146th Annual Meeting
American Neurological Association
Presented virtually
October 17–19, 2021
Opening Symposium: October 16, 2021
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ANA2021 Program

Sunday Poster Tour Sessions

Autoimmune Neurology

298. The Use of Routine Laboratory Parameters for Prediction of an Infectious or Autoimmune Etiology in Encephalitis

Hai E. Hoang, M.D.1, Jessica Robinson-Papp, M.D.2, Lan Mu, PhD3, Kiran Thakur, M.D.3, Carla Kim, M.D.3, Vivian Souko, M.D.3, Rachelle Dugue, M.D.3, Eileen Harrigan, M.D.3, Brittany Glassberg, M.D.2, Allison Navis, M.D.2, Jacqueline Sarah Gofsheyn, M.D.1, Mu Ji Huang, M.D.4, Nathalie Jette, M.D.2, Anusha K. Yeshokumar, M.D.2. 1Weill Cornell Medical Center, New York, NY, USA, 2Icahn School of Medicine at Mount Sinai, New York, NY, USA, 3Columbia University Irving Medical Center and New York Presbyterian Hospital, New York, NY, USA, 4New York Presbyterian Hospital, New York, NY, USA.

299. High Frequency of Asymptomatic Optic Nerve Enhancement in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder: Implication for Clinical Management and Trial Conduct

Shailee Shab, M.D.4, Padraig Morris, M.B., B.Ch.2, Marina Buciu, M.D.1, Deena Taifirouz, M.D.1, Dean Wingerchuk, M.D.3, Brian Weinschenker, M.D.1, Eoin Flanagan, M.B., B.Ch.1, Muhammad Tariq Bhatti, M.D.4, Sean Pittock, M.D.1, John Chen, M.D., Ph.D.4. 1Neurology, Mayo Clinic, Rochester, MN, USA, 2Radiology, Mayo Clinic, Rochester, MN, USA, 3Neurology, Mayo Clinic, Scottsdale, AZ, USA, 4Ophthalmology, Mayo Clinic, Rochester, MN, USA.

300. Parainfectious Neuromyelitis Optica Spectrum Disorder in a Patient with COVID-19 and Hepatitis B Co-Infection

Adil M. Ahmed, BS, Dmitriy Kosavlev, MD, Neeruika Thottempudi, MD, Elena Shanina, MD, PhD, Neurology, University of Texas Medical Branch, Galveston, TX, USA.

301. Clinical Outcomes Following Status Epilepticus in Anti-NMDAR Encephalitis

Seon-Jae Ahn, M.D., Soon-Tae Lee, M.D., Ph.D., Kon Chu, M.D., Ph.D. Seoul National University Hospital, Seoul, Korea, Republic of.

302. Investigations in Ca²⁺ Signaling in Anti-NMDAR Encephalitis

Charles A. Dean, BA1, Sarah R. Metzbeouver, PhD2, Scott K. Dosain, MD, PhD3, Thomas A. Blanpied, PhD2, David R. Benavides, MD, PhD4. 1Department of Neurology, University of Maryland School of Medicine, Baltimore, MD, USA, 2Department of Physiology, University of Maryland School of Medicine, Baltimore, MD, USA, 3Lankenau Institute for Medical Research, Wynnewood, PA, USA.

303. Analysis of Efgartigimod Efficacy Across Patient Populations and Myasthenia Gravis Specific Scales: Results of the Phase 3 ADAPT Study

Vera Bril, MD1, Hiroyuki Murai, MD2, Tuan Vu, MD3, Chafic Karam, MD4, Sujuan Peric, MD5, Temur Margania, MD6, Malgorzata Bilinska, MD7, Roman Shkarabshvili, MD8, Marek Smiłowski, MD9, Antonio Ciaglia, MD10, Peter Ulrichs, PhD10, Tony Vangeneugden, PhD10, Kimiaki Utsugisawa, MD11, Jan Vercruysen, MD12, Renato Mantegazza, MD13, James F. Howard, Jr., MD14, Ellen & Martin Prosserman Centre for Neuromuscular Diseases, University of Toronto, Toronto, Canada, 1Department of Neurology, International University of Health and Medicine, Tokyo, Japan, 2Department of Neurology, University of South Florida Morsani College of Medicine, Tampa, FL, USA, 3Penn Neurosciences Center, University of Pennsylvania, Philadelphia, PA, USA, 4Neurology, University of Belgrade, Belgrade, Serbia, 5Department of Neurology and Neuro-rehabilitation, New Hospitals, Tbilisi, Georgia, 6Department and Clinic of Neurology, Wroclaw Medical University, Wroclaw, Poland, 6Sarajishvili Institute of Neurology and Neurosurgery, Tbilisi, Georgia, 10Department of Hematology and Bone Marrow Transplantation, Medical University of Silesia, Katowice, Poland, 11argenx, Ghent, Belgium, 12Department of Neurology, Hanamaki General Hospital, Hanamaki, Japan, 13Department of Neurology, Leiden University Medical Center, Leiden, Netherlands, 14Department of Neuroimmunology and Neuromuscular Diseases, Fondazione Istituto Neurologico Carlo Besta, Milan, Italy, 14Department of Neurology, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

304. Genomic and Transcriptomic-Wide Analysis Identifies Novel Genetic Risk Loci and Prioritization of Therapies for Myasthenia Gravis

Ruth Chia, PhD1, Sara Saez-Aitienzar, PhD1, Natalie Murphy, BS3, Adriano Chiò, MD3,4, Cornelis Blauwendraat, PhD1, the International Myasthenia Gravis Genomics Consortium, 4, Ricardo H. Roda, MD3, Pentti J. Tenani, MD5,7, Henry J. Kaminski, MD6, Roberta Ricciardi, MD6, Melania Guida, MD6, Anna De Rosa, MD6, Loredana Petrucci, MD6, Amelia Eviol, MD10, Carlo Provenzano, MD10, Daniel B. Drachman, MD10, Bryan J. Traynor, MD10,7. 1Laboratory of Neurogenetics, National Institutes on Aging, National Institutes of Health, Bethesda, MD, USA, 2Rita Levi Montalcini Department of Neuroscience, University of Turin, Turin, Italy, 3Institute of Cognitive Sciences and Technologies, Rome, Italy, 4National Institutes on Aging, National Institutes of Health, Bethesda, MD, USA, 5Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA, 68.Research Program of Translational Immunology, Faculty of Medicine, Helsinki University Hospital, Helsinki, Finland, 7Research Program of Translational Immunology, Faculty of Medicine, University of
306. Challenging Diagnosis of Stroke in Young: A Case Report Reflecting Delayed Diagnosis of Takayasu Arteritis and Use of Ultrasound to Reveal Typical Inflammatory Vessels

Suzanne Odom, MD, Ana Giugliano, DO, Tamra Ransaning, MD. Wake Forest Baptist Health, Winston-Salem, NC, USA.

307. Hematologic Dysfunction in Aicardi Goutières Syndrome

Laura Adang, MD PhD MSTR, Francesco Gavazzi, MD, David Isaacs, BS (spring 2021), Noua Bronner, BS, Amanda Jan, BS, Zaida Flores, BS, Carly Scher, BS, Russell D’Alessio, MS, Justine Shults, PhD, Adeline Venderver, MD. 1Neurology, Children’s Hospital of Philadelphia, Philadelphia, PA, USA, 2Biostatistics, University of Pennsylvania, Philadelphia, PA, USA.

308. LGI4 is a Novel Autoantigen for Nodopathy/Paranodopathy Type Chronic Inflammatory Demyelinating Polyneuropathy

Xu Zhang, MD, PhD, Hidenori Ogata, MD, PhD, Tomohiro Imamura, MD, PhD, Takayuki Fujii, MD, PhD, Ryo Yamasaki, MD, PhD, Jun-ichi Kira, MD, PhD. 1Translational Neuroscience Center, Graduate School of Medicine, International University of Health and Welfare, Okawa, Japan, 2Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, 3School of Pharmacy at Fukuoka, International University of Health and Welfare, Okawa, Japan, 4School of Pharmacy and Department of Neurology, Fukuoka Central Hospital, International University of Health and Welfare, Fukuoka, Japan.

Behavioral Neurology

317. Genetic and Electrophysiological Biomarkers of Neuroplasticity Predict Post-Stroke Language Recovery

Haley C. Dresang, PhD, Denise Y. Harvey, PhD, Shreya Y. Parchure, BS, Roy H. Hamilton, MD, MS. 1Neurology, University of Pennsylvania, Philadelphia, PA, USA, 2Moss Rehabilitation Research Institute, Philadelphia, PA, USA, 3Engineering and Applied Science, University of Pennsylvania, Philadelphia, PA, USA.

318. Estimated Hypoperfusion Using Flair Predicts Presence and Severity of Hemispatial Neglect


335. Encephalopathy in Patients with COVID-19 Infection

Fatemeh Mohammadpour Touserkani, MD, Mohamed Elayed, MS, Lisa Calvo, MD, Loha Abdelwahab, MD, Dawen Zhang, BS, Sangni Park, MD, Patrick Arbor, MD, Movin Foroughi, MD, Malieheh Mohamadpour, MD, John Eduardo Maldonado, MD, Michael Silver, MPH, Ramaswamy Viswanathan, MD, DMSc, Yacov Anziska, MD. 1Neurology, SUNY Downstate Medical Center, Brooklyn, NY, USA, 2Psychiatry, SUNY Downstate Medical Center, Brooklyn, NY, USA, 3Pediatrics, SUNY Downstate Medical Center, Brooklyn, NY, USA, 4School of Public Health, SUNY Downstate Medical Center, Brooklyn, NY, USA.

360. Baseline Multimodal Imaging to Predict Longitudinal Decline in Atypical Alzheimer’s Disease

Ryan P. Coburn, MD, Jonathan Graff-Radford, MD, Peter R. Martin, MS, Keith A. Josephs, MD, Jennifer L. Whitwell, PhD, Hugo Botha, MBCM. Mayo Clinic, Rochester, MN, USA.

361. Inhibition of Hallucinations Through Electrical Stimulation of the Cerebellum

Athanasius Tochukwu Anasobi, MD, Lopez-Perez Macel, MD, Alan R. Hirsch, MD. 1All Saints University School of Medicine, Roseau, Dominica, 2Trinity School of Medicine, Ribishi, Saint Vincent and the Grenadines, 3Smell and Taste Treatment and Research Foundation, Chicago, IL, USA.

362. Central Precuneus Lesions Are Associated with Impaired Executive Function

Brooke E. Yeager, MS, Guillaume Herbet, PhD, Daniel Tranell, PhD, Aaron Boes, MD, PhD. 1Neurology, University of Iowa, Iowa City, IA, USA, 2Neurosurgery, University of Montpellier, Montpellier, France.

432. Assessing Symptom Severity of Primary Progressive Aphasia in Research Cohorts

Lynsey M. Keator, MA, Donna C. Tippett, MPH, MA. 1Center for the Study of Aphasia Recovery (C-STAR), Dept of Communication Sciences and Disorders, University of South Carolina, Columbia, SC, USA, 2Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

433. Behavioral Disturbances in Progressive Apraxia of Speech and Agrammatic Aphasia

Fatma Ozlem Hokelekli, MD, PhD, Joseph R. Duffy, PhD, Heather M. Clark, PhD, Rene L. Uriausuki, PhD, Hugo Botha, MB, ChB, Julie A. Sitterwalt, PhD, Edythe A. Strand,
PhD2, Mary M. Machulda, PhD2, Jennifer L. Whitwell, PhD3, Keith A. Josipov, MD, MST, MSc.1, Neurology, Mayo Clinic, Rochester, MN, USA, 2Division of Cardiology, Weill Cornell Medical College, New York, NY, USA, 3Department of Neurology, Feil Family Brain and Mind Research Institute and Department of Radiology, Mayo Clinic, Rochester, MN, USA.

Cerebrovascular Disease

319. Intraventricular Tissue Plasminogen Activator Use and Reduction of Parenchymal Hematoma Volume in the CLEAR III Trial
Jens Witsch, MD1, David Roh, MD2, Radhika Asadhan, MS3, Alexander E. Merkler, MD, MS1, Hooman Kamel, MD, MS2, Issam Awad, MD3, Daniel F. Hanley, MD3, Wendy C. Ziai, MD, MPH1, Santosh B. Murthy, MD, MPH1. 1Clinical and Translational Neuroscience Unit and Department of Neurology, Feil Family Brain and Mind and Translational Neuroscience Unit and Department of Neurology, Feil Family Brain and Mind, Weill Cornell Medical College, New York, NY, USA, 2Department of Neurology, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA, 3Brain Injury Outcomes Division, Johns Hopkins University School of Medicine, Baltimore, MD, USA, 4Department of Neurological Surgery, University of Chicago School of Medicine, Chicago, IL, USA.

320. Extrastriate Visual Cortex Damage and Temporoparietal Disconnection in Anton Syndrome
Elena Monari, MD1, Federica Palacino, MD1, Marta Bizzio, PhD2, Francesca Bernocchi, MD1, Lorenzo Pini, PhD2, Alessandro Salvataggio, MD2, Maurizio Corbetta, MD1,3.1 Department of Neuroscience, Clinica Neurologica, University of Padova, Padova, Italy, 2Padova Neurosciences Center (PNC), University of Padova, Padova, Italy, 3Padova Neuroscience Center (PNC), Venetian Institute of Molecular Medicine (VIMM), Fondazione Biomedica, Padova, Italy.

321. Left Atrial Strain and Atrial Cardiopathy in Embolic Strokes of Undetermined Source (ESUS)
Ajay Menon, Medical Student1, Jiyoung Kim, MD2, Hooman Kamel, MD1. 1Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute and Department of Neurology, Weill Cornell Medical College, New York, NY, USA, 2Division of Cardiology, Weill Cornell Medical College, New York, NY, USA.

322. Differences in Peripheral Leukocyte Subtypes Between Slow and Fast Progressors of Infarct Growth in Anterior Circulation Large Vessel Occlusion Stroke
Jiyoun Son, MD, Marcello Rocha, MD PhD, Neurology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA.

323. Early Deterioration, Hematoma Expansion, and Outcomes After Lobar Intracerebral Hemorrhage in the Fast Trial
Lindsey R. Kuohn, BA1, Stephanie Mayer, MD2, Thorsten Steiner, MD3, Kevin N. Sheth, MD4, Hooman Kamel, MD, MS5, Babak B. Navi, MD, MS5, Alexander E. Merkler, MD, MS5, Santosh B. Murthy, MD, MPH2, Jens Witsch, MD3. 1NYU Grossman School of Medicine, New York, NY, USA, 2New York Medical College, Valhalla, NY, USA, 3University of Copenhagen School of Medicine, Copenhagen, Denmark, 4Yale School of Medicine, New Haven, CT, USA, 5Weill Cornell School of Medicine, New York, NY, USA.

324. Adding MRI After CT is Not Associated with Improved Ischemic Stroke Outcomes at Discharge
Heitor C. Frade, MD1, Anne Beckwith, BS, CCNP2, Susan Wilson, DNP, ANP-BC3, William J. Powers, MD2. 1Neurology, University of Texas Medical Branch, Galveston, TX, USA, 2Neurology, University of North Carolina, Chapel Hill, NC, USA.

325. Elevated Initial Troponin I Levels in Patients with Spontaneous Intracerebral Hemorrhage Predict Poor Functional Outcome
Ahmed Abbas, MD1, Ammar Taradichi, MD1, Amber Fifer, PharmD2, Kristin Delfino, PhD3, Hesham Allam, MD1. 1Department of Neurology, Southern Illinois University School of Medicine, Springfield, IL, USA, 2Center for Clinical Research, Department of Neurology, Department of Psychiatry, Southern Illinois University School of Medicine, Springfield, IL, USA, 3Center for Clinical Research, Department of Surgery, Southern Illinois University School of Medicine, Springfield, IL, USA.

326. Reducing Readmission Rates by Improving Transitions of Care for Stroke Patients in the Pre-COVID and COVID Eras
Evan Kolesnick, MS1,2, Elise Lambertson, MSN3, Robin Dharia, MD3,1 Philadelphia College of Osteopathic Medicine, Philadelphia, PA, USA, 2Thomas Jefferson University, Philadelphia, PA, USA, 3Department of Neurology, Thomas Jefferson University, Philadelphia, PA, USA.

327. Stroke Severity and Post-Acute Care Discharge Setting Interact to Predict Mortality After Stroke
Mellanie V. Springer, MD MS, Lesli E. Skolarus, MD MS, Chunyang Feng, PhD, James F. Burke, MD MS, University of Michigan, Ann Arbor, MI, USA.

328. Duration of Heightened Ischemic Stroke Risk Following Hospitalization for Acute Systolic Heart Failure
Teহমিযাত Baj, Medical Student1, Desin J. Burke, MD1, Parag Goyal, MD2, Cenai Zhang, MS3, Alexander E. Merkler, MD, MS1. 1Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute and Department of Neurology, Weill Cornell Medicine, New York, NY, USA, 2Department of Medicine, Weill Cornell Medicine, New York, NY, USA.
341. The Mas Receptor Agonist TXA127 Blocks Neurovascular Inflammation Associated with Sars-CoV-2 Infection

Naoki Kaneko, MD/PhD1, Lea Guo, B.S.1, Jennifer An, B.S.2, Suman Dutta, Ph.D2, Davis Chong, B.S.3, Yutaro Komuro, Ph.D3, Fanny Elahi, MD/PhD3, Jason D. Hinman, MD/PhD4, Jason D. Hinman, MD/PhD4, Benjamin B. Gelman, MD, PhD5, Susan Morgello, MD6, neurology, ucla, los angeles, ca, usa, 2neurology, georgia institute of technology, atlanta, ga, usa, 3neurology, ucla, los angeles, ca, usa, 4neurology, ucsf, san francisco, ca, usa.

Dementia and Aging

363. Peripheral Inflammation and Depressed Mood Independently Predict Neurocognitive Worsening Over 12 Years

Ronald J. Ellis, MD, PhD1, Robert K. Heaton, PhD2, Bin Tang, MS3, Ann C. Collier, MD4, Christina Manna, MD5, Benjamin B. Gelman, MD, PhD6, Susan Morgello, MD6, David B. Clifford, MD3, Ned Sacktor, MD4, Scott L. Letendre, MD5. 1Neurosciences and Psychiatry, University of California, San Diego, San Diego, CA, USA, 3Psychiatry, University of California, San Diego, San Diego, CA, USA, 4Neurology, University of Washington, Seattle, WA, USA, 5Neurology, University of Washington, Seattle, WA, USA, 6Neurology, Baylor College of Medicine, Houston, TX, USA, 6Neurology, Neurosciences and Psychiatry, University of California, San Diego, San Diego, CA, USA.

364. Introducing DBM-21, a Novel and Potent Imaging Biomarker for Accurate and Non-Invasive Early Detection of Alzheimer’s Disease

Kaveh Vejdani, MD. Technology, Darmiyan, Inc, Berkeley, CA, USA.

366. Towards Universal Deep Learning Artificial Intelligence for Alzheimer’s Disease Magnetic Resonance Imaging

Raghav Tandon, BS1, Sivagami Nambi, BS2, Cassie S. Mitchell, Ph.D.1. 1Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA, USA, 2Georgia Institute of Technology, Atlanta, GA, USA.

367. A Machine Learning Approach to Analyze the Efficacy of Standard Clinic Metrics for Predicting Alzheimer Progression

Sri Vivek Vanga, MS1, Raghav Tandon, M.S.2, Anna Kirkpatrick, Ph.D.3, Cassie S. Mitchell, Ph.D.3. 1Computer Science, Georgia Institute of Technology, Atlanta, GA, USA, 2Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA, USA, 3Math, Georgia Institute of Technology, Atlanta, GA, USA.

369. Tractography Analysis of Supplementary Motor Area White Matter Tracts in Progressive Apraxia of Speech and Agrammatic Aphasia

Adrian Valls-Carbo, MD, PhD1, Robert I. Reid, PhD2, Nirubol Tosakulwong, BS3, Joseph R. Duffy, PhD4, Heather M. Clark, PhD5, Rene L. Uritanski, PhD6, Mary M. Machulda, PhD7, Hugo Bertha, MD2, Edythe A. Strand, PhD2, Stephen D. Weinland, MS2, Clifford R. Jack, Jr., MD2, Keith A. Josephs, MD2, Jennifer L. Whitwell, PhD1. 1Hosp. San Carlos, Madrid, Spain, 2Mayo Clinic, Rochester, MN, USA.

370. Abeta-Accelerated Neurodegeneration Caused by Alzheimer’s-Associated ACE Variant R1279Q is Rescued by Angiotensin System Inhibition in Mice

Robert Vassar, PhD1, Leah Cuddy, PhD1, Dmitry Prokopenko, PhD2, Rory Kirchner, PhD3, Oliver Hofmann, PhD4, Winston Hid, PhD5, Taleen Hanaian, PhD6, Steven Leiser, PhD7, Daniel Proce, PhD7, Peter Song, BA1, Rudolph Tanzi, PhD1. 1Neurology, Northwestern University, Chicago, IL, USA, 2Massachusetts General Hospital, Boston, MA, USA, 3Harvard T.H. Chan School of Public Health, Boston, MA, USA, 4University of Melbourne, Melbourne, Australia, 5Beth Israel Deaconess Medical Center, Boston, MA, USA, 6Psychogenics, Inc., Paramus, NJ, USA, 7Northwestern University, Chicago, IL, USA, 8Massachusetts General Hospital/Harvard, Boston, MA, USA.

371. Structural and Molecular Determinants of Repeat RNA Toxicity in Non-Amyloid Dementias

Peter K. Todd, MD/PhD. Neurology, University of Michigan, Ann Arbor, MI, USA.

428. Investigating the Utility of Common Linguistic Tasks in Distinguishing PPA Subtypes

Melissa D. Stockbridge, Ph.D., Donna C. Tippett, M.A., M.P.H., Bonnie L. Breining, Ph.D., Emilia Vitti, M.S., Argye E. Hillis, M.D. Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

429. Regional Atrophy Predicts Naming Decline in Primary Progressive Aphasia: A Comparison of Cross-Sectional and Longitudinal Analyses

Bonnie L. Breining, Ph.D.1, Andrea V. Faria, M.D., Ph.D.2, Donna C. Tippett, M.A., M.P.H.2, Melissa D. Stockbridge, Ph.D.1, Erin L. Meier, Ph.D.3, Olivia Herrmann, M.S.3, Alejandro Alfino, Ph.D.1, Aaron M. Meyer, Ph.D.4, Kyrana Tsapkini, Ph.D.1, Argye E. Hillis, M.D., M.A.1. 1Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2Radiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA, 4Communication Sciences and Disorders, Northeastern University, Boston, MA, USA, 5Neurology, Georgetown University, Washington, DC, USA.
Education

337. Assessment of the Efficacy of a Virtual Neurology Elective for Medical Students Developed During COVID-19
Kori A. Porosnicu Rodríguez, BA1, Christine E. Gummerson, MD2, Brian D. Lo, BS3, Zoe L. Coner, BS4, Dylan W. Hardenbergh, BA5, Diana M. Bongiorno, MPH6, Julia J. Waiinger, MPH7, Katherine Hu, BS8, Charlene E. Gamaldo, MD9, Rachel M.E. Salas, MD, MD10, Carlos G. Romeo, MD11, Doris G. Leung, MD, PhD12, 1Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2Neurology, Yale University School of Medicine, New Haven, CT, USA, 3Johns Hopkins University, Baltimore, MD, USA.

Epilepsy

338. Encephalopathy, Epileptiform Activity, and Seizures in Patients with COVID-19
Kaitlin Seibert, MD, Wonhee Lee, MD, Alexandra Eid, MD, Sara Klein, MD, Sumayyah Abumurad, MD, Fabiane Santos de Lima, MD, Naoun P. Isu, MD, PhD, Shaiba Wu, MD, PhD, Sandra Rose, MD, James X. Tao, MD, PhD. University of Chicago, Chicago, IL, USA.

342. Association of COVID-19 Infections with New-Onset and Breakthrough Epileptic Seizures
Hardik Bhaskar, BA1, Neeraj Singh, MD2, 1Department of Chemistry, Hunter College of City University of New York, New York, NY, USA, 2Department of Neurology, Northwell Health, Great Neck, NY, USA.

343. Anxiety, Depression and Medication Side Effects as Determinants of Quality of Life in People with Epilepsy
Leah Orozco, MS, Tianxia Wu, PhD, Sara Inati, MD, Shareaena Rahman, MD. National Institutes of Health, Bethesda, MD, USA.

344. Patient Reported Outcomes of Anxiety and Depression in Adults with Epilepsy: 6-month Outcomes During Usual Care in a Pilot Randomized Trial of Two Remote Outcome Assessment Methods
Heidi Munger Clary, MD, MPH1, Beverly Snively, PhD, Pamela Duncan, PhD, Umit Topaloglu, PhD, Gretchen Brenes, PhD. Wake Forest School of Medicine, Winston-Salem, NC, USA.

345. Increased Amplitude of Corticocortical Evoked Potentials Predicts the Site of Epilepsy Surgery
Adam Dickey, MD, PhD1, Jon T. Willile, MD, PhD2, Armin Vannoughi, MD3, Robert E. Gross, MD, PhD4, Nigel P. Pedersen, MBBS5, 1Emory University, Atlanta, GA, USA, 2Washington University, St. Louis, MO, USA.

346. Depression and Anxiety in Adult Persons with Epilepsy and Their Caregivers
Ioannis Karakis, MD, PhD, MSc1, Diane L. Teagarden, NP2, Hannah K. Villarreal, NP3, Matthew L. Morton, MD4, Nicholas J. Janoeck, MD5, Olivia Groover, MD6, David W. Loring, PhD7, Daniel L. Drane, PhD8, Konstantinos Tsamakis, MD, Msc, PhD9, 1Neurology, Emory University School of Medicine, Atlanta, GA, USA, 2Psychiatry, National and Kapodistrian University of Athens, Athens, Greece.

347. Long-Term Efficacy and Safety of Adjunctive Perampanel in Elderly Patients (Aged ≥60 years) with Focal-Onset Seizures (FOS): Post Hoc Analysis of Open-Label Extension (OLE) Studies by Enzyme-Inducing Anti-Seizure Medication (EIASM) Use
Robit Marawar, MD1, Ilo E. Leppik, MD2, Robert T. Wechsler, MD, PhD3, Anna Patten, PhD4, Leeck Y Ngo, PhD5, Manaaj Malhotra, MD6, 1Wayne State University, Detroit, MI, USA, 2University of Minnesota, Minneapolis, MN, USA, 3Idaho Comprehensive Epilepsy Center, Boise, ID, USA, 4Eisai Europe Ltd., Hatfield, United Kingdom, 5Eisai Inc., Woodcliff Lake, NJ, USA.

Global Neurology

339. Analysis of COVID-19 Brain Autopsies Reveals That Neuroinflammation is Not Caused by Direct SARS-CoV-2 Infection of the CNS
Kirtn T. Thakur, M.D.1, Emily H. Miller, MD2, Michael D. Glendinning, BA3, Osama Al-Dalahmah, MD, DPhil2, Matei A. Banu, MD1, Amelia K. Boehme, MD MSPH1, Alexandra L. Boubour, BA4, Samuel S. Bruce, MD5, Alexander M. Chong, BS6, Jan Claassen, MD, FNCS7, Phyllis L. Faust, MD, PhD8, Gunnar Hargus, MD PhD9, Richard Hickman, MD10, Sachin Jambhulikar, PhD11, Alexander G. Khandji, MD11, Carla Y. Kim, BS12, Robyn S. Klein, MD, PhD13, Angela Lignelli-Dipple, MD13, Chuan-Chieh Lin, MD, PhD14, Yang Liu, MD MS15, Michael M. Miller, MD, PhD16, Gul Moonis, MD17, Anna S. Nordvig, MD17, Andrew F. Teich, MD, PhD18, Drittan Agullia, PhD19, Anne-Catrin Uhlemann, MD, PhD20, Donna L. Rut, MD21, Allison Song, BS22, Kurenai Tanji, MD23, D. Glendinning, BA24, Peter D. Canoll, MD, PhD25, 1Dept. of Neurology, Columbia University Irving Medical Center, New York, NY, USA, 2Dept. of Pathology and Cell Biology, Division of Neuropathology, Columbia University Irving Medical Center, New York, NY, USA, 3Dept. of Medicine, Division of Infectious Diseases, Columbia University Irving Medical Center, New York, NY, USA, 4Dept. of Medicine, Columbia University Irving Medical Center, New York, NY, USA, 5Dept. of Radiology, Columbia University Irving Medical Center, New York, NY, USA, 6Dept. of Pathology and Laboratory Medicine, Washington University School of Medicine, St. Louis, MO, USA, 7Dept. of Pathology and Laboratory Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA.
Headache and Pain

385. A Phase 3 Randomized, Double-Blind, Sham-Controlled Trial of E-TNS for the Acute Treatment of Migraine (Team)
Deena E. Kuruvilla, MD1, Amael J. Starling, MD2, Stewart J. Tepper, MD3, Joseph I. Mann, MD1, Gregory Panza, PhD3, Michael Johnson, MD3, 1Westport Headache Institute, Westport, CT, USA, 2Neurology, Mayo Clinic, Phoenix, AZ, USA, 3Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA, 4Rochester Clinical Research, Rochester, NY, USA, 5CEFALY, Darien, CT, USA.

386. Efferent Projections of CGRP/Calcium-Expressing Parabrachial Neurons in Mice
Duke Huang, BS, Filan S. Grady, BS, Lila Pelekian, BS, Justin Lating, GED, Joel C. Geerling, MD PhD, University of Iowa, Iowa City, IA, USA.

387. Mindfulness-Based Stress Reduction (MBSR) vs. HA Education: A Randomized Clinical Trial Showing Mindfulness Targets Total Migraine Burden
Rebecca Erwin Wells, MD, MPH1, Nathaniel O’Connell, PhD1, Charles R. Pierce, MS1, Paige Estave, BS1, Donald B. Penzien, PhD1, Elizabeth Loder, MD, MPH1, Fadel Zeidan, PhD1, Timothy T. Houle, PhD4, 1Wake Forest Baptist Health, Winston Salem, NC, USA, 2Brigham and Women’s Hospital & Harvard Medical School, Boston, MA, USA, 3University of California-San Diego, San Diego, CA, USA, 4Massachusetts General Hospital and Harvard Medical School, Boston, USA.

388. Noninvasive Combined Occipital and Trigeminal Nerve Stimulation - Established Efficacy, Safety and Tolerability in the Acute Treatment of Migraine
Ronni Sharon, MD1,2, Daniel Oved, MD3, Stewart Tepper, MD4, 1Tel Aviv University, Sackler School of Medicine, Tel Aviv, Israel, 2Department of Neurology, Sheba Medical Center, Ramat Gan, Israel, 3Ramat Aviv Medical Center, Headache and Facial Clinic, Tel Aviv, Israel, 4Department of Neurology, Dartmouth Hitchcock Medical Center, Hanover, NH, USA.

389. Total Pain Burden in Patients with Treatment-Resistant Migraine: Effects of Galcanezumab in the CONQUER Phase 3B Trial
Jessica Ailani, MD1, J Scott Andrews, PharmD2, Antje Tockhorn-Heidenreich, MS3, Richard Wenzel, PharmD3, Mallikarjuna Rettiganti, PhD3, 1Medstar Georgetown University, Cambridge, MD, USA, 2Takeda Pharmaceuticals, Cambridge, MA, USA, 3Eli Lilly and Company, Indianapolis, IN, USA.

390. Sensory Predictors of Post-Traumatic Headache Related Disability
Cecilia Martindale, BA1, KC Brennan, MD, Melissa M. Cortez, DO. Neurology, University of Utah, Salt Lake City, UT, USA.

Movement Disorders

395. Sv2c is Required for Nicotine-mediated Rescue of Alpha-synuclein Toxicity
Sabrini Clemens, BS, Abby Olsen, MD PhD, Brigham and Women’s Hospital, Boston, MA, USA.

430. Patterns of Cortical Tau Pathology in LBD and PSP: A Multi-Center Digital Histology Study
David G. Coughlin, MD MTR1, Annie Hiniker, MD PhD2, Claire Peterson, BS3, Lucia Gianmini, MD4, Donald Pizzo, PhD3, Irene Litvan, MD3, Robert Risman, PhD2, Douglas Galasko, MD1, Daniel Weintraub, MD2, Andrew Siderowf, MD MScE1, John Q. Trojanowski, MD PhD2, Edward B. Lee, MD PhD2, Murray Grossman, MD1, David J. Irons, MD MTR1.

Multiple Sclerosis

340. Response to COVID-19 mRNA Vaccination in Patients with Multiple Sclerosis on anti-CD20 Disease Modifying Therapies
Andrew Wolf, MD1, Robert W. Pratt, MD1, Kirsty Crooks, PhD2, Tyler Borko, BS1, Jose Parra Gonzalez, BS1, Peter R. Martin, MS1, Joseph R. Duffy, PhD2, Heather M. Clark, PhD2, Rene L. Uitianski, PhD2, Edythe A. Strand, PhD2, Mary M. Machulda, PhD2, Hugo Botha, MD1, Nha Trang Thu Pham, BS1, Farwa Ali, MD1, Julie A. Stierwalt, PhD2, Marina Buciuc, MD2, Anthony J. Spychalla, BS2, Christopher G. Schwarz, PhD2, Robert I. Reid, PhD2, Matthew L. Senjem, MS2, Clifford R. Jack, MD2, Val J. Lowe, MD2, Dennis W. Dickson, MD2, Keith A. Josephs, MD, MST, MS2.1. Mayo Clinic, Rochester, MN, USA, 2Mayo Clinic, Jacksonville, FL, USA.

Neurogenetics

308. Reverse Transcriptase Inhibition as a Novel Therapeutic Approach for ADAR1-Related Aicardi-Goutières Syndrome
Akshata Almad, PhD1, Luis Garcia, BS1, Sarah Woidill, BS1, Asako Takanohashi, PhD4, Laura Adang, MD, PhD4.
Susan Weiss, PhD2, Adeline Vanderver, MD1. 1Department of Neurology, The Children’s Hospital of Philadelphia, Philadelphia, PA, USA, 2Department of Microbiology, University of Pennsylvania, Philadelphia, PA, USA.

354. Trio Exome Sequencing with In-Depth Phenotyping in Pediatric Epilepsy: A Prospective, Single-Centered Cohort Study with Return of Research Results to Patients

Hyunyong Koh, MD, PhD1, Lacey Smith, MS, CGC1, Archana Podary, BA2, Naisib Chouvaria, MD3, Emma Sexton, BS1, Devon Knight, BA1, Rebecca Pinsky, MSN, RN, CPNP4, Christelle Muafawad El Achkar, MD1, Christopher Yassaitis, MD, PhD1, Heather Olson, MD, MPH1, Beth Sheidley, MS, CGC1, Annapurna Poduri, MD, MPH1. 1Boston Children’s Hospital, Boston, MA, USA, 2Harvard Medical School, Boston, MA, USA, 3The University of Tennessee Health Science Center, Memphis, TN, USA.

Neuromuscular Disease

292. Neurotoxic Properties of Human Endogenous Retrovirus-K Envelope Protein and Detection in Cerebrospinal Fluid of Patients with Amyotrophic Lateral Sclerosis

Joseph Steiner, PhD1, Muzna Bachani, MS1, Nair Malik, PhD3, Wenxue Li, PhD4, Kevon Sampson, MS1, Myung-Hwa Lee, PhD1, Manju Bhaskar, PhD1, Bryan Smith, MD2, Lauren Reona, MD1, Joanna Brunel, PhD2, Benjamin Charvet, PhD1, Justine Pierquin, PhD2, Hervé Perron, PhD2, Avindra Nath, MD1. 1National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA, 2GeNeuro, Lyon, France, 3Geneuro, Lyon, France.

293. CK1ε-Dependent TDP-43 Phosphorylation in ALS

Vivian Ko, B.S., Sandra Diaz Garcia, Ph.D., Maria Rodriguez, B.S., John Raitts, M.D. Department of Neuroscience, University of California San Diego (UCSD), La Jolla, CA, USA.

294. Nuclear Accumulation of Chmp7 Initiates Nuclear Pore Complex Damage and Subsequent TDP-43 Dysfunction in Sporadic and Familial ALS

Alyssa Coyne, PhD1, C. Patrick Luk, PhD2, Frank Rigo, PhD3, Frank Bennett, PhD4, Jeffrey D. Rothstein, MD, PhD1. 1Neurology and Brain Science Institute, Johns Hopkins University, Baltimore, MD, USA, 2Cell Biology, Yale University, New Haven, CT, USA, 3Ionis Pharmaceuticals, Carlsbad, CA, USA, 4Ionis Pharmaceuticals, Carlsbad, CA, USA.

295. Sex and Age Impact the Role of the Immune System in Amyotrophic Lateral Sclerosis

Benjamin J. Murdock, Ph.D.1, Joshua P. Fannie, B.S.1, Caroline E. Pieruch, B.S.1, Kristen D. Raue, B.S.1, Cole H. Pieroni, B.S.1, Sebastian D. Iniguez, B.S.1, Jonathan Bou, B.S., M.S.2, Sehee Kim, Ph.D2, Lili Zhou, Ph.D2, Stephen A. Goutman, M.D.1, Eva L. Feldman, M.D., Ph.D.1. 1Neurology, University of Michigan, Ann Arbor, MI, USA, 2Biostatistics, University of Michigan, Ann Arbor, MI, USA.

296. The Gut Microbiome: Modulator of Environmental Insults in Amyotrophic Lateral Sclerosis

Claudia Figueroa-Romero, PhD1, Kai Guo, PhD1, Mohamed Noureldine, PhD2, Benjamin J. Murdock, PhD1, Stephen A. Goutman, MD1, Junguk Hur, PhD2, Stuart Bartterman, PhD1, Eva L. Feldman, MD PhD1. 1Neurology, University of Michigan, Ann Arbor, MI, USA, 2Department of Biomedical Sciences, University of North Dakota, Grand Forks, ND, USA, 3School of Public Health, University of Michigan, Ann Arbor, MI, USA.

297. Dynamic Network Stability Analysis for Prioritizing Experimental Combination Therapies for Amyotrophic Lateral Sclerosis

Sarab Bé, BS, Adam Krueger, BS, Eleanor Ridgeway, BS, Saktshi Deshpande, BS, Abad Khatri, BS, Albert Lee, BS, Cassie S. Mitchell, Ph.D. Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA, USA.

298. A Pilot Study on Hand Palmar and Digital Nerve Ultrasound in Peripheral Nerve Diseases

Jiping Zhou, MD1, Jun Li, MD, PhD2, Ryan Castoro, DO2. 1Department of Neurology, Wayne State University School of Medicine/Detroit Medical Center, Detroit, MI, USA, 2Division of Neuromuscular & Inherited Neuropathies, Department of Neurology, Wayne State University School of Medicine/Detroit Medical Center, Detroit, MI, USA.

299. Nadph Oxidase 5: A New Player in Peripheral Neuropathy

Stephanie A. Eid, PhD1, Faye Mendelson, B.S.1, John Hayes, B.S.1, Crystal Pacut, B.S.1, Kai Guo, PhD2, Junguk Hur, PhD2, Eva L. Feldman, M.D., Ph.D.,1. 1Neurology, University of Michigan, Ann Arbor, MI, USA, 2University of North Dakota, Grand Forks, ND, USA.

300. A Novel Pathologic Variant in MFN2

Leah Miller, BA, Noah Kolb, MD. University of Vermont Medical Center, Burlington, VT, USA.

Pain Mechanisms & Treatment

420. Peripheral Neuropathic Changes in Prurigo Nodularis

Baohan Pan, MD, PhD1, Shawn Kwatra, MD2, Xin Pan, MD3, Michael Polydefkis, MD1. 1Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA, 2Department of Dermatology, Johns Hopkins School of Medicine, Baltimore, MD, USA.
Monday Poster Tour Sessions

Autoimmune Neurology

311. Headaches and Neurologic Deficits with Cerebrospinal Fluid Lymphocytosis Syndrome Post SARS-CoV-2 Infection: A Case Report
Bismah Arif Hasan, BS, Nujub Farag, MD, Prashant Natteru, MD, Mary Alissa Willis, MD. University of Mississippi Medical Center, Jackson, MS, USA.

312. Can Clippers be Diagnosed without Pontine Involvement?
Edith L. Graham, MD, Elena Grebenciucova, MD. Northwestern University, Chicago, IL, USA.

405. A Rare Case of Rapidly Progressive Myasthenia Gravis with Coexisting Necrotizing Autoimmune Myopathy
Neeharika Thottempudi, MD, Sandeep Bhatt, MD, Ahmed Harazeen, MD, Neliaza Rivera Vega, MD, Chilvana Patel, MD, Xiangping Li, MD. Neurology, University of Texas Medical Branch, Galveston, TX, USA.

Cerebrovascular Disease

329. Sex Differences in Risk Factor Control Among Patients Undergoing Thrombectomy for Acute Ischemic Stroke
Adam P. Klein, DO1, Rakhee Lalla, DO1, Karen Yarbrough, ACNP1, Prachi Mehndiratta, MD1, Michael S. Phipps, MD1, Garuw Jindal, MD1, Carolyn A. Cronin, MD, PhD1, Marcella A. Wozniak, MD, PhD1, John W. Cole, MD1, Seenam Chaturvedi, MD1. 1Neurology, Medical University of South Carolina, Charleston, SC, USA.

330. White Matter Microstructure as a Predictor of Clinical Response to Transcranial Direct Current Stimulation in Post-Stroke Aphasia
Cori Cummings, MD4, Kyle Blidy, MS1, Janina Wilsnoketter, PhD2,4, Julius Fridriks, PhdB,4, Leonardo Bonilha, MD, PhD4. 1Neurology, Medical University of Kentucky, Lexington, KY, USA, 2S Sanders Brown Center on Aging, University of Kentucky, Lexington, KY, USA, 3Neurology and Sanders Brown Center on Aging, University of Kentucky, Lexington, KY, USA, 4Neurology, University of Kentucky, Lexington, KY, USA.

Dementia and Aging

372. Transcriptomic Analyses of Synaptic, Amyloid, and Tau Pathways in A20-Deficient Mice
Rawan Tarawneh, MD1, Maciej Pietrzak, PhD2. 1Neurology, The Ohio State University, Columbus, OH, USA, 2Biomedical Informatics, The Ohio State University, Columbus, OH, USA.

373. Differentiating the Cognitive Trajectory of TDP-43 vs. Alzheimer’s Disease Neuropathology in the Oldest Old
Kiana A. Scambray, BA12, Anne-Marie Leiby, BA, BS12, Hannah L. Nguyen, BS1,2, Giovanna Bubbico, PhD1,3, Michael J. Phelan, PhD1, Maria M. Corrada, ScD2,4, S. Ahmad Sajjadi, MD, PhD1,2. 1Neurology, University of California, Irvine, Irvine, CA, USA, 2Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, Irvine, CA, USA, 3Institute for Alzheimer’s Disease and Related Disorders, University of California, Irvine, Irvine, CA, USA.

374. Unsupervised Machine Learning to Identify Latent Relationships in Clinical Alzheimer Disease Relevant to Sub-Population Disease Progression
Robert Quinn, BS1, Velda Wang, BS2, Cassie S. Mitchell, PhD, D.2. 1Georgia Institute of Technology, Atlanta, GA, USA, 2Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA, USA.

375. Anti-Hypertensive Medication Use is Associated with Decreased Likelihood of Neurodegenerative Pathologies
Hannah L. Nguyen, BS, Kiana A. Scambray, BA, S. Ahmad Sajjadi, MD PhD. Department of Neurology, University of California, Irvine, Irvine, CA, USA.

376. Periventricular White Matter Hyperintensities Are a Potential Noninvasive Imaging Marker for Alzheimer- Like Cerebrospinal Fluid Amyloid β Levels in Cognitively Normal Aging Adults
Omar M. Al-Janabi, MD, MS, PhD1, Justin M. Barber, MS2, Katherine E. Snyder, BS2, Gregory A. Jicha, MD, PhD3. 1Neurology, University of Kentucky, Lexington, KY, USA, 2Sanders Brown Center on Aging, University of Kentucky, Lexington, KY, USA, 3Neurology and Sanders Brown Center on Aging, University of Kentucky, Lexington, KY, USA.
377. Preclinical Imaging of Microtubule Radioligand 11C-MPC-6827 in Animal Models of Alzheimer’s Disease

Ramesh Neelamegam, PhD1,2, Wei Zhang, PhD2, Michael O’Boyle, BS2, Veronica Galvan, PhD3, Jaya Prabhakaran, PhD4, Peter Fox, MD1,2, Sudha Seshadri, MD2, Dileep Kumar, PhD2. 1UT Health San Antonio/Glenn Biggs Institute, San Antonio, TX, USA, 2Radiology, Research Imaging Institute, San Antonio, TX, USA, 3Barshop Institute for Longevity and Aging Studies, San Antonio, TX, USA, 4Psychiatry, Columbia University Medical Center, New York, NY, USA, 5Feinstein Institutes for Medical Research, Manhasset, NY, USA.

378. Non-Invasive Deep Brain Modulation in Humans via Rhythmic Sensory Stimulation

Lou T. Blanpain, BA1, Michael Y. Walelign, BE2, James K. Park, BS1, Emily Chen, HSD1, Jon T. Willie, MD-PhD3, Annabelle C. Singer, PhD2. 1Emory University, Atlanta, GA, USA, 2Georgia Institute of Technology, Atlanta, GA, USA, 3- Washington University School of Medicine, St. Louis, MO, USA.

379. Written Language Impairments in Subgroups of Mild Cognitive Impairment

Hana Kim, Ph.D, Alex Walker, BA, Jennifer Shea, BA, Argye Hills, MD, Johns Hopkins School of Medicine, Baltimore, MD, USA.

380. Quantitative and Qualitative EEG Differences Between Dementia with Lewy Bodies and Alzheimer’s Disease

Jay R. Bronder, MD MBA1, Peter Kaplan, MBBS2, Paul B. Rosenberg, MD2, Jee Bang, MD2, Emily L. Johnson, MD2. 1Johns Hopkins Hospital, Baltimore, MD, USA, 2Johns Hopkins University School of Medicine, Baltimore, MD, USA.

382. Systemic Inflammation Elicits Distinct Brain Immune Signaling Dynamics in Female and Male Mice with AD Pathology

Sara Bitarafan, BS1, Supria Ramesha, Ph.D.2, Hailian Xiao, BS2, Benjamin J. Ahn, MD3, Srikanth Ranganaju, M.D.2, Levi B. Wood, Ph.D.4. 1Bioengineering, Georgia Institute of Technology, Atlanta, GA, USA, 2Neurology, Emory University, Atlanta, GA, USA, 3Biology, Georgia Institute of Technology, Atlanta, GA, USA, 4Mechanical Engineering, Georgia Institute of Technology, Atlanta, GA, USA.

383. Pathophysiological Changes in Soluble Amyloid Precursor Protein-β Turnover in Alzheimer’s Disease

Justyna A. Dobrowolska Zakaria, PhD1, Randall J. Bateman, MD2, Bruce W. Patterson, PhD1, Robert J. Vasiar, PhD1, 1Neurology, Northwestern University, Chicago, IL, USA, 2Neurology, Washington University in St. Louis, St. Louis, MO, USA, 3Medicine, Washington University in St. Louis, St. Louis, MO, USA.

384. Machine Learning Classification of Diagnostic Proteomics for Alzheimer Disease

Raghav Tandon, BS1, Nicholas Seyfried, Ph.D.2, Cassie S. Mitchell, Ph.D.1. 1Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA, USA, 2Biochemistry, Emory University, Atlanta, GA, USA.

391. Characterizing the Role of Genetic Variants Influencing α-Synuclein Seeding Activity Using Neuropathologically Characterized Human Brains

Naveen Kondru, DVM, PhD. Neuroscience, Mayo Clinic, Jacksonville, FL, USA.

422. The Association Between Sleep Apnea and Neurodegenerative Disorders: A Systematic Review and Meta-Analysis with an Emphasis on Precision-Medicine

Martin Guay-Gagnon, MD, PharmD, Philippe Desmarais, MD, MHSc. Division of Geriatric Medicine, Department of Medicine, Université de Montréal, Montréal, QC, Canada.

Epilepsy

348. Presurgical Evaluation Initiation Among Medicare Beneficiaries with Refractory Epilepsy

Chloe E. Hill, MD, MS, Chun Chieh Lin, PhD, MBA, Samuel W. Terman, MD, MS, Jack M. Parent, MD, Lesli E. Skolarus, MD, MS, James F. Burke, MD, MS. University of Michigan, Ann Arbor, MI, USA.

350. Looking Beyond Apnea: A Widespread Cortical Repertoire That Modulates the Rate and Depth of Breathing

Ganne Chaitanya, MBBS, PhD. Johnson P. Hampton, MSBME, Emilia Toth, PhD, Norma Hupp, A.A.S, John C. Mosher, PhD, Sandipan Pati, MD, Samden D. Lhatoo, MD, FRCP (Lon), Nuria Lecumberri Lacuey, MD, PhD. Neurology, University of Texas Health Science Center at Houston, Houston, TX, USA.

352. Failed Acute Stroke Interventions and High Ischemic Burden Increase Post-Stroke Epilepsy Risk

Alexandria L. Soto, BS1, Tejasvi D. Sudhakar, BA, MBS1, Hsin Yi Chen, BS2, Lindsey R. Kuoeh, BA3, Alison

Program and Abstracts, American Neurological Association S9
353. Total Daily Dosage of Anti-Epileptic Drugs in Women with Epilepsy with Somatic Pregnancies

Andrea V. Sanchez, MS, MS3, Maromi Nei, MD, Scott Mintzer, MD, Lindsay Higdon, MD, Brianna Casey, MD. Jefferson Comprehensive Epilepsy Center, Thomas Jefferson University, Philadelphia, PA, USA.

355. Non-Cell Autonomous Hyperexcitability Underlies Focal Epileptogenesis Mediated by Low-Level Brain Somatic Mutations in MTOR

Hyunyong Koh, MD PhD1,2, Jason Jang, Ph.D3, Sang Hyeon Ju, MD, Ryunhee Kim, Ph.D, Gyu-Bon Cho, MS4, Dong Seok Kim, MD PhD5, Jong-Woo Sohn, MD PhD6, Se-Bum Paik, Ph.D7, Jaong Ho Lee, MD PhD7,8, 1Neurology, Boston Children’s Hospital, Boston, MA, USA, 2Korea Advanced Institute of Science and Technology, Daejeon, Korea, Republic of, 3Severance Children’s Hospital, Seoul, Korea, Republic of, 4SoVarGen Inc., Daejeon, Korea, Republic of.

357. PV+ Interneurons Are Non-Cell Autonomously Dysregulated in Depd3-Associated Epilepsies

Tao Yang, Ph.D., Shuntong Hu, M.D. Ph.D., Yu Wang, M.D. Ph.D. University of Michigan, Department of Neurology, Ann Arbor, MI, USA.

358. Occurrence of Seizure Worsening and Clinical Toxicity During Postpartum Lamotrigine Taper in Women with Epilepsy

Elizabeth C. Shashkova, B.S., Page B. Pennell, M.D., Paula E. Voinescu, M.D., Ph.D., Stephanie R. Allen, P.A.-C. Neurology, Brigham and Women’s Hospital, Boston, MA, USA.

359. Natural Language Processing to Assess Seizure Frequency

Barbara M. Decker, MD1,2, Alexandra Turco, BS1, Jian Xu, MD PhD2, Samuel W. Terman, MD MS2, Nikitha Kosaraju, BA3, Kathryn A. Davis, MD MS2, Brian Litt, MD2, Colin E. Ellis, MD2, Pooya Khankhanian, MD1, Chloe E. Hill, MD MS2. 1University of Vermont Medical Center, Burlington, VT, 2University of Michigan, Ann Arbor, MI, USA.

Global Neurology

360. Levetiracetam Reduces Cerebral Lesions and Improves Biomarkers Related to Axonal Degeneration, Inflammation and Compromised Blood-Brain-Barrier in Patients with Adrenoleucodystrophy

Fanny Mochel, MD1, Florian Eichler, MD,2, Marc Engelen, MD2, Robin Lachman, MD,3, Ali Fatemi, MD2, Jacinda Sampson, MD2, Ettore Saisano, MD2, Josep Gamas, MD3, Maria Judith Mohar, MD2, Anna Vilalta, PhD10, Laura Rodriguez-Pascua, PhD10, Pilar Pizcueta, PhD10, Silvia Pascual, MS10, Anna Vila, PhD10, Maria Roira, MS10, Guillem Pina, MS10, Adriana Mantilla, MD2, Maria Pascual, PhD10, Marc Martinell, PhD10, Uwe Mey, MD10, Wolfgang Köhler, MD11. 1Hôpital La Pitié-Salpêtrière, ICM, Paris, France, 2Leukodystrophy Service, Massachusetts General Hospital, Boston, MA, USA, 3Pediatric Neurology, Amsterdam Medical Center, Amsterdam, France, 4Metabolic Medicine, National Hospital for Neurology and Neurosurgery, London, United Kingdom, 5Kennedy Krieger Institute, Baltimore, MD, USA, 6Neurology & Neurological Sciences, Stanford Hospital, Stanford, CA, USA, 7Clinical Neuroscience, Istituto Neurologico Carlo Besta, Milan, Italy, 8Neurology, Vall d’Hebron University Hospital, Barcelona, Spain, 9Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Budapest, Hungary, 10Minority Therapeutics, Mataro, Spain, 11Klinik und Poliklinik für Neurologie, Universitätsklinikum Leipzig, Leipzig, Germany.

Health Services Research

331. Evaluating the Impact of a New Model of Structured Interprofessional Bedside Rounding (TeaminguUP) on Climate Safety in an Inpatient Stroke Unit

Elizabeth Zink, MS, RN, CCNS, CNRN1, Eva Alexandra Barany, PharmD2, Mona Baborough, MD, PhD2,3, Rachel M. Salas, MD, MEd, FAAN, FANA4,5, Heather Watson, PhD, MSN, RN6, Tensie Shakes, RN7, Kathryn McDonald, PhD2,4, Anping Xie, PhD8, Ginger C. Hanson, PhD9, Bryan Hansen, MD, RN, APRN-CNS, ACNS-BC9, Dorna Hairston, PhD, RN, NEA-BC9, Elizabeth K. Tanner, PhD, RN, FAAN7. 1Johns Hopkins Hospital, Baltimore, MD, USA, 2Johns Hopkins University School of Nursing, Baltimore, MD, USA, 3Johns Hopkins University School of Medicine, Baltimore, MD, USA, 4Johns Hopkins University School of Nursing, Baltimore, MD, USA.

392. A Proposed Electronic Health Record Algorithm for Parkinson’s Disease Case Identification

Lauren E. Uhr, BS1, Aline Duarte Folle, MS, PhD1, Federica Agosta, MS1, Timothy S. Chang, MD, PhD1, Cooper Baddley, none1, Camille Malatt, MD4, Wesley Wu, none1, Betty Truong, none1.
BS1, Allan Wu, MD3, Andrew M. Wilson, MD, MS, MBA4,5. 1Department of Neurology, University of California Los Angeles, Los Angeles, CA, USA, 2Department of Epidemiology, University of California Los Angeles Fielding School of Public Health, Los Angeles, CA, USA, 3Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, CA, USA, 4Cedars-Sinai Medical Center, Los Angeles, CA, USA, 5Northwestern University Feinberg School of Medicine, Chicago, IL, USA, 6Department of Neurology, Greater Los Angeles Veterans Affairs Healthcare System, Los Angeles, CA, USA.

Chun Chieh Lin, PhD, MBA, Brian C. Callaghan, MD, MS, Kevin A. Kerber, MD, MS, James F. Burke, MD, MS, Lesli E. Skolarus, MD, MS, Chloe E. Hill, MD, MS. Neurology, University of Michigan Medical School, Ann Arbor, MI, USA.

Interventional Neurology
332. Early Inflammatory Markers in Acute Ischemic Stroke Patients
Mudassir Farooqui, MD, MPH1, Cynthia Zevallas, MD1, Darko Quispe-Orozco, MD1, Andrei Dajles, MS1, Alan Mendez Ruiz, MD2, Daniel Tranel, PhD1, Nitin Karandikar, MD1, Sterling Ortega, PhD1. Santiago Ortega-Gutierrez, MD, MSc1. 1University of Iowa, Iowa City, IA, USA, 2University of Iowa, Pittsburgh, IA, USA.

Movement Disorders
393. Satisfaction with Interdisciplinary Home Visits Among Individuals with Advanced Parkinson’s Disease and Their Caregivers
Jori E. Fleisher, MD MSCE1, Katheryn Woo1, Melissa Levin, B.S.2, Serena Hess, MA, MSN, RN2, Faizan Akram, B.S.1, Bichun OuYang, PhD1, Deborah Hall, MD, PhD1, Joshua Chodosh, MD, MSHS2,3. 1Neurological Sciences, Rush University Medical Center, Chicago, IL, USA, 2Geriatric Medicine and Palliative Care, New York University Grossman School of Medicine, New York, NY, USA, 3VA New York Harbor Healthcare System, New York, NY, USA.

396. Clusters of Offactory Performance Are Associated with Motor Decline in LRRK2G2019S Variant Parkinson Disease
Roberto A. Ortega, MS1, Rachel Gerber, BS2, Deborah Raymond, MSc3, Katherine Leaver, MD4, Nikita Urval, MD4, Viktoriya Katsnelson, MD4, Roy N. Acalay, MD, MS5, Anat Mirelman, PhD6, Michael C. Brumm, MS5, Christopher S. Coffey, PhD7, Tanya Simuni, MD8, Andrew D. Siderowf, MD9, Kenneth Marek, MD9, Nir Giladi, MD9, Karen S. Marder, MD, MPH2, Susan B. Bressman, MD1, Rachel Saunders-Pullman, MD, MPhD1. 1Neurology, Mount Sinai Beth Israel, New York, NY, USA, 2Neurology, Columbia University Irving Medical Center, New York, NY, USA, 3Neurology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, 4University of Iowa Carver College of Medicine, Iowa City, IA, USA, 5Biostatistics, University of Iowa, Iowa City, IA, USA, 6Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, 7Neurology, University of Pennsylvania, Philadelphia, PA, USA, 8Neurology, Institute for Neurodegenerative Disorders, New Haven, CT, USA.

397. Monogenic Hub of the Global Parkinson’s Genetics Program (GP2): The 500 Genomes Pilot Project
Niccolo E. Mencacci, MD, PhD1, Lara Lange, MD2, Enza Maria Valente, MD, PhD3, Shen-Yang Lim, MD, FRACP4, Ai Huey Tan, MD, PhD, FRCP5, Elsa-Juliane Vollstedt, MD6, Micol Avenali, MD7, Ignacio J. Keller Sarmiento, MD8, Harutyun Madoev, MS9, Peter Heutink, PhD9, Kishore R. Kumar, MBBS, PhD, FRACP10, Katja Lohmann, PhD10. 1Neurology, Northwestern University, Chicago, IL, USA, 2Neurology, Lübeck University, Lübeck, Germany, 3Department of Molecular Medicine, University of Pavia, Pavia, Italy, 4University of Malaya, Kuala Lumpur, Malaysia, 5Division of Neurology, University of Malaya, Kuala Lumpur, Malaysia, 6Lübeck University, Lübeck, Germany, 7University of Pavia, Pavia, Italy, 8German Center for Neurodegenerative Diseases, Tübingen, Germany, 9University of Sydney, Sydney, Australia.

398. ASN51, an Orally Bioavailable Small-Molecule O-GlcNAcase Inhibitor, Has Both Immediate and Disease-Modifying Benefits in Preclinical Models of Parkinson’s Disease and Epilepsy
Bruno Permanne, PhD, Ryan Schubert, MD, Astrid Sand, MSc, Solenne Ousson, MSc, Mdau Neny, MSc, Jennifer Hanson, MSc, Christoph Wiesner, PhD, Anna Quattropani, PhD, Dirk Beher, PhD, Asceneuron, Lausanne, Switzerland.

399. Effect of Hydrogen Sulfide on Alpha-Synuclein Aggregation
Elena Ostrakhovitch, PhD, Eun-suk Song, PhD. Tritia Yamasaki, MD PhD. Neurology, University of Kentucky, Lexington, KY, USA.
400. DYT-TOR1A Subcellular Proteomics Reveals Selective Vulnerability of the Nuclear Proteome to Cell Stress

Kunal Shroff, BS, Nicole Calakos, MD, PhD. Department of Neurology, Duke University School of Medicine, Durham, NC, USA.

402. CSF MicroRNA Analysis Reveals Angiogenesis and Autophagy Defects in Parkinson’s Disease Patients

Charbel Moussa, MD, Yasar Torres-Yaghi, MD, Fernando Pagan, MD. Georgetown University Medical Center, Washington, DC, USA.

426. Daytime Sleepiness in Parkinson’s Disease: Subjective and Objective Measures

Corina Catulin, MD1, Raima A. Memon, MD2, Allen Joop, MS3, Jennifer Pilkington, AM4, Kimberly H. Wood, PhD2, Amy W. Amara, MD, PhD2. 1University of Alabama at Birmingham, Birmingham, AL, USA, 2University of Alabama at Birmingham, Samford University, Birmingham, AL, USA.

K-401. Stabilization of Overall Quality of Life via Interdisciplinary Home Visits Among Individuals with Advanced Parkinson’s Disease

Jori E. Fleisher, MD MSCE1, Melissa Levin, B.A1, Katheryn Woon, MS, Serena Hess, MA, MSN, RN2, Faizan Akram, BS1, Bichun Ouyang, PhD1, Deborah Hall, MD, PhD2, Joshua Chodosh, MD, MS2. 1University of Pennsylvania, Philadelphia, PA, USA, 2Baylor College of Medicine, Houston, TX, USA.

Multiple Sclerosis

313. Functional Prioritization of Multiple Sclerosis-Associated Genetic Variants That Perturb Regulatory Element Activity in T Cells

Michael H. Guo, MD, PhD1,2, Koukue Mouri, PhD3, Carl G. de Boer, PhD4-5, Gregory A. Newby, PhD2-5, Matteo Gentili, PhD2, David R. Liu, PhD1,2, Nir Hacohen, PhD2-6, Ryan Teichey, PhD1, John P. Ray, PhD2-5. 1Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA, 2Broad Institute of Harvard and MIT, Cambridge, MA, USA, 3The Jackson Laboratory, Bar Harbor, ME, USA, 4School of Biomedical Engineering, University of British Columbia, Vancouver, BC, Canada, 5Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA, USA, 6Center for Cancer Research, Massachusetts General Hospital, Boston, MA, USA, 7Systems Immunology, Benaroya Research Institute, Seattle, WA, USA.

314. Psychosocial Impacts of COVID-19 in People Living with Multiple Sclerosis

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315. Interrogation of Extracellular Vesicle miRNA Repertoire in Adult and Pediatric MS

Setty Magana, MD, PhD1, Michelle Pleet, PhD2, Catherine DeMarino, PhD2, Maria Chiara Monaco, PhD2, Frances Andrada, CNP2, Anita Fletcher, MD2, Jemima Akinuanya, MD2, Karon Kauatra, BS2, Elizabeth Wells, MD1, Ilana Kahn, MD3, Margaret Parker, CNP2, Alyssa Beth Duda, BS3, William Sudovic, BS3, Gina Norato, MS4, Abdel Elkahloun, PhD2, Yong Zhang, PhD2, Kory Johnson, PhD2, Steve Jacobson, PhD2, Avindra Nath, MD2. 1The Research Institute at Nationwide Children’s Hospital, Columbus, OH, USA, 2NINDS, Bethesda, MD, USA, 3Children’s National Medical Center, Washington, DC, USA, 4NINDS, Bethesda, DC, USA, 5NHGRI, Bethesda, DC, USA.

Neurocritical Care

333. Natural Language Processing Model to Extract Acute Abnormalities from CT Head Reports

Victor M. Torres-Lopez, MA, Grace Rovenolt, B.A, Gabriella Garcia, MD, Sarah Chacko, B.S candidate, Angelo Olcese, MSE, Guido Falcone, MD, ScD, MPH, Sam Payabvash, MD, Richa Sharma, MD, MPH, Lauren Saning, MD, MS, FAHA, FANA, Kevin Sheth, MD, Jennifer A. Kim, MD/Ph.D. Neurology, Yale, New Haven, CT, USA.

334. Stroke as a Cause of Donor Brain Death and Prognostic Implication in Heart Transplantation

Takahisa Mikami, MD1,2, Shinobu Inagaki, MD3-2, Tomohiro Fujisaki, MD1,2, Toshiki Kuno, MD, PhD4,5,2, David P. Lerner, MD6-7, Joseph D. Burns, MD6-7, Anelch C. Anyanwu, MD8,2. 1Tufis Medical Center, Boston, MA, USA, 2Isahn School of Medicine at Mount Sinai, New York, NY, USA, 3Department of Cardiovascular Surgery, The Mount Sinai Hospital, New York, NY, USA, 4Isahn School of Medicine at Mount Sinai, New York, NY, USA, 5Department of Medicine, Mount Sinai St. Luke’s and West, New York, NY, USA, 6Department of Medicine, Mount Sinai Beth Israel, New York, NY, USA, 6Isahn Hospital & Medical Center, Burlington, MA, USA, 7Department of Neurology, Tufis University School of Medicine, Boston, MA, USA, 8Department of Cardiovascular Surgery, The Mount Sinai Hospital, Boston, MA, USA.
Neurogenetics

403. Comprehensive Analysis of PRKN in a Large Parkinson’s Disease Cohort Identifies Causative Mutations and Validates Population Scale Screening by Microarray
William Zhu, BSc1, Xiaoping Huang, MD1, Esther Yoon, BSc2, Sara Bandres-Ciga, PhD2, Cornelis Blauwendraat, PhD2, Joshua Cade, BSc2, Beverly P. Wu, BSc2, Janet Brooks, BSc1, J Raphael Gibbs, PhD3, Dena G. Hernandez, PhD2, Debra Ehrlich, MD, MS1, Andrew Singleton, PhD3, Derek P. Narendra, MD/PhD1. 1National Institute of Neurological Disorders and Stroke, Besthesda, MD, USA, 2National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA, 3National Institute of Aging, Besthesda, MD, USA.

404. Characterization of a Mouse Model of PDE10A-Related Autosomal-Dominant Movement Disorder
Nick Marotta, BSC, Niccolo Mencacci, MD/PhD, Milagros Pereira Luppi, MS, Rajeshwar Awatramani, PhD, Dimitri Krainc, MD/PhD. Northwestern University, Chicago, IL, USA.

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310. Geographical Variation in Proportion of Musk Antibody Myasthenia Gravis Around the World - A Multicenter Study

408. Muscle Biopsy in an Era of Neurogenetics: A Novel Mutation Leading to Becker Muscular Dystrophy
Erin McDevitt, B.S., Maryam Zulfiqar, MD, Prashant Natteru, MD, Saurabh Shukla, MD. UMMC, Jackson, MS, USA.

409. Brain Structure and Cognitive Endpoints in Myotonic Dystrophy Type 2
Artya Puwanant, MD1, Laura Flashman, PhD1, Carolina Burgos-Aguilar, MS2, Carly Olszewski, BS2, Joseph Rigdon, PhD3, Peggy Nopoulos, MD1. 1Neurology, Wake Forest University Health Sciences, Winston Salem, NC, USA, 2Wake Forest School of Medicine, Winston Salem, NC, USA, 3Psychiatry, University of Iowa, Iowa City, IA, USA.

410. Germline and Therapeutic Suppression of Tubulin Alpha 4a Rescues H-ABC Leukodystrophy in Mice
Sunetra Sase, PhD1, Julia Hacker, MS1, Akhata Ahmad, PHD1, Sarah Woidall, BS1, Asako Takanohashi, PhD1, Quasar Padiath, PhD2, Adeline Vanderveer, MD1. 1Department of Neurology, Children’s Hospital of Philadelphia, Philadelphia, PA, USA, 2Department of Human Genetics and Neurobiology, University of Pittsburgh, Pittsburgh, PA, USA.

411. Loss of TDP-43 Function and Rimmed Vacuoles Persist After T Cell Depletion in a Xenograft Model of Sporadic Inclusion Body Myositis
Chiseko Ikenaga, MD, PhD1, Kyla A. Britson, PhD1, Andrew Wilson, MS1, Nicole Reed, MS1, Philip C. Wong, PhD1, Thomas E. Lloyd, MD, PhD1. 1Department of Neurology, Johns Hopkins University, Baltimore, MD, USA, 2Department of Pathology, Johns Hopkins University, Baltimore, MD, USA.

412. Mitochondrial Replisome Protein Changes in Aging Mice
Ricardo Roda, MD/PhD. Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA.

414. Defects in Mitochondria-Lysosome Contact Site Dynamics in Charcot-Marie-Tooth-Type 2 Disease
George C. Shum, None, Jasmine Cisneros, BS, Yvette C. Wong, PhD. Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA.

Amy E. Rumora, PhD1, Faye Mendelson, B.S., John Hayes, B.S.2, John A. Maschek, PhD1, Liping Wang, PhD1, Scott Summers, PhD1, Eva L. Feldman, M.D., Ph.D.,2. 1University of Michigan, Ann Arbor, MI, USA, 2Neurology, University of Michigan, Ann Arbor, MI, USA, 3Biochemistry, University of Utah, Salt Lake City, UT, USA, 4Nutrition & Integrative Physiology, University of Utah, Salt Lake City, UT, USA.

Neuro-Oncology

K-316. Leukocyte Adhesion Causes Brain Capillary Obstruction During Neurotoxicity in a Mouse Model of Chimeric Antigen Receptor (CAR) T Cell Therapy
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423. New Insight Into REM Sleep Behavior Disorder Circuits in Living Humans

Maria G. Garcia Gomar, MD, PhD, Aleksandar Videnovic, MD, MSC, Katia Singh, PhD, Matthew Stauden, MD, Laura D. Lewis, PhD, Lawrence L. Wald, PhD, Bruce R. Rosen, MD, PhD, Marta Bianciardi, PhD. 1Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, USA, 2Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA.

424. Sleep Disturbances in Two Progressive Supranuclear Palsy Variants

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425. Global and Local Sleep Changes in Brain Oscillations After Stroke

Hanyang Miao, BS, Wei Chen, BS, Michelle J. Tang, BS, Eric C. Landsness, MD, PhD, Jin-Moo Lee, MD, PhD. Neurology, Washington University in St Louis, St Louis, MO, USA.

427. Effects of Lower-Sodium Oxybate on Functioning and Work Productivity in Participants with Idiopathic Hypersomnia

Michael J. Thorpy, MD, Nancy Foldvary-Schaefer, DO, MS, Patricia Chandler, MD, Luke Hickey, MSC, Dan Chen, MD, PhD, Richard K. Bogan, MD, Albert Einstein College of Medicine, Bronx, NY, USA, 2Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA, 3Jazz Pharmaceuticals, Inc., Palo Alto, CA, USA, 4Jazz Pharmaceuticals, Inc., Philadelphia, PA, USA, 5University of South Carolina School of Medicine, Columbia, SC, USA.

434. Poor Cognitive Outcome One Year After Mild Traumatic Brain Injury: Results from the TRACK-TBI Study

Andrea Schneider, MD, PhD, J. Russell Huie, PhD MPH, W. John Boscardin, PhD, Joel Kramer, PsyD, Kristine Yaffe, MD, Lindsey D. Nelson, PhD, Ramon Diaz-Arrastia, MD, PhD, Sonia Jain, PhD, Nancy Tenkin, PhD, Jason Barber, MS, Geoffrey Manley, MD, PhD, Raquel Gardner, MD. 1Neurology, University of Pennsylvania, Philadelphia, PA, USA, 2University of California San Francisco, San Francisco, CA, USA, 3Neurology, University of California San Francisco, San Francisco, CA, USA, 4Medical College of Wisconsin, Madison, WI, USA, 5University of California San Diego, San Diego, CA, USA, 6University of Washington, Seattle, WA, USA.

438. Associations of Pre-Injury Vascular Risk Factors with Traumatic Brain Injury Outcomes: A TRACK-TBI Study

Andrea Schneider, MD, PhD, Jason Barber, MS, Nancy Tenkin, PhD, Raquel Gardner, MD, Geoffrey Manley, MD, PhD, Ramon Diaz-Arrastia, MD, PhD, Danielle Sandmark, MD, PhD. 1Neurology, University of Pennsylvania, Philadelphia, PA, USA, 2University of Washington, Seattle, WA, USA, 3Neurology, University of Washington, Seattle, WA, USA, 4Neurology, University of California San Francisco, San Francisco, CA, USA, 5University of California San Francisco, San Francisco, CA, USA.

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487. Epigenetic Regulation of **ABCC8** and **TRPM4** is Associated with Intracranial Hypertension and Outcome After Severe TBI

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ANA2021 Abstracts

Autoimmune Neurology

001. A Case Report of Seropositive Neuromyelitis Optica Spectrum Disorder

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Neuromyelitis Optica Spectrum Disorder (NMOSD) involves immune mediated demyelination that primarily targets the optic nerve and spinal cord. It is characterized by the presence of aquaporin-4 (AQP4) antibodies. A minority of patients test positive for anti-myelin oligodendrocyte glycoprotein antibodies (MOG). The patient is a 62-year-old male who began having difficulties with depth perception in 2015. In April 2018, he started having left arm numbness and tingling which progressed to left sided torso and left leg numbness and weakness. On exam, he had brisk patellar and Achilles reflexes bilaterally, as well as decreased left torso and left leg sensation. Patient had a spastic gait and used a walker to ambulate. Strength was full bilaterally. MRI of the cervical spine in April 2018 showed left sided cord T2 hyperintensities with enhancement extending from C4 to C7. MRI of the brain revealed supratentorial T2 hyperintensities. CSF studies, including a multiple sclerosis panel, were negative. His AQP4 antibody was initially negative while he was on steroids. He then had a positive AQP4 antibody at 4.4 in August 2020. A diagnosis of NMOSD was made based on the 2015 international consensus criteria. Patient started Rituximab, followed by four courses of plasma exchange and steroids. He continued to have progression of his symptoms with persistent enhancement at the C5-C6 level. In October 2019, he began receiving Eculizumab. Since then, patent has not had any further relapses. There has been radiologic improvement as well; his September 2020 MRI showed subtle T2 hyperintensities from C4-C6 without any enhancement. Patient’s AQP4 antibodies have remained negative while on Eculizumab. NMOSD is a distinct entity from Multiple Sclerosis (MS). Relapses are common, with a quicker disability progression seen in comparison to MS. Recognizing and treating NMOSD early can slow progression of the disease and increase a patient’s quality of life.

002. Bifacial Palsy: A Presentation of Guillain-Barre Syndrome

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Background: Guillain-Barre Syndrome (GBS) is an autoimmune condition that most frequently causes demyelinating polyneuropathy. Several variants have been identified, with facial diplegia accounting for less than 2% of GBS presentations. We report a case of a woman who presented initially with unilateral facial nerve palsy that progressed to facial diplegia with no other symptoms suggestive of GBS.

Case Presentation: A 63-year-old female with a history of polyneuropathy presented to the emergency department with a two day history of right facial numbness and tingling and new onset slurred speech and right facial weakness. These symptoms were preceded by tenderness of her right temporal region and mandible. CT head revealed left periventricular white matter hyperintensity suggestive of an older infarct and CTA head and neck was unremarkable. She was admitted to the neuro critical care unit and started on aspirin 81mg and atorvastatin 40mg. On admission day 1, patient was started on valacyclovir for suspected Bell palsy without any improvement. By admission day 2, the patient had facial diplegia, scoring III-IV on the House Brackman scale. MRI brain revealed bilateral facial nerve enhancement (left > right), thus suggesting an autoimmune etiology. Valacyclovir was continued, aspirin discontinued, and prednisone was started without improvement. CSF studies showed albuminocytologic dissociation with increased protein. Otherwise laboratory work up was unremarkable (Meningitis panel, CSF culture, Lyme, EBV, HIV, VDRL, ANA, C-ANCA). In addition, NCS showed temporal dispersion and prolonged distal latencies, thus GBS was suspected. Valacyclovir was discontinued and IVIG was initiated for 5 days. There was clinical improvement after day 1 of IVIG, patient was able to better lift her eyebrows and close her eyes and lips. By day 5 of treatment, she opened and closed both eyes against resistance without difficulty, had an improved facial droop and was able to raise both eyebrows.

Discussion: Because this variant is only present in 2% of cases of GBS with an overall incidence of 1 per 5,000,000, it is infrequently seen in clinical practice and thus presents with diagnostic difficulty. Bifacial palsy can mimic conditions such as stroke, Lyme disease, and sarcoidosis with delayed treatment. This case is an important representation of the above statistics and adds to our knowledge of this condition.

Conclusion: Although rare, our case highlights the importance of increased awareness of this condition with training on diagnostic and therapeutic interventions that could result in quicker resolution of symptoms in patients with this GBS variant.

003. Guillain-Barre Syndrome After Complete Resolution of COVID-19 Infection in a Pediatric Patient

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Introduction: The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and its disease COVID-19, has devastated the world since its origin in Wuhan, China in late 2019. While SARS-CoV-2 can present like a respiratory illness in children and adults, its worst symptoms are caused by the body’s own inflammatory cascade and clotting system. Pediatric cases of COVID-19 has been shown to have more mild infectious disease course than in adults, but more severe complications can occur due to...
multi-inflammatory syndrome in children (MIS-C), a hyperinflammatory response that affects many organ systems in the body. We present a case of Guillain-Barré syndrome (GBS) following COVID-19 infection in a pediatric patient.

**Case Presentation:** A 17-year-old female presented to the emergency department with facial droop, facial numbness, and a bilateral lower extremity weakness 2 weeks after resolving COVID-19 infection. Physical examination demonstrated a distal weakness in all extremities with concurrent areflexia of the bilateral ankles. The patient was also found to demonstrate autonomic dysfunction, including tachycardia and elevated diastolic blood pressure. MRI lumbar was done showing posterior nerve root enhancement. CSF showed typical albuminocytological dissociation. Further workup to elucidate the etiology including other infectious process and autoimmune process such as ganglioside antibody panel were negative. She was subsequently diagnosed with acute inflammatory demyelinating polyradiculoneuropathy (AIDP) secondary to COVID-19 infection. The patient underwent a course of inpatient IVIg treatment, for which she endorsed subjective improvement in neurological symptoms. Following treatment, the patient was discharged with orders of two weeks of physical rehab.

**Conclusion:** An association between COVID-19 and GBS has been previously described in case reports of pediatric patients. This case report illustrates a unique presentation of GBS related to COVID-19 in a pediatric patient. The patient’s symptoms started after complete resolution of COVID19. This is in contrast to what has been previously reported in literature where GBS symptoms presented while patients were actively ill with COVID19, thus failing to differentiate between pure GBS vs critical illness polyneuropathy. Further studies are warranted to elucidate the association between COVID19 infection and GBS.

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**004. Bell’s Palsy a Neurological Manifestation of COVID-19**

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**Background:** Bell’s palsy is an idiopathic CN VII dysfunctions that presents as LMN facial droop. This report describes a COVID-19 positive patient who developed facial nerve paralysis and respiratory distress. Known viral causes of facial nerve paralysis include HSV-1, VSV, and Lyme disease. Damage to CN VII may be precipitated by direct viral damage, autoimmune mediated mechanisms, or ischemic injury secondary to inflammatory breakdown of the vasa nervorum.

**Case Presentation:** A 58-year-old male presented with chest pains, left-sided facial weakness, and numbness one week after testing positive for COVID-19. He had no associated hearing loss or diplopia. Relevant medical history includes a CVA (2010) with residual left-sided facial deficits and a left-sided facial trauma (2018). His neurological exam was remarkable for left peripheral CN VII palsy and decreased sensation in the V1-V3 distribution, dysphagia, and ageusia. The rest of his CNII-XII were intact, with normal strength and tone bilaterally. MRI brain showed no acute ischemia, hemorrhage or mass effect and no abnormalities along the facial or trigeminal nerve. Despite counseling the patient refused lumbar puncture. As there were no signs of encephalopathy there was low clinical suspicion for a bacterial meningitis. He was started on a 7-day regimen of 60 mg prednisone and valacyclovir 1 g TID. Although a focused neurological exam was not performed, improvement was noted by day 5. Chest pain workup with EKG and troponins was unremarkable. Initial CXR showed mild right upper lobe atelectasis. Respiratory symptoms were managed with tiotropium, fluticasone, and albuterol. He was initially stable. One week later he developed acute hypoxic respiratory distress treated with remdesivir, convalescent plasma and dexamethasone. His course was complicated by hospital acquired pneumonia managed with levofloxacin. Due to prolonged HFNC requirements he developed _S. aureus_ cellulitis resolved with doxycycline/mupirocin. Once oxygenating well on room air, he was discharged.

**Discussion:** Bell’s palsy is a rare presentation of COVID-19. In previous reports analysis of CSF usually demonstrates normal cellularity, glucose, and protein. Despite adequate counseling the patient didn’t consent to LP, thus CSF findings are unavailable. With supportive care, oral steroids and antivirals symptoms improved.

**Conclusion:** This case highlights Bell’s palsy as one of the neurological manifestations of COVID-19. Similar to other documented cases, with appropriate therapeutic measures adequate recovery was made.


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**005. The Cell Danger Response: Acute Respite or Chronic Energy Failure**

_Kelly Gibas, Doctorate, Ryan Singh, BS._

**Background:** Mitochondria are uniquely equipped to monitor the microenvironment for stress and modulate metabolism via retrograde signaling to nucleus and CNS. Therefore, mitochrondrial disturbance initiates systemic Cell Danger Responses (CDR) triggering evolutionarily conserved intracellular pathways to defend the host from metabolic threat. If chronically sustained, the ancient defenses damage cells. Clinically prescribed ketogenic diets are potent modulators of metabolic flexibility; clinical evidence suggests that ketogenesis mediates metabolic derangement via epigenetic deregulation of DNA methylation/acetylation. In addition, micro-dosed nasal insulin transverses the blood-brain barrier via trigeminal nerve awakening insulin sensing neurons in the midbrain/brainstem.

**Methods:** Adults with metabolic disease, including type II diabetes and mild Alzheimer’s disease, were supervised by medical professionals during an 8-week clinically prescribed ketogenic protocol with self-administration of nasal insulin (3x/day with meals). Participants were observationally studied by premedical students participating in a translational program. Primary outcome measures: MoCA, HOMA-IR, Triglyceride/HDL ratio, HbA1c and WHtR.

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Results: 59-year-old male previously diagnosed with type 2 diabetes and mild Alzheimer’s disease (MoCA @ 18/30), followed aforementioned protocol. Upon completion, the subject’s MoCA normalized @ 28/30, HOMA-IR dropped 90% to 2.3, HbA1c normalized @ 5.1% and Triglyceride/ HDL dropped 77% to 1.5; likewise, weight dropped 48lbs. and visceral adiposity significantly decreased (13% reduction in WHtR). The patient achieved statistically significant results in cognitive, metabolic and anthropometric measures.

Conclusion: The use of clinically prescribed ketogenic protocols coupled with micro-dosed nasal insulin is an effective treatment for neurocognitive disorders by alleviating CNS derived Cell Danger response thereby restoring mitochondrial efficiency.

006. Management of Ovarian Teratomas Associated with Autoimmune Encephalitis: A Case Report and Review of the Literature
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Problem Statement: NMDA encephalitis (NMDAE) is an autoimmune condition characterized by rapidly progressive psychiatric symptoms, cognitive impairment, seizures, abnormal movements, coma, and dysautonomia, sometimes requiring intensive care. Young females are mostly affected, with ovarian teratomas (OT) found in 18-50% of cases. Treatment includes OT resection; however, there is still insufficient evidence of the best management for NMDAE.

Methods: Case report and literature review.

Results: Case: A healthy 34-year-old female presented with bizarre behavior, emotional lability, disorganized speech and auditory/visual hallucinations for 48 hours. Found severely agitated, tachycardic and with pressured speech. Cerebrospinal fluid (CSF) showed lymphocytic pleocytosis and oligoclonal bands. Extensive metabolic and infectious workup was negated, tachycardic and with pressured speech. Cerebrospinal fluid (CSF) showed lymphocytic pleocytosis and oligoclonal bands. Extensive metabolic and infectious workup was negated, tachycardic and with pressured speech. Cerebrospinal fluid (CSF) showed lymphocytic pleocytosis and oligoclonal bands. Extensive metabolic and infectious workup was negated, tachycardic and with pressured speech. Cerebrospinal fluid (CSF) showed lymphocytic pleocytosis and oligoclonal bands. Extensive metabolic and infectious workup was negated, tachycardic and with pressured speech. 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headache, and encephalopathy are the most common neurological symptoms, whereas motor and sensory deficits, ataxia, and seizures appear uncommon. Here we present a case of acute anti-myelin oligodendrocyte glycoprotein [MOG] antibody longitudinally extensive transverse myelitis (TM) in an active COVID-19 patient.

Objective: To present a case of anti-MOG with longitudinally extensive TM in an active COVID-19 patient.

Methods: Case report

Case: A 33-year-old Caucasian female with a history of fibromyalgia and quiescent systemic lupus erythematous presented with multiple complaints in the setting of a COVID 19 infection, which she tested positive for 10 days prior to admission. Her symptoms included numbness and weakness in bilateral lower extremities (BLE) with associated diplopia, urinary retention, nausea, vomiting, and generalized aches. Initial neurological exam was positive for left gaze nystagmus, BLE pain with neck flexion and motor weakness 2/5, with an unremarkable remaining neurological exam. T2-FLAIR brain showed hyperintense lesions in the superior and middle cerebellar peduncules, and MRI cervical/thoracic/lumbar spine showed longitudinally extensive T2 hyperintense lesions involving C4-C7 and T11-T12. CSF analysis demonstrated elevated nucleated cells (98), predominately lymphocytes 91%, elevated protein 62, glucose 76, and lactate 2.4. Meningitis panel negative; oligoclonal bands negative; IgG synthesis elevated to 12.1 mg/day. Autoimmune panel was negative except for anti-MOG antibody. Given these results, she was diagnosed with anti-MOG Ab syndrome and initially treated for 3 days with high dose steroids without improvement, followed by 5 sessions of plasma exchange with improvement in BLE weakness to 4/5. She remained to have an unsteady gait and decreased sensation to T5-T12 distribution bilaterally. After discharge from inpatient rehab, final neurological exam demonstrated ability to walk alone with a walker. Given this workup, acute symptom presentation 10 days after a positive COVID test, and negative autoimmune panel apart from anti-MOG Ab, we believe coronavirus was the cause of her acute anti-MOG myelitis.

Conclusion: This is notable for the patient’s classic symptoms of anti-MOG longitudinally extensive TM after confirmed diagnosis of COVID-19. This case provides insight into the neuroimmunological response of COVID-19.

009. Dysphagia, Nystagmus and Ophthalmoplegia with Asymmetric Limb Weakness: An Atypical Presentation of Anti-GQ1b Antibody Syndrome

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Background: Most of the patients diagnosed with Guillain-Barre syndrome or some of its rare variants are seropositive for their glycolipid antibody profile, for example, anti-GQ1b antibody. Here we describe an atypical presentation of anti-GQ1b antibody syndrome with significant diplopia, dysphagia, asymmetric limb weakness, and preserved reflexes.

Case presentation: A 29-year-old, previously healthy white female presented with complaints of diplopia, dysarthria, dysphagia, and difficulty in walking for one week. She had bilateral partial 6th nerve palsy with horizontal diplopia, bilateral horizontal and vertical nystagmus, and mild bilateral facial diaphoresis on systemic examination. We also noted posterior lingual dysarthria, nasal quality speech, asymmetric limb weakness, and bilateral upper and lower extremity distal numbness. Additionally, she had proximal more than distal weakness in the left lower limb and distal more than proximal in upper limbs bilaterally. She also had diminished proprioception, intact reflexes, and the inability to stand without assistance. Brain MRI revealed diffuse linear abnormal symmetric enhancement involving bilateral trigeminal and VII/VIII cranial nerve complexes. The cerebrospinal fluid analysis only showed elevated protein. Electromyogram EMG/NCV on the third day of admission showed mild, sensory predominant, non-length-dependent axonal polyneuropathy. Our working diagnosis was GBS versus inflammatory disease of the central nervous system. She received a course of IV methylprednisolone and had a dramatic improvement in her symptoms. The patient’s glycolipid antibody profile turned out positive for the anti-GQ1b antibody (1:800). Thus, we called it an atypical presentation of anti-GQ1b antibody syndrome.

Discussion: The presence of anti-GQ1b antibody in our patient reflects a unique clinical spectrum, representing an existing continuum between several conditions (Fisher, Bickerstaff, and GBS) presenting with variable central and peripheral nervous system involvements. A more comprehensive term such as anti-GQ1b antibody syndrome could be used to include the common serological profile when referring to the clinical syndromes described by both Bickerstaff and Fisher. Nevertheless, the association of nystagmus (observed in our patient) with the anti-GQ1b syndrome was rarely reported in the literature, making this patient’s presentation an atypical one.

Conclusion: This case underscores the importance of recognizing atypical presentations of sensory deficits, asymmetric limb weakness, and CNS features such as nystagmus, which may be associated with anti-GQ1b antibody syndrome. Features consistent with myelitis and other multiple cranial neuropathies may create diagnostic and therapeutic difficulties for treating physicians.

010. Post-Influenza Vaccine Induced Acute Hemorrhagic Leukoencephalitis Treated with Plasma Exchange - A Case Report

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Objective: We present a rare case of AHLE after seasonal influenza vaccine promptly diagnosed with magnetic resonance imaging (MRI) brain which showed significant areas of hemorrhage with vasogenic edema including involvement of the pons. The patient was aggressively treated with plasma exchange and corticosteroids and had a favorable outcome.
Background: (AHLE) is a relatively rare, hyperacute and frequently fatal form of Acute Disseminated encephalitis (ADEM). Very rarely this can be a complication of vaccination. There is currently no consensus on the optimal treatment strategy of AHLE.

Design/Methods: Case Report

Results: A 74-year-old Caucasian female presented to the emergency department with acute symptoms of dizziness, headache, slurred speech and ataxia. Ten days prior hospitalization, she received virosomal influenza vaccine (FluZone High Dose Quad 20-21 PF). She was complaining of myalgia, fatigue and mental fog since receiving the vaccine. Nasopharyngeal swab for SARS COV-2 PCR was negative. Third day of hospitalization, she experienced a fall and became acutely encephalopathic with right side weakness and had to be intubated and transferred to the ICU. MRI brain with and without contrast demonstrated bilateral posterior frontal, parietal lobe and brainstem vasogenic edema. CSF studies showed 3 nucleated cells, mildly elevated glucose (73 mg/dL), significantly elevated CSF protein (108 mg/dL) and positive oligoclonal bands. Aquaporin-4 and MOG antibody were negative. She underwent 5 cycles of plasma exchange (PLEX) which started five days from initial presentation and received 5 days of IV solumedrol followed by steroid taper for 5 weeks. Repeat MRI brain without contrast fourteen days from initial presentation showed increased abnormal T2 hyperintensity and small amount of superimposed parenchymal hemorrhage involving the left parietal lobe, right parietal lobe and hemorrhage in pons. She was discharged eventually 5 weeks of IV solumedrol followed by steroid taper for 5 days. Repeat MRI brain without contrast fourteen days from initial presentation showed increased abnormal T2 hyperintensity and small amount of superimposed parenchymal hemorrhage involving the left parietal lobe, right parietal lobe and hemorrhage in pons. She was discharged eventually to a rehabilitation unit after significant improvement and was seen in an outpatient neurology clinic three months from initial presentation. She was ambulatory using a walker and only had mild right sided weakness and mild expressive aphasia.

Conclusions We illustrate a rare case of post-influenza vaccination AHLE treated with plasma exchange with a favorable outcome. This case highlights that a prompt diagnosis with MRI and early treatment with corticosteroids and plasma exchange may be warranted to offset the high fatality rate of AHLE in the future and further studies to explore treatments for this devastating disease are required.

011. Rapid Onset Stiff Person Syndrome
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Objective: To present a case of rapid onset Stiff Person Syndrome (SPS) in a non-classic patient and review diagnostic considerations associated with his presentation.

Background: SPS is a rare disorder, typically autoimmune or paraneoplastic in origin, characterized by fluctuating rigidity and stiffness of axial and proximal lower limb musculature with superimposed spasms and continuous motor unit activity on EMG.1 We present a case of SPS with an atypical onset.

Methods: A 24-year-old male presented with 1 week of left lower extremity pain and spasms that rapidly progressed to debilitating lumbosacral back, bilateral leg, and bilateral arm spasms. On examination, he was noted to have severe opisthotonus with dystonic posturing of his upper extremities and extensor posturing of both lower extremities. Brief periods of truncal extensor posturing lasting seconds accompanied by bilateral shoulder abduction were also observed. He was also found to have significant contraction of paraspinal muscles as well as increased tone and limited ROM at knees and elbows resulting in inability to ambulate. Symptoms had significant albeit transient improvement with valium. After diagnosis of SPS was confirmed, he received 3 days of IVIG and was started on Tizanidine. Examination after treatment was notable for resolution of opisthotonus and dystonic posturing with movement, normal tone, and normal strength. He was able to ambulate without any assistive device and was discharged home.

Results: EMG/NCS exteroceptive reflex testing revealed hyperexcitability with stimulation of the right median nerve. Serum workup including CBC, CMP, peripheral smear, TSH, PTH, AST, ALT, CK, folate, Vitamin B12, MMA, ceruloplasmin, Cu, Zn, GAD 65 were within normal levels. Serum anti-ampiphysin and paraneoplastic panel were negative. CTA intra/extracranial and MRI brain and cervical spine did not reveal significant abnormalities.

Conclusions: Here we show a non-classic patient presentation of SPS. Initial diagnostic considerations at presentation included seizure, acute dystonia, and functional/psychosomatic disorder. Although a rare disorder, SPS should be a diagnostic consideration in patients presenting with rigidity (diffuse and/or lateralizing as in this patient’s case) and spasms and may sometimes begin with stiff limb syndrome (classically a leg) before progressing to SPS. Treatment with benzodiazepines and/or IVIG can result in dramatic improvement in symptoms.


012. Idiopathic Acute Transverse Myelitis with Antecedent COVID-19 Infection
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Introduction: Coronavirus disease 2019(Covid-19), caused by SARS-CoV2, is known to trigger an inflammatory cascade affecting multiple organ system, including CNS. We here describe a case of transverse myelitis in the setting of COVID-19.

Case Description: A 72-year-old female patient presented to the emergency department with recurrent falls, urinary retention, numbness in both legs and right sided weakness. She also reported respiratory and gastrointestinal symptoms suggestive of COVID-19 for the past 1 month. Clinical examination demonstrated 4/5 strength in right upper extremity, 1/5 strength with right hip flexion, and 0/5 strength in right lower extremity. A sensory level to T2 was noted with 2+ reflexes and downgoing plantar response. Patient tested positive for COVID-19. MRI of cervical and
The thoracic spine demonstrated scattered STIR hyperintense, faintly enhancing lesions of C3-T1, primarily involving the dorsal columns and longer, linear lesions from T2-T4, consistent with transverse myelitis. Cerebrospinal fluid analysis demonstrated no pleocytosis or elevated protein, although this was obtained after initiation of treatment with glucocorticoids. Serum NMO and MOG testing were unremarkable.

The patient received a 7-day course of high dose IV methylprednisolone, antiretrovirals, and antibiotics with significant improvement, including resolution of her urinary retention and ability to walk with some residual lower extremity spasticity. Physical examination on a 6-month follow-up was notable for bilateral lower extremity foot drop, as well as mild lower extremity spasticity.

Repeat MRI demonstrated improvement of the foci of STIR hyperintensity throughout the cervical cord, with some residual abnormal signal at the thoracic spine, abdominal wall, and right iliac region. Methylprednisolone 1000mg x 5 days followed by IVIG 1 gm/kg x 2 days. Two days after starting high dose steroids, his mental status returned to baseline. One week later, he underwent an uncomplicated thymectomy.

Discussion: This case demonstrated how subacute symptoms of limbic dysfunction preceded the diagnosis of thymoma and how aggressive treatment with immune suppression and later tumor resection affected the course of the disease. It is important to consider autoimmune and neoplastic etiology when infectious causes are ruled out with patients presenting with encephalitis. Prompt treatment should be dictated by the etiology of the encephalitis, with appropriate follow-up and surveillance for malignancy or other autoimmune illnesses.

Objective: To describe an atypical presentation of Immunoglobulin G4-related disease (IgG4-RD).

Background: IgG4-RD typically affects middle-aged men, involving multiple organs including the pancreaticobiliary system, salivary and lacrimal glands, and retroperitoneal arteries. With a prevalence around 1/100,000 people, only during the past decade has it become recognized as a clinical disorder. Current diagnostic criteria is based on 2019 ACR/EULAR classification of IgG4-RD involves a stepwise classification and scoring process dependent on involvement of typical organ systems and clinical, serological, radiological, or pathological evidence.

Method: We report a 64-year-old female with remote history of Microscopic Polyangiitis (MPA) who presented with bilateral vision loss, scalp tenderness, eye pain, ptosis, jaw pain, and facial numbness as well as fatigue. The patient reported a prior episode of progressive painless vision loss, color desaturation, and vertical diplopia that had resolved spontaneously.

Results: Laboratory evaluation was notable for elevated inflammatory markers and serum IgG4 (210 mg/dL). Abdominal imaging revealed old circumferential abdominal aortic thickening. CSF analysis demonstrated lymphocytic...
pleocytosis with elevated protein. MRI of the brain showed pachymeningitis. Biopsy was required per 2019 ACR/EULAR classification of IgG4-RD, but temporal artery biopsy was performed rather than dural biopsy given the procedural risk. However, as no plasma cells were identified, IgG4 staining could not be performed. Nevertheless, the patient received pulse dose intravenous steroids with subsequent improvement in her vision. Patient did not tolerate a steroid taper despite concurrent azathioprine therapy and was started on Rituximab therapy.

Conclusion: While the patient’s recent presentation was consistent with IgG4-RD, it is worth considering whether her prior presentations were in fact related to IgG4-RD rather than MPA. This case represents an atypical presentation of IgG4-RD, a rare and recently described clinicopathologic syndrome, and also highlights the difficulties in obtaining a definitive diagnosis in clinical practice per 2019 ACR/EULAR criteria.

015. COVID-19 Complications - A Literature Review of Non-Vascular CNS Manifestations Associated with COVID-19

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Background: The data on neurological manifestations in coronavirus disease-2019 (COVID-19) patients has been rapidly increasing throughout the pandemic. However, data on CNS inflammatory non-vascular disorders in COVID-19 is still lacking. Here we performed a literature review of CNS inflammatory disorders associated with COVID-19.

Methods: All articles were screened that resulted from a search of PubMed, Google Scholar and Scopus, using the keywords; “SARS-CoV-2 and neurological complication”, “SARS-CoV-2 and CNS Complication” looking for reports of transverse myelitis (TM), longitudinally extensive transverse myelitis, neuromyelitis optica, myelitis, Myelin Oligodendrocyte Glycoprotein Antibody Disorder, Acute Disseminated Encephalomyelitis, Acute Hemorrhagic Necrotizing Encephalitis (AHNE)/Acute Hemorrhagic Leukoencephalitis, Cytotoxic lesion of the Corpus Callosum (CLOCC), Optic neuritis.

Results: Our literature search revealed 27 patients meeting the diagnosis of Myelitis, ADEM, AHNE or CLOCC. Statistical significance was observed when assessing severity of COVID-19 infection among patients with neurologic complications. Cases with acute myelitis were found occur in setting of non-severe COVID-19 infection and, cases of AHNE and CLOCC were found to occur during severe COVID-19 infection. CSF total proteins were also found to be elevated in 9 cases of TM and 3 cases of AHNE indicative of underlying neuroinflammatory process and changes in blood brain or blood meningeal barriers. Based on IDSA/ATS criteria of either requiring vasopressor for septic shock or mechanical ventilation, 46% (n=12) of the patients found in our literature search patients were considered to have a severe COVID infection, 15% (n=4) of cases were fatalities.

Conclusion: To our knowledge, this is among the first reviews that includes the clinical features, MRI neuroimaging, CSF findings and outcomes in COVID-19 associated CNS non-vascular inflammatory disorders. Our observational review study reveals that although rare, acute myelitis, ADEM, AHNE and CLOCC can be associated with COVID-19 infection. Further research using MRI imaging and CSF analysis in early diagnosis and intervention of these disorders is warranted.

016. Charcot-Marie-Tooth Type 2A Disease with Multiple Sclerosis: A Rare Occurrence

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Introduction: Charcot-Marie-Tooth disease (CMT) is a spectrum of inherited demyelinating or axonal neuropathies, and is synonymous with hereditary motor sensory neuropathy (HMSN). Overall estimated prevalence of CMT is 1 in 2500. The vast majority of cases are attributed to mutations in four genes: PMP22, MPZ, GJB1, and MFN2. CMT1, various autosomal recessive subtypes and X-linked CMT predominantly cause peripheral nerve demyelination and have evidence of co-existence with central demyelination and multiple sclerosis. CMT2A is primary axonal disease with no central nervous system involvement reported thus far. Central demyelination caused by multiple sclerosis (MS) is rare in patients with genetic neuropathies. We present a case of CMT2A with co-existing MS.

Methods: Case report and literature review.

Case: 53-year-old woman with a history of genetically diagnosed CMT2A, with a mutation in MFN2 gene with c227T>C variant and GAN gene with c805C>T variant, presented with progressive right eye painful vision loss over 3 days, secondary to optic neuritis as seen on MRI orbit with and without contrast. Examination findings were remarkable for right inferior visual field loss, pes cavus, hammer toes and distal symmetric sensory loss due to peripheral neuropathy. MRI brain with and without contrast showed subcortical and periventricular demyelinating lesions and MRI cervical spine showed prior asymptomatic demyelinating lesions in the cervical spinal cord. CSF studies were remarkable for 11 oligoclonal bands. She was therefore diagnosed with MS according to the McDonald criteria and consequently treated with IV solumedrol 1g daily for 3 days with complete restoration of vision.

Discussion: There is evidence of four cases of CMTX with mutation in CX32 who had subclinical CNS demyelinating lesions on MRI. Proposed mechanism involves presentation of myelin antigens to autoreactive T cells which may trigger an autoimmune reaction against CNS myelin. There are four cases of CMT1A in the literature that were diagnosed to have MS, the mechanism is thought to be due to the PMP22 gene, which is a component of myelin, and shares partial homology with other CNS proteins such as proteolipid protein, hence immune reaction against PMP22...
protein may affect similar CNS proteins. This makes our case one of its kind.

**Conclusion:** It is important to note that some pathogenic mutations in different types of CMT disease may be associated or act as a rare risk factor for developing an autoimmune reaction against CNS myelin leading to MS.

**017. Breast Carcinoma After Ocrelizumab Therapy in Multiple Sclerosis Patients: A Case Series and Literature Review**

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**Objective:** To present two unique cases of breast carcinoma after Ocrelizumab Therapy and the current literature on this possible adverse effect.

**Background:** Multiple Sclerosis is a debilitating disease with recent significant developments in immunomodulation therapies in the form of Disease Modifying Therapies (DMT) to prevent deterioration and disability. As the use of DMT increases, neurologists must be cognizant of the increased risk of infections and malignancy given the mechanism of action of these medications.

**Case 1:** A 67-year-old Caucasian woman with Primary Progressive Multiple Sclerosis (PPMS) was started on Ocrelizumab after diagnosis with clinical symptoms in addition to MRI and CSF findings. She had no personal prior history of malignancy or family history of malignancy. Cancer risk factors included only a remote tobacco use of 1.5 pack years 25 years prior. She was diagnosed with ER+/PR+/HER2- Invasive Ductal Carcinoma with Focal Associated Ductal Carcinoma in Situ (DCIS) of the left breast T1N0M0 stage1 after two years of Ocrelizumab infusions, which was then discontinued.

**Case 2:** A 42-year-old Caucasian woman with Relapsing Remitting Multiple Sclerosis (RRMS) was started on Ocrelizumab after MS exacerbation with new tumefactive lesions while on Teriflunomide. Cancer risk factors included prior excessive menorrhagia, Depo-Provera use, and remote tobacco use 10 years prior. She was on Ocrelizumab infusions for about 2 years prior to diagnosis of ER+/PR+/HER2- Invasive Ductal Carcinoma with Focal Associated Ductal Carcinoma In-Situ (DCIS) of the left breast T1N0M0 stage1. Ocrelizumab was again discontinued.

**Discussion:** This case series is the first suspected cases of development of breast cancer following Ocrelizumab therapy in patients with MS after FDA approval for RRMS and PPMS since 2017. Large trials such as OPERA 1 and ORATORIO found 4 and 11 cases of malignancy respectively. The suspected etiology of malignancy development is deactivation of protective mechanisms of the normal B-cells against tumor production and lysis of tumor. There are also multiple reports of increased risk of different malignancy in MS patients on DMT in general, though none of these are specific to Ocrelizumab therapy.

**Conclusion:** Given the increased usage of DMT such as Ocrelizumab, further investigation into risk of malignancy development as well as guidelines for monitoring for malignancy and MS treatment after malignancy development are necessary. This risk should also be included in risk vs benefit discussions with patients prior to initiating treatment.

**018. Characterization of a New Robust Neuromyelitis Optica Animal Model**

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**Introduction:** Neuromyelitis Optica (NMO) is an autoimmune disease of the Central Nervous System (CNS) characterized by T cell and antibody responses to a specific antigen, the water channel protein Aquaporin 4 (AQP4), affecting the spinal cord and optic nerve leading to paralysis and loss of sight. Currently employed NMO animal models are substandard inducing disease inconsistently and weakly, and not optimal for the development of new therapies. We have thus recently been successful in developing an NMO mouse model with a high disease incidence, robust severity and a more chronic disease course. Induction of robust disease requires that mice be immunized with the AQP4201-220 peptide epitope and be concomitantly treated with an antibody which neutralizes IFN-γ, or to induce disease in IFN-γ receptor knockout (KO) or IFN-γ KO (GKO) mice.

**Methods:** C57BL/6 mice were immunized subcutaneously with the AQP4201-220 peptide in Complete Freund Adjuvant (CFA) and treated with pertussis toxin (PTx) at day 0 and +2 post-immunization. Mice were treated weekly from day 0 with intraperitoneal injections of anti-IFN-γ antibody or isotype control. IFNGRKO and GKO mice were primed with the same regimen of peptide+CFA and PTx. Clinical scores were assessed daily. Splenic AQP4201-220 peptide-specific T cell proliferation and cytokine responses and H&E staining were used to levels of T cell activation and CNS histopathology.

**Results:** Both anti-IFN-γ-treated mice and KO mice (IFNGR and GKO) displayed ascendant paralysis following the AQP4201-220 peptide-specific T cell proliferation and cytokine responses and H&E staining were used when treating mice with a T cell activation

**Conclusions:** This new model shows the enhanced similarity to human NMO in terms of disease progression and severity, and has proven useful for testing tolerogenic immunotherapy. We are currently determining the underlying mechanisms by which IFN-γ regulates disease.

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019. Exploratory Study of Safety and Efficacy of Ocrelizumab in Autoimmune Encephalitis: A Randomized, Double-Blind, Placebo Controlled Trial
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Objective: To assess safety and efficacy of ocrelizumab to prevent clinical worsening in patients with antibody-mediated autoimmune encephalitis.

Methods: This was a single-center, 12-month, randomized, double-blind, placebo-controlled trial. Patients with autoimmune encephalitis were randomized in 1:1 fashion to placebo or ocrelizumab infusion. The primary endpoint of the study was clinical worsening defined as a perceived decline by the patient or clinician or a decrease in the Lawton and Brody Instrumental Activities of Daily Living Scale (IADL), along with either worsening on the Texas Functional Living Scale (TFLS) or hospitalization for symptoms of encephalitis.

Results: Among 21 potentially eligible patients, only three participants were enrolled in the study, with two in the ocrelizumab arm and one in the placebo arm. The single patient in the placebo arm (N-methyl-D-aspartate receptor [NMDA-R] antibody positive) met the primary endpoint at 12 weeks, and received open-label ocrelizumab with improvement. In the ocrelizumab arm, one participant (NMDA-R positive) demonstrated marked improvement, and the second (leucine-rich, glioma inactivated 1 [LGI1] antibody positive) remained clinically stable. There were no serious adverse events associated with ocrelizumab.

Conclusions: Clinical trial recruitment for autoimmune encephalitis is challenging, and our trial did not meet recruitment goals. In this small study, ocrelizumab appears safe and tolerable for use in autoimmune encephalitis, and appeared to prevent clinical worsening. Large, multicenter clinical trials are still needed. Instrumented functional rating scales will be valuable outcome measures for future studies.

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Objective: To report the case of a 35-year-old woman with treatment-resistant aquaporin-4 (AQP-4) immunoglobulin G (IgG) seronegative neuromyelitis optica spectrum disorder (NMOSD) successfully treated with eculizumab (a terminal complement inhibitor).

Methods: The investigational procedures and treatment regimens the patient received were documented over 8 years (2012 [first presentation] to 2020).

Results: The patient presented with subacute onset of lower-limb weakness and numbness, gait imbalance, and urinary incontinence. Magnetic resonance imaging (MRI) showed abnormalities in the thoracic spine from T7 to T10, but brain and cervical spine scans, visual evoked potential latencies, and IgG index were normal; cerebrospinal fluid pleocytosis and oligoclonal bands were both present. After treatment with intravenous methylprednisolone 1 g/day for 5 days, the patient was discharged without medication to acute rehabilitation but experienced relapses from 2012 to 2014. She was treated with oral prednisone (initiated at 40 mg/day in 2014; the dose was halved in 2015 due to weight gain) and mycophenolate mofetil (MMF) 1 g twice daily (from June 2015), but between 2014 and 2019 experienced 4-5 relapses/year, requiring treatment with intravenous methylprednisolone, with added maintenance plasma exchange from 2018 onwards. Although the patient tested negative for antibodies to AQP-4 and myelin oligodendrocyte glycoprotein, she was diagnosed with NMOSD in February 2017, based on recurrent episodes of longitudinal extensive transverse myelitis, MRI changes, and area postrema syndrome. By 2018 the patient needed a cane to walk. Prednisone and MMF were discontinued mid-2018, and rituximab was prescribed from July 2018 (maintenance regimen two 1 g doses 2 weeks apart every 6 months) but discontinued in July 2019 owing to lack of significant improvement. From July 2019 eculizumab was prescribed for 6 months (900 mg weekly for the first four doses, then 1200 mg every 2 weeks). The patient had no relapses or adverse events during and after eculizumab treatment (as of August 2020) and was able to walk unaided; her Expanded Disability Status Scale score improved from 4-5 during 2015-2018 to 2 in 2020 following eculizumab treatment.

Conclusion: Eculizumab shows promise as a treatment for AQP-4 IgG seronegative NMOSD and further studies are warranted.

021. CLIPPER Syndrome in a 57-year-old Patient: A Rare Neuroinflammatory Disorder
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Background: Chronic lymphocytic inflammation of pontine perivascular enhancement responsive to steroids (CLIPPERs) is a rare neuroinflammatory disorder. Its typical MRI appearance is perivascular enhancement involving the cerebral vasculature predominantly in the pons and the cerebellum. The signs and symptoms can range from ataxia to pseudobulbar affect. Currently, the etiology of this syndrome is unknown, and it can be misdiagnosed and mismanaged by physicians.

Case Presentation: Here, we present a case of a 57-year-old male presented in the emergency department with a five-month history of dysphagia, diplopia, dysarthria, vertigo, and
limb weakness. Additionally, he experienced a progressive decline in cognitive function. His neurological examination revealed lingual dysarthria, a positive finger-nose-finger test on the left side, and mildly increased tone in the bilateral lower extremity. The rest of the neurological and systemic examination was unremarkable. Extensive workup ruled out the possibility of vasculitis, CNS infection, demyelinating disease, paraneoplastic syndrome, sarcoidosis, and tuberculosis.

His MRI brain with contrast demonstrated innumerable tiny foci of contrast enhancement within the brain that do not geographically correspond to the areas of diffusion abnormality but involve a larger proportion of the brain. An MRI cervical spine with and without contrast showed patchy brainstem, middle cerebellar peduncle, and intramedullary signal abnormalities without contrast enhancement or spinal cord expansion. This pattern was initially believed to be consistent with a CNS lymphoma, but the brain biopsy ruled out any malignancy.

Based on a provisional diagnosis of CLIPPERS syndrome, he was commenced on a 5-day course of IV methylprednisone once daily, followed by a month-long prednisone taper with 40mg prednisone daily till his follow-up visit in the clinic. After three weeks, his follow-up brain MRI revealed a significant interval improvement. Although he did not respond immediately to corticosteroids in the hospital, by his 2nd week at home after discharge (week 3 of steroid), the patient reported marked improvement in his cognitive function. He continued to improve on a slow oral taper and was maintained on a final dose of 20 mg daily.

Conclusion: In summary, we have tried to raise the possibility that CLIPPERS syndrome may be more common than realized. As a recently defined syndrome, any reported case is pivotal in increasing the awareness of this disorder. Any new data would enhance our understanding of the natural course and treatment of the disease.

### 298. The Use of Routine Laboratory Parameters for Prediction of an Infectious or Autoimmune Etiology in Encephalitis

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**Objective:** This study aims to identify routine laboratory markers at presentation associated with infectious or autoimmune encephalitis (AE).

**Background:** The initial presentation for infectious, particularly viral, and autoimmune encephalitis may be similar. A definitive diagnosis often takes days to weeks, if determined at all, which may delay treatment and prolong hospitalization duration.

**Design/Methods:** This is a multi-center retrospective study at three tertiary care hospitals in New York City analyzing demographic and clinical data from patients diagnosed with definitive encephalitis based on a confirmed pathogen and/or autoantibody. Univariate analysis identified significant variables that were then inputted in a multivariate regression model to develop a scoring screen for predicting autoimmune versus infectious encephalitis.

**Results:** 333 individuals with confirmed encephalitis were included. A viral pathogen was identified in 151/333 (45.40%), bacterial pathogen in 95/333 (28.50%), and autoantibody in 87/333 (26.10%). The most common etiology in each group was herpes simplex virus, streptococcus, and anti-NMDA receptor antibodies, respectively. Univariate analysis confirmed that viral encephalitis was differentiated from autoimmune encephalitis by the presence of fever (viral 62.25%, AE 24.10%; p<0.001), higher CSF WBC (median 78 cells/μL vs. 8.00 cells/μL; p<0.001), higher CSF protein (76.50 mg/dL vs. 40.90 mg/dL; p<0.001), lower CSF glucose (58.00 mg/dL vs. 69.00 mg/dL; p<0.001), lower serum WBC (7.80 cells/μL vs. 9.72 cells/μL; p<0.050), higher ESR (19.50 mm/HR vs. 13.00 mm/HR; p<0.05), higher CRP (6.40 mg/L vs. 1.25 mg/L; p<0.005), and lack of antineuronal antibody titer (1:40; viral 11.54%, AE 32.73%; p<0.001). CSF to serum WBC ratio was significantly higher in viral compared to AE (viral 11.3, AE 0.99; p<0.001). Multivariate regression found the odds of an autoimmune etiology, compared to viral, were lower in individuals presenting with fever (OR 0.30 (95% CI 0.13-0.69); p<0.05), and elevated CSF WBC (OR 0.86 (95% CI 0.79-0.93); p<0.001). Individuals aged 12-29 years had higher odds (OR 4.72 (95% CI 1.49-14.93); p<0.05) of an autoimmune than viral etiology compared to those >65 years. Based on these findings, the predictive value of presenting with fever, CSF WBC ≥ 50 cells/μL, and CSF protein ≥ 75 mg/dL was explored in ruling-out AE. When all three criteria are present, an autoimmune etiology was found to be highly unlikely (sensitivity 92%, specificity 75%, negative predictive value 95%, and positive predictive value 64%).

**Conclusions:** Specific paraclinical data obtained at initial presentation may risk stratify which patients have an infectious versus autoimmune encephalitis.

### 299. High Frequency of Asymptomatic Optic Nerve Enhancement in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder: Implication for Clinical Management and Trial Conduct

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**Introduction:** Asymptomatic optic nerve (ON) enhancement in aquaporin-4-IgG (AQP4-IgG) positive neuromyelitis optica spectrum disorder (NMOSD) has been reported but is...
poorly characterized. Improved understanding has important implications for clinical care and adjudication procedures for evaluating disease activity in clinical trials.

Methods: 140 patients with optic neuritis meeting AQP4-IgG+ NMOSD criteria between 2000-2019 were retrospectively reviewed. 198 MRI brain/orbit scans were reviewed independently by neuro-radiologist/neuro-ophthalmologist/neuroimmunologist for consensus on interattack ON enhancement (>30 days after attack). Visual outcomes were reported as LogMAR.

Results: 107 interattack MRIs from 78 unique patients (66/78 [84%] female) were reviewed. 7 scans were done prior to any ON attacks (median 61 days before attack [range 21-271]) and 100 after clinical attack (median 400 days after attack [range 33 to 4623]). Median age at interattack MRI date was 47 years (range 8-85). Patients had a median 2 ON attacks (range 1-15) over 5.5 years (range 1-35). ON enhancement was present on 18/107 (16.8%; 15 unique patients) interattack scans (median 19.2 days from attack [range 33-2943]), encompassing 16 preceding ON attacks, 14 of which were treated with acute immunotherapy. On 15 scans, enhancement occurred at the site of prior attacks (lesion location unchanged, with improved lesion length), while 2 scans demonstrated new, asymptomatic lesions (prior scan demonstrating no enhancement). Another patient had ON enhancement and subjective visual changes, but no detectable abnormalities on eye examination until 15 days later. There was no difference in visual outcomes at preceding attack nadir between those with and without enhancement (LogMar VA of 1.7 versus 2.1; p=0.79) or long-term visual outcomes (0.4 versus 0.2, p=0.56).

Discussion: Asymptomatic ON lesions occurred in 17% of NMOSD patients and was largely attributable to enhancement at the site of prior attacks. New asymptomatic enhancement was only seen in two patients (1.8% of interattack scans), both of whom had prior optic neuritis. Asymptomatic enhancement may represent subclinical ON or intermittent blood-brain barrier breakdown in patients with prior ON. Blinded retrospective relapse adjudication is a mainstay of therapeutic clinical trials for NMOSD in assessing treatment efficacy. Clinical assessment may be insufficiently sensitive based on clinical thresholds for visual changes currently required for ON relapse. Incorporating ON MRI may minimize relapse misclassification, but close follow-up of patients with asymptomatic enhancement using clinical measures like OCT may further elucidate the clinical significance.

300. Parainfectious Neuromyelitis Optica Spectrum Disorder in a Patient with COVID-19 and Hepatitis B Co-Infection

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Background: Preliminary reports indicate that COVID-19 is associated with spectrum of neurological complications. Infections play a role in triggering immune-mediated inflammatory conditions of the central nervous system (CNS). We describe a case of parainfectious Neuromyelitis Optica Spectrum Disorder (NMOSD) in a patient positive for COVID-19/hepatitis B (HBV) and review the current literature.

Case Report: A 43-year-old Asian female with no past medical history presented with 10-day history of urinary retention and color vision loss. Her symptoms progressed rapidly, and she developed lower extremity numbness, thoracic sensory level, followed by quadriplegia and complete bilateral vision loss. Her respiratory status was normal. She tested positive for SARS-CoV-2 PCR IgM/IgG. Additionally, she was positive for HBV-antigen/HBeAB without clinically overt hepatitis. HIV and autoimmune panels were negative. MRI showed enhancement of the optic nerves, multiple T2-hyperintense lesions in the white matter, thalami, brainstem, periaqueductal grey, one large tumefactive lesion in the temporal lobe, and a longitudinally extensive enhancing lesion throughout the cervical and thoracic cord. CSF analysis showed mild pleocytosis, highly elevated myelin-basic protein and negative oligoclonal bands. Meningitis/encephalitis panel was negative. AQP4/MOG antibodies were absent. Patient was treated with combination of IV methylprednisolone/therapeutic plasma exchange (PLEX) and antiviral therapy with emtricitabine-tenofovir for occult hepatitis B. She recovered with resolution of weakness and sensory deficits, her visual acuity improved to 20/30.

Results: A PubMed database search revealed 23 cases of demyelinating disorders associated with COVID-19 infection, one case of transverse myelitis in COVID-19/HHV6 co-infection and one case of HBV-associated transverse myelitis. We describe the first case of COVID-19/HHV6 co-infection-associated NMOSD. Myelitis was the predominant finding present in 83% of all cases. Eight patients (35%) met criteria for AQP4 seropositive NMOSD, 4 with imaging-associated optic neuritis. From reported outcomes, 61% of patients showed significant improvement and 39% showed mild to moderate improvement. IV steroids alone were the most effective treatment, however various combinations of IV steroids, IVIG and PLEX were used.

Conclusions: COVID-19-associated immune-mediated CNS disorders can involve optic nerves, brain, and spinal cord. This unique case demonstrates simultaneous severe involvement of all these areas with excellent recovery after prompt treatment. Negative CSF COVID-19 PCR in most reported cases supports the view that this virus triggers an immune mediated process rather that direct neuro-invasion and should be considered a risk factor for developing neuro-inflammatory conditions.

301. Clinical Outcomes Following Status Epilepticus in Anti-NMDAR Encephalitis

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Background: Acute symptomatic seizure or status epilepticus (SE) are common presentations of autoimmune encephalitis. A favorable seizure prognosis is well known for anti-NMDAR encephalitis. Because status epilepticus itself causes epileptogenesis, we further researched clinical outcomes
following SE in anti-NMDAR encephalitis. SE etiology is one of the important outcome predictors in SE patients. Therefore, we studied and compared clinical outcomes following SE in both anti-NMDAR encephalitis and other new onset refractory status epilepticus (NORSE) patients.

**Methods:** We retrospectively reviewed 78 anti-NMDAR encephalitis patients in Seoul National University Hospital Autoimmune Encephalitis Registry. In the registry, 27 patients with history of status epilepticus were included in the study. Eight patients were excluded for short follow-up period (< 2 years). Clinical outcome (modified Rankin Score), seizure outcome, EEG findings, MRI findings, treatment and number of antiepileptic drugs (AEDs) were analyzed. For the comparison, 35 NORSE patients were analyzed in the same period. 18 patients were excluded for short follow-up period (< 2 years) or diagnosis of anti-NMDAR encephalitis. Finally, clinical features of 19 anti-NMDAR encephalitis patients and 17 other NORSE patients were compared.

**Results:** Compared to other NORSE patients, anti-NMDAR encephalitis had shorter duration of SE days (16.76±13.15 vs. 34.88±11.38, P<0.001). In the EEG findings, Other NORSE patient mostly showed periodic epilepto- form discharges (70.95%) while most of anti-NMDAR encephalitis showed rhythmic delta activities (78.95%). In seizure outcome, all 19 patients of anti-NMDAR encephalitis became seizure free, while only four patients became seizure free in other NORSE group (0/19 vs. 4/17, P<0.001). AED free rates were significantly higher in anti-NMDAR encephalitis (15/19 vs. 1/17, P<0.001). Clinical good outcome, defined as mRS ≤2, also differed between the two groups (16/19 vs. 8/17, P=0.02). The number of AEDs at disease onset showed no statistical difference (3.95±1.27 vs. 4.65±1.00, P=0.07). However, the number of AEDs at last follow-up in anti-NMDAR encephalitis was definitely lower (0.26±0.56 vs. 4.65±2.37, P<0.001).

**Conclusion:** Although anti-NMDAR encephalitis patients developed prolonged status epilepticus at disease onset, clinical outcome including seizure control were remarkably better compared to other NORSE patients. SE of anti-NMDAR encephalitis did not seem to cause epileptogenesis compared to other etiologies of SE. Clinical outcomes by etiologies of SE need to be further studied.

**302. Antigen Coupled PLG Nanoparticle Treatment Drastically Reduces Disease Severity in the Rodent Model of Neuromyelitis Optica**

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**Introduction:** Neuromyelitis Optica (NMO) is an autoimmune disease of the Central Nervous System (CNS) characterized by T cell and antibody responses to, the water channel protein Aquaporin 4 (AQP4). NMO causes severe disability in patients which often suffer from blindness and paralysis due to chronic damage to the optic nerves and spinal cord. Current treatments for NMO, are expensive, non-curative and fail to provide durable disease control. Here we use PLG particles coupled with the pathogenic AQP4 peptide in the animal model of NMO to induce tolerance. Our carboxylated biodegradable nanoparticles composed of the FDA-approved biopolymer (polylactide-co-glycolide) (PLG) to encapsulate proteins or peptides have been shown to induce T cell tolerance for the treatment of animal models of MS, as well as other autoimmune and allergic disease models where the antigen is known.

**Methods:** Mice were immunized with the pathogenic AQP4201-220 peptide emulsified with Freund’s Complete Adjuvant. PLG nanoparticles were coupled with the AQP4201-22 peptide or OVA323-339 control and administered intravenously to mice prophylactically 7 days prior to immunization. Clinical scores were recorded daily throughout the disease course. Spleens and lymph nodes were collected for determination of AQP4201-220 peptide-specific T cell proliferative and cytokine production.

**Results:** Treatment with PLG AQP4 coupled nanoparticles significantly reduced disease incidence and symptom severity as well as activation of autoreactive AQP4-specific Th1 and Th17 cells in the NMO mouse model. *Ex-vivo* recall of spleens and lymph nodes showed a significant reduction in T-cell reactivity to the AQP4 peptide compared to the OVA control group with less IL-17, GMCSF, IL-6, IFN-γ, and TNFα. This prophylactic treatment also inhibited clinical disease in our new and severe NMO mouse model induced in mice treated with anti-IFN-γ. Administration of PLG-AQP4201-220 in this case reduced the clinical score of NMO mice, prevented disease in almost all animals and *ex-vivo* recall showed reduced secretion of IL-17A from splenocytes and lymph node cells. These results provide evidence for anti-IFN-γ being an important orchestrator in the NMO disease as well as possibly contributing to the therapeutic effects of the PLG particles.

**Conclusion:** PLG nanoparticle treatment for the animal model of NMO shows promising results and significantly reduces disease. This treatment approach is likely to have beneficial and clinically relevant applications in future research.

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**303. Investigations in Ca2+ Signaling in Anti-NMDAR Encephalitis**

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N-methyl-D-aspartate receptors (NMDARs) are glutamate receptors that govern cellular mechanisms of learning and memory in neurons, including synaptic long-term potentiation (LTP), through Ca2+ permeability and induction of post-synaptic signaling cascades. Anti-NMDAR encephalitis (ANRE) is a neuroimmunological disease in which autoantibodies target the obligate GluN1 subunit of NMDARs, causing diverse neuropsychiatric symptoms, high neurologic...
morbidity, and death in severe cases. The molecular mechanisms that lead to clinical symptoms in ANRE remain incompletely defined. We measured NMDAR-dependent miniature, spontaneous Ca\textsuperscript{2+} transients in dissociated rat primary neurons treated with anti-GluN1 human monoclonal antibodies (hMAbs) derived from a patient with ANRE. Internalization of NMDARs following hMAb exposure was measured by surface biotinylation and quantitative immunoblotting. Our results show that ANRE hMAbs localize to neuronal synapses within 10 minutes, and decrease mSCaT amplitude without alterations to frequency. Surface biotinylation experiments also suggest that this alteration to synaptic Ca\textsuperscript{2+} influx through NMDARs occurs without significant loss of NMDARs from the neuronal cell surface. Spontaneously-activated NMDARs mediate synaptic homeostasis, and blockade of spontaneous release leads to potentiation of synaptic transmission. Therefore, the decreased mSCaT amplitude induced by ANRE hMAbs may lead to disruption of normal mechanisms controlling synaptic homeostasis and contribute to pathology in this way. This study contributes to our understanding of the underlying pathophysiology of neuroimmunological disorders involving antibodies targeting cell surface antigens.

304. Analysis of Efgartigimod Efficacy Across Patient Populations and Myasthenia Gravis Specific Scales: Results of the Phase 3 ADAPT Study

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**Purpose:** To evaluate the efficacy, tolerability and safety of efgartigimod, a human IgG1 antibody Fc-fragment that blocks FcRn in patients with generalized myasthenia gravis (gMG).

**Methods:** ADAPT was a phase 3, randomized, double-blind, placebo controlled, global multicenter 26-week study in patients with gMG (MG-ADL ≥5: ≥50% non-ocular symptom). Patients were randomized 1:1 to receive an initial treatment cycle of 4 weekly infusions of efgartigimod (10 mg/kg) or placebo. Subsequent cycles were initiated according to a patient’s clinical response. The primary endpoint was percentage of AChR-Ab+ patients who were MG-ADL responders (≥2 pts improvement sustained for ≥4 wks) after first treatment cycle.

**Results:** 167 patients (n=129 AChR-Ab+, n=38 AChR-Ab-) were randomized. In AChR-Ab+ patients, 67.7% of treated patients achieved MG-ADL responder status vs 29.7% placebo (p<0.0001). Within this population, 63.1% of treated vs 14.1% placebo patients were also Quantitative Myasthenia Gravis (QMG) responders (≥3 pts improvement sustained for ≥4 wks) in the first treatment cycle. In addition, AChR-Ab+ treated patients also had significant improvement in MGC and MG-QoL15r scores compared to placebo. The onset of effect reached significance after the first infusion in all the scales. Treated patients experienced significant improvement regardless of age, sex, or baseline scores MG-ADL scores. The overall population, experienced similar improvement in all outcome measures. Adverse events were predominantly mild or moderate, with few ≥ grade 3 severity.

**Conclusions:** Efgartigimod demonstrated significant efficacy in treating patients with gMG, with no significant safety issues.

305. Genomic and Transcriptomic-Wide Analysis Identifies Novel Genetic Risk Loci and Prioritization of Therapies for Myasthenia Gravis

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**Background:** Myasthenia gravis is a chronic autoimmune disease characterized by autoantibody-mediated interference...
of signal transmission across the neuromuscular junction. Though the genetic background plays a central role in disease pathogenesis, little is understood of the predisposition risks, the mechanisms that trigger the autoimmune cascade, or the biology underlying the different ages of onset and response to treatments.

**Methods:** We performed a genome-wide association study (GWAS) involving 1,873 patients diagnosed with acetylcholine receptor-positive myasthenia gravis and 36,370 healthy European-ancestry individuals to identify disease-associated genetic risk loci. We replicated our findings in an independent European cohort of 354 cases and 7,080 matched controls from the UK Biobank. We also performed a transcriptome-wide association (TWAS) using expression data from skeletal muscle, whole blood, and tibial nerve to identify disease-associated genes. We performed genetic correlation and two-sample Mendelian randomization between a target of the autoantibodies: a GWAS signal (rs35274388, p=3 x 10^{-8}, odds ratio (OR) =1.57) within the cholinergic receptor nicotinic alpha 1 subunit (CHRNA1) gene; and a TWAS association (rs4151121, p=3 x 10^{-4}, Z=4.67) with the cholinergic receptor nicotinic beta 1 subunit (CHRNA1) gene in skeletal muscle. Genetic correlation analysis and Mendelian randomization confirmed a genetic link between myasthenia gravis and other autoimmune diseases such as hypothyroidism, rheumatoid arthritis, multiple sclerosis and type 1 diabetes. Contrary to previous reports of cognitive impairment in myasthenic patients, we find no genetic correlation to the underlying genetics of dementia observed in Alzheimer’s disease, Parkinson’s disease, Lewy Body Dementia or Amyotrophic Lateral Sclerosis. Based on the genetic burden we identified from GWAS, Priority Index analysis identified multiple druggable genes/proteins that may be potentially effective targets in the treatment of myasthenia gravis. We nominated three existing therapies that are potentially useful in myasthenia gravis, particularly refractory cases, and suggest that clinical trials of one or more of these drugs could be prioritized.

**Conclusions:** This study provides insight into the genetic architecture underlying myasthenia gravis and demonstrates that genetic factors within the loci encoding acetylcholine receptor subunits contribute to its pathogenesis.

**Funding:** National Institute on Aging and the Myasthenia Gravis Foundation.

**306. Challenging Diagnosis of Stroke in Young: A Case Report Reflecting Delayed Diagnosis of Takayasu Arteritis and Use of Ultrasound to Reveal Typical Inflammatory Vessels**

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**Background:** Takayasu Arteritis (TA) is an idiopathic large vessel vasculitis mainly involving the aorta and its branches. It is most common in Asia, affects women more often than men, and predominantly presents in the second to fourth decades of life. There is a 15.8% prevalence of stroke and TIA in TA, therefore it is an important differential diagnosis of stroke in young patients. As undiagnosed patients develop cerebral vascular risk factors in middle age, stroke presentations can be easily attributed to atherosclerotic etiology, further delaying diagnosis. A high level of suspicion, awareness of TA presentation, and multimodal imaging is necessary to avoid serious complications.

**Case Report:** A 50-year-old Spanish-speaking female with a past medical history of hypertension, hyperlipidemia, type-2 diabetes mellitus, left carotid stenosis and remote stroke with residual right sided weakness presented with worsening baseline weakness and new left facial numbness. Her stroke was at age 15 and no etiology was identified. Physical exam revealed an absent left radial pulse, right carotid bruit, and systolic blood pressure discrepancy (right and left arms with 150 and 80 mmHg, respectively). CT angiogram demonstrated an occluded left common carotid, left subclavian and diminutive left internal carotid artery. Laboratory studies included a normal CRP and elevated ESR at 53. Brain MRI showed a remote left basal ganglia infarct. Carotid ultrasound revealed an occluded left common carotid and subclavian arteries, moderate circumferential homogenous thickening of the right common carotid artery wall, consistent with inflammatory disease rather than atherosclerotic plaque. Conventional angiogram confirmed the left common carotid and subclavian occlusion at the origin, left vertebral retrograde flow supplying the left upper extremity, stenosis of the thoracic aorta and fusiform right renal artery aneurysm. This constellation of findings and history of stroke at a young age is highly suggestive of previously undiagnosed TA. She was started on oral steroids with a plan to initiate glucocorticoid-sparing agent at outpatient follow-up.

**Conclusions:** There are multiple challenges in diagnosing TA, and the use of multimodal serial imaging can be helpful. A cohort study of 126 patients demonstrated a median delay in diagnosis of 17.5 months, it took 35 years in this case. Given the prevalence of stroke/TIA with TA, clinical awareness is essential in early diagnosis especially in stroke in young.

**307. Hematologic Dysfunction in Aicardi Goutières Syndrome**

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Aicardi Goutières Syndrome (AGS) is a genetic interferonopathy that results in severe neurologic disability coupled with complications systemic inflammation. AGS is caused by pathogenic variants in genes in complementary pathways related to RNA and DNA processing; nuclease activity (TREX1 (AGS1), RNASEH2A (AGS2), RNASEH2B
(AGS3), RNASEH2C (AGS4), SAMHD1 (AGS5),) RNA processing/sensing machinery [ADAR1 (AGS6), IFIH1 (AGS7)], and histone processing [LSM11 (AGS8), and RN7-1 (AGS9)]. Irrespective of the specific pathway, all forms of AGS result in IFN activation with elevated IFN-α levels. AGS is often referred to as a pseudo-TORCH infection because of its similarity to severe, congenital infection including cerebral calcifications, hepatitis, thrombocytopenia, and anemia. The hematologic dysfunction noted in case reports has been described as typically transient, but in rare cases require transfusions and/or immunosuppression. Despite its importance, we have limited understanding of the prevalence and extent of hematologic dysfunction in AGS. In this project, we characterized the extent of hematologic dysfunction using analysis of retrospective medical records in a cohort of children affected by AGS (n=141 subjects). The following variables were collected: age at sample collection, age at disease presentation, genotype, and complete blood counts (CBC). Laboratory values were extracted from electronic medical records whenever possible and supplemented with manual data extraction (n=9623 CBCs). Clinical context was collected as available for Grade 3-4 laboratory abnormalities. This included exposure to immunosuppressant medications, particularly baricitinib and corticosteroids, major medical events (including infection), and relevant concomitant medications. Each CBC parameter was considered as a categorical variable (grade) as well as a continuous variable. We grouped the graded dysfunction as: any abnormalities (grades 1-4), moderate-severe (grade 2-4) and severe (grade 3-4). Dysfunction for each individual for each parameter was classified as single transient, persistent, or recurrent transient. We found that the hematologic dysfunction is more prevalent and persistent than previously appreciated, with notable thrombocytopenia, anemia, and neutropenia occurring throughout the lifespan. With a better understanding of AGS-related dysfunction in these key cell lines, we can better guide clinical care and monitoring within future clinical trials.

309. LGI4 is a Novel Autoantigen for Nodopathy/Paranodopathy Type Chronic Inflammatory Demyelinating Polyneuropathy

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Background: Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common acquired immunemediated neuropathy that affects myelinated fibers. A fraction of CIDP patients carry autoantibodies against nodal/paranodal proteins, such as neurofascin (NF) 155 (NF155) and contactin 1 (CNTN1). Node/paranode antibody-positive CIDP presents distinct features compared with antibody-negative CIDP. However, CIDP patients with similar features to nodopathy/paranodopathy are occasionally negative for these antibodies.

Objective: To discover novel autoantibodies in anti-NF155 and anti-CNTN-1 antibody-negative CIDP patients demonstrating similar features to nodopathy/paranodopathy.

Methods: We screened autoantibodies that bind to mouse sciatic nerves and dorsal root ganglions (DRG) by tissuebased indirect immunofluorescence assays (IFA) using sera from 159 CIDP patients who were seronegative for anti-NF155 and anti-CNTN1 antibodies. Western blotting (WB) and cell-based RNA interference assay were used to identify the target antigens.

Results: Sera from four CIDP patients selectively bound to juxta-paranodal regions of the sciatic nerves and satellite glia in DRG. The predominant IgG subtype was IgG4 in all four patients. The patients’ IgG commonly stained a protein band around 60 kDa on WB using mouse DRG and sciatic nerve lysates. Based on these features, we hypothesized Leucine Rich Repeat LGI Family Member 4 (LGI4), which is mainly expressed in peripheral glial cells, such as Schwann cells, enteric glial cells, and satellite glia in the DRG, to be a candidate antigen. Commercial anti-LGI4 antibodies showed similar staining patterns of mouse DRG and sciatic nerves. All four patients’ IgG bound to LGI4-overexpression lysates. LGI4 siRNA effectively downregulated LGI4 in both rat Schwann cell line and LGI4-expressing human melanoma line cells and significantly reduced patients’ IgG binding compared with scrambled siRNA by IFA and WB. Anti-LGI4 antibody-positive CIDP patients had a relatively old age of onset (mean 59 years old, range 42 to 77 years old), and presented typical CIDP in 3 and MADSAM type in 1. The onset was subacute in 2 and chronic in 2. All patients had deep sensory impairment in addition to motor weakness and extremely high cerebrospinal fluid protein amounts.

Conclusion: Anti-LGI4 antibody is a novel autoantibody for nodopathy/paranodopathy type CIDP. Mutation of LGI4 is known to exhibit peripheral nerve hypomyelination. LGI4 secreted from Schwann cells interacts with ADAM22 on peripheral axonal membrane, and promotes myelination through Schwann cell-neuron communication. IgG4 anti-LGI4 antibodies may block LGI4-ADAM22 binding, which leads to dysfunctional axoglial interaction and demyelination.
neurological hemiparesis, aphasia, vision abnormalities, and hemisensory alterations temporally associated with moderate to severe headaches. Right hemibody clinical deficits have more commonly been reported than left-sided deficits in literature. Though it usually manifests as focal deficits, more diffuse manifestations such as an acute confusional state have also been described. The underlying pathophysiology is not well understood, but many reports suggest a migrainous, inflammatory, or viral etiology. To the authors’ knowledge, we describe the first documentation of a case of HaNDL syndrome in temporal association with the novel SARS-CoV-2 infection.

**Case Description:** A 23-year-old female with no past medical history except for SARS-CoV-2 infection about 2 months ago, presented with right-sided numbness and altered mental status. Since her SARS CoV-2 infection, the patient complained of multiple other transient neurological symptoms with several emergency department visits and hospitalizations, including short-lasting frontal headaches, associated with photophobia, right gaze preference, nausea, and vomiting with subsequent generalized weakness and slurred speech all lasting less than 24 hours. Diagnostic workup ruled out other etiologies like stroke, neurophilis, Lyme borreliosis, HIV, meningitis, encephalitis, and vasculitis of the central nervous system with CT angiography, contrasted brain MRI, and multiple lumbar punctures yielding lymphocytic pleocytosis. Patient transient symptoms and benign workup suggested the diagnosis of HaNDL syndrome post-SARS CoV-2 infection.

**Conclusion:** HaNDL syndrome is a rare condition that should be considered in the differential diagnoses of patients presenting with headaches and transient neurological deficits.

312. Can Clippers be Diagnosed without Pontine Involvement?

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**Introduction:** We present the case of a patient that clinically and histopathologically resembles chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), however, the imaging abnormality is centered in the brain and not the pons.

**Case Description:** A 60-year-old male with diabetes mellitus presented with gradual onset of bilateral lower extremity weakness. He was wheelchair-bound after two months. Initial magnetic resonance imaging (MRI) of the brain showed bilateral T2 hyperintense lesions involving the centrum semiovale and corpus callosum with associated linear and nodular enhancement in the perivascular distribution. MRI spine and MRA were normal. ANA screen was negative. ANCA screen showed a mildly elevated proteinase-3 antibody at 1.3 (reference <1.0) with repeat study negative. Anti-myelin oligodendrocyte glycoprotein and anti-aquaporin-4 antibody via cell-based-assay were negative. EMG was normal. Cerebrospinal fluid showed 6 nucleated cells, 218 red blood cells, glucose 76, protein 43, no oligoclonal bands, IgG index 0.46, IgG synthesis rate <0, Lyme IgG, VZV negative; cytology and flow cytometry were normal. CSF autoimmune encephalitis panel was negative. He was treated with IV methylprednisolone with rapid clinical improvement. Steroids were tapered two months later and his MRI brain showed worsening enhancement. Brain biopsy showed perivascular and parenchymal lymphocytic infiltrates composed predominantly of CD3-positive T lymphocytes with intermixed CD20-positive B lymphocytes. Microgliosis and scattered microglial nodules were present. Gram stain, AFB, fungal cultures, HSV 1/2, VZV, CMV, adenosivirus were negative. Molecular study for IgH was negative for clonal immunoglobulin heavy chain gene rearrangement. He was given dexamethasone post-biopsy with improvement in enhancement. The trend of worsening with steroid taper continued and he was started on mycophenolate mofetil and prednisone. MRI brain at 14 months showed near complete resolution.

**Discussion:** Overall, our case did not fit any current neuroinflammatory disease but most closely resembled CLIPPERS. Our patient’s subacute neurologic presentation, histopathology, and steroid responsiveness were the same. Just as in CLIPPERS, MRI T1 post-contrast lesions were not significantly bigger than T2 FLAIR lesions and pathology predominantly showed perivascular T cell infiltration with a paucity of B cells (Tobin et al. *Brain*, 2017). Given that CLIPPERS is not typically isolated to supratentorial compartment (Pittock S et al. *Brain* 2010), we would like to suggest that this may be a new presentation of this clinical entity and would like to describe our diagnosis as chronic lymphocytic inflammation with subcortical perivascular enhancement responsive to steroids (CLIPSPERS).

405. A Rare Case of Rapidly Progressive Myasthenia Gravis with Coexisting Necrotizing Autoimmune Myopathy

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**Background:** Necrotizing autoimmune myopathy (NAM) is a rare form of inflammatory myopathy characterized by necrosis and regeneration of myocytes without significant inflammation. Concurrence of inflammatory myopathy and myasthenia gravis (MG) is very rare but has been associated with thymoma and immune checkpoint inhibitors (ICI) in cancer immunotherapy. Here we present a rare case of NAM and MG after thymectomy.

**Case Presentation:** A 45-year-old Caucasian female with history of benign thymoma post resection in 2011, Crohn’s disease (previously on Infliximab and Ustekinumab) presented to the hospital for progressive extremity weakness, slurred speech, double vision and difficulty swallowing over the course of 3 weeks. Calf and triceps muscle pain was also reported. On physical examination she has severe dysarthria, bilateral prose noted after sustained up gaze, weak cough, distal more than proximal weakness in upper and proximal weakness in lower extremities. Laboratory testing revealed elevated CK at 1030, positive ANA, anti dsDNA, acetyl choline binding, blocking, modulating and anti-Titin antibodies. Rest of the laboratory workup including lumbar puncture,
extended myositis panel were negative. Electrophysiological studies showed evidence of motor syndrome, differentials including motor neuropathy or neuromuscular junction disorder or myopathy. Computed tomography (CT) chest demonstrated no residual or recurrent thymoma. Triceps muscle biopsy done later revealed changes of inflammatory/necrotizing myopathy. She received 5 doses of IVIG and was later started on pyridostigmine, prednisone with significant clinical improvement.

**Conclusion:** NAM and MG have been clinically associated with thymoma and immune checkpoint inhibitors (ICI) in cancer immunotherapy. The case described here highlights the association between NAM and MG may be present even after thymectomy. Although both Infliximab and Ustekinumab could increase the risk of autoimmune disorders, the last use of these medications was more than a year after thymectomy. Although both Infliximab and Ustekinumab could increase the risk of autoimmune disorders, the last use of these medications was more than a year after thymectomy.

**References:**

1. Patients with persistent symptoms following the acute infection exhibited a variety of neurological symptoms, most commonly cognitive and sensory symptoms. While blood tests and brain MRI did not show evidence of clear abnormalities, autonomic testing and evaluation of spinal fluid did reflect some changes that prompt additional investigation.

**Conclusions:** In this observational study of neurological function after COVID-19, patients with persistent symptoms following the acute infection exhibited a variety of neurological symptoms, most commonly cognitive and sensory symptoms. While blood tests and brain MRI did not show evidence of clear abnormalities, autonomic testing and evaluation of spinal fluid did reflect some changes that prompt additional investigation.

**K-488. Clinical Management of Aicardi Goutières Syndrome**

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**Objective:** Aicardi Goutières Syndrome (AGS) is a leukodystrophy characterized by early neurologic disability. Although AGS is genetically heterogeneous, all genotypes activate a common pathway: interferon (IFN) production leading to Janus kinase (JAK) activation and transcription of IFN-stimulated genes. While there is no approved treatment, there is great interest in targeting common steps along this autoimmune-inflammatory pathway.

**Methods:** We used existing literature to review the evidence surrounding therapeutic interventions from steroids and IVIG to reappropriation of targeted therapies such as reverse transcriptase inhibitors and janus kinase inhibition. Using data from our experience in over 50 individuals with AGS on janus kinase inhibitors, we used odds-ratios to compare the odds of having specific laboratory abnormalities at baseline and on study. We used common terminology of safety grading to describe the incidence of adverse events.

**Results:** Based on the abnormalities noted on trial and from our clinical experience, we propose clinical monitoring guidelines for the general AGS population. Overall, baricitinib is well tolerated. Common laboratory abnormalities included were thrombocytosis and neutropenia and additional monitoring of the immune system is recommended.

**Conclusion:** AGS is a systemic disorder of autoimmunity. Affected individuals necessitate a comprehensive plan for clinical monitoring and preventative care. Individuals on immunomodulatory medications require additional monitoring given the complexity inherent to AGS.
LB-455. The Consequence of Patient-Derived Anti-NMDA Receptor Autoantibodies in Neural Circuit Development and Subsequent Behavior

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Anti-NMDA receptor autoantibodies cause severe behavioral deficits and prominent abnormal movements in pediatric patients, indicating disruption of sensory-motor circuits. A key strategy for integrating sensory-motor information is the callosal connection between primary somatosensory cortices (S1). We have demonstrated that genetic disruption of NMDA receptor and antibody-mediated loss of function lead to defects in the somatosensory callosal projection in mice. We showed that disruption of axon guidance functions of the EPHRIN-B/EPHB pathway due to loss of NMDAR is the likely mechanism of this phenotype (Zhou et al., eLife, 2021). To further address whether exposure to patient-derived anti-NMDA receptor autoantibodies during callosal development disrupts callosal connectivity in S1, we generated anti-NMDA receptor monoclonal antibodies from the cerebrospinal fluid (CSF) of an anti-NMDA receptor encephalitis patient and identified two mAbs against two different subunits of NMDA receptor - mAb1 is against the NR2A subunit, mAb3 is against the NR1 subunit. Injections of either of these antibodies during callosal development in mice disrupts the ordered somatosensory callosal circuit. Injection of mAb1 caused small changes in the callosal projection but injection of mAb3 caused dramatically increased callosal innervation in the somatosensory cortex. Most interestingly, the disruption of a developmentally patterned circuit by the two patient-derived anti-NMDA receptor autoantibodies causes sensory-motor deficits in fine movement when these mice grew to adulthood. In particular, mAb3-treated mice show much worse performance in sensory-motor coordination tasks than mAb1-treated mice. This is the first demonstration that sensory-motor circuit deficits caused by patient-derived autoantibodies during development, cause subsequent sensory-motor behavior deficits in adulthood. This is relevant to the effects of this syndrome in pediatric and newborn patients and may also shed light on the protracted neurocognitive deficits experienced by anti-NMDA receptor encephalitis patients even after resolution of the acute phase of the illness.

Behavioral Neurology

022. Mickey Mouse Hand Syndrome: Macrosomatognosia with Haptic but without Parallel Visual Hallucinations During Panic Attacks

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Introduction: Macrosomatognosia, the perception of enlargement of one or more body parts, has been described with
myriad conditions including hallucinogenic substances (3,4-Methyl enedioxy methamphetamine, Lysergic acid diethylamide, cannabis (Montaclus, 2012), temporal lobe epilepsy (Kornitzer, 2015), stroke (Weijers, 2013), and psychiatric illnesses (schizophrenia, major depressive disorder, and panic disorder), but most frequently cited etiology is migraine (Mastria, 2016). In usual circumstances, there is concurrence of sensory input between haptic, somesthetic, and visual perception (Trousselard, 2003). A dissociation between visual sensory and haptic sensory perception of a body part with macrosomatognosia, as part of a panic attack, has not heretofore been described.

**Method:** Case study: This 33-year-old right-handed man presented with anxiety virtually everyday since 16 years old. Concurrent with this were frequent panic attacks, which manifest with 30 minutes of shortness of breath, blinking, and feelings of extreme anxiety. Along with these attacks, he would feel that his hands had grown to be extra large, and arms had shrunk to become stick thin, “like having Mickey Mouse hands.” Despite this sensation, when he would look at his hands and arms, they would appear to be of normal size. During these epochs, if he were holding a coke in his hands, the can would feel like it had shrunken and now possessed a miniature size, with the diameter as small as a pencil. It would seem strange to him that they would feel to be so small but visually appeared to be of normal size.

**Results:** Mental Status Examination: oriented x4. Immediate recall: 7 digits forwards and 2 digits backwards. Presidents are as follows: Trump, Obama, Clinton, ?. Able to remember 3 of 4 objects in 3 minutes without improvement with reinforcement. Despite having completed 13 years of education, he was unable to interpret proverbs.

**Discussion:** The lack of visual input overpowering haptic sensations, that only occur during panic attacks, suggests a temporary excess of limbic system discharge with visual cortical inhibition. Such a disconnection would explain not only his macrosomatognosia, but also the other manifestations of Alice in Wonderland syndrome (time and visual distortions). Peradventure, rather than having antecedent panic attacks as the origin of his symptoms, there might have been temporal lobe seizures or amigrainous migraine which then caused haptic distortions with sequelae of panic attacks. Further investigation into haptic or somesthetic predominance during macrosomatognosia is warranted.

**023. Neurofilament Light Chain is a Promising Biomarker in Alcohol Dependence**

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**Objective:** To explore the potential biomarker in the diagnosis and monitoring diseases of alcohol dependence patients.

**Methods:** ELISA was employed to detect the expression of serum nucleotide-binding oligomerization domain containing 3 (NLRP3) and Single-Molecule Array (Simoa) assay was used to detect the expression of serum neurofilament light (NFL) in 50 alcohol dependence patients and 50 controls with no drinking history. The alcohol consumption was measured by standard drinks. Neuropsychological assessments, including Montreal cognitive assessment (MoCA), Pittsburgh sleep quality index (PSQI), generalized anxiety disorder (GAD-7), and patient health questionnaire-9 (PHQ-9), were conducted to evaluate cognitive function and psychological states. The degree of white matter lesions (WMLs) was rated by the Fazekas scale using magnetic resonance imaging (MRI) analysis. The correlation between NLRP3 levels, NFL levels and neuropsychological dysfunction and the degree of WML were analyzed in alcohol dependence patients.

**Results:** Serum NLRP3 levels and NFL levels were higher in the alcohol dependence group. The NLRP3 levels were irrelevant to monthly alcohol assumption, MoCA, PSQI, GAD-7, PHQ-9 and Fazekas scale scores. The NFL levels were positively correlated with PSQI, PHQ-9 scores and the degree of WML, and negatively correlated with the MoCA scores. No associations were evident between NFL and monthly alcohol assumption and GAD-7 scores in the alcohol dependence group.

**Conclusion:** The study support the potential value of serum NFL as a non-invasive biomarker in alcohol dependence. The association with neuropsychological dysfunction and the degree of WMLs has implications to use NFL as a promising biomarker to assess the severity of brain damage, progression and prognosis of alcohol dependence.

**024. Relationships Between Body Composition, Leptin, and Cognition in Older People Living with HIV**

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**Background:** Although previous studies have suggested an inverse relationship between lower body fat and better cognitive performance in younger and mid-life adults, there is emerging evidence that this relationship changes in older adults with higher body mass associated with better cognitive performance. This protective effect may be due to leptin, a hormone released by adipose tissue cells. This relationship has not been well studied in certain neurodegenerative disease such as HIV-associated neurocognitive disorders (HAND). Due to combination anti-retroviral therapy (CART) persons living with HIV (PLWH) are living longer. We examined the relationships between body composition, leptin, and cognitive performance in older PLWH.

**Method:** Sixty-seven older (≥50 years old) PLWH who were virologically well-controlled (viral load <50 copies/mL) completed a dual-energy X-ray absorptiometry (DEXA) scan to calculate body composition (body mass index (BMI), total fat and lean mass, and total visceral adipose tissue (VAT) mass), a comprehensive cognitive battery assessing four domains (learning, memory, executive functioning, psychomotor speed), and a blood draw from which plasma leptin levels were derived. Spearman’s correlations were conducted to assess relationships between body composition, leptin levels, and cognitive performance. Analyses were performed separately in male (n=52) and female (n=15) participants due to potential sex differences in leptin levels and body composition.

**Results:** Higher BMI, total fat mass, total lean mass, and VAT mass were significantly associated with better
psichomotor speed and learning performance in older male PLWH, while higher total fat mass was associated with better executive functioning in older female PLWH (p-values <.05). Higher plasma leptin levels were positively associated with body composition variables for male PLWH (p-values <.01), but these relationships did not reach significance in female PLWH. Additionally, higher leptin was associated with better learning performance in both male (p=.04) and female (p=.03) PLWH, with a trend-level relationship with better executive functioning in female PLWH (p=.06).

Conclusions: Higher BMI and other measures of body composition were significantly associated with better cognitive performance in older PLWH. Increased levels of leptin, which were associated with high body composition values, may mediate this relationship. Further analyses of a larger sample of PLWH and HIV- controls, especially female PLWH, are needed to more fully understand the interactions between these variables and the impact of body composition on cognition.

025. Do Regional MRI Patterns Predict Treatment Outcomes for Cerebral Adrenoleukodystrophy
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Objective: Childhood cerebral adrenoleukodystrophy (ccALD) is a rare neurologic disorder characterized by rapidly progressive demyelinating brain lesions that lead to death if untreated. Standard therapy to halt the progression of ccALD lesions is hematopoietic stem cell transplantation (HCT). In the most common variant of ccALD, disease initially appears in the splenium of the corpus callosum (CC) and then extends posteriorly to parieto-occipital white matter. In rare cases, however, lesions are initially detected in the genu of CC, advancing to frontal cortical tissue. This investigation examined whether outcomes after treatment with HCT differ in individuals with the variant frontal ccALD disease pattern.

Methods: Retrospective chart review identified 7 pediatric patients with frontal pattern ccALD and MRI severity score <10, who underwent a single HCT at our center. MRI changes, neurocognitive and psychiatric outcomes at a mean of 1.2 years post-HCT were compared with a group of 7 boys with the parietal-occipital disease pattern. MRI severity score. Transplant outcomes were evaluated for overall survival (OS), engraftment as well as HCT related complications.

Results: The 5-year post-HCT OS was 100% in both groups. A similar rate of post-HCT complications was noted in both groups (2/7 patients developed Grade I/II acute graft versus host (aGVH) disease in each group; with one additional Grade IV aGVH in the frontal cohort). Radiographic disease advancement (change in MRI severity score) was slightly greater in the parietal-occipital disease group (1.4 points increase for frontal pattern and 3 for parieto-occipital disease at an average of 1.2 years post-HCT). Neurocognitive outcomes were broadly similar across the groups, with more frequent working memory deficits in the individuals with frontal disease. Psychiatric problems including hyperactivity, attention problems, aggression and atypical behavior were considerably more common and severe among patients with the frontal ccALD pattern.

Conclusion: Transplant outcomes and the risk for cognitive decline was generally similar regardless of MRI pattern in ccALD. Psychiatric manifestations are a very common concern among patients after HCT, and were especially prevalent among patients with the frontal ccALD pattern. Comprehensive care for ccALD should address the needs for psychiatric care and management.

026. Effect of Post-Stroke Aphasia Severity on Treatment Outcomes Following Combined TMS and Speech-Language Therapy
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Introduction: For persons with aphasia (PWA), behavioral treatment represents the standard of care, yet benefits of these treatments are often variable. Repetitive transcranial magnetic stimulation (rTMS) has shown promise in enhancing the effectiveness of behavioral interventions. The goal of the current study is to investigate whether rTMS paired with speech-language therapy (SLT) confers greater benefits than SLT alone. We contrast four patients who received active or sham rTMS paired with SLT to assess whether initial aphasia severity influences treatment response.

Methods: Four participants with chronic aphasia following left ischemic stroke (> 6 months post-stroke) completed the study protocol. Two participants (P1 and P2) received active rTMS: at baseline, P1 presented with Broca’s aphasia (WAB-AQ: 76.7) and P2 presented with Conduction aphasia (WAB-AQ: 84.3). Two participants (P3 and P4) received sham rTMS: at baseline, P3 presented with Broca’s aphasia (WAB-AQ: 34.0) and P4 presented with Anomic aphasia (WAB-AQ: 85.4). After baseline assessment, participants received 10 sessions of active/sham low-frequency rTMS administered over the right hemisphere Broca’s area homologue immediately followed by 60 minutes of SLT, involving scaling from picture naming of nouns and verbs to production of full sentences. Treated and untreated SLT items were probed at ≤ 10 days (T0), 3- and 6-months post-treatment (T3 and T6, respectively). Outcome measures

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included clinically meaningful change in WAB-AQ (≥ 5 points) and SLT item performance change evaluated with by-item statistical analysis of noun, verb, and sentence production accuracy.

**Results:** P1’s WAB-AQ improved at T6, and all SLT outcome measures improved at T0, which was maintained at T6 for nouns, but did not generalize to untreated items. P2’s WAB-AQ remained stable across all time points, but all SLT outcome measures improved with maintenance through T6 and generalization to untreated nouns and sentences at T3 and T6. P3 showed no effect of treatment for WAB-AQ or SLT items at any time point. P4’s WAB-AQ improved at T6 and all SLT outcome measures improved at T0 with maintenance at T6 for verbs and sentences, but no generalization to untreated items.

**Conclusions:** This combination of interventions may be most beneficial for PWA who exhibit moderate impairments, as seen by comparing outcomes between patients in the same treatment group. Critically, comparisons between active/sham for patients matched on severity (P2 and P4) suggests active rTMS facilitates long-lasting generalization to untreated items.

**027. Assessing Glutamate Concentration as a Predictor for Social Behavioral Changes in Asd Due to Memantine**

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**Background:** Autism spectrum disorder (ASD) is characterized by repetitive behaviors and impaired social communication. Differences in neural excitability/inhibitory ratios have been previously reported in ASD. Magnetic Resonance Spectroscopy (MRS) has been shown as an effective technique to measure concentrations of the neurotransmitter glutamate, which general causes increases in neural excitability. Memantine is a glutamatergic antagonist that has been studied in ASD with mixed results. It is therefore possible that this MRS be used as a predictor for the efficacy of pharmacological interventions in ASD such as memantine.

**Method:** MRS data from adult participants with ASD was processed to determine differences in glutamate concentration in the cerebellum and dorso-lateral prefrontal cortex (DLPFC). Social behavior was assessed before and after a 12 week trial of Memantine using the Clinical Global Impression-Severity (CGI-S) scale. Changes in social behavior were compared to concentrations of glutamate in both ROIs to determine if glutamate concentration may serve as a predictor of changes in social behavior due to Memantine.

**Results:** A positive correlation was discovered between glutamate concentration in left DLPFC and changes in CGI scores related to social interaction. There was no relationship between glutamate concentration in either cerebellum or DLPFC with regard to aberrant or abnormal behavior, repetitive behavior, verbal or nonverbal communication, hyperactivity, anxiety, hypo or hyper sensitivity, or restricted interest.

**Conclusions:** More work is needed to further assess the efficacy of biomarkers acquired using MRS in predicting treatment response to memantine, but these initial results suggest that it may be possible that these biomarkers can predict changes in social interaction.

**028. Clinical Correlation of Cerebrospinal Fluid P-tau Levels and Mmse Score in a Memory Clinic**

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**Background:** P-Tau protein levels in cerebrospinal fluid is a biomarker of Alzheimer disease. We correlated MMSE severity to CSF p-tau levels in a large memory clinic sample.

**Method:** We retrospectively analyzed data from patients attending a memory clinic in the south shore of Boston from 2010 to 2021, and had a lumbar puncture to obtain CSF p-tau levels. We correlated CSF p-tau levels to MMSE scores. Univariate analyses used Spearman correlation due to data being non-normal. A multivariate regression model was created including covariates of age, sex, and race.

**Results:** Total sample size analyzed, N=136, with age median=73, mean=70 SD=14. Race and gender results showed 84.3% White and 58.6% Male. P-tau distribution showed median=54, mean=63.8, SD=32.7. MMSE distribution showed median=23 mean=21, SD=7.3. Cognition as measured by MMSE total was not correlated to p-tau levels in the CSF, rho=-0.08, p=0.34.

**Conclusion:** In a large memory clinic sample, CSF p-tau levels did not correlate to MMSE scores.

**029. Tuberous Sclerosis Complex-Associated Neuropsychiatric Disorder (TAND) in a Low-Resource Setting**

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Tuberous sclerosis complex (TSC) patients commonly present with neuropsychiatric symptoms - grouped as TSC-associated neuropsychiatric disorder (TAND) - incorporating Autism Spectrum Disorder (ASD) symptoms, intellectual and learning disabilities, psychiatric and behavioral problems. A structured symptomatic assessment known as the TAND-checklist can be useful in reviewing these symptoms systematically and comprehensively. A 21-year-old woman presented with delusions of reference, auditory hallucinations, irritability, restlessness, aggressive behavior, new-onset tremors and rigidity in both upper limbs, and refusal of food and medication intake for 1 week. She has a history of several seizure episodes since 3 years of age which was controlled on oral sodium valproate, carbamazepine, and clobazam. MRI revealed tubers in frontal and insular cortex. Ultrasound of the abdomen showed bilateral renal angiomyolipomas. She was diagnosed with TSC with psychotic symptoms. TSC2 mutations usually present early with epileptic spasms (ES), complex epilepsies, intellectual and cognitive deficits, cardiac rhabdomyomas, and subependymal giant-cell astrocytomas (SEGAs) with high tuber-to-brain
proportions (TBP). There is also a remarkable symptom overlap between autism spectrum disorder (ASD) and TSC with behavioral/psychiatric disorders. Social and behavioral problems seen in our patient may be a manifestation of either TSC, ASD, or both. Cost-effectiveness and pragmatism must be considered for TAND-patients in low-resource settings. While it may be theoretically valid to seek genetic testing, TBP-measurement, and mTOR-inhibitor therapy to address TAND-symptoms, they are impractical when compared to TAND-checklist during follow-up.

030. Zugzwang Syndrome with Denigrating Hallucinations

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Background: Zugzwang syndrome can be described as a condition in which a person finds themselves in a situation where one is obligated to make a move but are paralyzed by denigrating hallucinations judging their every move and decision as being wrong. This has not been previously reported in patients with denigrating hallucinations.

Methods: Case report: A 40 year old right-handed man has experienced voices telling him that every movement he intends to make is wrong. He describes the movements as being as simple as moving to sit on the bed, picking up an object, walking from one spot to another or playing cards. As soon as the intention of mobilizing begins, he immediately starts hearing voices that force him to second guess his actions, deeming them incorrect. He states that these are not command hallucinations rather denigrating hallucinations. In response to those denigrations, he has assumed an almost catatonic position where he doesn’t move. However, even in an immobile state, he reports persisting denigrations. These voices have gotten progressively worse to the point that the patient has attempted to end his life and “stop moving altogether”. Patient also indicates trouble sleeping and frequent twitching, which he attributes to the stress and anxiety from the denigrating hallucinations. Lack of sleep worsens these symptoms and when the patient is finally able to sleep, he reports hearing the voices less. Patient is distressed as not only is he not able to control the reactions, but also feels powerless to the reactions he has towards them.


Conclusion: This study was important because it shines a light on psychiatric patients with denigrating hallucinations as being high risk of self-harm. It’s long been reported that patients with command hallucinations are distressed and were at high risk to comply with self-harm (Shawyer et al, 2003). Controlled trials for the management of command hallucinations have shown reduction in compliance behaviors using cognitive therapy for command hallucinations (Trower et al, 2004). A formalized trial for the management of denigrating hallucinations is warranted.

317. Genetic and Electrophysiological Biomarkers of Neuroplasticity Predict Post-Stroke Language Recovery

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Background: Variability in post-stroke aphasia has been attributed to several factors, like age, lesion size, and time post-stroke. However, predicting language recovery remains imprecise. We examine whether genetic biomarkers and electrophysiological indicators of neuroplasticity improve abilities to predict language recovery, measured by aphasia severity (Western Aphasia Battery-Aphasia Quotient [WAB-AQ]; Kertesz, 2007). We specifically investigate whether language recovery predictions are improved by examining interactions between 1) a common genetic polymorphism, the brain-derived neurotrophic factor gene (BDNF) and 2) neurophysiological indicators of plasticity - cortical excitability measured through motor-evoked potentials (MEPs) before and after continuous theta burst stimulation (cTBS).

Methods: Participants were 19 adults with chronic aphasia subsequent to a left-hemisphere ischemic stroke. We collected MEPs pre- and post-cTBS to primary motor cortex and obtained saliva samples for genotyping. We evaluated the extent to which BDNF Val66Met polymorphism interacted with pre-cTBS cortical excitability (log-transformed MEPs [LnMEPs]), and cTBS-induced MEP-suppression (10 minutes post- minus pre-cTBS LnMEPs) to predict language recovery (WAB-AQ). These predictors were added to established predictors of age at stroke, lesion volume, and log-transformed time post-stroke. We fit a forward stepwise linear regression model with these factors.

Results: We found significant interactions between BDNF genotype and the following predictors of language recovery: lesion volume, age at stroke, pre-cTBS cortical excitability, and cTBS-induced MEP-suppression. First, although Val66Val and Val66Met carriers both showed lower WAB-AQ as lesion volume increased, lesion volume had a stronger effect on language recovery in Val66Val carriers (β=-0.08, p<0.001). Second, increased age at stroke was associated with lower WAB-AQ for both groups, but again had a stronger effect for Val66Val carriers (β=-0.50, p<0.001). Third, cortical excitability was positively associated with WAB-AQ for Val66Val carriers, but negatively associated with WAB-AQ for Val66Met carriers (β=16.60, p<0.001). Last, increased MEP-suppression was associated with higher WAB-AQ for both groups (β=3.47, p<0.001); however, this effect was stronger for Val66Met than Val66Val carriers.

Conclusion: Neurophysiological indicators and genetic markers of neuroplasticity improve ability to predict post-stroke language recovery. The Val66Val genotype is associated with stronger neuroplasticity than Val66Met, so factors

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like age at stroke and lesion volume have a stronger effect for Val66Val carriers, who have relatively preserved plasticity. In addition, MEPs may be a biomarker for neuroplasticity, and BDNF genotype may account for cortical excitability post-stimulation. These findings provide novel insights into potential sources of variability in stroke recovery and may improve aphasia prognostics.

318. Estimated Hypoperfusion Using Flair Predicts Presence and Severity of Hemispatial Neglect

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Severity of spatial neglect in acute right hemisphere stroke correlates more strongly with total dysfunctional tissue (volume of hypoperfusion + infarcted tissue measured with DWI and PWI) than infarct alone. However, PWI is not always attainable. Hypoperfusion volume can be estimated on FLAIR by counting arteries with loss of flow voids, or Hyperintense Vessels (FHV). FHV ratings correlate with PWI measured hypoperfusion but has yet to be shown to correlate with functional deficits.

Hypothesis: 1. Neglect severity correlates with volume of dysfunctional tissue, estimated with FHV + DWI infarct. Neglect is associated with FHV in MCA and PCA territories

Methods: Right ischemic stroke patients (n=135) had neglect testing + MRI <48 hours of onset. We tested neglect with cancellation, scene copy and line bisection. We measured severity by left omissions in cancellation. We examined 6 areas for FHVs: ACA territory, PCA territory; and MCA frontal, temporal, parietal and insular regions. We rated each area as 0=0 FHV, 1=1-2 FHV on ≤2 slices or 2=3+ FHVs, and summed ratings. Penumbra was calculated as estimated hypoperfusion minus infarct volume. Total dysfunctional tissue was penumbra + infarct. We tested associations between continuous variables using Pearson correlations and multivariable linear regression and associations with dichotomous outcomes with χ² and multivariable logistic regression.

Results: Forty-one (30.4%) patients had neglect. Severity correlated with total dysfunctional tissue (r=.63; p=.0007) and less with penumbra (r=.54; p=.006) and infarct volume (r=.22; p=.02). In linear regression with age, infarct volume, hyperperfusion volume and dysfunction in each area as dependent variables, severity of neglect was independently predicted only by dysfunction in MCA temporal (r=2.97, p=0.008). Presence of neglect was associated with dysfunctional tissue in MCA temporal (q2=5.83; p=.01) and PCA (q2=4.99; p=.02) areas. Risk of neglect was independently associated with dysfunctional tissue in PCA territory (OR=5.64, p=.001) or MCA temporal (OR=2.47, p=.04) and age (OR=1.05, p=.003). FHV rating can be used, in comparison with infarct volume, to identify hypoperfusion associated with neglect and candidates for improved function with reperfusion.

335. Encephalopathy in Patients with COVID-19 Infection

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Introduction: COVID-19 presents with a wide range of symptoms, including neurologic, most commonly manifesting as encephalopathy or change in mental status, headache, dizziness, and stroke. While certain encephalopathic patients possess other co-morbidities, others lack obvious systemic or organ dysfunction to explain the impaired mentation. This study aims to characterize this latter group of patients.

Methods: Medical records of patients hospitalized at the University Hospital of Brooklyn from March 1, 2020 to May 1, 2020 with a positive COVID-19 PCR test were reviewed, and patients with clinically documented encephalopathy were selected for detailed chart review. Patients without change in mentation or who were intubated prior to admission were excluded from further review. Patient with encephalopathy were then classified into primary vs secondary encephalopathy groups. Those patients who had an accompanying medical comorbidity that could be an etiologic factor were classified into the secondary encephalopathy group and the rest were placed in the primary encephalopathy group. We defined the following etiologies for secondary encephalopathy: hypoglycemia, hyperglycemia, hyponatremia, hypernatremia, uremia, post-ictal status, diabetic ketoacidosis, respiratory failure, and structural etiologies (including acute ischemic or hemorrhagic stroke, diffuse cerebral edema). Clinical, laboratory, and radiologic variables were extracted from patients’ charts. Data analysis was performed using Wilcoxon rank sum test for continuous and Fisher exact test for categorical variables.

Results: Out of 721 patients with positive COVID-19 PCR testing in the defined time period of 7 weeks, 214 (29.7%) were identified as developing encephalopathy. 136 (63.6%) patients were in the primary, and 78 (36.4%) were in the secondary encephalopathy groups. Patients in the primary encephalopathy group had lower WBC counts and procalcitonin levels, better renal function, and were more likely to present with fever and fatigue compared to patients in the secondary encephalopathy group.

Conclusion: Patients with primary encephalopathy in the setting of COVID-19 infection tended to have better renal function and presented more frequently with constitutional symptoms compared to secondary encephalopathy group. There were no significant differences in other laboratory measures or inflammatory markers, except for procalcitonin. These findings suggest the presence of an isolated
encephalopathy in COVID patients that cannot be explained by concurrent medical issues typically seen in COVID patients. The etiology for this primary encephalopathy is unclear, but possibilities include systemic inflammation causing damage to the blood-brain barrier and results in cerebral dysfunction and less likely to be direct neurotoxicity of COVID-19 infection.

336. Neuropsychological Profile of Patients Recovering from Mild COVID-19 Infection
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Objective: To examine cognitive functioning in post-acute COVID-19 patients who suffered mild infection.

Background: COVID-19 can cause acute primary and secondary brain involvement, raising risk of persistent neurocognitive sequelae. Although lingering deficits might be expected following severe illness and hospitalization, recent reports suggest that many who sustained even mild illness continue to experience cognitive symptoms months after recovery. The term “brain fog” has emerged in the media and scientific literature, largely reflecting patients’ self-report; however, we aimed to delineate the specific cognitive domains affected in post-acute patients based on objective cognitive assessment.

Methods: Participants included 10 post-COVID-19 patients (9 women, mean age: 46.1 ± 12.5; mean education years: 15.6 ± 2.6) who did not require hospitalization for their COVID-19 infection, referred consecutively for neuropsychological assessment due to subjective cognitive decline or impaired 5-minute MoCA performance on neurological examination. All patients underwent comprehensive remote video-conference assessment of general intelligence, memory, verbal fluency, naming, attention, mental flexibility, and working memory, and screening for symptoms of depression and anxiety. Test scores were compared to demographically referenced normative data. Pearson correlations assessed the relation between age, time post-infection and performance. All patients consented to inclusion in the Columbia University Medical Center Neuropsychology Registry.

Results: Patients were assessed 8.2 ± 2.3 months (range: 3-12) post COVID-19 illness. Overall, patients exhibited normal intelligence (mean FSIQ: 100.3 ± 14.3), marked variability in verbal memory (43 %ile ±34), mild difficulty in working memory and mental flexibility (mean: 18 %ile ± 19.6), and response inhibition (31 %ile ±8.7) and marked impairment in naming (< 1/ %ile). Psychological screens revealed moderate depressive symptoms and mild anxiety. There was no relation between age and cognitive performance (all p > .05). Time since infection correlated only with performance on one demanding measure of response inhibition and mental flexibility (r = .81, p = .05). There was no relation between psychological symptoms and cognitive performance.

Conclusion: In this small series of patients who suffered only mild COVID-19 infection, neuropsychological assessment revealed specific cognitive deficits in working memory, mental flexibility, response inhibition, and word finding. Level of difficulty was unrelated to age, and with one test as the exception, unrelated to time since infection, suggesting that individuals across a range of ages may be equally vulnerable to cognitive sequelae, and that abnormalities may persist post infection. Continued follow-up and assessment of a larger series will further inform extent of impairment and recovery trajectory.

360. Baseline Multimodal Imaging to Predict Longitudinal Decline in Atypical Alzheimer’s Disease
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Background: There are recognized neuroimaging regions of interest in typical Alzheimer’s disease (AD), which have been used to track disease progression and aid prognostication. However, there is a need for validated imaging markers at baseline to predict clinical decline in atypical AD. We aimed to address this need by studying the association between baseline multimodal imaging measures and longitudinal clinical measures.

Methods: Data from 46 atypical AD patients with a diagnosis of logopenic variant primary progressive aphasia (LPA) (N = 24) or posterior cortical atrophy (PCA) (N = 22) were used in our analysis. Patients underwent MRI, FDG-PET and Tau-PET imaging and a full neurologic battery at two time points. We used the Schaefer functional atlas to extract network based and regional gray matter volume or PET SUVR values from baseline imaging. Penalized regression (Elastic Net) was used to predict scores on testing at Time 2 while controlling for baseline performance, education, age, sex, and diagnosis.

Results: The degree of baseline involvement on neuroimaging was predictive of future performance on cognitive testing while controlling for the above measures. For example, metabolism in left dorsal attention regions were associated with ideomotor praxis, left cognitive control regions were associated with sentence repetition, left temporal-parietal and cognitive control regions were associated with naming, and right dorsal attention regions were associated with performance on simultanagnosia and visual object perceptual testing. In unimodal models it appeared that baseline FDG showed the greatest associations and MRI the least. Then, in an exploratory analysis we included regions from all modalities and found many regions which were important in unimodal models survived regression, with regions on FDG again showing the greatest association on most models.

Conclusions: Our findings support three important conclusions. First, the important regions for predicting decline differed based on the cognitive domain, suggesting that a single region or summary metric will likely not suffice to track disease severity in LPA and PCA. Second, the fact that baseline imaging can predict longitudinal performance independently of baseline performance supports an important prognostic role of imaging. Third, FDG-PET outperformed MRI and Tau-PET, suggesting it may be a more sensitive marker of the extent of involvement. In summary, our
Findings suggest that incorporating baseline neuroimaging measures can help predict future decline in a domain specific manner, which may be helpful for prognostication and stratification of future studies.

361. Inhibition of Hallucinations Through Electrical Stimulation of the Cerebellum

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Background: While transcranial magnetic stimulation of the cerebellum has been found to increase the frequency of auditory verbal hallucinations (Pinheiro, 2020), cerebellar stimulation through intracranial implants has not heretofore demonstrated impact on hallucinations.

Case Report: A 62-year-old right-handed male, at age 34, began to constantly shake, especially upon intention. His mother, brother, and sisters had similar tremors. Because of such uncontrollable shaking, he underwent implants in bilateral ventral intermediate nuclei of the thalam. Prior to implantation and for the first two years after placement, the patient experienced no hallucinations. After two years of using the implant, the energy of the battery drained, at which point, his cerebellar symptoms recurred. Within one week of his implants running out of power, he began to experience a new onset of visual, auditory, olfactory, gustatory, and haptic hallucinations which were constant, all day and night. The visual hallucinations consisted of birds, animals, and vehicles. These were black and white, like cinema. He also experienced auditory hallucinations, which were not voices, but rather high pitched tinnitus, bilateral. Concurrently, he also smelled phantoms, which was flowery and paper-like, emanating from both nostrils, which persisted despite squeezing his nostrils closed. They were 8/10 in severity (with 10 being most intense), and were reduced by eating or chewing gum. He simultaneously noted gustatory hallucinations of the taste of cigarettes. In addition, he perceived haptic hallucinations, as if someone was touching both shoulders. These epochs occurred every two years, whenever the implant batteries ran out of energy. Both the hallucinations and the cerebellar motor symptoms resolved once the batteries were replaced.


Conclusion: The multiple hallucinations that occurred concurrently suggest that the cerebellum may have a supracortical governing role to inhibit hallucinations. This is consistent with cerebellar discharge functioning to inhibit conditioned hallucinations and that diseases of the cerebellum are associated with auditory hallucinations including focal cerebellar lesions, spinocerebellar ataxia, and frontotemporal dementia (Pinheiro 2020). Further investigation into cerebellar stimulation to help symptomatic management of hallucinations is warranted.

362. Central Precuneus Lesions Are Associated with Impaired Executive Function

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Background: The precuneus is a major node within the default mode network (Raichle, M. E., Proceedings of the National Academy of Sciences, 2001), yet its functional role is poorly understood. Recent work has proposed three functional subdivisions of the precuneus based on distinct patterns of functional connectivity, including an anterior region involved in representing the body, a central region involved in cognition, and a posterior region involved in higher order visual processes (Margulies, D. S., Proceedings of the National Academy of Sciences, 2009). A recent lesion study supported these functional subdivisions within the precuneus by showing a role for the antero-dorsal precuneus in body awareness (Herbet, G., Brain, 2019). In this study we set out to evaluate cognitive outcomes following focal precuneus lesions, with a focus on executive function assessed with the Trail-Making Test (TMT), and specifically to test the hypothesis that lesions of the central precuneus are associated with impaired executive function to a greater extent than other regions of the precuneus.

Method: We identified 17 subjects from the Iowa Lesion Registry and from Montpellier University Hospital's Department of Neurosurgery with focal lesions involving the precuneus. Using the difference score between TMT part A and TMT part B as our primary measure of executive functioning, subjects were divided into two groups, those with executive deficits (n=7) and those without impairment, with the threshold of impairment set at Z scores of < −1.65 relative to normative scores. Lesion location was compared between these groups using proportional subtraction and results were compared to a previously identified ‘central’ precuneus region of interest (Margulies, D. S., Proceedings of the National Academy of Sciences, 2009).

Results: 4 of the 7 subjects with TMT impairments had lesions that overlapped with the left central precuneus region, and a proportional subtraction analysis showed that lesions of the left central precuneus were proportionally higher in subjects with impaired executive function (peak MNI coordinate -5, -65, 49), consistent with our a priori hypothesis.

Conclusions: Using the lesion method, we show that, in a sample of 17 subjects with focal acquired lesions involving the precuneus, the left central precuneus is maximally associated with chronic executive function impairment based on TMT performance. These results further support the notion of a tripartite division in the precuneus, with the left central precuneus having a role in cognition.
**432. Assessing Symptom Severity of Primary Progressive Aphasia in Research Cohorts**

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**Objectives:** A global measure of symptom severity in primary progressive aphasia (PPA) would assure equivalent comparison cohorts [e.g., logopenic variant PPA (lvPPA), nonfluent agrammatic PPA (nfaPPA), semantic variant (svPPA)] in clinical research. We hypothesized that the Clinical Dementia Rating-Sum of Boxes (CDR-SB) (Berg et al, 1992, *Annals of Neurology*; Hughes et al, 1982, *British Journal of Psychiatry*; Morris, 1993, *Neurology*) and FTLD-specific Clinical Dementia Rating (FTTLD-CDR) (Knopman et al, 2008, *Brain*; Knopman et al, 2011, *Alzheimer & Dementia*) would correlate with scores on the Revised Boston Naming Test (BNT) (Goodglass et al, 2000) rather than symptom duration. We predicted that these correlations would be strongest in svPPA because the selected rating scales capture the language and behavioral characteristics primarily associated with svPPA.

**Design/Methods:** Sixty-four individuals with PPA (mean age = 67.61 ± 7.53; 39 female; mean education = 15.95 ± 2.68; average symptom duration = 36.08 ± 21.93) were rated on the CDR-SB and FTLD-CDR, including 26 with lvPPA, 20 with nfaPPA, and 18 with svPPA. PPA subtype was diagnosed by an experienced behavioral neurologist on the basis of history, comprehensive neurological examination, imaging, and a battery of cognitive/language tests, and classified using consensus criteria for each variant (Gorno-Tempini et al, 2011, *Neurology*).

**Results:** Correlations were weak between symptom duration and CDR-SB (r = 0.306, p = 0.014) and FTLD-CDR (r = 0.279, p = 0.025). There were moderate significant correlations between BNT scores and CDR-SB (r = -0.521, p < 0.001) and FTLD-CDR (r = -0.676, p < 0.001). After correcting for multiple comparisons (Bonferroni), there were significant moderate correlations between BNT scores and FTLD-CDR for lvPPA (r = -0.612, p = 0.005) and nfaPPA (r = -0.616, p = 0.011).

**Conclusions:** As expected, the correlations between the rating scales and BNT scores were stronger than the correlations between the rating scales and symptom duration. Surprisingly, there were no significant correlations between the rating scales and BNT in svPPA. This is explained by uniformity and severity of ratings on language in this group (median score = 3, interquartile range = 0) and likely poor performance on BNT, even early in the disease course. These findings suggest that different indicators of severity should be reported as each measure has its own limitations in capturing the multifactorial nature of symptom severity.

**433. Behavioral Disturbances in Progressive Apraxia of Speech and Agrammatic Aphasia**

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**Introduction:** Patients with primary neurodegenerative speech-language disorders can display behavioral symptoms. However, little is known about how behavioral disturbances differ across progressive apraxia of speech and/or agrammatic aphasia. In this study, we investigated the behavioral symptomatology across 3 distinguishable speech-language disorders: those with pure speech apraxia, those with pure agrammatic aphasia, and those with mixed speech apraxia and agrammatic aphasia.

**Methods:** This study included 89 prospectively recruited patients with speech-language difficulties, of whom 40 had isolated speech apraxia and met criteria for primary progressive aphasia of speech (PPAOS), 11 had isolated agrammatic aphasia and were designated progressive agrammatic aphasia (PAA), and 38 had both (AOS-PAA). A total of 238 visits were performed, with on average 2.37 visits per patient. Behavioral disturbances were evaluated using two questionnaires: the frontal behavior inventory (FBI) and a novel 20-item behavioral assessment (20-BAS), the latter developed in our laboratory over the past two decades to address behavioral symptoms not covered by other behavioral inventories and reported for the first time here. We analyzed FBI total score, FBI negative behavior and FBI disinhibition behavior subscores, as well as individual items in both inventories. We also checked the evolution of behavioral disturbances across groups over visits.

**Results:** All patients in this study, regardless of diagnosis, endorsed at least one symptom on the FBI at the baseline visit, most frequently verbal apraxia (100%) and logopenia (95.6%), as well as irritability (55.9%), and apathy (42.6%). On the 20-BAS, 47.6% of the patients endorsed at least one symptom, most commonly ‘crying more easily’ (19.5%) and personality change (18.3%). Supported by both of these inventories, across variants, PPAOS was the least behaviorally affected group. Negative behaviors were different between PPAOS and AOS-PAA (p = 0.001) while disinhibition was more common in PAA than PPAOS (p = 0.037). Overall, behavioral disturbances in all measures worsened over time but there were no differences in the rate of change across groups.

**Conclusions:** Behavioral disturbances are frequent in aphasic more than apraxic speech patients, even early in the disease course, and worsen as the disease progresses. They should therefore be assessed in PAA, AOS-PAA and PPAOS patients even in the early stages of the syndromes.

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**K-496. Differential Behavioral Outcomes of Cerebellar Disruption in Early Mouse Development**

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Neurodevelopmental disability arising from prematurity poses a large and increasing disease burden and has been associated
with cerebellar pathogenesis. Cerebellar development coincides with the third trimester in humans, a developmental period during which establishment of brain networks supports neurotypical outcomes. During this period there is a massive expansion of cerebellar foliation, including the establishment of the cerebellar cortical circuitry that houses the majority of the neurons in the nervous system. In addition, increasing evidence points to extensive anatomic and functional connectivity between the cerebellum and the entire nervous system. Together these observations suggest a hypothesis by which cerebellar function during this developmental window is a key component in the establishment of typical neurodevelopment and the underlying physiologic substrates that support it. Using an inducible, conditional approach of silencing Purkinje cell neurotransmission through cre-mediated excision of the vesicular GABA transporter specifically in Purkinje cells, cerebellar function is dynamically altered both early (in utero) and late (postnatal day 20) in mouse development. Early disruption of Purkinje cell neurotransmission leads to pervasive behavioral dysfunction across developmental domains, while late disruption leads to behavioral disruptions primarily in functional behavioral domains. Preliminary data suggests that there are discrepant anatomic and electrophysiologic alterations resulting from these manipulations, which points to a mechanistic insight into the role of cerebellar dysfunction in neurodevelopmental outcomes.

K-516. Prediction of Cognitive Function with Multimodal Brain MRI
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Cognitive health reflects the ability to effectively think, learn, and remember and is key to accomplishing day-to-day activities and maintaining functional independence in an ever-changing environment. A valid brain-based biomarker that predicts cognitive function at the individual level could help uncover the neural basis underlying cognition and promote the development of clinical tools for the early detection of vulnerability to cognitive decline. Here we develop and validate prediction pipelines of crystallized and fluid aspects of human cognitive function using multimodal magnetic resonance imaging (MRI) derived brain features. Each MRI modality — structural MRI (i.e. gray matter morphometry), diffusion MRI (i.e., white matter fractional anisotropy), resting state functional MRI (i.e., functional connectivity, frequency domain measures, and graph measures), and task-evoked functional MRI (i.e., working memory, category-specific representations, gambling, language processing, social cognition, relational processing, and emotion processing) — demonstrated significant predictive power, with a multimodal prediction pipeline explaining more than 35% of the variance in total cognitive function in an independent testing dataset (n=80, r²=0.368). Finally, we contrasted the prediction of the fluid and crystallized components of cognitive function. Predictive performance was higher for crystallized (r²=0.380) than fluid (r²=0.236) cognitive processes. We conclude that MRI-based prediction pipelines can provide objective and neurobiologically-based measures of cognitive function. These measures may provide insight into the relationship between the brain and cognitive health and may prove to have diagnostic value as well as prognostic and predictive value in health and disease.

LB-465. Encoding Behavioral Information by Dynamic Reorganization of a Prefrontal Microcircuit
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Changes in multineuron activity within the brain underlie cognitive processes. However, the nature by which information is encoded is unclear. We reasoned that modulation of the temporal patterning of neuronal groups into behavior-specific patterns might both contribute to specific computational processes and increase the reliability by which information might be transmitted between neurons during behavior. We utilized calcium imaging to record the activity of many neurons simultaneously as mice engaged in a variety of social and anxiety-provoking behaviors to generate multidimensional datasets. We then utilized machine-learning approaches to identify specific ensembles of neurons whose activity was modulated during each behavior. We show that the activity of identified ensembles convey information that is specific for each behavior with little overlap between ensembles and different behaviors. Demonstrating that the temporal patterning of neuronal activity is critical, shuffling datasets randomly reduces the performance of our classifier to chance, whereas shuffling data in a manner that preserves correlations maintains above-chance accuracy. We reason that in neurodegenerative or neurodevelopmental disorders this temporal patterning may be altered both due to changes input or changes in the function of the local microcircuit.

LB-471. Nidus for Delusions: Neurologic Dysfunction Induced Sensory Illusions - A Case Series
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Introduction: The construct that altered sensory perception can be misperceived as an illusion and then integrated into a delusional system is consistent with the idea that delusions originate with the sensory focus, as in tactile or kinesthetic phenomena (Angyal, 1935). However, no case series has hitherto been described confirming such an assumption. Three such cases are reported.

Methods/Results: Case Report: Case 1: A 23-year-old right-handed woman with Marfan’s Syndrome experienced a feeling she was being stretched, as if being tortured on a rack
or nailed to a crucifix and her extremities were being disarticulated from her body and at times, she actually believed she was being crucified. For a decade she has had falling spells with a feeling of unreality, and ideas of reference. She admits to frequent déjà vu and auditory hallucinations, and has been diagnosed with focal seizures. Results: Abnormalities on Physical Examination: General: Height 6 feet, Arachnodactyly, Pes Planus. Neurologic Examination: Reflexes: Absent. MRI of Thoracic and Lumbar Spine: Dural sacs with septation at S1-S2. Case 2: A 28-year-old right-handed man presented with a history of visual, auditory, and haptic hallucinations of the Grim reaper since the age of five. The Grim Reaper was seven feet tall with a scythe, covered in a long black cape and skull faces. The Grim Reaper would appear in epochs of 30 seconds and grabs his arm, “the touch of death”. He experienced déjà-vu every three days, but denied jamais-vu, cataplexy, and drug use. Results: Abnormalities in physical examination: Neurological Examination: Hoffman Reflex: positive bilaterally. Magnetic resonance imaging of brain with and without contrast: normal. Three-day electroencephalogram revealed temporal lobe status epilepticus with bilateral foci. Case 3: A 21-year-old right-handed cisgender female two months prior to presentation felt generalized stiffness in her muscles and as if she couldn’t move. On admission her chief complaint was “I am a tree”, standing motionless. She had a past history of trauma but would not disclose any further details about this. Neurologic examination: she would stand still for long periods of time, refusing blood pressure to be obtained, expressing fear of constraining “flow”.

Discussion: In each of the cases of delusional disorder described herein, nidus for the delusion was a sensory phenomenon. In those with delusions, investigation as to presence of a neurologic abnormality, functioning as the primary source of sensation from which the delusion is built upon, is warranted.

Cerebrovascular Disease

031. Right-to-Left Shunt Detection Using Transforaminal Insonation of the Basilar Artery

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Objective: To assess the accuracy of transforaminal insonation of the basilar artery (TIBA) in detecting right-to-left shunt (RLS) in patients with cryptogenic strokes (CS) and acoustically insufficient temporal windows.

Background: PFO screening is routine practice in patients with CS, as PFO closure in select CS patients is currently advised for secondary stroke prevention. Transcranial Doppler ultrasound (TCD) with bubble is non-invasive, reproducible and has high sensitivity for PFO screening. However, about 10% of the population has insufficient temporal bone windows to perform standard TCD monitoring of the middle cerebral arteries (MCA). We aimed to determine if TIBA could be used for PFO screening in individuals unable to undergo standard TCD bubble study. Methods: We performed a retrospective, single-center, observational study of TIBA in patients with CS and inadequate temporal windows. We compared the PFO screening accuracy using TIBA versus echocardiogram, either transthoracic (TTE) or transesophageal (TEE).

Results: Sixteen females and 4 males were included (mean age 63.2 years; range 22-86 years). All patients underwent TTE, and only 10 (50%) underwent the gold-standard TEE. Nine patients had positive RLS with both TCD and echocardiogram. Two patients with negative echocardiogram had TCD-positive RLS. Three patients had RLS detected on echocardiogram, whereas TCD was negative. Six patients had absent RLS with both TCD and echocardiogram. The sensitivity and specificity of TBAI for RLS detection were 75%, positive predictive value 82% and negative predictive value 67%. 9 out of 12 shunts detected by TIBA had medium or large size.

Conclusion: PFO screening accuracy using TIBA was somewhat lower than standard transtemporal insonation. This may be due to the lack of standardization and optimization of a protocol that has yet to be created for TIBA. Prospective evaluation of CS patients with TIBA and comparison to the gold-standard TEE should be performed to further guide clinical practice.

032. Vertebral Artery Dissection After CrossFit Workout

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Background: Spontaneous vertebral artery dissection (VAD) accounts for nearly 20% of strokes in patients younger than 45. They are commonly seen in cases of trauma or neck manipulation such as chiropractic maneuvers but have also been reported to occur during or after intense exercises. We present a case involving a young woman who experienced a VAD during a vigorous CrossFit routine.

Case Presentation: A 30-year-old woman with no past medical history presented to the emergency department with sudden onset left sided weakness, numbness and light-headedness. These symptoms developed while clean-and-pressing 95 lbs overhead. She had no history of smoking, alcohol or recreational drug use. She exercised 6 days a week at a CrossFit gym. Upon admission her vitals were stable (140/80, HR-70-80) with an NIH Stroke Scale (NIHSS) score of 3. CT head was unremarkable, but CT angiogram head and neck revealed a segmental stenosis of right vertebral artery (V1) segment. In addition, there was 4 mm out-pouching concerning for dissection and complete occlusion of the right posterior cerebral artery (P2) segment. She was given IV thrombolytic therapy, tissue plasminogen activator (tPA). During transfusion of tPA, patient developed left sided homonymous hemianopsia. Her NIHSS score was between a 3 and 4 with the addition of a headache. A repeated CT head was unremarkable but a CT Perfusion scan revealed a 7 mm area of ischemic penumbra in the right occipital lobe with no
core infarct. She was admitted to the neurology critical care unit and started on Dual Antiplatelet therapy 24 hours after administration of tPA. She was discharged 72 hours later with no residual defects. She followed up in stroke clinic in 6 months with complete resolution of neurological and radiological findings.

Discussion: Although rare, this case illustrates the potential for vertebral dissections and subsequent posterior circulation stroke with intense exercises including CrossFit. Incidence of spontaneous VAD is only 1-1.5 per 100,000 with 0.97 per 100,000 occurring secondary to trauma elicited by intense exercise. This case adds to these statistics and suggests that VADs may occur due to high-intensity workouts such as CrossFit more often than initially proposed.

Conclusion: Although incidence of posterior circulation stroke during vigorous workouts is rare, our case highlights the importance of being vigilant during high intensity exercises and demonstrates the importance of posterior circulation stroke education in younger population.

033. Hydration Practices for Hospitalized Stroke Patients at the University Teaching Hospital in Zambia

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Objective: Evaluate baseline hydration practices for hospitalized stroke patients at the University Teaching Hospital in Lusaka, Zambia.

Background: Stroke prevalence and case-fatality rates in sub-Saharan Africa (SSA) are amongst the highest in the world. Volume contracted state (VCS) at stroke onset may worsen stroke outcomes; therefore, providers may consider administering increased rehydration in these patients. Thus, we sought to understand current hydration practices after stroke in Zambia.

Methods: A consecutive series of adults with stroke were enrolled in this prospective study. All participants were screened for thirst (none/mild/significant) during the first 10 days of hospitalization, and amount of intravenous fluids (IVF) administered each day was recorded. Blood urea and creatinine were recorded when obtained as standard care and categorized as: elevated urea (>7.10 mmol/L), moderate VCS (urea:creatinine ratio >100:1), and mild VCS (urea:creatinine ratio >75:1). We analyzed whether these states were associated with in-hospital mortality, self-reported thirst, and amount of IVF.

Results: Of 125 enrolled participants, 76 were female (61%) with mean age 59±16 years, and 22 (18%) were people with HIV. Stroke types were: 67 (54%) ischemic, 38 (30%) hemorrhagic, and 20 (16%) unknown (no imaging obtained). Approximately one-third of participants reported thirst each of the first 10 days of admission. Within 10 days of hospitalization, 28% (n=35) received IVF. When IVF was administered, 65% received ≤500 mL. Elevated urea but not VCS (mild or moderate) was associated with higher mortality. Self-reported thirst did not differ by laboratory measures of hydration status and was not associated with IVF administration on any day. Participants with elevated urea, mild VCS, and moderate VCS were more likely to receive IVF on hospitalization day 2 than participants without these factors but not on other days. Still, <50% of participants meeting these parameters received IVF during the first 3 days of their hospitalization.

Conclusion: Only a small proportion of adults hospitalized with stroke in Zambia receive IVF including <50% of our participants with VCS. Optimization of hydration protocols may represent a low-cost and scalable intervention for stroke patients in Zambia and similar settings. Further work is needed to understand perceptions underlying hydration practices of local clinicians to address this gap.

034. Vertebrobasilar Insufficiency as a Cause of Drop Attack, A Case Report and Literature Review

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Background: The vertebral arteries merge to form the basilar artery and thus the posterior circulation of the brain. Inadequate blood flow in these vessels is termed vertebrobasilar insufficiency (VBI) and can have dire consequences including disability and death as this area supplies the cerebellum, medulla, midbrain, and occipital cortex. The most common symptom is vertigo with 60% of patients reporting dizziness/syncope. Less common symptoms can include, diplopia, ataxia, altered mentation, weakness, incontinence, or drop attacks. We present a case of a woman with drop attacks and an atypical presentation of VBI.

Case Presentation: A 68-year-old Caucasian woman with a past medical history of TIA, Hepatitis C, psoriatic arthritis, diabetes, and 2-3 Packs per week smoking history presented with 3 years of gait instability that had been non-progressive until 3 months prior. She was referred by her PCP who had concerns of normal pressure hydrocephalus (NPH) versus other neurological etiology due to a 3-month history of worsening instability and urinary incontinence as well as new-onset aphasia. These episodes consisted of unsteady gait, feeling off-balance, and drop attacks where her legs would give out or her knees would buckle, leading to stumbling and falls. She also complained of progressive speech problems with word finding difficulty, word salad, and losing train of thought for seconds at a time. She denied loss of consciousness, syncope or presyncope, dizziness, vertigo, diplopia, or vision changes. Her Neurological examination was unremarkable. MRI brain Without Contrast showed no acute abnormality. CTA Head and Neck showed 70% stenosis of the left vertebral artery and 30% stenosis of the right vertebral artery bilaterally in the V1 segment with no other significant findings. Patient was further evaluated with diagnostic cerebral angiogram to assess posterior circulation flow and possibility of vertebral stenting.

Discussion: While this patient does have vascular risk factors associated with VBI, her presentation is atypical when considering her normal neurological exam and lack of vertigo/syncope. With up to 25% of elderly patients presenting with instability and increased fall risk caused by VBI, prompt management is necessary to limit dangerous sequelae like trauma or stroke.
Theory: Although drop attacks are usually cardiogenic or vestibular in etiology, this case presents them as a manifestation of an insidious and dangerous etiology, VBI. Increased awareness of drop attacks as a presenting symptom without typical vertigo/syncope can lead to prompt evaluation, diagnosis, and intervention.

035. Different Neurological Manifestations in Brothers with Hypermobile Ehler-Danlos Syndrome
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Background: Ehlers-Danlos Syndrome (EDS) is a heterogeneous group of connective tissue disorders characterized by joint hypermobility, hyperextensible skin, poor wound healing, and easy scarring. There are numerous subtypes with various characteristics. The objective of this case report is to highlight two brothers with hypermobile EDS with different neurological manifestations including moyamoya, transient ischemic attacks, migraines, and cognitive decline.

Case Description: Two brothers presented to our institution with a known diagnosis of hypermobile EDS. Brother A with a history of postural orthostatic tachycardia syndrome (POTS), presented with an acute episode of right-sided facial paresthesia and right upper extremity paresthesia. Workup revealed right-sided moyamoya and neuropsychology testing revealed bifrontal (left>right) and bitemporal (left>right) involvement, thought to be due to left-hemispheric transient ischemic attack, with likely contributions from right-hemispheric vascular insufficiency. Brother B presented after experiencing an episode of confusion, dizziness, and right-sided weakness followed by persistent academic difficulties, chronic migraines, chronic tension headaches, and dysautonomia. Neuropsychology testing revealed bifrontal involvement with reductions in processing speed, mental flexibility, and verbal and visuospatial recall, representing a decline from his prior functioning based on premorbid estimates.

Conclusion: Neurologic manifestations associated with EDS include headaches, Chiari I malformation (CMI), segmental kyphosis and instability, memory and concentration problems, tethered cord syndrome, neuropathic pain, and cardiovascular dysautonomia causing secondary neurologic symptoms. Even though both brothers had hypermobile EDS, they went on to have different types of neurological manifestations. Although vascular EDS has been reported to be associated with stroke in the young, the presence of vascular sequelae in both brothers indicates a possible association between cerebral vascular accident and hypermobile EDS as well.

036. A Rare Case of Spontaneous Bilateral Internal Carotid Artery Dissection in a Young Healthy Female
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Background: Carotid artery dissection attributes to about 20% ischemic strokes in young adults. Etiology could be spontaneous, traumatic or due to underlying arteriopathy/vascular tissue disorder. Spontaneous bilateral internal carotid artery dissection is rare with unknown incidence due to its varied presentations ranging from local symptoms like isolated headache or neck pain to stroke.

Case Presentation: A 43-year-old Hispanic female with no significant medical history presented to emergency department with sudden onset transient left arm weakness and holocranial pressure-type headache that started while performing push-ups before a kick boxing class. Neurological examination on presentation was essentially non-focal. Computed tomography (CT) head did not show any acute abnormality. CT angiogram (CTA) head and neck demonstrated severe narrowing of bilateral distal cervical internal carotid arteries (ICA’s) concerning for dissection. Magnetic resonance imaging (MRI) brain did not show any acute infarct. Diagnostic cerebral angiogram confirmed arterial dissection involving high cervical segments of both ICA’s with severe focal arterial stenosis. Laboratory testing including genetic testing for connective tissue disorders causing aortic or vascular aneurysm, dissection was unrevealing. During hospitalization, she developed another episode of transient left arm weakness in the setting of cerebral hypoperfusion secondary to systemic hypotension requiring blood pressure augmentation with vasopressors. A repeat cerebral angiogram was done with stent placement within dissected right ICA. Following an uneventful hospital course, she was discharged home on dual anti-platelet therapy with plans for follow up cerebral angiogram.

Conclusion: Spontaneous bilateral internal carotid arterial dissection is a rare cause of acute ischemic stroke with potentially serious complications in young otherwise healthy patients. Cerebral angiogram provides a better diagnostic opportunity by not only providing details regarding collateral circulation and can also guide therapeutic treatment options.

037. Bilateral Carotid Endarterectomy for Thrombosis from Coronavirus
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A 50-year old female, SARS-CoV-2 positive patient with no risk factors for stroke, presented to the emergency room for headache and dyspnea. This patient underwent computed tomography angiography for suspicion of cerebrovascular accident which revealed aortic thrombus at the proximal descending and abdominal area, bilateral carotid thrombus, and findings suggestive of stroke involving the frontal and parietal lobes. This patient underwent bilateral carotid endarterectomy and was discharged on dual antiplatelet therapy. SARS-CoV-2 has recently been reported to be involved in hypercoagulable states, coagulopathic changes, and large vessel occlusions of intracranial vessels. This coagulopathic process can proceed to stroke, however, this is most commonly seen in the setting of risk factors: Hypertension, diabetes, hyperlipidemia, and smoking. Our study demonstrates the need for a high degree of suspicion for stroke in cerebral angiogram.
patients with no risk factors who test for SARS-CoV-2 and the need for early imaging for vascular thrombosis so that appropriate protocol can be started efficiently. It points to the severe disruption that SARS-CoV-2 has on Virchow’s triad of blood stasis, hypercoagulability, and endothelial damage.

038. Intracerebral Hemorrhage in the Setting of Acute COVID-19 Infection

**Kyra Curtis, B.S., Yousef Ajam, M.D., Prashant Rai, M.D., Sama Elahi, B.S., University of Texas Medical Branch, Galveston, TX, USA.**

**Background:** Although cerebrovascular disease has been identified as a common complication of SARS-CoV-2 infection, intracerebral hemorrhage (ICH) has been less documented. Despite the low incidence of ICH (0.7%), the mortality is high (48.6%). We describe a case where the patient expired from an ICH during COVID-19 infection.

**Case summary:** A 53-year-old male with a past medical history of hypertension, hyperlipidemia, chronic kidney disease, diabetes mellitus type II, and glaucoma presented to an outside emergency department after an unwitnessed fall following a brief syncopal episode. Per family the patient had been experiencing a sore throat and chills for a week. In the ED he tested positive for COVID-19 and a CT head showed a 3.4 x 6.1 cm ICH of the right temporal lobe with surrounding vasogenic edema, small subdural hematoma overlying the right cerebral convexity, small subarachnoid hemorrhage of the left temporal lobe, and a 5mm right to left midline shift. Given significant brain edema and hemorrhage, the patient was intubated and transferred to UTMB for further care. He was placed on Keppra and hypertonic saline as neurosurgery did not recommend an acute surgical intervention. Per neurology consult, it was determined that he likely experienced a hemorrhagic stroke leading to a fall rather than a hemorrhage due to the fall. After a week, the patient was extubated but had another unwitnessed fall on the same day. Imaging did not show any acute injury but the patient became bradycardic so he was re-intubated and placed on pressors. Nearly two weeks later, a tracheostomy was placed. The patient went on to develop aspiration pneumonia followed by a PEG tube placement. He was discharged to a skilled nursing facility as he was A&O, unable to communicate via board due to visual impairment, and ability to only move RUE. The patient expired 2 months after discharge.

**Discussion:** Although ICH is a relatively rare complication of COVID-19, it carries a high mortality rate. The pathophysiology of ICH in the setting of SARS-CoV-2 is still unclear but is thought to be related to pre-existing conditions, age, and overexpression of angiotensin converting enzyme 2 (ACE2). Case reports such as this one are important in better understanding this complication of COVID-19.

**Conclusion:** The incidence of ICH in COVID-19 patients is low but indicates a poor prognosis. Further study is needed in order to better understand its pathophysiology and increase appropriate prevention measures.

039. Acute Ischemic Stroke in the Setting of COVID-19

**Saloni Gyani, BSA, Yousef Ajam, MD, Prashant Rai, MD, University of Texas Medical Branch, Galveston, TX, USA.**

**Background:** Although SARS-CoV-2 is a predominantly a respiratory virus emerging evidence suggest it has an array of neurological presentations including stroke. The virus enters host cells via the ACE-2 receptor which is also expressed on neurons and endothelial cells making them vulnerable targets. Activation of ACE-2 precipitates a systemic inflammatory response and cytokine storm with elevated IL-6 and TNF-α. Between direct viral invasion, stasis, and endothelial damage the virus induces a hypercoagulable state increasing the probability for acute ischemic stroke.

**Case Presentation:** A 62-year-old male with a 1-month history of shortness of breath was admitted for acute hypoxic respiratory failure secondary to COVID-19 pneumonia. Pertinent history includes hyperlipidemia, rheumatoid arthritis interstitial lung disease, wheelchair restriction and tobacco use. The patient was on DVT prophylaxis (Enoxaparin 1mg/kg/d and Aspirin 81mg/day). On admission day 4 stroke activation was called for altered mental status, aphasia, and right-sided weakness. He scored 14 on the NIHSS. Physical examination was remarkable for expressive/receptive aphasia, right sided hemi-neglect, and absent right-sided response to painful stimuli. Strength was diminished in the right upper extremity (1/5) and preserved in the lower extremity (4/5). D-dimer increased from 4.23 at admission to 49.72. CT head without contrast revealed left temporal lobe, parietal lobe, left insular cortex and lentiform nucleus hypodensity. CTA revealed complete occlusion of the left M2 inferior branch. The patient was out of t-PA window period(24 hours from symptom onset). Additionally, he wasn’t candidate for endovascular clot retrieval as CT perfusion showed complete infarct. Anticoagulation was held due to risk of hemorrhage. Hypertonic saline was initiated to decrease edema. Permissive hypertension up to 220/110 was employed to improve cerebral perfusion. Oxygen requirements began to increase, and he deceased on day 9.

**Discussion:** Prior studies report that the proportion of acute ischemic stroke(large vessel disease) among patients hospitalized from COVID ranges between 1-3%. Independent of COVID-19 status cardiovascular disease and advanced age increase stroke predisposition. However, in the setting of COVID-19 the mortality rate from stroke increases by 2-fold and may be attributed to the virus’s pro-thrombotic state.

**Conclusion:** This case highlights acute ischemic stroke large vessel disease as a rare complication of COVID-19, particularly in the setting of the pre-existing autoimmune dysfunction, immobility, and cardiovascular disease seen in our patient. Given his elevated D-dimer the etiology of his stroke was likely secondary to a hypercoagulable state. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7670261/ https://www.ahajournals.org/doi/10.1161/STROKEAHA.120.031786

040. Intracerebral Hemorrhage in the Setting of Anticoagulation and COVID-19

**Saloni Gyani, BSA, Yousef Ajam, MD, Prashant Rai, MD, Bhanu Gogia, MD. University of Texas Medical Branch, Galveston, TX, USA.**

**Activation of ACE-2 precipitates a systemic inflammatory response and cytokine storm with elevated IL-6 and TNF-α. Between direct viral invasion, stasis, and endothelial damage the virus induces a hypercoagulable state increasing the probability for acute ischemic stroke.**
Background: SARS-CoV-2 uses the ACE-II receptor to gain entry to cells. This receptor plays a key role in blood pressure regulation and is found not only in the lung parenchyma but also in the cerebral vasculature and circumventricular organs. It is hypothesized that viral disruption of the receptor interferes with cerebral autoregulation leading to blood pressure spikes which cause arterial damage and hemorrhage. This case describes a patient who had multifocal intracerebral hemorrhage in the setting of anticoagulation therapy.

Case Report: A 73-year-old COVID-19 positive male was hospitalized for over 3 weeks on prolonged heparin anticoagulation, intubation, and a multidrug respiratory therapy regimen. While on a sedation holiday the patient was unable to follow commands. CT showed a 9 mm right inferior temporal hemorrhage and subdural hematoma. Secondary findings included multifocal hemorrhages overlying the right parietal, and occipital lobes, scattered subarachnoid hemorrhage, trace intraventricular hemorrhage of the lateral ventricle occipital horn, and a mild right-to-left mass effect. His neurological status continued to decline. Grimace and pain response was absent, gaze was deviated rightwards and pupils were sluggish. Repeat CT and MRI showed mild expansion of the original temporal contusion (now 1.3 cm). MRV was negative for venous sinus thrombosis. Because imaging findings were incongruent other differentials such as PRES and seizure were considered. EEG was remarkable for moderate diffuse slowing suggestive of but negative for epileptiform discharges. The patient then developed right upper extremity weakness. Repeat MRI showed worsening of the right subdural hematoma, however clinical symptoms improved. Right-sided strength returned, mental status improved (A&Ox4), gaze deviation regressed, and pupils were reactive.

Discussion: Intracerebral hemorrhage is a rare complication of COVID-19 occurring in 0.7% of affected patients. Imbalance between coagulation and fibrinolysis can lead to ischemic stroke or hemorrhage. Our patient’s D-dimer was 3.63 μg/mL indicating skew towards fibrinolysis. COVID-19 evokes a hyperfibrinolytic state by elevated plasminogen, tPA, and urokinase levels. Additionally, viral proteases may provide an alternative fibrinogen cleavage pathway. Finally, as seen in our patient, in critical care settings patients are often placed on prolonged anticoagulation therapy, increasing their risk for acute bleeding.

Conclusion: Between the damage COVID-19 inflicts on cerebral vasculature, the pro-fibrinolytic state, and prolonged anticoagulation therapy our patient developed multiple hemorrhages across his parietal, temporal, and occipital lobe. Once the acute setting passed, with supportive measures such as blood pressure control our patient’s mental status and function improved. doi/10.1016/j.jstrokecerebrovasdis.2021.105603 https://pubmed.ncbi.nlm.nih.gov/32322398/

044. Intracerebral Hemorrhage from Pro-fibrinolytic Balance with COVID-19 Infection
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Objective: Reviewing 2 cases of intracerebral hemorrhage in COVID-19 patients presenting with reversible ischemic stroke/TIA and severe hypotension in prolonged non-ophthalmic surgeries.

Background: Viral proteases may provide an alternative fibrinogen cleavage pathway. Finally, as seen in our patient, in critical care settings patients are often placed on prolonged anticoagulation therapy, increasing their risk for acute bleeding. COVID-19 increases the risk of developing ischemic stroke and even ILT. ILT is an uncommon finding among acute stroke/TIA patients with prevalence being 1.6%. It is most often caused by atherosclerosis. Management includes combination antithrombotics, which partially or completely resolve 75% of ILTs within one week, such as with this patient.

Conclusion: There are increasing COVID-19 patients having strokes, and this report presents just one of many. Our patient fortunately recovered with no residual deficits. This case highlights both the importance of a thorough workup in possible stroke patients with COVID-19 and the benefits of using antithrombotics to treat ILTs.

Reference: https://www.ahajournals.org/doi/pdf/10.1161/STROKEAHA.118.023015

042. Lights, Christmas Tree, Animals and People: Charles Bonnet Syndrome Due to Perioperative Posterior Ischemic Optic Neuropathy
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Objective: Revisiting Charles Bonnet Syndrome and perioperative posterior ischemic optic neuropathy due to impaired blood supply to the optic nerve in the setting blood loss or hypotension in prolonged non-ophthalmic surgeries.

Background: This case report serves to highlight the rare presentation of sudden onset of vision loss followed by
formed visual hallucinations in an individual with no underlying psychiatric illness, after cystectomy due to posterior ischemic optic neuropathy (PION).

**Design/Methods: Case Report:** 71-year-old, man who presented with sudden onset painless bilateral vision loss following a six-hour long cystectomy. It was reported that his BP was 90/50 throughout the surgery and he remained on Trendelenburg position. After some time, he stated he was seeing lights, bright colors & shapes, later he started seeing a Christmas tree, some animals and people. He was aware of visual hallucinations. On exam his extra-ocular movement intact, bilateral pupils 2.5 mm with slow constriction. On fundoscopy we found optic nerve sharp borders with no edema, macula showed normal vessels. MRI brain revealed no acute intracranial infarcts. Metabolic and inflammatory markers were normal, of note ESR:13 & CRP:48. Vasculitis was ruled out. Patient was counselled for poor prognosis.

**Conclusion:** Posterior ischemic optic neuropathy (PION) should be considered as a possible cause of vision loss after surgical procedures. Charles Bonnet Syndrome can be a part of presentation, awareness of CBS is critical to reassure patients that they are not suffering from a mental disorder. Prognosis is poor.

**043. Monro-Kellie Doctrine: A Case of Paradox**

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Orthostatic headaches are a common clinical finding in Spontaneous Intracranial Hypotension (SIH) and as its name indicates a low pressure in the cranial vault. Head imaging usually shows a venous distension sign which presents as subdural fluid collection and “Brain Sagging”. On the flip side cerebral venous thrombosis (CVT) usually results in an increased intracranial pressure secondary to venous congestion. We present a case of a patient where these co-exist. The Monro-Kellie Hypothesis has been used to explain the mechanism mass enhancing lesions play on ICP, but can it explain the relationship between CVT and SIH. We report a 48 year old woman with a past medical history of migraines who presented to the ED as a stroke alert with left hand and face numbness with dysarthria. Initial computed tomography (CT) head and angiogram revealed an empty delta sign indicating cerebral venous thrombosis and intracranial hypotension noted on magnetic resonance imaging (MRI) of the brain. She was started on heparin and admitted to the ICU for cerebral hemorrhage monitoring. Patient also underwent an MRI of her entire spine which did not reveal any obvious CSF leak. Patients hypercoagulable workup was unrevealing, and malignancy workup on CT chest revealed hilar adenopathy with biopsy consistent with sarcoidosis. This case highlights an important correlation for an extensive workup in patients with CVT, which is known to be caused by sarcoidosis. Our patients SIH though is not well explained by sarcoidosis and we hypothesize if the Monro-Kellie doctrine can be used to explain SIH as a mechanism to compensate for the elevated ICP caused by CVT.

**044. Bilateral Madelung Deformities Associated with a Persistent Hypoglossal Artery**

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**Objective:** To describe a case of vertigo in the setting of a persistent hypoglossal artery and bilateral Madelung deformity.

**Background:** Madelung deformity is a rare congenital condition characterized by shortening of the forearm. It is caused a mutation in the SHOX gene. Persistent hypoglossal artery (PHA) is a rare congenital carotid-basilar anastomosis with a reported prevalence of 0.03-0.09%. It has also been reported as a potential risk factor for embolic stroke in patients with atherosclerotic disease.

**Case Presentation:** A 67-year-old female with past medical history of treated latent tuberculosis, diabetes mellitus and right middle cerebral artery aneurysm s/p clipping presented to the emergency with chief complaint of vertigo. She described the symptoms as “feeling ceiling was spinning and she was falling into an abyss”. The symptoms were worsened when lying flat and resolved on sitting up. On physical examination the patient was noted to have bilateral Madelung deformities. Normal motor examination was noted. Cranial nerve examination was unremarkable except hearing loss to high and low frequencies bilaterally. Patient was noted to have severe vertigo with right beating nystagmus induced upon performing the Dix-Hallpike maneuver to the right. The patent was unable to tolerate any subsequent repositioning. A CT scan of the head showed a right sided craniotomy for clip ligation of an aneurysm at the right middle cerebral artery bifurcation. Further evaluation by CT angiogram of the head and neck showed a persistent right hypoglossal artery (PHA) originating from the external carotid artery feeding the basilar artery. MRI could not be performed due to history of aneurysmal clip. Patient further revealed similar wrist abnormality in her mother suggestive of an autosomal dominant SHOX gene disorder. Given the symptoms and initial work up including imaging findings, presentation was consistent with a diagnosis of BPPV. She was prescribed meclizine and an Epley maneuver worksheet and reported improvement in symptoms on a follow up visit after a month.

**Conclusion:** Our patient had an inherited congenital Madelung deformity suggestive of a SHOX gene disorder along with PHA. SHOX genes has been reported to be involved in craniofacial development so there may be an association with PHA. Another question worth investigating would be if inherited congenital Madelung deformity of a SHOX gene disorder may be associated with a higher risk of stroke.
045. Acute Spastic Hemiparesis as a First Sign of an Ischemic Stroke: A Rare Presentation and Pathology
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Objective: Objective of this poster is to discuss a unique case of acute ischemic stroke presentation as spasticity of the affected side.

Background: Hemiparesis after ischemic stroke is a common presentation, but spasticity presenting as an acute sign of cortical ischemic stroke is a rare phenomenon. Spasticity usually develops weeks after the stroke but not acutely.

Design/Methods: N/A

Result: 67 year old African American male with past medical history of hypertension presented to ED with 3 hours history of left upper (LUE) and left lower extremity (LLE) weakness with stiffness. On examination NIHSS of 3 (1 LUE drift, 1 LLE drift, 1 for ataxia LUE) was given. Interestingly, patient had moderate to severe spasticity of LUE and LLE. CTH was unremarkable. CTA showed occlusion of right Anterior cerebral artery (ACA) A2 segment. After obtaining consent, tissue plasminogen activator was given. MRI brain was done that showed acute ischemic infarct involving the right ACA and right ACA- MCA (middle cerebral artery) watershed area of the cortex.

Conclusion: Spasticity is defined as a velocity dependent increase in muscle tone due to increased excitability of the muscle stretch reflex. In the cortex, frontal area which is involved in pyramidal pathway, premotor and supplementary motor cortices which participate in sequencing and modulation of all voluntary movements and anterior cingulate cortex as cortical suppressant, play an important role in muscle tone and activity. Disruption to these areas due to stroke or injury could lead to disruption of inhibitory projections to lower motor neurons with resultant spasticity.

046. A Rare Case of Mollaret’s Meningitis Presenting as a Cryptogenic Stroke
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Objective: We describe a rare case of Mollaret’s Meningitis who was eventually diagnosed after suffering an acute ischemic cerebellar stroke. He was successfully treated with antiviral therapy and had complete resolution of his symptoms on follow-up.

Background: Mollaret’s Meningitis is characterized by recurrent episodes of Aseptic Meningitis commonly caused by Herpes Simplex Virus (HSV type 2). Patients present with recurrent bouts of aseptic meningitis that last two to seven days with spontaneous resolution of symptoms and no residual neurological deficits. It is an extremely rare and challenging diagnosis due to its variable presentation and often normal imaging findings.

Design/Methods: Case Report

Results: An 81-year-old male with a past medical history of Atrial fibrillation status post watchman device placement and hypertension was hospitalized due to symptoms of nausea, vomiting and diarrhea for about 1 week. During hospitalization, patient had an acute episode of right sided weakness with expressive aphasia and dysarthria and MRI brain with and without contrast was performed which showed a 1 cm acute ischemic stroke in right superior cerebellum. MR angiogram head and neck did not reveal any significant intra or extra cranial stenosis. Transthoracic Echocardiogram did not reveal any embolic source. Electroencephalogram showed broad based low frequency generalized periodic discharges and Lumbar Puncture (LP) was performed due to his nonspecific encephalopathy. Cerebrospinal fluid (CSF) analysis showed lymphocytic predominant pleocytosis with 300 cells, elevated protein of 156, low glucose of 26 and HSV 2 PCR was positive. Patient was started on intravenous acyclovir for 2 weeks. Patient presented again after 2 weeks with an episode of expressive aphasia. MRI brain did not show any acute findings and LP was repeated which continued to show lymphocytic predominant pleocytosis with 109 Nucleated cells with positive HSV-2 PCR, protein 153 and glucose of 18. Patient was further treated with 7 days of IV Acyclovir and was transitioned to oral Valacyclovir twice daily. He was followed up in clinic after one year without any further hospitalizations with gradual resolution of his symptoms.

Conclusions: We present a rare case of Mollaret’s Meningitis successfully treated with antiviral therapy after presenting as a cryptogenic stroke. We postulate that the etiology of stroke was most likely secondary vasculopathy from underlying HSV-2 infection. Mollaret’s Meningitis though extremely rare should be considered in the differential diagnosis as an etiology of cryptogenic stroke.

047. Giant Cell Arteritis of the Superior Mesenteric Artery Presenting with Wernicke Encephalopathy from Thiamine Deficiency
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Background: Giant cell arteritis (GCA) is one of the most common systemic vasculitides in adults, with incidence ranging from 15 - 35 per 100,000 individuals. The disorder is commonly included in the differential diagnosis of maladies producing atypical facial pain / headache, visual loss / amaurosis fugax, jaw pain, elevated inflammatory markers, and anemia. Patients tend to be over the age of 50, with a peak incidence in the seventh decade. The disorder is well known to affect cranial arteries, and hence typical physical exam findings include tenderness of palpation to the temporal arteries and cranial neuropathies. Clinical diagnosis is supported by new headache, temporal artery abnormality,
048. Left Bias in Nihss is Greatest for Mca Stroke

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Background and Aim: NIHSS score has been shown to be higher for left vs right hemisphere strokes of equal volumes (Fink et al. 1999; Woo et al. 1999). Differences in each vascular territory have not previously been evaluated. We hypothesized that right MCA strokes are associated with lower NIHSS scores than left MCA ischemic strokes, after controlling for age and stroke volume. As NIHSS is used for trials or treatment criteria in patients with strokes, this difference might be useful to account for the scale bias, since NIHSS tends to award more points for tests of presumed left-MCA territory function.

Methods: From the 1,878 patients admitted to our hospital (2009-2019) with evidence of acute ischemic stroke (2-24h post-onset) on Diffusion-weighted MRI (DWI), 1,298 had lesions affecting exclusively one major arterial territory. The delineation of the stroke core was defined on DWI. Considering only patients with NIHSS recorded at admission, on the same occasion as the MRI, the largest groups were MCA (n=437) and PCA strokes (n=209). In an initial exploratory analysis, we stratified patients by NIHSS (<5 (n=368) and >5 (n=233)) to access differences in mean volumes between left or right strokes, using t-tests. We then used multiway analysis of variance (ANOVA) for testing the effects of stroke side, volume, age and sex on NIHSS.

Results: There were no difference in the incidence of left or right strokes. Except for severe PCA strokes (NIHSS>5), which did not show asymmetry in volumes, right hemisphere strokes were larger than left hemisphere strokes when groups were categorized by NIHSS, in agreement with previous studies. This difference was greatest in the MCA strokes. Only patients with MCA strokes showed NIHSS score affected by the hemisphere when controlling for stroke volume, age, and sex. This difference was greater in the more severe strokes (NIHSS>5). In addition, stroke volume and age significantly correlated with NIHSS.

Conclusion: Right MCA strokes are associated with lower NIHSS scores than left MCA ischemic strokes, after accounting for age and stroke volume. As NIHSS is used for trials or treatment criteria in patients with strokes, this difference might be useful to account for the scale bias, since NIHSS tends to award more points for tests of presumed left-MCA territory function.

049. Characteristics of Moyamoya Disorder in a Racially Diverse Adult and Pediatric Cohort

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Introduction: Moyamoya disease or syndrome is not well-characterized in the United States (US). Limited studies reported epidemiologic and clinical characteristics of moyamoya in the US that differ from Asia while differences by race and ethnicity are not well described. Most of the large population-based studies in the US have been on patients treated in the inpatient setting, which limits generalizability. We describe epidemiologic and clinical characteristics of moyamoya in a racially diverse cohort of patients identified from the outpatient setting.

Methods: Using ICD-9 codes, we identified charts for patients with coded diagnosis of moyamoya between 1/1/10 and 6/30/20. We excluded patients who did not have supporting evidence for the diagnosis. Epidemiologic and clinical characteristics were abstracted. We compare characteristics by age and race/ethnicity using Fischer’s exact tests and logistic regression analyses.

Results: Of 139 charts identified, 123 patients were included. Average age at diagnosis was 31.5 (SD 15.4), with bimodal distribution (peaks 19 and 34). Race/ethnic distribution was 28.5% Non-Hispanic White, 35.8% Non-Hispanic Black, 8.9% Asian, 18.7% Hispanic, 8.1% other/unknown. We compared features by age group at diagnosis and race.
children and adults, there were higher proportions of females and ischemic stroke at presentation. Antiplatelet treatment was more common in adults (p=0.002) who were also more likely to have vascular risk factors (RFs). Children had more sickle cell disease. There were no racial differences in the prevalence of vascular RFs, age at diagnosis, or management.

Conclusions: In this study of patients identified from an outpatient setting in a diverse metropolitan city, we characterized adult and pediatric moyamoya patients from non-White and non-Asian populations, which are not previously well-described. Future studies should follow US moyamoya patients prospectively to better define clinical course and cause.

050. Missing the Mark: Altered Mental Status with No Focal Weakness
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Background: There is a broad differential for patients with altered mental status (AMS) and no focal weakness on exam. Presentation of metabolic, infectious, and cerebrovascular etiologies may overlap, making diagnosis challenging. Here, we describe a case of a patient presenting with AMS with no focal weakness, diagnosed with bilateral thalamic infarct from an Artery of Pecheron (AOP) occlusion.

Case Presentation: A 69-year-old male with history of alcohol abuse and hypertension, was brought to the ED after being found unresponsive. He was binge drinking the day prior to admission. In the ED, he was noted to have anisocoria and GCS 3. He was intubated for airway protection. Comprehensive laboratory studies was unremarkable, including glucose 92 and ethanol level 60. EKG showed new-onset atrial fibrillation (AFib) with rapid ventricular response. Non-contrast CT Head was unremarkable. He was started on IV thiamine and vitamin B12 to address Wernicke’s encephalopathy; as in this case. This V sign is reportedly a characteristic neuroimaging finding in AOP infarction. Symptoms vary: hyper somnolence, memory impairment, vertical gaze palsy, and pupillary abnormalities are the four most documented manifestations. Successful thrombolysis of AOP has been reported. Timely diagnosis in patients with this clinical presentation is imperative to provide appropriate treatment and to prevent unnecessary testing.

051. Sexual Asphyxia Causing Vertebral Artery Dissection and Stroke
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Background: Sexual asphyxia is a practice of intentional participation in oxygen deprivation for enhanced sexual excitement and arousal. This practice can be achieved by hanging, strangulation, chest compression, or suffocation. This form of sexual gratification can have neurological corollaries. There are case reports of sexual asphyxia causing death, carotid artery injury, and Horner’s syndrome. However, to the authors’ knowledge, vertebral artery dissection by sexual asphyxiation leading to stroke has not been reported.

Case Description: A 21-year-old female with a history of migraines developed an acute onset of bilateral vision loss and headache. Vision gradually improved over the next 3 days. She underwent a head and neck computed tomography angiogram (CTA) that showed proximal left posterior cerebral artery (PCA) high-grade stenosis. Brain magnetic resonance imaging (MRI) showed scattered infarcts in the left PCA territory. A transthoracic and transesophageal echocardiogram, cerebrospinal fluid studies, serum hypercoagulable studies were unremarkable except for a borderline elevation of immunoglobulin M anticardiolipin antibody which subsequently normalized 8 weeks later. She was started on aspirin 325mg daily and atorvastatin 40mg daily. The etiology for stroke remained cryptogenic and she was referred to an outpatient vascular neurology clinic. At her fiance’s urging, she reluctantly volunteered information about their sexual asphyxia practices. Upon closer review of the CTA head and neck images, bilateral vertebral artery dissections were discovered that were missed on the initial radiology report.

Conclusions: In young adults presenting with stroke, it is important to obtain a thorough history, review images, and specifically, explore any alternative practices that could provide clues to stroke etiology.

052. Does COVID-19 Worsen Outcome in Stroke Thrombectomy?
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Background: Nasopharyngeal and pulmonary infection with Severe Acute Respiratory Coronavirus 2 (SARS CoV2) is...
recognized by the World Health Organization as the cause of “2019 novel coronavirus disease,” the COVID-19 pandemic. We assessed 90-day outcome after mechanical thrombectomy (MT) performed to treat acute ischemic stroke (AIS) in patients with confirmed SARS CoV2 infection.

**Methods:** All MTs undertaken for treatment of AIS at an academic medical center serving the Appalachian region of Kentucky were surveyed over 12 months during February 2020 – 21. In a retrospective case-control study, 6 subjects with SARS CoV2 infection and AIS were identified and compared to non-infected patients matched for age, sex, and vascular distribution of ischemic brain injury.

**Results:** The subject cohort included 5 women and one man (mean age 69 yrs; range 53 - 86). Each subject had active COVID-19 infection, as shown by nasopharyngeal swab revealing presence of SARS CoV2 ribonucleic acid. Among 3 subjects with atrial fibrillation (50%), 2 were not anticoagulated and one presented on subtherapeutic anticoagulation. Two subjects (33.3%) underwent cerebral thrombolyis before MT. Median pre-procedural NIH Stroke Scale was 25 points (range 15 - 31). All subjects underwent general endotracheal anesthesia. Mean time between last known well and arterial puncture for catheter access was 436 ± 287 min. Five subjects had middle cerebral artery (MCA) occlusions (isolated M1 segment [n=3]; M2 branch [n=2]). The remaining subject had “T” occlusion of the supraclinoid internal carotid artery and branching A1 (anterior cerebral artery) and M1 segments. Suction thrombectomy was performed in all cases; 2 subjects required conjoint use of stent retrievers. For 5 subjects, recanalization graded on the Thrombolysis in Cerebral Infarction scale equated or exceeded 2b. In the sixth subject, tear of the successfully recanalized MCA prompted intra-operative coil embolization to control intraparenchymal hemorrhage. Within 90 days afterward, 3 of 6 subjects had died (50% mortality) and one remained hospitalized for 44 days.

**Discussion:** In our single-center cohort of SARS CoV2-infected subjects, MT was performed successfully to treat AIS in 83.3% of cases. However, 90-day outcome was affected by high mortality or extended disability in 66.7%. Factors that drove unfavorable outcome included sepsis and coagulopathy (n=1) or delayed cardiorespiratory complications of COVID-19 (n=3).

**Conclusion:** Concomitant infection with SARS CoV2 may impair recovery from large-vessel occlusion causing AIS. Mechanical thrombectomy remains highly effective at reperfusing ischemic brain, but 90-day outcome is burdened by complications attributed to COVID-19.

**053. The Clinical Characteristics and Potential Mechanism of Patients with Occult Malignant Tumors First Onset of Cerebral Hemorrhage**

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**Objective:** To investigate the clinical characteristics and potential mechanism of patients with occult malignant tumors first onset of cerebral hemorrhage.

**Methods:** Patients with occult systemic malignancies with cerebral hemorrhage as the first manifestation in the First Affiliated Hospital of Zhengzhou University from January 2017 to December 2020 were chosen as the tumor group, and patients without occult tumors in the same period were chosen as the control group, who were matched for age and sex according to the ratio of 1:4. The clinical data were compared between the two groups.

**Results:** A total of 23 patients were enrolled in the tumor group and 92 patients were enrolled in the control group. Compared with the control group, the tumor group has less hypertension patients (52.2% vs 76.1%, P<0.05) and NLR was significantly decreased in group (2.74 vs 5.35, P<0.05), more patients in the tumor group with bleeding sites located in the brain lobe (43.5%, 19.6%, P<0.05) and coagulopathy (52.2%, 29.3%, P<0.05) than in the control group. In the multivariate logistic regression analysis, hypertension was less (OR: 0.318 95%CI: 0.112-0.904), the bleeding site (OR: 3.465 95%CI: 1.177-10.243), and coagulation dysfunction (OR: 3.176 95%CI: 1.131-8.913) is independent predictors of occult tumors.

**Conclusions:** The previous absence of hypertension, the location of hemorrhage in the lobe of the brain, and coagulation dysfunction may have a certain prompting effect on patients with cerebral hemorrhage accompanied by occult malignancies.

**054. Neurologic Manifestations of COVID-19 in a Mainly Hispanic Population in South Florida**

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**Introduction:** We aim to describe neurologic symptoms in COVID-19 positive patients in a mainly Hispanic population in South Florida. It is important to recognize these manifestations to determine accurate morbidity and mortality of the disease, anticipate complications during hospitalization, and educate the public on possible symptomatology. Background: COVID-19 infection is associated with multiple neurologic manifestations including, among others, anosmia, dysgeusia, headache, migraine, encephalitis, seizure, weakness, encephalopathy, and stroke-1-9. It is undetermined if certain demographics are at higher risk of neurologic manifestations than others.

**Methods:** International Review Board (IRB) expedited approval was obtained. We performed a retrospective, observational review study on patients who were 2019-Sars-CoV positive via polymerase chain reaction (PCR) or antigen testing. EMR records of COVID-19 patients were evaluated for subjective data, objective data, and assessments that were consistent with specific neurologic diagnoses.

**Results:** 70 patients that were hospitalized at a South Florida facility were analyzed and were 2019-Sars-CoV positive via PCR or antigen testing. The average age of the patient was 74.5 years old (minimum age: 24, maximum age: 98). 40% of patients were Male and 100% were White Hispanic. 40% of patients resided at an assisted living facility (ALF). The neurology service was consulted on 10% of the patients.
in this cohort. 24.29% of patients had a history of neurologic disease other than dementia, 28.57% were demented, 22.86% had a documented co-infection present during their hospitalization, and 28.57% of patients died. The most frequent manifestations were encephalopathy, dizziness, and presyncope/syncope. Discussion: Similar to other published studies, our results recognize encephalopathy as one of the most prevalent neurologic manifestations of COVID-19. It is undetermined if this is due directly from the neurotropism and neuroinvasion of the virus or from other biologic and metabolic factors. Limitations: Analyzed data was subjective and dependent on provider documentation. Intubated and demented patients were difficult to obtain accurate subjective data from. Other underlying infectious processes may contribute to the symptomatology of some patients. Only hospitalized patients in the acute phase of infection were studied.

Conclusion: Hispanic patients with confirmed COVID-19 infection experienced neurologic manifestations of disease that were consistent with published data of other demographic populations. More studies should be done with larger sample sizes to confirm the findings of our case series.

055. Evaluating the Impact of Stroke Subtype on Cognitive Impairment in Ischemic Stroke Patients
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Introduction: Ischemic stroke (IS) is associated with cognitive impairment, but how this differs by IS subtype is unknown. Study aim: To understand how IS subtype influences post-stroke cognition.

Methods: Patients met study inclusion criteria as part of a parent study: adults with acute IS confirmed on MRI admitted to Johns Hopkins Hospital (2017-2019). IS was classified according to TOAST algorithm by a reviewer masked to patient characteristics. Cognition was assessed by telephone using the Six Item Screener (SIS, 0-6) which tests orientation (day, month, year) and recall (grass, paper, shoe). Ordinal logistic regression was used to determine association of IS subtype with SIS score (dependent variable), adjusting for age, race, sex, NIHSS, and IS volume. Multivariable logistic regression determined the association of dichotomized SIS score with IS subtype. A sensitivity analysis imputed low SIS scores for those lost to follow-up.

Results: 130 patients met inclusion criteria (male=57%, black=60%, mean age=61yo), 74 answered the phone, and 63 consented. There was no significant difference in IS subtype between patients who did and did not answer the phone. Those who answered were more likely hypertensive (p=0.04) and had higher BMI (31.57 kg/m² v. 26.86 kg/m², p<0.001). The median number of days post-stroke at time of assessment was 316 (IQR=224-528) with average SIS of 4.5 (SD=1.3). The most prevalent IS subtypes among patients who completed the SIS were small-vessel (29%), cardioembolic (22%), and large-artery (22%). Cardioembolic IS patients had 3.16 times elevated odds (95% CI=0.87-11.54) of having 1-point higher (better) SIS compared to other subtypes, while large-artery IS patients had lower odds (OR=0.37, 95% CI=0.10-1.40) of having a 1-point higher SIS, although neither were statistically significant. There were non-significantly higher odds of scoring in the "high" SIS category among those with cardioembolic IS (OR=2.32, 95% CI=0.38-13.97) and non-significantly lower odds among those with large-artery IS (OR=0.37, 95% CI=0.07-1.95). When assuming those who did not answer the phone scored in the "low" SIS category (N=56) the effect estimate remained non-significant but attenuated for cardioembolic IS (OR=1.93, 95% CI=0.70-5.31).

Conclusion: In this single-center prospective cohort study, there is a suggestion that cognitive function post-stroke may differentiate across IS subtype, although the effects were not statistically significant, likely attributable to sample size. As post-stroke cognitive impairment can be devastating, IS subtype may be an important factor to consider in cognition recovery.

056. Safety and Efficacy of Endovascular Therapy Referred by Telephone-Based vs In-Person Consultations
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Background: Endovascular therapy (EVT) is an effective mode of treating acute ischemic stroke caused by a large vessel occlusion. Telephone-based consults may be a way to screen for candidacy for this therapy but have not been well-studied. We sought to elucidate whether EVT initiated by telephone-based consultation is safe and efficacious compared to in-person referral.

Methods: Demographics, clinical characteristics, and outcomes of acute ischemic stroke patients referred for EVT from 2008-2017 by The Johns Hopkins Hospital (JHH, where consults are performed in person) and by Howard Country General Hospital (HCGH, where consults are performed over the telephone) were compared. All EVT was performed at JHH, and all acute stroke decisions were made by the same group of stroke neurologists. Primary outcome was intracerebral hemorrhage after EVT. In addition, patients who did not receive EVT were compared by referral hospital, and those who received EVT vs those who did not at each referral hospital were also compared. We further ran multi-variable analyses on patients who received EVT with respect to the outcomes intracerebral hemorrhage after EVT, discharge to home, discharge to rehabilitation, and discharge as deceased.

Results: Among patients who received EVT, age, admission National Institutes of Health Stroke Scale (NIHSS), intracerebral hemorrhage after EVT, discharge NIHSS, and discharge destinations were similar regardless of whether the referral was made in person (n=99) or via telephone consultation (n=7). Further, door-to-EVT time (153 (41-281) min vs 156 (109-322) min, p=0.60; notably this referred to door to HCGH for patients referred by HCGH) and onset-to-EVT.
time (386 (272-520) min vs 267 (257-368) min, p=0.10) were similar between JHH and HCGH. Among those not referred for EVT, HCGH patients (n=427) were older and had greater NIHSS than JHH patients (n=772), potentially suggesting a higher threshold for transfer to JHH for EVT. By referral hospital, patients referred for EVT vs those who were not had greater admission NIHSS but were similar in age. In multivariable analyses, referral hospital was not associated with important endpoints (e.g., intracerebral hemorrhage after EVT, discharge to home, discharge to rehabilitation, discharge as deceased).

Conclusions: Telephone-based consultations leading to EVT appear to be as safe and efficacious as those conducted in person. Remarkably, important time metrics were similar by referral hospital despite a requirement to transfer from HCGH to JHH in order to receive EVT. Additional HCGH patients could potentially be considered for EVT.

057. Characteristics of Patients with Acute Ischemic Stroke and COVID-19: A Mississippi Academic Center Cohort

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Objective: To identify patients’ clinical and demographic characteristics presenting with acute ischemic stroke and simultaneous COVID-19 infection.

Background: Coronavirus 2019 (COVID-19) was declared as a global pandemic in March of 2019 and has been reported to cause neurologic disease, including cerebrovascular disease. The Stroke Belt carries a risk of stroke one third the national average. Sparse data is available regarding COVID-19 infection and stroke from the southern states, especially Mississippi. This cohort aims to describe the characteristics of patients with both acute ischemic stroke (AIS) and COVID-19 infection.

Methods: Single center, retrospective cohort study of adult patients admitted to University of Mississippi Medical Center (UMMC) from March 1, 2020 - December 31, 2020. The UMMC COVID cohort explorer was used to collect demographic, socio-economic, clinical and laboratory characteristics. Descriptive statistics are used to characterize this population.

Results: Out of 3,031 patients with COVID-19 admitted in UMMC, 111 (3.6%) adult patients had an acute stroke and COVID-19. They were mostly African American (71, 64%) males (64, 58%), with a mean age of 65.71 ± 14.54 SD. The majority of the patients were insured. The most common comorbidity is hypertension (90.09%), followed by type two diabetes mellitus (T2DM) (59.45%). The mean initial procalcitonin, d-dimer, LDH, and absolute lymphocyte count levels were 2.41 ± 5.59, 2078.74 ± 3907.25, 313.77 ± 129.8 and 0.8 ± 0.71, respectively. Overall mortality for this cohort was 28% (n=31) in addition the mortality rate of African Americans was higher than Caucasians (28% vs 20.7%).

Conclusion: We present one of the first descriptions of patients with COVID-19 and strokes in Mississippi. Most of our patients are African American males with an overall mortality rate of 28%. Further studies are needed to characterize this population and to analyze predictors of outcome.

058. 65-Year-Old Male with an Atypical Presentation of CNS Vasculitis

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Primary central nervous system (CNS) vasculitis is a rare inflammatory condition that targets small and medium-sized vessels of the brain and spinal cord. CNS vasculitis can also occur in the context of systemic inflammatory disease or an infectious process. It is important to recognize and diagnose CNS vasculitis promptly, especially in atypical presentations, as treatment is effective and largely affects prognosis. It is also vital to exclude infectious causes given that the treatment consists of immune suppressive agents. Below, we discuss the case of a 65-year-old male who presented with a four-month history of progressive cognitive decline which was initially attributed to Alzheimer’s Disease in the outpatient setting.

059. Cerebral Venous Sinus Thrombosis Following Mild SARS-CoV-2 Infection: Infection Related Hypercoagulability or Adverse Effect of Novel Therapy?

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Background: Thromboembolic events have been a topic of interest during the COVID-19 pandemic both as one of the notable non-respiratory complications of the infection and as a possible side effect of the Astra-Zeneca and Johnson & Johnson vaccines. The FDA has approved emergency use authorizations for multiple pharmaceuticals during the coronavirus pandemic including vaccines, antivirals, and monoclonal antibody treatments. Bamlanivimab, a monoclonal antibody, received emergency authorization in November 2020 for the treatment of patients with mild to moderate SARS-CoV-2 infections who are considered at high risk for progressing to severe disease. We present a patient with a relatively mild infection who was treated with this novel therapy and later went on to develop a cerebral venous sinus thrombosis (CVT).

Case Presentation: A 42-year-old female healthcare worker with a history of iron deficiency anemia and obesity (BMI 41.6) experienced dyspnea, fatigue, and myalgias. Nasal swab PCR confirmed SARS-CoV-2 infection. Due to obesity, she qualified for bamlanivimab therapy and received an infusion seven days later. Six days following the infusion she developed a new headache and altered mental status. On arrival to the hospital she was found to have severe receptive and expressive aphasia. CT brain revealed left temporal and
occipital hemorrhage and CTV demonstrated thrombosis of the left transverse and sigmoid sinus with extension into the internal jugular vein. Intravenous unfractionated heparin was initiated and she was eventually transitioned to a direct oral anticoagulant. At discharge she was alert and communicative with mild residual mixed aphasia. A detailed inquiry of the patient’s personal and family medical history revealed no history of venous thromboembolism, hypercoagulability, or rheumatologic disease, and the patient denied use of oral contraceptives or tobacco use.

Conclusion: This is a case of an otherwise healthy woman, without traditional thrombotic risk factors, who developed cerebral venous sinus thrombosis following a relatively mild COVID-19 infection and treatment with bamlanivimab monoclonal antibody therapy. Based on review of the literature, CVTs associated with COVID-19 tend to present 1-2 weeks following diagnosis but have been reported in patients with more severe disease. To date, there are no other reported cases of CVT specifically following bamlanivimab therapy. Development of venous thrombosis, including CVT, should be monitored with continued use of the drug.

060. Prevalence of Food Insecurity Among Stroke Survivors
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Background: Stroke is a leading cause of death and disability among U.S. adults. Social determinants of health (SDOH) are associated with stroke risk and outcomes. Food insecurity, which refers to the lack of access to food for an active lifestyle because of insufficient resources, is present in 11.1% of the U.S. population (Coleman-Jensen 2019). Food insecurity is a SDOH that is associated with increased risk for vascular disease, yet is understudied in stroke survivors. We sought to assess the prevalence of food insecurity among stroke patients following in an outpatient clinic and to examine whether food insecurity was positively associated with demographic variables and vascular risk factors.

Methods: Demographic and clinical data were obtained from a prospective clinical registry (January to March 2021). A validated 2-item food insecurity screener was used to assess food insecurity (Hunger Vital Sign, 2009). Patients who responded affirmatively (sometimes true or often) to at least one of the items was considered to be food insecure. Student t-tests, chi-squared, and Fisher’s Exact tests were used for descriptive analyses. Univariate and multivariate logistic regression analyses were used to assess the relationships between food insecurity and key demographic and clinical variables.

Results: Among 103 stroke survivors, 99 patients with complete food insecurity data were included. Food insecurity was seen in 14.1%. Patients who experienced food insecurity did not differ from those who did not experience food insecurity in regards to age (58.6 years vs. 60.8 years) or sex (42.9% male vs 36.5% male). Among Non-Hispanic White, Non-Hispanic Black, Hispanic, and Asian groups, 8.7%, 24.1%, 15.0%, and 0%, respectively had food insecurity (p=0.37). In univariate regression, patient with coronary disease had 4.46 higher odds of food insecurity (95%CI 1.10-18.0, p=0.03) and Black patients had a 3.34 high odds (trend) of food insecurity than Non-Hispanic Whites (95%CI 0.88-12.7, p=0.09). Medical history of hypertension, diabetes, hyperlipidemia, atrial fibrillation, heart failure, and obstructive sleep apnea were not associated with increased odds of food insecurity. In the multivariate logistic regression including age, gender, race and coronary artery disease, only coronary artery disease showed a borderline significant association with food insecurity (OR 5.06, 95%CI 0.99-25.98, p=0.05).

Conclusion: Food insecurity was seen in 14.1% of patients in our cohort, which is higher than that observed in the general population. It is a key SDOH that should be further explored and addressed in stroke survivors.

061. Ruptured Infective (Mycotic) Intracranial Aneurysm Secondary to Bacterial Meningitis: A Case Report and Review of Literature
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Mycotic aneurysm (MA), a rare complication of systemic infections, is a result of degradation and dilation of the arterial wall. Etiology can be due to endovascular seeding of infective emboli (e.g. infective endocarditis, bacteremia) or extravascular spread of infection (e.g. meningitis, osteomyelitis, orbital cellulitis). Infective intracranial aneurysms (IIA) are extremely rare and account for a small fraction of all intracranial aneurysms. Most IIA are caused by bacterial or fungal infections. IIA has a higher risk of rupture as compared to other aneurysms due to their rapid progression and increased vessel fragility. Diagnosis is mostly based on clinical history and neurovascular imaging. Medical management and endovascular intervention can be considered the first-line treatment for unruptured IIA. Open surgery is done in cases of complications or failed endovascular intervention. A case of suspected ruptured IIA secondary to bacterial meningitis is discussed in detail along with a review of the literature. Certain proposals on diagnosis, management, and complication have been put forth.

062. Left Atrial Strain and Atrial Cardiopathy in Embolic Strokes of Undetermined Source (ESUS)
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Background and Objective: Most strokes are categorized as ischemic. Of these, 20% lack a clear cause. Most of these
cryptogenic strokes appear embolic in nature and can be referred to as embolic strokes of undetermined source (ESUS). Emerging evidence suggests that one potential source of ESUS is atrial cardiopathy in the absence of atrial fibrillation/flutter. The emergence of speckle-tracking echocardiography enables the identification of atrial cardiopathy beyond left atrial structure and size alone through the quantification of atrial strain, which is a sensitive marker of atrial function. We hypothesized that peak atrial longitudinal strain (PALS) would be more impaired in ESUS than in strokes of known non-cardioembolic origin.

Methods: Among 2,945 ischemic stroke patients registered in the Cornell Acute Stroke Academic Registry (CAESAR) from 2011 through 2018, 2,203 (75%) had a transthoracic echocardiogram (TTE) performed within 3 weeks of their index stroke. Stroke subtypes were determined by neurologists according to the TOAST classification and consensus ESUS definition. PALS was measured by a trained reader, blinded to TOAST subtype, using the Image-Arena 2D Cardiac Performance Analysis software (Version 4.6, TomTec Imaging Systems, Unterschleissheim, Germany) in both two- and four-chamber views of the most recent 324 of these TTEs. Forty-two patients were excluded from this analysis due to an incomplete stroke evaluation or multiple potential causes.

Results: Of 282 included patients, 100 (35.5%) had cardioembolic stroke, 104 (36.9%) had ESUS, and 78 (27.6%) had known non-cardioembolic stroke (small-vessel occlusion, large-artery atherosclerosis, or other determined cause). PALS was significantly lower in ESUS (24.4 ±10.8) than in known non-cardioembolic strokes (30.9 ±15.9) (P for t-test = 0.002) when analyzed via two-chamber view. Although PALS was lower in ESUS (27.5 ±12.7) versus non-cardioembolic strokes (29.3 ±11.8) when analyzed via four-chamber view, this difference was not significant (P for t-test = 0.32). Patients with cardioembolic stroke had significantly lower PALS than both ESUS and non-cardioembolic strokes in both views.

Conclusion: We found more impaired left atrial strain in patients with ESUS versus known non-cardioembolic stroke. These findings support the growing theory of left atrial derangements playing a key pathogenic role in strokes that are currently labeled as ESUS. Left atrial strain represents a promising tool for identifying atrial cardiopathy in patients with ESUS.

063. Venous Sinus Thrombosis in the Setting of Oral-Contraceptives
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Background: Oral contraceptive pills (OCP) can rarely cause venous thromboembolism (VTE) because they promote upregulation of the coagulation cascade and downregulation of the anticoagulation mechanisms. Plasma concentrations of pro-coagulation factors including fibrinogen, prothrombin, factors VII, VIII, and X levels are elevated while concentrations of hemostasis inhibitors, antithrombin and tissue factor are decreased. Additionally, the biological activity of protein C, an anticoagulant, is reduced due to an increase in its inhibitors, α1-antitrypsin, α2-macroglobulin. Moreover, OCP users are resistant to the anticoagulation effects of protein C. This is known as acquired protein C resistance (APC) and is thought to be related to elevated levels of sex hormone binding globulin (SHBG). Third generation OCP’s are associated with more thrombotic events, possibly because they contain higher concentrations of estrogen, and SHBG increases synergistically with estrogen.

Case Presentation: A 52-year-old female presented with a 1-week history of flat affect and recall difficulties. Physical exam was remarkable for paraphasic error and mild speech slurring. NIHSS = 0. There were no focal neurological deficits. CT/CT-Angiogram were unremarkable. MRI revealed T2 flair hyperintensities in the bilateral thalami with a mild hyperintense signal on DWI. MRV showed contrast enhancement in straight sinus and internal cerebral veins indicating deep venous sinus thrombosis. Heparin anticoagulation was initiated, and mentation improved. Hypercoagulable workup was negative. Lumbar puncture revealed elevated WBC (20), protein (112) and low glucose (45). Prophylactic acyclovir, vancomycin and ceftriaxone was begun. Meningitis/encephalitis panel came back negative and medications were discontinued. Of note patient received COVID-19 vaccine 2 weeks prior. Titers revealed elevated IgG and IgM. Etiology of thrombotic event likely associated with OCP use.

Discussion: VTE is a rare occurrence in OCP users. It occurs more frequently in users greater than 40 years old. This correlation is likely because age is an independent prognostic factor for the development of thrombosis. Rarer among VTE’s is the event of cerebral venous sinus thrombosis in a patient who takes OCPs.

Conclusion: VTE in the setting of OCP is due to a disproportionate shift towards coagulation as there is an increase in pro-coagulation factors, a decrease in anticoagulation factors, and acquired protein C resistance. Our patient developed venous sinus thrombosis of the straight sinus and internal cerebral veins. Her COVID vaccination status was likely unrelated to this event as she had predisposing risk, advanced age and OCP use. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6714678/

064. The Thalamus and Vertical Gaze
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The thalamus plays a crucial role in neurological functions such as processing sensory information, executing motor activity, regulating sleep and emotions and processing memory. Though thalamic strokes are common, their presentations vary due to both the complex organization of thalamic nuclei and frequent anatomical variations of arterial supply. Thalamic infarcts without midbrain involvement presenting with isolated features of vertical gaze palsy are extremely rare, only three cases have been reported in the past. Vertical gaze...
palsy is typically recognized as manifestation of midbrain lesion involving the mesencephalic rostral interstitial nucleus of the medial longitudinal fasciculus, the interstitial nucleus of Cajal, the posterior commissure and the peri-aqueductal gray matter. We report a case of vertical gaze palsy associated with acute unilateral hemiplegia and speech disturbance in a 77 year-old-man. A magnetic resonance imaging (MRI) of the brain showed acute unilateral thalamic infarct with no mid brain involvement.

065. A Case Report of Cerebral Amyloid Angiopathy Related Inflammation

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Introduction: Cerebral amyloid angiopathy (CAA) is caused by the deposition of beta amyloid in the walls of cerebral vasculature making them prone to rupture and bleed. There is a rare, yet clinically distinct variation of CAA where edema and inflammation appears around the affected vessels. This is referred to as cerebral amyloid angiopathy-related inflammation (CAARI) due to an autoimmune reaction to cerebrovascular β-amyloid deposits.

Case Description: 80 year old female with a past medical history of Alzheimer’s dementia, presented to ER with increasing confusion, falls and episodes of loss consciousness over 4 weeks. Her medications included donepezil, fluoxetine and levothyroxine. Vital signs were stable. Cognitive assessment revealed she was alert, oriented to self and place only, with poor short term memory and concentration. Rest of neurologic exam was non-focal showing no weakness, dysmetria and her gait was normal. MRI of the brain showed few micro-hemorrhages in both cerebral hemisphere more in the right temporo-occipito-parietal lobes likely related to amyloid angiopathy, with surrounding subcortical and deep white matter edema and mild regional mass effect and associated regional leptomeningeal enhancement. EEG showed focal slowing in the right temporoparietal & occipital region with sharp waves. The area was felt to be epileptogenic so patient was placed on Keppra 500 mg BID. CT venogram was negative for venous sinus thrombosis. A whole body CT did not demonstrate any primary cancers, making brain metastasis less likely cause. The lack of parenchymal enhancement on MRI made primary glioma unlikely. Family decided not to pursue lumbar puncture. Patient met criteria for probable cerebral amyloid angiopathy-related inflammation (CAARI). Patient received IV dexamethasone for 3 days resulting in improvement with cognitive function, followed by prednisone taper over 6 weeks. Repeat MRI of the brain after 2 months of discharge showed significant improvement of right hemispheric edema.

Discussion: Cerebral amyloid angiopathy-related inflammation responds well to anti-inflammatory/immunosuppressive treatment which can improve symptoms. While cerebral biopsy is required for definitive diagnosis, clinicians have created non-invasive criteria for probable diagnosis such as the ones suggested by Chung et al.: 1. acute/subacute onset 2. Age more than 40, 3. One or more of the following symptoms: Headache, mental/behavioral changes, focal neurologic deficits, or seizure. 4. MRI demonstrates unifocal or multifocal white matter hyper-intensity lesions in an asymmetric pattern. 5. Evidence of CAA in the form of cerebral micro/macronuclear bleeds, 6) Absence of neoplastic or infectious causes.

066. Temporal Patterning of Neurofilament Light as a Blood-Based Biomarker for Stroke: A Meta-Analysis

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Multiple recent studies have examined leakage of the neuronal cytoskeleton protein neurofilament light (NFL) into the bloodstream after stroke and chronic cerebrovascular disease and generally support its use as a stroke biomarker. However, measurement of NFL on different assay platforms and in varying clinical cohorts with cerebrovascular disease has created confusion about the true absolute detection of blood NFL levels in post-stroke periods. A clear understanding of the phasic nature of NFL release into the bloodstream after stroke can assist in identifying patterns of recovery and clearly delineating therapeutic windows that may exist for post-stroke therapeutic interventions. We conducted a PRISMA-conforming meta-analysis of the existing literature measuring blood NFL in stroke and cerebrovascular disease. Using available summary data from common platform immunoassays measured in human subjects (n=3,325; 9 studies), we created a phasic model of serum/plasma NFL values corresponding to distinct time periods after stroke and identified reasonable cutoff values for the prediction of stroke. Weighted averages and interquartile ranges vary across the temporal epochs of acute (0-7d - 83.73 pg/mL [IQR 44.87-176.37]), subacute (8-90d - 584.38 pg/mL [IQR 255.03-3447.73]), and chronic (90d+ - 35.02 pg/mL [IQR 23.83-57.48]) stroke. Blood NFL levels notably peak between 14-21 days after stroke and then decline steeply but remain above control and chronic cerebrovascular disease levels. To determine the relationship of plasma NFL values between time periods after stroke, we generated a series of random effect linear mixed models across time periods using the mean NFL values and variance from included studies. NFL values were significantly higher in the acute phase compared to control (difference = 17.53 pg/mL; t=3.96, p<0.05). In the subacute phase, NFL values were substantially elevated above control (difference = 67.06 pg/mL; t=5.83, p<0.05). In the chronic phase after stroke, NFL values decline but remain above control (8.74 pg/mL; t=2.75, p<0.05). A blood NFL value of approximately 47.5 pg/mL generated a likelihood ratio above 2 indicating reliable detection of stroke. To support the functionality of this model, we developed a web-based interface allowing subject level queries to estimate the likelihood of stroke and determine the most...
Objective: To determine the spectrum of acute cerebrovascular disease (CVD) among COVID-19 patients admitted to Ochsner-Louisiana State University Health Sciences Center, Shreveport (OLSU-S) after SARS-CoV-2 positive results.

Background: Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is now known to cause a broad range of neurological manifestations. COVID-19 infection causes a pro-inflammatory, hypercoagulable state and there is an increased risk of CVDs which can have many adverse outcomes compared to other neurological complications.

Methods: We conducted a retrospective, observational study of hospitalized adult patients (age > 18 years) admitted to OLSU-S with laboratory confirmed SARS-CoV-2. All clinical data was reviewed including epidemiology, clinical features, laboratory data, neuroradiological findings, hospital management and course from 34 patients hospitalized for COVID-19 management with neurological symptoms at OLSU-S between March 15, 2020 to March 15, 2021.

Results: We screened 34 patients admitted to OLSU-S with COVID-19 who either presented with or developed neurological complications during their hospital course. Of these patients with neurological complications and acute COVID-19 infection (Neuro-COVID), 15 (44.1%) were diagnosed with CVD. In our Neuro-COVID cohort, CVD was more common in male patients (11 [73.3%]). Hypertension was the most common underlying comorbidity (10 [66.6%]), followed by diabetes (5 [33.3%]), and obesity (5 [33.3%]). There were 5 (33.3%) patients who had a previous history of CVDs. Of those with acute CVD, 3 (20%) received tPA, 3 (20%) received endovascular thrombectomy, and the remainder were not candidates for hyperacute interventions. Patients with COVID-19 related CVD had more serious clinical courses with 8 (53.3%) patients admitted to the intensive care unit, 5 (33.3%) patients requiring ventilation, and 7 (46.7%) patient deaths. EEG abnormalities were noted in 6 acute CVD patients, which ranged from mild to moderate encephalopathy and one case of unilateral focal slowing. Neuroimaging showed severe and unique types of strokes. This included an intraventricular hemorrhage, hemorrhage of the basal ganglia, venous infarct of the thalamus, and 11 acute ischemic strokes. Of the acute ischemic strokes, 5 had hemorrhagic transformation.

Conclusions: Our observations confirm the increased incidence of acute CVDs seen in Neuro-COVID patients. Acute CVDs associated with COVID-19 tended to be more severe, leading to poor prognosis and more mortality.

Introduction: Viral infections are often an under-recognized cause of acute stroke. Although most of them are characterized by fever or other systemic signs and symptoms, on rare occasions they can cause an isolated central nervous system vasculitis that can present as an acute ischemic event with sudden onset loss of neurological function.

Case Presentation: A 43 year old woman presented with sudden onset paraparesis. She was in her usual state of health prior to presentation without any complaints. Exam revealed right sided facial weakness, dysmetria and ataxia. She had no fever, skin rash or systemic symptoms. Magnetic Resonance Imaging (MRI) showed an acute to subacute bilateral pontine infarction. A conventional angiography showed multifocal stenosis, particularly affecting the bilateral posterior circulation. CSF studies were positive for VZV without other abnormalities. The patient was treated with intravenous Acyclovir and steroids with some improvement of her symptoms.

Discussion: Varicella zoster virus (VZV) is a neurotropic herpesvirus that causes chickenpox, most commonly in the unvaccinated pediatric population. After the symptoms of fever and rash resolve, the virus remains latent in cranial or dorsal root ganglia. When the host immune system is weakened by any reason, for example old age, malnutrition or other disease, the virus reappears and causes shingles. VZV vasculopathy has been studied as a manifestation of active viral replication during initial infection (chickenpox) or reactivation (shingles). Interestingly, VZV is the only virus known to replicate in the cerebral vasculature. The manifestations of VZV vasculopathy can include ischemic stroke, transient ischemic attack (TIA), myocardial infarction (MI) or intracerebral hemorrhage secondary to aneurysm rupture. In fact, multiple studies have showed that the increased risk of ischemic stroke can peak at up to 26 weeks after shingles, especially if the rash affects the ophthalmic dermatome. Histopathology of intracerebral VZV vasculopathy is characterized by granulomatous inflammation with extensive lymphocytic infiltration, thickening of the elastic lamina and progressive intimal thickening. In our patient, VZV vasculopathy was not a straightforward diagnosis because she did not present with the typical rash seen with zoster, she was not immunocompromised and the multifocal stenosis were all in the anterior circulation without any obvious vascular abnormalities to account for the acute to subacute bilateral pontine stroke. However, the multifocal arterial

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irregularities raised suspicion for a vasculitic inflammatory or infectious process, hence a lumbar puncture was deemed necessary to provide adequate management.

069. Acute Quadriplegia Caused by an Atraumatic Hematomyelia: A Case Report

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Background: Intramedullary spinal cord hemorrhage (hematomyelia) is a rare cause of myelopathy and can present acutely, sub-acutely, stepwise, or chronically. It is most associated with trauma, but other nontraumatic etiologies include vascular malformations, bleeding disorders, tumors, syphilis, syringomyelia, and myelitis. Diagnosis of hematomyelia requires recognizing the myelopathy syndrome (central, anterior, posterior, transverse, or hemi-cord) accompanied by sudden, severe neck, back, or at times radicular pain. The imaging modality of choice is magnetic resonance imaging (MRI) of the brain with and without gadolinium. We present a case of an acute hematomyelia extending from the cervicomedullary junction to T11.

Case Report: A 67-year-old woman with a past medical history of hypertension, diabetes mellitus, seizures, Hepatitis C with cirrhosis, and thrombocytopenia was transferred to our center after complaining of acute onset neck pain and left-sided hemiparesis. Before transfer, spine imaging showed an increased T1 signal from the cervicomedullary junction up to the T10 segment. Upon arrival, she was nonverbal, had no movements in any of the extremities except the right upper. She was intubated and admitted to the neurocritical ICU. A repeat MRI of the spine showed an extension of hematomyelia to T11 along with cord expansion and diffuse edema, while she progressed to quadriplegia on clinical exam. CT angiogram was negative for an AVM. Workup included CSF xanthochromia (RBC 1,500, WBC 4), glucose 39 g/dl, and protein of 318 mg/dl. The meningitis/encephalitis panel was negative. Serum RPR 1:1, but FTA-Ab was nonreactive. HIV negative. ANA+ 1:1280, speckled pattern, positive Smith, RNP and chromatin antibodies, normal C3, C4, mildly elevated CRP, normal ESR. Platelet count was at her baseline in the 50-100K range. Hematology recommended maintaining her platelet counts above 75K. Folate, vitamin B12, and other coagulation studies were within normal limits. She received pulse steroids to stabilize declining platelet counts despite recurrent platelet transfusions. Her hospital stay was complicated by intercurrent Pseudomonas, Citrobacter, Klebsiella infections which were all treated appropriately. Her condition remained poor throughout her hospital stay and she was eventually transferred to a long-term acute care facility.

Conclusion: Hematomyelia can present in several different ways, sometimes making it difficult to diagnose especially if blood obscures the underlying pathology on imaging. Treatment is usually directed towards the underlying etiology. In our patient, after extensive workup, the etiology of hematomyelia was directed to the refractory thrombocytopenia due to her pre-existing liver cirrhosis secondary to Hepatitis C infection.

070. Widespread Embolic Strokes Involving the Bilateral Supra- and Infratentorial Brain Territory: A Unique Radiological Manifestation of Candida Endocarditis

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Objective: To highlight a distinctive radiological manifestation of Candida endocarditis with widespread anterior and posterior brain circulation acute ischemic strokes attributable to septic emboli.

Background: Incidence of infectious endocarditis in patients with stroke is 8-11%, out of which fungal endocarditis accounts for 1.3-6% of cases. Males appear to be affected more between ages 44-48 years. Candida spp is the main etiology of fungal endocarditis and of all the Candida spp, Candida albicans accounts for 53-67.8% of cases. Involvement of the bilateral supra- and infratentorial brain regions due to septic emboli in the setting of fungal endocarditis is very rare and here we report one such case of Candida endocarditis with widespread involvement of the brain circulation.

Methods: Case report.

Results: 40-year-old man with medical history of type 1 diabetes, peripheral arterial disease s/p right toe amputation, left foot gangrene, grade D esophagitis, Becker’s muscular dystrophy (paraplegia with anti-gravity motion in arms bilaterally) and intravenous (IV) methamphetamine use admitted to our hospital for having diabetic ketoacidosis, right lower lobe pneumonia, upper gastrointestinal bleed and progressively worsening encephalopathy for the last 5 days. He was intubated within first 24 hours of admission due to rapid decline in GCS (4). EEG was unremarkable for seizures. CT head showed loss of gray-white differentiation and subtle hypodensities in posterior cerebral hemispheres. MRI of brain showed innumerable embolic infarcts in the bilateral anterior and posterior circulation. Blood cultures showed growth of Candida glabrata, ur sine culture and tracheal aspirate showed growth of Candida albicans. He was started on broad-spectrum antibiotics and vasopressors for septic shock. Transthoracic echocardiogram (TTE) showed 0.5cm x 1.5cm mobile mass on the tricuspid valve concerning for thrombus/vegetation with presence of right to left shunt. He was initially on micafungin for candidemia but after the finding of vegetation on TTE, it was switched to IV amphotericin B and flucytosine for better CNS penetration. Patient improved over time with discharge to long-term acute care (LTAC) facility.

Conclusion: Presentation of Candida endocarditis with septic emboli causing widespread bilateral supra- and infratentorial acute ischemic infarcts is rarely reported in the literature and it is essential to take into account such radiological presentation of this entity.
071. Disease Read Books: A Pure Gerstmann Syndrome
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Objective: To report a case of pure Gerstmann syndrome without any associated cognitive deficits in a patient with parieto-occipital subacute ischemic stroke attributable to cardioembolic phenomena. Background: Gerstmann in 1924 described the features of Gerstmann syndrome (GS). It has a high value in localization and the lesion is mainly localized to angular gyrus of the dominant hemisphere. It is manifested by a tetrad of agraphia, acalculia, finger agnosia, and right-left disorientation, which is often incomplete and is mostly associated with cognitive deficits including alexia, aphasia, apraxia and some perceptual disorders. Here we present a patient with left parieto-occipital subacute infarct of cardioembolic etiology who had pure Gerstmann syndrome without any significant cognitive issues.

Method: Case report
Results: 46-year-old woman with medical history of controlled diabetes mellitus type II, and hypertension who was admitted to our service for acute right parietal and posterior tempor-occipital subacute infarct complicated by cerebral edema & hemorrhagic transformation (7.2 x 2.6 x 2.9cm) as seen on MRI brain, due to cardioembolic phenomena in the setting of atrial fibrillation. It was manifested by confusion, agraphia without alexia, acalculia, finger agnosia, right-left disorientation, very mild expressive aphasia, right homonymous hemianopsia, mild right-sided weakness/numbness, ataxia on the right finger to nose, NIHSS 3, preadmission mRS 1. No TPA was given or thrombectomy done due to the subacute nature of infarcts. He was started on apixaban 5mg BID 10-14 days after repeat CTH that was stable. Concluded with mRS 1 on 3-month follow-up. Conclusion: Carotid web should be in differentials for etiologies whenever encountering stroke in young patients without typical stroke risk factors. Failure to recognize carotid web can result in misdiagnosing stroke etiologies to cryptogenic/ idiopathic. Identification of the underlying carotid web can lead to successful carotid revascularization, which is an effective therapy without reported recurrence.

072. Tale of a Carotid Web: Rare Etiology of Ischemic Stroke in a Young Patient
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Introduction: Carotid web is amongst rare etiologies of ischemic stroke. It is an uncommon form of focal fibromuscular dysplasia which leads to turbulent blood flow and stagnation resulting in thromboembolism. We aim to highlight a case of a young female who had an underlying carotid web and had a resultant acute ischemic stroke. Method: A case report. Results: 46-year-old woman with medical history of controlled diabetes mellitus type II, and hypertension who was admitted to our service for acute right parietal and posterior insular ischemic stroke secondary to right proximal internal carotid artery web per CT angiogram, manifested by left homonymous hemianopsia, left hemimotor-sensory loss, NIHSS 8, mRS 0 s/p tPA and thrombectomy TICI3 flow achieved, repeat NIHSS improved to 5. The patient was started on Aspirin 81mg daily and Plavix 75mg daily (continue for 3 months). She had R ICA stent placement for the carotid web with distal protection by neurosurgery. She was stable to be discharged to home with home health. Repeat mRS 1 on 3-month follow-up. Conclusion: Carotid web was an uncommon cause of ischemic stroke in a young patient with carotid web and distal protection. We attribute the improved outcome to early presentation, and appropriate treatment for the carotid web.

073. The Enigma of Changing Exam During IV Alteplase Administration in Acute Stroke
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Introduction: We present a case of an 85 years old female undergoing IV alteplase administration for acute stroke who had an exam change during alteplase administration. We will review a rare cause of change in exam in this group of patients.

Methods: This is a case-report.
Case Description: Patient is an 85 years old female who was admitted with soft tissue pre-vertebral fluid collection from C3-C5 vertebrae concerning for an infection. She has past medical history of hypertension and atrial fibrillation. She also has past surgical history of C3-C7 cervical fusion. She was taken off of anticoagulation for needle aspiration of this fluid and started on combination of vancomycin, cefepime and metronidazole. An inpatient stroke page was called after patient developed acute onset aphasia, right-left disorientation and left side gaze preference. Patient was evaluated by the stroke team and was determined to be having a stroke. Her CT head showed subtle changes in the posterior left middle cerebral artery (MCA) distribution consistent with an acute stroke. There was no large vessel occlusion (LVO) and patient had perfusion changes in the same posterior left MCA distribution. IV alteplase was started after the risks vs benefits discussion. Twenty minutes into the alteplase administration, patient started to move her right side but remained aphasic. Ten minutes later patient developed right side gaze preference and left-sided weakness. Patient underwent a stat repeat CT which ruled out any hemorrhagic complications. Patient could not undergo a repeat CTA given the previous contrast load or a MRI due to implanted hardware. Due to concern for seizure, patient was empirically treated with lorazepam 1 mg without improvement and placed on continuous EEG. Patient completed the IV alteplase dose and was admitted to neuro-critical unit for further care. A follow-up CT head was obtained at 24 hours which showed a large right MCA stroke.
Conclusion: Change in exam during alteplase administration for acute stroke usually raises concerns for hemorrhagic complications or seizure. We present a case where patient initially started with left MCA stroke and during alteplase administration, developed right MCA stroke. In conclusion, possibility of a new stroke during alteplase administration should be kept in the differential for change in neurological exam in these patients.

074. Acute Progressive Ischemic Stroke in the Young: Think of Syphilitic Angitis - A Case Report and Review of Literature
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Background: Syphilis is the second least prevalent sexually transmitted disease in the United States, behind Hepatitis B. It is known as the “great imitator” because of its varied systemic manifestations. Neurosyphilis affecting the central nervous system can occur in any stage of the disease. Early stage neurosyphilis is characterized by infectious cerebral vasculitis involving small and medium sized vessels, middle cerebral artery being the most common. About 3% of neurosyphilis can present with strokes. There is a paucity of literature from the US on neurosyphilis presenting with stroke, likely owing to low incidence. Most studies are out of middle and low income countries. The largest cohort consisted of 53 neurosyphilis patients who developed stroke, more than half presented with focal symptoms. In a Brazilian study, the prevalence of positive syphilis serology was noted in 13% of stroke patients, mostly the young.

Case Presentation: A 28 year old gentleman with history of hypertension, presented with sudden onset right sided weakness and right facial droop that started two days ago. He was admitted for stroke evaluation. MRI demonstrated multiple small acute infarcts in the left frontal, parietal, temporal and occipital lobes. CT angiogram showed bilateral mild M1 stenosis. Vasculitis was suspected, since the infarcts crossed different vascular territories. An infectious and autoimmune work up was initiated for the same. His serology returned positive for Treponema pallidum antibodies. This prompted CSF studies which revealed a positive CSF VDRL. Of note, patient did not have any cutaneous manifestations of syphilis. On day two of admission, patient developed new onset aphasias and worsening of the right sided weakness, with no new infarcts on repeat MRI. He was started on intravenous penicillin G and within days, there was notable improvement in his speech. He was discharged to a rehabilitation facility.

Conclusion: Through our case, we highlight the following issues. Although rare, stroke is a serious manifestation of neurosyphilis. It is important to consider this differential diagnosis in young individuals presenting with a stroke. A similar rapidly progressive course of syphilitic stroke has been described previously in literature. This makes timely diagnosis important to initiate antibacterial treatment. Its occurrence in asymptomatic individuals also makes the diagnosis challenging. Neurosyphilis is a critical public health issue. It is a preventable infection among youth that has a potential to cause significant disability.

075. Severe Vasoconstriction Leading to Massive Stroke Post Traumatic Subdural Hemorrhage
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Objective: We present a case of severe vasoconstriction post traumatic subdural hemorrhage leading to a massive stroke.

Background: Cerebral vasospasm is a phenomenon commonly seen as a sequelae of aneurysmal subarachnoid hemorrhage. Severe cerebral vasospasm followed by ischemic stroke event after traumatic subdural hemorrhage does not occur commonly but needs to be considered as a potential serious complication.

Case Description: 20-year-old male with no significant past medical history was admitted to the hospital after undergoing a motor vehicle accident resulting in a large left subdural hematoma measuring 13mm with 10mm of midline shift requiring evacuation by neurosurgery. There was no associated traumatic subarachnoid or intraparenchymal hemorrhage. Three days post craniotomy, patient started having difficulty speaking and seemed to be agitated. After ruling out underlying seizures a CT angiogram was performed showing concern for cerebral vasospasm. A diagnostic cerebral angiogram followed showing findings of severe left ICA and ACA vasospasm treated with verapamil and milrinone. Despite treatment, patient developed right upper extremity weakness and right lower face paralysis due to ischemic infarcts involving the posterior left frontal and parietal lobe.

Conclusions: Severe vasospasm after post-traumatic subdural hematoma in a young individual with no past medical history, is rare but could result in secondary stroke if not considered or treated. Healthcare providers are aware of this complication following aneurysmal subarachnoid hemorrhage. It has also described in moderate to severe traumatic brain injury with multi-compartment hemorrhages. In this clinical scenario, CTA was performed to be certain that a dissection wasn’t missed causing his symptoms, but vasospasm discovered. This case is presented in order to demonstrate the possibility of a severe large vessel vasospasm as a complication following a subdural hematoma.

076. Completing the NIHSS Prior to CT Scan in an Attempt to Reduce Time to Acute Intervention for Stroke
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Introduction: Ischemic stroke is a leading cause of morbidity and mortality in the United States. Two acute stroke interventions exist including tissue plasminogen activator (tPA) and mechanical thrombectomy. Unfortunately, both are highly time sensitive and outcomes depend on quick intervention. The typical patient will lose 1.9 million neurons per minute during acute stroke. Therefore, it is in the best interest of patients and our health system alike that patients have rapid times to intervention for acute stroke.

Methods: The FOCUS-PDSA model was used to determine how our stroke alert process could be improved. The stroke alert process previously involved initiation of the
NIHSS as a patient arrived to the ED, viewing images in real time and then following the patient back to their ED room to complete the examination before calling for acute intervention (tPA or thrombectomy). An opportunity for improvement was identified in which the NIHSS examination could be completed outside of the CT scanner and prior to imaging. By eliminating interruptions in the examination, we hoped tPA and thrombectomy could be initiated while reviewing imaging. A multidisciplinary team was developed including members who had extensive knowledge about the process. The change in process was made in July, 2020. Data was analyzed for 6 months before and after to determine whether the new protocol had improved times to tPA and times to thrombectomy.

**Results:** Times to tPA before and after intervention were compared. 52 patients received tPA prior to intervention and 36 received tPA after intervention. The average times to tPA increased after intervention from 53.25 minutes to 63.20 minutes. We further broke this data down into four categories and found that there were 12 (27.27%) in the >60 minute group pre-intervention and 14 (40%) in the post intervention group. When analyzing the other categories, there was a shift from the 46-60 minute group to the 31-45 minute group after intervention. Time to thrombectomy improved after intervention from an average of 52.46 minutes to 43.63 minutes.

**Conclusions:** Door-to-needle times did not change significantly by allowing neurology residents to complete the NIH Stroke Scale prior to CT scan. Time to thrombectomy did improve with this intervention. A larger sample size is required to effectively address this clinical question. This should prompt additional analysis of the barriers to rapid tPA administration in appropriate patients and warrants further investigation.

319. Intraventricular Tissue Plasminogen Activator Use and Reduction of Parenchymal Hematoma Volume in the CLEAR III Trial

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**Background and Purpose:** Intraventricular thrombolysis reduces intraventricular hemorrhage (IVH) volume in patients with intracerebral hemorrhage (ICH), but it is unclear if a similar relationship exists with parenchymal ICH volume. We evaluated the association between intraventricular alteplase administration and parenchymal ICH volume, and functional outcomes.

**Methods:** We performed a post-hoc analysis of the Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) trial, where patients with ICH (<30 mL) and large obstructive IVH were randomized to receive periodic administration of either intraventricular alteplase or normal saline. The primary outcome was a change in hematoma volume between stability and end-of-treatment computed tomography scans. Secondary outcomes were poor outcome (modified Rankin score > 3) and mortality, assessed at 6 months. We assessed the relationship between alteplase and change in ICH volumes, and the association between change in ICH volume and 6-month outcomes, using multiple linear and logistic regression models, respectively.

**Results:** Of 454 enrolled patients with ICH, 230 (51%) received intraventricular alteplase. The alteplase group had a greater mean reduction in ICH volume compared to the placebo group (1.8 mL versus 0.4 mL, p<0.001). Multiple linear regression adjusted for demographics, admission ICH and IVH volumes, ICH location, and antithrombotic therapy, showed a significant association between alteplase administration and decrease in parenchymal ICH volume (beta 0.51, 95% CI, 0.36-0.77, p<0.001). Secondary analysis did not show an association between decrease in ICH volume and poor outcome (aOR, 1.2; 95% CI, 0.9-1.5), or with mortality (aOR, 1.1; 95% CI, 0.8-1.4), likely due to the burden of remaining IVH.

**Conclusions:** In this secondary analysis of the CLEAR III trial, intraventricular alteplase was associated with a small reduction in parenchymal ICH volume, highlighting a possible communication between the ventricular cavity and brain parenchyma. These results highlight exploring this novel treatment for decreasing ICH volume and potentially improving outcomes.

320. Extrastriate Visual Cortex Damage and Temporoparietal Disconnection in Anton Syndrome

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Anosognosia, the lack of awareness for a neurological deficit, is an intriguing but still unclear phenomenon that negatively impacts rehabilitation after stroke. Anton syndrome (AS), or anosognosia for cortical blindness, is among the most striking forms of anosognosia but the underlying mechanisms are not clear. Previous studies involved single case reports. Furthermore, they employed a lesion-based approach to link clinical symptoms to the site and/or volume of a focal injury. However, focal lesions induce functional and structural changes that extend beyond the primary damage on apparently intact regions of the brain. Here, for the first time, we analyzed a sample of AS cases looking for common regions of damage responsible for the most severe visual anosognosia. We measured both the overlap of lesions across patients, as well as the overlap of secondary structural disconnection (SDC)
321. Left Atrial Strain and Atrial Cardiopathy in Embolic Strokes of Undetermined Source (ESUS)

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Background and Objective: Most strokes are categorized as ischemic. Of these, 20% lack a clear cause. Most of these cryptogenic strokes appear embolic in nature and can be referred to as embolic strokes of undetermined source (ESUS). Emerging evidence suggests that one potential source of ESUS is atrial cardiopathy in the absence of atrial fibrillation/flutter. The emergence of speckle-tracking echocardiography enables the identification of atrial cardiopathy beyond left atrial structure and size alone through the quantification of atrial strain, which is a sensitive marker of atrial function. We hypothesized that peak atrial longitudinal strain (PALS) would be more impaired in ESUS than in strokes of known non-cardioembolic origin.

Methods: Among 2,945 ischemic stroke patients registered in the Cornell Acute Stroke Academic Registry (CAESAR) from 2011 through 2018, 2,203 (75%) had a transthoracic echocardiogram (TTE) performed within 3 weeks of their index stroke. Stroke subtypes were determined by neurologists according to the TOAST classification and consensus ESUS definition. PALS was measured by a trained reader, blinded to TOAST subtype, using the Image-Arena 2D Cardiac Performance Analysis software (Version 4.6, TomTec Imaging Systems, Unterschleissheim, Germany) in both two- and four-chamber views of the most recent 324 of these TTEs. Forty-two patients were excluded from this analysis due to an incomplete stroke evaluation or multiple potential causes.

Results: Of 282 included patients, 100 (35.5%) had cardioembolic stroke, 104 (36.9%) had ESUS, and 78 (27.6%) had known non-cardioembolic stroke (small-vessel occlusion, large-artery atherosclerosis, or other determined cause). PALS was significantly lower in ESUS (24.4 ± 10.8) than in known non-cardioembolic strokes (30.9 ± 15.9) (P for t-test = 0.002) when analyzed via two-chamber view. Although PALS was lower in ESUS (27.5 ± 12.7) versus non-cardioembolic strokes (29.3 ± 11.8) when analyzed via four-chamber view, this difference was not significant (P for t-test = 0.32). Patients with cardioembolic stroke had significantly lower PALS than both ESUS and non-cardioembolic strokes in both views.

Conclusion: We found more impaired left atrial strain in patients with ESUS versus known non-cardioembolic stroke. These findings support the growing theory of left atrial derangements playing a key pathogenic role in strokes that are currently labeled as ESUS. Left atrial strain represents a promising tool for identifying atrial cardiopathy in patients with ESUS.

322. Differences in Peripheral Leukocyte Subtypes Between Slow and Fast Progressors of Infarct Growth in Anterior Circulation Large Vessel Occlusion Stroke

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Background: Stroke due to anterior circulation large vessel occlusion (ACLVO) leads to high morbidity and mortality that depends on early infarct growth rate. Fast progressors experience rapid infarct growth after ACLVO stroke onset, whereas slow progressors experience slow infarct growth despite a delayed presentation. The pathophysiology of fast and slow progressors remains poorly understood, but changes in leukocyte (WBC) subtypes have previously been associated with stroke severity. We aimed to compare the relative neutrophil, lymphocyte and monocyte counts between fast and slow progressor phenotypes of ACLVO stroke.

Methods: Single-center retrospective study of patients admitted with occlusion of the middle cerebral artery or intracranial internal carotid artery from 2014-2017. Baseline CTP or MRI were obtained within 24 hours of stroke onset. Fast progressors (ischemic core > 70 ml, 0 - 6 hours after onset) and slow progressors (ischemic core ≤ 30ml, 6 - 24 hours after onset) were identified. Lymphocyte, neutrophil, monocytes percentages were compared in three groups: fast vs. non-fast progressors (0 - 6 hour epoch), slow vs. non-slow progressors (6 - 24 hour epoch), fast vs. slow progressors. Mann-Whitney test was used for univariate comparisons. Multivariable logistic regression tested the independent association of WBC subtypes with progressor status.

Results: Of 185 patients with mean age of 71, median NIHSS of 17, and median WBC count of 9.9 x 10^3 cells. In the early presentation epoch, fast progressors had increased neutrophil percentage (79 vs. 73 %, p=0.04) and decreased lymphocyte percentage (9 vs. 15 %, p=0.06) relative to non-fast progressors. In the 6 - 24 hour epoch, slow progressors had significantly decreased monocyte percentage relative to non-slow progressors (6 vs. 8 %, p=0.01). After adjusting for age, NIHSS and sex on multivariate regression,
only the monocyte percentage (OR 0.68, 95% CI 0.53 - 0.88) was independently associated with slow progressor status, but not that for neutrophils (OR 0.99, 95% CI 0.92 - 1.07) or lymphocytes (OR 1.01, 95% CI 0.92 - 1.12).

**Conclusions:** Peripheral WBC subtypes differ between fast and slow progressors of acute ACLVO stroke. Together, the data suggest that circulating monocytes may play a role in the pathophysiology of early infarct growth due to ACLVO. Moreover, use of point of care WBC differential may help predict fast and slow progressor phenotypes in the emergency setting.

### 323. Early Deterioration, Hematoma Expansion, and Outcomes After Lobar Intracerebral Hemorrhage in the Fast Trial

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**Background and Purpose:** Prior studies in patients with intracerebral hemorrhage (ICH) suggest that early neurologic deterioration (END) is more common in lobar hemorrhages while hematoma expansion (HE) and poor functional outcome is more frequent in deep hematoma location. Here we assessed the relationship between HE, END, and functional outcome by analyzing a patient cohort that underwent admission brain imaging early after symptom onset.

**Methods:** We performed a secondary analysis of the Factor-VII-for-Acute-Hemorrhagic-Stroke-Treatment (FAST) trial including all patients with supratentorial hemorrhage. Patients were enrolled in the FAST trial from May 2005 to February 2007. All patients underwent brain imaging within 3 hours of symptom onset and 24 hours after study treatment. Multivariable logistic and ordinal regression analyses were used to test the association between ICH location (lobar versus deep) and three pre-specified outcomes: HE (increase of ≥33% or 6mL from baseline ICH volume), END (decrease in Glasgow coma score by ≥2 points or increase in NIHSS score by ≥4 points within 24 hours of admission), and functional outcome at 90 days (modified Rankin Scale score). Multivariable models of functional outcome adjusted for patient demographics, baseline GCS score, time from symptom onset to treatment, study treatment, and 24-hour neuroimaging characteristics (HE, ICH volume, presence of intraventricular hemorrhage, midline shift distance, and perihematomal edema volume).

**Results:** Of 841 FAST trial participants, we included those with supratentorial hemorrhages (mean age 76, 38% women; deep ICH n=640, lobar ICH n=113); 215 (30%) had HE and 145 (19%) had END. In patients with lobar compared to those with deep ICH, HE (44 vs. 27%, p=0.001) and END (32 vs. 18%, p=0.001) were more common. Outcome was worse in those with lobar compared to those with deep ICH (median mRS score 5 vs. 4, p=0.03). However, when adjusting for 24-hour neuroimaging characteristics, lobar ICH location was associated with better outcome (OR 0.51, 95% CI 0.28-0.95, p=0.04). There was no interaction between study treatment and ICH location when predicting functional outcome (p-interaction=0.4).

**Conclusions:** In this secondary analysis of randomized trial patients with supratentorial ICH, patients with lobar ICH demonstrated higher rates of HE, END, and unfavorable outcome compared to those with deep hemorrhages. Adjusted analyses suggest that patients with ICH in lobar locations may have had a propensity for better outcomes, but worse 24-hour neuroimaging characteristics influenced poor outcomes.

### 324. Adding MRI After CT is Not Associated with Improved Ischemic Stroke Outcomes at Discharge

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**Background:** Diagnostic imaging is an important driver of healthcare costs in the United States, but there are few data addressing the impact of imaging on clinical outcomes in neurological diseases. A large study based on the National Inpatient Sample reported that inpatient brain MRI in patients with acute ischemic stroke (AIS) was associated with favorable inpatient outcomes. However, this study lacked information on important baseline predictors of outcome.

**Objectives:** To compare outcomes at hospital discharge in patients with AIS who did or did not receive subsequent MRI in addition to CT using propensity-score matched cohorts.

**Methods:** Patients hospitalized at a United States comprehensive stroke center from 2015 to 2017 with admission diagnosis of AIS based on clinical evaluation and CT were identified by retrospective medical record review. Eligible subjects who received or did not receive subsequent MRI were propensity score matched using a 1:1 nearest neighbor approach, with a caliper width of 0.1, and without replacement. Propensity scores were estimated using a logistic regression model based on sex, age, time from last known normal, admission NIHSS, modified Rankin Scale (mRS) at baseline, serum glucose level, statin pretreatment, hypertension, hyperlipidemia, diabetes, coronary artery disease, myocardial infarction, atrial fibrillation, heart failure, peripheral artery disease, chronic kidney disease, obstructive sleep apnea (OSA), previous transient ischemic attack, previous AIS, body mass index, cancer, current tobacco use, Charlson Comorbidity Index, use of alteplase, and use of endovascular treatment. The primary outcome was favorable mRS at discharge of 0-2. Discharge NIHSS score, mortality and hospital length of stay were compared between groups as secondary analyses.

**Results:** Of 579 eligible patients with complete data. Propensity score matching yielded 135 cases with subsequent MRI and 135 without. Standardized mean difference (SMD) was less than 0.100 for all covariates except OSA.
(SMD 0.104). Favorable outcome was achieved in 49.6% of MRI cases and 50.4% of CT only controls (OR 1.03; 95% CI 0.64-1.66; p = .903). There were also no differences in discharge NIHSS (p = .394), mortality (4.4% in MRI cases and 3.7% in controls, p = .758) or hospital length of stay (p = .345).

**Conclusion:** In patients with admission diagnosis of AIS based on clinical evaluation and CT, subsequent MRI was not associated with improved outcomes at discharge in this propensity-score matched cohort study.

### 325. Elevated Initial Troponin I Levels in Patients with Spontaneous Intracerebral Hemorrhage Predict Poor Functional Outcome

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**Background:** Elevated initial Troponin I levels have been associated with poor outcomes in acute ischemic stroke. However, the relationship in symptomatic intracerebral hemorrhage (sICH) has not been extensively explored and prior studies focused on the association with in-hospital mortality. The aim of this study is to investigate the association between initial Troponin I levels and poor functional outcome, mortality and hematoma expansion in sICH.

**Methods:** We retrospectively reviewed the electronic health records (EHR) of 290 patients with sICH admitted to our comprehensive stroke center between January 1st 2009 and December 31st 2018. Demographic data, Troponin I level, severity scores, risk factors and functional/mortality outcomes were obtained from the EHR and hematoma characteristics were obtained from CT scans. Descriptive statistics were computed for all study variables. Logistic regression analysis was used to assess the association of initial Troponin I with poor functional outcome (defined by modified Rankin Scale 4-6 at 45-180 days) as well as of hematoma expansion and mortality.

**Results:** Of the 290 patient charts reviewed, Troponin I levels were obtained within 24 hours in 213 patients (73.4%). 164 patients fulfilled our inclusion/exclusion criteria and were included in the final analysis. Initial Troponin I level was elevated (>0.03ng/ml) in 28 patients (17.1%). There was no statistically significant difference in the age, mean Glasgow Coma Scale, mean ICH score, risk factors and hematoma characteristics between normal and elevated troponin group. There was a statistically significant association between elevated initial Troponin I level and poor functional outcome (OR=3.46; 95% CI 1.09-10.90; p=0.03). A statistically significant association was not observed with neither mortality (OR=1.51; CI 0.66-3.47; p=0.32) nor hematoma expansion (OR=13.56; CI 0.78-16.17; p=0.09).

**Conclusion:** Our study shows that elevated initial Troponin I level is associated with poor functional outcome in patients with sICH suggesting a utility of this test in the prognostication and risk stratification of this patient population. No association was found between initial Troponin I with neither mortality nor hematoma expansion.

**References:**


### 326. Reducing Readmission Rates by Improving Transitions of Care for Stroke Patients in the Pre-COVID and COVID Eras

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**Introduction:** Despite advances in secondary stroke prevention, acute cerebrovascular disease continues to rank among the top causes of 30-day readmission in the United States. To improve quality of care and reduce healthcare costs, increasing attention has been given to improving transitions of care (TOC) for stroke patients. The objective of our study was to determine if evaluating patients within 1-3 weeks after discharge in a stroke TOC clinic would reduce 30-day readmission rates.

**Methods:** Potential participants were identified by ICD-10 diagnoses corresponding with stroke or transient ischemic attack at Thomas Jefferson University Hospital (TJUH). Starting in January of 2019, an in-person TOC clinic visit with a vascular neurologist or nurse practitioner was automatically scheduled for individuals discharged to home. When coronavirus precautions began, these visits were transitioned to telemedicine. Follow-up telephone surveys assessing self-efficacy, confidence and perceived value of TOC clinic were administered to attendees within 6-months of their appointment. Readmission statistics were collected from the TJUH electronic health record. Preliminary data analysis was performed in SPSS.

**Results:** 208 individuals (113 in-person, 95 telemedicine) seen in TOC clinic between January of 2019 and February of 2021 were included in the preliminary analysis. The 30-day all-cause readmission rate was 5.8% (12 patients). Of these readmissions, 2 were in-clinic visits (2.1%) and 10 were evaluated via telemedicine (8.8%). Chi Square revealed a between group difference (X² = 4.318, p = 0.038). Participants in both the in-person group (u = 8.421, SD = 1.835) and telemedicine group (u = 8.100, SD = 1.875) considered TOC a valuable experience. Analysis of perceived TOC value did not differ between groups (t = 0.654, p = 0.515).

**Discussion:** Stroke readmissions represent a significant source of morbidity, mortality and healthcare spending in the United States. Overall, TJUH TOC clinic patients experienced fewer readmissions compared to institutional and
national 30-day stroke readmission rates. Ongoing qualitative surveys also confirmed that TOC visits correct misunderstandings about medications, clarify diagnoses and ease fears after discharge. We posit that the promising results of this quality initiative support an increase in clinic appointment availability and may serve as a model for initiatives in departments with similarly complex patients.

327. Stroke Severity and Post-Acute Care Discharge Setting Interact to Predict Mortality After Stroke
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Background: Limited nationwide data exists on stroke outcomes in the US, yet these data may be important for informing decisions about care preferences. We used a national dataset to assess US stroke survivor outcomes based on two main predictors: post-stroke function and post-acute care discharge setting.

Methods: This study was a retrospective cohort study of Medicare beneficiaries hospitalized with acute ischemic stroke or intracerebral hemorrhage in 2013. We followed subjects for at least 1 year post-discharge for the primary outcomes of unplanned readmission and mortality. We performed multivariate logistic regression to estimate 90-day odds ratios and cox proportional hazards regression to estimate post 90-day hazard ratios on each outcome, adjusting for demographics, Charlson comorbidities, the risk of ischemic stroke was highest in the first 30 days after discharge from the acute systolic HF hospitalization for patients with atrial fibrillation. We excluded patients with and without atrial fibrillation in the first post-acute care setting, and setting-function interactions.

Results: There were 167,000 patients with a mean follow-up period of 441 days. In the unadjusted analysis, mortality and unplanned readmission at 90 days were higher in patients discharged to SNF (22.9% for 90-day mortality, 32.2% for 90-day unplanned readmission) compared to IRF (7.7%, 26.9%) and HHA (6.7%, 24.5%). Post-stroke function (OR 0.23, 95% CI 0.19-0.27 comparing highest to lowest quintile of post-stroke function) and discharge setting (OR 4.05, 95% CI 3.78-4.33 for SNF vs. IRF) were strongly associated with mortality within 90 days. There was an interaction between setting and function such that the lowest function SNF patients had a mortality of 64.1% at 1 year vs. 29.6% in IRF.

Conclusions: Post-acute care discharge setting, initial post-discharge function, and their interaction are strongly associated with mortality one year after stroke. These findings may have relevance for prognostication during stroke hospitalization.

328. Duration of Heightened Ischemic Stroke Risk Following Hospitalization for Acute Systolic Heart Failure
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Background: The duration of increased stroke risk after hospitalization for acute systolic heart failure (HF) remains uncertain.

Methods: We performed a retrospective cohort study using claims between 2008 and 2018 from a nationally representative 5% sample of Medicare beneficiaries aged ≥66 years old. Both acute systolic HF and ischemic stroke were ascertained using previously validated International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), diagnosis codes. Patients with claims for ischemic stroke before or during index hospitalization for acute heart failure were excluded. We fit Cox regression models separately for the groups with and without acute systolic HF to examine its association with ischemic stroke after adjustment for demographics, stroke risk factors, and Charlson comorbidities. We stratified the cohort by patients with and without atrial fibrillation prior to or during the hospitalization for acute systolic HF. We used the corresponding survival probabilities to compute the hazard ratio (HR) in each 30-day interval after discharge. Confidence intervals (CI) were computed using the nonparametric bootstrap method.

Results: Among 2,077,501 eligible beneficiaries, 94,641 were hospitalized with acute systolic HF and 210,583 for ischemic stroke. After adjusting for demographics, stroke risk factors, and Charlson comorbidities, the risk of ischemic stroke was highest in the first 30 days after discharge from the acute systolic HF hospitalization for patients with atrial fibrillation ( Hazard ratio (HR): 2.4; 95% CI, 2.1-2.7) and without atrial fibrillation (HR: 4.6; 95% CI, 4.0-5.3). The risk of stroke remained elevated for 60 days in patients with atrial fibrillation (HR, 1.4; 95% CI, 1.2-1.6) and was no longer significantly elevated afterward. The risk of stroke remained significantly elevated through 330 days in patients without atrial fibrillation (HR: 2.1; 95% CI, 1.7-2.7) and was no longer significantly elevated afterward.

Conclusion: Hospitalization for acute systolic HF is associated with a prolonged increased risk of ischemic stroke. The risk of stroke appears especially prolonged in patients without atrial fibrillation.

329. Sex Differences in Risk Factor Control Among Patients Undergoing Thrombectomy for Acute Ischemic Stroke
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Introduction: There are class 1 recommendations for the management of common stroke risk factors. Despite this,
there are sex inequalities in risk factor control with previous studies showing that women are treated less appropriately for atrial fibrillation (AF) and hyperlipidemia (HLD). The purpose of this study is to estimate the percentage of large vessel strokes that are potentially preventable with adequate management of vascular risk factors and how this may differ by sex.

Methods: A retrospective chart review was conducted on patients undergoing endovascular therapy (EVT) from 2012-2019 at a single tertiary stroke center. Risk factors identified prior to admission including hypertension (HTN), diabetes mellitus (DM), HLD, AF, history of vascular disease and smoking were recorded. Preventable stroke was defined as having at least one of the following: untreated AF, untreated HLD, poorly controlled HTN (presence of left ventricular hypertrophy on transthoracic echo), vascular disease not on an antplatelet agent, poorly controlled DM (A1c>10), current smoking. Our analysis focused on differences in risk factor control among sexes.

Results: Our sample included 396 patients who underwent EVT (mean age 65, 50% female). Most patients (78%) had at least 1 poorly controlled risk factor. 42% of patients with AF were not on anticoagulation, 31% of patients with HLD were untreated, 39% of patients with HTN were poorly controlled, 27% of patients with a history of vascular disease were not on an antplatelet, 14% of patients with DM were poorly controlled, and 46% of patients were smokers. Overall there was no difference in rates of untreated risk factors between males and females (48% vs 52%, p=0.30). Men had higher rates of poorly controlled DM (p=0.015), untreated vascular disease (p=0.013), and were more likely to be smokers (p=0.026). Differences between men and women in untreated AF (men>women) and untreated HLD (women>men) did not reach statistical significance.

Conclusions: There are sex-specific differences in risk factor control seen prior to admission for large vessel stroke. Our data correlated well with prior literature regarding control of smoking, HTN, and HLD, but did not correlate with prior data on control of diabetes, AF or vascular disease. Some differences may be due to the smaller sample size in our study. Nevertheless, a focus should be placed on improving primary prevention with awareness of sex differences, especially when treating patients with risk factors for large vessel strokes.

330. White Matter Microstructure as a Predictor of Clinical Response to Transcranial Direct Current Stimulation in Post-Stroke Aphasia
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Introduction: Aphasia continues to be a debilitating deficit for many stroke patients, many of whom experience incomplete recovery despite intensive speech therapy. Prior research has highlighted anodal transcranial direct current stimulation (A-tDCS) as a potential adjunct to speech therapy, with promising results for improving clinical outcomes. Our study investigates if baseline white matter microstructure predicts clinical response to A-tDCS in patients with post-stroke aphasia.

Methods: Using MRI brain images from 22 subjects enrolled in the tDCS vs sham study, which were eddy current corrected with PyDesigner, T1 white matter was segmented and normalized to diffusion space in SPM (MatLab). Spheres identifying regions of interest according to tDCS anode placement were created in MRicroGL, and tracts within these spheres were analyzed using DSI studio. Baseline and one-week Philadelphia Naming Test (PNT) scores were used to calculate Proportion Maximum Gain (PMG).

Results: Of 22 subjects, 9 (40.9%) received A-tDCS, and 13 (59.1%) received S-tDCS. Despite similar baseline PNT scores, A-tDCS patients had higher PMG than S-tDCS (p=0.008). Baseline tract characteristics were similar, however, in A-tDCS patients, Superior Longitudinal Fasciculus 3 (SLF3) trunk volume was associated with higher PMG (p=0.002).

Conclusion/Discussion: Our results found correlation between baseline SLF3 volume and PMG for A-tDCS subjects. This suggests SLF3 volume as a potential marker for patients with improved A-tDCS rehabilitation potential.

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341. The Mas Receptor Agonist TXA127 Blocks Neurovascular Inflammation Associated with Sars-CoV-2 Infection
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Infection with Sars-CoV-2 is associated with a significant increased risk of cerebrovascular events including a 7-fold increased risk of ischemic stroke as well as atypical stroke syndromes including cerebral venous thrombosis and intracerebral hemorrhage. The mechanisms of this increased risk of stroke associated with Sars-CoV-2 infection are unknown but may result from direct viral infection of the cerebral endothelia in a process modulated by cerebral blood flow (Kaneko et al. Stroke 2021). Binding of Sars-CoV-2 spike protein to ACE2 disrupts the normal enzymatic activation of angiotensin II into Ang-(1,7), a peptide moiety that activates the Mas receptor (MasR). Agonism of MasR may blunt the detrimental vascular effects induced by Sars-CoV-2 spike protein binding to ACE2. We used a series of in vitro cell culture paradigms to examine the role of Sars-CoV-2 in activating neurovascular inflammation that potentially underlies stroke pathology in COVID-19. In monolayer cultures of human
brain microvascular endothelial cells, exposure to recombinant Sars-CoV-2 spike protein trimer triggers specific 1.3-fold up-regulation of complement C3 that is absent in human umbilical vein endothelial cells. Using a novel endothelialized 3D-printed precision cerebrovascular model of the middle cerebral artery cultured under flow conditions (>30 dynes/cm²) that promotes ACE2 expression, recombinant spike protein leads to 2.2-fold up-regulation of complement C3. Increased levels of C3 can be detected in conditioned media and endothelial exosomes released from brain endothelia after spike protein exposure. To test whether activation of MasR can reduce spike-protein-induced C3 expression, we used the MasR agonist TXA127 (1 μm). Spike protein-induced activation of the complement cascade in brain endothelia can be robustly blocked by the Mas receptor agonist TXA127. After exposure to live Sars-CoV-2 virus, TXA127 can effectively inhibit C3 expression and reduce complement activation in conditioned media and endothelial exosomes in monolayer and 3D models endothelialized with human brain microvascular endothelial cells. Identification of the neurovascular inflammatory cascades activated by Sars-CoV-2 can play a critical role in developing therapeutic approaches to reduce the burden of cerebrovascular disease in COVID-19.

479. Monocyte Transcriptomic Analysis of High-Risk Carotid Atherosclerosis
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Background: Carotid atherosclerosis remains an important cause of ischemic stroke and new therapeutic interventions are needed to mitigate the stroke risk associated with carotid plaques. Intraplaque macrophages have a pivotal role in plaque progression and rupture. They also secrete cytokines that might affect gene expression in peripheral monocytes. We aimed to evaluate differences in monocytes gene expression in patients with symptomatic (high risk) and asymptomatic (low risk) carotid atherosclerosis.

Methods: Peripheral monocytes were isolated from 15 patients with symptomatic carotid atherosclerosis (stroke due to carotid plaque) and 21 patients with asymptomatic carotid atherosclerosis (14 with stroke not due to carotid atherosclerosis and 7 without stroke). Total RNA was isolated and processed with NEB library preparation and Illumina NovaSeq 6000 sequencer. We applied a log-normal linear regression adjusted for statin treatment to identify genes differentially expressed in symptomatic versus asymptomatic carotid atherosclerosis (genelist1), and in patients with severe (>70%) carotid stenosis versus mild (<50%) or moderate (50-69%) stenosis (genelist2). Genes common to both lists were considered as key determinants of monocyte differentiation into pro-atherogenic macrophages. The ability of genes common to both lists to separate patients with symptomatic carotid atherosclerosis from those with asymptomatic carotid atherosclerosis was visualized using principal component analysis and hierarchical clustering. Functional pathways associated with the differentially expressed genes in both lists were also identified.

Results: There were 40 genes common to genelist1 (n=1029) and genelist2 (n=147). The 40-gene panel correctly identified 93.3% of the patients with stroke due to carotid stenosis and displayed a good ability to separate patients according to their grade of stenosis. Functional analysis identified a predominance of genes relevant to programmed cell death-ligand 1/programmed cell death protein 1 checkpoint pathway (PD-L1/PD-1) and hypoxia-inducible factor 1 alpha signaling pathway (HIF-1α). There was a lower expression of HIF1A in patients with stroke due to symptomatic carotid atherosclerosis than in those with asymptomatic carotid atherosclerosis (FC = -1.35, p<0.001) and a higher expression of CD274 (PD-L1) in patients with severe stenosis than in those with mild stenosis (FC=+3.02, p = 0.03).

Conclusion: Peripheral monocytes have a distinctive gene expression profile in high-risk carotid atherosclerosis with increased expression of CD274 and decreased expression of HIF1A. Further studies will determine whether these differences could inform the design of new biomarkers and drugs for the management of carotid atherosclerosis.

K-452. Angiogenesis and Neurogenesis in the Human Germinal Matrix
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The vasculature is increasingly recognized to impact brain function in health and disease. In a striking example of vascular contributions to neurodevelopmental disorders, 20% of extremely preterm babies experience hemorrhage specifically in an area of the brain called the ganglionic eminences (GE). This region contains abundant radial glia that produce the majority of cortical interneurons. Consequently, hemorrhage in this area can cause permanent brain damage and death. However, it remains unclear why developing vasculature in the GE is particularly vulnerable. Endothelial and mural cells compose the main structural and functional elements of the vasculature. Brain endothelial cells are thought to originate from a perineural vascular plexus external to the brain parenchyma, whereas the ontogeny of mural cells remains elusive. One major limitation of these studies, however, is that most of them are performed in animal models. Accordingly, the mechanisms regulating angiogenesis in a highly neurogenic niche in prenatal human brain, such as GE, remain poorly understood. Using cell type-specific markers, we characterized the development of endothelial and mural cells in the human GE during prenatal brain development. At early ages, these experiments revealed a predominance of endothelial and mural cells located directly next to the ventricle. Endothelial cells in this region displayed abundant filopodia and increased branching, features of active angiogenesis. These experiments suggest a new source of vascular cells deep...
within the brain and contrast with the traditional view of vascular cells as originating external to the brain parenchyma. To delineate the specific stages of vascular development in this vulnerable region, we used fluorescence-activated cell sorting and single-cell RNA-sequencing to characterize brain endothelial and mural cells in the second trimester. This approach revealed distinct subtypes and stages of maturation for these cells and uncovered a group of novel progenitors in the ventricular-subventricular zones with transcriptomes that overlapped with radial glia, the canonical neural stem cells. When placed in cultures or in brain organoids, these progenitors can produce both vascular and neural lineage cells. In sum, these results support the existence of a remarkably plastic vascular progenitor in the ventricular zone of the developing human brain, and its potential involvement in disease.

**K-493. Disregulation of Nrg1-ErbB4 and BDNF-TrkB Pathways and Their Link to the Deficit in Hippocampal Parvalbumin (PV)+ Interneurons After Neonatal Hypoxia-Ischemia**

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**Background:** Neonatal hypoxia-ischemia (HI) reduces the number of parvalbumin (PV)+ interneurons (INs). BDNF supports maturation and maintenance of interneurons. ErbB4 activation by Nrg1 results in an activity-dependent increase in expression of PV, as well as escalation of dendritic complexity. Satb1, a transcription factor, maintain mature MGE-derived INs. Thus, we hypothesize that the Nrg1 and BDNF disregulation by neonatal HI results in dysmaturation of MGE-derived INs.

**Methods:** C57BL6 mice received cerebral HI at P10. HI mice were randomized to normothermia (NT, 36°C) or therapeutic hypothermia (TH, 31°C) for 4h vs. sham. Mice were sacrificed at 24h, 5d, 8d, and 30d after injury to study in hippocampus; i) BDNF and Nrg1 levels (ELISA), ii) phospho total TrkB and ErbB4 ratios (WB), and iii) Nrg1, ErbB4, PV, SST, Satb1 and markers of E/I balance (Vglut2/ Syt2) expression in the dorsal CA1 (IF-IHC). Images were processed using ImageJ/FIJI, IMARIS software, and analyzed using SPSS.

**Results:** By P15, the number of PV+INs almost doubled and continue increasing until P18. These changes occurred while hippocampal BDNF levels progressively increased (R² 0.48, p<0.001) and Nrg1 levels decreased (R² 0.56, p<0.001) from P11 to P40. While, HI did not decrease the number of SST+INs, it did decrease the number of PV+INs in the dorsal CA1 as early as P18. Preceding the deficit of PV+INs, Nrg1 levels were increased by 66% and 31% in NT at P11 and P15, respectively; while BDNF levels were unchanged. Nrg1 increased was most abundant in Py layer. Although, ErbB4 immunoreactivity (IR) increased on PV+INs and ErbB4 phosphorylation matched the Nrg1 increase (~60%), the phosphoErbB4 was not increased. At P18 and P40, ErbB4 activation was decreased by 70% after HI, as it was BDNF levels by 62% and TrkB phosphorylation by 71%. In sham mice nuclear Satb1 was more commonly identified in SST+INs than in PV+INs. Twenty percent of SAth1 + cell do not express either PV, or SST.

**Conclusion:** Early increase in Nrg1 expression in pyramidal cells and ErbB4 receptor in the membrane of PV+INs after HI, may be part of a mechanism intended to recapitulate an immature MGE-derived phenotype to redirect their cellular fate. Whether the delayed and late deficits in the activation of TrkB and ErbB4 receptors plays a role in memory deficits and hippocampal neurodegeneration after neonatal HI, needs further investigation.


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**Background:** Intracerebral hemorrhage and arterial ischemic disease share risk factors, but the association between the two conditions remains unknown. Our objective was to determine whether intracerebral hemorrhage is associated with an increased risk of incident ischemic stroke and myocardial infarction.

**Methods:** An analysis of pooled participant-level data from four population-based, longitudinal cohort studies in the United States: the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), and the Northern Manhattan Study (NOMAS), and the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. Patients were enrolled from 1987-2007, and the last available follow up was December, 2018. The exposure was intracerebral hemorrhage, as determined by an adjudication committee based on pre-defined clinical and radiological criteria. The primary outcome was an arterial ischemic event, defined as a composite of ischemic stroke or myocardial infarction, centrally adjudicated within each study. Secondary outcomes were ischemic stroke and myocardial infarction. We excluded participants with prevalent intracerebral hemorrhage, ischemic stroke, or myocardial infarction at their baseline study visit. Cox regression was used to examine the association between intracerebral hemorrhage and subsequent arterial ischemic events after adjustment for baseline age, sex, race, vascular comorbidities, and antithrombotic medications.

**Results:** Among 55,131 participants, 47,866 were eligible for analysis, with a mean age of 62 years (SD, 10), and 20,227 (42.3%) participants were men. During a median follow up of 12.7 years (interquartile range, 7.7-19.5), there were 318 intracerebral hemorrhages and 7,648 arterial ischemic events. The incidence of an arterial ischemic event was
3.6 per 100-person years after intracerebral hemorrhage versus 1.1 events per 100 person-years among those without intracerebral hemorrhage. In adjusted models, intracerebral hemorrhage was associated with arterial ischemic events (HR, 2.3; 95% CI, 1.7-3.1), ischemic stroke (HR, 3.1; 95% CI, 2.1-4.5), and myocardial infarction (HR, 1.9; 95% CI, 1.2-2.9). In sensitivity analyses, intracerebral hemorrhage was associated with arterial ischemic events when updating covariates in a time-varying manner (HR, 2.2; 95% CI, 1.6-3.0), when using incidence density matching (OR, 2.3; 95% CI, 1.3-4.2), when including participants with prevalent ischemic stroke or myocardial infarction (HR, 2.2; 95% CI, 1.6-2.9), and when using death as a competing risk (sub HR, 1.6; 95% CI, 1.1-2.1).

Conclusions: We found that intracerebral hemorrhage was associated with a heightened risk of ischemic stroke and myocardial infarction. These findings suggest that intracerebral hemorrhage may be a novel risk marker for arterial ischemic events.

K-517. Reasons for Delay in Hospital Arrival After Stroke Onset in an Urban Community

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Background: Treatments for stroke are time-sensitive and depend on early hospital arrival. Black Americans are less likely to receive stroke treatments, such as tissue plasminogen activator due in part to delayed hospital arrival. We sought to identify the reasons for delay in hospital arrival and reasons for hesitancy to activate 911 in an urban primarily Black American community.

Methods: We created a survey that assessed reasons for delay in hospital arrival after stroke symptom onset and attitudes about calling 911. Survey questions were based on the theory of planned behavior. We partnered with the stroke coordinator at an urban hospital who administered surveys to hospitalized adult stroke patients who arrived 3 or more hours after symptom onset. We excluded patients who woke up from sleep with their symptoms or who could not read English. Surveys were analyzed by coding responses into the theory of planned behavior and based on the frequency of responses.

Results: We enrolled 19 participants with a mean age (± standard deviation) of 57 ± 8 years old from December 2020 - April 2021. Participants were 58% men, 63% Black Americans, and 63% with at least some college education. Of all participants, 47% knew that they were having a stroke. Of the participants who did not know that they were having a stroke, 70% attributed their symptoms to one of their medical problems. Frequent reasons for delay in hospital arrival included waiting for symptoms to resolve, not thinking that the symptoms were serious, and not wanting to miss work. A frequent first action after symptom onset was to call family or to lie down. The most frequent reasons for eventually coming to the hospital included being advised by family or if their symptoms did not go away. The majority of people thought they would have to pay for an ambulance, but only 16% of participants cited cost as a reason for delay.

Conclusion: Education about the importance of early hospital arrival after stroke symptom onset should emphasize that symptoms might not self-resolve, the seriousness of symptoms, and the importance of early activation of emergency medical services to be considered for stroke treatment. We plan to adapt a stroke preparedness intervention to include these messages and perform cognitive interviewing to ensure that community members understand the intervention materials as intended.

K-519. Admission CT Radiomic Signatures Outperform Hematoma Volume in Predicting Baseline Clinical Severity and Functional Outcome in Intracerebral Hemorrhage

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Purpose: Only 40% of ICH patients regain functional independence while there is yet no effective treatment - highlighting the importance of early risk stratification for personalized treatment decisions and enrollment in clinical trials. To date, hematoma volume is the most widely used and strongest imaging predictor of clinical outcome. We investigated the utility of ICH radiomics in predicting the severity of clinical symptoms at admission and long-term functional outcome.

Methods: Utilizing the dataset gathered by the “Antihypertensive Treatment of Acute Cerebral Hemorrhage II” trial, we extracted a set of n=1130 radiomics features reflecting hematoma shape, density and texture from hematoma lesions of n=895 patients on admission non-contrast CT. Subjects were randomly allocated to a discovery (n=448) and independent validation cohort (n=447). Following exclusion of features with low inter- and intra-rater reproducibility and high multicollinearity, we generated separate “radiomics signatures” associated with admission GCS, admission NIHSS, and 3-month follow-up modified Rankin scale (mRS) scores using LASSO-regularized ordinal logistic regression models in the discovery cohort. Features with non-zero coefficients were linearly combined and weighted by their respective coefficients to devise the signatures. Spearman’s correlation (rho) between radiomics signatures and target scores was compared with the correlation between ICH volume and target scores.

Results: Radiomics signatures, compared to ICH volume, demonstrated significantly stronger correlation with GCS (rho=0.47 vs 0.44, p=0.008), NIHSS (0.69 vs 0.57, p<0.001), and mRS scores (0.44 vs 0.32, p<0.001) in the discovery cohort. Similarly, in independent validation, the radiomics signatures exhibited significantly stronger association with GCS (0.43 vs 0.41, p=0.02), NIHSS (0.64 vs
Conclusion: Automatically extracted ICH radiomics features characterizing the density, shape, and heterogeneity of hemorrhagic lesions on baseline non-contrast CT can provide imaging correlates of patients’ clinical presentation and outcome beyond hematoma volume. These results could lead to a paradigm shift where imaging biomarkers of cerebral parenchymal injury in addition to the size of hemorrhagic lesions may potentially improve current models for prognostication, risk-stratification, and treatment triage of ICH patients.

K-524. Precise CRISPR Base-Editing in Arctic Ground Squirrel Cells Reveals Novel Mechanisms of Metabolic Resilience
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Introduction: Arctic ground squirrels (AGS) are extreme hibernators capable of withstanding months of freezing temperatures by suppressing metabolic rate. Hibernation is characterized by low cerebral blood flow and relative brain tissue hypoxia. Curiously, hibernation is interrupted by bouts of arousal in which perfusion is quickly restored, yet AGS suffer no ischemic or reperfusion injuries. Laboratory models of stroke or anoxic brain injury also demonstrate decreased neuronal injury in AGS in vivo. In vitro experiments on neurons derived from AGS stem cells similarly demonstrate remarkable tolerance to metabolic stressors.

Methods: We identified new metabolic resilience phenotypes in AGS neurons in vitro and performed a functional genomic cDNA screen to identify overexpression candidates facilitating stress resilience. Using a bioinformatics pipeline, we further screened AGS cytoprotective proteins for protein sequence adaptations in regions of high conservation. Numerous highly-adapted and cytoprotective protein candidates emerged including ATP5G1. A combination of base editing knock-in and Cas9 knock-out approaches were used to generate loss-of-function variants in a subset of AGS proteins to identify mechanisms of AGS adaptive responses to metabolic stress.

Results: Expression of AGS-specific protein variants compared to human variants leads to improved metabolic stress tolerance. Conversion of the Ag Atp5g1 allele into a human allele in AGS neural cells with a CRISPR adenine base editor attenuated AGS stress resilience and partially abrogated mitochondrial functional and survival phenotypes. Mechanistically, the AGS-specific ATP5G1 amino acid substitutions lead to altered abundance of ATP synthase dimers.

Conclusions: The results point to a role for ATP5G1 in regulating cellular adaptations in oxidative phosphorylation and imparting neuroprotection in our in vitro model. We gained key functional insights into how an AGS-specific amino acid substitution can alter mitochondrial function to impart cytoprotection. This detailed dissection of the AGS optimized adaptive stress response pathway can serve as a template for the development of new neuroprotective treatments.

K-524. Mechanisms of Post-Stroke Plasticity in the Mouse Somatosensory Cortex
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Circuits in the healthy central nervous system (CNS) have the capacity for reorganization and remapping of functionality. It has been widely hypothesized that after cortical injury, such as stroke, circuits will remap such that spared neurons will assume the functionality of those lost to injury. The peri-infarct cortex is often suggested as a site of functional remapping as this region exhibits changes that could support circuit re-wiring, including increased dendritic spine turnover, axonal sprouting, and expression of genes promoting circuit plasticity. However, after a lesion targeting an individual barrel (C1) in the barrel field of mouse primary somatosensory cortex (S1BF), we have recently found that circuit remapping is actually inhibited in the surrounding cortex. Using longitudinal in vivo two-photon calcium imaging after a stroke that destroys the C1 barrel, we did not find any increase in the number of C1 whisker-responsive neurons in adjacent, spared barrels. In addition, spared C1 whisker-responsive neurons showed diminished sensory-evoked neuronal responses. In an attempt to promote plasticity after stroke, in another cohort of animals, we employed a forced-use paradigm and plucked all whiskers except C1 after stroke. This led to an increase in the reliability of sensory-evoked responses in C1 whisker-responsive neurons, but again, did not result in increased numbers of C1 whisker-responsive neurons in spared surround barrels. These data suggest that maladaptive circuit changes occur that limit, rather than promote, recovery, and we are now investigating the mechanism underlying these changes. GABAergic parvalbumin-expressing (PV) interneurons are major regulators of the excitation:inhibition (E/I) ratio, shape cortical sensory representations, and regulate circuit plasticity. We hypothesize that PV cells may be key regulators of local cortical circuit excitability and remapping following focal cortical strokes. We are testing this hypothesis directly, using in vivo calcium imaging to record PV cell sensory-evoked activity in the peri-lesional cortex throughout recovery. We expect that PV cell activity may be increased following focal cortical stroke, reducing pyramidal cell activity and, thus limiting remapping. In the future, we will further test this hypothesis by manipulating PV cell activity with inhibitory DREADDs to promote remapping.

LB-460. Non-Dolichoectatic Vertebral Artery Compression of the Medulla: A Comprehensive Literature Review
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Objective: Vertebral artery compression of the medulla is a rare vascular finding that causes a variety of clinical
Dementia and Aging

077. Prevalence of Triple Disease (AD, WMD, DLB)  
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**Objective:** Alzheimer’s disease (AD), Lewy body disease (LBD), and white matter disease (WMD) are common in the elderly. Although these diseases are observed together pathologically, the extent to which these diseases occur together clinically is uncertain. To address this question, we analyzed the clinical-neuroimaging data of Japanese patients.

**Patients and Methods:** This was a prospective study with a 3.0-year recruiting period, a prospective follow-up period of ≥1×/year visits. We recruited 770 referred subjects who had undergone three neuroimaging markers: brain magnetic resonance imaging (MRI), dopamine transporter (DAT) scanning, and metaiodobenzylguanidine (MIBG) myocardial scintigraphy.

**Results:** Among the 770 patients, 731 fulfilled the criteria of some or all of the three diseases as follows: WMD (n=46), WMD + AD (n=110), WMD + LBD (n=89), WMD + AD + LBD (n=86), AD (n=118), LBD (n=239), and AD + LBD (n=43). In total, there were patients with WMD (n=331), AD (n=357), and LBD (n=414) (with overlap); dual diseases (n=242; 33%) and triple diseases (n=86; 12%). Clinically, pure WMD showed overactive bladder but mild gait/cognitive disorder. Pure AD showed cognitive disorder alone. Pure LBD showed cognitive, gait, and sleep/autonomic disorders. Triple/dual diseases showed combined clinical features, depending on the underlying diseases. However, these differences did not reach statistical significance.

**Conclusion:** Forty-five percent of the patients who visited dementia/movement disorder/sleep-autonomic disorder clinics showed either triple or dual diseases. It is important to follow such patients from the viewpoint of disease progression and necessary care.
Methods: 500 AD patients and 500 healthy controls were recruited in this study. AD was diagnosed by neurologist specialized in dementia base on NINCDS-ADRDA criteria. Blood samples from AD patients and healthy controls were used for DNA extraction and Polymer chain reaction (PCR). Student t test and Chi-square analysis was used for statistical analysis.

Results: The dominant model and the recessive model of HMOX-1 rs2071746 were shown statistically significant between AD patients and control after adjustment of age, gender and education (Dominant model: p value: 0.047, OR: 1.34, 95% CI: 1.00 - 1.78, adjusted; recessive model: p value: 0.049, OR: 1.34, 95% CI: 1.00 - 1.80, adjusted). There is also a trend of association between dominant model and LOAD after adjustment of age, gender and education (Dominant model: p value: 0.084, OR: 1.37, 95% CI: 0.96 - 1.95, adjusted).

Conclusions: We found the association of the dominant model and the recessive model of HMOX1 rs2071746 with AD. More large and multicenter studies are warranted.

080. Aphasia in Dementia of Lewy Body Disease
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Dementia with Lewy Body Disease (DLB) clinically manifests as dementia with any combination of parkinsonism, psychosis, rapid eye movement (REM) sleep behavior disorder and autonomic dysfunction. Cognitive deficits are reported to disproportionately affect attentional/executive and visuospatial function and relatively spare episodic memory and language. We investigate clinical and neuroimaging features of 24 patients with DLB who exhibited the core clinical features of DLB, including visual hallucinations, fluctuating cognition, and rapid eye movement sleep behavior disorders (RBD). They were all evaluated by a behavioral neurologist and speech and language pathologists. Eleven patients were male and 13 was female; median age [range] (82.0 [68-90]); none had a family history of a neurodegenerative disorder. Brain magnetic resonance imaging (MRI), N-isopropyl-p-[123I] iodoamphetamine single-photon emission computed tomography (SPECT), and dopamine transporter (DAT) SPECT imaging with [123I]-ioflupane were conducted for investigating neuroimaging features. Three out of 13 patients full filled criteria of primary progressive aphasia (PPA). On MRI these three patients showed diffuse cortical atrophy with a focus of involvement in the left lateral temporal lobe. DLB can present as a PPA in the absence of distinct focal areas of atrophy on MRI. Presence of aphasia, therefore, should not exclude underlying DLB.

081. Pharmacotherapy in Behavioral Variant Frontotemporal Dementia: A Literature Review
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Background: Behavioral variant frontotemporal dementia (bvFTD) is a clinical syndrome characterized by deficits in executive function and changes in behavior. bvFTD is the commonest condition in the frontotemporal (FTD) spectrum, particularly in adults under the age of 65. There is no known cure; pharmacological intervention is primarily symptomatic. This literature review was conducted to examine existing practices in pharmacotherapy for bvFTD and identify commonly used therapeutic agents.

Methods: A literature search was conducted using the PubMed database in accordance with the PRISMA 2020 guidelines. Search terms included “behavioral variant frontotemporal dementia”, “treatment”, and “pharmacotherapy”. Articles published from 2000-2021 were included. Exclusion criteria included non-English studies and animal studies.

Results: The literature search yielded 48 articles. 25 articles were included in the final literature review. For management of apathy, bupropion, oxytocin, agomelatine, and memantine were suggested treatments. Improvements in behavioral symptoms were seen with the use of trazodone, low-dose atypical antipsychotics, and selective serotonin/norepinephrine reuptake inhibitors including fluoxetine, fluvoxamine, sertraline, and paroxetine. However, memantine and paroxetine were associated with negative results in other studies reviewed. Case reports indicated that clomipramine may be effective in reducing compulsive behaviors and topiramate may be useful in abnormal eating behavior associated with FTD. In general, cholinesterase inhibitors showed either negative effects or were ineffective in treating bvFTD.

Conclusions: There has been limited progress in targeted pharmacotherapy for bvFTD over the past several decades. Current literature is primarily comprised of small scale clinical trials and case reports, which show mixed results relating to treatment efficacy. There is a clear need for managing symptoms associated with bvFTD, which supports the need for further research using existing medications and novel drug development.

082. Association Between Global Cortical Atrophy and Magnetoencephalography (MEG) Resting-State Alpha and Beta Peak Frequencies
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Introduction: Decreased alpha and beta peak frequencies (PF) have previously been found in individuals with mild cognitive impairment (MCI) [1] and Alzheimer’s disease (AD) [2] compared to controls and to be associated with hippocampal atrophy [1]. This study aims to investigate the association between global cortical atrophy and MEG resting-state alpha or beta PF in cortical regions that show early AD neuropathology.
Methods: Eleven cognitively impaired adults (mean: 68.1 years, 45% female) and 11 age-and-sex-matched controls (mean: 67.8 years, 27% female) were included in this analysis. All subjects completed a 6-minute resting-state MEG scan and T1w structural brain MRI. MEG data underwent standard preprocessing (Signal-Space Separation, 0.5-150Hz band pass filtering, and artifact rejection using Independent Component Analysis). Artifact-free data was source localized using a beamforming approach and normalized using 3-minutes of empty-room data acquired the same day. Brain activity was filtered into canonical frequency bands: alpha (8-12 Hz) and beta (15-29 Hz). PF were computed for 12 regions: left and right angular gyri, anterior cingula, hippocampi, parahippocampal gyri, posterior cingula, and precuneus. Global cortical brain volumes normalized by intracranial volume were computed for the structural MRI data using FreeSurfer 6.0. Generalized linear regression modeling was performed for each region with an interaction term of cognitive status and global cortical volumes (GCV) normalized by intracranial volumes. Regional alpha or beta PF was the outcome and age centered at 65 years and sex were covariates.

Results: Normalized GCV was associated with regional beta PF in cognitively normal individuals in the left hippocampus ($\beta=1.3275$, $p=0.0024$) and left parahippocampal gyrus ($\beta=1.0361$, $p=0.0418$). The interaction term of cognitive status and normalized GCV was significant in the left hippocampus ($\beta=1.5510$, $p=0.0018$), right hippocampus ($\beta=1.3396$, $p=0.0212$), and left parahippocampal gyrus ($\beta=1.2797$, $p=0.0262$). Normalized GCV was not associated with regional alpha PF in either cognitive group.

Conclusions: Decreased regional beta PF in the left hippocampus and parahippocampal gyrus was associated with global cortical atrophy in cognitively normal individuals. There was heterogeneity of cognitively impaired diagnoses, MCI-possible n=4, MCI-probable n=4, dementia n=3, which contributed to variability within the group. Additional data will be needed to elucidate the association between regional beta PF and global cortical atrophy in the cognitively impaired and to determine whether that association differs amongst subjects with MCI and dementia.


083. Annexin A6 in Alzheimer’s Disease
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BACE1 is the β-secretase enzyme that initiates Aβ production and is a prime therapeutic target for Alzheimer’s disease (AD). Drugs that inhibit BACE1 enzyme activity are in clinical trials for AD, but early termination of a recent trial raises concerns regarding safety and efficacy of these agents. Animal studies suggest that BACE1 inhibition may cause multiple neurological side effects. Thus, it is crucial to develop alternative therapeutic strategies that reduce BACE1 cleavage of APP without impairing essential BACE1 functions. We have shown that global BACE1 protein levels are markedly elevated in APP transgenic mouse and AD brains. Elevated BACE1 is concentrated within dystrophic axons surrounding amyloid plaques and is associated with increased generation of BACE1-cleaved APP fragments and Aβ42. Our preliminary results show that Aβ elevates resting [$Ca^{2+}$]i in primary neurons, and peri-plaque dystrophic axons in 5XFAD mice also show elevated resting [$Ca^{2+}$]i and disrupted microtubules. We hypothesize a feed-forward mechanism in which plaque-associated Aβ causes axonal dystrophy, BACE1 accumulation, and accelerated Aβ generation that drives amyloid progression. Our goal is to understand the mechanisms of dystrophy formation and target these pathways as a potential therapeutic approach. Aβ interaction with membrane can result in disruption of the phospholipid bilayer, allowing calcium leak and potentially cell death. Cells have developed membrane resealing mechanisms to recover from plasma membrane damage and augmenting these pathways can have therapeutic benefit in muscular dystrophy models. Extrapolating from this, we hypothesize that membrane resealing mechanisms play a role in dystrophic neurite formation around plaques, and enhancement of resealing may be protective against amyloid pathology. Here we show that Annexin A6, a key player in membrane resealing in muscle is expressed in neurons in the murine brain and accumulates in a subset of dystrophic neurites of 5XFAD mice. In vitro, endogenous A6 accumulates at sites of membrane disruption in primary neurons, and exogenously added A6 also accumulates at injury sites. Preliminary data suggests that overexpressing A6 in neurons of 5XFAD mice reduces Aβ measured by dot blot. We are also measuring the effects of A6 dominant negative on resealing in vitro and in vivo, and on amyloid and dystrophic neurite pathology in 5XFAD brain.

084. Facilitating Early Detection of Creutzfeldt-Jakob Disease Mimics in Clinical Practice
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Background: The advent of real-time quaking-induced conversion (RT-QuIC) assays capable of detecting prions in CSF has greatly improved the antemortem diagnosis of Creutzfeldt-Jakob disease (CJD). Yet, despite the acronym, RT-QuIC testing cannot be performed quickly, with a turnaround time of approximately 14 days. There is a need to leverage clinical features and the results of readily available tests to distinguish patients with CJD from those with other causes (‘CJD mimics’), including patients with potentially treatment-responsive causes of rapidly progressive dementia (RPD).

Methods: Patients with definite (pathology-confirmed) or probable CJD with positive RT-QuIC were identified...
through retrospective review of Mayo Clinic Enterprise (n=79) and Washington University in St. Louis records (n=10; Jan-2014 to Oct-2020). “CJD Mimics” were identified through review of records from patients enrolled within longitudinal studies of RPD at study sites (n=135); mimics met clinical criteria for probable CJD but did not have CJD.

Results: CJD mimics comprised 10/155 (6.5%) of patients enrolled with RPD at study sites. Mimics were diagnosed with autoimmune encephalitis (n=7), neurosarcoidosis, frontal temporal lobar degeneration with motor neuron disease, and unknown dementia. Age-at-symptom onset (median 65.6 [21.9-81.5] vs 63.7 [44.6-76.4] years; p=0.14), gender distribution (44% vs 50% females; p>0.99) and symptoms/signs were similar between groups. Motor signs (i.e., faciobrachial dystonic seizures, myoclonus, dyskinesias, parkinsonism) were more common in mimics (49/93 vs. 10/10; p=0.01). On readily available tests, electroencephalogram abnormalities and MRI findings typically ascribed to CJD (73/93 vs 8/10; p=0.99) were reported in similar proportions of CJD cases and mimics. Elevations in CSF leukocytes (>5 cells/hpf: 4/92 vs 5/10) and protein >45 mg/dL (39/92 vs 9/10) were more common in mimics (p<0.01). Neural-specific autoantibodies associated with autoimmune encephalitis were detected within the serum (4/9) and CSF (5/10) of mimics, but not CJD cases (CSF, 0/78; serum 0/71). Low-titer of other autoantibodies (e.g., GAD-65) were detected within the serum of 9 CJD patients (12.6%).

Conclusions: Autoimmune encephalitis, neurosarcoidosis and select neurodegenerative diseases may mimic CJD at presentation. CJD mimics should be considered in patients with early motor dysfunction and abnormal routine CSF studies, providing an opportunity for early treatment.

085. Efficacy of Transcranial Alternating Current Stimulation (tACS) in the Enhancement of Working Memory Performance in Healthy Adults: An Exploratory Meta-Analysis
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Introduction: Working memory is a short-term memory process that allows for information to be maintained, manipulated, or reorganized when it is no longer present in the environment. This cognitive process is fundamental to general cognition and is known to decline with advanced age in healthy individuals. Noninvasive brain stimulation techniques, such as transcranial alternating current stimulation (tACS), which is capable of altering cortical oscillations in the brain via entrainment, has shown promise in improving working memory performance (e.g., accuracy or reaction time) in healthy individuals. However, the overall efficacy of tACS in the enhancement of working memory behavior is not well understood.

Aim and Hypothesis: The aim of this meta-analysis is to systematically evaluate the efficacy of tACS in the enhancement of working memory behavior in healthy adults. Sub-analyses explore the magnitude of tACS effects and examine potential moderators that may influence stimulation outcomes (e.g., cognitive load, stimulation parameters, demographics). We hypothesized that active tACS during working memory task performance would result in significantly enhanced behavioral outcomes over sham stimulation.

Methods: A systematic computerized database search identified eight tACS studies that met inclusion criteria, and provided 25 effects in the overall analysis. Standard mean differences (SMDs) for change in behavioral performance from baseline to post-stimulation on working memory tasks were evaluated.

Results: Random effect models revealed a significant, heterogeneous, and moderate effect for active tACS in the enhancement of working memory performance in healthy adults over sham (Cohen’s d=0.553; CI=0.353-0.753; p=0.0001). Findings from this meta-analysis demonstrate that cognitive load is important for state-dependent effects from brain stimulation, an effect found to be largely driven by more challenging tasks (i.e., 2-Back version of the N-Back task over 1-Back) (Cohen’s d=1.71; CI=0.822-2.59). Moreover, we found a significant, heterogeneous effect of stimulation region that was largely driven by parietal lobe stimulation (Cohen’s d= 0.788; CI=0.015-0.550).

Conclusions: Collectively, these data support the efficacy of tACS in the improvement of working memory abilities in healthy adults. Randomized controlled trials are needed to determine the maintenance (short-term versus long-term) of tACS behavioral gains in working memory abilities in healthy adults. Moreover, future research is needed to optimize tACS parameters to enable the greatest gains for working memory enhancement in healthy aging and patient populations that experience deficits in working memory abilities.

086. Lysosomal Activation by Farnesyltransferase Inhibitors Decreases Amyloid Pathology in 5XFAD Mice
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A persistent accumulation of aggregated proteins characterizes age-related neurodegenerative disorders. Increasing evidence suggests that impaired cellular clearance of pathological proteins leads to aggregation over time. The lysosomal system is a major pathway of cellular clearance, and aging, mutations, or misfolded proteins cause lysosome function to decline. Thus, therapies restoring lysosome function may be effective for various neurodegenerative disorders. Recent studies have identified small-molecule farnesyltransferase inhibitors (FTIs), previously tested as potential cancer therapies, as lysosome activators. We previously showed that Parkinson’s disease α-synuclein perturbs the physiological response to lysosomal stress by impeding the SNARE protein ykt6. Activating ykt6 by a small-molecule FTI LNK-754 restored lysosomal activity and reduced α-synuclein in patient-derived neurons and mice1. Another recent study found that the FTI lonafarnib reduced pathogenic tau inclusions and microgliosis in rTg4510 mice by activating lysosomes2. Here, we evaluate amyloid pathology in 5XFAD mice treated with LNK-754 or...
lonafarnib for three months. Immunofluorescence microscopy showed that FTIs reduced plaque number and size in 5XFAD mice. Aβ42 levels were measured by ELISA and were significantly decreased in FTI-5XFAD mice. Total tau and pathogenic tau protein levels were also reduced significantly in 5XFAD mice treated with LNK-754 or lonafarnib. As expected, FTI-treatment increased lysosomal activity and LAMP1 levels in 5XFAD mice. However, LAMP1 and BACE1 accumulation in dystrophic neurites surrounding plaques was decreased, suggesting an effect of FTIs on axonal lysosome trafficking. We next investigated the impact of FTIs on axonal lysosome trafficking in mouse primary forebrain neurons by performing live-cell imaging. We observed a significant increase in retrograde lysosomal transport in FTI-treated neurons compared to vehicle-treated controls. Velocity and distance traveled of lysosomes were also significantly increased by FTI treatment. Finally, we analyzed microglia and astrocyte activation in FTI-5XFAD mice and FTI-treated primary forebrain neurons. LNK-754, but not lonafarnib, caused a dramatic proliferation of microglia both in vivo and in vitro. Our findings suggest that FTI treatment could provide a potential therapeutic for Alzheimer’s disease by reducing dystrophic neurite formation. BACE1 levels, and Aβ accumulation. 1. Cuddy et al. Stress-Induced Cellular Clearance Is Mediated by the SNARE Protein ykt6 and Disrupted by α-Synuclein. Neuron. 2019 2. Hernandez et al. A farnesyltransferase inhibitor activates lysosomes and reduces tau pathology in mice with tauopathy. Science Translational Medicine. 2019

087. Attenuation of ERK Signaling by Brain Permeant MEK Inhibitor Suppresses Microglia-Mediated Neuroinflammation in a Sex-Dependent Manner

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Background: Activation of the mitogen-activated protein kinase (MAPK) pathway called extracellular signal-regulated kinase (ERK), represents a central patho-mechanism of Alzheimer’s disease (AD). We recently found that activated microglia in AD mouse models are characterized by ERK hyper-activation, and ERK inhibition in-vitro inhibits pro-inflammatory and neurodegeneration-associated microglial responses. If effective in in-vitro models, existing FDA-approved drugs (eg. MEK inhibitors) could be re-purposed for neuroinflammatory and neurodegenerative disorders.

Objectives: To assess the ability of small molecule MEK inhibitor selumetinib to (1) engage the ERK pathway in the brain, and (2) suppress microglia-mediated neuroinflammatory and neurodegeneration-associated responses in an in-vitro model.

Methods: Selumetinib (50mg/kg IP x 1 dose) was administered to C57BL/6J mice and brain was collected 1h and 6h after administration. Phospho-proteins from the MAPK pathway were measured by multiplexed ELISA. We then used the systemic lipopolysaccharide (LPS)-induced neuroinflammation model (LPS 75mg/kg x 4 daily IP doses) that partly recapitulates pro-inflammatory and neurodegeneration-associated microglial responses seen in AD pathology, to test the efficacy of systemic selumetinib (Veh, Veh+Sel, LPS, LPS +Sel, 3M+3F/group, age 6-7 mo). For in-vivo studies, brain cytokine levels and microglial transcriptomic profiling (Nanostring) were used as endpoints. CD11b+ MACS-purified microglia were used for transcriptomic studies.

Results: A single dose of IP selumetinib attenuated brain phospho-ERK levels by 50% at 6h but not at 1h confirming target engagement. LPS increased inflammatory cytokines (e.g., TNF-α, IL-6, G-CSF, Eotaxin, and MCP-1) in female mice and this was partly attenuated by selumetinib. LPS induced pro-inflammatory (Lcn2, Cda72, C4a, Iftim3, Ihi30) and neurodegeneration-associated (ApoE, Tyrobp, Gm1, Axl, Clec7a) gene expression in microglia isolated from both males and females, although selumetinib treatment impacted LPS-induced changes only in females (n=163 differentially-expressed genes in females vs. 3 in males). Selumetinib most strongly suppressed LPS-mediated upregulation of Cda72, Ptpcr, AD-related genes Cotl1, Msn, Tlr2, Axl, Tyrobp in females only.

Conclusions: We provide in-vivo evidence for the ability of systemically administered MEK inhibitor selumetinib to achieve target engagement in the brain, and suppress microglia-mediated neuroinflammation. We also identified novel sex-based differences in ERK-dependent mechanisms of neuroinflammation. Ongoing studies will determine the ability of selumetinib to modify neuropathology and identify biofluid biomarkers of ERK suppression in AD mouse models.

088. Criminal Act Leading to a Diagnosis of Alzheimer Disease

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Objective: To report a case with a criminal act leading to the diagnosis of Alzheimer Disease.

Background: New onset socially unacceptable behaviors, delinquency and criminality in the elderly can be the sign of an underlying neurodegenerative process. Behavioral changes and judgement impairment can initially be subtle and missed by family members of the patient with cognitive impairment.

Methods: Case report and literature review.

Results: 71-year-old man with controlled hypertension, family history of unspecified dementia, initially seen in 2017 for recent word-finding difficulties and memory complaint. He had no behavioral issues, was independent in all ADLs/ IADLs though he was described as docile by family members. Neuropsychological testing was significant for mild deficit in verbal memory and attention, but not substantial enough to support a formal diagnosis. He subsequently missed his next appointments. A traffic incident in 2018 reported later by his
wife raise concern for ongoing cognitive decline. In 2019, during a family altercation, he grabbed a gun and accidentally killed his daughter, which led to his incarceration. A repeat neuropsychological assessment in 2020 showed significant progression with amnestic profile and language deficit coherent with Alzheimer disease. Judgement was also impaired. Brain computed tomography (CT) showed diffuse atrophy, non-specific microvascular changes and one lacune in the left caudate nucleus. PET scan showed decreased uptake in the bi-temporoparietal lobes. In January 2021, he scored 19/30 on the Montreal Cognitive Assessment (MoCA) test, and was formally diagnosed with Alzheimer Dementia.

**Discussion:** Neurodegenerative diseases can affect personality, judgement, emotional processing and control of behaviors, executive functions and social cognition. Frontal and anterior temporal lobes structures are key in these processes. Behavioral dysfunctions may lead to early socially unacceptable behaviors. Though more frequent in the behavioral variant of frontotemporal dementia (bvFTD) (50% of cases), primary progressive aphasia (PPA) semantic type or Lewy body dementia (LBD), it can still be present in at least 10% of patient with Alzheimer’s disease. Men are classically more affected than women. Depression can be one of the first sign of an underlying neurodegenerative process. A high degree of suspicion is required to identify subtle behavioral symptoms.

**Conclusion:** New onset delinquency and criminality in the elderly should raise concern for an underlying neurodegenerative process. Early detection and appropriate management is key.

**009. TardbpGene with a Mutation with Spastic Speech Disorder**

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Motor neuron disease is an adult-onset neurodegenerative disease that occurs due to the degeneration of motor neurons located selectively in the motor cortex, brainstem and spinal cord. While 5-10% of the cases are familial, most cases are sporadic cases without a family history. 1-3% of motor neuron patients come across as primary lateral sclerosis. Primary lateral sclerosis proceeds with progressive upper motor neuron involvement without lower motor neuron involvement. An eighty-year-old female patient is presented. Her speaking difficulty has been starting at the age of 76. Her speech gradually had become worse for four years. She has begun crying or laughing, although there is not any emotional situation. The tremor of her left hand has occurred while resting for two years. Her speech was anarthria; comprehension, writing, and reading comprehension are preserved, there is no praxis defect. The tongue is atrophic and spastic; fasciculation is not detected. Her left upper extremity finger abduction and adduction were 4/5 MRC, it is intentional and rest tremor with low amplitude on the left hand, in additionally there is left wrist rigidity. There is also bradykinesia, increased glabellar reflex, snout reflex is present, jaw reflex is detected, bilateral Hoffmann reflex is present, deep tendon reflexes are globally increased, Babinski reflex is present bilaterally. As a result of DNA sequence analysis performed in terms of neurodegenerative diseases on progressive spastic dysarthria and finally anarthria, first motor neuron involvement, and parkinsonism, the clinical significance of the TARDBP gene in the 6th exon (Variant of Unknown Significance; VUS) is a heterozygous c.800 A> G change (N267S); VUS, heterozygous c.803G> C change in exon 3 of the POLG gene and; VUS, heterozygous c.1301G> A change in exon 14 of the AAAS gene. The patient is diagnosed with primary lateral sclerosis and asymmetric tremor dominant parkinsonism, which may be related to sporadic TARDBP gene mutation. The first case presents primary lateral sclerosis and asymmetric tremor dominance parkinsonism due to TARDBP mutation in our country.

**090. Innate Immune cGAS/STING Pathway Dysregulation in a Murine Model of Midlife Obesity and Prediabetes May Contribute to Cognitive Decline**

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Obesity, prediabetes, the metabolic syndrome, and diabetes are growing in prevalence around the world. These conditions also predispose patients to the development of neurological complications, including cognitive decline. This is especially true for patients with midlife obesity and diabetes. A potential shared mechanism that may be responsible for this increased risk is chronic inflammation. One innate inflammatory pathway that has received recent attention is the intracellular double stranded DNA sensing cGAS/STING pathway. Therefore, we performed a pilot study using our non-transgenic murine model of obesity and prediabetes, which develops insulin resistance and nervous system complications, to investigate the potential role of cGAS/STING in midlife obesity and prediabetes-mediated cognitive decline. At 1 yr of age, male C57/BL6 mice were started on either standard diet (SD; n=10) or a 60% high fat diet (HFD; n=10) composed primarily of lard. Animals were fed their respective diets for 12 weeks, at which time they were assessed for cognitive changes using social recognition testing. After 13 weeks on diet, metabolic phenotyping was performed with glucose tolerance testing and general inflammatory phenotype was carried out via ELISA. Hippocampi were isolated and assessed by western blotting for cGAS/STING pathway protein expression. As expected, animals fed HFD had impaired glucose tolerance compared to SD controls. Additionally, they had increased circulating levels of the cytokine tumor necrosis factor alpha and the chemokine monocyte chemoattractant protein-1, indicating a pro-inflammatory phenotype. When looking at central nervous system specific hippocampal changes, STING protein expression was lower in HFD animals compared their SD.
counterparts. Interestingly, HFD mice also had deficits in short and long term memory. Taken together, these data indicate that HFD-induced obesity and prediabetes in mice promote cognitive decline and that this may be, at least in part, due to changes in inflammatory profiles and specifically regulation of the cGAS/STING pathway. However, more studies are warranted to fully understand these potential links and to understand underlying mechanisms of cGAS/STING involvement in obesity, prediabetes, and cognitive decline.

091. The Association of New Onset Seizures with the Risk of Incident Dementia Among Stroke Patients
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Introduction: Post-stroke dementia (PSD) is a dementia syndrome that affects one in three stroke survivors. The impact of new onset seizures in young stroke survivors on subsequent development of dementia is poorly understood.

Methods: The IBM Watson Health MarketScan® Commercial Claims and Encounters database, for the years 2006 through 2014 served as the data source for this study. Using the International Classification of Diseases, Ninth Revision (ICD-9), we identified patients aged 18-60 years with ischemic strokes (433.x1, 434.x1, and 436) and hemorrhagic strokes (430, 431, 432.0, 432.1, and 432.9) between January 1, 2006, and December 31, 2009, which constituted our baseline study cohort. At baseline, all included participants were free of claim for dementia, brain tumors, toxin exposure, traumatic brain injury, and neuro-infectious diseases, identified using ICD-9 codes. Additionally, they had at least 1-year continuous enrollment before the index stroke diagnosis and 5 years after, and no seizure within 1 year after the index date. The exposure of interest seizures: a time-window 1-year before the index stroke diagnosis and 5 years after, and no seizure within 1 year after the index date. The exposure of interest seizures: a time-dependent variable. The study outcome of interest was dementia (ICD-9: 290.0, 290.10-13, 290.20-21, 290.3, 290.40-43, 291.2, 292.82, 294.10-11, 294.20-21, 294.8, 331.0, 331.11, 331.19, and 331.82), which occurred during the follow-up period from January 1, 2010, to December 31, 2014. A Cox proportional hazards regression model was applied to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the independent association of seizures with the occurrence of dementia, adjusting for potential confounders such as demographics and major chronic diseases.

Results: At the end of the baseline period, a total of 23,680 stroke patients were identified, including 20,642 and 3,038 with ischemic and hemorrhagic strokes, respectively. The cumulative incidence of seizure was 6.7%, 6.4%, and 8.3% for all strokes, ischemic strokes, and hemorrhagic strokes, respectively. The cumulative incidence of dementia was 1.3%, 1.4%, and 0.9% for all strokes, ischemic strokes, and hemorrhagic strokes, respectively. After multivariable adjustment, young patients with stroke who developed seizures had greater risk of dementia compared with those without seizures (All strokes adjusted HR: 2.53, 95%CI 1.83-3.48), Ischemic strokes: 2.52, 1.79-3.53). Borderline significant association was found for Hemorrhagic strokes (2.66, 0.99-7.12).

Conclusion: These findings suggest that the onset of seizures in young stroke survivors is associated with a 2.53-fold risk of developing dementia. Whether systematically screening and treating stroke survivors for seizures can reduce the onset of dementia remains to be validated.

092. A Case of Frontal Temporal Dementia with Pathogenic Variant in LRRK2 Gene
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Background: A genetic etiology of frontal temporal lobar degeneration (FTLD) is common in those with a positive family history of dementia. We report a case of FTLD with strong family history of early dementia and learning disability, found to have a pathogenic variant in Leucine-rich repeat kinase 2 (LRRK2) gene. The LRRK2 gene mutation is a common cause of inherited Parkinson’s disease, however recent neuropathological studies suggest it may play a role in non-Lewy body neuropathological changes, with varying clinical phenotypes including dementia, dystonia and amyotrophy.

Methods: Case report

Results: Over 5 years a 60-year-old bilingual left-handed male developed deficits in language function and short-term memory impairing his ability to work as a Spanish translator. His wife noted confabulation, depression and nightmares. Family history was striking for multiple members with complex neurocognitive phenotype of early dementia, intellectual disability, and dysmorphism in an apparently autosomal dominant manner. Examination was notable for stuttering speech and mild amplitude postural and kinetic tremor, worse on the left. Kokmen short test of mental status was 23/38. Neuropsychological testing showed impaired word reading, phonemic fluency, and semantic fluency consistent with greater dominant hemisphere dysfunction, overall concerning for semantic variant frontotemporal lobar degeneration. MR brain revealed scattered foci of white matter T2 hyperintensity, without focal atrophy, but FDG-PET showed hypometabolism of the right greater than left prefrontal cortex. Genetic evaluation was negative for pathogenic variants in C9ORF72, MAPT, and progranulin. Chromosomal micro-array suggested mild consanguinity. Whole exome sequencing revealed a pathogenic variant in LRRK2 (p.Gly2019Ser: c.6055 G>A in exon 41).

Conclusion: This is a unique case of frontal temporal lobar degeneration in a patient with strong family history of dementia and intellectual disability, without features of parkinsonism. This finding supports growing evidence for genetic pleiotropy in neurodegeneration.
093. Ambiguity with the Diagnosis of Vascular Dementia in Clinical Practice
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Background: Vascular dementia (VaD) includes a wide spectrum of clinical phenotypes ranging from vascular cognitive impairment to dementia. It is typically defined as a step-like pattern of decline in memory with each vascular insult. It is a type of subcortical dementia with modifiable risk factors and therefore requires critical thinking. Due to its overlapping features and co-existence with Alzheimer’s disease (AD) and it is commonly mislabeled. However, it is imperative to distinguish the two as the pathophysiology is different and so is the management. Currently, there exist neuroimaging modalities such as MRI (Magnetic Resonance Imaging) brain, PET (positron emission tomography) scan, and DTI (Diffusion Tensor Imaging) which can help distinguish VaD from AD.

Methods: We ran a search for “vascular dementia” on our electronic medical record clinic database that is used in our university. A retrospectively chart review of these patients was performed and the data was collected in a Microsoft Excel sheet.

Results: A total of 39 clinical charts were reviewed. The age range of the reviewed patients was 62-100 years with 18 males and 21 females. Sixteen patients were seen and evaluated by a neurologist in an outpatient setting while the remaining were managed by geriatric/primary care physicians. Seventeen patients (~44%) carried a diagnosis of AD as well. About 5 patients had MMSE (mini-mental status examination) score and formal neuropsychological testing during a clinic visit at some point. Of the 39 patients, nine had moderate to severe microvascular ischemic changes or evidence of prior ischemic infarct on MRI brain, 6 had mild microvascular ischemic changes with cortical atrophy and 24 patients did not have MRI brain. None of the patients had PET or DTI scan done.

Conclusions: VaD often co-exists with AD; however, misdiagnosis of VaD is a common occurrence in clinical practice. Despite the advancement of neuroimaging techniques and neuropsychological testing, patients with possible vascular dementia do not undergo a thorough workup and are often mislabeled.

094. Uncovering Aggregate Trends in Alzheimer Disease Through Meta-Analysis and Feature Selection of Pre-Clinical APOE Literature
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Background: It has been difficult to develop broadly effective treatments for Alzheimer’s Disease since heterogeneous results in the literature suggest that a complicated relationship exists between age, APOE genotype, gender, treatment, and cognition. The present meta-analysis leveraged statistical and machine learning methodologies to gain insight into the extent that cognition in mice is affected by these various features, as measured by escape latency from the Morris Water Maze.

Methods: PubMed was queried using the key search terms “Alzheimer’s Disease”, “APOE”, and “Morris Water Maze”. A total of 32 peer-reviewed papers met all of the requirements for inclusion, where quantifiable experimental data examining APOE knockin (KI), APOE knockout (KO) and wild type (WT) mice were used to curate a database with 98.8% transcription accuracy. After null value removal, 1,251 data points were used in analysis. T-tests between genotypic mouse groups were performed at an alpha level of 0.05 with pairwise Boneferroni correction for multiple comparison. To further examine the effect of treatment, the mean age of treated and untreated groups was equalized before performing a t-test at an alpha level of 0.05. Lastly, a supervised random forest model was produced in Python to predict the importance of each feature on MWM escape latency.

Results: Results indicate a significant 11.5% difference in escape latency between WT and ApoE KO (t-test, p<0.001), a significant 8.7% difference between WT and ApoE KI (t-test, p<0.01), and an insignificant 2.8% difference between ApoE KO and ApoE KI (t-test, p=0.5). A significant 10.5% difference was observed between treated versus untreated groups after correcting for mean age (t-test, p<0.01), with an effect size of 1.98. Random forest model results show the following feature importance: [Day of MWM Testing, Age, Treatment, Wild Type, Male Gender, Female Gender, KO Type, KI Type, Mixed Gender, and Unknown Gender] = [0.34, 0.32, 0.11, 0.06, 0.05, 0.04, 0.03, 0.02, 0.02, 0.01].

Conclusion: Meta-analysis results illustrate the mixed protective and destructive effects of APOE. Collective aggregate study results demonstrate that APOE modifying treatment(s) and age are the most important factors in predicting cognition, whereas gender and genotype appear to be less impactful in predicting cognition in the AD mouse model. The normalized 10.5% treatment effect supports further study and development of clinical modulators of protective subtypes of APOE.

095. Utilizing Literature-Based Discovery Methods to Assess Alzheimer Disease Comorbidities and Risk Factors Relating to Metabolism
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Introduction: Multiple studies have identified relationships between Alzheimer’s Disease (AD) and metabolic system disturbances. It is hypothesized that antecedent or comorbid conditions impacting metabolism could alter future risk of Alzheimer’s disease. Recent systems biology analysis has particularly implicated hypothyroidism as a condition of interest. The goal of the present study was to utilize literature-based discovery (LBD) tools to establish connections between AD and metabolism-adjacent areas of interest by text mining nearly 30 million PubMed abstracts.

Methods: SemNet, a custom software that utilizes machine learning algorithms for text mining and ranking
functionality for LBD, was used to query a modified version of the National Library of Medicine’sSemMedDB to find source nodes (SNs) relating AD and hypothyroidism. This query resulted in a list of 607 nodes that relate to both AD and hypothyroidism, where each was grouped by Unified Medical Language System (UMLS) semantic types and ranked by importance based on an adjusted HeteSim unsupervised feature ranking metric. A custom 3-dimensional interactive visualizer was constructed to further evaluate identified text relationships within the network. In this study, seven UMLS node types were used, including pharmacologic substance and disease or syndrome. A sub-list was compiled for each semantic group, where the top 5 SNs were manually reviewed in an extensive literature context survey aided by SemNet.

Results: Of the 35 selected and filtered source nodes, dexamethasone, (node type = pharmacologic substance), propranolol (node type = organic chemical), and type 2 diabetes (node type = disease or syndrome) had particularly highly ranked interactions involving AD and hypothyroidism. All three of these SNs either attenuate or degrade aspects of AD while also having a measurable effect on the thyroid. A node neighborhood was used to visualize and overlay these and numerous other interactions between AD and hypothyroidism. Thirty-five nodes connecting AD and hypothyroidism were prioritized for further assessment.

Conclusion: The concepts connecting AD and hypothyroidism, as well the 35 filtered SNs, consistently correlate to shared metabolic networks. Literature findings, aided by SemNet and other LBD tools, have shown strong connections between AD and metabolic systems. Altered metabolism has also been cited in recent large-scale clinical Alzheimer’s patients proteomic studies. Further examination of specific identified metabolic connections between Alzheimer’s Disease and antecedent conditions impacting metabolism are warranted.

096. Clinical Correlation of GAD7 to Tau PET-Imaging
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Background: Anxiety symptoms are a risk factor for developing Alzheimer’s dementia (AD) in patients with MCI. General Anxiety Disorder-7 (GAD-7) scale is typically given to determine symptomatology severity. In addition, brain tau positron emission tomography (PET) imaging is sensitive to diagnose AD. Currently, there is a lack of insight on the association between tau-PET status and GAD7 scores.

Objective: Assess the relationship between GAD-7 scores and tau-PET status, which could influence AD diagnosis and treatment.

Methods: A retrospective cohort study was conducted. Patients attending a Boston neuropsychiatry clinic from 2016 to 2021 with GAD-7 test scores and tau-PET scans were included. We studied the association between GAD-7 scores and tau-PET scan binary results with Spearman correlation as data were not normally distributed. Additionally, covariates (age, sex, and race) were evaluated by a multivariate regression model.

Results: Sample (N=964) expressed a mean age of 70.1 years (SD= 14.36), with 88.34% white and 58.61% female. Thirty-three patients fulfilled the study criteria with available PET scan results. Spearman correlation between Tau-PET scan and GAD7 score had a rho of 0.126 and a p-value= 0.51. Multivariate analysis confirmed the lack of association of GAD7 to Tau PET.

Conclusion: Tau-PET scan results did not correlate with GAD-7 scores, a frequently used as a clinical measure to determine anxiety severity.


097. Heterogeneity of Rate of Cognitive Decline in Alzheimer’s Disease is Associated with the APOE Genotype
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Objective: Whether the APOEe2 and e4 alleles impact the clinical progression of Alzheimer’s disease (AD) is critical for clinical trial design, yet remains controversial. Here we tested the hypothesis that, compared to APOEε3, the APOEε2 and e4 alleles differentially impact AD cognitive trajectory, and that these effects are independent of APOE allele effects on neuropathology.

Methods: We applied novel reverse-time longitudinal modeling with latent class shared with survival model, 3-year change point, and right truncation adjustments on a convenience sample of 1,102 subjects from the National Alzheimer’s Coordinating Center Neuropathology dataset from September 2005 to November 2018. Subjects selected had sufficient AD neuropathological changes at autopsy to warrant eligibility for current biomarker-based therapeutic AD clinical trials (CERAD neuritic plaque score moderate or frequent and Braak neurofibrillary tangle stage III or above), age of death 50+ years, and last clinical evaluation within 2 years of autopsy. Exclusion criteria were: primary neuropathological diagnosis other than AD neuropathological changes; cognitive impairment due to medical illness, medications, or alcohol; and APOE genotype not available or ε2/ε4. The cognitive trajectories of APOEε2 and APOEε4 carriers were compared with APOEε3 homozygotes as reference group and CDR-SOB and MMSE scores as outcome measures.

Results: We found a statistically significant difference in rate of cognitive decline across APOE genotypes. APOEε4 carriers exhibited ≈1.5 times faster CDR-SOB increase than APOEε3 homozygotes (2.12 versus 1.44 points/year), and...
098. The Impact of Mild Cognitive Impairment on the Neural Dynamics Serving Verbal Working Memory: A Magnetoencephalography Study

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Background: In healthy adults, neural oscillatory activity within a predominantly left-lateralized network of brain regions underlies verbal working memory (VWM) performance (Proskovec, Human Brain Mapping, 2016), but how mild cognitive impairment (MCI) impacts these oscillatory dynamics is not well characterized. The present study utilized the spatiotemporal precision of high-density magnetoencephalographic (MEG) brain imaging to investigate the effects of MCI on the neural oscillations serving specific phases (i.e., encoding, maintenance) of VWM. In congruence with the compensation-related utilization of neural circuits hypothesis (CRUNCH; Grady, Nature Reviews Neuroscience, 2012), we hypothesized that MCI patients would recruit greater neural resources during VWM.

Methods: Fifty-five adults (11 clinically-diagnosed MCI, 44 controls; 26 females; M age: 63.4, age range: 38-81) completed a Sternberg-type VWM task during MEG. First, an empty 2x3 grid was presented (1.4 ± 0.1 s). Next, six letters were displayed within the grid for 2.0 s (encoding). Subsequently, the letters disappeared from the grid for 3.0 s (maintenance). Finally, one test letter appeared for 0.9 s (retrieval). Participants were instructed to respond via button press as to whether or not the test letter was in the previous encoding set. Only correct trials were analyzed, and the average number of trials included did not differ between groups. All MEG data underwent standard preprocessing, were transformed into the time-frequency domain, and significant neural oscillatory responses relative to baseline were imaged using a beamformer. To determine the effect of group (MCI vs. controls), ANCOVAs were performed on the resulting encoding and maintenance whole-brain maps with age as a covariate.

Results: Throughout encoding and maintenance, decreases in alpha/beta (9-16 Hz) oscillatory activity were seen in left fronto-temporal regions, which were significantly larger in MCI patients during the encoding phase (p < .05, corrected). Additionally, significant group differences were detected in right inferior frontal and superior temporal cortices throughout both encoding and maintenance, such that MCI patients exhibited decreased alpha/beta activity within these regions, while these responses were absent in controls (p < .01, corrected). As expected, MCI patients performed worse on the VWM task (p < .05).

Conclusions: While both groups recruited a similar left-hemispheric cortical network during VWM encoding and maintenance, individuals with MCI recruited some nodes more strongly and additionally recruited right fronto-temporal regions. Our results offer supporting evidence for CRUNCH.

363. Peripheral Inflammation and Depressed Mood Independently Predict Neurocognitive Worsening Over 12 Years

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Background: Neurocognitive (NC) impairment in people with HIV (PWH) is associated with important adverse outcomes, but no markers exist to predict long-term NC decline. We evaluated depressed mood and markers of persistent inflammation, oxidative stress and altered amyloid processing (all common in PWH) as predictors of NC worsening over 12 years.

Methods: PWH were enrolled and followed longitudinally in the CNS HIV Antiretroviral Effects Research (CHARTER) study at six US sites. We quantified biomarkers
of inflammation in blood at entry: (interleukin-6 [IL-6], C-reactive protein [CRP], monocyte chemotactic protein type 1 [MCP-1], D-dimer, soluble sCD14 (sCD14), soluble tumor necrosis factor receptor - type II [sTNFR-II], neopterin, and soluble CD40 ligand [sCD40L]), oxidative stress (protein carbonyls, 8-oxo-2′-deoxyguanosine [8-oxo-dG]) and altered amyloid processing [amyloid beta (Ab)-42, soluble amyloid precursor protein-alpha (sAPPα)] using commercial immunoassays. The Beck Depression Inventory-II (BDI-II) assessed depressed mood at entry. NC decline over 12 years was evaluated using the summary (global) regression-based change score (sRBCS). A factor analysis reduced dimensionality of the biomarkers. Univariable and multiple regression models tested the relationship between baseline predictors and outcomes.

**Results:** Participants were 191 PWH, 37 (19.4%) women; at study entry mean (SD) age 44.0 (7.55) years, estimated duration of HIV infection (median, IQR) 9.82 [4.44, 14.5] years, nadir CD4 104/uL (19, 205), current CD4 568/uL (356, 817), 80.1% plasma HIV RNA < 50 c/mL, 46.6% African American, 43.5% non-Hispanic white, 8.83% Hispanic, 15.7% white, 1.6% other, enrolled between 2003 and 2007; median (IQR) duration of follow-up 12.4 [9.69, 16.2] years. Three factors were identified: F1 (loading on plasma IL-6, CRP), F2 (sTNFR-II, neopterin) and F3 (sCD40L, sAPPα). Participants with higher F1, reflecting worse systemic inflammation at entry, had greater decline in global neurocognition (r = -0.168, p = 0.0205). NC change was not significantly related to the other Factors, nor to demographics, nadir and current CD4, viral suppression or NC confound status (incidental, contributing, confounding). Individuals with worse depressed mood at entry experienced more NC decline (r = -0.1734, p = 0.0006). Both BDI-II (p = 0.0324) and Factor 1 (p = 0.0325) contributed independently to NC decline; their interaction was not significant.

**Conclusions:** Participants with greater systemic inflammation and more depression at entry had greater NC decline over 12 years. These findings suggest that targeted therapies, such as anti-inflammatory and antidepressants, could prevent NC worsening.

**364. Introducing DBM-21, a Novel and Potent Imaging Biomarker for Accurate and Non-Invasive Early Detection of Alzheimer’s Disease**

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**Background:** A patient is recently diagnosed with amnestic mild cognitive impairment (aMCI). “Do I have Alzheimer’s disease?” they ask. Today, there is no reliable and fully objective early detection method for Alzheimer’s disease. Instead, we rely on a battery of inaccurate, non-conclusive, expensive, and sometimes invasive tests, such as PET or CSF biomarkers. Neurocognitive assessments such as MMSE, MOCA, and CDR are relatively poor predictors of aMCI prognosis, with a 5-year accuracy below 70% [Mauri, 2012]. Similarly, MR-based volumetry and PET biomarkers provide 5-year prognostic accuracies in the ~60-75% range [Ferrari, 2019]. Darmiyan Inc. has developed a novel, non-volumetric, magnetic resonance imaging (MR)-based imaging biomarker, Darmiyan Biomarker 21 (DBM-21), for early detection of Alzheimer’s disease at the aMCI stage. DBM-21 is derived from Darmiyan’s proprietary “Virtual Microscope” algorithm, which estimates neural tissue properties at the sub-voxel level by combining standard, non-contrast T1, T2, and diffusion-weighted MR signals.

**Methods:** DBM-21 was compared against various composite combinations of cognitive measures, MR volumetry features, and ApoE genotype. For cognition, MMSE (total) and CDR (all 6 boxes) were used. For MR volumetry, regional brain volumes and regional cortical thicknesses were measured using FreeSurfer v6.1. For side-by-side comparative analysis, 81 aMCI patients from the ADNI dataset met all the data availability and clinical follow-up requirements. Of these, 29 had not progressed to Alzheimer’s disease dementia (AD-dementia) for at least 5 years (Non-converters), and 52 had progressed to AD-dementia within 5 years (Converters). Composite models were generated using standard machine learning techniques, and mean balanced accuracies of 5-fold cross-validation iterations of each model was reported and compared against the accuracy of DBM-21 biomarker alone. Sensitivity (Sen) and specificity (Spec) of each model was also compared against DBM-21.

**Results:** The balanced accuracies of various composite models, versus DBM-21 alone, were as follows:
- Cognition (MMSE + CDR): 80.3 % (Sen 82.7, Spec 77.8)
- Cognition + volumetry: 84.7 % (Sen 85.6, Spec 83.8)
- Cognition + volumetry + ApoE: 85.1 % (Sen 85.8, Spec 84.5)

Darmiyan’s DBM-21 alone: 88.3 % (Sen 85.8, Spec 90.8)

**Conclusion:** Darmiyan’s novel, MR-based, non-volumetric biomarker, DBM-21, is a potent imaging biomarker for predicting aMCI’s 5-year prognosis (or early detection of Alzheimer’s disease) non-invasively. On side-by-side comparison with various composite models including cognitive measures, MR volumetry, and ApoE genotype, DBM-21 alone outperforms all other models alone or combined.

**References:** Mauri M, Functional Neurology, 2012/Ferrari BL, Medicine (Baltimore). 2019

**366. Towards Universal Deep Learning Artificial Intelligence for Alzheimer’s Disease Magnetic Resonance Imaging**

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**Introduction:** Neuroimaging data such as brain magnetic resonance imaging (MRI) scans can be useful for assessing the diagnosis and progression of Alzheimer’s Disease (AD) by revealing spatiotemporal changes occurring in the brain as it progresses from a more cognitively healthy state to dementia. The goal of the present study is to employ a deep learning (DL) approach to assist in classifying brain structural MRI scans into cognitively healthy controls and AD. Specifically, this study assesses important methodological choices in the
367. A Machine Learning Approach to Analyze the Efficacy of Standard Clinic Metrics for Predicting Alzheimer Progression

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Introduction: Alzheimer’s disease broadly progresses through three disease stages: Cognitive Normal (CN), Mild Cognitive Impairment (MCI) and Alzheimer’s disease (AD). The Alzheimer’s disease neuroimaging initiative (ADNI) has released a dataset tracking patients’ Alzheimer’s disease progression, patients’ time-varying and time-independent attributes. The objective of this study was to utilize the ADNI dataset to explore which variables are most important for predicting if and when a patient will transition to each stage.

Methods: MRI data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) is used to train a convolutional neural network (CNN) to classify controls from AD subjects. The data fed to the CNN (ResNet architecture) passes through pre-processing steps such as intensity homogenization, brain tissue extraction, image registration and spatial smoothing, all of which impact the final dataset preparation and the subsequent classifier performance. The present study utilizes and quantitatively assesses the respective contribution of pre-processing algorithm choice and classification model choice on ultimate model accuracy (i.e. correct classification outcome based on ground truth labels given by clinical records). Statistical bootstrapping using multiple CNN simulations with subsets of data are used to calculate classification performance variance due to either pre-processing or classification algorithm choice.

Results: Results illustrate that pre-processing choices are critical to obtaining consistently accurate classifier results in a large multi-site study such as ADNI. Findings illustrate that while classification algorithm choice is important, it is highly correlated and closely dependent on the pre-processing procedure. MRI data is subject to dataset specific biases, based on the MRI protocols, technical specifications of the MRI machine utilized, and site operating procedures. A uniform pre-processing protocol can be helpful in undoing these dataset specific biases and make the overall process more interpretable.

Conclusion: Prior DL work on AD MRIs has largely focused on classification algorithm optimization with less emphasis on optimal and uniform pre-processing steps to insure compatibility of analysis across multiple clinic sites. Study results illustrate the application of a detailed, universal pre-processing protocol is imperative for widespread accurate and interpretable adoption of DL artificial intelligence for AD research and care.

368. Assessing Cell Survival and Immunosuppression Efficacy in Intracranial Human Neural Stem Cell Transplantation

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Highly developed and effective immunosuppression protocols to prevent graft rejection are key to clinical translation of cellular therapies for the treatment of neurological disorders. Although Tacrolimus is a frequently used immunosuppressive agent for xenotransplantation applications, intracranially transplanted human cell survival is generally variable and short-term on this regimen. Additionally, graft survival is typically not evaluated until terminal histology, making it challenging to efficiently assess immunosuppression in vivo. Bioluminescence Imaging (BLI) is a molecular imaging tool that uses light generated from a Luciferase enzyme-substrate
369. Tractography Analysis of Supplementary Motor Area

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Progressive aphasia of speech (AOS) is a motor speech disorder affecting the ability to produce phonetically and prosodically normal speech. Progressive AOS can present in isolation or co-occur with agrammatic aphasia and is associated with degeneration of the supplementary motor area (SMA). We aimed to assess breakdowns in structural connectivity from the SMA in patients with progressive AOS and/or agrammatic aphasia to determine which SMA tracts are specifically related to AOS. Eighty-five patients with progressive AOS and/or agrammatic aphasia were recruited by the Neuodegenerative Research Group and underwent neurological, neuropsychological and speech/language assessments, as well as 3T diffusion MR imaging. Of the 85 patients, 36 had AOS in isolation (primary progressive aphasia of speech (PPAOS)), 41 had AOS and agrammatic aphasia (AOS-PAA), and eight had agrammatic aphasia in isolation (progressive agrammatic aphasia (PAA)). Tractography was performed to identify 5 distinct tracts connecting to the SMA. Fractional anisotropy (FA) and mean diffusivity (MD) were assessed along the lengths of the tracts to construct tract profiles, and median FA and MD were calculated across each tract. Decreased FA and increased MD were observed along the commissural SMA fibers in all three groups compared to controls. PPAOS had abnormal diffusion in the SMA-putamen and SMA-prefrontal tracts, with greatest abnormalities observed closest to the SMA. AOS-PAA showed abnormal diffusion in the left SMA-putamen tract compared to controls and PPAOS, as well as the left frontal aslant tract (FAT), left SMA-prefrontal and left SMA-motor tracts compared to controls. PAA showed abnormalities in the left FAT and SMA-prefrontal tract compared to both PPAOS and AOS-PAA, with PAA showing greatest abnormalities furthest from the SMA. These findings provide insight into how agrammatism and AOS are differentially related to disrupted diffusivity, with progressive AOS associated with abnormalities close to the SMA, and the FAT being particularly associated with agrammatic aphasia.

370. Abeta-Accelerated Neurodegeneration Caused by Alzheimer’s-Associated ACE Variant R1279Q is Rescued by Angiotensin System Inhibition in Mice

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Recent genome-wide association studies identified the angiotensin-converting enzyme gene (ACE) as an Alzheimer’s disease (AD) risk locus. However, the pathogenic mechanism by which ACE causes AD is unknown. Using whole-genome sequencing, we identified rare ACE coding variants in AD families and investigated one, ACE1 R1279Q, in knockin (KI) mice. Similar to AD, ACE1 was increased in neurons, but not microglia or astrocytes, of KI brains, which became elevated further with age. Angiotensin II (angII) and angII receptor AT1R signaling were also increased in KI brains. Autosomal dominant neurodegeneration and neuroinflammation occurred with aging in KI hippocampus, which were absent in the cortex and cerebellum. Female KI mice exhibited greater hippocampal electroencephalograph disruption and memory impairment compared to males. ACE variant effects were more pronounced in female KI mice, suggesting a mechanism for higher AD risk in women.
Hippocampal neurodegeneration was completely rescued by treatment with brain-penetrant drugs that inhibit ACE1 and AT1R. Although ACE variant-induced neurodegeneration did not depend on β-amyloid (Aβ) pathology, amyloidosis in 5XFAD mice crossed to KI mice accelerated neurodegeneration and neuroinflammation, whereas Aβ deposition was unchanged. KI mice had normal blood pressure and cerebrovascular functions. Our findings strongly suggest that increased ACE1/angII signaling causes age-dependent, Aβ-accelerated selective hippocampal neuron vulnerability and female susceptibility, hallmarks of AD that have hitherto been enigmatic. We conclude that repurposed brain-penetrant ACE inhibitors and AT1R blockers may protect against AD.

371. Structural and Molecular Determinants of Repeat RNA Toxicity in Non-Amyloid Dementias

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Transcribed repeat expansions cause multiple neurodegenerative disorders, including C9orf72 associated Amyotrophic Lateral Sclerosis/Frontotemporal Dementia (C9 ALS/FTD) and Fragile X-associated tremor/ataxia syndrome (FXTAS). Repeat RNAs sequester RNA-binding proteins (RBPs) into nuclear foci and undergo repeat-associated non-AUG (RAN) translation into toxic peptides in the cytoplasm. To identify proteins involved in these processes, we employed a repeat RNA-tagging system to capture CGG and GGGGCC repeat proteins involved in these processes, we employed a repeat RNA-tagging system to capture CGG and GGGGCC repeat transcriptional profiling, and determined the impacts of these structures on RBP interactions and RAN translation efficiency. We identified several SR (serine/arginine-rich domain) proteins that interact selectively with both CGG and GGGGCC repeats basally and under cellular stress. These same proteins modify toxicity in Drosophila models of FXTAS and C9 FTD/ALS. Genetic or pharmacological targeting of serine/arginine protein kinases (SRPKs) inhibits RAN translation in cells and toxicity in both FXTAS and C9 ALS/FTD model flies and in rodent neurons. We also elucidated how repeat-structures directly influence RBP interactions and RAN translation from both CGG and GGGGCC repeats. Taken together, these findings demonstrate underappreciated roles for in vivo repeat RNA structures and interactions in pathological neurodegenerative disease cascades while supporting further evaluation of SRPK inhibitors in modulating toxicity associated with repeat expansion disorders.

372. Transcriptomic Analyses of Synaptic, Amyloid, and Tau Pathways in A20-Deficient Mice

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Background: Growing evidence supports the role of dysregulated innate immunity in Alzheimer disease (AD) pathogenesis. However, the molecular mechanisms and pathways by which dysregulated innate immunity contributes to synaptic injury in AD remain to be elucidated. A20 is a regulatory protein for the nuclear factor kappa B (NF-kB) which plays an important role in regulating microglial activity during CNS homeostasis and pathology. We here investigate whether the pro-inflammatory milieu associated with A20 deficiency influences the transcription of genes involved in maintaining synaptic integrity and/or function.

Methods: We analyzed RNA-Seq transcriptomic datasets of wild-type and A20-deficient mice [1]. We performed differential gene expression (DEG) on these datasets using the Bioconductor Package edgeR. Functional pathway analyses were performed using Ingenuity Pathway Analysis (IPA, Qiagen) and Kyoto Encyclopedia of Knowledge (KEGG). Figures and graphical illustrations were generated using R and STRING.

Results: Our findings suggest that n=3019 genes were differentially expressed in A20-deficient mice compared to WT (p<0.05). Of these differentially expressed genes, n=13 genes have been implicated in AD pathogenesis (Table 1). APOE (log FC=1.22, p=8.51E-25), APP (log FC=0.32, p=1.48E-05), PSEN1 (log FC=0.37, p=9.08E-08), SORL1 (log FC=1.11; p=7.51E-15), CX3CR1 (log FC=1.33, p=1.55E-39), and TREM2 (log FC=0.2, p=0.004) were differentially expressed in A20-deficient compared to WT mice before lipopolysaccharide (LPS) injection (Figure 1). Importantly, our findings suggest that n=540 of the differentially expressed genes are directly involved in synaptic plasticity and/or repair. Our pathway enrichment analyses implicate synaptic plasticity, synaptic transmission, amyloid formation, amyloid clearance, lipid metabolism, microglial regulation, and clathrin-mediated endocytosis among the most enriched pathways for the genes differentially expressed in A20-deficient mice compared to WT.

Conclusions: Findings from this study suggest that dysregulated innate immunity plays an important role in synaptic dysfunction and impaired synaptic plasticity in a mouse model with no evidence of AD pathology. Findings from this study have important implications in the role of dysregulated immunity in mediating synaptic injury in AD independently of other AD pathologies.


373. Differentiating the Cognitive Trajectory of TDP-43 vs. Alzheimer’s Disease Neuropathology in the Oldest Old

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Background: Alzheimer’s disease neuropathology (ADNP) and TAR DNA-binding protein 43 (TDP-43) are important degenerative neuropathologies in the oldest-old, yet their individual contributions to cognitive decline are unclear.

Methods: 264 participants of The 90+ Study with longitudinal assessments and neuropathological data were included. Participants were divided into three groups according to their cognitive status at death: cognitively normal (CN), cognitively impaired with no dementia (CIND), and dementia. Neuropathologies were assessed at postmortem and dichotomized. Presence of TDP-43 in at least hippocampus and NIA-AA designation of “high” ADNP likelihood were our criteria for positivity. The Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) was used as a validated measure of clinically relevant cognitive impairment. A cumulative logit model, adjusted for age, sex, and education assessed the probability of an increased CDR-SB score based on the type of neuropathology. Age at follow up was decomposed as cross-sectional age at death and longitudinal years until death.

Results: Of 264 study participants, 87 were CN (mean age at death=97.5 years), 82 had CIND (mean age at death=97.6 years), and 95 had dementia (mean age at death=97.6 years) at the time of death. TDP-43 was present in 13 (15%) of the CN, 25 (30%) of the CIND, and 41 (43%) of the dementia individuals. Also, 22 (26%) CN, 27 (33%) CIND, and 41 (43%) dementia group participants had ADNP. There were no discernible differences in CDR-SB trajectory between the pathologies in the CN group. In CIND group, on the other hand, participants who had TDP-43 pathology were more likely than the ADNP group to have a higher CDR-SB score at baseline which was 10 years before death. This difference was maintained up to 3 years prior to death but disappeared by the time of death due to faster rate of cognitive decline in the ADNP group. Conversely, among those with dementia, the TDP-43 group had a faster rate of decline and a higher CDR-SB score at the time of death when compared with ADNP group.

Discussion: Our findings suggest TDP-43 has a significant contribution to cognitive decline of the oldest old individuals. While TDP-43 related cognitive decline seems to have a more protracted trajectory than ADNP at the less advanced stages of cognitive impairment, it is associated with a faster rate of cognitive decline in those who die with dementia.
Methods: Data were extracted from 4475 participants in the National Alzheimer’s Coordinating Center (NACC) database. The following dichotomized neuropathologies were considered: cerebral amyloid angiopathy (CAA), arteriolar narrowing, atherosclerosis, Alzheimer’s disease (AD), Lewy bodies (LB), hippocampal sclerosis (HS), frontotemporal lobar degeneration (FTLD), and TAR DNA-binding protein 43 (TDP-43). Hypertension was defined using four measures: systolic blood pressure (SBP) >130mmHg, diastolic blood pressure (DBP)>80mmHg, mean arterial pressure (MAP)>100mmHg, and pulse pressure (PP)>60mmHg. Participants’ blood pressure measures were averaged across visits excluding the last visit prior to death. Use of the following anti-hypertensive medications was assessed individually and as a group: antihypertensive agents, ACE inhibitors (ACEIs), antihypertensive combination therapy, angiotensin receptor blockers (ARBs), beta-blockers (BB), calcium channel blockers (CCBs), diuretics, and vasodilators. Linear regressions adjusted for age of death, sex, and education explored the association of degenerative pathologies with various blood pressure measures as well as anti-hypertensive medications.

Results: Among 4475 participants 54.2% were male, 57.4% had college education, and average age of death was 81.1 years. After Bonferroni correction, none of the dichotomized hypertension measures were associated with any pathology. On the other hand, use of anti-hypertensive medications was associated with reduced likelihood of AD (t=-6.644, p<0.001), LB (t=-5.688, p<0.001), TDP-43 (t=-4.641, p<0.001), CAA (t=-4.082, p<0.001) and HS (t=-3.525, p<0.001), but increased likelihood of atherosclerosis (t=3.327, p<0.001). Considering different classes of anti-hypertensives, diuretics were associated with a lower likelihood of AD (t=-6.239, p<0.001), HS (t=-4.104, p<0.001), CAA (t=-3.562, p<0.001), and LB (t=-2.586, p=0.010). ARBs were associated with a lower likelihood of LB (t=-2.889, p=0.004). BB were associated with lower likelihood of AD (t=-2.871, p=0.004) and LB (t=-2.654, p=0.008), and CCBs were associated with greater likelihood of atherosclerosis (t=2.991, p=0.003).

Discussion: We found use of anti-hypertensive medications was associated with lower likelihood of most neurodegenerative pathologies and diuretics were the class most strongly associated with this decreased likelihood. These findings suggest that anti-hypertensive medications play an important role in protecting the brain against development of neurodegenerative pathologies in those with hypertension.

Background: Cognitively normal elderly persons with lower CSF Aβ levels are classified as having preclinical Alzheimer’s disease (pAD). Identifying pAD is important for targeted recruitment in clinical trials of Alzheimer’s disease (AD) therapies. To date, amyloid PET and CSF are the only FDA-approved biomarkers used to identify pAD, but both are expensive and burdensome. Structural imaging markers such as hippocampal and other regional volumes as well as regional cortical thickness signatures have been used to stage AD but have not been shown to be reliable for the identification of pAD. However, recent studies have found associations between posterior periventricular-occipital WMHs (PVWMH) and AD-like CSF Aβ levels.

Method: Participants were recruited from the UK Sanders-Brown Center on Aging longitudinal cohort. Participants were classified as cognitively intact (CDR = 0; CI) or MCI (CDR = 0.5) using Clinical Dementia Rating™ Scale (CDR). CSF Aβ levels were used to classify participants as having elevated (≥250pg/ml; Aβ+) or non-elevated (>250pg/ml; Aβ-) brain amyloid. History of hypertension (HTN) was a dichotomous variable. Hippocampal volumes were quantified using FreeSurfer. The PVWMH volume was quantified using our previously published methods. Standard descriptive and comparative statistics including t-tests, chi-square tests, and logistic regression models were used for analyses.

Results: PVWMH data was available for 84 participants, including 41 CI and 43 MCI participants. There were no differences between CI and MCI for age, education, or sex (p > 0.52). Aβ+ CSF levels (p = 0.009) and HTN (p < 0.001) were more prevalent in the MCI (67.4% and 79.1%) compared to CI group (39% and 45.2%). The interaction between HTN and PVWMH demonstrated a trend for the prediction of CSF Aβ status (p = 0.09) even after controlling for age, sex, and education. This interaction was not significant when only MCI were included in analysis (p = 0.11); it was significant when only CIs were included (p = 0.05).

Conclusion: For CI participants with HTN, greater PVWMH increased the likelihood of Aβ+ CSF status suggesting that this may be a low cost, non-invasive biomarker for identifying pAD in research and clinical work. The development of low-cost, non-invasive pAD biomarkers is a critical priority in the field.

376. Periventricular White Matter Hyperintensities Are a Potential Noninvasive Imaging Marker for Alzheimer-Like Cerebrospinal Fluid Amyloid β Levels in Cognitively Normal Aging Adults
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Objectives: The existing Positron Emission Tomography (PET) tracers used in Alzheimer’s disease (AD) have limited...
utility in prognosis and in revealing reliable clinicopathologic correlations of disease. Microtubules (MTs) are abundant in brain and loss of MTs in brain occurs in the early to advanced stages of neurodegenerative disorders (NDs) and correlates with neurodegeneration leading to motor and cognitive dysfunctions. Since, MT loss is sensitive to alterations of a large number of mutated proteins, post-translational modifications and inflammation, it may provide a higher signal-to-noise ratio for monitoring disease stages in NDs compared to other biomarkers representing only a subset of abnormalities in neurodegeneration. At present, the first BBB penetrating MT PET tracer, $^{11}$C[MPC-6827] is available for in vivo imaging. Here, we report the in vivo imaging of $^{11}$C[MPC-6827] in J20 (Aβ pathology) and hTau (tau pathology) animal models of AD and compared the binding with a amyloid PET tracer $^{[11]}$C[PiB] in J20 mice and tau PET tracer $^{[18]}$F[MK6240] in hTau mice groups.

**Methods:** Automated radiosynthesis of $^{[11]}$C[MPC-6827], $^{[11]}$C[PiB] and $^{[18]}$F[MK-6240] were achieved by reacting corresponding precursors using GE Tracerlab modules. microPET imaging (50±10 μCi) were performed in 9-month-old J20 (n=3), 15-month-old hTau (n=3) and with corresponding age matched control mice (n=3) using a Siemens Focus scanner for 30-minute dynamic acquisitions. Image analyses were performed with vendor-provided software on reconstructed data. Mean activity in region of interests in whole brain, brain regions were measured and plotted against imaging time to generate time-activity curves (TACs) and standardized uptake values (SUVs).

**Results:** The synthesis of radiotracers were achieved in 40±10% radiochemical yield in >99% radiochemical purity with a molar activity of 2±0.5 Ci/μmol. $^{[11]}$C[MPC-6827] has higher SUV compared to $^{[11]}$C[PiB] and $^{[18]}$F[MK-6240] in both transgenic (Tg) and control groups. J20 and hTau mice show lower binding of $^{[11]}$C[MPC-6827] in whole brain in comparison to controls. Whereas, $^{[11]}$C[PiB] and $^{[18]}$F[MK-6240] exhibit a marginal higher binding in Tg group compared to control group. However, $^{[11]}$C[MPC-6827] binding shows higher effect size compared to $^{[11]}$C[PiB] and $^{[18]}$F MK-6240.

**Conclusions:** Our preliminary studies show that in amyloid and tau Tg mice, binding of the MT PET ligand $^{[11]}$C[MPC-6827] is reduced in whole brain, hippocampus and cortex compared control mice and is inversely correlated with $^{[11]}$C[PiB] and $^{[18]}$F[MK-6240]. Therefore, $^{[11]}$C[MPC-6827] could be used for preclinical and human brain imaging of AD and other NDs. Details of PET imaging data will be presented.

## 378. Non-Invasive Deep Brain Modulation in Humans via Rhythmic Sensory Stimulation

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**Background:** Our limited means to non-invasively modulate deep brain circuits constrain the development of new therapeutic strategies for various disorders such as Alzheimer’s disease (AD). Several studies have shown that precise rhythmic light flashes and sounds, or sensory flicker, modulate neural activity, decrease pathology, and rescue spatial memory deficits in mouse models of AD. Furthermore, sensory flicker modulates neural activity and immune function in healthy animals and in deep brain circuits required for memory. These results suggest that sensory flicker could be a general tool to non-invasively manipulate neural and brain immune functions. However, we lack understanding of how sensory flicker affects neural activity across brain regions in humans, including deep regions involved in AD. We hypothesize that exposure to sensory flicker in humans modulates activity beyond sensory regions, including deep circuits such as the hippocampus.

**Methods:** We studied the effects of sensory flicker in six epileptic patients undergoing presurgical intracranial monitoring with depth electrodes (stereoelectroencephalography). Subjects were exposed to repeated visual and/or auditory stimuli at frequencies of 5.5Hz, 20Hz, 40Hz, 80Hz, or random irregular patterns. We additionally controlled for potential noise induced by sensory flicker, using an occluded condition. Local field potentials (LFP) were recorded from around 900 electrode contacts across medial and lateral frontal, temporal, parietal, and occipital cortices, including visual and auditory regions. We compared the degree of entrainment across regions by measuring the relative increase in power in the frequency band of stimulation, under each condition. Moreover, we recorded single neuron activity in a subset of patients in the hippocampus and cingulum and analyzed neurons’ propensity to fire as a function of the stimulus phase.

**Results:** We found sensory flicker of different frequencies and modalities to quantitatively entrain LFP across broad brain regions, including in regions not canonically involved in primary sensory processing, such as hippocampus and cingulum. Furthermore, our data suggests that sensory flicker can modulate single unit activity in the hippocampus and cingulum.

**Conclusion:** This study is one of the first to show that sensory flicker entrains LFP broadly across superficial and deep brain regions and may modulate single neuron activity in memory and limbic structures. These results suggest that sensory flicker may be an effective non-invasive method to modulate brain activity at multiple frequencies and in multiple brain circuits, opening new avenues to optimize non-invasive therapeutic stimulation of circuits implicated in disease.

## 379. Written Language Impairments in Subgroups of Mild Cognitive Impairment

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**Background:** Amnestic mild cognitive impairment (aMCI) has received much attention in research for its high progression rate to dementia. From a neuropsychological point of view, the aMCI can be classified into two different subtypes: single-domain amnestic MCI (Sa-MCI) and multiple domain...
amnestic MCI (ma-MCI). Sa-MCI is characterized by isolated memory deficits while Ma-MCI shows additional impairments in other cognitive domains along with memory deficits. Previous studies have reported heterogeneous clinical manifestations between the two subtypes of MCI in terms of cortical thickness (Gu et al., 2019; Seo et al., 2007; Zhou et al., 2020) and etiology process of dementia (Aerts et al., 2017). However, differences in behavioral characteristics between the two subgroups of aMCI have been under investigated.

**Aims:** The aims of our study were to: 1) investigate whether the two subtypes of aMCI present distinct linguistic profiles in written language and 2) explore the extent to which linguistic features derived from written language could predict aMCI’s conversion to dementia.

**Methods & Procedures:** 129 individuals with aMCI (Sa-MCI = 68, Ma-MCI = 61) were included in the study. Written language samples were collected using the Cookie Theft picture from Boston Diagnostic Aphasia Examination (Goodglass et al., 2001). Analysis of written language samples were completed in three linguistic domains: lexical content (total number of words, lexical diversity, and number of nouns, verbs, adjectives, adverbs, and closed class words), syntactic structure and complexity (number of words in sentences, number of complete sentences, number of embeddings), and spelling errors (phonologically plausible errors, phonologically non-plausible errors- deletions, insertions, substitutions, transpositions). Out of 129 participants, 62 individuals with aMCI have been reassessed to determine their progression to dementia. Logistic regression was performed using the full set of written linguistic variables, age, and education as predictors, and conversion status to dementia as the binary outcome variable.

**Results & Conclusion:** Individuals with Sa-MCI showed greater production of verbs (p = .019) and adverbs (p = .016) compared to individuals with Ma-MCI. In binary logistic regression, the more words (p = .041, OR = 46.730), fewer nouns (p = .035, OR = .018), fewer verbs (p = .043, OR = .018), and fewer errors in letter substitutions were the predictors of the progression to dementia. The overall predictive value of the model was found to be 85.2%. Clinical implications will be discussed.

### 380. Quantitative and Qualitative EEG Differences Between Dementia with Lewy Bodies and Alzheimer’s Disease

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**Objective** Recent studies1,2 have demonstrated that there are significant differences in quantitative EEG between early stage Dementia with Lewy Bodies (DLB) patients and Alzheimers Disease (AD) patients. If these differences are detectable on routinely collected EEGs, EEG could represent a low-cost screening tool to differentiate dementias. We therefore conducted this retrospective study to determine if there are significant quantitative or qualitative EEG differences between patients diagnosed with DLB and AD on standard clinically obtained EEGs, at any stage in the disease progress.

**Methods:** We identified 145 patients diagnosed with either AD or DLB over the past 5 years (2015-2020) who also underwent EEG. Each patient file was reviewed and included in the study if the patient had either possible or probable AD or DLB based on NIA-AA criteria. Patients were excluded if the EEG contained excessive artifact or if the EEG was obtained in the setting of active seizure, stroke, or trauma. This resulted in 36 patients included in the study; 23 with AD (11 Probable, 13 Possible) and 13 with DLB (9 Probable, and 4 Possible). Patients included in both groups ranged in disease progression from mild to severe disease. EEGs were also assessed visually and graded on a scale (1-5) with a higher number representing increased abnormality by two board certified epileptologists.1,2,3 We performed a fast Fourier transform to analyze the power spectrum between the groups. Five artifact-free epochs (8 seconds long) were selected for each patient and averaged for the intergroup comparison. Additionally, we measured a posterior dominant rhythm for each patient and compared the two groups.

**Results:** The DLB patients had a lower posterior head power spectrum in the (alpha 1) 8-10 Hz range (p=0.041) compared to AD patients. The DLB patients also had a higher posterior head region Theta/Alpha (4-8 Hz/8-13 Hz) power ratio compared to AD patients (p=0.046). The posterior dominant rhythm was lower for the DLB patients compared to AD patients, but not significantly so. Additionally, the DLB patients had a higher average visual EEG score compared to AD patients; however, this was not statistically significant.

**Conclusion:** This study demonstrates that there are detectable differences in clinically-obtained EEG between DLB and AD patients, regardless of disease progression. Future studies with larger numbers could help refine EEG as a classification tool in diagnosing dementia.

### 381. The Feasibility of Home-Based, Non-Invasive Brain Stimulation for Memory in Adults with Dementia Due to Alzheimer’s Disease

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Loss of memory is an early and debilitating symptom in patients with Alzheimer’s Disease Related Dementia (ADRD). There are currently limited therapeutic options. Recently, we identified the dysregulation of gamma oscillations in the angular gyrus of ADRD patients as captured by high-density electroencephalography (hd-EEG) during a memory task. Here, we report on the feasibility and efficacy of a remotely monitored, caregiver-administered, home-based transcranial alternating current stimulation (tACS) protocol.
to entrain gamma oscillations in the angular gyrus of ADRD individuals (n = 10, M = 74.33 years old, SD = 10.54 years, 7 males). Caregivers completed 3 on-site laboratory visits for tACS administration training. After caregivers passed a competency evaluation, they were instructed to administer 5 to 6 tACS sessions per week for 14 weeks. On average, each tACS session lasted an hour (15-30 min for set-up, 20 min for tACS, 10 min for equipment cleaning). We employed a 6-gel-electrode montage (2 anodes and 4 cathodes) with a maximum inject current of 2mA per electrode and 4mA overall to generate an average electric field of 0.25 V/m.

Before and after tACS, participants recorded any stimulation side effects using a 5-minute remotely monitored safety questionnaire. The primary outcome measure was the change in Montreal Cognitive Assessment (MoCA) and dependent National Alzheimer’s Coordinating Center’s Uniform Data Set (NACC)-defined sub-scores from baseline to treatment completion. A total of 658 sessions were assigned across all participants. 58 sessions were not completed, of which 3 were due to tACS-induced discomfort. Two participants dropped out due to the time demand of daily sessions. Two other participants temporarily paused the intervention schedule: one participant due to study-related scalp skin lesions and one due to an unrelated illness. MoCA and Memory Index Sub-scores (MIS) increased for all participants between baseline and completion of the study (mean ∆MoCA = + 6 points, SD = 4.12; ∆Moca-MIS = +7.56, SD = 3.57). Our findings suggest that home-based tACS is feasible and safe, with all experienced side effects being mild and expected. All participants showed a benefit in memory and overall cognition, encouraging the pursuit of a larger, randomized controlled trial.

382. Systemic Inflammation Elicits Distinct Brain Immune Signaling Dynamics in Female and Male Mice with AD Pathology

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**Background:** Women are disproportionately affected by Alzheimer’s disease (AD), even after adjusting for age and socioeconomic status. Sex-based biological differences in immune response, including hormonal and X-linked immune genes, may contribute to differences in disease progression. However, we have limited understanding of the role of sex in modulating immune response and how these differences are affected by AD pathology. Here, we hypothesized that female and male mice would exhibit distinctive neural immune signaling in response to challenge with the pro-inflammatory stimulus lipopolysaccharides (LPS), and that these differences would be exacerbated in male 5xFAD mice compared to wild-type controls.

**Methods:** Female and male six-month-old 5xFAD amyloid beta (Aβ) and wild type (WT) littermate mice were interperitoneally injected daily with LPS for 1, or 4 days or saline (N=6). Luminox multiplexed ELISAs was used to quantify inflammatory cytokines, MAPK intracellular signaling phospho-proteins in cortical tissues.

**Results:** As expected, in wild type mice we observed no significant differences between females and males after either one or four daily injections of LPS. In saline-treated mice, we observed that 5xFAD male mice demonstrated greater MAPK phosphorylation (p38, Atf2, and Stat1) compared to other groups. Interestingly, however, LPS administration decreased MAPK phosphorylation in 5xFAD males after 1 or 4 doses, but did not affect other treatment groups (WT males, WT females, or 5xFAD females). As expected, LPS increased expression of multiple pro-inflammatory cytokines (Eotaxin, IP-10, RANTES) after 1 dose and further increased their expression after 4 doses. Importantly, expression of these cytokines were amplified in female 5xFAD mice compared to other groups, suggesting distinctive responses in males and females.

**Conclusions:** Our data reveal that although sex is not a significant determinant of neural immune response in WT mice, it significantly affects neural immune response to LPS challenge in 5xFAD mice. These data suggest distinctive immune processes in female vs male 5xFAD mice that are not present in healthy controls. Future work will consider the effects of Aβ pathology on these results.

383. Pathophysiological Changes in Soluble Amyloid Precursor Protein-β Turnover in Alzheimer’s Disease

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The amyloid hypothesis posits that increased production and/or decreased clearance of amyloid-beta (Aβ) will lead to higher order amyloid structures that initiate a cascade of events, culminating in neuronal death manifesting as Alzheimer’s disease (AD). These pathophysiological processes are put in motion decades before clinical symptoms. Sequential cleavage of Amyloid Precursor Protein (APP) generates Aβ. APP may be processed in one of at least two pathways, initially being cleaved by either α- or β-secretase (BACE1). BACE1 cleavage of APP releases soluble APP-β (sAPPβ) and subsequent cleavage by γ-secretase produces Aβ. Aβ formation is precluded if α-secretase cleaves APP, producing soluble APP-α (sAPPα). We hypothesize most of the AD and non-demented Amyloid+ populations overproduce Aβ because of varying degrees of increased BACE1 activity. Our objective is to measure sAPPβ and sAPPα turnover, as surrogate markers of BACE1 activity, in human cerebrospinal fluid (CSF) to determine if, and by how much, BACE1 activity is increased in these subjects. We employed stable isotope labeling kinetics/immunoprecipitation/liquid chromatography-tandem mass spectrometry methods, to quantitate sAPPβ and sAPPα in CSF from human Amyloid+ (AD) and Amyloid- (control) subjects who had undergone [U-13C6]-leucine
labeling and hourly CSF collection. The fraction of metabolite derived from de novo synthesis was measured by calculating normalized metabolites’ hourly mole fraction labeled (MFL), over 36 hours. Normalized MFL was multiplied by the metabolites’ absolute concentration to quantitate newly generated metabolites. Regression analyses were performed to determine the extent of the relationship between these parameters, brain amyloid load, and CSF Aβ. Herein we present interim analyses of 60 subjects. Both sAPPα and sAPPβ turn over slower than Aβ, and sAPPα turns over a little faster than sAPPβ in most subjects. This difference was more pronounced in participants that had brain amyloid deposition. There is almost a significant amyloid effect on the whole system fractional turnover rate (FCR) for both sAPPα and sAPPβ. Newly generated sAPPβ, and the newly generated sAPPβ/sAPPα ratio, were significantly elevated in Amyloid+.

Results: The ML algorithm identified a small subset of 29 important proteins out of the 3300+, which can differentiate AD cases from control control cases with high accuracy. However, 88 proteins of 3300+ are necessary to differentiate AD from asymptomatic AD with high accuracy. Notably, the ML algorithm is able to differentiate cases and controls even when amyloid beta levels (measured through Amyloid Precursor Protein) are not used in the classification, showing that classification does not hinge solely upon amyloid beta. Using previously published modules for protein function, a function ontology was overlaid on the selected proteins to determine which functions are more or less represented. The subset of selected proteins was significantly enriched for metabolic function, namely glucose metabolism.

Conclusion: ML classification can be used to successfully identify a subset of the most discriminative proteins useful for AD clinical diagnostics and etiological research pursuit. Future work in predictive medicine can incorporate such algorithms for further patient personalized risk assessment and treatment recommendations.

384. Machine Learning Classification of Diagnostic Proteomics for Alzheimer Disease

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Introduction: Protein changes and aberrant protein accumulation is a hallmark of Alzheimer’s Disease (AD). Thousands of different proteins can be measured in clinical patients. However, in the sake of etiological understanding and for developing a more succinct and universally available AD protein diagnostic panel, prioritizing which proteins are most associated with a particular AD disease state is helpful. The objective of the present study was to investigate a large set of clinical proteomic markers from the brain tissues (dorsolateral prefrontal cortex) and determine a subset that is best for differentiating healthy controls, asymptomatic AD cases, and AD cases.

Methods: A machine learning (ML) based protein selection approach is applied to published clinical proteomic datasets, which had over 3300+ measured proteins. Four published data sets were used to construct and train the model while two published data sets were used to independently validate the model results. The machine learning approach involved recursive elimination of the “less useful” proteins, until a pre-determined number of proteins remained that successfully classified the patient cohorts. The final protein subset is a small fraction of all the proteins measured in the data (less than 1% of all proteins to start with).

In order to avoid chance selections, the recursive feature selection strategy is performed with different algorithmic choices, including support vector machine and logistical regression. Classification performance is quantified using area under the receiver operating curve (AUROC).

391. Characterizing the Role of Genetic Variants Influencing α-Synuclein Seeding Activity Using Neuropathologically Characterized Human Brains

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Background: Parkinson’s disease (PD), Dementia with Lewy bodies (DLB), and Multiple system atrophy (MSA) are all synucleinopathies, which are characterized by the accumulation of pathological α-synuclein (α-syn) protein aggregates in the brain. Differing pathological presentations in PD, DLB, and MSA do not always result in distinct clinical phenotypes between diseases therefore collectively termed Parkinsonian disorders or parkinsonism. Neuropathologic examination of human brains report compelling evidence on the existence of distinct α-syn strains between disease types. These strains can be used as a molecular biomarker to distinguish between diseases; however, neither the role of genetic variants nor the distribution of α-syn strains across susceptible brain regions in PD, DLB, and MSA have been defined.

Methods: Real-time quaking-induced conversion (RT-QuIC) is an ultrasensitive detection technology for quantifying and characterizing misfolded proteins, and has a greater sensitivity and specificity compared to conventional approaches, such as immunohistochemistry. We have previously established RT-QuIC and implemented it to detect α-syn in brain and cerebrospinal fluid (CSF) from PD and MSA and has a sensitivity and specificity level ranging from 95-100%. We have optimized the RT-QuIC assay to assess large cohorts of pathologically confirmed diseased brain tissues to explore α-syn seeding activity in synucleinopathies, and whether α-syn is a suitable biomarker of disease type and progression.

Results: We have generated quantitative measures of α-synuclein seeding kinetics using RT-QuIC assays to characterize α-syn strains in PD, DLB, and MSA brains. These measures have been overlayed with available genomic and clinical data to determine genetic markers influencing α-syn
422. The Association Between Sleep Apnea and Neurodegenerative Disorders: A Systematic Review and Meta-Analysis with an Emphasis on Precision-Medicine

**Introduction:** There has been great interest recently regarding the possible link between sleep apnea (SA) and dementia. Previous meta-analyses on the topic have reported a statistically significant association between these conditions. However, these meta-analyses have included cohorts with patients having self-reported diagnoses of SA as exposures and non-specific cognitive diagnoses as outcomes, undermining clinical implications. We aimed to assess the association between SA and specific neurodegenerative causes of dementia and to review the use of precision-medicine tools supporting clinical diagnoses in studies.

**Methods:** We performed a systematic review and meta-analysis in conformity with the PRISMA guidelines. Two investigators searched the Web of Science Core Collection databases from inception to March 1st, 2021. Longitudinal studies were included if they: 1) used either polysomnography (PSG) or International Classification of Diseases (ICD) codes for SA diagnosis, and 2) measured the risk of all-cause dementia, mild cognitive impairment, Alzheimer’s disease (AD), vascular dementia (VaD), Parkinson’s disease (PD), Lewy body dementia (LBD), frontotemporal dementia (FTD), and/or mixed dementia. The use of biomarkers to support clinical diagnoses in eligible studies was collected. Studies of cross-sectional design, that used self-administered questionnaires for the diagnosis of SA, or that measured solely cognitive scores as outcomes were excluded. Pooled analyses of hazard ratios (HR) were obtained for every type of dementia using a random effects model.

**Results:** Among the 1,191 records identified, 8 studies were included, representing a total of 1,249,975 patients. Patients with SA had a 43% increased risk of developing any of the aforementioned types of dementia (HR: 1.43 [1.26-1.62], 95% CI). They were 34% more likely to develop all-cause dementia (HR: 1.34 [1.15-1.57], 95% CI), 28% more likely to develop AD (HR: 1.28 [1.16-1.41], 95% CI) and 54% more likely to develop PD (HR: 1.54 [1.30-1.84], 95% CI). No statistically significant association was found with VaD. One study reported a two-fold increased risk of LBD with SA. No study used biomarkers such as regional cortical atrophy on brain imaging or genetic testing. Results remained consistent after sensitivity analyses.

**Conclusion:** While SA appears to be associated with an increased risk of all-cause dementia, notably for AD, PD and LBD, future studies will have to be conducted using more rigorous precision-medicine tools in order to better characterize the specific associations between these conditions.

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428. Investigating the Utility of Common Linguistic Tasks in Distinguishing PPA Subtypes

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**Introduction & Aims:** Primary progressive aphasia can be further distinguished for many individuals into one of three variants: semantic variant PPA (svPPA), non-fluent/agrammatic variant PPA (nfavPPA) and logopenic variant PPA (lvPPA). Each subtype is associated with a distinct constellation of relatively impacted cognitive-linguistic capacities; however, there is little evidence to guide the optimal combination of behavioral instruments for distinguishing each the variant from the others. The aim of this work is to provide insight into the relative utility of numerous commonly-used language tasks for distinguishing each of the three PPA variants.

**Methods:** Two hundred twenty-two patients (86 lvPPA, 63 nfavPPA, and 73 svPPA) evaluated in an outpatient clinic between 2008 and January 2021 were included in analysis. Testing included the National Alzheimer’s Coordinating Center’s frontotemporal lobar degeneration module (FTLD), augmented with additional lexical access, semantic anagram, semantic association, recognition, description, and written tasks. Area under the receiver operating characteristic (AUROC) analysis was used to determine the diagnostic utility of each task for each subtype. For each subtype, an AUROC of 0.7 was used as a cutoff to identify the most useful tasks, which were then entered together into a binomial logistic regression to predict that subtype.

**Results:** Thirteen of the 29 tasks resulted in high diagnostic utility (AUROC ≥ 0.7). NfavPPA was best predicted by high scores in noun and verb naming (oral and written), noun and verb recognition, and delayed complex figure copy scores. These assessments together significantly predicted nfavPPA diagnosis, $\chi^2(7)=42.99$, p<0.001, and correctly classified 77% of cases. SvPPA was best predicted by low scores in noun and verb naming (oral and written) and recognition, semantic association tasks targeting both nouns and verbs, spelling, and receptive single word vocabulary. Together, these predicted svPPA status, $\chi^2(11)=63.24$, p<0.001, and correctly classified 86% of cases. No single task from the battery demonstrated high utility in predicting lvPPA; however, the ratio of the FTLD module’s sentence reading to sentence repetition performance demonstrated diagnostic utility (AUROC=0.70) and resulted in a significant model, $\chi^2(1)=19.65$, p<0.001, that correctly classified 69% of cases.

**Conclusion:** This analysis provides evidence that many tasks demonstrate limited utility in predicting any one PPA subtype, suggesting extended cognitive-linguistic evaluations of this population may have diminishing returns. We further suggest an abbreviated battery of high utility tasks based on these results to facilitate diagnosis of PPA variant.
429. Regional Atrophy Predicts Naming Decline in Primary Progressive Aphasia: A Comparison of Cross-Sectional and Longitudinal Analyses

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Background: Many investigations of brain-behavior relationships in primary progressive aphasia (PPA) consider only one timepoint. However, true atrophy quantitation requires comparing individual brains over time. Therefore, longitudinal investigations may better characterize disease progression and cognitive consequences. Here, we used longitudinally-collected data to compare the results of more traditional cross-sectional analyses associating naming performance with regional volume at each timepoint to longitudinal analyses that directly related change in naming to change in volume. We investigated whether naming decline in PPA is linked to continuing atrophy of critical language regions that are first affected, or to atrophy of additional regions that may initially have played a compensatory role in processing.

Methods: Participants (N=62; 31 female; mean age=66.8±7.37 years) with the three recognized variants of PPA completed the Boston Naming Test (BNT) and MRI twice (mean=343.89±208.98 days apart). Atlas-based analysis in the MRI Cloud platform (www.mricloud.org) was used to segment each T1-weighted anatomical scan into regions of interest (ROIs) and calculate the volume of each region normalized by total cerebral volume. Cross-sectional analyses related BNT performance and volume in 22 ROIs at each timepoint using LASSO regression. Longitudinal analysis evaluated changes in BNT performance and volume in the same ROIs. Change in volume of each ROI was quantified as the Jacobian determinant derived from the deformation field comparing the two scans for each individual using DiffeoMap, with values <1 indicating shrinkage and >1 indicating expansion.

Results: Cross-sectional analyses at both timepoints identified left inferior frontal gyrus pars opercularis, superior temporal pole, middle temporal gyrus, and inferior temporal gyrus as critical for naming. Greater overall atrophy predicted poor performance at the later but not earlier timepoint, reflecting increasingly diffuse atrophy as the disease progresses. In the longitudinal analysis, increasing atrophy in left supramarginal gyrus and middle temporal pole predicted greater naming decline. Female sex and longer intervals between timepoints also predicted greater decline.

Discussion: Cross-sectional analyses identified classic language areas that were consistently related to poor performance at multiple timepoints. In contrast, the longitudinal analysis identified nearby but distinct language regions where increasing atrophy predicted decreasing performance. This suggests that further behavioral decline is driven by atrophy of additional regions, not by continuing atrophy of the critical regions that were first affected. These results demonstrate that directly examining atrophy over time furthers understanding of decline in PPA.

441. Palmitate Increases Amyloid Precursor Protein Exosome Secretion: A Missing Link Between Metabolic Syndrome and Alzheimer’s Disease

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Type 2 diabetes (T2D) and Alzheimer’s disease (AD), share several pathological features, including elevated inflammation, oxidative stress, abnormal protein processing, insulin resistance (IR), and mitochondrial dysfunction. Metabolic syndrome (MetS), which constitutes obesity, dyslipidemia, and hypertension, is a risk factor for and frequent T2D precursor. MetS and T2D increase AD risk, but the precise mechanism is elusive. IR, which develops from a diet rich in saturated fatty acids such as palmitate, is central to MetS, T2D, and AD. Exosomes are also a point of convergence among these conditions, and palmitate stimulates exosome production. However, the role of palmitate-induced IR in the brain and its potential link to exosomes in AD is unknown. We demonstrate that palmitate induces IR and amyloid precursor protein (APP) phosphorylation in primary rat embryonic cortical neurons and human cortical stem cells, which is blocked by metformin activation of AMP-activated protein kinase. Palmitate also increases phosphorylated APP secretion from cortical neurons via exosomes, which transfect naïve neurons to induce tau phosphorylation, suggesting a novel theory underlying the increased risk of AD in MetS. Funding: Robert E. Niederlander Sr. Program for Alzheimer’s Research (BK), N019685 IDNC (ELF) and the NeuroNetwork for Emerging Therapies.

472. Gamma Frequency Sensory Stimulation in Probable Mild Alzheimer’s Dementia Patients: Results of a Preliminary Clinical Trial

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Background: Non-invasive gamma frequency light and sound stimulation at 40Hz was shown to reduce Alzheimer’s disease (AD) pathology and improve performance during behavioral testing in mouse models of AD (Iaccarino et al., Nature, 2016; Martorell et al., Cell, 2019; Adaikkan et al.,...
Neuron, 2019). Sensory stimulation inducing 40Hz entrainment reduced amyloid burden and hyperphosphorylated tau and prevented brain atrophy in different models of AD. In addition, performance on tasks testing short-term memory and spatial learning improved after 6 weeks of daily 40Hz stimulation. Based on these studies, we hypothesized that gamma entrainment with light and sound is worth pursuing as a potential disease-modifying therapeutic for AD.

Methods: We conducted a placebo-controlled, randomized control trial (n=15) in subjects with probable mild AD dementia to use our light and sound device at home for one hour daily (NCT04042922). Control devices delivered constant light and white noise while devices with the active setting produced patterned and synchronized light and sound at 40Hz. We report interim results after 3 months of daily 40Hz stimulation. Electroencephalogram (EEG) was used to evaluate safety and entrainment when using the 40Hz stimulation. Weekly phone questionnaires were used to assess safety. Magnetic resonance imaging was used to evaluate brain structure and actigraphy was used to record sleep. Face-name association delayed recall was done to assess changes in cognition.

Results: Patients with mild AD dementia were highly compliant with device usage in both the control and active groups, in some cases, with care-partner’s assistance. EEG data show that our novel light and sound device safely and effectively induced 40Hz entrainment in participants with mild AD dementia. After 3 months of daily stimulation, the group that received 40Hz entrainment had less longitudinal hippocampal atrophy and ventricular enlargement than the control group (p = 0.034, p = 0.024, respectively). Circadian rhythmicity was better in the 40Hz stimulation group (p=0.03). Performance on the face-name association delayed recall test improved in the 40Hz stimulation group but not in the control group (p=0.027). There were no significant adverse effects.

Conclusion: Gamma frequency light and sound stimulation can be used safely daily for 3 months and preliminary biomarker and cognitive data suggest that it should be further evaluated as a potential treatment for AD. Induced entrainment using sensory stimulation at 40Hz shows promise as a novel disease modifying therapeutic for Alzheimer’s dementia.

474. Imaging Prodromal Neuromelanin and Iron Pathology in REM Sleep Behavior Disorder

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Background: Patients with REM sleep behavior disorder (RBD) and no other neurological diagnosis are at high risk of developing synucleinopathy, i.e. Parkinson’s disease (PD), dementia with Lewy bodies (DLB) or multiple system atrophy (MSA). Neuromelanin loss and iron accumulation are key features of neurodegeneration in these conditions. Neuromelanin-sensitive MRI (NM-MRI) and R2* relaxometry are MRI methods capable of quantifying neuromelanin- and iron-associated contrast, respectively. We used these imaging modalities to assess for prodromal synucleinopathy effects in RBD.

Methods: 19 patients with polysomnographically confirmed RBD and no neurodegenerative disease diagnosis were recruited from the Emory Sleep Clinic. 38 healthy older adult controls were recruited. Demographic data were collected. Participants were scanned with a 3T Siemens Prisma fMRI scanner. NM-MRI data was acquired using a magnetization transfer prepared 2D gradient-echo (GRE) pulse sequence, and LC and SNc volumes measured using a highly reproducible approach (Langley et al., 2017, MAGMA). Multi-echo GRE data was acquired and R2* values determined (Langley et al., 2019, Mov Disord). SNc and lateral-ventral SNc (LV-SNc) regions of interest (ROIs) were selected using NM-MRI contrast-derivated atlas for accuracy and reproducibility (Huddleston et al., 2017, Hum Brain Mapp). The Harvard-Oxford Subcortical Brain Atlas in FSL was used to define putamen, globus pallidus (GP), and caudate ROIs. A custom red nucleus (RN) atlas was used. Group demographic characteristics were compared. SNc volume, LC volume, SNc R2*, LV-SNc R2*, putamen R2*, GP R2*, caudate R2* and RN R2* were compared between groups using ANCOVA to correct for demographic differences.

Results: The groups differed significantly at baseline in gender (RBD=94.7% men, Control=31.2% men, p < 10^-4), age trended older in controls (RBD=57.0±3.4, Control=63.4±1.6, p=0.098), and there were no significant differences in race or education. ANCOVA including age and gender as covariates found significant group differences for LC volume (Mean ± SE; Control=8.1±0.5, RBD=4.4±1.0, p=0.011), SNc R2* (Control=26.6±0.6, RBD=31.7±1.6, p=0.002), LV-SNc R2* (Control=30.2±0.9, RBD=37.2±2.0, p=0.001), GP R2* (Control=34.6±0.7, RBD=37.4±1.2, p=0.002), and RN R2* (Control=31.9±0.7, RBD=36.4±1.6, p=0.008). SNc volume did not differ controlling for age and sex. However, controlling for age alone SNc volume was reduced in RBD (Control=439.2±19.3, RBD=350.6±33.1, p=0.022). No significant group differences in putamen R2* or caudate R2* were observed.

Conclusions: NM-MRI and R2* relaxometry detect neuromelanin loss and iron accumulation, respectively, across a range of brainstem and basal ganglia ROIs in RBD. These measures represent candidate imaging markers for prodromal synucleinopathy and warrant further study.

475. Autophagy & Neurons: Targeting Protein Quality Control for Modifying Proteostasis and Discovering Therapeutic Targets for Neurodegenerative Diseases

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One of the most characteristic pathologic features shared among neurodegenerative diseases is the deposition of misfolded proteins into insoluble, detergent-resistant inclusions. At a basic level, these inclusions imply that vulnerable
neuronal populations harbor impairments in protein quality control mechanisms, including that of the highly conserved pathway of autophagy. In line with this, stimulating autophagy is sufficient to not only degrade aggregates of disease-associated proteins, but also rescue cell death in multiple model systems of neurodegenerative diseases. However, neurons are refractory to well-established methods for stimulating autophagy, and prior studies implicate distinct regulatory mechanisms controlling autophagy in neurons. Together, these observations not only constrain the therapeutic potential of targeting autophagy in neurodegeneration, but also underscore the need to define the cell type-specific mechanisms that confer selective vulnerability to proteotoxic insults in neurons. Using genome-wide measurements of mRNA stability and assessments of protein expression, we identified neuron-specific upregulation of myotubularin-related phosphatase 5 (MTMR5), which suppresses autophagy by dephosphorylating membrane inositides critical for autophagy initiation. MTMR5 knockdown in iPSC-derived neurons restores autophagy induction in response to Torin1 treatment, while MTMR5 overexpression produces a neuron-like insensitivity to Torin1 in undifferentiated iPSCs. Furthermore, novel, non-invasive, and optical methods for measuring autophagic flux in live cells found that MTMR5 knockdown significantly enhanced degradation of the proteolytic substrate, TDP-43. By precisely identifying a determinative mechanism through MTMR5 that regulates autophagy within neurons, we are establishing molecular and genetic targets for maximizing neuronal autophagy, a goal with broad and fundamental therapeutic implications for mitigating neurodegenerative disease.

483. Pulse-Chase Proteomics of the APP Knock-In Mouse Models of Alzheimer’s Disease Reveals Synaptic Dysfunction Originates in Presynaptic Terminals

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Alzheimer’s disease (AD) is an incurable brain disorder that currently debilitates millions of people worldwide. Historically, the etiological model has been that early alterations at synapses cause changes in the activity of neuronal circuits, which occur many years prior to the presentation of clinically impaired cognition. Consistently, synapse loss represents an important and early feature of AD that correlates with the severity of dementia. The mechanisms leading to synaptic dysfunction and loss are not fully understood and both direct and indirect effects of Abeta peptides and Tau pathology are recognized as key drivers.

Our team recently used dynamic metabolic isotopic labeling with 15N and mass-spectrometry-based proteomics to investigate changes to protein turnover in the APP knockin (APP KI) mice. In these preclinical Alzheimer’s disease mouse models, we found that proteostasis in the presynaptic terminal is specifically altered. Notably, synaptic vesicle (SV)-associated proteins functioning in exo- and endocytosis have impaired degradation and elevated levels in the cortex and hippocampus. Finally, we found that the readily releasable SV pool and presynaptic potentiation is enhanced at the earliest stages of amyloid beta accumulation.

Due to numerous failed clinical AD trials focused on reducing Abeta levels, the importance of the amyloid cascade has been brought into question. Intriguingly, we observe a relationship between these observations and the effects of the atypical antiepileptic drug levetiracetam that is currently the subject of several Phase II clinical trials for AD. Our preliminary studies demonstrated that levetiracetam selectively normalizes SV endocytosis machinery abundance and restores non-amyloidogenic processing of APP which is anti-correlated to our disease progression observations in APP KI mice. Thus we have uncovered a potential mechanism that may explain the therapeutic benefits of levetiracetam as well as targets for future therapeutic intervention.

K-494. Therapeutic CRISPR Gene Editing Approaches to C9orf72 FTD/ALS in Patient Cells

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Expansion of the GGGGCC hexanucleotide repeat in the C9orf72 gene is the most frequent known genetic cause of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) (termed C9-FTD/ALS). Although the cellular dysfunction caused by this disease is multifactorial, targeting the gene itself by CRISPR/Cas9 editing could be curative. The most pressing challenge to implementing this technology effectively is identifying edits that neutralize the C9orf72 mutation without introducing unintended cellular dysfunction. We have taken three approaches to editing the C9orf72 gene using CRISPR in human patient-derived iPSC cells: (1) bi-allelic excision of non-coding DNA harboring the repeat expansion region, (2) allele-specific excision of the mutant allele containing the repeat expansion, (3) regulatory region disruption to selectively silence the C9orf72 repeat expansion. We have additionally engineered our cell lines with inducible neuron-specific transcription factors as a high-throughput method for producing disease-relevant cell types (cortical and motor neurons). By studying the effects of these genetic manipulations in induced neurons we not only interrogate gene editing approaches, but also advance our understanding of the normal regulation of the C9orf72 gene.

K-498. Combining Postmortem Single Cell Analysis with an Induced Pluripotent Stem Cell Model to Study Dysregulated Pathways in FTD

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Frontotemporal dementia (FTD) is a heterogeneous group of early-onset dementias leading to an impairment of behavior, language and cognition. FTD can be caused by mutations in the MAPT gene encoding the microtubule-associated protein tau resulting in pronounced atrophy of the frontal and temporal lobes, basal ganglia and brain stem areas. Here, we
performed single nucleus RNA sequencing (snRNA-seq) on postmortem brain tissue from FTD patients carrying the MAPT N279K mutation and from healthy control individuals to identify dysregulated pathways in patient neural cells at single cell resolution. Amongst others, we found significant changes in pathways related to cell metabolism and neuroinflammation in patient neurons that we tested further in a stem cell model of FTD using patient-derived and control individual-derived induced pluripotent stem cells (iPSCs). Patient iPSC-derived neurons with the MAPT N279K mutation demonstrated altered metabolic response to inhibition of mitochondrial respiration. FTD neurons also showed altered metabolic profiles with an increased basal mitochondrial respiration, increased ATP production and an increased maximal respiratory capacity as measured by neuronal oxygen consumption indicating an increased energy demand in these cells. Interestingly, iPSC-derived FTD neurons also had a significant effect on the survival of host neurons and on glial cell responses when transplanted into the brains of immunocompromised mice indicating a potential immunomodulatory role of patient neurons in vivo. These findings demonstrate that a combinatorial approach applying snRNA-seq on patient brain tissue and a dynamic iPSC cell model comprises a powerful tool to identify disease phenotypes in neural cells at risk in FTD. Such stem cell model of FTD could also be used as a cellular platform for high-throughput drug screening assays to identify potential therapeutic targets in FTD.

K-499. Tau Splicing Regulates Interaction with 14-3-3 Proteins
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Introduction: We have shown that in the developing human brain, tau is extensively phosphorylated, similar to that seen in Alzheimer disease and related dementias, without apparent adverse effects. The ubiquitous 14-3-3 family of chaperone proteins is known to affect tau phosphorylation and degradation, but the role of these proteins in the pathogenesis of neurodegenerative tauopathies remains unclear.

Methods: Human fetal, adult and AD brain samples obtained from the Iowa NeuroBank were homogenized, subject to co-immunoprecipitation with anti-tau antibody-linked beads and the resulting eluted proteins identified by mass spectrometry. We then used heterologous transfection and co-immunoprecipitation using bead-linked antibodies in HEK cells to validate interactions and characterize the effect of developmental changes in tau splicing.

Results: We found that three 14-3-3 family proteins - 14-3-3-beta, gamma and eta, interacted with tau in the adult and AD brain, which expresses both long and short tau isoforms, but not during development, when only the short (3R) tau isoform is expressed. When we coexpressed FLAG-tagged 14-3-3-beta with 4R and 3R tau in a heterologous HEK cell system, only 4R tau was pulled down with 14-3-3-beta. 3R tau did not interact with 14-3-3-beta regardless of phosphorylation status.

Conclusions: There are significant differences in the phospho-tau interactome between fetal and AD brain. AD, but not fetal brain shows tau interactions with 14-3-3-beta, gamma and eta, which may interact specifically with 4R tau. This suggest that the mechanisms for tau aggregation may differ between 4R/mixed and pure 3R tauopathies.

K-518. Prefrontal Neuron Anatomy After Viral-Mediated Overexpression of Human Alpha-Synuclein in Cortical Neurons in Mouse
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Lewy Body Dementias (LBD), including Parkinson’s disease dementia and Dementia with Lewy Bodies, are characterized by widespread intracellular alpha-synuclein protein deposits, including in the cortex. LBDs cause cognitive changes, including abnormalities in executive function, hallucinations, altered sleep, and cognitive fluctuations. The cause of these symptoms is still unclear, but it is known that duplication/triplication of alpha-synuclein increases the risk of developing Lewy Body disease. One possibility is that accumulation of alpha-synuclein in the cortex perturbs synaptic and cellular function, leading to some of these symptoms. In order to investigate the effects of cortical (rather than brainstem) alpha-synuclein we used local, viral overexpression of human alpha-synuclein protein. We used 2-photon microscopy to evaluate the effect on neurons by quantifying changes in morphology, dendritic spine density and turnover, and differences in cellular activity. Mice genetically expressing YFP in layer V pyramidal neurons were used to evaluate dendritic spine and axonal bouton turnover before and after virally-mediated overexpression of alpha-synuclein. After cranial window implant and initial imaging, mice were randomized to injection with virus coding for alpha-synuclein or mCherry alone. In vivo 2-photon imaging was then conducted in awake animals in one-week intervals for 2 months in order to observe dynamic changes in these structures. Using this technique, we found an increase in the relative spine density in mice with local overexpression of alpha-synuclein. The density changes were secondary to transient changes in formation rate of spines, without changes in elimination rate. These data suggest that local overexpression of alpha-synuclein does not cause spine loss over a two-month period. As there is some evidence for hyperexcitability in the cortex during the early stages of neurodegenerative disease, future experiments will determine if these changes in spine density are associated with abnormal cellular activity.

LB-462. Comprehensive Genetic Evaluation of APOE in Dementia with Lewy Bodies Implicates Distinct Disease Subgroups
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Background: The genetics of dementia with Lewy bodies (DLB) is still poorly understood, but APOE has consistently
arisen as top risk locus. However, DLB has been mostly studied as one entity without considering the extent of Alzheimer’s disease (AD) co-pathology. There are mixed reports on whether APOE is an independent driver of α-synuclein pathology in DLB.

**Methods:** We analyzed whole-genome sequencing data in 2,466 DLB cases and 2,928 neurologically healthy controls aged over 50. First, we used APOE ε4 as a proxy for Alzheimer’s disease co-pathology and performed genome-wide association analyses (GWAS) comparing 1,286 DLB cases without APOE ε4 to 2,271 controls without APOE ε4 and 1,180 DLB cases with APOE ε4 to 657 controls with APOE ε4. Then, we divided 495 DLB cases into three subgroups based on the severity of the AD co-pathology: (1) pure DLB (pDLB, n=88; Braak stages 0-2 and CERAD scores 0-A), (2) DLB with intermediate AD co-pathology (DLB + iAD, n =66; Braak stage 3 and CERAD scores A-C), and (3) DLB with high AD co-pathology (DLB + AD, n =341; Braak stages 4-6 and CERAD scores B-C). We analyzed the association of APOE ε4 with these neuropathological subgroups against the 2,928 controls.

**Results:** In the GWAS comparing DLB cases and controls without APOE ε4, GBA was the only locus that reached genome-wide significance (rs2230288, p = 6.58x10-9, odds ratio [OR] = 3.41, 95% confidence interval [CI] = 2.25-5.17). In the GWAS comparing DLB cases and controls with APOE ε4, there were no genome-wide significant loci. The top association signal was within the histamine receptor H1 (HRH1) gene (rs9858388, p = 2.00x10-7, OR = 1.47, 95% CI = 1.27-1.71). In the neuropathological subgroup analysis, APOE ε4 was strongly associated with DLB + AD (p = 1.29x10-32, OR = 4.25, 95% CI = 3.35-5.39) and DLB + iAD (p = 0.0011, OR = 2.31, 95% CI = 1.40-3.83) but not with pDLB (p = 0.31, OR = 0.75, 95% CI = 0.43-1.30).

**Conclusions:** APOE ε4 is not an independent driver of α-synuclein pathology in DLB, rather, the association is explained by intermediate to high AD co-pathology. In contrast, GBA is associated with low or absent AD co-pathology separating DLB genetically into two potentially distinct subgroups. The severity of AD co-pathology should be assessed in future DLB genetic studies.

**LB-463.** Examining the Role of Obesity in Hippocampal Microglial Activation Using Single Cell RNA-Sequencing

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**Background:** Obesity is a risk factor for developing cognitive impairment and dementia, however, the pathologic mechanisms contributing to cognitive deficits remain elusive. Our lab, and others, have shown that mouse models of obesity induced by a high fat diet (HFD) rich in saturated fatty acids display hippocampal-dependent memory deficits. Microglia, macrophage-like immune cells of the CNS, are activated in mouse models of obesity and contribute to cognitive impairments (Cope, J Neurosci 2018). The effects of HFD on the progression of microglial activation over time are largely unexplored. Here we examined the effect of HFD on the microglial inflammatory phenotype using single cell RNAseq to interrogate the heterogeneous population of microglial subtypes.

**Methods:** At 5 wks of age, C57BL/6J mice were begun on either 60% fat HFD chow or 10% fat control chow. After 1 month and 3 months diet, animals were sacrificed and hippocampal CD45low/CD11bhigh cells were collected by fluorescence activated cell sorting and sequenced on the 10X Chromium platform. Reads were quality filtered and mapped to the mouse genome using CellRanger and then read into Seurat (Stuart, Cell 2019). Principal Component Analysis followed by Uniform Manifold Approximation and Projection (UMAP) of principal components was performed.

**Results:** Transcriptomic analysis of isolated cells confirmed a pure population of Itgam (Cd11b) and Ptprc (Cd45) expressing cells. The majority of sequenced cells expressed the microglial marker genes Tmem119, Cx3cr1, and P2ry12. Twelve clusters were identified in both the control and HFD samples, including four homeostatic microglia types, interferon related microglia, inflammatory microglia, macrophages, and neutrophils, among others. DESeq2 was used for differential gene expression analysis in control versus HFD clusters, and identified a select number of differentially expressed genes (DEG). Cell-to-cell communication pathways were analyzed using CellChat (Jin, Nature Communications 2021), and distinct pathways were identified in HFD vs control microglia, such as complement and BAFF signaling. Additional analyses are ongoing.

**Conclusions:** HFD has been shown to induce microglial activation by morphological measures, and our findings suggest that the transcriptome is subtly affected; all clusters were present in both control and HFD animals, and DEGs between clusters from each group were few in number. CellChat analysis identified multiple immune related pathways present in only the HFD microglia. Future work will investigate the significance of the select DEGs in each group, and ongoing work will correlate transcriptomic effects with morphological measures of activation.
2D T1-weighted magnetic resonance imaging. Naming was measured using Boston Naming Test and Category and Lexical Fluency. Executive function was evaluated using TMT-B/A Ratio. Voxel-based morphometry (VBM) analysis was used to characterize regions of atrophy in bvFTD as compared to HC using t-test. Regional GM volume loss associated with naming and executive measures in bvFTD, was calculated using regression analysis.

**Results:** T-test results showed regions of significant bilateral atrophy in frontal and temporal regions as expected ($p < 0.0001$, uncorrected). VBM analysis showed significant correlation between BNT scores and cortical volume in the left temporal lobe extending from anterior to posterior temporal regions. We found significant correlations between Category Fluency and cortical volume within the left lateral temporal and dorsolateral frontal cortex (DLPFC). Sixty eight percent of Category Fluency variance was accounted for by GM volume loss in temporal lobe, and 38% was accounted by atrophy in the dorsolateral frontal lobe. For the TMT-B/A scores, we found significant correlation between cortical volume in bilateral DLFPC and anterior cingulate cortices (ACC).

**Conclusion:** Our findings demonstrate a correlation between left lateral temporal atrophy and confrontation naming in bvFTD. Impairment in Category Fluency, however, was related to atrophy in a larger network including left dorsolateral frontal and left lateral temporal regions. Not shown in previous investigations, perisylvian atrophy accounted for most, but not all of Category Fluency variance. TMT-B/A scores were related to atrophy bilateral DLPFC and ACC pointing to a network of frontal regions supporting executive function for this test. Our results help with better understanding of the neural signatures of naming and executive deficit in bvFTD.

**Education**

**099. Central Nervous System Cryptococcosis Mimicking Stroke**

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**Background:** We present a unique case of central nervous system (CNS) cryptococcosis in a patient with hepatitis C cirrhosis and intravenous drug abuse who presented as a stroke alert for right arm weakness and headache.

**Case Summary:** A 39-year-old man with a history of hepatitis C cirrhosis, hepatic encephalopathy, upper gastrointestinal bleeding, and intravenous drug abuse presented to the emergency department for headache and right arm weakness. The remainder of the exam was unremarkable. CT head w/o contrast demonstrated a small left centrum semiovale hypodensity. CTA head/neck showed no arterial stenosis or occlusion. MRI brain w/o contrast showed multiple enhancing lesions in the left midbrain, bilateral basal ganglia, bilateral internal capsules, right thalamus, and right cerebellar hemisphere. Restricted diffusion within the left midbrain lesion was suggestive of abscess. Differential for these lesions included an infectious process, such as septic emboli, fungal infection, or toxoplasmosis, and less likely neoplastic or demyelinating. Lumbar puncture was performed with opening pressure of 10 cm H2O. CSF analysis revealed glucose 54, protein 30, cell count 7 (94% lymphocytes), and positive Cryptococcal antigen with titer of 1:20. CSF Gram stain, KOH, India ink, menigitis/encephalitis PCR panel, West Nile, and VDRL were negative. HIV, EBV, JC polyoma virus, and MS profile were negative. Serum studies revealed pancytopenia. Patient was considered immunosuppressed due to chronic liver cirrhosis. Patient’s treatment plan for CNS cryptococcosis included induction therapy with amphotericin and fluconazole for 6 weeks, followed by consolidation therapy with oral fluconazole. However, patient’s hospital course was complicated by E. coli bacteremia, decompensated cirrhosis, esophageal variceal bleeding with acute blood loss anemia requiring numerous blood transfusions and banding, hepatic encephalopathy, and acute kidney failure. Unfortunately, the patient expired due to complications related to hepatic failure.

**Discussion:** Worldwide, nearly 220,000 new cases of cryptococcal meningitis occur each year, resulting in an estimated 181,000 deaths. Management of CNS cryptococcosis in immune-compromised hosts involves treatment targeting the fungal pathogen, reducing the intracranial pressure, and improving the immune status of the patient.

**Conclusion:** We present this case of CNS cryptococcosis presenting as a stroke mimic to highlight the risk factors, characteristics, and challenges in diagnosis and management of this emerging disease in the U.S.

100. Dearth of Recognition Awards Given to Underrepresented in Medicine Individuals by Major US Neurological Societies

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**Introduction:** Influential American medical societies such as the American Academy of Neurology (AAN) and the American Neurological Association (ANA) play a pivotal role in publicly recognizing accomplished physicians/researchers. Underrepresented in Medicine (UIM) researchers (vs. Non-Hispanic Whites) are less likely to receive NIH grants, be promoted, or report high career satisfaction. The extent to which the AAN and ANA give awards to UIM physicians/scientists has not been investigated.

**Methods:** We searched and manually extracted data from the AAN and the ANA awards history available online from 1950-2020 for the AAN and from 1950-2020 for the ANA, focusing on those that exclusively or primarily aimed at individual physician recipients, and recognized as any physician/scientist who self-identified or whom phenotypic appearance
and/or origin name was from any of the following racial/ethnic categories: African American or black, Hispanic or Latino, American Indian or Alaska Native, or Native Hawaiian or Pacific Islander. Primary outcomes were the total number and proportion of awards given to UIM US physician/scientists.

**Results:** Between 1990 and 2019, the AAN presented a total of 222 awards in 15 categories to US physicians/scientists, including 8 (3.6%) to UIM physicians/scientists; of these UIM award recipients, 4 (1.8%) were Black, 3 (1.3%) were Hispanic, and 1 (0.4%) was a Pacific Islander. The first award presented to a UIM physician/scientist (a Black physician), the Michael S Pessin Stroke Leadership Prize, was in 2008. Between 1950 and 2020, the ANA presented 183 awards in 7 categories, including 5 (2.7%) to UIM physicians/scientists, all of whom were Hispanic. The first award presented to a UIM physician/scientist, the Soriano Lecture-ship was in 1989.

**Conclusion:** UIM physicians/scientists rarely receive recognition awards from US Major Neurological Societies. This issue should be further investigated and addressed.

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**101. Olfaction is in the Nose of the Beholder - Effect of Visual Input on Olfactory Threshold Testing**

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**Introduction:** It has long been recognized that visual input can impact upon olfactory perception. This has been demonstrated with effects of color on intensity and characteristics of smell (Dematte, 2008; Piqueras-Fiszman, 2015; Zellner 2015). Visual stimuli enhanced olfactory detection upon presentation of congruent pictures, but threshold measurements were not noted (Gottfried, 2003). This has been postulated to be due to a cortical top down phenomena, effect of odors on affect, impact of suggestion, or expectation effect (Engen, 1972). Despite this, Bhise et al demonstrated lack of impact of visual stimuli on olfactory threshold testing using the Phenyln Ethyl Alcoholic Threshold Test (Bhise, 2010). The Alcohol Sniff Test (AST), another threshold test, is standardized with eyes closed to eliminate such visual stimuli (Davidson, 1997; Alpert, 2000). The effects of eyes open while performing this test of olfactory function has not heretofore been described.

**Methods: Case Study:** A 42-year-old right-handed male with chronic sinus infections, one year prior to presentation, underwent cardiac ablation for atrial fibrillation. One week later he noticed a sudden complete loss of taste and smell.

**Results:** Olfactory testing: Anosmia on: phenylethyl alcohol threshold: Left (L) > -2.0, Right (R) > -2.0; Brief Smell Identification Test: 3; Olfactometer N-butanol Threshold Test: L = 0.0, R = 1.0; University of Pennsylvania Smell Identification Test: L = 11, R = 8. Sniff Magnitude Test: Sniff magnitude ratio: 0.92. Sniff-n-Sticks: Threshold: L <1, R <1. Odor Memory Test: 10 sec: 1, 30 sec: 1, 60 sec: 1, total: 3; Retronasal Olfaction: Retronasal Smell Index: 1 (anosmia); AST performed repetitively with eyes closed: 0 cm (anosmia); AST performed with eyes open: 9 cm (hyposmia).

**Conclusion:** The structure responsible for the retrieval of semantic associations is attributable to the hippocampus, and the rostromedial orbitofrontal cortex may be the primary site for olfactory-visual integration (Gottfried, 2003). Moreover, the intraparietal sulcus is a potential site for odor source localization and attention orientation (Gottfried, 2003). Expectation effect, which has been described to occur with olfactory stimuli (Zellner, 1991), may most effectively explain this patient’s findings. When performing olfactory threshold tests, elimination of visual stimuli may best serve to reduce any impact of suggestion or expectation effect and would generate more standardized results.

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**102. Low-Pressure Hydrocephalus in Adults- Review of a Rare Clinical Entity**

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**Objective:** Low-pressure hydrocephalus (LPH) is a rare clinical entity defined by the presence of ventriculomegaly and gradual neurological decline at intracranial pressure (ICP) below the expected level (<70 mm H2O). Our study aims to provide a comprehensive review of the available LPH literature focusing on the recent advances in management.

**Method:** The review was conducted according to the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We performed a literature search on PubMed/MEDLINE and Google Scholar for all cases of LPH from 1994 to 2020. Articles in the English language involving adults at least 18 years, with clinical presentation and brain imaging consistent with hydrocephalus and failure of resolution with standard drainage pressures, were included in our study. Articles involving pediatric age group (<18 years) and without confirmatory imaging were excluded from the review. The recorded data for the descriptive analysis included patient demographics like age and gender, primary etiology, clinical presentation, bridging and definitive interventions, and patient outcomes.

**Results:** The literature search identified 540 records, and after screening and applying eligibility criteria, we included 41 full-text articles. The studies contained data of 148 adults. Among these patients, 61 (41.2%) were females, 82 (55.4%) were males, and five had unspecified gender. The three most common etiology of LPH included hemorrhage (67- 45.2%), trauma (32- 21.6%), followed by neoplasm (23- 15.5%). Affected individuals commonly presented with a reduced level of consciousness which was evident among 84 (56.7%) patients. An external ventricular...
drain was placed in 42 (28.3%) patients, and the commonly used bridging intervention was sub-atmospheric cerebrospinal fluid drainage, done in 68 (45.9%) patients. The frequently employed definitive form of treatment was shunt insertion or revision, done among 64 (43.2%) patients. With appropriate intervention, 70 (47.2%) patients returned to their pre-LPH neurological baseline, and the overall mortality was 10.8% (16 patients).

**Conclusion:** LPH is a paradox: hydrocephalus with low pressure. It is a challenge to diagnose for the practicing physician. The rationale for any treatment option in LPH is to resolve ventriculomegaly and improve neurological function. Ventriculoperitoneal shunt procedures are the most commonly performed procedure, while endoscopic third ventriculostomy appears to be an acceptable alternative. Large-scale randomized clinical trials exploring new interventions and comparing the available treatment modalities are required to develop a standardized algorithm to manage LPH patients.

### 104. Race/Ethnic Disparities Publications in Neurological Journals During an Era of Heightened Awareness to Issues of Diversity, Equity and Inclusion

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**Introduction:** The extrajudicial killing of George Floyd and others, and the disproportionate effects of Covid-19 on communities of color, have led to greater awareness of structural racism in healthcare. As a result, several neurological departments, medical societies and neurological journals are increasingly committed to enhancing institutional race/ethnic diversity and healthcare delivery to underserved populations. Yet the impact of antiracism efforts on the content of journals, as measured by publications related to diversity, equity and inclusion (DEI) is unclear. Our goal was to determine the yearly rates of DEI-related publications in the top general neurology and neurological sub-specialty journals and compare them to other biomedical journals. We further sought to gauge journal editorial board diversity.

**Methods:** We included publications from general neurology and neurological subspecialty journals between 2015 and 2020 including: JAMA Neurology, Annals of Neurology, Neurology, Stroke, Epilepsy, Multiple Sclerosis, Headache, Sleep, Movement Disorders, Journal of Neurooncology, Pediatric Neurology, Muscle & Nerve, Neurorehabilitation and Neural Repair. For comparison we included the five most impactful biomedical journals as measured by H-Index. We performed a PubMed search in each using MESH and title search terms related to race, ethnicity, gender, equity and diversity. Rates of DEI-related publications were calculated using total yearly publications as the denominator. Linear regression and a right-tailed F-test were used to analyze the data. Finally, we polled editors-in-chief to gauge the diversity of their journal’s editorial boards.

**Results:** Combined yearly rates of DEI-related publications in neurological journals were 1.45, 1.40, 1.41, 1.07, 1.76, and 0.81 for consecutive years 2015 to 2020. There was no change in rate of DEI publications by year in neurological journals as a whole ($R^2 = 0.156$, $p=0.44$). Yearly rates of DEI-related publication in the top-cited medical journals were 0.64, 0.74, 0.83, 1.20, 1.19, and 2.20. The top cited medical journals saw a statistically significant linear increase in DEI related publication between 2015 and 2020 ($R^2 = 0.7919$, $p=0.017$). Of the 13 neurological journals polled, we received three responses that included information about 68 associate editors, of which 20 (30%) were women and 5 (7%) underrepresented in medicine.

**Conclusion:** While neurological journals had a higher baseline rate of DEI-related publications vs. top cited biomedical journals, unlike the top cited medical journals, during a period of heightened awareness, DEI-publications in neurological journals did not increase between 2015-2020.

### 105. Need for Enhancing the Knowledge of Medical Students Regarding Autism Spectrum Disorder (ASD) and Neurodevelopmental Disorders

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Autism Spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and the presence of restricted and repetitive behaviors. The behavioral phenotype of ASD varies considerably from person to person. A 2018 report from the Centers for Disease Control and Prevention (CDC) indicates that 1 in 59 children are diagnosed with ASD. We performed a search of common electronic databases including Medline, Scopus and reviewed studies related to primary care providers’ knowledge of ASD and evidence-based interventions for ASD and other neuropsychological disorders. We also conducted a literature search through PubMed and reviewed data regarding medical student clerkship curricula from various universities posted on their websites, and examined our own medical school curriculum to see how much knowledge about ASD and neurodevelopmental disorders was provided. Our search revealed that very few schools had disability specific content incorporated into medical school curricula. An excellent example of such an initiative was a partnership between the Nisonger Center and the Ohio State University (OSU) College of Medicine. Here, the disability specific content is incorporated into the medical school curriculum to ensure that students have the knowledge, skills, attitudes and competence necessary to provide quality, effective and compassionate care to patients with autism spectrum disorder (ASD) and other neurodevelopmental disorders. At Penn State College of Medicine, we gave psychiatry grand rounds for neurology and psychiatry physicians and trainees. Zoom polls were used to assess their knowledge about ASD and other neurodevelopmental disorders. Our results clearly indicated a need for more education in this area and to create a training program to address this need. This is particularly important in view of the increasing prevalence of ASD and other neurodevelopmental disorders. Our initiative will target medical
schools, as today’s medical students are tomorrow’s physicians. We plan to implement it for third-year medical students and assess its long term impact by using the Kirkpatrick model. We plan to use resources such as “Autism Curriculum Guide” provided by the Nisonger Center. The curriculum will also include a component of diversity. Improving the medical curriculum in this way will help our students empower individuals with disabilities and improve their skills. attitudes and knowledge about persons from diverse cultural backgrounds with ASD and other neurodevelopmental disorders.

106. Social Networks and Social Media in Neurology Education: Key Applications and Potential Use for Educational Purposes

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Background: According to recent estimates, almost four billion people globally use social networks and social media. From the launch of Facebook to the latest TikTok videos, in less than two decades, they have revolutionized the modality of interactions and opened up a new world. Here, we reviewed the key applications of seven among the most used platforms worldwide within neurology and neuroscience education. We highlighted benefits and disadvantages, and discussed their potential use for educational purposes.

Methods: The social platforms studied via explorative analysis and peer-reviewed papers were Facebook, YouTube, WhatsApp, WeChat, Instagram, Twitter and TikTok.

Results: YouTube is the largest online repository of educational videos on a plethora of neurological topics, and measures for quality assessments, including neuroaxial block and lumbar puncture, have been defined. WhatsApp and WeChat have been adopted as telemedicine and training tools after the outbreak of the COVID-19 pandemic. While YouTube and Facebook videos are used as platforms to share, simplify, and summarize basic and advanced neuroanatomy concepts, Instagram posts seem to be more frequently exploited for schematic representations of fundamental aspects. Instagram and Facebook can additionally be used to highlight role models from history and contemporary neurology, promote diversity and showcase the variety of neurology research areas to potentially fight neurophobia. Twitter allows online journal clubs, case studies, virtual rounds, live and asynchronous Q&As, and added a new learning and networking dimension to seminars and conferences. Specific hashtags favour the retrieval of mentoring advice on Twitter and Instagram, which, moreover, can be utilized to create a sense of identity and belonging across all the steps of a neurologists’ career, from match day to retirement. TikTok and Instagram Reels can give a glimpse, either as a humorous representation or a genuine one, of clinical neurologists’ life. They might also be used to sustain identity development. Furthermore, social media platforms can be part of public engagement initiatives and outreach activities within different digital communities.

Conclusions: Considering the reported advantages, which includes scalability, quick incorporation, reception on the learners’ side and the increasing numbers of online users, and the limited number of disadvantages, careful use of social media platforms may enrich the educational experience for learners and faculty alike.

107. Cervical Tethered Cord: Capturing the Elusive

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Though tethering of the cord is seen in a multitude of conditions, its predilection to lumbar region is most common. Majority of the reported cases are mostly due to occult spinal dysraphisms. Here we report an unusual case of tethering in the cervical region in a post operative case of multilevel cervical laminectomy done many years ago. The region of tethering and the cause assume significance and have never been reported earlier.

108. Underrepresented in Medicine: Identifying Representation in Neurology Subspecialty Society Recognition Awards

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Objective: To evaluate the proportion of individuals who self-identify as part of an ethnic/racial group considered underrepresented in medicine (UIM) among recognition award recipients from neurology subspecialty societies over the past two decades.

Background: The presence of gender disparities in medicine, including neurology, has been established. Moreover, gender disparities have been noted in various medical and neurology subspecialty societal recognition awards. While there have been attempts to analyze representation amongst those from UIM groups throughout the entire physician workforce, there remains a paucity of evaluations regarding UIM inequities within medical subspecialties. Therefore, it is unclear if inequities exist within neurology subspecialties for UIM. We hypothesized that those UIM will be disproportionately underrepresented in neurology subspecialty societies’ recognition awards.

Methods: Lists were obtained from 6 neurology subspecialty society websites’ award pages. The 6 neurology subspecialty societies were the American Association of Neuromuscular & Electrodiagnostic Medicine, American Epilepsy Society, American Headache Society, Neurocritical Care Society, North American Neuro-Ophthalmology Society, and the American Neurological Association.
Society of Vascular and Interventional Neurology. The lists included the names of individual recognition awardees over the past 20 years (2000 - 2020). Contact information was obtained for awardees by searching publicly available records online (ie. PubMed). A 6-question anonymous survey was emailed to all awardees to inquire from which society they won an award and self-identifying questions based on US Census racial/ethnic classifications (US Census 2020). The 2004 AAMC definition was used to define races included as UIM. The survey was sent on April 12, 2021 and will be closed on April 30, 2021. The primary outcome measure is the percentage of UIM award winners among total award winners within each society and compared to overall UIM representation within the physician workforce. This study was reviewed and exempted by the Michigan State University Institutional Review Board (IRB).

**Results:** Surveys were sent to 96 total awardees from 6 neurology subspecialties. Currently, we have a survey response rate of 15% (14 of 96) surveys with 13/14 (93 %) of respondents self-identifying from non-UIM racial/ethnic groups. Additional data collection and analysis is pending.

**Discussion:** Our results are preliminary, and the survey is still open. Further data collection and analysis is needed to support or refute our hypothesis. Our results may help us to identify an area in which our profession can improve.

337. Assessment of the Efficacy of a Virtual Neurology Elective for Medical Students Developed During COVID-19

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**Introduction:** As a result of the COVID-19 pandemic, in-person medical electives were widely suspended in March 2020. To address the need for curricular alternatives, the Johns Hopkins Neurology Clerkship Team developed a virtual neurology elective to serve as an introductory neurology course and foster telemedicine skills development.

**Objectives:** (1) To increase student confidence in telemedicine skills. (2) To assess the efficacy of a variety of virtual medical education tools.

**Methods:** We piloted a 2-week course titled “Virtual Patient Rounds in Neurology” which was held once in April 2020 and once in May 2020. The curriculum consisted of: (1) a virtual rounding component, (2) a lecture series with international medical education leaders titled “JHNeuroChats”, and (3) asynchronous educational activities including the AAN’s NeuroBytes modules and AMA’s Health Systems Science modules. Students completed surveys before and after the course. Student’s t-tests were used in the analysis.

**Results:** In total, 14 students enrolled in the two iterations of the course, with 64% (9 of 14) students having taken 0-1 virtual electives prior. During the virtual rounding experience, faculty leaders directly supervised 50% (7 of 14) of students as they conducted tele-histories and 14% (2 of 14) of students as they conducted tele-neurology physical exams. At course completion, students reported increased confidence in conducting both tele-histories (2.14 to 3.93; p<0.0001) and tele-neurology physical exams (1.36 to 3.14; p<0.0001). All students reported that faculty provided effective teaching, with 93% (13 of 14) reporting satisfaction with the overall quality of their educational experience. Student satisfaction with the elective components were as follows: 100% (14 of 14) with the virtual rounding, 93% (13 of 14) with the “JHNeuroChats” lecture series, 93% (13 of 14) with the AAN Neurobytes modules, and 64% (9 of 14) with the AMA Health Systems Science modules. Overall, 57% (8 of 14) of students reported an increased likelihood of pursuing a career in neurology.

**Conclusion:** Our virtual neurology elective successfully increased student confidence in their telemedicine skills. There was high student satisfaction with virtual rounding, our lecture series taught by international medical education leaders, and asynchronous educational materials made available through professional societies. Future steps should include increasing supervised history-taking and physical examination on virtual platforms in telemedicine electives and clerkships.

109. Focal Status Epilepticus from Posterior Reversible Encephalopathy Syndrome in a COVID-19 Patient

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**Introduction:** We present a patient who developed focal status epilepticus and Posterior Reversible Encephalopathy Syndrome (PRES) associated with COVID-19. To date, only one such case has been reported in the literature [1].

**Case Report:** A 51-year old female was transferred to our hospital for worsening respiratory distress and mechanical ventilation eight days after being diagnosed with COVID-19. On hospital day 26, the patient started to desaturate, and her blood pressure started to increase, with a peak pressure of 212 mmHg. On hospital day 27, the patient started having a right-sided nystagmus and a tonic/clonic seizure localized to the right arm. The patient was given five successive doses of lorazepam (2 mg) over the next two hours. EEG showed continuous 2.5-3 Hz rhythmic 100-200 μV sharp and slow wave discharges over the left occipital region, consistent with non-convulsive status epilepticus. Levetiracetam (1500 mg) was administered thereafter, after which the seizures ceased. A brain CT showed a bilateral posterior hypodensity suggestive of PRES. On hospital day...
31, this was confirmed with an MRI. The patient was thereafter started on a regimen of levetiracetam (1500 mg b.i.d.), phenytoin (100 mg t.i.d.), and clobazam (10 mg b.i.d.).

**Discussion:** The MRJ/CT findings suggested that this was PRES possibly induced by COVID-19. To further our hypothesis, it has been suggested in the literature that endothelial dysfunction caused by SARS-CoV-2 might lower the blood pressure thresholds to trigger PRES [2]. Therefore, when the patient became hypertensive when she started desaturating on hospital day 26, this increase may have been enough to cross this lowered threshold and cause PRES. In establishing that the patient’s PRES was uniquely due to COVID-19, it is important to rule out any underlying hypertension, since 75% of patients who develop PRES in absence of COVID-19 have moderate-to-severe hypertension [3]. Our patient therefore notably did not have a history of hypertension and was almost exclusively normotensive during the hospitalization.

**Conclusion:** We have presented here, to our knowledge, only the second case of a COVID-19 patient who presented with PRES and focal status epilepticus. The patient’s seizure activity is currently controlled with levetiracetam, phenytoin, and clobazam, and she is recuperating in in-patient rehabilitation.


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**Purpose:** In the US, perampanel is approved for focal-onset seizures (FOS; adjunctive and monotherapy) in patients aged ≥ 4 years and generalized tonic-clonic seizures (GTCS; adjunctive) in patients aged ≥12 years. Some anti-seizure medications can exacerbate myoclonic and absence seizures in patients with generalized seizures. Here, we performed a post hoc pooled analysis of Phase III and Phase II studies to assess the efficacy and safety of adjunctive perampanel for myoclonic and absence seizures in adult, adolescent, and pediatric patients.

**Methods:** In Study 332 (NCT01393743), adolescent/adult patients aged ≥12 years with idiopathic generalized epilepsy and GTCS received placebo or adjunctive perampanel 8 mg/day. In Study 311 (NCT02849626), pediatric patients aged 4 to <12 years with FOS or GTCS received open-label perampanel up to 16 mg/day. In Study 232 (NCT01527006), pediatric patients aged 2 to <12 years with epilepsy received open-label perampanel up to 0.18 mg/kg/day. For these analyses, data from patients with myoclonic and/or absence seizures during baseline were pooled. Assessments included median percent change in seizure frequency per 28 days, 90% responder rates, and treatment-emergent adverse events (TEAEs).

**Results:** Of 393 patients, 66 had myoclonic seizures (placebo, n=23 [mean (standard deviation) age: 28.1 (8.9) years]; perampanel, n=43 [18.8 (11.9) years]) and 72 had absence seizures (placebo, n=33 [28.8 (13.2) years]; perampanel, n=39 [21.0 (12.2) years]) at baseline; patients with both seizure types are counted in both groups. Median percent reductions in seizure frequency per 28 days were observed in both the placebo and perampanel groups: myoclonic, 52.5% and 24.6%; absence, 7.6% and 25.1%, respectively. For placebo and perampanel, 90% responder rates were: myoclonic, 26.1% (n=6/23) and 14.0% (n=6/43); absence, 18.2% (n=6/33) and 25.6% (n=10/39), respectively. TEAEs with placebo and perampanel occurred in 18 (78.3%) and 36 (83.7%) patients with myoclonic seizures, and 25 (75.8%) and 34 (87.2%) patients with absence seizures, respectively. With perampanel, the most common TEAEs were dizziness and fatigue.

**Conclusions:** Despite small patient numbers, these data suggest adjunctive perampanel does not worsen myoclonic or absence seizures in adult, adolescent, and pediatric patients. Seizure reductions were observed for both seizure types; however, this analysis was not powered to make comparisons between placebo vs perampanel.

**Funding:** Eisai Inc.

**111. Population Pharmacokinetics and Its Relationship with Adverse Events of Oxcarbazepine in Adult Patients with Epilepsy**

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**Objective:** This study aimed to develop a pharmacokinetic (PK) model of oxcarbazepine (OXC) and analyse the relationship between monohydroxylated derivative (MHD), an active metabolite of OXC, and the adverse events of OXC.

**Methods:** We obtained 711 OXC samples from 618 patients with epilepsy who were enrolled in the Epilepsy Registry Cohort of Seoul National University Hospital from February 2011 to January 2014. To develop a PK model, we combined data from a PK study of 40 patients evaluating a single oral dose of 30 mg/kg OXC. The plasma PK model was developed using a nonlinear mixed-effect modelling method with NONMEM (ver 7.3). The differences in PK variables between the groups with and without the adverse events were statistically analysed.

**Results:** A one-compartment model with a first-order absorption model and proportional residual error adequately described the MHD concentration-time profiles. The only covariate incorporated for CL/F and V/F was body weight. Of the 447 patients analysed, 28 (6.26%) had dose-related adverse events (DRAEs), which were dizziness, somnolence, headache, and diplopia. For DRAE occurrence, the cut-off values of the MHD trough and AUC were 12.27 mg/L (specificity 0.570, sensitivity 0.643) and 698.5 mg h/L (specificity, sensitivity 0.571), respectively. Multivariate analysis showed the sole dizziness symptom was significantly

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associated with both the MHD trough and the AUC (p=0.013, p=0.038, respectively).

**Conclusion:** We newly developed a population PK model using sparse sampling data from patients with epilepsy, and the model better reflects the actual clinical situation.

112. Testing the Salzburg Criteria in Cefepime Induced Non-Convulsive Status Epilepticus

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**Objective:** To test the Salzburg criteria for non-convulsive status epilepticus (NCSE) in cefepime induced NCSE.

**Background:** Cefepime is a fourth-generation cephalosporin known to cause neurotoxic effects. Cefepime has been associated with encephalopathy and NCSE which usually becomes apparent 2-8 days after initiating cefepime. Generalized periodic discharges (GPDs) with or without triphasic morphology are the most common electroencephalogram (EEG) pattern which fall in the ictal-interictal continuum pattern on EEG making definite diagnosis of NCSE and its treatment difficult.

**Case Description:** 50-year-old male with history of spina bifida, hydrocephalus, ventriculo-peritoneal shunt placement, hypertension, chronic urinary tract infections (UTI) and epilepsy on lacosamide, levetiracetam, and oxcarbazepine, was admitted with encephalopathy, which was deemed secondary to UTI and started on cefepime. His usual seizure semiology was focal (right upper extremity shaking) to bilateral tonic-clonic seizures. Initial EEG showed 1-3 Hz GPDs with triphasic and biphasic morphology with no improvement with IV lorazepam 2 mg, IV lacosamide 400 mg and IV fosphenytoin 1900 mg, hence, it was deemed non-ictal based on the modified-Salzburg criteria. Cefepime was discontinued. The encephalopathy worsened 48-hours after and the repeat EEG showed persistent above mentioned EEG pattern. At that point, cefepime induced non-convulsive status epilepticus was considered and ketamine infusion (1.5mg/kg load, 2.5 mg/kg/hr infusion) was started. Clinical improvement and resolution of EEG pattern was noticed within 24 hours. The patient was subsequently discharged home.

**Conclusions:** Time interval used to assess EEG and clinical changes after IV anti-seizure medications to define NCSE is not defined. Initial attempt to classify the pattern as ictal using clinical and EEG improvement from IV anti-seizure medications in this case failed, but both EEG and clinical improvement was seen after 24 hours of IV ketamine infusion. Our report highlights need to quantify the time interval that should be used to define NCSE in the Salzburg criteria through the trial of IV anti-seizure medication.

113. Status Epilepticus in the Setting of COVID-19 Infection

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**Background:** COVID-19 has been associated with many neurological presentations, some of the most frequently reported are acute epileptic seizures, and Status Epilepticus (SE). The cause of these neurological issues is believed to be due cytokine storm and the resulting inflammation. However, there are various other mechanisms that could cause seizures in COVID patients such as hypoxia, metabolic imbalances, and fever. Treatment of seizures during an active COVID infection poses several challenges including respiratory depressive effects of benzodiazepines used to break status epilepticus as well as drug interactions between many anti-seizure medications and antivirals.

**Case Presentation:** A 79-year-old female with hypertension and hyperlipidemia was admitted with a 10-day history of shortness of breath, fever, and dry cough. The patient tested positive for COVID via RT-PCR. Patient continued to have progressively increased O2 demands and was transferred to the Medical Intensive Care Unit (MICU) and intubated on day 6 of hospital stay. The patient’s hospital course was further complicated by sepsis with blood cultures positive for *E. coli* and superimposed MRSA pneumonia. The patient was treated with vasopressors and antibiotics including Ertapenem. The patient further deteriorated into multi-organ failure. The patient began having seizure-like activity on 30 day of hospital stay. The patient had left arm jerking, head shaking and facial deviation to the left during these episodes. EEG showed focal seizure activity originating from the right hemisphere with secondary generalization lasting 2-3 minutes in a near continuous fashion. Patient’s seizures were eventually controlled with Keppra 2g BID, Vmpat 200mg BID, Depakote 750mg BID, and Propofol in addition to midazolam drip. The patient was later taken off ventilatory support according to family wishes due to worsening respiratory status and multi-organ failure.

**Discussion:** SE is a serious condition that can arise from COVID-19 infection. Onset of SE in COVID-19 patients commonly occurs after the development of GI/respiratory symptoms. While the patient was taking a carbapenem which can lower seizure threshold, the risk difference between carbapenems and non-carbapenems is negligible. The patient’s SE was likely due to the patient’s underlying infection.

**Conclusion:** While the exact mechanism of how COVID-19 causes SE is currently unknown, COVID-19 has been associated with various neurological conditions. Our patient developed a convulsive SE originating focally from the right hemisphere associated with severe COVID-19 infection.

114. Electroencephalographic Patterns in Patients with Covid-19: A Single Center Observational Study

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**Background:** COVID-19 related encephalopathy has been widely recognized. EEG is the cornerstone of diagnostic testing in suspected cases. Data on specific EEG findings is
sparse. We sought to study the electrographic patterns in hospitalized patients with SARS-CoV 2 (COVID-19) infection on electroencephalogram (EEG).

**Methods:** We included adult patients admitted with COVID-19 infection at Hartford Hospital between March 1st 2020 and June 1st 2020 who underwent EEG testing.

**Results:** A total 30 patients met inclusion criteria. The mean age was 68.4 years, with 67% of the patients being men. Clinically, their mental status was categorized as alert (27%), lethargic (23%), stuporous (33%) and comatose (17%). Electrographically, 93% (28/30) had encephalopathy. Based on EEG classification, 30% had mild, 40% had moderate and 23% had severe encephalopathy. A total 28 patients had some degree of encephalopathy on EEG, 16 of whom were classified as having moderate to severe encephalopathy. Around 20% (6/30) of patients were found to have focal slowing all of whom had structural lesions on imaging (stroke, craniotomy, chronic subdural hematoma, and meningioma). Around 6% (2/30) were found to have epileptiform discharges (EDs) specifically frontal sharps and temporal sharps. 1 patient without focal slowing but with severe encephalopathy was found to have epileptiform discharges. 2 of the 3 patients with EDs were found to have structural lesions on imaging; these lesions included bilateral subdural hematomas and a chronic left MCA infarction.

**Conclusions:** In our study we found encephalopathy to be the most common finding but no other specific EEG features in patients with COVID-19 infection. We did note some discrepancy in the clinical and electrographic grades of encephalopathy with seemingly alert patients having moderate to severe encephalopathy on EEG. We did find a higher percentage of patients with epileptiform discharges than reported. Larger studies are needed to study these patterns further.


115. Complete Heart Block Mimicking Recurrent Seizures: A Case of Convulsive Syncope

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**Objective:** To highlight the importance of video-EEG (electroencephalogram) with simultaneous ECG (electrocardiogram) recording in the workup of patients with recurrent seizures with unclear epilepsy diagnosis. Background: Convulsive syncope is a common mimic for seizures and as many as 20% to 30% of patients with epilepsy may be misdiagnosed. Abnormal movements such as tonic flexion, extension or myoclonus can occur and are due to cerebral hypoxia in the setting of syncope rather than from actual brain epileptiform discharges. When these movements are present, it may occasionally be difficult to make a diagnosis on clinical grounds. Convulsive syncope occurs in many causes of syncope including cardiovascular causes such as cardiac arrhythmias or heart block. In this case, we describe a patient who presented with recurrent tonic seizure-like activity but was found to have complete heart block.

**Methods:** Case report.

**Results:** 60-year-old woman with history of hypertension, chronic kidney disease, type 1 diabetes, alcoholic hepatic cirrhosis, Grave’s disease, atrial fibrillation, and rheumatoid arthritis, severe deconditioning and debility, who presented to the emergency department with seizure-like episodes. These were manifested by generalized tonic posturing with extension of limbs, grunting, pupillary dilation, and head turning to left side, lasting a few seconds followed by lethargy for few minutes. She had also been having worsening frequent falls, preceded by light-headedness, in the prior three weeks. Physical exam including neurologic and cardiac exam was unremarkable. CT brain was unremarkable. Labs were normal except for elevated B-type natriuretic peptide (BNP) to 1048. Patient was loaded with levetiracetam and started on 500mg BID maintenance. Patient had a video EEG which captured three episodes of unresponsiveness followed by generalized tonic-like posture and showed diffuse generalized slowing with no epileptiform discharges. The EKG correlate demonstrated that all these episodes were preceded with brief asystole (absent QRS complex) suggesting complete heart block lasting for few seconds with no escape rhythm. Cardiology was consulted and a dual chamber pacemaker placed with complete resolution of the seizure-like spells while her levetiracetam was discontinued.

**Conclusion:** In the clinical setting, convulsive syncope needs to be considered in the differential diagnosis of recurrent seizures-like episodes. Video EEG with simultaneous EKG recording is very key in making the distinction between the two diagnoses as it can reveal syncope from a cardiovascular cause such as a heart block or cardiac arrhythmia which can prevent a misdiagnosis of epilepsy.

116. Sub-Cortical Structural Changes and Network Involvement in Medial Temporal Lobe Epilepsy: A VBM Meta-Analysis

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**Background:** Medial temporal lobe epilepsy (MTLE) is the most common form of adult epilepsy referred for surgery. Structural changes in the hippocampus of patients with MTLE are associated with positive surgical outcomes but subtle extra-hippocampal changes show the opposite correlation. Voxel-based morphometry (VBM) detects these
changes, but VBM literature contains variable results; a meta-analytic approach is needed. Two meta-analyses (Barron et al., 2013; Eslami et al., 2020) studied VBM data in MTLE but used a small sample size and did not accommodate for contralateral coordinates, respectively; neither corrected for database bias towards spurious convergence. This VBM meta-analyses uses a larger dataset and more statistically robust approach, cluster-wise family wise error (FWE), to confirm prior reports and identify additional remote structural changes in MTLE.

Methods: The literature search inclusion criteria required manuscripts to be peer-reviewed, published in English, and report 3-D standard-space coordinates from whole-brain imaging contrasts of MTLE patients with controls. This yielded 31 manuscripts, 43 experiments, and 404 foci, representing 1209 MTLE patients. BrainMap Tools (http://www.brainmap.org/) were used to enter data into the BrainMap database (Sleuth 3.6), create a workspace of MTLE coordinates (Sleuth 3.0.4), and perform activation-likelihood estimation (GingerALE 3.0.2); cluster-wise FWE was included in GingerALE parameters. This was done for R-MTLE, L-MTLE, and the combined Recti fl to R-MTLE.

Results: Structural changes in each group are reported in Talairach space, with labels from the Talairach Daemon. R-MTLE: ipsilateral hippocampus (32, -16, -12), Brodmann area (BA) 27 (24, -32, -2), medial dorsal nucleus (MDN) (2, -18, 10), and sub-lobar thalamus (12, -16, 12), and contralateral ventral posterior medial (VPM) nucleus (-14, -18, 8). L-MTLE: ipsilateral hippocampus (-30, -16, 14), MDN (-6, -16, 12), BA 30 (-24, -36, 2), pulvinar coordinates (-12, -28, 10)/(-18, -34, 10), and medial geniculum body (-18, -26, 2), and contralateral MDN (2, -18, 6) and lateral posterior nucleus (LPN) (14, -18, 10). Rectified: ipsilateral hippocampus (30, -16, -14), MDN (-6, -16, 12), BA 27 (22, -36, 0), MDN (4, -16, 12), pulvinar (18, -34, 10), and caudate coordinates (8, 8, 10)/(6, 2, 12)/(12, 14, 6), and contralateral LPN (14, -18, 10).

Conclusions: This coordinate based meta-analysis demonstrates a robust statistical corroboration of Barron (2013) and Eslami (2020) in identification of hippocampal and thalamic structural changes in MTLE. The analysis also identifies changes in the contralateral VPM and MDN; these regions should be explored as potential markers of seizure laterality. Changes in pulvinar and caudate structure were also identified and a network model of MTLE should be pursued with the inclusion of these regions as nodes. This will permit future per-subject functional connectivity assessments of resting-state fMRI data.

117. Hemimegalencephaly with Seizure: A Rare Congenital Malformation in a 22 Months Old Boy
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Introduction: Interpreting studies from patients undergoing intracranial pre-surgical evaluation requires precise anatomical information about electrode location. Several toolboxes are available for this registering the pre- and post-implant brain images and visualizing the electrodes within the brain. However, not all have the same features or are equally adapted for research use.

Method: Here, we comprehensively review available toolboxes from the literature. We have noted the operating system/language platform and which features are present. We then discuss which features are needed for a comprehensive suite that can address the needs of SEEG practitioners and researchers.

Results: We found a total of 14 open-source toolboxes, that met inclusion criteria (open-source and for research purposes). Most had several software dependencies: for pre-implant MRI segmentation, and pre- and post-implant CT/MRI coregistration tools such as FreeSurfer, FSL, ITK-SNAP were used in the development/usage of these pipelines.

Isolated hemimegalencephaly (HME) is a rare congenital malformation of brain development, remarkable for its extreme asymmetry, and is characterized by the overgrowth of part or whole hemisphere. The enlarged hemisphere is manifested by hamartomatous characteristics with a dysplastic cell array of atypical morphology. Traditionally the genetic theories regarding the pathogenesis of HME are considered due to disturbance in cell signaling during neuroblast migration, cell differentiation, and proliferation, patterning, and symmetry. HME can present as isolated or associated with several neurocutaneous syndromes. The clinical picture varies depending on the severity of the malformation; however, HME patients typically exhibit refractory epilepsy, macrocephaly, colpocephaly, global developmental delay, intellectual disability, hemibody hypertrophy, and hemiparesis. Early diagnosis is crucial because despite neuroimaging and pathologic evidence, hemimegalencephaly sometimes still is unrecognized. Also, misdiagnosed as obstructive hydrocephalus or cerebral neoplasm can lead to unnecessary surgical procedures. Although hemispherectomy has high morbidity, it is recommended early for patients with severe, intractable epilepsy. We report a diagnosed case of a 22-month-old boy hemimegalencephaly who presented with seizures and was successfully treated with antiepileptic medications.
Ten of the toolboxes were based on MATLAB (SEEGview, iELVIS, iEEGview, iElectrodes, IntraNat Electrodes, Ntools, moviEEG, FieldTrip, eConnectome, BrainMapper), three on Python (IELU, img_pipe, and 3dSlicer), and one on C++ (BioImage Suite). Many used either Visualization Toolkit (VTK, Kitware Inc.) or Insight Toolkit (ITK) toolboxes for visualization. Regarding operating system dependencies, most of the tools were compatible with both Linux and Mac OS X, while some of them also were executable in Windows. One of the most important features for research is to have group data analysis features, which to our knowledge six of the toolboxes are capable of performing.

Discussion/Conclusion: Post-implant electrode localization and visualization are necessary for proper analysis of SEEG and ECoG data, including accurate localization of these electrodes, visualization, and more importantly using the same pipeline for analysis of multiple patients. While there are a large number of toolboxes, not all have all the features that are required for all settings and research studies. We suggest the development of comprehensive standard tools for this process, drawing on the strengths of available software and adding some key new features. Important features include adding databasing of contacts for identifying patients based on electrode location; inclusion of clinical information; fusion of physiologic data with imaging; fusion with other modalities such as diffusion imaging; and, performing group analysis - of utmost importance when dealing with bigger data sets.

119. The Future of Telemedicine in Epilepsy Patients
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This quality improvement study aims to determine the “show-rate” of epilepsy patients during telemedicine, explore factors behind the “show-rate,” and survey patient satisfaction with telemedicine. This study comprises a retrospective chart review of patient encounters with Drs. Ching Tsao and Valeriya Poukas at Temple University Hospital from March 16, 2020 to August 1, 2020 along with administering a prospective survey. We found a significantly higher “show-rate” in patients with a suspected or confirmed diagnosis of epilepsy (80.0%) than compared to visits the year prior (71.2%), t(384) = 2.130, p = 0.034 and all-time (74.7%, t(417) = 3.873, p < 0.001). Phone surveys revealed that 54.1% of patients either preferred phone visits or had no preference between phone or in-person visits. Patients spent on average $15.02 per visit to travel to appointments. We conclude that telemedicine should be offered more regularly to epilepsy patients, with the option for in-person visits for those who prefer them.

120. Postpartum Depression in Women with Epilepsy
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Introduction: Sex hormone fluctuations are known to affect the neurobiology of epilepsy and mood disorders. In this study, we test the hypothesis that women with epilepsy (WWE) who experience seizures early postpartum have a higher risk of postpartum depression (PPD). We chose WWE on lamotrigine, the most commonly prescribed antiseizure medications during pregnancy, with known mood-stabilizing effects.

Methods: We included all WWE on lamotrigine monotherapy followed at Brigham and Women’s Hospital Epilepsy-Obstetric clinics between January 2018 and December 2020. Clinical data on seizure types and frequency, therapeutic drug monitoring during pregnancy was collected in a longitudinal prospective database. Chart review was performed to obtain additional information on seizure frequency from preconception year through 6 weeks postpartum, medical and surgical history, Edinburgh Postnatal Depression Score (EPDS) score at 6-weeks postpartum. We utilized t-tests, chi-squared analysis, and multivariate logistic regression to compare variables of interest between women with different EPDS scores. Exclusion criteria: medication changes during pregnancy, aborions, non-epileptic seizures, and poor adherence.

Results: Amongst 54 WWE on LTG monotherapy, 46 met the inclusion criteria, but only 31 had adequate information on seizures and mood to be included in the analysis. Mean age was 35 years and 87% (n = 27) were white. EPDS data is as follows: 74% (n=23) women scored 0-6 (minimal depression), 10% (n=3) women scored 7-13 (mild depression), 13% (n=4) scored 14-19 (moderate depression), and 3% (n=1) scored 20-30 (severe depression). 80% (n=25) had focal epilepsy while the rest had generalized epilepsy. 20 women remained seizure free throughout pregnancy and postpartum; 11 were refractory. PPD was identified in 18% (n=2) of women with refractory epilepsy and 20% (n=4). Multivariate regression analysis demonstrated that a prior history of depression was significantly correlated with a higher EPDS score (p = 0.024), while none of the other factors tested (age, race, epilepsy type, seizure freedom status, seizure frequency changes in postpartum compared to pregnancy or in pregnancy compared to preconception) were significant.

Conclusion: Results suggest that history of depression is associated with a higher risk of depressed mood in early postpartum WWE. Seizure occurrence during postpartum period did not have a strong correlation with a depressed mood in our small cohort. Future studies may benefit from comparing WWE on lamotrigine to WWE on other antiseizure medications to clarify the role of lamotrigine for seizure control and mood stabilization in this cohort.

338. Encephalopathy, Epileptiform Activity, and Seizures in Patients with COVID-19
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Objectives: Neurological manifestations are commonly observed in patients with COVID-19. However, the...
associations of encephalopathy and seizures with COVID-19 have not been fully established. The aim of this study is to determine the risk of encephalopathy, epileptiform activity and seizures in patients with COVID-19.

Methods: We performed a retrospective review of medical records from 131 consecutive patients with COVID-19 who underwent EEG studies during hospitalization, with a total of 166 EEG studies between March 1, 2020 and February 28, 2021. Data were extracted on demographics, clinical history and EEG features.

Results: The mean age of the 131 patients was 60.9 ± 17.0 years (mean ± SD, range: 19 to 93). Seventy-two (55.0%) patients were male and 59 (45.0%) were female. Of 166 EEG studies, 52 (31.3%) were 40 minutes and 144 (60%) ran for more than four hours. Normal EEG background frequency (8-12Hz) was observed in only 27 (16.2%) studies. Mild encephalopathy (7-8 Hz) was present in 39 (23.5%) of studies, moderate encephalopathy (5-6 Hz) was present in 66 (39.8%) of studies, and severe encephalopathy (<5 Hz) was present in 34 (20.4%) of studies. Interictal epileptiform continuum (IIC) patterns were observed in 23 (13.8%) studies. Interictal epileptiform discharges (IEDs) were observed in 10 (6.0%) studies, and electrographic seizures were observed in 9 (5.4%) patients. Five patients (3.8%) had either subclinical seizures or nonconvulsive status epilepticus.

Conclusions: These findings demonstrate that there is a substantial risk of encephalopathy, epileptiform activity and subclinical seizures including status epilepticus in patients with COVID-19. Future studies are needed to assess the impact of these findings on long-term clinical outcomes.

342. Association of COVID-19 Infections with New-Onset and Breakthrough Epileptic Seizures
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Objective: This study explores the relationship between the incidences of COVID-19 infections and new-onset or breakthrough epileptic seizures in the largest patient sample to date in a single New York-based hospital system.

Background: Since the advent of the COVID-19 pandemic, anecdotal reports have indicated a possible relationship between COVID-19 infections and new-onset and breakthrough seizures. We analyzed 917 patient admissions that were positive for COVID-19 infections and administration of antiepileptic medications between 14 February and 14 June 2020 within a single health system in New York City and adjacent counties.

Design/Methods: Patients were included in this case control study if they were admitted to a hospital in the health system and had a confirmed positive test for COVID-19 infection during the admission. Only patients who were administered antiepileptic medications during the admission for any reason were included in this study. These patients were divided into those with and those without a known history of epilepsy. The incidences of new-onset and breakthrough seizures and mortality rates were compared between these groups using Pearson’s chi-squared test, and then statistical significance with Fisher’s exact test and odds ratios (OR) were calculated. One-way ANOVA and Tukey’s HSD test were used to compare the lengths of stay between patients with new-onset seizures and those without them.

Results: Patients without a known history of epilepsy had over three times greater odds of having new-onset seizures than patients with a known history of epilepsy to have breakthrough seizures (p<0.0001, OR=3.15). Patients with new-onset seizures had a longer average length of stay (26.9 days) than patients with a known history of epilepsy, whether they presented with breakthrough seizures (12.8 days, p<0.0001) or did not (10.9 days, p<0.0001). Mortality rates were higher among patients who had new-onset and breakthrough seizures than those who did not (p=0.03, OR=1.41). There was no difference in mortality rates between all patients who had a history of epilepsy and those who did not, regardless of whether they had new-onset seizures (p>0.47).

Conclusions/Discussions: Among patients with COVID-19 infections, new-onset seizures were more likely than breakthrough seizures. Those patients with new-onset seizures had longer lengths of stay and higher mortality rates. Further research is needed to investigate the roles of proinflammatory cytokines, blood brain barrier permeability, hypoxia, and abnormal coagulation associated with COVID-19 infections in seizure onset.

343. Anxiety, Depression and Medication Side Effects as Determinants of Quality of Life in People with Epilepsy
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Objective: We investigated how anxiety, depression, and adverse side effects of anti-seizure medications (ASMs) influence quality of life (QOL) in epilepsy patients evaluated at the National Institutes of Health (NIH) Clinical Center.

Background: Symptoms of depression and anxiety affect approximately 23% and 20% of people with epilepsy (PWE). Previous studies have independently found that anxiety, depression, and medication side effects may both impair and also serve as predictors of QOL in PWE.

Design/Methods: Validated screening questionnaires, including GAD7 for anxiety, NDDI-E for depression, Liverpool Adverse Event Profile (LAEP) for medication side effects, and QOLIE-31 for QOL were completed by a cohort of 132 patients. Additional clinical data including seizure frequency, disease duration and ASM treatment were extracted from medical records. Pearson correlation coefficient was used to assess the linear relationship between questionnaire scores. ANCOVA with gender, disease duration, and seizure frequency was used to evaluate the association between ASMs and questionnaire scores.

Results: Of 132 patients, 65 (49%) were female, with mean age of 38 (range 17-67) years, and mean seizure onset at 24 (range 0.02-55) years. Anxiety (r=0.80, p<0.0001), depression (r=-0.74, p<0.0001), and medication side effect
Patients taking zonisamide reported lower cognitive well-being scores (p = 0.04, p=0.03). Patients taking oxcarbazepine reported less depressive symptoms (p=0.01). Medication side effect scores were positively correlated with quality of life (QOL) in our cohort. Medication side effects (p<0.05) when compared to males, suggesting a gender difference across these variables. Compared to other ASMs, patients taking lacosamide and topiramate indicated less depressive symptoms (p=0.01).

**Conclusion:** Our study reinforces the effect of psychiatric state and medication side effects on quality of life in PWE. Gender may also play a role in susceptibility to these effects. Furthermore, female PWE may be more susceptible to anxiety, depression, and medication side effects, with resultant impacts on QOL. ASMs appear to have differential effects on side effect profiles which should be taken into account when selecting ASMs. These findings have important clinical implications, underscoring the importance of identifying and addressing both psychiatric symptoms and medication side effects to improve QOL in PWE.

**344. Patient Reported Outcomes of Anxiety and Depression in Adults with Epilepsy: 6-month Outcomes During Usual Care in a Pilot Randomized Trial of Two Remote Outcome Assessment Methods**

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**Objective:** In a pilot randomized trial of pragmatic outcome collection methods, to assess 3- and 6-month changes in quality of life and other patient-reported health outcomes during usual care among adults with epilepsy and high or borderline anxiety or depression symptoms.

**Methods:** Prospective outcome collection occurred during usual epilepsy care in a randomized pilot trial comparing methods of patient-reported outcome assessment (health record patient portal questionnaires versus telephone interview). Adults (N=30) with high or borderline anxiety or depression scores at a tertiary epilepsy visit were recruited via patient portal EHR questionnaires or telephone interview. Participating patients were randomized to complete the health record patient portal questionnaires versus telephone interview. Of those completing the health record patient portal questionnaires, 57% had at least one hospitalization or urgent care visit coded in the EHR during the 6-month period (7 of 12 with action plan documented, 58%). Health care utilization was high, with 40% (12 of 30) having at least one hospitalization, emergency visit, or urgent care visit reported by the patient and/or documented in the EHR. Of those with hospitalizations or emergency/urgent care visits, one third (4/12) failed to report a hospitalization or urgent visit via telephone interview or electronic questionnaire.

**Conclusion:** In this prospective outcome collection among epilepsy patients with borderline or high anxiety or depression symptoms over 6 months of usual care, quality of life and anxiety/depression symptoms did not significantly improve. Participants also under-reported anxiety and depression management plans and major health care utilization outcomes compared to EHR data sources.

**345. Increased Amplitude of Corticocortical Evoked Potentials Predicts the Site of Epilepsy Surgery**

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**Objective:** The main goal of in patients undergoing intracranial recording for the treatment of intractable epilepsy is to determine the region of cortex for resection or ablation. We studied whether large amplitude corticocortical evoked potentials (CCEPs) in the area of early ictal spread could help identify the clinically-determined region of ablation. However, we first needed to control for the confound of distance, as CCEP amplitudes are known to be largest on electrodes nearby the site of stimulation.

**Methods:** Single pulse electrical stimulation (1 Hz, 20 second train) was performed at multiple sites in 9 patients with refractory epilepsy undergoing stereo-EEG monitoring. Resulting CCEPs were averaged and amplitude was defined as the root mean squared deviation from the end of the stimulus artifact to 100 ms after the stimulus. We computed the Euclidean distance between each stimulated and recording electrode, and compared the effect of distance of the CCEP amplitude using the traditional referential montage and the alternative bipolar montage. For each stimulated electrode, we compared the median CCEP amplitude (using the bipolar montage) in areas of early seizure versus control cortex using a one-tailed Wilcoxon ranksum test. We defined +CCEP-ictal overlap as a p-value < 0.05. Finally, we compared whether +CCEP-ictal overlap was detected more often when stimulation was triggered inside the ablation zone.

**Results:** We found that using a bipolar montage rather than the traditional referential montage attenuated the distance confound - the predicted CCEP amplitude drops

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between 100 uV at 14 mm, significantly less than 37 mm for the referential montage (p<0.001, paired t-test). We stimulated 37 electrodes within the ablation zone and 91 electrodes outside the ablation zone. 17/37 (46%) of electrodes inside the ablation zone had +CCEP-ictal overlap (using the bipolar montage), significantly more than 10/91 (11%) of electrodes outside the ablation zone.

**Conclusions:** Using a bipolar montage, rather than a traditional referential montage, attenuates the confounding effect of distance on CCEP amplitude. A measure of CCEP-ictal overlap (larger amplitude CCEPs in areas of early ictal activity) attenuates the confounding variables.

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### 346. Depression and Anxiety in Adult Persons with Epilepsy and Their Caregivers

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**Objective:** Contrary to patients, the psychological impact of epilepsy to caregivers has not been adequately investigated. This study aimed to evaluate the prevalence and determinants of mood disorders in adult persons with epilepsy (PWE) and their caregivers.

**Methods:** Adult PWE and their caregivers attending the outpatient Epilepsy clinic or admitted to the Epilepsy Monitoring Unit completed surveys about demographic, disease-related and psychosocial characteristics. Prevalence and determinants of mood disorders were evaluated using the Beck Depression Inventory (BDI) and Anxiety Inventory (BAI) scores. Univariate and multivariate analysis was performed using the presence of any mood disorder (depression and/or anxiety) as dependent variable and the collected patient and caregiver characteristics as independent variables.

**Results:** One hundred patients (62% female, mean age 35 years) and 100 caregivers (66% female, mean age 44 years) were recruited. Most patients suffered from epilepsy for approximately 14 years averaging 7 seizures per month despite being on polypharmacy. Most caregivers were spouses cohabitating with the patients. A mood disorder was present in 89% of patients [67% had depression with a mean BDI score of 16 (mild to moderate range) and 84% had anxiety with a mean BAI score of 21 (moderate range)] and 56% of caregivers [42% had depression with a mean BDI score of 10 (mild range) and 47% had anxiety with a mean BAI score of 11 (mild range)]. Patient and caregiver depression and anxiety levels weakly correlated (r=0.22, p=0.02 for depression and r=0.21, p=0.03 for anxiety). In the univariate analysis, the presence of mood disorder in the patient was associated with being unmarried, unemployed, frequent hospitalizations, increased side effects from polypharmacy, heightened patient felt stigma, poor patient quality of life, increased caregiver anxiety level and higher caregiver burden. In the multivariate analysis, only medication side effects sustained as an important determinant (β=0.22, p=0.05). In the univariate analysis, the presence of mood disorder in the caregiver was associated with increased seizure frequency, increased patient anxiety level, poor patient quality of life, heightened caregiver felt stigma and higher caregiver burden. In the multivariate analysis, only the patient anxiety level and caregiver burden sustained as important determinants (β=0.08, p=0.004 for patient anxiety and β=0.05, p=0.01 for caregiver burden).

**Conclusion:** Adult persons with epilepsy and their caregivers experience high rates of depression and anxiety. These are associated by specific demographic, disease-related and psychosocial factors that could act as targets for future intervention trials.

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### 347. Long-Term Efficacy and Safety of Adjunctive Perampanel in Elderly Patients (Aged ≥60 Years) with Focal-Onset Seizures (FOS): Post Hoc Analysis of Open-Label Extension (OLEX) Studies by Enzyme-Inducing Anti-Seizure Medication (EIASM) Use

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**Purpose:** In the US, perampanel is approved for FOS (adjunctive/monotherapy) in patients aged ≥4 years and generalized tonic-clonic seizures (adjunctive) in patients aged ≥12 years. Since EIASMs are known to increase the clearance of perampanel, this post hoc analysis evaluated the long-term (up to 4 years) efficacy and safety of adjunctive perampanel in elderly patients (aged ≥60 years) with FOS by concomitant EIASM use during Studies 307 (NCT00735397) and 335 OLEX (NCT01618695).

**Methods:** Patients completing randomized, double-blind, Phase III studies could enter OLEX Studies 307 (16-week blinded Conversion; 256-week Maintenance) or 335 OLEX (4-week Pre-conversion; 6-week Conversion; ≥46-week Maintenance) to continue receiving perampanel (maximum: 12 mg/day). Here, outcomes were stratified by baseline concomitant EIASM use (defined as carbamazepine, eslicarbazepine, phenytoin, oxcarbazepine). Efficacy and safety were evaluated over Years 1-4 (the start of Year 1 corresponds with initiation of perampanel treatment).

**Results:** The Safety Analysis Set included 71 patients: 39 patients were receiving EIASMs and 32 patients were receiving non-EIASMs at baseline. During Years 1 and 2, respectively, median percent reductions in seizure frequency were 36.6% (n=39) and 42.7% (n=19) in theEIASM group vs 55.5% (n=32) and 53.4% (n=19) in the non-EIASM group. Seizure reductions were observed during Years 3 and 4 in both groups and were higher in the non-EIASM group vs the EIASM group, but patient numbers were small (n=≤10). During Years 1 and 2, respectively, treatment-
emergent adverse event (TEAE) incidence was similar with EIASMs (87.2% [n=34/39] and 55.6% [n=15/27]) and non-EIASMs (87.5% [n=28/32] and 60.9% [n=14/23]). During Years 3 and 4, respectively, TEAE incidence was higher with non-EIASMs (60.0% [n=6/10] and 75.0% [n=6/8]) vs EIASMs (33.3% [n=3/9] and 33.3% [n=2/6]), but small patient numbers limit comparisons. The most common TEAE during Year 1 was dizziness (EIASMs, n=21 [53.8%]; non-EIASMs, n=13 [40.6%]). During Year 2, dizziness and fall (both n=4 [14.8%]) were most common with EIASMs, and diarrhea and pneumonia (both n=3 [13.0%]) were most common with non-EIASMs.

Conclusions: Adjunctive perampanel was well tolerated with sustained seizure reduction for up to 4 years in elderly patients with FOS, regardless of concomitant EIASM use. However, patients receiving concomitant EIASMs may require a higher perampanel dose to achieve similar efficacy to those receiving only non-EIASMs.

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348. Presurgical Evaluation Initiation Among Medicare Beneficiaries with Refractory Epilepsy
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Objective: For the ~1 million people in the United States with refractory epilepsy, continued antiseizure medication (ASM) trials offer a <5% chance of seizure freedom while epilepsy surgery offers a 30-70% chance of seizure freedom. Yet, utilization of epilepsy surgery is low. To begin to understand the drivers of underutilization, we explored patient, provider, and geographic factors associated with completion of inpatient EEG monitoring, the first step of the presurgical pathway.

Methods: Using Medicare files (Parts A, B, and D) from 2008-2018, we identified patients with incident refractory epilepsy using validated criteria of 1) ≥2 distinct ASMs, and 2) ≥1 encounter with a refractory epilepsy diagnosis code, then excluded patients with <2 years of pre-diagnosis and <1 year of post-diagnosis enrollment. We used logistic regression to evaluate the association between our primary outcome (inpatient EEG monitoring) and patient factors (age, sex, race, diagnosis year, comorbidities, epilepsy type, ASM number, and epilepsy-related healthcare utilization), diagnosing provider type, and geography (hospital referral region neurologist density and proximity to an accredited comprehensive epilepsy center).

Results: We identified 12,054 patients with an incident refractory epilepsy diagnosis. Mean age was 58 years; 55% were female; 73% were white and 16% were black; 45% had a focal epilepsy diagnosis. Most patients were initially diagnosed by a neurologist (68%). In total, 17% underwent inpatient EEG monitoring subsequent to their refractory epilepsy diagnosis (median time to evaluation 53 days, interquartile range 2-459); another 6% underwent inpatient EEG monitoring prior to diagnosis but not afterward. Only 1% underwent epilepsy surgery. Factors associated with inpatient EEG monitoring were age <65 (adjusted odds ratio 1.5 [95% confidence interval 1.3-1.8]), female gender (1.2 [1.1-1.3]), not dual eligible (1.3 [1.2-1.5]), traumatic brain injury (1.3 [1.1-1.7]), headache (1.2 [1.1-1.4]), focal epilepsy diagnosis (1.6 [1.4-1.8]), diagnosing physician specialty (neurology 1.6 [1.4-1.9], neurosurgery 1.7 [1.03-2.7], emergency medicine 1.6 [1.3-2.1]; reference is primary care), prior epilepsy hospitalizations (1.1 [1.01-1.2]), prior epilepsy emergency visits (1.1 [1.1-1.1]), prior inpatient EEG [2.9 [2.5-3.4]), residing <50 miles from an epilepsy center (1.5 [1.3-1.7]), and residing in high neurologist density regions (1.5 [1.2-1.8]).

Interpretation: A small proportion of Medicare beneficiaries with refractory epilepsy initiated the presurgical evaluation pathway. Younger age, focal epilepsy diagnosis, non-primary care diagnosing physician, and measures of access to care (prior EEG evaluation, epilepsy center proximity, neurologist density) were the strongest predictors. Interventions aimed at improving access may facilitate use of epilepsy surgery.

349. Proteins Involved in Ictogenesis and Seizure Clustering: Insights from Temporal Proteomics Profiling in Chronic Epilepsy
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Background: Seizure clustering is a common phenomenon in chronic epilepsy. Protein expression profiles in different phases of a seizure cluster might reflect the key pathomechanism underlying the ictogenesis. We performed proteomics analysis to identify the proteins with a specific temporal pattern of expression during the seizure cluster phases and demonstrate their potential pathomechanistic role.

Methods: In a mouse pilocarpine epilepsy model with chronic spontaneous recurrent seizure with a seizure cluster pattern, mice were sacrificed at the onset of the seizure cluster (group 1), peak of the seizure cluster (group 2), end of the seizure cluster (group 3), and mid seizure-free period (group 4). The proteomics analysis was performed in the hippocampus and the cortex. Differentially expressed proteins (DEPs) were identified and classified according to the expression patterns. Involved biological processes were analyzed and key proteins were identified for the DEP classes.

Results: 317 DEPs from 6,976 quantified proteins in the hippocampus and 332 DEPs from 6,412 quantified proteins in the cortex were identified. The DEPs in each locus were classified into five classes. For the hippocampal DEP classes (HC-classes), temporal expression pattern and involved biologic process indicated that HC-class 1 (66 DEPs) represents disrupted homeostatic cell metabolism due to clustered seizures, HC-class 2 (63 DEPs) anti-ictogenic proteins, HC-class 3 (42 DEPs) ictogenesis-related proteins, and HC-class 4 (103 DEPs) consequences of clustered seizures spread over the brain, while HC-class 5 (42 DEPs) did not exhibit a specific expression pattern. Expression patterns and involved proteins in HC-class 3 were specific to the hippocampus. Especially, DEPs in HC-class 3 were involved in
axonogenesis, synaptic vesicle assembly, and neuronal projection, indicating pathomechanistic role of those processes in ictogenesis. Five key proteins in HC-class 3, Dnm3, Cadps, Sry2, Sry6, and Fscn1, had abundant involvement in the enriched biological processes and were interconnected with each other.

**Conclusions:** This study provides comprehensive information about spatial and temporal regulation of protein expression during a seizure cluster. HC-class 3 provide novel insight regarding the biological processes involved in ictogenesis and its key proteins might serve as a seizure biomarker or as a treatment target for reducing seizures in chronic epilepsy.

350. Looking Beyond Apnea: A Widespread Cortical Repertoire That Modulates the Rate and Depth of Breathing

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**Introduction:** Propagation of seizures into cortical structures involved in breathing regulation may lead to respiratory dysfunction, contributing to fatal outcomes such as sudden unexpected death in epilepsy (SUDEP). Seizure-induced central apnea is mainly observed in temporal lobe epilepsies. While electrical stimulation studies have shown that amygdala and hippocampus stimulation can cause apnea, the complete ensemble of forebrain structures that regulate breathing remains to be identified. We hypothesized that direct cortical stimulation can assist in causal discovery of forebrain nodes that modulate breathing rate, depth, and volume.

**Methods:** Ten consenting patients with drug-resistant epilepsy undergoing invasive stereo-EEG investigation for localization of epilepsy, were included in the study protocol where multiple temporal (amygdala, hippocampus, temporal pole, entorhinal and lateral-temporal cortex) and extratemporal (orbitofrontal and anterior cingulate) regions were systematically stimulated (N=759trials; 50Hz; 200μs; increasing current strengths: 1-15mA). Respiratory biosignals from multimodal wearables (i.e., thermistor airflow) were analyzed to quantify significant changes in tidal volume (TV), minute ventilation (MV), and breathing rate (BR). A one-sample t-test was used to find the threshold and an inter-regional comparison was done using univariate analysis with false discovery rate (FDR) correction.

**Results:** Electrical stimulation of various forebrain regions evoked subclinical changes in breathing parameters. Along with amygdala and hippocampus, entorhinal and orbitofrontal cortices also inhibited breathing by decreasing TV (t< -5.9, p<0.001) and MV (t<-2.9, p<0.001) by more than 40%. The mesial nuclei in amygdala contributed to a greater decrease (i.e., accessory basal > basal > lateral nucleus) in TV (t<-5.9, p<0.001) and MV (t<-3.5, p<0.012). Temporal pole and cingulate stimulations enhanced breathing, evidenced by a greater than 45% increase in TV and greater than 43% increase in MV. A 15% decrease in BR was noted with stimulation of cingulate, hippocampus, orbitofrontal, and rhinal cortices.

**Conclusion:** We identified multiple forebrain regions that modulate breathing. For the first time, we demonstrated breathing enhancement by stimulation of anterior cingulate and of temporal pole cortex, making these candidate neuromodulation targets for breathing support.

351. A Single-Center Retrospective Analysis of Occipital Lobe Epilepsy Surgery Outcomes at Mayo Clinic Arizona

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**Introduction:** Occipital lobe epilepsy (OLE) is a rare focal epilepsy (5-10% of focal epilepsy) characterized mainly by visual symptoms including flashing lights, visual distortions, hallucinations, and ictal blindness. Although rare, OLE can be refractory to anti-seizure medications (ASMs) and debilitating to patients’ quality of life. Non-medication options such as vagus nerve stimulation (VNS) and surgical resection have been reported as beneficial. Further characterization of epilepsy surgery outcomes in this patient population is needed. We provide a single center case series characterizing post-epilepsy surgery outcomes in patients with drug-resistant OLE.

**Methods:** This is a retrospective, single-academic center review of patients who presented to Mayo Clinic Arizona for neurosurgery between 1998 and 2020. The primary endpoint was seizure freedom at 4 months, 12 months, and 18 months. Secondary endpoints include pre- and post-epilepsy surgery ASM quantity/dosing, as well as postoperative visual field outcomes.

**Results:** We identified 781 surgical procedures that met initial search criteria, with 4 patients meeting criteria: (1) drug-resistant OLE diagnosis (2) OLE surgery and (3) greater than 1 year of post-operative follow-up. 75% of patients were female. The mean age was 36.25 (range: 27-50). 75% of the patients had an abnormal MRI, and etiologies included bilateral occipital encephalomalacia, occipital focal cortical dysplasia, right occipital glioma, and one patient had an unknown etiology. 50% of patients (n=2) reported having no seizures at 12 months. The remaining 50% of patients (n=2) experienced self-reported notable reduction in seizure frequency and intensity. The average number of pre-operative scheduled anti-seizure medications was 2.5, which was reduced to a mean of 1.25 at 12 month post-operative follow-up. With respect to visual outcomes, 25% of patients (n=2) experienced no change in visual outcomes, 50% (n=2) of patients demonstrated some degree of visual field decline including a right homonymous hemianopsia and a monococular peripheral loss pattern of unknown etiology. 100% of patients with VNS (n=2) had improvement in seizure control following surgery.
Conclusions: Our case series shows that OLE surgery can be associated with favorable postoperative seizure-freedom, with 50% of patients reporting no seizures at 12-month follow-up and the other 50% of patients reporting improvement in seizure frequency and intensity. Additionally, ASM quantity and dose reduction was noted, with a 50% reduction in ASMs at 12-month postoperative visit. Further characterization of OLE surgery outcomes is warranted to help predict seizure freedom outcomes and risk stratify patients.

352. Failed Acute Stroke Interventions and High Ischemic Burden Increase Post-Stroke Epilepsy Risk
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Background: Post-ischemic stroke epilepsy (PISE) is a serious and disabling complication of ischemic stroke. Recent advances in acute stroke intervention have improved survival rates and clinical outcomes but may increase the population at risk for developing PISE. Prior studies concluded that patients undergoing IV-tPA and/or mechanical thrombectomy (MT) are more likely to develop PISE. However, the independent influence of stroke severity on this relationship remains unknown; thus, the interaction between acute stroke interventions, stroke severity, and PISE requires further analysis.

Objective: To explore the independent associations of acute stroke interventions and stroke severity on epilepsy risk.

Methods: Patient’s enrolled in Yale’s Acute Brain Injury Biorepository were evaluated for PISE (≥1 seizure in month 2-12 post-stroke). PISE patients were matched 1:3 with non-PISE controls based on admission NIHSS, age, and sex. We excluded patients with a history of seizures/epilepsy. The associations between PISE and patient demographics, past medical history, acute stroke interventions, hospitalization characteristics, and imaging biomarkers were evaluated by univariable and multivariable logistic regression. We assessed model performance using receiver-operating characteristic (ROC) analysis.

Results: Out of 2014 ischemic stroke patients, we identified 41 PISE patients and 123 non-PISE matched controls. We did not find an association between IV-tPA or MT and PISE. In univariable analyses, we found that stroke severity proxies associated with PISE included smaller changes in NIHSS (ΔNIHSS, p=0.001), hemorrhagic transformation (ΔNIHSS, p=0.007), higher infarct volume (manual) (ΔVI, p=0.021), and atrial fibrillation (ΔAF, p=0.010). Combined, these factors exhibited an area under the ROC curve of 0.81 for predicting PISE.

Conclusion: Patients with persistent stroke deficits, high infarct volume, and hemorrhagic transformation were at increased risk of PISE, potentially implicating stroke severity rather than acute interventions in PISE development. Additionally, patients with complete reperfusion (TICI3) exhibited an inverse association between MT and PISE, suggesting that PISE risk may be modifiable. Future studies validating our findings are warranted.

353. Total Daily Dosage of Anti-Epileptic Drugs in Women with Epilepsy with Subsequent Pregnancies
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Background: Anti-epileptic drug (AED) levels often change during pregnancy in women with epilepsy (WWE). Dose adjustments during pregnancy happen after levels change. However, level fluctuations as well as difficulties in obtaining timely levels may lead to seizures and contribute to an increased adverse risks in epilepsy. Ideally, it would be useful to be able to predict necessary dose changes during pregnancy and implement changes in advance to prevent significant fluctuations and obviate the need for frequent blood testing during pregnancy, particularly during a successive pregnancy on the same WWE. It is unknown whether levels and dosing are similar between pregnancies in the same WWE on the same AED(s) during successive pregnancies. We hypothesized that dose requirements between successive pregnancies in the same WWE on the same AED would follow a similar pattern throughout both pregnancies.

Methods: A retrospective chart review was conducted in 17 WWE with >1 pregnancy between 01/01/1997 to 04/13/2021. WWE who had at least 2 pregnancies on the same medication(s) and had blood levels drawn during pregnancy were included with a total of 14 WWE in final analysis. There were seven WWE on lamotrigine (LTG), and one each on valproic acid (VPA), levetiracetam (LEV), carbamazepine (CBZ), oxcarbazepine (OXC), and phenytoin (PTH). One WWE in both pregnancies was on LEV and OXC and another WWE in both pregnancies was on topiramate (TOP), lacosamide (LMC), and zonisamide (ZON). 13 were seizure-free, while one on LTG had a seizure four days after delivery.

Results: For the 14 LTG patients, the difference in dose change between pregnancies ranged between 200 to 400 mg. The VPA patient required an increase in dose toward the end of her first pregnancy only, from 750 mg to 1000 mg. LEV patient had no change in dose throughout. The OXC patient had a similar dose increase in pregnancies.

Conclusion: Our study suggests that total daily dosages used in women with subsequent pregnancies follow a similar
pattern for most patients except for LTG patients where results were more variable. This variation may reflect differences in the timing of level testing, variability in practitioner dosage change during different pregnancies amongst other factors. The doses used during an initial pregnancy may be useful in guiding dose management in successive pregnancies, but frequent testing of levels may still be needed. Larger studies are needed to evaluate and confirm these preliminary findings.

355. Non-Cell Autonomous Hyperexcitability Underlies Focal Epileptogenesis Mediated by Low-Level Brain Somatic Mutations in MTOR
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Low-level somatic mosaicism in the brain has been shown to be a major genetic cause of intractable focal epilepsy including focal cortical dysplasia (FCD) and hemimegalecephaly (HME) (D’Gama et al., Annals of Neurology, 2015). However, how relatively few mutation-carrying neurons are able to induce epileptogenesis at ‘the local network level’ remains poorly understood. We generated FCD type II model mice having a somatic mutation in MTOR L2427P presenting seizures by in utero electroporation and ascertained the number of mutated neurons (MTORL2427P) throughout the whole brain in the mice and FCD type II patient-derived tissue identified with MTOR somatic mutation. To probe the origin of epileptogenesis, we measured the excitability of neurons with MTOR mutation and nearby non-mutated neurons (L2427Pnormal) recorded by whole-cell patch-clamp and array-based electrodes comparing the topographic distribution of the mutation. Computational connectivity using the leaky-integrate-and-fire model recapitulates network changes based on measured properties. Interestingly, the seizure-triggering hyperexcitability was originated from non-mutated neurons near mutation-carrying neurons which proved to be less excitable than non-mutated neurons. To examine the underlying mechanism, we measured excitatory and inhibitory synaptic inputs in MTOR2427P and L2427Pnormal neurons by electrophysiological and immunofluorescence methods using the mouse model and postoperative FCD and HME human brain tissue. The net balance between excitatory and inhibitory synaptic inputs onto mutated neurons remained unchanged, implying that intrinsic synaptic changes driven by MTOR somatic mutation are less likely to be explanatory. To explain non-cell autonomous hyperexcitability, an inhibitor of adenosine kinase (ADK), which translation is increased by MTOR2427P in ribosome profiling (Kim et al., J. Clin. Invest., 2019), was injected into mice to enhance adenosine signaling and to mitigate hyperactivity of L2427Pnormal neurons. Additionally, we found that inhibition of ADK, which can affect adenosine metabolism and neuronal excitability, reduced the hyperexcitability of non-mutated neurons. Taken together, providing an example of how low-level brain somatic mutation can change the entire brain activity, this study showed that neurons carrying somatic mutations in MTOR lead to focal epileptogenesis via non-cell autonomous hyperexcitability of nearby non-mutated neurons.

357. PV+ Interneurons Are Non-Cell Autonomous Dysregulated in Depdc5-Associated Epilepsies
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MTOR-related malformation of cortical development (MCD) is the most common cause of medically refractory epilepsy in children. It is still unclear which cell subtypes with MTOR hyperactivation contribute to the pathogenesis and epileptogenesis of MCD. Clinical and experimental data have suggested that MTOR hyperactivation in dorsal progenitors-derived cells, but not ventral progenitors-derived interneurons, generates pathognomonic cellular changes, overall cortical overgrowth, and severe epilepsies. However, studies have also reported impaired inhibitory pre-synaptic transmission as well as the reduction of interneuron number in MTOR-associated MCD, raising a critical question how genetically intact interneurons are impaired. In this study, we used Depdc5 conditional knockout mouse lines to show that Depdc5 deletion in cortical dorsal progenitor, but not in ventral progenitors, is necessary and sufficient to generate thickened cortex, cytomegalic neurons, and severe epileptic seizures. Astrocytes-specific deletion of Depdc5 failed to produce these pathognomonic features of MTOR-related MCD. We further found that perineuronal nets (PNN) and parvalbumin (PV) + interneuron (IN) are impaired non-cell autonomously through microglial-mediated neuroinflammation in a response to the downregulated microglial inhibitory molecule, CD200, and the severely disrupted homeostasis in mutant cortical excitatory neurons. Therapeutically, treatment with Everolimus restored both cell-autonomous pyramidal neuron and non-cell autonomous PV+ IN impairments, and rescued severe seizures, suggesting critical roles of PV+ INs in the epileptogenesis of MTOR-related MCD.

358. Occurrence of Seizure Worsening and Clinical Toxicity During Postpartum Lamotrigine Taper in Women with Epilepsy
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Objective: Postpartum tapering of antiseizure medications (ASMs) in women with epilepsy (WWE) has long been a practice in clinical settings, yet a standardized method has not been developed. ASM postpartum taper plans are individualized and require consideration of ASM-specific pharmacokinetics as well as patient’s ASM plasma concentrations and dose adjustments from preconception through late pregnancy. Lamotrigine (LTG) is the most widely used ASM for pregnant WWE. LTG clearance increases dramatically and
requires frequent dose increases throughout pregnancy, but clearance drops rapidly during the early postpartum period, possibly leading to LTG toxicity if dose is not decreased. Conversely, rapid LTG dose decreases may increase the risk of seizure breakthrough. We reviewed patterns of postpartum tapers for LTG to determine key factors for maintaining seizure stability and preventing clinical toxicity.

**Methods:** 54 WWE on LTG monotherapy were followed throughout pregnancy/postpartum in the Brigham and Women’s Hospital Epilepsy-Obstetrics program between 2012-2021. Clinical data on seizure types and frequency concurrent with therapeutic drug monitoring during pregnancy was collected in a longitudinal prospective database. A retrospective chart review was performed to confirm this information and corroborate with reports of toxicity to LTG symptoms (blurry vision, dizziness/balance problems) in the postpartum period. Dose changes were calculated as the difference between ASM dose on delivery day and end taper dose. Changes in seizure frequency were evaluated by comparing preconception seizure frequency to seizure frequency during first six weeks postpartum.

**Results:** Of the 54 patients analyzed, 7 (12.96%) experienced seizure worsening and 8 (14.81%) reported symptoms of toxicity in the six-week postpartum period, as compared to their preconception seizure frequency and symptoms. The average decrease in LTG dose during the postpartum taper was 46.18% (n=54). The average decrease in dose was similar (p>0.01) for patients with stable seizure frequency 45.35% (range, 0-85.7%, n=47) and patients with worsening seizure frequency 51.73% (range, 37.5-78.13%, n=7). The average decrease in dose was also similar (p>0.01) for patients with clinical toxicity 49.68% (range, 35.71-78.13%, n=8) and asymptomatic patients 45.57% (range, 0-85.7%, n=46).

**Conclusions:** There was not a significant difference in the total dose change between the stable and worsening seizure frequency groups or between the symptomatic and asymptomatic groups. The trend towards higher dose changes in the group with seizure worsening supports the need for larger studies. Further research is necessary to establish key factors for effective and safe postpartum tapers.

359. Natural Language Processing to Assess Seizure Frequency

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**Objective:** To develop a natural language processing (NLP) algorithm to abstract seizure frequency from the electronic health record (EHR).

**Background:** Seizure frequency is the primary clinical outcome for patients with epilepsy, and seizure frequency documentation is a key quality measure outlined by the American Academy of Neurology Epilepsy Quality Metrics. Yet lack of standardized language and sparse data abstraction capabilities are critical barriers to easy, accurate capture of seizure frequency from the EHR. NLP can efficiently mine structured and unstructured EHR text. In this study, we present an algorithm that can extract seizure frequency from EHR unstructured text and can report numeric frequency descriptors for unique semiotics. We evaluate the algorithm’s accuracy across two epilepsy centers.

**Methods:** We developed a rules-based NLP algorithm to recognize terms related to seizures and terms related to frequency, time, or number that occur in close proximity within note text. The gold standard for seizure frequency was manual annotation by two human reviewers. The algorithm was developed in an iterative manner from 100 clinic notes from institution #1 (development set). The algorithm was then tested on a separate set of 220 notes from institution #1 (internal validation set) that contained 248 unique mentions of seizure frequency. To assess generalizability across institutions, the algorithm was also applied to a set of 100 notes from institution #2 (external validation set) that contained 124 unique mentions of seizure frequency. Algorithm performance was measured by recall (sensitivity), precision (positive predictive value), and F1 score (geometric mean of precision and recall; a value of 1 indicates perfect accuracy).

**Results:** In the internal validation set, the algorithm demonstrated 70% recall (173/248), 95% precision (173/182), and 0.80 F1 score, as compared to manual review. In the external validation set, performance of the algorithm was lower with 22% recall (27/124), 73% precision (27/37), and 0.40 F1 score; the algorithm performed particularly poorly with statements of seizure freedom (precision 0/24).

**Conclusions:** Our rules-based NLP tool for seizure frequency extraction from clinical notes showed acceptable performance within the development institution and did not generalize well to a second institution. These results suggest that NLP text extraction of clinically meaningful outcome measures is feasible, and also highlight the importance and the challenge of generalizability across institutions for large scale implementation.

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occur across the lifespan. Surgical candidacy is based on clinical examination and noninvasive (neuropsychological evaluation, scalp electroencephalographic monitoring, structural and functional imaging) and invasive techniques (Wada testing, intracranial monitoring). Within this context, some patients require stereo-electroencephalographic (sEEG) mapping to better define the epileptogenic zone. For these patients, functional mapping using electrocortical stimulation (ESM) and high gamma activity (HGA) assessment can be utilized to define language and memory lateralization and guide surgical intervention. We present a case in which language and memory mapping were performed using three different modalities.

Methods: A previously typically developing, right-handed, late adolescent male underwent an extensive presurgical workup for refractory dominant (left) temporal lobe epilepsy that was thought to be secondary to numerous sports-related concussions.

Results: Neuropsychological findings indicated most cognitive abilities were within age-expected ranges and not strongly lateralizing or localizing, showing mild weakness with verbal output consistent with left frontal dysfunction, and weakness in visual memory suggestive of right temporal lobe dysfunction. These results were inconsistent with positron emission tomography/computerized tomography and EEG findings, both of which showed left temporal lobe abnormalities. Initial MRI findings were noncontributory, whereas a subsequent functional MRI (fMRI) indicated a left temporal pole encephalocele with associated encephalomalacia and left lateralized language. Wada testing was done to clarify verbal and visual memory dominance and indicated left lateralized language and bilateral independence in auditory-verbal and visual memory. Spontaneous seizures were originating from the left temporal pole with rapid involvement of the hippocampus. ESM results implicated the left temporal pole and hippocampus during an expressive language task. Stimulating the left temporal pole also reproduced the patient’s habitual seizures. HGA mapping implicated left pars triangularis in expressive language and the left hippocampus in encoding. Following the workup, the patient underwent an uncomplicated left temporal polectomy with hippocampal transection, after which he did not exhibit language, memory, or motor deficits. He has been seizure free since surgery.

Conclusion: The overlap of the epileptogenic zone with eloquent cortex makes surgical planning challenging. However, detailed presurgical language and memory mapping using traditional methods such as the Wada test and fMRI, when complemented by ESM and HGA mapping using depth electrodes with sEEG (“electrical Wada”), provides additional information for optimal surgical planning that can improve postsurgical outcomes.

K-478. Sleep Disruption in a Mouse Model of Medial Temporal Lobe Epilepsy
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Background: Epilepsy affects more than three million people in the US alone, with most reporting a relationship between seizures and sleep-wake patterns, and about one million having sleep disorders. Furthermore, many of the comorbidities of epilepsy, such as mood disorder, attentional and executive difficulties, memory dysfunction, and psychosis, are worsened by disrupted sleep, not to mention the association of sudden unexpected death in epilepsy and sleep. Despite this long-appreciated and robust relationship between sleep-wake and epilepsy, little is known about the underlying mechanisms of this interaction. We sought to examine sleep disruption in a model of medial temporal lobe epilepsy and found that this model recapitulates several human findings.

Methods: Mice were implanted with a pre-configured head plate that includes hippocampal cannula targeting the amygdala, along with dural screws and EMG electrodes for standard sleep scoring. After recovering from surgery, mice underwent continuous video-EEG recording for one week (baseline), continuing during intraamygdala kainic acid injection and for three subsequent weeks. Mice were then perfused for histology.

Results: Sleep is significantly decreased (~15%) in both the light and dark periods in mice with spontaneous seizures after intraamygdalal kainic acid (ANOVA P=0.032, n=6,6). Moreover, seizure frequency was correlated with sleep disruption (P=0.046, R2=0.37). There were significantly more transitions between sleep and wake (P=0.004). Seizures were also more frequent and longer during sleep than during wakefulness (P=0.013).

Conclusions: These findings mirror documented human sleep disorders in epilepsy with prominent insomnia and sleep disruption. In concert with epidemiological data, showing increased sleep disorders in people with epilepsy, these results are consistent with sleep disruption being a key and novel comorbidity of epilepsy. Moreover, as a topic for further study, we hypothesize that sleep disruption may in turn contribute to other comorbidities of epilepsy. These would particularly include affective and cognitive complaints.

K-480. Real-Time Longitudinal Tracking of Neuronal Death and Seizures After Perinatal Oxygen-Glucose Deprivation
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Rationale: Neonatal seizures in the setting of hypoxia-ischemia (HI) are common in newborns and associated with significant mortality and other poor outcomes. However, definitive data indicating whether they are independently harmful or not after HI is a critical gap in the field. This information is essential to determine how aggressively to treat patients. The central hypothesis of this project is that neonatal seizures independently worsen brain injury after HI. Key barriers to testing this hypothesis include insufficiently effective seizure treatments that are potentially harmful as well as methodological limitations measuring cell death and injury. To address this question, we developed a system to longitudinally track neuronal survival after oxygen-glucose deprivation (OGD). We used sustained emission of
transgenically-expressed fluorescent proteins as a robust biomarker of neuronal viability (Arrasate et al. Nature 2004) and genetically encoded calcium indicators to follow seizure activity in real-time for up to 2 weeks following OGD.

**Methods:** Organotypic hippocampal slices prepared from neonatal mice expressing a neuronal red fluorescent protein and green calcium indicator (pAAV-hSyn1-mRuby2-2SG-P2A-GCaMP6s-WPRE-pA, Addgene) underwent 20 min of OGD. Chronic high resolution two-photon imaging of the pyramidal cell layer was performed. Neuronal death was quantified using the fluorophore quenching assay (Balena et al. in prep). All analyses were performed in ImageJ.

**Results:** 1) After OGD, calcium imaging demonstrated recurrent seizures that began with a latency of 23±1 sec (mean ± SE). 2) Neurons dying after OGD could be separated into two cohorts based on time course: immediate (<24 hours) and later death (1 - 14 days). 3) OGD induced an excess of acute and chronic neuronal death compared to controls. 4) Neurons that died late after OGD participated in seizure activity. 5) Neurons that died late after OGD had similar ictal calcium activity compared to neurons that survived.

**Conclusions:** This is the first study to longitudinally study neuronal death as well as seizure activity in real-time after perinatal acute injury. We found that neurons died with time courses consistent with both early necrotic and late apoptotic deaths. Neurons that eventually underwent apoptosis participated in seizure activity after OGD, and their participation was largely indistinguishable from the participation of neurons that survived OGD and seizures. We next hope to perform these studies in vivo, and to suppress seizure activity in a subpopulation of neurons to test whether this improves neuronal survival after injury.

K-481. Cortico-Hippocampal Circuit Dysfunction in a Mouse Model of Dravet Syndrome

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**Rationale:** Dravet syndrome (DS) is a severe epileptic and developmental encephalopathy, characterized by pharmacoresistant infantile-onset seizures, intellectual disability, autism spectrum disorder, and sudden death. DS is primarily caused by pathogenic variants in SCN1A, which encodes the Nav1.1 sodium channel alpha subunit. Mechanisms of seizure generation and chronic epilepsy in DS remains unclear, but convergent data suggest that disease pathogenesis may involve dysfunction of the hippocampal dentate gyrus (DG). Here, we investigated cortico-hippocampal circuit pathology and ictogenesis in a well-characterized mouse model of DS (SEN1A+/- mice).

**Methods:** We used 2-photon (2P) calcium imaging with the genetically-encoded calcium indicator GCaMP7s to determine the large-scale responses of DG granule cells (GCs) to perforant path (PP) input in acute brain slices. We compared the response of SEN1A+/- mice versus wild-type littermate controls at two developmental timepoints (early postnatal and young adult) using a mixed model analysis approach. We followed this up with electrophysiological analysis of different circuit elements in DG. We next performed in vivo optogenetic stimulation of entorhinal cortex in SEN1A+/- versus wild-type control mice. Finally, we coupled optogenetic activation of SEN1A+/- parvalbumin-expressing interneurons (PV-Is) with 2P calcium imaging in slice.

**Results:** We identified a profound impairment in the normal function of the DG in filtering PP input in young adult SEN1A+/- mice. The intrinsic excitability of SEN1A+/- PV-Is was near-normal, but we identified a marked increase in the strength of monosynaptic excitatory input to SEN1A+/- GCs. We confirmed in vivo hyperexcitability of the cortico-hippocampal circuit, demonstrating that optogenetic stimulation of entorhinal cortex was highly ictogenic in SEN1A+/- mice, using parameters that did not reliably evoke seizures in wild-type controls. Selective optogenetic activation of SEN1A+/- PV-Is rescued this circuit impairment in slice, decreasing the GC response to approximately one third of that to PP stimulation alone.

**Conclusions:** This work uses dynamic multicellular imaging and optogenetics in SEN1A+/- mice to link across scales and demonstrate a circuit-level abnormality and mechanism of ictogenesis in a well-validated preclinical experimental model of epilepsy. This circuit hyperexcitability can be acutely rescued by recruitment of PV-Is, suggesting potential therapeutic approaches towards seizure prevention or termination in DS. As mouse models of acquired temporal lobe epilepsy have also identified a breakdown of this cortico-hippocampal circuit, we propose that this circuit deficit may be convergent across epilepsies of entirely different underlying etiologies.

K-506. Zebrafish Models of SLC6A1/GAT1 Hypofunction and a Novel Cell-Based Fluorescence Assay to Identify Positive Modulators of GAT1

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**Rationale:** Solute carrier (SLC) transporters are targets of major interest for drug development due to their role in numerous important physiological processes. Loss of function variants in SLC6A1 which encodes GABA transporter 1 (GAT1) have been described in a genetic epilepsy known as myoclonic atatic epilepsy (aka Doose syndrome), but how genetic loss of GAT1 function leads to epilepsy remains unclear and there are no existing precision therapies. Here we describe our approach to 1) dissect the developmental versus constitutive effects of GAT1 hypofunction using pharmacological and genetic approaches in zebrafish, and 2) develop a fluorescence-mediated cell-based assay of GAT1 function to
identify positive allosteric modulators by high-throughput drug screening. Genetic models of GAT1 hypofunction have been generated using CRISPR/Cas9 targeting slc6a1a and slc6a1b genes in zebrafish. Loss-of-function (LOF) has been validated by QPCR, and fish are currently being bred to F3 generation for further characterization. Meanwhile, pharmacologic inhibition of GAT1 by tiagabine (TGB) at 3 different doses (10 uM, 100 uM, and 1 mM) during different developmental intervals demonstrates increased spontaneous seizure-like activity and increased susceptibility to PTZ based on calcium fluorescence in Gcamp6s fish at day post fertilization (dpf) 5 only in the “chronic TGB minus” (CT- group, TGB from dpf 0 - 4) and is not observed in “chronic TGB plus” (CT+, TGB from dpf 0 - 5) or “acute TGB” (AT, TGB from dpf 4-5) versus controls, which may suggest a developmental effect. Phenotypes from both genetic and pharmacologic analyses will be further validated by orthogonal assays including tectal EEG, and light sheet microscopy of calcium fluorescence. A fluorescent cell-based assay of human GAT1-mediated GABA uptake has been developed using a genetically encoded GABA sensor (iGABA-Snfr) for high-throughput drug screening. Assay performance was evaluated over a 5-log dose range of extracellular GABA (1uM - 10mM) with and without GAT1 inhibitor (TGB, 260uM) and co-expressed hGAT1. A specific hGAT1-mediated increase in iGABA fluorescence is observed in the presence of 1-100uM extracellular GABA, which is blocked by tiagabine, and is not observed in the absence of hGAT1. Additional optimization to improve the dynamic range of the assay in the [GABA] = 0-100uM range was successful. These preliminary results demonstrate proof-of-concept for this assay to identify molecules that enhance GAT1-mediated GABA uptake. Taken together, these studies will advance our understanding of the developmental and constitutive roles of GABA signaling in epilepsy and take steps towards identifying novel compounds to ameliorate GAT1 hypofunction.

K-515. Ectopic Spiking in Parvalbumin-Expressing Inhibitory Interneurons of the Neocortex
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A basic property of axons involves their ability to propagate action potentials in both orthodromic (“forward”) and antidromic (“backward”) directions, e.g. (Brain Res Rev. 21(1):42-92). Neuronal spikes are usually generated in axon initial segments, then propagate orthodromically down the axon to terminals. In some cases, however, they are initiated elsewhere, further down the axons. The literature generally refers to such spikes as ‘ectopic’ action potentials. Recently, ectopic spiking has been demonstrated in approximately 80% of NPY-expressing interneurons of the hippocampus, which comprise a relatively small proportion of hippocampal interneurons (Nat Neurosci. 14(2):200-209). The same study demonstrated that only very few parvalbumin-expressing interneurons (PV+ cells) generated ectopic spikes. We (Theyel, et al. in prep) have discovered that the majority (70/73) of PV+ cells in both orbitofrontal and somatosensory cortices are capable of ectopic firing. Spike patterns of ectopics are variable, and last for up to tens of seconds. We also recorded from a handful of somatostatin positive interneurons, and found that the majority (778) were capable of ectopic spiking. However, they never fired high frequency trains of ectopics, and fired far fewer ectopics than PV+ cells. Further, it took highly intense stimulation not likely to be possible in an awake behaving animal’s brain to elicit ectopics in somatostatin cells. PV+ cells, often referred to in the literature as “fast-spiking” interneurons, had a relatively low initiation threshold for ectopic spikes, requiring a few hundred spikes over the course of tens of seconds, and often (~75%) of the time) fired trains of ectopic action potentials rather than just one or a handful. Given that recordings of these cells in vivo suggest that they fire at rates sufficient to yield spiking that is far beyond this threshold, it is likely that ectopics occur in awake, behaving animals. Given PV+ cells’ strong inhibition onto excitatory cells, and their role in generating network gamma rhythms, ectopic spiking may have significant implications for network activity and cognitive processing. Several studies have implicated abnormalities in PV+ interneurons in schizophrenia (J Neurosci, 29:8, 2344-2354; Trends Neurosci, 35(1), 57-67), Autism Spectrum Disorder (PLoS One, 10(3), e0119258; Mol Psychiatry, 20(10), 1161-1172), and epilepsy (Neuron, 95(1):92-105; Epilepsia, 57(7):1109-19). Our future work will focus on whether ectopic spiking behavior changes in PV+ interneurons of animal models of both disorders.

K-520. Utilizing Human Brain Organoids to Model Hippocampal and Cortical Neural Circuit Activity
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Human brain organoids are a 3D culture system where brain-like structures are created from human embryonic or induced pluripotent stem cells (hESCs or hiPSCs). In recently completed studies we generated “fusion” organoids in which cortex-like organoids predominantly containing excitatory neurons and ganglionic eminence (GE)-like organoids primarily with inhibitory neurons integrate. These fusions resulted in organoids with complex network activity including neural oscillations with similar frequencies as observed in human cortex in vivo. Here we expanded on this approach and generated hippocampus-GE in addition to cortex-GE fusion organoids. Like cortex, hippocampus fusions generated neural oscillations at multiple frequencies, but additionally generated sharp wave ripple complexes. The latter are a unique class of oscillation associated with hippocampal memory consolidation. We next generated organoids from the hiPSCs of a patient with developmental epileptic encephalopathy-13 (DEE-13) due to a pathogenic gain of function mutation in the SCN8A sodium channel. Using two photon-based calcium indicator imaging and extracellular recordings of local field potentials we found substantial hyperexcitability as well as a loss of sustained oscillatory activity in the cortex-GE fusions compared to isogenic controls. In contrast, in DEE-13 hippocampus fusion organoids we
did not observe overt hyperexcitability. Instead, we found more subtle changes including a loss of theta and alpha oscillations with relative preservation of gamma activity. In addition, we observed fewer instances of spontaneous sharp wave ripple complexes. These data suggest that (1) hippocampus and cortex fusion organoids generate complex and distinct network activities and (2) that human brain organoids may provide unique insights into brain-region specific changes that result from the same pathogenic SCN8A mutation.

K-521. The Neurophysiology and Cognitive Profile of Late Onset Unexplained Epilepsy
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Background: Late onset unexplained epilepsy (LOUE) after the age of 60 has been associated with a higher risk of dementia. The reasons for this elevated risk are unclear, and the impact of epileptiform abnormalities on cognition in this patient population have not been described. The goal of the study was to characterize the cognitive profile and EEG findings of patients with LOUE.

Methods: Patients were recruited from Brigham and Women’s Hospital and affiliated hospitals. Inclusion criteria: new onset seizures ≥60yo, onset <3 years, absence of cortical lesions on MRI and of provoking factors. Patients underwent the Clinical Dementia Rating (CDR) Scale and a neuropsychological battery to assess 4 cognitive domains: global cognition (Preclinical Alzheimer Cognitive Composite), delayed verbal recall (Free and Selective Cued Reminding Test and Logical Memory), processing speed (Trailmaking Test A, Digit Symbol Substitution Test), and executive function (Trailmaking Test B and Controlled Oral Word Association Test). A 24-hour EEG was also obtained within 1 year of cognitive assessment and then assessed for the presence or absence of focal slowing, and epileptiform abnormalities including spikes/sharp waves and lateralized rhythmic delta activity.

Results: We enrolled 32 patients. Mean (±SD) age was 69.5 ± 6.1 years. 50% were female. Global CDR scores were 0.0 (n=21) and 0.5 (n=11); CDR sum-of-boxes ranged from 0.0-3.5. Ambulatory EEG findings included focal slowing (n=19), bi-temporal (n=6), left-temporal (n=6), right-temporal (n=3), and right frontal-parietal (1) epileptiform abnormalities. 24 subjects were on antiseizure medicine monotherapy, and 2 were not on medications. The mean z-score for global cognition was −0.48 (range −3.44, 0.98), delayed verbal recall −0.81 (−3.64, 1.17), processing speed −0.40 (−6.45, 1.67), and executive function −1.06 (range −7.78, 1.67). Gender differences were noted with females exhibiting higher delayed verbal recall scores (mean ±SD -0.34±1.1 v.s. mean -1.3±1.1, p=0.02). There were no differences on cognitive testing noted between subjects with or without focal slowing or epileptiform abnormalities.

Conclusions: LOUE is associated with cognitive deficits at time of presentation, most notably executive difficulties. Delayed verbal recall scores were better in females. The presence of epileptiform abnormalities did not correlate with worse cognitive performance. Future studies need to evaluate the cognitive trajectory of LOUE and predictors of cognitive decline.

K-526. Convolutional Neural Networks Applied to Rey Complex Figure Drawings for Epilepsy Diagnostic Classification
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Rationale: Although widely used, the Rey Complex Figure Copy Task (RCFT) is poorly diagnostic of non-dominant temporal lobe dysfunction using conventional scoring methods. Convolutional Neural Networks (CNNs) are a class of deep learning algorithms applied to visual imagery recognition which can discover ambiguous features in drawings. We explored the use of a pre-trained CNN on a retrospective dataset of RCFT drawings to distinguish between focal epilepsy diagnoses.

Methods: RCFT copy and 30-min delay drawings generated by 197 adult patients with epilepsy (66 LTLE, 71 RTLE, 60 ETLE) at a single center and 45 healthy controls (HC) were analyzed. Epilepsy localization was adjudicated based on seizure semiology, MRI, and EEG. A synthetic dataset was generated by all combinations of the standard 18 RCFT features (218 = 262,144), then augmented through rotation, perspective shifts, and line thinning and thickening. This dataset was used to pre-train a CNN, which was applied to each subject drawing to generate a 512-dimensional embedding. The top principal components were isolated via principal component analysis (PCA), then clustered by K-means clustering. A clustering method maximally differentiating seizure diagnoses was selected. Descriptive, ANOVA, and Chi-squared statistics were performed on resulting clusters.

Results: Subjects were 53% F, 38.2 (±14.3) years old, with IQ 93.68 (±15.23), and 14.4 (±2.5) years of education. Three clusters were generated from the CNN-derived embeddings of copy and delay drawings. Clusters for delay drawings were more heterogeneous than the copy drawings. Among delay clusters, there was no difference in age, education, or IQ. Epilepsy diagnoses differed between the 3 clusters of delay drawings (χ² = 29.844, p < 0.0001). HCs more likely belonged to Cluster A (p <0.0001), ETLE patients belonged to Cluster B (p < 0.0001), and RTLE patients belonged to Cluster C (p = 0.001). RCFT scores differed between clusters (χ²(2) = 42.096, p < 0.0001), with Cluster A (19.1 ± 7.7) scoring higher than Cluster B (10.6±5.3) (p <0.0001), or Cluster C (10.5±6.2) (p < 0.0001).

Conclusions: RTLE and ETLE patients produce delay drawings with different features than those generated by HCs, discovered by a pre-trained CNN model. Even when RCFT delay scores were similar, CNNs could distinguish between drawings made by RTLE and ETLE patients. CNNs can be applied to RCFT delay drawings to improve epilepsy diagnosis, and generate new hypotheses regarding non-dominant temporal and extratemporal lobe contribution to delayed visual recall.
LB-443. Commonly reported Magnetic Resonance Imaging (MRI) findings in hyperglycemia induced encephalopathy and seizures include transient cortical T2 hyperintensity, restricted diffusion, and often gyral and/or adjacent leptomeningeal contrast enhancement. We report the case of a 55 year old male with no known past medical history who came in with hypertension to systolic blood pressure (SBP) 190s and hyperglycemic to 443, presenting with several days of visual and auditory hallucinations, subsequently witnessed to have a seizure in the Emergency Department with left gaze deviation and left arm shaking progressing to generalized shaking followed by a postictal state. MRI brain with and without contrast revealed a region of cortical T2/Fluid-Attenuated Inversion Recovery (FLAIR) hyperintensity with subcortical T2/FLAIR hypointensity and associated diffusion restriction in the temporal/parietal lobes. Also noted was a region of curvilinear focus of contrast enhancement in a gyrus and adjacent sulcus in the right inferior lobule. Postictal Electroencephalogram (EEG) obtained showed sharply contoured right parieto-occipital slowing that correlated with the MRI findings. Hyperglycemia induced MRI findings of subcortical T2 hypointensities have been reported, seen in both ketotic and non ketotic hyperglycemia. Our case aims to reaffirm this neuroradiological finding as a “hallmark” in hyperglycemic seizures.

LB-464. Microglial Dysfunction in Comorbid Alzheimer’s Disease and Seizures
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Background: Mounting evidence suggests a role of seizures in worsening Alzheimer’s Disease (AD) neuropathology, with reports of comorbidity between these conditions ranging from 1.5% to 64% (Friedman D, CNS Neurosci Ther, 2012). We hypothesized that dysregulation of microglial immune function may lead to neuroinflammation, underlying this relationship.

Methods: We examined human temporal lobe tissue from AD cases with and without known seizure history and controls. Quantitative immunohistochemistry was used to determine the percentage of β-amyloid (Aβ) coverage in the grey matter (GM) and white matter (WM). Then we performed multiplex Lumixex assays to evaluate expression levels of two critical microglial immune regulators: TREM2, which stimulates microglial phagocytic capacity, and RANTES, a C-C chemokine (CCL5) that promotes microglial recruitment and activation. Samples were grouped into four categories: Alzheimer’s disease (AD), Alzheimer’s with seizures (AD+S), Alzheimer’s without seizures (AD-S), and controls. Controls to AD and AD+S to AD-S were compared via unpaired t-tests. Potential correlations between the microglial markers and Aβ1-42 were examined via simple linear regressions.

Results: Aβ levels were significantly higher in AD compared to control cases, both in the GM (3.76±0.43%; n=22 in AD versus 0.31±0.16%; n=17 in controls; p<0.0001) and WM (0.56±0.15% compared to 0.02±0.01%; p<0.01). AD+S cases had higher levels of Aβ than AD in the WM (1.16±0.43% in AD+S, n=6 versus 0.34±0.09% in AD-S, n=16; p<0.05), while the difference in the GM (4.50±1.01% in AD+S compared to 3.48±0.46% in AD-S) was not significant (p=0.3028). Lysates from AD patients had reduced TREM2 concentrations (133.0±12.14 ng/mL, n=20) compared to controls (151.2±15.50 ng/mL, n=5; p=0.4871), with AD+S cases showing significantly reduced TREM2 levels compared to AD-S (108.8±12.04 ng/mL versus 157.2±18.63 ng/mL, n=10 each; p<0.05). RANTES was significantly elevated in AD cases (19.57±2.55 ng/mL, n=20) compared to controls (5.24±1.98 ng/mL, n=5; p<0.05), but there was no significant difference between AD+S cases (22.68±4.22 ng/mL, n=10) and AD-S (16.46±2.74 ng/mL, n=10; p=0.2322). However, RANTES was positively correlated with Aβ1-42 across patients, regardless of group (p<0.05, R²=0.1888).

Conclusions: Our findings support the notion that seizures worsen Alzheimer’s pathology and provide preliminary evidence of microglial dysregulation in a pro-inflammatory manner based on seizure phenotype, suggesting that therapies targeting microglia may attenuate disease progression in patients with AD and seizures. Supported by: National Institute on Aging: Institutional National Research Service Award T32AG000255-23 (AB), National Institute of Neurological Disorders and Stroke R21NS105437 (FEJ), R37NS115439 (FEJ) and R01NS101156 (DMT).

Global Neurology

121. Neurological Manifestations of Patients with Mild-to-Moderate COVID-19 Attending a Public Hospital in Lima, Peru
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Background: Peru has reported more than 1 million COVID-19 cases and about 40,000 deaths as of February 2021 in a country of 33 million inhabitants. Despite this burden, few studies have assessed non-respiratory signs or symptoms of mild-to-moderate infection in Latin America and none have assessed this in Peru. We sought to determine the prevalence and characteristics of the most common neurological manifestations in Peruvian patients with mild-to-moderate COVID-19.

Methods: We conducted a single-center prospective, cross-sectional study at an isolation center functioning as a public health
Augusto Aliaga Plaza, MD
Chemosensory Recovery

122. Nonplus from COVID-19 Vaccination: acute-care hospital during the COVID-19 pandemic in Lima, the capital city of Peru. This was a convenience sample of patients with acute COVID-19 infection and mild-to-moderate respiratory symptoms who presented for hospital admission between September 25 and November 25, 2020. We interviewed participants following provision of informed consent and collected demographic, medical history and clinical presentation data. All participants underwent a complete physical and neurological examination. Descriptive statistics and prevalence ratios (PR) with corresponding 95% confidence intervals and p-values were calculated to explore between-groups differences.

**Results:** There were 199 patients with mild-to-moderate COVID-19 enrolled in this study. Mean age was 43+/−15 years and female patients made up more than half (57%) of the cohort with no significant differences in age or sex between those who had neurological symptoms vs. those who did not. Many (42%) had no prior past medical history. The prevalence of neurological symptoms was 83% with participants having at least one neurological symptom (mean symptom duration 8 +/- 6 days). The most common neurological symptoms were headache (72%), hypogeusia or ageusia (41%), hyposmia or anosmia (40%) and dizziness (34%). Less common neurological symptoms included ataxia (7.5%), focal motor deficit (7%), impaired consciousness (3.5%) and seizure (0.5%). Presence of at least 1 neurological symptom was independently associated with fever, dyspnea, cough, poor appetite, sore throat, chest tightness or diarrhea (each p<0.05), but not with comorbid conditions, such as hypertension, hyperlipidemia or diabetes.

**Conclusions:** This cross-sectional study found that headaches, and smell and taste dysfunction are common among patients presenting with mild-to-moderate acute COVID-19 in Lima, Peru and may be used to identify those with COVID-19 who may not have access to scarce testing. International longitudinal studies are needed to determine the long-term neurological sequelae of COVID-19 during the acute and post-infectious period.

123. Implementation and Evaluation of an Objective Structured Clinical Examination Tool for Neurology Post-Graduate Trainees in Lusaka, Zambia
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**Background:** Despite the high burden of neurologic disease in Zambia, a lower-middle income sub-Saharan African country of eighteen million people, there are currently few Zambian neurologists. The first neurology residency program in Zambia was established at the University of Zambia School of Medicine and the University Teaching Hospital in Lusaka in 2018. The Objective Structured Clinical
Examination (OSCE) is a clinical education tool widely adopted in U.S. training programs. We evaluated the feasibility of implementing a modified OSCE to teach and assess clinical skills for the new Zambian trainees.

Methods: The neurology training program began in October 2018, and its three enrolled trainees completed the OSCE exercise in February 2019. The exercise involved using a smartphone to videotape trainees performing a physical examination and oral presentation in the neurology clinic with real patients with various neurologic findings. Trainees and neurology faculty reviewed the videos independently and assessed performance using a standardized rubric. Faculty members and trainees then met in person and discussed the activity and scoring rubric to identify strengths and areas for improvement in a formative manner. The trainees who participated completed pre- and post-OSCE surveys in which they rated their confidence in elements of the history and neurological examination and provided feedback about the OSCE exercise.

Results: Trainees’ average self-confidence scores improved from the pre- to post-OSCE survey in every category assessed (pre-OSCE: mean score 6.84, range 4.8-7.8, SD 0.92; post-OSCE: mean score 7.9, range 5.67-9.33, SD 0.86). Qualitative responses showed that trainees found the OSCE helpful, routinely applied feedback, and would appreciate repeating the OSCE exercise every few months.

Conclusions: This study demonstrated that OSCEs can be modified and successfully implemented in a neurology post-graduate training program in a resource-limited setting, and still result in improved self-confidence among trainees. Important modifications to the OSCE involved using smartphones to videotape the OSCEs and real patient encounters rather than standardized patients. Because there are many neurology patients and few providers in Zambia, embedding the experience within a busy clinic day was practical, directly applicable, and efficient. Future work should expand use of OSCEs both within the Zambian neurology residency program and among non-neurology training programs. Including additional video reviewers could add to the validity of clinical skills assessment. Videos created could also be used for remote mentorship and teaching purposes.

124. Outcomes of Cryptococcus Meningoencephalitis and Associated Magnetic Resonance Imaging Findings

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Objective: In Cryptococcus Neoformans meningoencephalitis, brain MRI findings might reflect the pathomechanism of disease progression that is fungal accumulation in the periventricular space and consequent invasion into the parenchyma. This study analyzed serial brain MRI findings in Cryptococcus meningoencephalitis in association with the disease progression and outcomes.

Methods: In this retrospective study, 76 patients diagnosed with Cryptococcus meningoencephalitis and performed baseline and serial follow-up MRI evaluations were included. Clinical, treatment, and cerebrospinal fluid profiles were analyzed. MRI parameters included the enlarged periventricular space (ePVS) score (range 0–8), periventricular lesion extension, cryptococcoma, and hydrocephalus. Clinical outcomes at 2-week, 10-week, and 6-month were evaluated using modified Rankin scale (mRS) scores.

Results: At 6 months, 15 (19.7%) patient died and 34 (44.1%) had poor neurological outcomes (mRS scores >2). In multivariate analysis, an ePVS score of ≥5 (Odds ratio [OR]: 94.173, 95% confidence interval [95% CI]: 7.507–1181.295, P<0.001) and periventricular lesion extension (OR: 51.965, 95% CI: 2.592–1041.673, P=0.010) in baseline MRI, and presence of encephalitis feature at baseline (OR: 44.487, 95% CI: 1.689–1172.082, P=0.023) were associated with 6-month poor outcomes. Presence of two or more risk factors at baseline was highly associated with the 6-month poor outcomes (area under the curve [AUC]: 0.978, 95% CI: 0.950–1.000, P<0.001) and mortality (AUC: 0.836, 95% CI: 0.745–0.927, P<0.001). In serial MRI analyses, disease progression was associated with interval development of cryptococcoma and hydrocephalus.

Interpretation: In Cryptococcus meningoencephalitis, brain MRI findings might be useful in predicting poor outcomes and monitoring the disease progression.

125. Vestibular Neuritis with Right CN VIII Enhancement on Internal Auditory Canals (IAC) MRI Months out from COVID-19 Exposure

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Background: Ischemia, hemorrhage, and leukoencephalopathy are common neurologic sequelae of COVID-19. Cranial neuritis, neuropathy, Guillain-Barre, and cauda equina syndromes are less frequently described2. Vertigo is rarely reported3. Neurologic symptoms occur in the peri-infectious period. A single case of vestibular nerve enhancement has been recognized3. The following presents a patient with vertigo diagnosed with post-infectious vestibular neuritis with MRI findings ten months out from initial COVID-19 exposure.

Case Summary: A 63-year-old male veteran with hyperlipidemia and bradycardia presented as a telephone visit with complaints of non-positional vertigo and unsteady gait. The vertigo resolved after four weeks and gait imbalance persisted for six months. He denied nausea, vomiting, tinnitus, or hearing loss. COVID-19 rapid PCR testing was negative. He only recalled upper respiratory symptoms three months prior to onset while in Spain when several close contacts became severely ill. An in-person clinic examination was negative including Dix-Hallpike and sensory changes. MRI brain with IAC reported subtle linear enhancement along the superior margin of the right internal auditory canal suggesting possible neuritis. SARS-CoV-2 antibodies were checked given suspicion for prior infection and returned positive. Patient underwent gait training with resolution of symptoms.

Discussion: Acute vertigo is a described complication of COVID-19 infection. Vestibular neuritis is a clinical
diagnosis involving symptoms of vertigo, nausea, and gait imbalance that accompanies or is preceded by viral infection. Rarely are there associated MRI findings. Cranial neuritis in COVID-19 has been described in the literature with reports of olfactory bulb, optic nerve, facial nerve, and infrequently vestibular nerve enhancement on MRI. Identification usually occurs in the peri-infectious period. This case is unique in that symptom onset and neuroradiologic findings of vestibular neuritis occurred many months out from initial infectious exposure. Thus, there is diagnostic utility of MRI IAC in patients presenting with vestibulopathy with a remote history of COVID-19 infection.


126. Measuring Ambulation, Motor, and Behavioral Outcomes (MAMBO) with Post-stroke Fluoxetine in Tanzania: A Phase II Trial
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Background and Purpose: Fluoxetine may improve post-stroke motor recovery, beyond its antidepressant effects, but has yielded mixed therapeutic and safety results in mostly Western populations. The impact of post-stroke fluoxetine in resource-poor Sub-Saharan African populations, who are overall younger, has not been studied.

Methods: Adults with acute ischemic stroke, seen within 14 days of new-onset motor deficits at Muhimbili National Hospital, Dar es Salaam, Tanzania, were enrolled in a single-arm, open-label phase II trial of daily fluoxetine 20mg for 90 days, from November 2019-October 2020. The primary outcome was safety with secondary outcomes of adherence and tolerability.

Results: 34 participants were enrolled (11 female, mean age at onset 52.2 years, 65% <60 years old; mean 3.3 days since symptom onset). Participants had hypertension (74%), diabetes (18%), and smoked cigarettes (18%). The median NIHSS at enrollment was 10.5, and the median FMMS was 28.5 (upper extremity 8, lower extremity 17.5). 32/34 participants (91%) survived to 90 days. There were 8 serious and 2 non-serious adverse events.

Deaths during the study period occurred due to (1) gastrointestinal illness with low serum sodium (nadir 120 mmol/L) with seizure (fluoxetine stopped two weeks prior; fluoxetine duration 25 days) and (2) gastrointestinal bleed from gastric cancer (fluoxetine duration 38 days). Two others were lost to 90-day follow up but survived. Of the 30 remaining participants, the average sodium level at 90 days was 139 mmol/L (range 133-146) and alanine transaminase was 28 U/L (range 10-134). 96% of pills were taken. The median mRS among survivors at 90 days was 2 and FMMS was 66 (upper extremity 40, lower extremity 27). Median 90-day PHQ-9 and Montgomery-Åsberg scores were 3.5 and 4 (minimal depression).

Conclusions: Fluoxetine administration for 90 days post-stroke in Sub-Saharan Africa was generally safe and well-tolerated, but comorbid illness presentations were fatal in 2/34 cases, even after careful participant selection.

127. Long-Term Neuro-Cognitive Effects in COVID-19 Patients Following Hospital Discharge - A Systematic Review
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Introduction: There are many studies describing complications and burden of coronavirus disease SARS-CoV-2 (COVID-19) disease since the pandemic has begun and many more studies mentioned long term effect of COVID-19 amongst patients discharged from the hospitals, but the literature on post-COVID-19 neurological séquels has been limited.

Aim: Primary aim of this systematic review is to evaluate long-term neurological effects of COVID-19 amongst patients discharged from hospital. Post-discharged COVID-19 neurological sequelae were defined as headache, anosmia, sleep disturbance, concentration, myalgia, fatigue, dysgeusia, PTSD, suicidality, and depression.

Methods: We have extracted the data on post-discharged COVID-19 neurocognitive effects and epidemiology of such patients from observational studies with a consensus of three independent reviewers from September 1, 2019 to present following PRISMA guideline and MOOSE protocol. We identified epidemiological characteristics and prevalence of neuro-cognitive symptoms amongst post-discharged COVID-19 patients.

Results: Total of 7 studies with 3377 post-discharged COVID-19 patients were identified. 1471 (43.56%) were
male. Mean age was 56 years (Range: 34-70). 986 (20.20%) were having persistent post-discharged COVID-19 (one or many) symptoms. Symptoms persist between 30-60 days. Amongst persistence symptoms, neuro-cognitive symptoms like sleep disturbance 381 (63,1%), confusion (32.6%), headache 555 (27.8%), fatigue 335 (26.7%), myalgia 252 (23.14%), anosmia 198 (22.8%), difficulty to concentrate 22 (22%), and dysgeusia 86 (12,1%) and psychiatric symptoms like PTSD 31 (31%), feeling depressed 141 (20%), and suicidality 2 (2%) were having higher prevalence following post-hospitalization.

Conclusion: In our systematic review sleep disturbance, confusion, headache, fatigue, myalgia, and difficulty to concentrate were highly prevalent amongst discharged patients. Since these symptoms are also associated with a poor quality of life, long term follow up may mitigate the neuro-cognitive disability related burden amongst discharged patients following COVID-19 infection.

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Objective: This comprehensive literature review aims to highlight the neurological complications and neuroimaging findings in COVID-19 infection, help clinicians timely address the neurological complications and emphasize the need for close follow-up and monitoring in hospitalized COVID-19 patients.

Background and Review: The COVID-19 infection, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), typically manifests as a self-limiting respiratory illness. However, 20% of COVID-19 patients are known to present with extrapulmonary and multi-organ system manifestations. A staggering number of COVID-19 patients presenting with neurological complications add to the concept of neuro-invasion as a worrisome matter that SARS-CoV-2 may have evolved and presented as a new neuropathogen. Neuro-radiologists have reported many cases worldwide concerning the detrimental effect of COVID-19 infection on the nervous system. CT scan and MRI results of the brain have shown that once within the CNS, COVID-19 produces neurological manifestations, including aneurysm,encephalitis, polynueopathy, anosmia, ageusia, ischemic and hemorrhagic strokes. These findings indicate the close affiliation of the new coronavirus with neurological symptoms, but our understanding of these sequel remains in the early stages. COVID-19 isolation and contact precaution measures have limited the ability to screen for COVID-19 induced neurological complications early on. Therefore, patients presenting with the novel coronavirus-induced neurological manifestations must be followed for months after recovery to report any symptoms worsening.

Conclusions: Studies have indicated that although SARS-CoV-19 predominantly involves the respiratory system, it is a neurotropic virus as well with well-documented neurological manifestations of different severities worldwide. These range from isolated hypoguesia and hyposmia to seizures, acute stroke, encephalitis, and Guillain Barre Syndrome. The gustatory and olfactory symptoms are the most common and predominantly occur due to direct viral damage to the receptors. This literature review will also aid in reporting the neuropathological effects of the COVID-19 virus and its representation on neuroimaging with non-contrast CT, MRI, and CTA, along with microscopic studies, will assist in directing future research and development efforts and help better understand the pathophysiology in COVID-19 patients, ultimately leading to a compromise of neurological function. More data will be collected to study the SARS-CoV-2’s short and long-term effects on patients’ neurological and functional outcomes internationally for an in-depth understanding of this aspect.

129. Transient Focal Neurological Deficits Due to Charcot-Marie-Tooth Neuropathy X-Linked Type 1 Mimicking Acute Disseminated Encephalomyelitis. Case Report and Literature Review
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Objective: Acute disseminated encephalomyelitis (ADEM) is an immune-mediated demyelinating central nervous system (CNS) disorder, manifested by polyfocal neurologic symptoms occurring mainly in childhood, associated with characteristic MRI findings. Charcot-Marie-Tooth disease X-Linked Type 1 (CMTX1) can mimic ADEM but has distinct MRI findings and pathophysiology. We describe one patient with three episodes of transient neurologic deficits, associated with white matter abnormalities on MRI and confirmed to have a hemizygous pathogenic variant of gap junction protein beta 1 (GJB1) gene.

Background: Charcot-Marie-Tooth disease (CMT) is the most common inherited neuropathy but has significant phenotypical and genetic heterogeneity, manifesting with variable motor, sensory and autonomic involvement. CMT X-Linked represents 10-15% of all CMT cases, and 90% of patients have mutations in GJB1 gene encoding connexin 32 (CMTX1), expressed in Schwann cells, oligodendrocytes, and astrocytes as part of gap junctions. Manifestations of CMTX1 include slowly progressive motor and sensory
130. Horner’s Syndrome with Multiple Cranial Nerve Palsies: An Unusual Neurological Manifestation of Granulomatosis with Polyangiitis
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Objective: To report Horner’s syndrome with cranial nerve (CN) palsies as an unusual neurological presentation of Granulomatosis with polyangiitis (GPA) in the setting of granuloma invasion and thickening of the external and internal carotid artery.

Background: GPA (also known as Wegener’s disease) is a rare necrotizing vasculitis that can affect any body organ, but most frequently, it seems to involve the upper/lower respiratory tract and kidneys. Neurological manifestations of GPA are rare (seen in approximately 8% of cases) and usually present as mononeuritis multiplex mainly involving cranial nerves, subacute/chronic meningitis, less frequently seizures, cerebritis, myelitis, stroke, myopathy, etc. GPA presenting as Horner’s syndrome with numerous CN palsies has not been previously reported.

Design/Methods: A case report

Results: A 25-year-old man with medical history of hypertension presented with a 5-month history of worsening nasal congestion and productive cough. Neurology consulted for admission for a 1-month history of symptoms concerning for left-sided Horner’s syndrome (ptosis and miosis), left cranial nerve V, IX, X, XII palsies manifested by left facial hyposthesia, left temporalis/masseter weakness, dysphagia, dysarthria, and left tongue atrophy/fasciculations with deviation to left respectively. Labs were remarkable for transaminits (AST/ALT 59/167), direct hyperbilirubinemia (1.4) and elevated inflammatory markers ESR (75), CRP (101). Rheumatological panel was positive for c-ANCA and anti-proteinase-3 antibodies. Infectious workup (including blood cultures, sputum cultures and CSF cultures) unremarkable. CT chest showed multiple cavitary lesions in the right lung. MRI brain with contrast showed enhancement over anterior (left>right) and basal (left) frontal lobes, extending to the interhemispheric fissure along with extensive sinus disease. MRI also revealed bilaterally enhancing carotid sheath thickening causing narrowing of the left upper cervical internal carotid artery just beneath the skull base. CT-guided lung biopsy showed necrotizing granulomatous inflammation. Patient was diagnosed with mononeuritis multiplex secondary to chronic meningitis with GPA along with partial left Horner syndrome due to infiltration of left internal carotid plexus at the left internal carotid sheath. He was started on high-dose methylprednisone followed by rituximab infusion with clinical improvement.

Conclusion: GPA must be considered in the differential diagnoses of Horner’s syndrome with multiple CN palsies, as this diagnosis can be easily overlooked. It needs to be recognized and properly localized by the neurologists to help with early diagnosis and management of this entity.

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presentation, and he would liberally apply condiments and preferred spicy foods.


**Conclusions:** COVID-19 induced phantosmia, not as a direct effect, but rather as an indirect unintended consequence of health preventive measures (wearing a face mask) has not been reported. While other harmful effects of pandemic preventive behaviors, i.e., inhalation or ingestion of bleach cleaning products and hand sanitizers has been reported (Kuehn, 2020), negative health effects of mask wearing to prevent COVID-19 have not been described. It is possible that air flow during exhalation, rather than diffusing into the ambient atmosphere, remains in the crypto-climate under the mask. Thus, odor suffused exhaled aroma is reintroduced to the nasal cavity, which is interpreted as a phantosmia. Query is to the perception of phantosmia in those wearing face masks may detect an iatrogenic correctable complication within the pandemic.

133. Predictive Value Regarding Neurological Outcome Following Spinal Surgery Utilizing Pre-Operative Somatosensory Evoked Potential Electrophysiological Monitoring Data

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**Objective:** To examine the sustainability and neurological predictive value of the onset latency of intra-operative SSEP improvements in patients undergoing spinal cord surgery.

**Methods:** We collected data from twenty-one patients who underwent spinal cord surgery and analyzed changes in the pre-operative, post-operative and intra-operative median and posterior tibial nerve SSEP’s. Post-operatively, we assessed light touch, vibration, and pin prick sensation, and muscle strength and tone in the upper and lower extremities for which SSEP studies have been performed. We explored correlations between the results of the post-operative neurological outcome and changes of the intra-operative SSEP onset latency.

**Results:** Statistically, there was a strong correlation between the intra-operative, and pre-post-operative SSEP latency changes, and between intra-operative SSEP onset changes and light touch and pin prick testing results. There was no correlation with vibration testing. There a trend towards, but not statistically significant correlation with clinical motor outcome.

**Conclusion:** The results support the hypothesis that improvement in the intra-operative SSEP onset latencies during spinal cord surgery are sustainable and assist in predicting post-operative clinical sensory outcome, and trend towards assisting in predicting the overall neurological outcome.

**Significance:** Intra-operative SSEP onset latencies assist in predicting post-operative sensory outcome and may assist in predicting overall post-operative neurological outcome.

134. CNS Vasculitis Secondary to Lymphoid Interstitial Pneumonia

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**Introduction:** Cerebral vasculitis can have a variety of clinical manifestations and required brain biopsy to diagnose. In this case presentation, we will discuss a case of granulomatous vasculitis of the CNS secondary to idiopathic lymphoid interstitial pneumonia (LIP), presenting with atypical cerebral lesions. On the grounds that both the diagnoses of LIP and the secondary granulomatous vasculitides were confirmed by biopsy, this case illustrates the importance of biopsy as a tool for diagnostic workup.

**Case Presentation:** 46-year-old female initially presented with complaints of a dry cough in August of 2020. An extensive workup of this complaint resulted in a LIP-positive core biopsy of the lung. She then presented with altered mentation in January of 2021, exhibiting global aphasia, motor weakness, diminished tendon reflexes and poor response to sensory stimuli. MRI within the cerebral hemispheres, cerebellum and brainstem showed innumerable, predominantly small, foci of abnormal signal intensity and enhancement with T2 prolongation and robust contrast enhancement with the larger lesions exhibiting a ring like morphology. Infection workup and metagenomic next generation sequencing results were negative. Brain biopsy was indicative of granulomatous vasculitis of the CNS with a markedly increased CD4:CD8 T cell ratio (60:1) and no significant B cell population identified. Patient initially improved on a combination of cyclophosphamide, corticosteroids, and plasma exchange sessions, however the patient’s lesion size worsened suggesting poor prognosis, and palliative care was discussed.

**Discussion:** Although CT/MRI may be able to show abnormalities of the cerebral vasculature, they are not specific for vasculitis encouraging the usage of brain biopsy for true diagnosis. In our case, neuroradiological evaluation did not strengthen the differential of the cerebral lesions as they were not consistent with cerebral vasculitis. The challenge in this case was that, regardless of diagnostic workup being negative for infection and other vascular abnormalities, the patient exhibited lesions upon imaging and a deteriorating neurological condition that was quickly exacerbated with the tapering of steroids. In the case of ambiguous cerebral lesions in patients presenting with immunological infiltration, we are strongly encouraging early biopsy and CSF metagenomic next generation sequencing to rule out infection, followed by prophylactic steroid and immunomodulating therapy, regardless of negative diagnostic cerebral angiogram.
135. The Childhood Epilepsy Treatment Gap in Northern Nigeria

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Background: The childhood epilepsy treatment gap in sub-Saharan Africa’s low- and middle-income countries has been estimated at 67-90%. Epilepsy treatment gap estimates are important for developing, testing and implementing strategies for enhancing epilepsy care access. Prior estimates of the epilepsy treatment gap often did not utilize a systematic search for non-motor seizures, or specifically included only convulsive epilepsy.

Methods: As part of the Bridging the Childhood Epilepsy Treatment Gap in Africa (BRIDGE) project, mothers of children in three northern Nigerian cities (Kano, Zaria, and Kaduna) were administered a previously-validated Hausa-language epilepsy screening and seizure classification tool that screened for possible generalized and focal-onset epilepsy, including non-convulsive epilepsy. Children who screened positive underwent further diagnostic evaluation for epilepsy. Children with previously untreated epilepsy were identified and offered enrollment in the BRIDGE non-inferiority cluster randomized clinical trial (cRCT) comparing care provided by epilepsy-trained community health workers (CHWs) versus physician epilepsy care. Screening was performed in pediatric clinics, in community door-to-door surveys, and at schools. Prior to the epilepsy screening an extensive community education and awareness campaign was executed that included weekly radio broadcasts in Hausa on epilepsy as an often undiagnosed and treatable medical disorder.

Results: Between June 2020 and April 2021, 620 of 10,953 children in clinics (5.7%), and 1135 of 30,507 children (3.7%) in communities screened positive for epilepsy. None of the 29 children who were screened in schools screened positive for epilepsy. 612 of 620 children (99%) who screened positive in clinics and 1113 of 1135 children (98%) who screened positive in the community were diagnosed with epilepsy. Some children who screened positive and were diagnosed with epilepsy were brought to screening sessions after their parents listened to the epilepsy education radio broadcasts. 1664 of the 1725 children identified with epilepsy (96.5%) were untreated and were eligible for enrollment in the BRIDGE cRCT, of which 1659 were enrolled.

Conclusion: The childhood epilepsy treatment gap in three large cities of northern Nigeria is higher (96.5%) than what has been previously reported in studies from other areas of Africa. The inclusion of non-convulsive epilepsy and focal onset epilepsy in the screening tool, screening by epilepsy-trained community health workers who were from the local communities, and the utilization of a comprehensive community education and outreach program with radio broadcasts all likely played a role in the increased ascertainment of children with untreated epilepsy.

Funding: NINDS, FIC/NIH (R01 NS113171).

136. The Reliable Plane for Cortical Thickness and Cortical/ Subcortical MR Volumetry Study Employing FreeSurfer

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Objectives: We tried to select a reliable acquisition plane for the brain magnetic resonance (MR) volumetry analysis through FreeSurfer.

Methods: Seven hundred sixty-nine (454 men, 315 female) healthy adults, aged 19-72 years, were enrolled between March 2016 and March 2021 from a tertiary hospital. Cortical reconstruction and volumetric segmentation from 3D T1-weighted axial, coronal, and sagittal images from 5 MR scanners with 3.0 magnetic field strength (Phillip scanners, Koninklijke Phillips N.V.) were estimated using the Freesurfer image analysis suit (v6.0) under the 3 workstations with exactly same hardware setups. MR sequences were as followings: FOVs were 220 or 224 in axial and sagittal images and those in coronal images were 224. The acquisition matrix = 224 x 224, The number of row and column = 1024 x 1024, the thickness of slice = 1 mm. TE = 4.6 ms, TR = 99 ms, Flip angle = 8°. Cortical/subcortical volumetry was done from 58 regions of interest (ROI) including amygdala, hippocampus, caudate, pallidum, putamen, thalamus, and nucleus accumbens. Total 148, grey matter regions were estimated bilaterally for cortical thickness and were diagnosed with epilepsy were brought to screening sessions after their parents listened to the epilepsy education radio broadcasts. 1664 of the 1725 children identified with epilepsy (96.5%) were untreated and were eligible for enrollment in the BRIDGE cRCT, of which 1659 were enrolled.

Conclusion: The childhood epilepsy treatment gap in three large cities of northern Nigeria is higher (96.5%) than what has been previously reported in studies from other areas of Africa. The inclusion of non-convulsive epilepsy and focal onset epilepsy in the screening tool, screening by epilepsy-trained community health workers who were from the local communities, and the utilization of a comprehensive community education and outreach program with radio broadcasts all likely played a role in the increased ascertainment of children with untreated epilepsy.

Funding: NINDS, FIC/NIH (R01 NS113171).
respectively. Combined proportion of excellent and good rate, the correlations of Cortical/ subcortical volumetry were 91.9 %, 93.5 %, and 95.1 % and those in cortical thickness were 95.4 %, 96.1 %, and 96.1 % from the above same sequential, paired combinations of acquisition plane.

**Conclusion:** Our results showed the proportion of excellent correlation of ICC was higher in cortical/ subcortical volumetry than those of the cortical thickness. Considering The proportion more than good rate, acquisition from any plane for cortical/ subcortical MR volumetry and cortical thickness measure employing FreeSurfer could yield reliable results.

339. Analysis of COVID-19 Brain Autopsies Reveals That Neuroinflammation is Not Caused by Direct SARS-CoV-2 Infection of the CNS

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**Background:** Many patients suffering from a SARS-CoV-2 infection develop neurological symptoms; however, it is unclear whether they are a consequence of direct viral infection of the CNS or due to secondary sequelae from the virus-induced systemic inflammatory response syndrome.

**Methods:** In order to understand the mechanisms by which the SARS-CoV-2 systemic infection induces neurological symptoms, we collected brain samples from 41 consecutive COVID-19 patients undergoing autopsy at our medical center from April - June 2020. We characterized the degree of neuroinflammation in these cases by performing histopathological analysis of multiple brain regions and immunohistochemistry (IHC) for cell-specific markers, including macrophages and microglia (CD68 and Iba1), astrocytes (GFAP), lymphocytes (CD3 and CD20), and inflammatory cell adhesion molecules (VCAM-1). We also analyzed the integrity of the blood-brain barrier and blood-CSF barrier by staining for tight junction proteins (CLAUDIN5 and ZO-1) and basement membrane proteins (Collagen IV and Lamina). In parallel, we analyzed whether there was a direct invasion of the SARS-CoV-2 virus into the brain parenchyma via IHC, quantitative reverse-transcriptase PCR (qRT-PCR), and RNA in situ hybridization (RNAscope), targeting both the spike and nucleocapsid regions of the SARS-CoV-2 virus.

**Results:** The mean age was 74 years (38-97 years), 27 patients (66%) were male and 14 (33%) were of Hispanic/Latinx ethnicity. Every patient showed some degree of hypoxic/ischemic injury, and several had hemorrhagic infarcts. The blood-brain and blood-CSF barriers were largely intact. We found in a majority of patients microglial activation (80.5%), most prominently in the brainstem, and often with microglial nodules accompanied by neuronophagia (63.4%). In contrast, there was sparse T lymphocyte infiltration in either perivascular regions or brain parenchyma, and no evidence of vasculitis. qRT-PCR revealed very low viral RNA levels in the majority of brains, which were substantially lower than those in nasal epithelia from the same patients, and when present did not correlate with histopathological evidence of neuroinflammation. Furthermore, RNAscope and IHC failed to detect viral RNA or protein in COVID-19 brains.

**Conclusion:** Our analyses suggest that neuroinflammatory findings observed in COVID-19 patients do not result from direct viral infection of the brain parenchyma, but instead are likely a result of systemic inflammation, perhaps with synergistic contribution from hypoxia/ischemia.

356. Epilepsy Stigma in the Republic of Guinea and Its Demographic, Social, and Clinical Associations: A Cross-Sectional Analysis

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**Background/Objective:** Epilepsy stigma in Sub-Saharan Africa is linked to various demographic, social, and clinical factors, some of which may be modifiable. Identifying and addressing these factors may mitigate stigma and its consequences. In West Africa, where traditional healing is ubiquitous and access to epilepsy expertise is limited, there are few reports on epilepsy-associated stigma. We aim to quantify the degree of stigma perceived by people living with epilepsy (PLWE) in the Republic of Guinea (2019 gross national income per capita, 930USD) and analyze factors associated with epilepsy stigma.

**Methods:** As part of the Guinea Epilepsy Project, a prospective convenience cohort of PLWE was recruited at the Ignace Deen Hospital in Conakry. All participants were evaluated by U.S. and Guinean physicians. A survey instrument exploring demographic, social, and clinical variables was
administered to PLWE, and their guardians if PLWE were children (age <18 years). The primary outcome measure was the Stigma Scale of Epilepsy (SSE), a 24-item scale previously validated in SSA with scores ranging from 0 (least stigma) - 100 (most stigma). Regression models were fit to assess possible associations between SSE scores and 16 pre-selected demographic, social, and clinical variables of interest.

**Results:** 249 PLWE (112 female; mean age=20.0 years; 22% from rural locale; 14% of participants >16 years old with no formal schooling; 11% seizure-free for 6 months) had an average SSE score of 46.1 (standard deviation=14.4). Children had an average SSE score of 45.2, and adults had an average score of 47.0. There were no significant differences between self- and guardian-reported SSE scores (means=45.8 and 46.5, respective), p=.86.

In univariate analyses, higher stigma scores were associated with lesser wealth (p=0.03), more seizures (p=0.005), and more depressive symptoms (p=0.01); age, sex, education level, and social support were not associated with stigma perceptions (all p>0.05). In a multivariate model including sex, educational level, household wealth, generalized tonic-clonic seizures, seizure frequency, and seizure-related burns, only low household wealth (β=4.05, p=0.03) and higher seizure frequency (β=2.34, p=0.03) were significantly associated with higher SSE scores.

**Conclusions:** In this Guinean cohort of people living with poorly-controlled epilepsy, participants reported moderate perceptions of epilepsy stigma. Stigma was associated with lesser household wealth and higher seizure frequency—both potentially modifiable factors. Programs targeting consistent antiseizure treatment of PLWE would have the highest downstream impacts on stigma reduction, especially for PLWE with lesser household wealth.

406. Leriglitazone Reduces Cerebral Lesions and Improves Biomarkers Related to Axonal Degeneration, Inflammation and Compromised Blood-Brain-Barrier in Patients with Adrenomyeloneuropathy

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**Objectives:** Effects of leriglitazone (MIN-102) on imaging and biochemical parameters in plasma.

**Background:** Leriglitazone is a brain penetrant peroxisome proliferator-activated receptor γ (PPARγ) agonist.

**Design/Methods:** Data from a 2-year, placebo-controlled study in adult male patients with 2:1 randomization were analyzed with respect to progression of cerebral lesions and Loes scores, and biochemical parameters in plasma. Three serial MRIs at Baseline, Weeks 48 and 96 of treatment were rated by investigators and 2 independent central readers blinded to treatment. Plasma levels of Neurofilament Light Chain (NFL) were measured at Baseline, Week 48 and Week 96 by SIMOA technology. Matrix Metalloproteinase 9 (MMP-9), Interleukin-18 (IL-18), Interleukin-1beta (IL-1β), Interleukin-1 Receptor Antagonist (IL-1ra), and Macrophage Inflammatory Protein 1-beta (MIP-1 β) were measured in plasma at Baseline and Week 96 by Luminex system.

**Results:** 116 patients were randomized (77 leriglitazone, 39 placebo). Thirty-eight (49.4%) patients on leriglitazone and 22 (56.4%) had Loes scores >0 at Baseline. Leriglitazone reduced lesion growth by Loes score change (p = 0.024 ANCOVA). Six patients, all in the placebo arm with 3 of them having arrested cALD with non-enhancing lesions at Baseline, showed progressive cerebral ALD by clinical assessment of the investigators and agreed by central readers (p = 0.0015 Fisher test). Further 5 patients were only assessed by central readers as “progressed”, totaling the number of cases to 11 with 8 patients in the placebo arm and 3 patients in the leriglitazone arm (p = 0.0066 Fisher test). Leriglitazone significantly reduced plasma MMP-9, IL-18 (p<0.0001 and p<0.001 respectively, Fisher LSD), IL-1β, IL-1ra (p<0.01 Fisher LSD) and MIP-1 β (p<0.05 Fisher LSD) levels compared to the placebo group. NFL plasma levels remained stable at Week 96 compared to Baseline in the leriglitazone group but showed elevation in those 6 patients in the placebo group who by investigators’ judgment showed progressive cerebral ALD (p<0.001 Fisher LSD).

**Conclusions:** Leriglitazone may reduce the risk of lesion progression in patients with adult cerebral ALD. Results on biomarkers related to inflammation, blood-brain-barrier permeability and neuronal damage supported the impression obtained by imaging that leriglitazone slowed the progression of cerebral lesions.


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Introduction: Epidemiological studies on the global impact of pain-related disorders (PRDs) are poorly explored, generating a misrepresentation of them in the global health policy agenda, and reducing the awareness among health professionals and the general population.

Aim: This study describes and compares the global and regional burden of PRDs by age and sex from 1990 to 2019.

Methods: Data were extracted from the Global Burden of Disease (GBD) 2019 Study. The included PRDs were: A) Conditions with a direct relationship (included pain as part of their definitions): migraine, tension-type headache, rheumatoid arthritis, osteoarthritis, low back pain, neck pain, gout, and other musculoskeletal disorders. B) Conditions with an indirect relationship (highly associated with pain over the course of the disease): Opioid use disorders, urolithiasis, sickle cell disorder, falls, and injury by mechanical forces. Age, sex, and region-specific analyses were conducted to estimate the Disability-Adjusted Life Years (DALYs), years lived with disability (YLDs), and Years of life lost (YLLs), with their uncertainty intervals (UIs).

Results: The overall burden of PRDs represented 10.64% of the global burden in 1990 and 18.11% in 2019. This places PRDs as the leading group of burden-causing diseases in the world in 2019. The Global DALYs of pain-related disorders were 276.7 million (95% UI: 168.9 million-426.1 million) in 1990 and increased by 66.78% to 461.4 million (95% UI: 281.8 million-708.9 million) in 2019. The disability measure (YLDs) represented the highest proportion of this burden with almost no change from 1990 to 2019 (89.48% vs. 91.97%, respectively). This burden is produced mainly by direct PRDs in both 1990 (82.6%) and 2019 (85.2%). In 2019, the conditions that generated the highest-burden were: 1) Low back pain, 2) Tension-type headache, and 3) Migraine. The Burden was higher (50% higher) in females than males in both 1990 and 2019. Middle-aged adults (35-49 years of age) from high-income countries had the highest-burden; however, the burden is rapidly increasing in older adults (+40.6%) and adults from low- and middle-income countries (LMICs) (+89.8%) from 1990 to 2019.

Conclusions: PRDs are the leading global cause of burden and disability. Even though, these estimates are not including neuropathic and cancer pain. Greater awareness is urgently needed to mitigate this increasing burden. Health system strengthening to improve pain prevention, diagnosis, and management should be priorities in LMICs.

K-490. Socioeconomic Status and Cognitive Function in Children with HIV in Zambia

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Background: Multiple prior studies have identified a detrimental effect of pediatric HIV on cognitive function. Socioeconomic status (SES) is one of the strongest predictors of cognitive performance, and may affect the relationship between HIV and cognition.

Methods: As part of the ongoing HIV-Associated Neurocognitive Disorders in Zambia (HANDZ) study, a prospective cohort study, we recruited 208 participants with HIV and 208 HIV-exposed uninfected controls, all aged 8-17 years. A standardized questionnaire was administered to assess SES, and all participants had comprehensive neuropsychological testing. An NPZ8 score was derived as a summary measure of cognitive function. Logistic and linear regression were utilized to model the relationship between SES and cognitive function, and mediation analysis was used to identify specific pathways by which SES may affect cognition.

Results: Children with HIV performed significantly worse on a composite measure of cognitive function (NPZ8 score -0.19 vs. 0.22, p <0.001) and were more likely to have cognitive impairment (33% vs. 19%, p=0.001). Higher SES reduced the risk of cognitive impairment (OR 0.8, 95% CI 0.75-0.92, p<0.001) in both groups, with similar effects in HIV+ and HEU groups. SES was more strongly correlated with NPZ8 score in children with HIV than in uninfected controls (Pearson’s R 0.39 vs 0.28), but predicted NPZ8 in both groups. Mediation analysis suggested that the effect of SES on cognition was most strongly mediated through malnutrition.

Conclusion: Cognitive function is strongly correlated with SES in children with HIV, suggesting a synergistic effect of HIV and poverty on cognitive function.

Headache and Pain

137. Treatment of Nummular Headaches with Topiramate Monotherapy: A Case Report

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Background: Nummular headache is an emerging diagnosis within the field of neurology. It has a unique clinical picture that distinguishes it from other primary headache disorders. Nummular headaches present as constant or intermittent pain within a fixed, circular or ovoid region of the scalp that measures between 1-6cm. Since its first description in 2002 only a few hundred cases have been recorded making this a fairly rare headache.

Case Report: We report on a case of a 66-year-old male with a history of migraine-like headaches and mild compressive cervical radiculopathy, who presented with sudden onset head pain. The pain was restricted to a circular area on the right temporal scalp approximately the size of a golf ball and was a dull, pressure-like sensation that was intermittent and throbbing. It did not radiate and was not alleviated by over-the-counter ibuprofen (200-400mg). Patient denied symptoms of nausea, vomiting, phonophobia, or photophobia. Based on the initial presentation and thorough history, this patient’s headache was classified as a nummular headache and was started on topiramate 25mg. Despite two weeks of treatment, the headache did not resolve which increased suspicion for an underlying structural abnormality such as a solid tumor or...
hemangioma. MRI and MRA revealed no intracranial abnormalities which reinforced the initial suspected diagnosis of nummular headache. By week three of no improvement, the patient opted to discontinue topiramate and not pursue any other medical therapy. Over the following three-month period the patient observed a gradual resolution of his nummular headache. Occasionally he reports experiencing an infrequent pressure-like sensation in the same location. However, it does not interfere with his activities of daily living.

**Discussion:** According to the current literature and guidelines, there are no definitive treatments for nummular headache. For patients who experience severe pain, such as this patient, prophylactic or abortive therapy would significantly improve quality of life. There have been reports of neuromodulators helping some patients; however, antiepileptics are a class of neuromodulators that have not been attempted as monotherapy. This case supplements the current knowledge regarding types of successful medical therapy available for nummular headaches.

**Conclusion:** While most cases of nummular headaches can be managed with analgesics, some patients may have severe refractory pain. Topiramate did not yield immediate results; however, patient noted a significant decrease in pain in the subsequent months suggesting that it may be a possible treatment option for those suffering from refractory pain.

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138. Intracranial Subdural Hematoma as a Rare Complication of Spinal Epidural Anesthesia Treated with Burr Hole Hemtoma Evacuation

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**Background:** Intracranial subdural hematomas are a rare, but serious complication of epidural anesthesia. There are very few cases reported in literature, though one study cited an incidence of 1:500,000 [1]. Dural puncture can lead to CSF leak and subsequent reduced intracranial pressure. This decrease in intracranial pressure can cause a downward displacement of brain structures, tearing of subdural veins, thereby creating a subdural hematoma [2-4].

**Case presentation:** A 36-year-old woman presented to the emergency department (ED) complaining of a holoc cephalic positional headache 4 days after receiving epidural anesthesia during spontaneous vaginal delivery. Initially, the patient was diagnosed with post dural puncture headache. She was treated with autologous blood patch with only minimal improvement in her headache. Three days after her blood patch, she returned to the ED due to worsening positional headache. She was found to have an unremarkable neurologic exam, though CT head revealed the presence of a right 8 mm intracranial subdural hematoma with 3 mm midline shift. MRA and MRV head did not show any evidence of vascular anomalies including aneurysms, dural fistulas, or sinus thrombosis. The patient underwent burr hole craniotomy for evacuation of the subdural hematoma. She had significant improvement in her headache and a benign post-operative clinical course.

**Conclusion:** Postpartum headache after receiving epidural anesthesia is a common complication. However, failure of conventional medical therapy, along with other modalities of management including blood patch, should raise suspicion for rare and serious causes including intracranial hemorrhage. CT head should be considered to evaluate for subdural hematoma in patients with refractory post puncture headache.


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139. Chronic Pain and Suicide: A Systematic Review and Meta-Analysis

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**Objective:** To conduct a systematic review and meta-analysis on suicidality (ideation, plan, and attempt) and death by suicide in patients with chronic head, neck, and back pain.

**Background:** Suicide is the 10th leading cause of death in the United States. Chronic pain is a known risk factor for suicidal behavior and death. However, there is a paucity of comprehensive review and meta-analysis to better understand whether the risk of suicidality is significantly different in those with chronic head pain versus chronic back and neck pain.

**Method:** Search was performed using PubMed, Embase, and Web of Science from the date of the first available article through the end of 2020. This review included adult participants with migraine, tension headache and cluster headache, as well as chronic neck/back pain. A total of 14 studies were included in the systematic review. We performed meta-analysis using a random effects model on 11 studies to estimate the pooled odds ratios (ORs) and 95% confidence intervals (95%CI) for the association between suicidality and these chronic pain conditions.

**Results:** A total of 186,123 migraine patients and 135,790 patients with chronic neck/back pain were included in the meta-analysis. The meta-analysis showed that the estimated risk of suicide ideation/planning is increased by two-fold [OR: 2.03; 95%CI: 1.92-2.16] and risk of suicide attempt is increased by more than three-fold [OR: 3.47; 95%CI: 2.68-4.49] in patients with migraine as compared to healthy controls. Additionally, the risk of suicidality in migraine patients [OR 2.49; 95%CI: 2.15-2.89] is higher than that in patients with chronic back/neck pain [OR 2.00; 95%CI: 1.63-2.45]. Furthermore, the risk of suicide attempt in
migraine patients is statistically higher than in those with chronic neck or back pain (OR 2.53; 95% CI: 2.05-3.12) [z test, p=0.04]. No Meta-Analysis was performed for cluster and tension headache due to limited study numbers.

Conclusions: Suicidality risk is higher in migraine than in chronic neck and back pain patients. Especially, risk of suicide attempt is significantly higher in patients with migraine than in those with chronic neck and back pain. This study underscores the critical needs for suicide prevention in migraine patients.

140. Idiopathic Intracranial Hypertension Presenting as Cyclic Vomiting Syndrome in a Child; A Case Report

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Background: Idiopathic Intracranial Hypertension (IIH) is a disorder of increased intracranial pressure in the absence of cerebrospinal outflow obstruction, mass lesion, or other underlying cause. It is a rare phenomenon in prepubertal children and is most typically found in women of child-bearing age. The classic presentation consists of headaches, nausea, vomiting, and visual changes; however, children present more atypically. We report a case of IIH in an otherwise healthy, 4 year-old child with atypical symptoms resembling that of cyclic vomiting syndrome (CVS).

Case Presentation: A 4 year-old Caucasian, otherwise healthy, male child who presented to our emergency department with episodic intermittent early morning vomiting occurring once every 1-3 weeks without inter-episodic symptoms, starting 10 months prior. With outpatient metabolic, autoimmune, endocrine, allergy, and gastroenterology work-up all unremarkable, he was initially diagnosed with CVS. Discovery of mild optic nerve sheath distension on MRI Brain 10 months after symptoms onset led to inpatient admission and a lumbar puncture notable for an opening pressure of 47cmH2O, with normal cell count and protein levels. He had no changes in visual acuity or optic disc edema on dilated fundoscopic exam. Patient was started on acetazolamide, with resolution of episodic emesis at his last follow-up visit 12 weeks after discharge.

Conclusions: IIH presents atypically in prepubescent children with about one-fourth presenting asymmetrically, and only 13-52% presenting with “classic” symptoms. With a prevalence of only 0.6 - 0.7 per 100,000, much remains unknown regarding the underlying pathophysiology in this demographic. Cyclic vomiting syndrome (CVS) however, has a much higher prevalence in this age group; with a prevalence of 0.4-1.9 per 100. It is thought to be an idiopathic, periodic disorder of childhood, often linked to neurological conditions such as abdominal migraines, epilepsy, mitochondrial disorders, and structural lesions such as chiari malformation and posterior fossa tumors. While CVS is thought to have a benign course, untreated IIH can have long-term detrimental effects; such as visual loss or even blindness. We present a case of IIH presenting with symptoms resembling CVS in a 4 year-old child, diagnosed 10 months after initial onset of symptoms. We aim to demonstrate the need for a high level of clinical suspicion and the need for further investigation into underlying pathophysiology in this vulnerable population.

141. Efficacy of Long-Term Fremanezumab Treatment in Patients with Chronic or Episodic Migraine and Prior Inadequate Response to Multiple Migraine Preventive Medication Classes

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Introduction: Fremanezumab, a fully-humanized monoclonal antibody (lgG2Δα) that selectively targets the calcitonin gene-related peptide (CGRP), has been approved for migraine preventive treatment in adults. The long-term efficacy of fremanezumab was evaluated in patients with chronic migraine (CM) or episodic migraine (EM) and documented prior inadequate response to 2-4 migraine preventive treatment classes during the 12-week double-blind (DB) period (DBP) followed by a 12-week open-label extension (OLE) in the phase 3b FOCUS study.

Methods: After a 28-day baseline period, patients were randomized (1:1:1) to quarterly or monthly fremanezumab or placebo for the DBP. In the OLE, patients who had been on monthly fremanezumab continued monthly dosing; patients who had been on quarterly fremanezumab or placebo switched to monthly dosing. Outcomes are summarized by DB randomization group.

Results: During the DBP, reductions in monthly migraine days (MMD) from baseline were significantly greater with quarterly and monthly fremanezumab versus placebo for CM patients (n=509; least-squares mean changes: quarterly, -3.9 and monthly, -4.5 vs placebo, -0.8) and for EM patients (n=328; quarterly, -3.7 and monthly, -3.8 vs placebo, -0.6); all P<0.0001 vs placebo. Reductions in MMD increased to the end of the OLE across all DB randomization groups for CM patients (n=493; mean changes from baseline: quarterly fremanezumab, -5.1; monthly fremanezumab, -5.8; placebo, -5.3) and for EM patients (n=313; quarterly fremanezumab -5.1; monthly fremanezumab, -5.1; placebo, -3.9). With both dosing regimens of fremanezumab versus placebo, significant reductions from baseline were also observed in monthly headache days of at least moderate severity during the DBP for CM and EM patients (all P<0.0001 vs placebo) that increased during the OLE. In the quarterly fremanezumab, monthly fremanezumab, and placebo groups, respectively, the proportion of patients with a ≥50% reduction in MMD was 27%, 29%, and 8% for CM patients and 47%, 43%, and 10% for EM patients during the DBP (all P<0.0001 vs PBO) and was 35%, 40%, and 31% for CM patients and 63%, 56%, and 49% for EM patients during the OLE.
Conclusions: Fremanezumab demonstrated long-term efficacy in CM and EM patients with prior inadequate response to multiple preventive classes, including those switching from quarterly to monthly fremanezumab.

142. Relative Frequency of Medically Diagnosed Migraine in the Veterans Health Administration: A 12-year Cohort Study

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Objective: Describe the relative frequency of medically diagnosed migraine in men and women by age among veterans served by the Veterans Health Administration (VHA). Background: U.S. studies indicate the one-year prevalence of migraine is 6-10% in men and 18-21% in women. The VHA is the largest integrated healthcare system in the United States. Veterans may be at increased risk of migraine compared to the general United States population due to military exposures and comorbidities.

Methods: This is a 12-year cohort study evaluating the relative frequency of medically diagnosed migraine in the VHA by age and gender using administrative data. An adapted validated algorithm identified all veterans with a physician diagnosis of migraine for at least one outpatient VHA visit from October 1, 2007 through September 30, 2019. Age and gender were extracted at the time of the first migraine encounter during the cohort period. Age and gender characteristics were also extracted for all veterans who received care in the VHA during the study period. Age was divided in 2 to 5-year bands. Descriptive statistics and chi-square tests evaluated differences between men and women.

Results: The relative frequency of medically diagnosed migraine was 5.3% (n = 567,121/10,789,815) in the total VHA population, 19.6% (157,837/805,641) in women, and 4.1% (409,284/9,984,174) in men, p < .001. Women had higher relative frequency of migraine than men in every age band, p < .001. For women, migraine increased from age 18-19 (1.7%), 20-24 (12.6%), 25-29 (22.9%) and peaked at age 30-34 (29.8%). After this peak, the relative frequency of migraine in women declined as age increased (35-39: 28.7%; 40-44: 25.8%; 45-49: 21.9%; 50-54: 17.8%; 55-59: 15.1%; 60-64: 11.3%; 65-69: 8.8%; 70-74: 4.7%; 75-79: 3.5%; 80-84: 1.3%; 85+: 1.0%). Men demonstrated a similar shaped, flatter curve with migraine relative frequency increasing as age bands increased from 18-19 (0.7%) to 20-24 (5.3%), 25-29 (9.5%), peaking at age 30-34 (12.7%). After this peak, migraine in men declined as age bands increased (35-39: 10.7%; 40-44: 9.0%; 45-49: 7.1%; 50-54: 5.2%; 55-59: 3.5%; 60-64: 2.7%; 65-69: 2.5%; 70-74: 1.5%; 75-79: 0.9%; 80-84: 0.6%; 85+: 0.5%).

Conclusions: The VHA has served over half a million veterans with migraine over the past 12 years, representing 5.3% of the VHA population. The relative frequency of migraine was lower than expected which could indicate under-ascertainment, particularly in men.

143. Reductions in Migraine Frequency with Fremanezumab Treatment by Baseline Migraine Frequency Category in Patients with Chronic and Episodic Migraine

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Introduction: Fremanezumab, a fully-humanized monoclonal antibody (IgG2Δa) that selectively targets the calcitonin gene-related peptide (CGRP), has been approved for preventive treatment of migraine in adults. Migraine patients with more frequent attacks may have greater disease burden. This pooled analysis assessed the shift in migraine frequency category for patients treated with fremanezumab from three phase 3, double-blind, placebo-controlled trials (HALO CM, HALO EM, and FOCUS).

Methods: In all 3 studies, patients with chronic migraine (CM) or episodic migraine (EM) were randomized 1:1:1 to quarterly fremanezumab, monthly fremanezumab, or matched monthly placebo. The percentages of patients with a shift of at least 1 category down during 12 weeks of treatment were evaluated by baseline frequency category (high-frequency CM [HFCM; ≥19 monthly migraine days (MMD)]; low-frequency CM [LFCM; 15-18 MMD]; high-frequency EM [HFEM; 10-14 MMD]; moderate-frequency EM [MFEM; 4-9 MMD]).

Results: At baseline, 659 patients had MFEM, 515 had HFEM, 511 had LFCM, and 500 had HFCM. Higher proportions of patients with MFEM receiving quarterly (53%) and monthly (52%) fremanezumab experienced a shift of 1 category down to LFEM (<4 MMD) versus placebo (29%). Among patients with HFEM at baseline, higher proportions of patients receiving quarterly and monthly fremanezumab versus placebo experienced a shift of at least 1 category down in to MFEM or LFEM (quarterly, 77%; monthly, 75%; placebo, 58%). Similarly, among CM patients divided by baseline migraine frequency, higher proportions of patients receiving quarterly and monthly fremanezumab versus placebo experienced a shift of at least 1 category down in the baseline HFCM subgroup to HFEM, MFEM, or LFEM (quarterly, 73%; monthly, 76%; placebo, 57%) and in the baseline HFCM.
subgroup to LFDM, HFEM, MFEM, or LFEM (quarterly, 57%; monthly, 59%; placebo, 44%). In addition, higher proportions of patients with MFEM, HFEM, and LFDM receiving placebo experienced a shift of at least 1 category up versus quarterly and monthly frumazenil.

**Conclusions:** Treatment with quarterly and monthly frumazenil was associated with greater reductions in migraine frequency compared with placebo, regardless of migraine frequency at baseline.

**144. Long Term Efficacy and Safety of AXS-07 (MoSEIC™ Meloxicam-Rizatriptan) for the Acute Treatment of Migraine: Results from the MOVEMENT Phase 3 Trial**

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**Background:** Migraine is a leading cause of disability. Surveys of migraineurs indicate that >70% are dissatisfied with current treatments, nearly 80% would try a new therapy, and treatments that work faster, more consistently, with less symptom recurrence are desired. AXS-07 is a novel, oral, rapidly-absorbed, multi-mechanistic investigational medicine for the acute treatment of migraine. AXS-07 is thought to act by inhibiting CGRP release, reversing CGRP-mediated vasodilation, and inhibiting neuro-inflammation, pain signal transmission, and central sensitization. Meloxicam is a new molecular entity for migraine enabled by MoSEIC™ technology, which results in rapid absorption of meloxicam while maintaining a long half-life. In prior controlled-trials, AXS-07 demonstrated superiority over placebo, MoSEIC™ meloxicam and rizatriptan (MOMENTUM), and over placebo (INTERCEPT), for the acute treatment of migraine.

**Methods:** MOVEMENT was a Phase 3, long-term, open-label study that enrolled patients who had completed previous pivotal trials of AXS-07: MOMENTUM and INTERCEPT. Patients could treat up to 10 migraine attacks/month over the up to 12-month period, using one dose of AXS-07 (20 mg MoSEIC™ meloxicam/10 mg rizatriptan) for each migraine.

**Results:** MOVEMENT enrolled 706 patients and treated >21,000 migraine attacks. AXS-07 treatment resulted in rapid, and substantial relief of migraine pain and most bothersome migraine-associated symptoms (MBS). Within 1 hour of dosing, pain relief was achieved in 39% of treated migraines, demonstrating the rapid onset of AXS-07. Two hours after dosing, pain relief was achieved in 68% of treated migraines, and pain freedom in 38%. Freedom from MBS was achieved within 2 hours of dosing in 47% of treated migraines. Pain relief with AXS-07 was durable. Rates of sustained pain relief from 2-24 and 2-48 hours for treated migraines were 60% and 59%, respectively. Rates of sustained pain freedom from 2-24 and 2-48 hours for treated migraines were 33% and 32%, respectively. Rescue medication was not required through 24 hours for 85% of migraine patients treated with a single dose of AXS-07. AXS-07 was generally safe and well tolerated with long-term dosing. The safety profile of AXS-07 over 12 months was consistent with that observed in short-term controlled trials. The most commonly reported AEs (≥3%) were nausea, dizziness, and vomiting.

**Conclusions:** AXS-07 rapidly, substantially, and durably relieved migraine pain and MBS over 12 months. These long-term data confirm the robust efficacy and well-tolerated safety profile of AXS-07 observed in controlled trials.

**145. Improvement in Migraine Disability from Mindfulness is Mediated by Improvements in Pain Catastrophizing and Depression**

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**Introduction & Objective:** Our randomized clinical trial evaluating Mindfulness-Based Stress Reduction (MBSR) vs. Headache (HA) Education in adults with migraine (n=89) showed that mindfulness may improve disability in adults with migraine. The objective of our current study was to evaluate potential mediators of mindfulness meditation’s effect on disability.

**Methods:** The effect of MBSR on disability was assessed in adults with migraine (n=77) randomized to MBSR or HA Education who completed four study visits (baseline, 12, 24, and 36 weeks). Independent mediation analyses were conducted for MBSR treatment on disability (Migraine Disability Assessment, MIDAS) through each of our candidate mediators, which included the Pain Catastrophizing Scale (PCS), Headache Management Self-Efficacy (HMSE), depression (Patient Health-Questionnaire-9, PHQ-9), anxiety (Generalized Anxiety Disorder-7, GAD-7), emotion regulation (Difficulty in Emotion Regulation Scale, DERS), and pain acceptance (Chronic Pain Acceptance Questionnaire; CPAQ). The mediator and outcome models used for the mediation analysis were fit via linear mixed models with treatment (MBSR vs. HA education), time (treated as a factor variable), and baseline MIDAS as predictors, with random intercepts for each patient. Statistical significance was based on the estimated Average Causal Mediation Effects (ACME), which was estimated for each candidate mediator following the Quasi-Bayesian Monte-Carlo method over 5,000 simulations, with statistical significance determined at a 0.05 level.

**Results:** Reductions in PCS (p=0.026) and PHQ-9 (p=0.001) were significant mediators of reductions in MIDAS between the MBSR vs. HA Education groups. We found non-significant mediating effects for increases in HMSE (p=0.098) and CPAQ (p=0.12), and reductions in GAD-7 (p=0.083). Changes in DERS did not mediate the MBSR (vs. HA Education)-related changes in MIDAS (p=0.53).

**Conclusions:** Our results suggest that a decrease in migraine disability in MBSR participants is significantly mediated by improvements in pain catastrophizing and depression. These results suggest mindfulness may impact migraine-related disability through the Fear-Avoidance Model. Future research should continue to evaluate mechanisms of mindfulness-based interventions.
Introduction & Objective: Emerging research demonstrates that mindfulness may decrease the total migraine burden. The objective of our research was to better understand the mechanisms of mindfulness meditation in adults with migraine through patient perceptions.

Methods: Adults with migraine randomized to Mindfulness Based Stress Reduction (MBSR) in two separate randomized clinical trials (n=43) participated in semi-structured in-person qualitative interviews conducted after the interventions. Interviews querying participants on impact of mindfulness in their lives and on migraine were audio-recorded, transcribed, and summarized into a framework matrix. A master codebook was created until data saturation was reached and magnitude coding established code frequency. Themes and subthemes were identified using a constructivist grounded theory approach.

Results: Participants were mostly women (91%), Caucasian (89%) with an average age (SD) of 44 (13), 9.8 (3.3) headache days/month with 26 (14) years lived with migraine and severe disability (average HIT-6 of 63 (7)). Themes demonstrated that mindfulness increased awareness of external experiences (e.g., external sensations and awareness of self/world) and internal sensations (e.g., increased interoception, meta-cognition, emotional awareness, non-reactivity, and non-judgmental awareness), with resulting improvements in overall well-being, enhanced relationships, and meaningful behavior changes. Mindfulness specifically impacted migraine and pain experience through changed awareness, perspective, and reactivity of pain experience and perception, with a changed experience of pain during heat pain testing and decreased reactivity to pain. After learning mindfulness, participants experienced an altered response to migraine attacks with increased interoception and resulting earlier migraine attack awareness and treatment, along with improved emotion regulation around migraine experiences, and use of class techniques as an acute treatment. The group mindfulness setting also had benefits for participants with migraine in providing support and changing personal migraine perspectives.

Conclusions: Participants with migraine reported that mindfulness provided overall life and migraine-specific benefits. In particular, participants reported mindfulness improved interoception, resulting in earlier migraine awareness and treatment. Mindfulness may also modify pain perception and improve emotion regulation related to living with migraine. These findings provide fruitful preliminary data for future empirical research on the benefits and mechanisms of mindfulness in migraine.
The parabrachial nucleus is located at the midbrain-pons junction. It contains genetically diverse neurons surrounding the superior cerebellar peduncle. One of these genetic subpopulations expresses Calca, which encodes the neuropeptide CGRP. Calca-expressing neurons in this region have been implicated in a variety of homeostatic functions, but their distribution and overall pattern of axonal projections remain unclear. To map the efferent projections of Calca neurons in this region, we performed Cre-dependent anterograde tracing with synaptophysin-mCherry in Calca-Cre mice (8-19 weeks, male and female, heterozygous and homozygous). Calca-expressing PB neurons heavily target subregions of the amygdala, bed nucleus of the stria terminalis, basal forebrain, thalamic intralaminar and ventral posterior parvicellular nuclei, brainstem reticular formation, and some cranial motor nuclei. The projection pattern in each case depended on the location of the injection site within the PB region, and injections involving the locus coeruleus produced additional, diffuse labeling in the cerebral cortex. We confirmed the unexpected projections to the brainstem with tracer injections of Fluorogold into the medullary reticular formation, which retrogradely labeled Calca-expressing and CGRP-immunoreactive neurons in the rostral-ventral PB and supratrigeminal nucleus. We also identified populations of neurons in and around the PB that contain Calca mRNA or CGRP immunoreactivity, including the locus coeruleus and motor trigeminal nucleus. In the PB, most neurons that express Calca form a dense cluster in the outer portion of the external lateral PB subnucleus, and most of these prominently express the mu-opioid receptor (Oprm1). A small number of these Oprm1-expressing Calca neurons distribute rostrally, just dorsal to the Kolliker-Fuse nucleus. This information provides a detailed neuroanatomical framework for interpreting experimental work involving CGRP/Calca-expressing neurons and opioid action in the PB region.

**387. Mindfulness-Based Stress Reduction (MBSR) vs. HA Education: A Randomized Clinical Trial Showing Mindfulness Targets Total Migraine Burden**

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**Background:** Migraine is the second leading cause of disability worldwide. Most patients with migraine discontinue medications due to ineffectiveness or side effects. Mindfulness-based stress reduction (MBSR) may provide benefit. Our objective was to determine if MBSR improves migraine outcomes and affective/cognitive processes compared to Headache (HA) Education.

**Methods:** We conducted a randomized clinical trial of MBSR vs. HA Education (n=89) in adults with 4-20 migraines/month. Blinding occurred of participants (to active vs. comparator group assignments) and PI/data analysts (to group assignment). The interventions were MBSR (standardized training in mindfulness/yoga) and HA Education (migraine information) delivered in eight weekly two-hour groups. **Primary outcome:** change in migraine day frequency (baseline to 12 weeks). Secondary outcomes: changes in disability, quality of life, self-efficacy, pain catastrophizing, depression scores, and experimentally induced pain intensity and unpleasantness (baseline to 12, 24, 36 weeks).

**Trial Registration:** clinicaltrials.gov Identifier: NCT02695498.

**Results:** Most participants were female (92%), 43.9 years (SD 13.0), with 7.3 (SD 2.7) migraines/month and high disability (HIT-6: 63.5 (5.7)), attended class (median attendance 7/8), and followed-up through 36 weeks (73% of both groups). Participants in both groups had fewer migraine days at 12 weeks (MBSR: 1.6 migraines/month; 95% CI: [-0.7, -2.5]; HA Education -2.0; [-1.1, -2.9]), without group differences (p=0.51). Compared to HA Education, MBSR participants had improvements from baseline at all follow-up time points (reported in terms of point estimates of effect differences between groups) on measures of disability (5.92 (95% CI 2.8, 9.0) p<0.001); quality of life (5.1 (1.2, 8.9) p=0.01); self-efficacy (8.2 (0.3, 16.1, p=0.04); pain catastrophizing (5.8 (2.9, 8.8), p<0.001); depression scores (1.6 (0.4, 2.7) p=0.008), and decreased experimentally induced pain intensity and unpleasantness (p=0.004 and 0.005, respectively, at 36 weeks. See Table and Figure demonstrating improvements in well-being (panel 1) and changes in experimental pain intensity and unpleasantness (panel 2) of MBSR compared to headache education. One reported adverse event was deemed unrelated to study protocol.

**Conclusions:** Both MBSR and HA Education improved migraine frequency, but only MBSR also improved disability, quality of life, self-efficacy, pain-catastrophizing, and depression out to 36 weeks, with decreased experimentally induced pain suggesting a potential shift in pain appraisal. MBSR may help treat total migraine burden. A larger more definitive study will help further investigate these results.

**388. Noninvasive Combined Occipital and Trigeminal Nerve Stimulation - Established Efficacy, Safety and Tolerability in the Acute Treatment of Migraine**

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**Background:** Peripheral, noninvasive neuromodulation offers a potential innovative solution in the acute treatment of migraine. Combined occipital and trigeminal nerve...
stimulation (COT-NS) was only previously available through implanted devices. A novel non-invasive, self-administered, multichannel COT-NS device (Relivion®, Neurolief Ltd.) provides a synergistic analgesic effect on the trigemino-cervical complex and the cortico-thalamic network. A cloud database platform gathering treatment data offers potential for treatment adaptation and optimization over time, providing further headache relief for migraineurs. Following two double-blind, randomized, sham controlled clinical trials, the Relivion® device has established efficacy, safety, and tolerability as an abortive treatment for migraine.

Objective: To review the safety and efficacy of a non-invasive combined occipital and trigeminal nerve stimulation device (Relivion®) in the acute treatment of episodic and chronic migraine following two successful double-blind, randomized, sham-controlled clinical trials.

Methods: Two independent prospective multicenter, randomized, double-blind, sham-controlled trials were conducted with the Relivion® device on a total of 164 patients meeting the diagnostic criteria for episodic and chronic migraine. Following a self-administered one-hour treatment with the Relivion® device, pain level was measured at time points including 1, 2 and 24 hours post treatment.

Results: Both clinical studies met their primary and secondary endpoints with highly statistical significance. An initial study consisting of 55 participants revealed significant pain relief at all time points compared to sham (group difference at 1-hour 41%, p=0.0002, 2-hours 33%, p=0.03, 24-hours 36%, p=0.02). Pain freedom at 2-hours for subjects at baseline level of moderate-severe pain was significantly higher in the treatment group compared to the sham group (43% vs. 11%, p=0.02). In a larger subsequent trial of 109 participants, pain relief was significantly higher in the active group than the sham group at 2 hours post treatment (60% vs. 37%, p=0.018). Following 2 hours post-treatment, 46% of patients in the active group reached complete pain freedom compared to only 11.8% in the control group (p<0.0001). When evaluating MBS freedom, 75% of patients in the active group reached complete MBS freedom 2-hours after treatment, compared to 46.7% in the control group (p=0.009). Complete freedom of migraine symptoms (pain as well as MBS) at 2-hours was also significantly higher (47.2% vs.11.1%, p=0.0003). No serious adverse events were reported.

Conclusions: The Relivion® device provides a new, innovative, highly effective and safe option in the acute treatment of migraine for migraine sufferers.

Introduction: Total pain burden, a composite measure encompassing frequency of migraine headache days, duration, and severity, was previously used to characterize response to galcanezumab in patients with migraine. Here it is used to measure response in patients with treatment-resistant migraine.

Methods: CONQUER trial patients (N=458), 18-75 years old with 2-4 prior migraine preventive treatment category failures, were randomized (1:1) to monthly placebo or galcanezumab 120mg with 240-mg loading dose. For each patient, monthly total pain burden in severity-weighted hours was calculated by multiplying daily migraine headache duration (hours) by maximum severity (0=none, 1=mild, 2=moderate, 3=severe) for each migraine day, then summing daily scores for the monthly score. Changes from baseline in monthly total pain burden across Months 1-3 were analyzed post hoc using mixed-model repeated measures. Spearman correlations between total pain burden and Migraine Specific Quality-of-Life Questionnaire (MSQ) and Migraine Disability Assessment Scale (MIDAS) were assessed at baseline.

Results: Mean (standard deviation) baseline monthly total pain burden was 192.1 (158.3) and 188.2 (197.4) severity-weighted hours for galcanezumab-treated and placebo-treated patients, respectively. Across the 3-month double-blind period, galcanezumab-treated patients experienced significantly greater mean reductions from baseline in monthly total pain burden compared with placebo-treated patients, both for mean change (standard error (SE)) (galcanezumab: -82.7 (7.5), placebo: -15.8 (7.5), difference from placebo (95% confidence interval): -66.8 (-85.5, -48.2, p<0.001) and percent change (SE) (galcanezumab: -38.6% (5.7), placebo: 9.4% (5.7), difference from placebo (95% confidence interval): -48.1% (-62.3, -33.9), p<0.001). Furthermore, baseline total pain burden correlated with MSQ score (r=-0.39) and MIDAS score (r=0.40), suggesting good association of total pain burden with quality-of-life outcomes.

Conclusions: Total pain burden may be an additional meaningful measure for clinicians when discussing migraine preventative therapy.

389. Total Pain Burden in Patients with Treatment-Resistant Migraine: Effects of Galcanezumab in the CONQUER Phase 3B Trial
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Candidate variables included: sensory and affective symptom questionnaires, and clinical characteristics, including sex and age. Measures of anxiety, depression, and disease groupings were excluded as non-significant contributors (p<0.2), while AlloDynia Symptom Checklist (ASC-12; score range 0-24), Khalfa Hyperacusis Questionnaire (HQ; score range 0-42), and Photosensitivity Assessment Questionnaire (PAQ; score range 0-1) scores were included (p<0.2). Our model included 102 subjects with complete scores for all variables (average age=42, 84.9% female), with a mean of 15.96 headache days per month (SD=10.38). Fifty-three percent reported no history of recurrent headaches pre-injury. MIDAS scores ranged from 2 to 200 (mean=68.7, SD=51.70). Mean ASC-12 score was 8.55 (range 1-20, SD=4.14), mean PAQ score was 0.61 (0-1, SD=0.29), and mean HQ score was 20.1 (3-35, SD=7.97). Our independent variables reliably predicted MIDAS score (p=0.0015). Percent change in MIDAS score, associated with each independent variable was calculated using exponentiated β values: PAQ 5.9%, ASC-12 4.0%, and HQ 2.0%. Increased allodynia, hyperacusis, and photosensitivity are associated with increased headache-related disability in this sample of ARMR participants with PTH. When all other variables are held constant, an increase of one point in the HQ corresponds to a 2.0% increase in MIDAS score; an increase of one point in the ASC-12 corresponds to 4.0% increase in MIDAS score, and an increase of one tenth of a point in the PAQ corresponds to a 5.9% increase in MIDAS score. Symptoms of sensory amplification likely contribute to PTH-related disability, and merit ongoing investigation as to their potential as disease markers and treatment targets.

K-501. Modeling of Human and Rodent Responses to ipRGC Signaling to Examine Neuronal Pathways in Migraine-Associated Photophobia

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Migraine is a common, debilitating neurologic disorder characterized by headache as well as associated symptoms. Photophobia is a pathognomonic symptom of migraine where light is perceived as painful or exacerbates the headache. Calcitonin gene-related peptide (CGRP) is a key mediator of migraine and a recent target of multiple new pharmacologic agents, and we and others have shown CGRP can induce light aversive behavior in mice, providing a rodent model of migraine-associated photophobia. However, a key gap in knowledge is the neuronal circuitry that facilitates photophobia. Clinically, we have shown that targeted stimulation via silent substitution of either cones, melanopsin (the opsin contained in intrinsically photosensitive retinal ganglion cells, ipRGCs), or the combination of both evokes heightened visual discomfort in participants with migraine compared to headache-free controls. Based on a model we developed, people with migraine do not differ in how cone and melanopsin signals are combined, rather people with migraine demonstrate an enhanced response to the integrated ipRGC signals for visual discomfort, an explicit measure of light sensitivity. This integrated signal likely stems from extrinsic cone input on ipRGCs and intrinsic melanopsin stimulation within ipRGCs. As an implicit measure of light sensitivity, we assessed orbicularis oculi EMG activity and blinking in human subjects. Participants with migraine with aura showed significantly heightened responses to stimulation of cones, melanopsin, or the combination of both as compared to participants with migraine without aura or headache-free controls. This discordance in responses between our extrinsic and intrinsic measures indicates there are distinct pathways that mediate photophobia depending on the presence of aura in migraine. To further dissect these pathways, we are examining the interaction of ipRGC and trigeminal pathways in the mouse model of migraine-associated photophobia. To determine whether cone and melanopsin signals facilitate light aversion in mice, we have developed digitally controlled LED panels which contain three different LEDs (red, blue, and UV wavelengths) that can be combined to create stimuli that target melanopsin and/or cone stimulation or flicker at various rates. Here I will show preliminary data using this LED light source as follows: 1) CGRP induced light aversion in wildtype mice; 2) c-fos activity in response to CGRP and bright light; 3) aversive responses to various frequencies of flickering light. The overall goal of these studies is to create new opportunities for investigation of novel therapeutic targets for migraine and photophobia.

K-514. Validation of Treatment Expectation Scale in Children and Adolescents with Headache

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Background: Patient response to treatment may be affected by the patient’s expectations before starting treatment. This expectation may contribute to placebo responses in clinical trials, as well as positive and negative outcomes in clinical care. The Stanford Expectations of Treatment Scale (SETS) was developed and validated to measure positive and negative treatment expectancies in adults with pain, but no such tool exists for use with children.

Purpose: In this study we adapted the SETS for use with children and adolescents, then validated this adapted scale, the PedSETS.

Methods: We simplified the language of the questions in the SETS to a 5th grade reading level, and reviewed multiple iterations with patients in clinic until verbal interviews confirmed that the concepts were understood consistently. This adapted version, the PedSETS, was then administered to two groups of patients ages 7-17 years: 1) preventive: patients in neurology clinic who were about to start an oral preventive treatment or receive onabotulinum toxin injections for headache, and 2) acute: patients seen for an exacerbation of headache who were treated with either nerve block (in outpatient neurology clinic) or IV medications (in the emergency

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LB-448. CT- or Heavily T2-Weighted MR-Myelography for the Initial Evaluation of Patients with Spontaneous Intracranial Hypotension?

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Objective: To compare the diagnostic accuracy of spine MRI including heavily T2- weighted MR-myelography (MRM) to post-myelography CT (CT-myelography [CTM]) for the identification of spinal CSF leaks in patients with spontaneous intracranial hypotension (SIH).

Methods: This cohort study was conducted using data from a prospectively maintained database of patients who meet the International Classification of Headache Disorders (ICHD)-III criteria for SIH. The patient population consisted of a consecutive group of patients with SIH who underwent both CTM and MRM at our institution without any intervening therapeutic interventions. The primary endpoint was the non-inferiority comparison of the two imaging modalities regarding the diagnosis of CSF leak.

Results: Among the 576 patients who met the inclusion criteria, 276 (47.9%) were diagnosed with an extradural CSF collection on both CTM and MRM (absolute difference: 0.01%, upper limit of one-sided 95% CI: 3.2%, p<0.001 for non-inferiority) and 292 (50.7%) patients did not have an extradural CSF collection by both CTM and MRM (absolute difference: 0.01%, upper limit of one-sided 95% CI: 3.2%, p<0.001 for non-inferiority) and 292 (50.7%) patients did not have an extradural CSF collection by both CTM and MRM (absolute difference: 0.01%, upper limit of one-sided 95% CI: 3.2%, p<0.001 for non-inferiority). Patients were predominantly female (78%), White (77%) adolescents with a median age of 16 years. The positive expectancy subscale of the PedSETS demonstrated a moderate correlation with the PGIC, with a stronger correlation in the acute group (Spearman’s rho = 0.63, p=0.0002) than the preventive group (Spearman’s rho=0.447, p=0.0006). The negative expectancy subscale of the PedSETS was limited by floor effects, with a substantial portion of participants indicating no or low levels of concern about side effects prior to treatment.

Conclusion: The PedSETS is simple to administer, score, and interpret, and the positive expectancy scale has a moderate correlation with treatment outcome. Ongoing work will examine the relationship between positive expectancy and placebo response in a clinical trial.

LB-453. Acute Stroke in a 21-Year-Old Woman with Migraine with Aura

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We present a case of a 21-year-old female with a past medical history of migraine with aura who presented to the emergency room with complaints of migraine with an aura of 20 minute duration and was found to have an acute stroke on MRI brain using diffusion weighted imaging. On presentation the patient complained of dizziness and headache. She has had migraines since adolescence and suffers from attacks 1-2 times per year, however this recent migraine was more severe. She described her typical aura as visual scotomas that persist for 30-60 mins. She reported that she was recently seen in another hospital for similar complaints and at that time she had an MRI brain with and without contrast done which showed non-enhancing foci of restricted diffusion on DWI consistent with acute infarction. Consequently, a CT angiogram of the head was performed, which showed no high-level stenosis. The diagnosis of vasospasm was given at this time and she was started on verapamil and aspirin and referred to outpatient neurology clinic for evaluation by a headache specialist. Migrainous infarction is defined as a stroke that occurs during a migraine with aura attack, and the aura symptoms persists for at least 60 minutes. Here we present a case of migraine with aura and acute stroke. In this case presentation migraine aura lasted only 20 minutes and the headache lasted between 1-2 hours. This case is of interest because this clinical presentation of short migraine aura duration and infrequent migraine attacks is not classic for migrainous infarct. We propose that further investigation needs to be done regarding correlation between duration of migraine aura and ischemic infarction.

Health Services Research

147. Assessing the Impact of the COVID-19 Air-Travel Ban on Neurology Faculty in Setting of the Global Climate Change Emergency

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Background: The University of Pennsylvania began an ongoing air-travel ban for all faculty in March 2020 due to the COVID-19 Pandemic. This ban resulted in inability of faculty to travel by air. Many national organizations cancelled or
began to hold meetings virtually. Prior to pandemic, air travel accounted for greater than 10% of University of Pennsylvania’s carbon footprint. Since the ban, carbon footprint from air travel is non-existent at the University, creating a question regarding the need for academic travel versus the benefit to the environment.

Methods: A confidential online survey was emailed to all Neurology Faculty at University of Pennsylvania. Faculty were asked about effect of the Pandemic and Air-travel ban on their academic, clinical, and research careers and development. They were asked whether conferences they typically attended were cancelled and whether they attended or declined to attend virtual conferences. They were asked to provide any additional comments regarding the benefits of live or virtual conferences.

Results: 53 faculty responded to the survey which reflected an appropriate cross-section of the department for rank and track. The Pandemic appears to have had minimal (40%) to moderate (28%) effect on academic careers. The pandemic on average had minimal effect on clinical and research careers. On average, the air travel ban itself had minimal to no effect on faculty’s academic, research and clinical careers and development. 92% of faculty attended virtual conferences during the ban with faculty attending an average 2.1 virtual conferences. 68% of faculty had a conference fully cancelled by the pandemic. 45% of faculty did not attend a conference because it was virtual while 43% of respondents were able to attend virtual meetings they typical would not have attended. Majority of comments from faculty stressed the loss of networking and social interactions while other comments centered on improved flexibility and access inherent with virtual meetings.

Conclusion: The air travel ban along with necessary use of virtual conferencing appears to have had minimal effect on academic neurologist careers. Neurologist will need to consider their impact on environment when they choose to travel by air to live conferences in the future. Conferences organizers will need to consider offering virtual curriculum options for future conferences and virtual conference developers will need to work on ways to improve networking and interactive options.

148. Evaluation of Crowd-Sourced Fundraising to Cover Health Care Costs for Neurological Conditions in the United States

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Background: The annual cost of treating neurologic disorders in the US is greater than $800 billion. Both the rising costs of prescription medications, which show some of the steepest increases among neurologic drugs, as well as the aging of the American population have been implicated. Crowdfunding platforms have gained traction as patients search for alternate ways to finance their health care. Previous studies have examined the role of crowdfunding platforms in financing the care of cancer patients. We assessed the use of the GoFundMe crowdfunding platform among patients with neurological conditions.

Methods: We used custom scripts for web-scraping to gather information about 11,274 medical campaigns on GoFundMe using a set of 15 search terms corresponding to the most common ICD-10 neurological conditions. The information gathered included the fundraising goal, amount raised, and the number of donors. Between December 2020 and March 8, 2021, 2,203 of these campaigns were coded using a data extraction tool to capture information i.e. neurological condition(s), patient demographics, and expenses cited. Analysis of remaining campaigns is anticipated to be completed in July 2021.

Results: The majority of campaigns were for males (56.6%) and adults (66.5%). For patients whose insurance status was known (n=732), 74.6% had insurance and 25.4% did not. On average, the campaigns studied raised $17,019 (SD=$25,383) for a target average goal of $41,145 (SD= $234,066) with an average of 174 donors per campaign (SD=302). Traumatic brain injury represented the greatest share of campaigns (24.6%), followed by neuroinfectious diseases (18.3%), epilepsy (10.8%), and dementias (7.8%). Rehabilitation was the most common expense cited by campaigns (39.8%), followed by surgical expenses (32.8%), lost income (31.1%), transportation costs (21.0%), funerals (16.9%), and medication expenses (16.7%).

Conclusions: This study highlights how many with neurological illness are relying on fundraising to cover their medical costs. Rehabilitation, surgery, and lost income are among the push factors toward using crowdfunding. Neurologists must work in concert with policymakers to address rising financial burdens among patients with neurological illness.

331. Evaluating the Impact of a New Model of Structured Interprofessional Bedside Rounding (TeaminguUP) on Climate Safety in an Inpatient Stroke Unit

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Research Question: Does implementing an intervention designed to improve bedside rounding, an adapted model of Structured Interprofessional Bedside Rounding (SIBR): Teaming-Up®, enhance the patient safety climate on an inpatient stroke unit?

Introduction: Interprofessional bedside rounds provide a consistent method for patients, families, and clinicians from different disciplines to collaborate in daily discussions of care and clinical decision-making. Since health care team coordination issues continue to be an important source of medication errors, current guidelines recommend optimizing
communication and medication safety, and more broadly, patient safety, by integrating nurses and pharmacists within the inpatient care team. We hypothesize that the implementation of TeamingUP®, a customized SIBR model, will enhance communication, teamwork, and collaboration among interprofessional health care team members, improve quality of care, and improve the efficiency of delivery and patient safety climate on the unit.

**Sample/Methods:** We use a quasi-experimental pre-post design without control to evaluate the impact of SIBR TeamingUP® on an acute inpatient stroke unit at a large academic center. All clinicians (n=137) responsible for patient care on the stroke unit were eligible to participate in the Safety Attitudes Questionnaire (SAQ): Unit Safety Climate and Psychological Safety survey subscales.

**Results:** A total of 53 clinicians (38.7% response rate) from all disciplines caring for stroke patients (case managers, nurses, pharmacists, physicians, therapists, and social workers) completed the pre-SIBR implementation survey. The baseline results indicate targeted opportunities for improvement; for example, 8% of clinicians reported not knowing the proper channels to direct questions regarding patient safety, while 15% reported it being challenging to discuss these errors on the unit. After TeamingUP® implementation, pre/post score changes in the aforementioned subscales, along with specific safety issues, will be reported with recommendations for improving quality and climate safety on a stroke unit.

**Conclusions and Implications for Practice:** Safety is foremost in delivering care, and especially for stroke patients who are at risk of medical complications such as falls, aspiration pneumonia, and medication errors. SIBR TeamingUP® is a novel method for efficiently rounding and planning interprofessional team-based care, with emphasis on improving the climate of safety in at-risk stroke patients.


**392. A Proposed Electronic Health Record Algorithm for Parkinson’s Disease Case Identification**

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**Background:** Algorithms using electronic health record (EHR) data for case identification are important for population health management, disease surveillance, and clinical trials recruitment. While ICD codes are commonly used to identify cases, algorithms that incorporate additional clinical detail may improve the accuracy of case ascertainment. We developed an enhanced EHR-based algorithm to identify patients with Parkinson’s disease (PD) for use in the California Parkinson’s Disease Registry (CPDR).

**Methods:** To generate a gold-standard, we performed manual chart review on 460 patients with at least one of six PD-related ICD codes (G20, G23.1, G31.83, G90.3, G23.3, G31.85) seen at UCLA between 10/01/2018 and 12/31/2018. Patients were categorized as Probable, Possible, or Not PD based on consensus of two abstractors. We combined EHR elements to construct a three-tiered classification algorithm with two thresholds: lower (separating Probable-Possible from Not PD) and upper (separating Probable from Possible-Not PD). EHR elements included ICD code(s) (G20 only versus PD-related), disease duration, and anti-parkinsonian drug use (APDs) for ≥6 months. We calculated precision (positive predictive value), recall (sensitivity), and F1 scores (summary measure of precision and recall) for each threshold and built an independent optimal algorithm for a three-tiered classification.

**Results:** From chart review, 352 (77%) patients were determined to be Probable, 97 (21%) as Possible, and 11 (2%) as Not PD. Lower threshold filters had precision and recall ranges of 0.99-1.00 and 0.53-0.96, respectively. G20 ICD code best differentiated Probable-Possible from Not PD (precision=0.99, recall=0.96, F1=0.98). Upper threshold filters had precision and recall ranges of 0.81-0.95 and 0.64-1.00, respectively. G20 ICD code and APDs best differentiated Probable from Possible-Not PD (precision=0.87, recall=0.93, F1=0.90). When combining thresholds to define a three-tiered algorithm that mirrors the gold-standard, we found using PD-related ICD codes as the lower threshold and G20 ICD code, APDs, and disease duration >1 year as the upper threshold outperformed alternative algorithms (F1=0.82). Requiring documentation by a neurologist for this algorithm improved the precision by 1 but lowered recall by 3 percentage points, resulting in a lower F1 score.

**Conclusion:** Using data elements common across EHRs, we demonstrate the systematic development of an algorithm to distinguish tiers of PD diagnostic certainty that closely match an abstractor’s judgment. Validation of algorithm performance on prospective datasets is pending. This algorithm is intended to be widely scalable and for use in population-wide cohort registries such as the CPDR.


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**Objective:** Neuropathy, headache, and low back pain (LBP) are common neurologic conditions requiring pain management. Yet little is known about opioid use for these conditions or whether access to particular specialists impacts opioid
prescription. We aimed to identify factors associated with opioid initiation.

Methods: We identified patients with incident neuropathy, headache, or LBP diagnoses from 2010-2017 in a 20% Medicare sample, excluding those with prior opioid use or other chronic pain conditions. Opioid initiation was defined as first opioid prescription filled at or after diagnosis date. Disease-related opioid initiation was defined as first opioid prescription filled within 7 days after a disease-specific claim. Multivariate logistic regression using generalized estimating equations was used to determine the association of patient demographics, provider types, and regional characteristics (physician specialty density) with disease-related opioid initiation, accounting for within region correlation.

Results: We identified 20,086 neuropathy, 49,415 headache, and 71,347 LBP Medicare patients. Of these, 10,730 (54%) neuropathy, 26,665 (54%) headache, and 43,957 (62%) LBP patients initiated opioids and 479 (2%), 3818 (8%), and 15,845 (22%) had disease-related opioid initiation, respectively. Opioid initiation substantially declined from 2010-2017 (neuropathy: 75% to 25%, headache: 73% to 24%, LBP: 80% to 35%) as did disease-related opioid initiation (neuropathy: 3% to 2%, headache: 10% to 5%, LBP: 27% to 15%). Certain physician specialty visits were associated with lower likelihood of disease-related opioid initiation as compared with primary care: neurology visits for all three conditions (neuropathy: odds ratio 0.7 [95% confidence interval: 0.57-0.87]), headache: 0.72 [0.64-0.8], LBP: 0.61 [0.44-0.86]), podiatry visits for neuropathy (0.47 [0.34-0.65]), and orthopedic surgery (0.85 [0.77-0.92]) and neurosurgery visits (0.59 [0.43-0.82]) for LBP. Emergency medicine visits were associated with increased likelihood of disease-related opioid initiation for headache (2.33 [1.95-2.77]) and LBP (2.22 [1.92-2.57]). Greater access to certain physician specialties was associated with lower likelihood of disease-related opioid initiation: residence in high neurologist density regions for headache (0.62 [0.49-0.78]) and LBP (0.59 [0.51-0.7]), high podiatrist density regions for neuropathy (0.46 [0.33-0.65]), and high PM&R specialist density regions for LBP (0.82 [0.71-0.96]). Residence in high primary care density regions had increased likelihood of disease-related opioid initiation for LBP (1.17 [1.01-1.36]).

Conclusions: We found that >50% of patients initiated opioids after their neurologic diagnoses with much lower rates of disease-related opioid initiation, particularly for neuropathy and headache. Neurology visits and greater access to neurology, podiatry, or PM&R were associated with lower likelihood of disease-related opioid initiation. These data could inform future studies that evaluate interventions to attenuate opioid use in neurologic conditions.

LB-442. Prevalence and Risk Factors for Inpatient Falls Among Adults Hospitalized with Status Epilepticus

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Introduction: Inpatient falls are common preventable adverse events experienced by nearly 10% of individuals hospitalized for medical and/or surgical conditions. Aside from adding to the patients’ injury burden, inpatient falls also contribute significantly to the cost burden on the hospital itself, by increasing the length of stay and opening avenues of litigation. The current study aims to understand the prevalence and risk factors associated with inpatient falls in adult patients hospitalized with status epilepticus. The findings of the study would assist hospital administrators and patient providers in improving fall precautions and/or fall-risk stratification protocols for these vulnerable patients.

Methods: The 2005 to 2014 National Inpatient Sample was queried using International Classification of Diseases 9th Edition (ICD-9) diagnosis code 345.3 to identify adult (age 18 years and above) patients who were hospitalized with status epilepticus. The ICD external injury code E849.7 was used to identify occurrences of falls that happened when the individual was hospitalized. Multivariate logistic regression analyses were used to identify risk factors associated with occurrences of inpatient falls.

Results: A total of 137,410 adult patient with status epilepticus were included in the study - out of which 2,942 (2.1%) experienced an inpatient fall. Risk factors associated with experiencing an inpatient fall included increasing age (p<0.05), male gender (OR 1.38 [95% CI 1.28-1.49]; p<0.001), individuals having median household income in the higher quartile (OR 1.42 [95% CI 1.27-1.58]; p<0.001), anemia (OR 1.56 [95% CI 1.43-1.71]; p<0.001), chronic lung disease (OR 1.19 [95% CI 1.08-2.09]; p<0.001), coagulopathy (OR 1.85 [95% CI 1.64-2.09]; p<0.001), depression (OR 1.15 [95% CI 1.03-1.28]; p=0.012), having uncomplicated diabetes mellitus (OR 1.24 [95% CI 1.12-1.37]; p<0.001), chronic liver disease (OR 1.42 [95% CI 1.21-1.67]; p<0.001), electrolyte disorders (OR 1.29 [95% CI 1.20-1.39]; p<0.001), psychiatric comorbidity/depression or anxiety (OR 1.59 [95% CI 1.43-1.76]; p<0.001), pulmonary circulatory disorder (i.e. hypertension) (OR 1.54 [95% CI 1.18-2.00]; p=0.002), cardiac valvular disorder (OR 1.33 [95% CI 1.09-1.62]; p=0.004), chronic weight loss (OR 1.35 [95% CI 1.19-1.55]; p<0.001), and being admitted in July (OR 1.27 [95% CI 1.13-1.44]; p<0.001).

Conclusion: Up to 2% of individuals who are hospitalized with status epilepticus experience an inpatient fall. Furthermore, a number of modifiable and non-modifiable risk factors are associated with experiencing these potentially avoidable events. Understanding patient profiles and risk-stratifying would be imperative in developing fall-risk policies aimed at ameliorating the occurrences of these costly events.

LB-450. Association of Hospital Volume and Outcome Following Status Epileptic in the United States

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Introduction: Prior studies have shown hospital volume (HV) is associated with poor outcomes following elective procedures and in-patient medical hospitalizations. It is unknown if HV impacts in-patient outcomes after hospitalization for status epilepticus (SE). The objective of this study...
was to assess the impact of HV on the outcome of SE patients with regards to in-patient medical complications.

Methods: The 2005 to 2013 National Inpatient Sample (NIS) database was queried using ICD-9 diagnosis code 345.3 to identify patients with SE. The NIS hospital ID was used as a unique facility identifier to calculate the average volume of SE patients seen in a year. Using 3 distinct tertials, the study cohort was divided into three groups: Low volume hospital (LVH) (0-7 SE patients/year), Medium volume hospitals (MVH) (8-22 SE patients/year), and High volume hospitals (HVH) (>22 SE patients/year). Multivariate logistic regression analyses were used to assess whether higher HV (i.e. Medium or High) had lower rates of inpatient medical complications, as compared to LVH.

Results: A total of 137,410 patients with SE were included in the analysis - out of which 37% (N=50939) were treated in LVH, 42724 (31%) were treated in MVH, and 18% (N=25207) were treated in HVH. Following adjustment for baseline demographics and hospital-level factors, patients undergoing treatment a MVH (vs. LVH) had slightly lower odds of cardiac complications (OR 0.92 [95% CI 0.84-0.99]; p=0.033), pulmonary complications (OR 0.95 [95% CI 0.91-0.97]; p=0.001), metabolic complications (OR 0.83 [95% CI 0.79 - 0.87] p<0.001), renal complications (OR 0.91 [95% CI 0.86 - 0.96 p=0.001), and neurological complications (OR 0.86 [95% CI 0.80 - 0.91] p<0.001). Apart from a lower rate of neurological, metabolic and renal complications, HVH had slightly higher odds of pneumonia (OR 1.12 [95% CI 1.04 - 1.20] p=0.009), urinary tract infections (OR 1.17 [95% CI 1.11 - 1.23] p=0.001), sepsis (OR 1.12 [95% CI 1.02 - 1.23] p=0.014), stroke (OR 1.16 [95% CI 1.01 - 1.34] p=0.027). Additionally, a longer length of stay (>3 days) was significantly higher for MVH and HVH, whereas disposition to a care facility was significantly lower.

Conclusion: It appears that there exists a volume-outcome relationship for SE. Higher rates of complications at HVH may be explained by patient/disease complexity or a surveillance bias at bigger healthcare centers. Further research is warranted to better understand how increasing hospital volume may impact care of patients.

Interventional Neurology

149. A Complicated Case of Cerebral Hyperperfusion Syndrome in Association with Pial Arteriovenous Fistula After Complex Carotid Artery Stenting
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Learning Objectives: To highlight diagnosis and treatment of a rare case of cerebral hyperperfusion syndrome (CHS) after complex carotid artery stenting (CAS) for a patient with ischemic stroke with significant expressive aphasia and later discovery of a pial arteriovenous fistula.

Background: Cerebral Hyperperfusion is a well-known but rare complication after carotid endarterectomy (CEA) or CAS. Diagnosis can be difficult due to nonspecific neurological symptoms. Early recognition of CHS is important to reverse and prevent neurological complications.

Clinical Findings: A 49-year-old lady with history of untreated hypertension and smoking was admitted for acute word finding difficulty which started two-days ago. On examination, patient demonstrated significant expressive aphasia with intact comprehension. MRI of brain without contrast showed multifocal acute ischemic strokes in the left middle cerebral artery (MCA) territory. CT angiography of the head and neck revealed hemodynamically significant vascular stenosis of the left internal carotid artery (ICA). Patient was treated medically with dual antiplatelet therapy and statin and referred for prompt cerebral angiography which revealed critical 99% stenosis of the left ICA in the upper cervical region with near occlusion and post-stenotic dilatation. A 7.7x4.9x7.3 mm bilobed aneurysm of the anterior communicating artery and a small 3mm aneurysm of the right MCA were also found. Patient was treated with endovascular angio-plasty and stenting of the left ICA in the mid cervical segment. Post-operative evaluation showed hemodynamic improvements and subjective improvement of her speech. Twenty-one days later, patient presented to neurology clinic with intermittent episodes of right sided numbness and right eye blurry vision lasting a minute. A routine EEG revealed intermittent periods of left temporal rhythmic delta activity with epileptogenic potential. Patient was started on Levetiracetam with resolution of the episodes. The patient further underwent successful stent-Coil embolization of the AComm aneurysm but was found to have a new left sided pial arteriovenous fistula arising from distal left middle cerebral artery branches with cortical venous drainage. Surgical management of the pial arteriovenous fistula is planned.

Conclusion: We present a rare case of Cerebral Hyperperfusion Syndrome presenting with episodic focal neurological symptoms with abnormal EEG findings treated with antiepileptic after a complex case of carotid stenting for critical ICA stenosis. On the follow-up cerebral angiogram, patient was also found to have a new pial arteriovenous fistula which is going to be surgically treated.

150. Developing an Integrated Tool for Identifying Certified Stroke Centers in the United States
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Introduction: Stroke is a leading cause of morbidity, mortality and healthcare spending in the United States. Acute management of ischemic stroke is time-dependent and evidence suggests improved clinical outcomes for patients treated at designated certified stroke centers. As a result, there is an increasing trend among hospitals to obtain certification as designated stroke centers. Presently, there are four levels of certification based on hospital capabilities. A common source or integrated tool providing information on all available stroke centers and their locations irrespective of the certifying organization is not currently available. The objective of our research is to create a readily accessible unified platform providing the most current information on the location and level of stroke centers for Emergency Medical Services (EMS) and public access.

Methods: Data on stroke center certification was obtained from each of the three main certifying organizations: The Joint Commission (TJC), Det Norske Veritas (DNV) and Healthcare Facilities Accreditation Program (HFAP). Geographic mapping of stroke center locations was performed using ArcGIS Pro. The most current data on stroke centers is presented in an interactive format and the information is frequently updated to represent newly recognized centers. Utility of the tool and its analytics are provided.

Results: Aggregate data analysis at the time of submission revealed 1,788 total certified stroke centers. TJC-certified stroke centers represent the majority with 91 Acute Stroke Ready (ASR), 1,089 Primary Stroke Centers (PSCs), 41 Thrombectomy Capable Centers (TSCs) and 185 Comprehensive Stroke Centers (CSCs). DNV has certified 316 programs including 36 ASRs, 143 PSCs, 18 PSC Plus (thrombectomy capable) and 119 CSCs. Since the end of 2019, DNV has certified 72 new stroke centers with at least 25 hospitals pending certification. HFAP has certified 66 centers composed of 11 ASRs, 49 PSCs, and 6 CSCs.

Discussion: Stroke treatment and clinical outcomes are time-dependent and prompt assessment and triage by EMS directly to appropriate designated stroke centers is therefore critical. A readily available electronic platform providing location and treatment capability for all nearby stroke centers will enhance regional stroke systems of care, including rapid inter-hospital transfers for advanced intervention.

151. Repeated Spontaneous Short Interval Recurrences in a COVID-19 Large Vessel Occlusion

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Background: In the new era of COVID-19 pandemic, comprehensive stroke centers face new challenges with complex stroke cases due to the cascade of inflammatory thrombosis. Thus, early reocclusion in successful thrombectomies has become more prevalent. We present a case of a large vessel occlusion ischemic stroke with multiple short interval spontaneous recurrences resistant to intravenous alteplase (tPA) and five successful thrombectomy passes.

Case Presentation: A 56-year-old male with hypertension and diabetes presented to the emergency department as a Code Stroke at 17:48 with left middle cerebral artery (MCA) syndrome; last known well was 17:00. Initial National Institutes of Health Stroke Scale (NIHSS) was 25 for global aphasia, leftward gaze, right facial droop, dense right-sided hemiplegia and hemineglect. Computerized tomography (CT) head was unrevealing for hemorrhage with an Alberta Stroke Program Early CT (ASPECT) score of 8. Patient received the tPA bolus at 17:56 and infusion at 18:01. CT angiography revealed an acute left M1 MCA occlusion. CT perfusion showed a core infarct of 8cc and penumbra volume of 162cc, prompting neurointervention. The first aspiration catheter pass was successful. Patient clinically improved, spoke a few words with antigravity movement in his right arm. Within minutes, he abruptly became aphasic; repeat angiogram demonstrated reocclusion of the left M1 MCA. A second pass was performed successfully, but was followed by a short interval reocclusion. Patient was loaded with aspirin 300mg and heparin 70units/kg. A third pass was performed successfully, also followed by a short interval reocclusion. The patient was then loaded with ticagrelor 180mg. Again, a fourth successful thrombectomy was performed, followed by a short interval reocclusion. A stent was placed in the fifth pass with intra-arterial tPA at 20:24. A post-stenting angiogram showed a Thrombolysis in Cerebral Infarction (TICI) III flow. COVID-19 polymerase chain reaction test returned positive. A follow-up platelet function test (P2Y12) confirmed therapeutic antiplatelet effect. After a 24-hour CT, dual antiplatelet therapy was started with aspirin and ticagrelor. On day 3, a repeat CT angiography showed occlusion of the stent; magnetic resonance imaging showed a large infarct of entire left MCA territory.

Conclusion: The hypercoagulable nature of COVID-19 poses a new array of complications to conventional stroke interventions, which was uniquely highlighted by this case’s aggressive medical and interventional therapies. This raises consideration for protocol amendments of interventions for ischemic strokes with COVID-19, a novel and distinctive risk factor.


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Introduction: An increase in volatile components including those subjected to heat influences the degree to which aroma and flavor is perceived. Previous studies of taste indicate that sensitivity was optimal at a food temperature of 30°C. A decrease and increase of temperature from this level lower
taste sensitivity (Moskowitz, 1973). A patient with hypogeusia who was paradoxically able to perceive taste better in refrigerated food has not heretofore been reported.

Methods: Case Report: This 64-year-old right-handed male had a progressive loss of smell and taste over twelve years, attributed to severe allergies and chronic rhinitis. He was able to smell strong cooking odors of garlic and onions as well as gasoline, but nothing else. One month prior to the initial consult, he noticed a decreased ability to taste food rating his ability to be 10% of normal. Although he is able to identify the four basic tastes, he was unable to perceive flavor. Four years after the presentation, he noticed that he was able to perceive flavor better with refrigerated food (about 4°C) including lemon chicken, steak, and salmon.


Discussion: Retronasal smell could be the major factor in his inability to perceive flavors, which improved when he ate cold foods. Possible explanations for this include direct stimulation of TRPM8 receptors that are implicated in taste, improvement in oral or lingual blood flow, increased cGMP and related proteins after cold stimulation, and improvement of retronasal smell through an alternative neural pathway that links to other cranial nerves supplying the pharyngeal area. Cold stimulation induces swallowing after stroke (Cola, 2012; Kaatzke-McDonald, 1996). Because both taste and retronasal pathways terminate in the nucleus tractus solitarius, there is the possibility of a connection between these and swallowing functions. Odorants targeted to stimulate the retronasal smell receptors can also stimulate the cranial nerves that induce swallowing (Welge-Lusse, 2009). In addition, trigeminal stimulation through temperature-sensitive receptors may have a role in enhancing retronasal smell.

Conclusion: Cold enhancement of taste as seen in the patient opens a possible target for treatment in those patients who suffer from chemosensory loss. Further evaluation may be worthwhile.

332. Early Inflammatory Markers in Acute Ischemic Stroke Patients
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Introduction: Ischemic brain injury in acute stroke results in an inflammatory response characterized by interleukins and cytokines. However, the exact mechanism of this inflammatory mechanism and its interaction among these ischemic stroke (IS) patients is still ambiguous. The aim of this study was to characterize the early inflammatory response and its interaction at the site of occlusion among these IS patients.

Methods: Patients with large vessel occlusion acute ischemic stroke (LVO-AIS) eligible for Mechanical Thrombectomy (MT) were recruited within 24 hours from their symptom onset. Blood samples were collected proximal and distal to the occlusion site during the procedure. Control samples were collected from the femoral artery and median cubital vein. 20-Plex assay and ELISA was used for the analysis of cytokines and chemokines. Graph-pad prism and R-software was used for evaluating the differences among the molecules across the site of occlusion and control.

Results: A total of 19 (male: 13 and female: 6) patients were included. Cytokine quantification observed a significant increase in MMP-9 and IFN-g proximal to the occlusion, whereas, there was a decrease in IL-2, IL-4, IL-5, IL-6, IL-7, IL-15, IL-17, GM-CSF, TNF-α, IP-10, VEGF, MIP-1a, and MIP-1b distal to the clot. The levels of IL-8, MCP-1, and MIG were comparable across the sites.

Conclusion: Our results characterized the local environment and immediate inflammatory molecules, within few hours of the ischemic brain injury. These observations indicate the evidence of initial activation of inflammatory response. This will help better understand the molecular patho-physiology and identify molecular biomarkers of ischemic stroke progression and subsequent modulating therapeutic interventions.

LB-452. A Randomized, Triple-Blind, Placebo-Controlled Phase I Study of Single and Multiple Ascending Doses of NVG-291 in Healthy Subjects
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Background: There are no approved treatments that directly promote neural repair through axonal regeneration, remyelination, or neuroplasticity after CNS injury, whether due to trauma (e.g. spinal cord injury [SCI]) or disease-specific mechanisms (e.g. multiple sclerosis [MS], Alzheimer’s disease [AD]). Substantial data from animal models of SCI, MS and AD supports that chondroitin sulfate proteoglycans (CSPGs), the major plasticity-inhibiting component of the perineuronal net, are increased at sites of CNS damage and inhibit endogenous repair mechanisms. The inhibitory effect of CSPGs is mediated through protein tyrosine phosphatase receptor (PTP)σ, which is the principal receptor for CSPGs in the CNS. NervGen is developing a novel, first-in-class PTPσ inhibitor, NVG-291, a systemically administered peptide for treatment of nervous system damage due to trauma or disease. In addition to its unique targeted mechanism of action, in animal models NVG-291 has demonstrated the ability to cross the blood brain barrier by virtue of its cell-penetrating tag.

Objectives: This randomized, blinded, placebo-controlled trial will assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single (SAD) and multiple ascending doses (MAD) of NVG-291 administered subcutaneously once-daily in healthy subjects.

Materials and Methods: Part 1 (SAD portion) is being conducted in up to 32 healthy adult volunteers randomly
assigned into 6 cohorts of placebo or NVG-291 (doses ranging from 0.032 mg/kg to 0.864 mg/kg, and in the range where preclinical efficacy was observed). Following completion of the single dose escalation, an additional cohort of 4 subjects will be treated at the highest tolerated dose for cerebrospinal fluid (CSF) collection and evaluation of PK/PD. Part 2 (MAD portion) will proceed after Part 1, and dose up to 18 subjects randomly assigned into 3 dose cohorts to receive NVG-291 or placebo once-daily for 14 days. An additional cohort of 6 subjects will receive NVG-291 for 14 days at the mid-dose level for CSF analysis. Safety assessments and cognitive testing will be conducted for all cohorts.

Results and Discussion: Recruitment started in May 2021 and is expected to be completed by Q1 2022. NVG-291 has been safe and well-tolerated in subjects dosed to date. The study will establish whether NVG-291 is safe and well-tolerated at doses expected to be biologically active in humans, and will assess exposure in the CNS, in order to support advancement to clinical trials in patients with SCI, MS, and AD.

Movement Disorders

153. Nilotinib is Safe and Stabilized Motor, Cognitive and Functional Symptoms in Parkinson’s Disease Patients Over 27 Months
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Background: Nilotinib is FDA-approved for leukemia and this open label study investigated the safety, tolerability and potential clinical effects of nilotinib in medically optimized Parkinson’s disease patients.

Objectives: Safety and tolerability were primary objectives and clinical outcomes were exploratory.

Methods: Sixty-three patients completed a 15-month Phase 2, double-blind, placebo-controlled study and were randomized 1:1 into an open label study of nilotinib, 150mg versus 300mg, for 12 months.

Results: Nilotinib was safe and tolerated, no adverse effects seemed to be related to the drug and no differences in adverse events were observed between groups. Exploratory clinical outcomes showed that nilotinib, 300mg, was remarkably stable from baseline to 27 months using partial and total UPDRS. Nilotinib, 150mg versus 300mg, significantly declined using partial or the sum of UPDRS I and II. There was no significant difference in nilotinib, 150mg versus 300mg, using UPDRS III (ON Levodopa) and total UPDRS I-III. Sub-group analysis showed that late start nilotinib, 150mg, significantly worsened using the sum of UPDRS II +III and total UPDRS I-III compared to late start nilotinib, 300mg. Quality of life using PDQ-39 in nilotinib, 150 mg, significantly declined between 15 and 27 months compared to nilotinib, 300 mg, and there was no change in cognition using MoCA between groups.

Conclusions: This study provides evidence that nilotinib is safe and tolerated in Parkinson’s disease. The exploratory clinical data will inform an adequately powered larger study to evaluate the efficacy of nilotinib, 300mg, in PD.

154. The Implications of Pyramidal Signs in Multiple System Atrophy
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Objective: To determine pyramidal signs in multiple system atrophy (MSA) and the associations with other clinical characteristics.

Background: The clinical manifestations of MSA are comprised with symptoms of four domains: autonomic, parkinsonism, cerebellar, and pyramidal systems. However, the involvement of pyramidal system, manifesting as upper motor neuron (UMN) symptoms and signs, are frequent yet insufficiently studied in MSA.

Methods: We reviewed 40 autopsy-confirmed MSA cases from New York Brain Bank and assessed the pyramidal signs using UMN burden scores (0-36, calculated by scoring deep tendon reflexes, muscle tone, and corticospinal tract signs). Based on UMN burden scores, MSA patients were divided into those with high UMN burden (HUMN) ≥ 18 and low UMN < 18 (LUMN). We compared the clinical characteristics of MSA cases with HUMN vs. LUMN using Chi-Square and independent t-test. We investigated if UMN burden is associated with the presence of autonomic, parkinsonism, and cerebellar features. We conducted a multivariable linear regression to examine if UMN burden is associated with survival. We investigated whether cases with more severe gial cytoplasmic inclusion deposition (GCI score ≥ 2) in the motor cortex have higher UMN burden scores compared to less severe cases (GCI score < 2).

Results: MSA cases with HUMN (35%, n = 14) and those with LUMN (65%, n = 26) have similar age, sex, age of onset, and disease duration. MSA cases with HUMN are more likely to be MSA-P than those with LUMN (p = 0.016). MSA patients with HUMN are more likely to have urinary incontinence (OR = 4.00, p = 0.046), but less likely to have orthostatic hypotension (OR = 0.24, p = 0.043) and erectile dysfunction (OR = 0.03, p = 0.006). The HUMN cases do not differ from LUMN in regards to bowel dysfunction, stridor, and dry eyes. Patients with HUMN and those with LUMN are not different in survival. Cases with more severe GCI deposition (GCI ≥ 2), compared to the less severe group (GCI < 2), has higher UNN burden (43.7 ± 16.8 vs. 29.0 ± 20.2, p = 0.039). High GCI burden is more commonly seen in MSA-P than MSA-C (p = 0.013).

Conclusion: Pyramidal signs are associated with different MSA subtypes and autonomic features. Further studies are needed to fully characterize this often-neglected clinical domain for MSA.
155. Diabetic Striatopathy in a Choctaw Female
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Objective: To describe a case of diabetic striatopathy in a 55-year-old female.

Background: Diabetic Striatopathy (DS) is an uncommon complication of chronically uncontrolled diabetes mellitus (DM). Pathophysiology of DS is not entirely understood; theories include GABA depletion and proliferative vascular abnormalities. DS is a rare clinical entity; one 2018 review recognized only 7 cases over 15 years at a US referral medical center. It is thought to be underdiagnosed in Western populations. DS has a predominance for female, Asian, and elderly people. Patients present with hyperglycemia and acute onset hemichorea. The contralateral basal ganglia are hyperdense/hyperintense on CT or MRI.

Methods: Retrospective chart review and literature review.

Our Case: Our patient was a 55-year-old Choctaw female with a past medical history of coronary artery bypass graft, type II diabetes, and oxygen dependence following Covid-19 infection. She presented with acute onset of involuntary right upper limb movements. The movements were suppressed during sleep and resumed upon waking. On exam, her right arm writhed violently in a choreiform fashion. Her right face and right leg were involved too. Her exam was otherwise normal. She reported two family members with these symptoms in the past. CT head revealed a hyperdensity in the left basal ganglia, with no mass effect. CTA revealed enlarged veins in the left putamen. Lab studies revealed a hemoglobin A1C of 14.7 and glucose of 281. She was admitted and given haloperidol and lorazepam which did not alleviate symptoms. Endocrinology was consulted to improve glycemic control. Multiple attempts to obtain MRI failed due to our patient’s inability to lie still. On the sixth day of admission, our patient’s movements were controlled with improved diabetes management and clonazepam.

Conclusions: DS is an uncommon complication of uncontrolled Type II diabetes that can be corrected with glycemic control and should be considered in presentations of acute hemichorea. Our report is unique as no case report in existence, to our knowledge, presents this rare disorder in a person of Choctaw heritage.

156. Late-Onset Familial Segmental Dystonia with Novel GNAL Mutation
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Objective: Report a unique onset of dystonia in family affected by tremor and segmental dystonia

Background: A 66-year-old woman of Norweigan descent with several months of progressive blepharospasm, leading to functional blindness. Botulinum toxin helped reduce the symptoms initially, but she then developed lower face spasms, dysarthria, and hypophonia, without dysphagia. She began to have jerky anterocollis, with complaints of shortness of breath and increased respiratory rate. Imaging and testing was normal. Despite medical and botulinum toxin treatment, she continued to progress, and bilateral GPi DBS was performed. Improvement with DBS is modest but she is undergoing continued adjustments. There was an extensive family history of dystonia: mother had onset in the neck in her 30s, with gradual spread to the spine, resulting in lateral spine posture and retrocollis; 3 maternal uncles with cervical dystonia; and daughter and niece with tremor.

Methods: Case report and literature review with genetic testing.

Results: A dystonia genetic testing panel from Centogene (including a total of 88 genes tested through next-generation sequencing and copy number variant analysis) revealed a positive result. This likely pathogenic variant identified is a heterozygous frameshift mutation, c.1302_1303del (p. Asn435Hisfs*21), in the GNAL gene, which causes a shift in the reading frame starting at codon 435 in the protein product. The new reading frame ends in a stop codon 20 positions downstream. The predicted protein-length change affects a non-repetitive conserved region and is predicted to be likely pathogenic. This result is consistent with a genetic diagnosis of DYT-GNAL (formerly known as DYT25). The phenotype of DYT-GNAL is that of adult-onset segmental dystonia, typically with later onset (mean 32 years, range 7-54) with cervical and cranial dystonia that may also spread to the arms. There are over 30 different GNAL pathogenic variants, mostly heterozygous in nature, which are noted over the entire gene, with variable penetrance.

Conclusions: Adult-onset dystonia with familial occurrence and relatively rapid spread caudally is unusual and genetic causes must be explored. Involvement of the respiratory muscles is unusual but can be disabling. DBS is a potential treatment option for long-term reduction of dystonia severity if medical treatment fails. This case expands the phenotype (old age, diaphragm involvement, rapidity of spread) and genotype of DYT-GNAL.

157. Effects of Once-Daily Opicapone 50 mg on the Pharmacokinetics of Levodopa Administered as Carbidopa/Levodopa Extended-Release Capsules: An Open-Label Phase 1 Study
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Background: Opicapone, an oral long-acting catechol-O-methyltransferase inhibitor, is approved as a once-daily adjunctive treatment to oral carbidopa/levodopa (CD/LD) in patients with Parkinson’s disease (PD) experiencing OFF-episodes. It has been previously demonstrated that the addition of opicapone to immediate-release CD/LD decreases plasma peak-to-trough fluctuation index, thus providing more consistent exposure to levodopa (LD) in patients with PD. There has been no prior evaluation of opicapone with the CD/LD extended-release (CD/LD-ER) formulation, a common treatment used in
the United States. This study was conducted to assess the effects of opicapone 50 mg on the pharmacokinetics (PK) of LD and its metabolite, 3-O-methylidopa (3-OMD), when administered with CD/LD-ER capsules in healthy individuals.

**Methods:** 18 healthy subjects (9 male, 9 female) were included in this Phase 1 open-label study. CD/LD-ER 23.75/95 mg was administered as follows: 1 capsule three times a day (TID) on Days 1 and 16; 2 capsules TID on Days 2-3 and Days 17-18 every 7 hours at 07:00, 14:00, and 21:00. Opicapone 50 mg once-daily was administered at 22:00 on Days 4-18. Blood samples for the assessment of LD and 3-OMD plasma concentrations were collected on Days 3-4 (CD/LD-ER without opicapone) and Days 18-19 (CD/LD-ER with opicapone) every 30 minutes from 07:00 to 21:00, and every 2 hours from 23:00 until 09:00 the next morning. Samples for soluble COMT (S-COMT) activity were collected on Day 1 and Day 19.

**Results:** Administration of once-daily opicapone with CD/LD-ER resulted in increased trough, peak, and overall LD exposure; decreased peak and overall exposure to 3-OMD; and markedly decreased S-COMT activity.

**Conclusions:** Providing more consistent LD levels through the day is a central treatment strategy for the management of motor fluctuations in PD. Administering once-daily opicapone with CD/LD-ER resulted in increased overall LD exposure, decreased 3-OMD exposure, and reduced S-COMT activity. The effects of OPC on this extended-release formulation of CD/LD may contribute to more consistent LD exposure throughout the day, which continues to be a challenge and goal in treating PD.

**158. OPTI-ON: A Longitudinal Real-World Study of Opicapone in Patients with Parkinson’s Disease and Motor Fluctuations**

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**Background:** Motor fluctuations and wearing-off of medications are common complications as Parkinson’s disease (PD) progresses. Opicapone is an oral once-daily catechol-O-methyltransferase (COMT) inhibitor for adjunctive treatment to carbidopa/levodopa (CD/LD) in patients with PD and OFF-episodes. The efficacy and safety of opicapone was demonstrated in two phase 3 studies that were conducted in Europe and Asia (BIPARK-1, BIPARK-2). An observational phase 4 study in the United States (US), OPTI-ON (Opicapone Treatment Initiation Open Label Study [NCT04787965]), is currently underway. This study examines treatment patterns, clinical outcomes, safety and tolerability of opicapone as an adjunctive treatment to CD/LD in patients with PD who are experiencing OFF-episodes.

**Methods:** OPTI-ON is an ongoing, prospective, multicenter, open-label study of opicapone as an adjunctive treatment to CD/LD. Approximately 250 clinically eligible patients with PD and OFF-episodes are being enrolled at about 50 sites in the US. Participation in the study is expected to continue for up to 6 months. Assessments include patient demographics and clinical history, opicapone treatment decisions (reasons for initiation or discontinuation), use of other PD medications, and changes in PD medications. Clinician- and patient-rated outcomes (PROs) include: Clinician Global Impression of Change; MDS-Unified Parkinson’s Disease Rating Scale, Parts 1A and 4 (clinician), Parts 1B and 2 (patient); Patient Global Impression of Change; Patient Global Impression of Severity in ON- and OFF-states; and 8-item Parkinson’s Disease Questionnaire. This is also the first longitudinal study to implement the new clinician- and patient-rated Non-Motor Fluctuation Assessment. Assessments are completed online by patients (electronic PROs) and performed by clinicians during office visits or via telemedicine.

**Results:** Up-to-date findings will be presented.

**Conclusions:** Results from the OPTI-ON study are expected to provide real-world information about the patterns of use and outcomes with adjunctive opicapone for treatment of PD in clinical practices throughout the US. These results will expand upon findings from the phase 3 clinical trials, which established the efficacy and safety of once-daily opicapone in patients with PD and OFF-episodes.
(≥50% improvement by Wk4 through Wk48); early/ sustained (≥30% by Wk4 through Wk48); early (≥30% at Wk4 and Wk48); delayed (≥30% at Wk8 and Wk48); late (≥30% at Wk12 or later and Wk48); poor/none (none of the 5 response groups). Based on Schoolder-Kane criteria, remission was defined as absence of TD (scores ≤2 [mild or better] in ≤1 AIMS item and ≤1 for all other items) at last study visit or last 2 visits (sustained remission).

**Results:** Analyses included 158 patients. The percentage of patients with AIMS ≥2-point improvement increased from Wk4 (57.0%) to Wk48 (97.1%); 2.9% had ≥2-point worsening at Wk48. Response results were as follows: early/ sustained/strong (10.8%), early/sustained (14.6%), early (3.2%), delayed (29.1%), late (27.8%), poor/none (14.6%). 62.0% and 48.1% of patients met the criteria for remission and sustained remission, respectively.

**Conclusions:** Patterns of improvement may vary but robust and long-term TD improvements can be expected with once-daily valbenazine. Patients responding within 4 weeks may be likely to maintain that response throughout treatment. Others may require ≥8 weeks of treatment before responding, but with long-term outcomes that are comparable to “early responders”. Some patients may achieve TD remission within 1 year of valbenazine treatment.

160. Eye Blink-Associated Saccadic Intrusions

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Saccades function to bring targets of interest into the field of view. They are one of four types of basic eye movements in humans, all of which are generated and modulated by components of a complex eye movement network, involving cortical eye fields, thalami, basal ganglia, cerebellar, and brainstem structures. Similarly, blinks are presumed to be generated by a blink center involving complex cortical and subcortical pathways. An association between saccades and blinks is well established; when these circuits are disrupted, normal saccadic parameters change. A 49 year old female presented with fatigue and weakness. She had a complicated medical history, including drug-resistant epilepsy with subsequent vagus nerve stimulator (VNS) placement, right anterior temporal lobectomy, craniotomy, and a second right temporal lobectomy and amygdalohippocampectomy to remove remaining epileptogenic tissue. The latter was complicated by ischemic right middle cerebral artery (MCA) territory stroke. She had resultant left hemiplegia. Neurology was consulted for evaluation of the change in the patient’s functional status. Her examination was unremarkable with regards to the presenting complaints, but one unique finding was observed; she demonstrated abnormal conjugate eye movements to the left with each blink. They continued to be present even after the patient’s ability to fixate on an object was removed with the use of Frenzel goggles. She denied any subjective changes in her vision and exhibited normal extraocular movements. It was unclear how long this finding had been present as the patient and her caregiver were unaware of these eye movements. Review of her MRI of the brain from 10 months prior showed encephalomalacia and surrounding gliosis in the right MCA territory, right temporal laminar necrosis, right basal ganglia and parietal lobe microhemorrhages, ex vacuo dilatation of the right lateral ventricle, and a resultant rightward 5 mm midline shift. The change in functional status was attributed to recent medication changes and she was deemed safe for discharge. Saccadic abnormalities have been reported in a variety of conditions. The blink-associated saccadic intrusions seen here are rare. To our knowledge, only one other patient has been reported with similar blink-associated eye movements after brain injury, which was following a right MCA territory stroke. The exact mechanism underlying these eye movements is unclear, but may involve aberrant or disrupted neuronal signaling in cortical and/or basal ganglia components of the eye movement network.

161. Ten-year Patient Experience: Deep Brain Stimulation in Early-Stage Parkinson’s Disease

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**Background:** The demonstrated safety and efficacy of deep brain stimulation (DBS) in Parkinson’s disease (PD) motivated the first and only clinical trial evaluating its application in very early-stage PD. Vanderbilt completed a single-blind pilot clinical trial (NCT00282152) with thirty early-stage PD patients (medication duration 6 months-4 years; without history of dyskinesia/motor fluctuations) randomized 1:1 to early DBS plus optimal drug therapy (DBS+ODT) or optimal drug therapy alone (ODT). Patients completed 7-day inpatient therapeutic washout assessments ON and OFF treatment biannually for the first two years after randomization, ON outpatient assessments annually through five years, and a longitudinal follow-up study ON and OFF after ten years. Given the risks associated with DBS surgery, we aimed to understand the motivations, reservations, and satisfaction among patients who completed the pilot over 10 years ago.

**Methods:** Patients approached for enrollment in the ten-year follow-up study were also offered participation in this study (IRB#191728). One-hour, semi-structured interviews were audio recorded and transcribed. A hierarchical coding system was developed using the interview guide and preliminary transcript review. Interviews were coded by three trained coders, then compared to resolve discrepancies. Coded transcripts were analyzed using an iterative inductive-deductive approach. The structure, frequency, and interrelationships of coded quotes were integrated into a conceptual framework.

**Results:** Ten participants (6 ODT, 4 DBS+ODT) were interviewed. Motivations for enrolling in the trial included desire to maintain careers and independence, hope that DBS would slow disease progression, and motivation to benefit future PD patients. Reservations about study participation...
included the unappealing nature of the surgery and hesitance to accept the risks of brain surgery while still functioning adequately. Some patients emphasized the thoughtful nature of the expanded, three-part informed consent process as a helpful factor in making their decision to participate. While patients described challenges related to their washout experience and some early ODT patients were dissatisfied with their treatment assignment, many expressed satisfaction with study participation due to positive interactions with study personnel, benefits of early DBS therapy, and/or gaining a means by which to fight back against the disease.

**Conclusion:** After more than 10 years since joining the only clinical trial of DBS in early-stage PD, patients reflected meaning and satisfaction from their participation. These results are encouraging for enrollment in future trials evaluating DBS in very early-stage PD. The FDA has approved a phase III clinical trial evaluating DBS in early-stage PD (IDE#G050016).

**163. Clonazepam Responsive Nonketotic Hyperglycemic Hemiballismus**

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**Background:** Nonketotic hyperglycemic hemiballismus (NHH) is a rare presentation in setting of uncontrolled diabetes. The typical triad includes unilateral involuntary movements, contralateral striatal abnormalities (hyperdensity on computed tomography (CT) & striatal hyperintensity on magnetic resonance imaging (MRI)) and nonketotic hyperglycemia. Clinical improvement is typically seen with blood glucose correction with first line pharmaceutical therapy being neuroleptics targeting D2 receptors. Other agents considered include tetrabenazine, anti-epileptics, and benzodiazepines.

**Case:** A 72-year-old man with diabetes mellitus type 2 presented with worsening left sided involuntary movements of 3 weeks’ duration. Symptom onset was six weeks prior, with involuntary left foot tapping which progressed to debilitating flinging movements involving proximal and distal left upper and lower extremity. He denied recent medication changes, illicit drug use, or illnesses. Neurological examination revealed involuntary high amplitude, nonrhythmic, multidirectional choreiform motions involving the entire left upper and lower extremities, consistent with hemiballismus. Spot blood glucose testing revealed hypoglycemia with blood glucose level of 32 initially and 16 on repeat testing. The movements persisted despite correction of blood glucose with 50% dextrose. He received intravenous haloperidol without adequate relief. Subsequently, patient was intubated with propofol infusion, where the involuntary movements were still elicitable with minimal stimulation. CT head was unremarkable but MRI brain revealed hyperintensity in the right putamen with corresponding contrast enhancement. Work up revealed HbA1c of 9.2%. Given lack of improvement with haloperidol and EKG changes, patient was switched to Clonazepam with significant improvement. Patient was able to perform fine finger movements and ambulate independently at the time of discharge.

**Conclusion:** Several features make this case unique in addition to the rare occurrence of hemiballismus involving the striatum. Although NHH occurs in the setting of...
hyperglycemia with clinical improvement from blood glucose correction, our patient was noted to be hypoglycemic on presentation with no improvement despite glucose correction. Typical striatal abnormalities on the CT scan was not seen. Hemiballismus persisted despite propofol sedation until he was switched to clonazepam. In nonketotic hyperglycemic states, brain metabolism shifts to an anaerobic pathway, rapidly depleting GABA. Thus, it is plausible for Clonazepam to have better efficacy as it enhances the effects of GABA compared to neuroleptics targeting dopamine receptors. Additionally, diabetes is associated with a higher prevalence of QTc prolongation and cardiac complications, making diabetic patients poor candidates for neuroleptics. Our case highlights the utility of clonazepam in treating these metabolic movement disorders.

164. Leriglitazone Reduces Iron Accumulation in the Dentate Nucleus and Improves Further Relevant Disease Biomarkers and Clinical Parameters in a Phase 2 Clinical Study in Friedreich’s Ataxia (FRDA)
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Objectives: Proof-of-concept study to investigate the effects of leriglitazone on biochemical, imaging and clinical parameters in FRDA.

Background: Leriglitazone is a brain penetrant peroxisome proliferator-activated receptor γ (PPARγ) agonist.

Design/Methods: This was a double-blind placebo-controlled study in 39 patients with FRDA (age 12-60 years), randomized 2:1. Primary endpoint was change in spinal cord area, secondary endpoints included Quantitative Susceptibility Mapping (QSM) for dentate nucleus iron concentration, tNAA/mIns ratio by Magnetic Resonance Spectroscopy (MRS) in the spinal cord, Composite Cerebellar Functional Severity Scale (CCFS), Scale for the Assessment and Rating of Ataxia (SARA), Activities of Daily Living, Quality of Life, Fatigue Severity Scale and Clinician-and Patient based Global Impressions of Improvement.

Results: 26 patients received leriglitazone, and 13 placebo. 32 patients (20/12) completed the study. Leriglitazone was safe, with edema and weight gain as the most frequently reported adverse events. The primary endpoint was not reached, as the expected area change in the placebo group did not occur, probably due to long disease duration with patients already reaching a plateau of spinal atrophy at baseline. Leriglitazone reduced iron accumulation in the dentate nucleus by QSM (p = 0.050, ANCOVA). A composite endpoint of “response” on QSM, CCFS and MRS favored leriglitazone (p=0.043, O’Brien sum of ranks test). Subpopulation analysis revealed efficacy trends in SARA and Activities of Daily Living.

Conclusions: Leriglitazone showed favorable effects on relevant disease markers such as iron accumulation in the dentate nucleus, spinal cord metabolism and upper limb ataxia with no major safety concern, prompting further consideration as a potential therapeutic for FRDA.

165. Evaluating Patients’ Preferences for Parkinson’s Disease Treatments
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Background: OFF-episodes between levodopa/carbidopa (LD/CD) doses can be burdensome for patients with Parkinson’s disease (PD). New treatments, such as opicapone, have the potential to reduce OFF-time; however, little is known about patients’ willingness to tradeoff the side effects of adjunctive treatments to gain reductions in OFF-time. A survey was developed to identify patient preferences for attributes of oral medications that are added to levodopa or LD/CD regimens to reduce OFF-time for PD patients.

Methods: The survey was developed based on prior research and the treatment landscape. Input on the survey design came from patient advisors on the study team and through cognitive debrieﬁng interviews with adult patients recruited by the Michael J. Fox Foundation for Parkinson’s Research using the following criteria: self-reported diagnosis of PD; current treatment with LD/CD; and ≥90 mins of total OFF-time per day. The survey presented a series of choices between medications that varied in efﬁcacy (minutes of additional ON-time), potential side effects (more minutes of troublesome dyskinesia, risk of diarrhea, risk of change in urine/sweat/saliva color), and dosing frequency. Results from the interviews will be used to develop an online survey.

Results: Of the patients who completed the interviews, 9/15 (60%) were male; mean age (±SD) was 62±8 years. Although patients were taking 3-6 LD/CD doses per day, 7/15 (47%) reported >90 mins of OFF-time each day and 5/15 (33%) took rescue medications for OFF-time. When choosing between hypothetical medicines, patients verbalized their personal reasoning for tradeoffs between efﬁcacy and side effects. When presented with a medication that would provide 1-2 hrs of additional ON-time, 8/15 (53%) patients always selected adjunctive medicine despite adding another treatment with side effects to their regimen. Some
participants were willing to forgo 30-60 mins of additional ON-time to avoid troublesome dyskinesia, diarrhea, or change in urine, sweat, or saliva color.

Conclusions: Patient feedback provided valuable insights on patient preferences that will be incorporated into a future online survey. Patients indicated that OFF-episodes are not well-controlled with currently available medications, and this research contributes to the literature on patients’ experiences with motor fluctuations to support identification of appropriate treatment strategies for OFF-episodes.

166. Hot Cross Bun Sign in Progressive Ataxia with ELVOL4 Mutation
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A 65 year old woman presented to the clinic for trouble with her gait as well as speech. Her earliest symptoms included difficulty with riding a bike at 30 years of age. Around her mid-50s she developed trouble with speech, swallowing as well as double vision. She needed support of a cane for ambulation. Age 60 years of age she transitioned to a walker due to worsening gait problems and falls. By the time she was seen at our clinic she had developed autonomic dysfunction including, bowel and bladder incontinence. On further investigation she had family history of similar issues in her daughter, mother, maternal aunt, maternal grandmother and maternal great aunt.

On examination patient was noted to have gaze evoked nystagmus and square wave jerk on right and left gaze. She had reduced optokinetic response in vertical and horizontal directions. Her gait was wide based with ataxia and she used a walker to ambulate. Patient had 4/5 strength on bilateral hip flexion and bilateral foot drop. She had significant dysmetria on finger to nose testing and finger chasing. There was trace bradykinesia on finger tapping and hand movements. She had hyperreflexia throughout. Her exam was asymmetric with worsened findings on the left side.


ELOVL4 mutations have been associated with rare dermatological disorders, subtypes of macular dystrophy and spinocerebellar ataxia.

SCA type 34 is an autosomal dominant disorder with typical onset during young adulthood with slow progression. This may involve skin manifestations in addition to nystagmus, dysarthria as well as ataxia. To our knowledge this is the second case report that identifies an individual with this exact ELVOL4 mutation with SCA, MRI hot cross bun sign (which is more commonly associated with multiple system atrophy) and without erythrokeratodermia. This case exemplifies the varied phenotype associated with this mutation.

167. 31P Magnetic Resonance Spectroscopy as a Tool to Identify Mitochondrial Dysfunction in Parkinson’s Disease In-Vivo
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Objective: To determine if 31P magnetic resonance spectroscopy (31P-MRS) can identify mitochondrial dysfunction in Parkinson’s disease (PD) and if this correlates with in-vitro measures of mitochondrial function obtained from patient derived fibroblasts.

Background: PD is increasingly recognized as an aetiologically heterogeneous disorder. Identification of the distinct mechanism contributing to neuronal cell loss in an individual will be crucial to develop future “Precision Medicine” approaches. 31P-MRS is a non-invasive tool that measures relative quantities of key compounds involved in energy metabolism, such as adenosine triphosphate (ATP) and phosphocreatine.

Methods: 31P-MRS scans were undertaken in 35 patients with PD and 25 healthy age and sex matched controls using a multi-voxel 2D chemical shift imaging sequence with image-selected in-vivo spectroscopy localised to the midbrain and putamen. Spectra were analysed using the jMRUI software package and the AMARES spectral fitting algorithm (Vanhamme L, JMRI, 1997). All participants had a 3mm punch skin biopsy to establish fibroblast cell lines for assays including total cellular ATP, mitochondrial membrane potential and mitochondrial count per cell. Clinical assessment included the Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS), Non-Motor Symptom Scale, genetic analysis and the calculation of predicted risk of disease progression (Veleboer DC, Neurology, 2016).

Results: 35 PD patients (19 male, 16 female, mean age 60.06 ± 10.74) and 25 controls (12 male, 13 female, age 60.64 ± 10.96) have been assessed. The mean disease duration was 13.71 ± 7.50 months (maximum 32 months), with a median modified Hoehn & Yahr of 2, mean MDS-UPDRS part 3 motor scores 32.60 ± 9.89 and a mean total levodopa equivalent daily dosage of 370.43 ± 218.44mg. Interim analysis of 31P-MRS data revealed a significant difference in variance in total normalised ATP levels in the midbrain between PD and controls (F test, p <0.01), a third of patients had ATP values > 2 standard deviations from the control mean. Total normalised phosphocreatine in the midbrain as a third of patients had ATP values > 2 standard deviations from the control mean. Total normalised phosphocreatine in the midbrain showed a significant linear relationship with the risk of predicted disease progression (p<0.01, r²=0.519).

Conclusions: 31P-MRS may help to identify a PD subgroup with significant mitochondrial dysfunction or at high risk of rapid progression. 31P-MRS may therefore become useful to stratify patients for future neuroprotection trials. Assessment of mitochondrial function in fibroblast cell lines...
is on-going and will allow us to determine a possible correlation between central and peripheral measures of mitochondrial dysfunction.

168. Treatment Patterns in a Real-World Sample of Patients with Parkinson’s Disease and Motor Fluctuations

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Background: Levodopa is the most effective treatment for Parkinson’s disease (PD), but motor fluctuations (MFs) and OFF-episodes are important clinical considerations as the disease progresses. Strategies for managing MFs include increasing frequency/dose of levodopa, switching to different formulations, and/or adding adjunctive medications. This study was conducted to evaluate real-world treatment patterns in patients with PD experiencing MFs.

Methods: A retrospective medical chart review study of adult patients with PD (mean age: 70.9 years) who began experiencing MFs between 01/2014 and 04/2019 while taking carbidopa/levodopa (CD/LD). Patient and clinician questionnaires were implemented to ascertain which factors are most important when selecting a PD treatment. Data were extracted from patients’ medical charts to characterize treatment patterns, including changes in CD/LD treatments (dosing strength and frequency, formulation) and adjunctive therapy use. All outcomes were analyzed descriptively.

Results: Of 310 patients, 61% were male and 93% were white. Mean ages (±standard deviation) at PD onset and MF onset were 64.6±10.0 and 69.1±9.4 years, respectively. The cohort comprised 193 (62.3%) patients who had MFs for <2 years and 117 (37.7%) for ≥2 years. Both physicians and patients rated motor symptom suppression and OFF-period reduction as most important when selecting medications, but patients rated the following as “extremely/very important” more often than physicians: pill burden (44.4% vs 17.9%), pain reduction (57.5% vs 25.0%), drug costs (56.5% vs 42.9%). Of 350 CD/LD regimens taken after MF onset, 71.4% were CD/LD immediate-release, 12.0% were CD/LD controlled-release, and 11.4% were CD/LD extended-release. No standardized approach to MF treatment was observed. Of 129 CD/LD regimens with a change in dosing strength and/or frequency, frequency change was the most common first step (38.8%), followed by strength change (31.8%), and both simultaneously (29.5%). Various medications were used conjunctively with CD/LD regimens, with dopamine agonists (52.5%) and monoamine oxidase-B (MAO-B) inhibitors (46.5%) being the most common adjunctive therapies.

Conclusions: Patients with PD and MFs were more likely than physicians to rate pill burden, pain reduction, and drug costs as important factors when selecting a medication. Changes in CD/LD doses and/or frequency were common, and various medications were used conjunctively with CD/LD regimens. These results indicate a lack of a standard treatment algorithm and the need for more effective medications with less burden for managing PD with MFs.

169. Exploring Knowledge Gaps in Functional Neurological Disorders

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Background: Functional Neurologic Disorders (FND) are common and often disabling group of conditions, comprising around 16% of Neurology outpatient referrals; in one study, stroke-like presentation of functional etiology comprised of 8.7% of inpatient stroke admissions, many of whom underwent intravenous thrombolysis. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has removed psychological stressors from the diagnostic criteria. It has been encouraged to replace terminologies such as psychogenic disorders and hysteria with the more neutral term functional disorder. Furthermore, FND is no longer a diagnosis of exclusion but rather relies on positive clinical findings. Despite evolving understanding and updated diagnostic criteria for FND, it is not known whether this knowledge is widely disseminated and understood. As Emergency Department (ED) is often the first point of contact for patients presenting with FND, it creates a valuable opportunity for early and proper identification of FND; delayed diagnosis and treatment may lead to deleterious consequences such as unnecessary testing, prolonged duration of disease, increased economic burden and functional impairment.

This study’s aim was to evaluate the current understanding, perceptions and management of FND by ED providers.

Methods: This is a cross-sectional study surveying ED healthcare providers (physicians, nurse practitioners, and physician assistants) (n=273). Electronic surveys were created using REDCap and sent to providers and anonymous responses were automatically uploaded to a secure database.

Results: There were 68 respondents. Familiarity with the terms FND or FMD were 6.7% and 1.7%, respectively. The most frequent terms often used were psychogenic non-epileptic seizures (25%) and stress-induced/stress-related (21.7%). Vast majority of respondents felt that overall experience working with an FND patient was either more or much more difficult than other patient populations in the ED. The level of understanding of FND was rated “somewhat well” or less in close to 85%. Overwhelming majority of the respondents (98.5%) were unfamiliar with any FND resources and at least 81% had a desire to learn more about this condition.

Conclusion: Despite evolving understanding and updated diagnostic criteria for FND, knowledge gaps exist in our current healthcare system. This survey calls for FND awareness efforts in the healthcare community.
170. A Case of MELAS Mimicking PSP
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Case: A 69-year-old, right-handed, 4’11” female with a history of type II diabetes with associated retinopathy and nephropathy and hearing loss dating back 2-3 decades presented with 1 year of rapidly progressive gait imbalance, falls, cognitive decline and headaches. Examination revealed hypomimia, reduced blink rate, frontalis activation and saccadic intrusion of horizontal pursuit eye movements. She had mild generalized bradykinesia, axial rigidity and a parkinsonian gait with postural instability. An MRI was obtained which revealed midbrain, superior and middle cerebellar peduncle and hippocampal atrophy, mild ventricular dilation in the setting of global atrophy, moderate leukoaraiosis and remote lacunar infarcts in the deep subcortical white matter. CSF assessment with removal of 30mL showed no improvement of her gait with an unremarkable CSF analysis, including paraneoplastic studies. Based on her clinical exam findings and neuroimaging findings of mid-brain atrophy, the diagnosis was thought to be Progressive Supranuclear Palsy (PSP) Richardson’s Syndrome. Two years later, the patient presented to the emergency department with encephalopathy progressive over several days. She was afebrile and had stable vital signs. On neurologic examination she was awake with spontaneous eye opening, and symmetric semi-purposeful movements, withdrew and grimaced with painful stimuli, could track and fixate but was unable to follow commands or speak. Metabolic workup was normal except for neutrophilic leukocytosis (15.7). Her peak serum lactate was 4.2 mmol/L. No systemic infection was found. CSF evaluation was unremarkable. Prolonged video EEG monitoring did not show any epileptiform abnormalities. An MRI brain scan showed confluent areas of T2 hyperintensity in the anterior right greater than left temporal gyrus showed a subacute infarct and absence of beta-amyloid and tau on immunostaining. The patient died one month later. Next Generation Sequencing for mitochondrial disorders revealed an m.3243A>G change in the MT-TL1 gene (15.7). Her peak serum lactate was 4.2 mmol/L. No systemic infection was found. CSF evaluation was unremarkable. Prolonged video EEG monitoring did not show any epileptiform abnormalities. An MRI brain scan showed confluent areas of T2 hyperintensity in the anterior right greater than left temporal lobes with new evolving and migrating cortical diffusion restriction in the temporo, hippocampal and para-hippocampal region with patchy enhancement. A biopsy of the right middle temporal gyrus showed a subacute infarct and absence of beta-amyloid and tau on immunostaining. The patient died one month later. Next Generation Sequencing for mitochondrial disorders revealed an m.3243A>G change in the MT-TL1 gene which was considered pathogenic. An autopsy was performed, showing multiple cortical and subcortical infarcts and “infarct-like” lesions of variable age with relative preservation of the substantia nigra, locus ceruleus and subthalamic nuclei and no evidence of alpha-synuclein or tau-immunoreactive lesions. The final diagnosis was consistent with mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS).

Conclusions: The initial presentation met diagnostic criteria for PSP and is the first report, to our knowledge, of MELAS mimicking PSP.

171. Progressive Worsening in Tandem Gait Step-Width in Parkinson’s Disease
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Objective: To define the progression of objective deficits in tandem gait in Parkinson’s disease (PD).

Background: Tandem gait abnormalities have been reported to increase with advancing age (Virmani et al., Gait Posture 2018), play a role in fall-prediction in PD (Lindholm et al., J. Neurol. 2016) and distinguish PD from atypical parkinsonism (Aerts et al. J. Neurol. 2015). We also previously reported a wider step-width with more advanced PD (Sharma et al., Parkinsonism Relat. Disord. 2019).

Methods: Participants with PD and age matched controls performed a tandem walk, one-length of a 20-foot instrumented gait mat (Protokinetics), approximately every 6 months. Data was collected and analyzed using PKMAS software. Participants completing at least 30 months of assessments were analyzed (PD=20, controls=20). The annual rate of change in the means and variability of tandem gait variables (step-length, step-width, step-time and stride-velocity) were calculated. A student’s t-test was used for group comparisons.

Results: The mean age at enrollment (PD: 65.9 ± 5.6, controls: 63.2 ± 7.5 years), and mean duration of follow-up (PD: 3.5 ± 0.8, controls: 4.0 ± 0.9 years) was comparable in both groups. At enrollment, PD participants had a mean disease duration of 6.3 ± 5.0 years, Hoehn & Yahr staging score of 1.7 ± 0.5, and motor and total Unified Parkinson’s Disease Rating Scale (UPDRS) scores of 11.9 ± 5.3 and 20.2 ± 7.2 respectively. None of the PD participants reported freezing of gait. Compared to controls, there was a higher rate of increase in mean step-width (mean difference = 8.7 ± 3.9 percent/year, 90%CI: 2.1-15.2, p=0.03), and a higher rate of decrease in step-width variability (mean difference = 8.5 ± 3.5 percent/year, 90%CI: 2.6-14.5, p=0.02) in PD participants. While there were trends towards higher rate of increase in mean stride-velocity in PD compared to controls (mean difference = 3.1 ± 1.9 percent/year, 90%CI: -0.2-6.3, p=0.12), the rate of change in mean step-length (mean difference = 0.4 ± 0.6 percent/year, 90%CI: -0.7-1.4, p=0.55) and mean step-time (mean difference = 2.4 ± 2.1 percent/year, 90%CI: -1.1-5.9, p=0.26) were similar between groups. The annual rate of change in variability in step-length, step-time and stride-velocity was similar between the groups.

Conclusions: Tandem gait decline in Parkinson’s disease leads to wider step-width with decreased step-width variability over time. This could suggest greater involvement of cerebellar pathways as the disease progresses.

172. Off-Time and Sleep in Patients with Parkinson’s Disease and Motor Fluctuations
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Background: Opicapone is approved as a once-daily adjunctive treatment to levodopa/carbidopa (LD/CD) in patients with Parkinson’s disease (PD) who experience OFF-episodes. OFF-episodes can contribute to sleep impairment, a common but poorly addressed problem in patients with PD. Data from two Phase 3 studies of opicapone (BIPARK-1, BIPARK-2) were pooled and analyzed post hoc to explore OFF-time and sleep in patients.

Methods: Study participants received 14-15 weeks of once-daily opicapone, entacapone, or placebo added to their current LD/CD regimen. Baseline data from 24-hour patient PD diaries were analyzed to assess the following OFF-time outcomes: OFF before sleep onset (OBS); OFF after sleep onset (“nighttime” OFF [NTO]); early morning OFF (EMO) after waking up. Sleep metrics included: total sleep time; duration of longest uninterrupted sleep period; number of awakenings after sleep onset (including waking up in OFF); and percentage of sleep time spent awake. Data were analyzed descriptively; mean values are presented with standard deviations.

Results: The overall pooled study population included 1010 participants. At baseline, 34.4% (332/964) of participants had OBS (mean OBS duration: 1.8±1.2 hours). After sleep onset, 16.4% (158/964) woke up at least once for any reason; of these, 81.0% (128/158) woke up in an OFF-state (mean NTO duration: 1.0±0.5 hours). 89.4% (898/1005) of participants had EMO at baseline (mean EMO duration: 1.5±0.9 hours). Mean total sleep time was 7.6±1.5 hours (n=964). Mean duration of longest uninterrupted sleep was 7.2±1.9 hours, and on average, participants with sleep interruptions awoke 1.3±0.7 times. The mean percent of sleep time spent awake for any reason was 15.8±10.5%; mean percent of sleep time spent awake in an OFF-state was 15.4±9.6%.

Conclusions: These results characterize OFF-time and sleep in a large cohort of patients with PD and motor fluctuations, with an aim to better understand the potential impact of OFF-time on sleep. Key findings include the high percentages of study participants who experienced OFF-time before sleep, awoke in an OFF-state at night after falling asleep, or awoke in the morning in an OFF-state. Improving OFF-periods before, during, and after nighttime sleep may be an important avenue for better sleep in patients with PD, which in turn may have positive effects on daytime motor performance and quality of life.

173. Roles of Mitochondria-Lysosome Contact
Regulation and Function in Neurodegenerative Disease
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Multiple neurodegenerative diseases including Parkinson’s disease have been genetically and functionally linked to defects in mitochondria and lysosomes, suggesting that proper regulation of these two organelles is critical for maintaining neuronal homeostasis. Inter-organelle contact sites between mitochondria and lysosomes have been shown to form and tether together before undergoing subsequent untethering events. However, the precise roles and regulation of mitochondria-lysosome contact sites are not fully understood. Moreover, identifying the functions of this pathway may provide significant insights into the pathogenesis of multiple neurodegenerative diseases. Using advanced imaging live cell confocal microscopy techniques, we have examined how mitochondria-lysosome contact sites are dynamically regulated and their roles in regulating mitochondrial and lysosomal functions. Mitochondria-lysosome contacts mediate the bidirectional regulation of both mitochondrial and lysosomal network dynamics, and are further regulated by multiple proteins on both organelles. Furthermore, mitochondria-lysosome contact regulation and functions are disrupted across several neurodegenerative diseases. These findings further support a key role for this pathway in regulating neuronal homeostasis and in potentially driving the etiology of multiple neurodegenerative diseases including Parkinson’s disease which are associated with mitochondrial and/or lysosomal dysfunction.

174. Generalized Myoclonus in a COVID-19 Patient
Case Report
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Objective: To describe a case of a new onset generalized myoclonus in a patient with Covid-19 infection.

Background: Covid-19 infection has been associated with several neurological manifestations and complications, from anosmia and headache to encephalopathy and stroke. Some cases of generalized myoclonus have been reported. We present here a new case that supports this association.

Method: Case report and review of the literature.

Results: 73-year-old man with history of hypertension presented with sub-acute worsening generalized multifocal myoclonic jerks in the setting of one week history of Covid-19 infection with mild flu-like symptoms. Myoclonus was characterized by very frequent multifocal asymmetric jerks presenting in all four limbs and face, affecting patient’s speech and all his voluntarily movements. It worsens by movements and auditory and tactile stimuli with exaggeration in startle response. Rest of neurologic exam was unremarkable including normal mental status and cognitive function. Full work up of toxic, metabolic, infectious, autoimmune, and structural causes, including MRI, was noncontributory. EEG was not performed due to limitations in context of Covid-19 infection. However, there were no significant improvement with IV Benzodiazepine, and epileptic myoclonus was thought to be unlikely. Trial of pulse steroids was also unsuccessful. Intravenous (IV) levetiracetam lead to improvement then resolution of the myoclonus after up titration. Patient’s hospitalization was complicated with worsening of respiratory status and he was intubated briefly for few days after ten days of admission. Patient was eventually extubated and discharged to LTAC with complete resolution of his myoclonus along with normal neurologic exam.

Discussion: Several cases of generalized myoclonus have been reported in Covid-19 patients. Previously described
cases exhibit features supporting brainstem myoclonus origin, as in our patient. Starting time is closely related to the infection, and a para or post infectious auto-immune response is hypothesized, though a direct trans-neuronal spread of the virus through the olfactory bulb to the brainstem is also a possibility with some publications supporting this physiopathology. More research is needed.

**Conclusion:** Our case along with previously described cases suggest generalized brainstem myoclonus as a possible complication of SARS CoV-2 infection. A para or post infectious auto-immune mechanism is thought more likely, though a trans-neuronal spread is also possible. This association warrants further evaluation to clarify the underlying pathophysiological mechanism and to govern optimal treatment.

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**175. Unusual Brain Findings in Fragile X Associated Tremor/Ataxia Syndrome**

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**Introduction:** Fragile X-associated tremor ataxia syndrome (FXTAS) is an X-linked disorder due to FMR1 gene premutation which corresponds to a 55 to 200 CGG repeat expansion (1). FXTAS mostly occurs after 50 years of age in men and mainly consists of cerebellar ataxia and intentional tremor (1). MRI mostly demonstrates fluid attenuated inversion recovery (FLAIR) middle cerebellar peduncle (MCP) lesions (2). In the absence of known family history, this diagnosis continues to be a diagnostic challenge due to the rarity of the condition and multiple mimics. We present a case of tremor and ataxia in a 70 year old man with no significant family history and unusual brain MRI findings, who was eventually diagnosed with FXTAS.

**Case Description:** 70-year-old man with no significant past medical history or family history presented with shaking in upper extremities for 5 years. He reports difficulty using tools, holding a cup and using utensils. He also complains of balance impairment for three years which leads to recurrent falls. Shaking and balance impairment are gradual in onset and progression. Exam was notable for mild distal left upper extremity postural tremor, mild-moderate distal bilateral upper extremities action tremor and mild head tremor. Resting tremor, dystonia, rigidity and bradykinesia were not noted. Mild ataxia in the left upper extremity and bilateral lower extremities and has gait ataxia. MR head revealed non-enhancing T2 hyperintensities of bilateral dentate nuclei and anterior corpus callosum. Mild atrophy of corpus callosum and global cerebral atrophy were also noted. Genetic testing revealed 89 repeats of the FMR1 CGG repeat consistent with a premutation and confirming a diagnosis of FXTAS.

**Discussion:** Our case is unique and interesting because of no known family history of FXTAS or fragile X syndrome and less common brain imaging findings noted in FXTAS. MCP hyperintensities is the frequent brain imaging finding in FXTAS (2) but our patient’s imaging reveals lesions in anterior corpus callosum and dentate nucleus. Our case is an example to re-emphasize that FXTAS should also be considered when tremor exists with MCP hyperintensities even in the absence of family history of FXS. Unfortunately, there is no curative treatment for FXTAS and treatment focuses on symptom management. However, early diagnosis can benefit patients by guiding medical management and introducing genetic counseling.


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**176. Genotype at Parkinson’s Disease Risk SNPs Associated with Lysosomal Protein Concentrations in CSF**

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**Objective:** To determine if variation at Parkinson’s disease (PD) genetic risk loci is associated with concentrations of lysosomal proteins in CSF of PD patients.

**Background:** Lysosomes play an important role in PD pathogenesis and degrade α-synuclein, the neuropathological hallmark of PD, through the lysosomal-degradation pathway. Lysosomal failure also causes α-synuclein aggregation in cell models. Furthermore, lysosomes exhibit disrupted membrane permeability and degradative function prior to brain dopaminergic cell death. Large genome-wide association studies have identified genetic loci associated with PD risk. However, the effect of variation at PD risk genetic loci on lysosomal protein concentrations is unknown. Here we evaluated whether genotypic variation at PD risk-associated single nucleotide polymorphisms (SNP) associated with concentrations of a panel of lysosomal proteins in cerebrospinal fluid (CSF) from people with PD.

**Methods:** Blood and CSF was obtained from 176 people with PD at the University of Pennsylvania. DNA was isolated from blood and genotype was determined using the NeuroX or Illumina Global Screening Arrays for 19 SNPs selected based on (1) strong association with PD, (2) likely effects on mRNA expression of one or more genes, and (3) prior experimental evidence of roles in PD progression. The concentrations of 17 lysosomal proteins represented by 45 individual peptides were analyzed using parallel reaction monitoring mass spectrometry. Linear regression models were used to determine the association between additively coded SNP genotype and CSF protein concentration with covariates of age at sample collection, plate, and sex.

**Results:** 124 male (70.4%) and 52 (29.5%) female patients with PD were included in the study. The mean age of participants at time of sample collection was 67.6 years (SD: 8.1), and the median disease duration was 8.0 years (IQR: 4-11). PD-risk genotype at SNP rs7910668 (intergenic near ITGA8) was associated with a lower concentration of cathepsin B in CSF, and PD-risk genotype at rs126575663 (CAMLG missense) was associated with elevated levels of cathepsin F, cathepsin L, beta-hexosaminidase, and tripeptidyl-peptidase I in CSF.
177. SHBG, and Possibly Other Sex Hormones, Are Associated with the Risk for Parkinson’s Disease: A Mendelian Randomization Approach
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Objective: To assess the association between sex steroid hormones (Sex Hormone Binding Globulin (SHBG), Testosterone, Estradiol, DHEAS) with Parkinson’s disease (PD).

Background: Sex hormones may protect dopaminergic neurons, possibly preventing or delaying the onset of Parkinson’s disease (PD). However, studies of PD based on reproductive characteristics have been inconclusive.

Methods: We performed inverse-variance weighting (IVW) MR analysis using external GWAS summary data to estimate the effects of genetic variants on measured sex hormone levels, stratified by sex. The associations between genetic variants and PD were estimated in two population-based studies (PASIDA, Denmark, and PEG, USA) that enrolled 1,737 females (825 PD, 912 controls), and 2,430 males (1,218 PD, 1,212 controls) of European ancestry. We included independent variants (linkage disequilibrium R²>0.1) and a P-value of 5x10⁻⁸ in the GWAS for sex hormones. Sensitivity analyses included using alternate MR techniques and varying P-value thresholds except with MR-Egger. Among females, per 10 pmol/L increase in estimated SHBG concentration PD risk increased by 19% (OR: 1.19; 95%CI: 1.10 to 1.30, P: 6.7 x 10⁻⁵). Results were consistent using a weighted median MR analysis and also with varying P-value thresholds.

Results: Among females, per 10 pmol/L increase in estimated SHBG concentration PD risk increased by 19% (OR: 1.19; 95%CI: 1.10 to 1.30, P: 6.7 x 10⁻⁵). Results were consistent using a weighted median MR analysis and also with varying P-value thresholds except with MR-Egger. Among the other sex hormones, there is some indication that an increase in sex hormone concentration is associated with a decrease in PD risk, however, these findings were not statistically significant in our preliminary findings.

Conclusions: Higher estimated SHBG concentrations were associated with an increased risk of PD among women. Among the other sex hormones there is an indication for a protective effect on PD. Unfortunately, our findings for testosterone, estradiol and DHEAS might be limited due to weak instrument bias. Our preliminary findings indicate that sex hormones may influence PD risk, further supporting the hypothesis that sex hormones may be neuroprotective.

178. Discriminating Alpha-Synuclein Strains and Sub-Strains in Synucleinopathies
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Background: Synucleinopathies are a diverse group of neurodegenerative diseases characterized by misfolding aggregation and accumulation of misfolded alpha-synuclein (αSyn) in neurons or glial cells, which include Parkinson’s disease (PD) multiple system atrophy (MSA) and dementia with Lewy bodies (DLB). Although they share the same pathological protein, different synucleinopathies present distinct clinical and pathological phenotypes. Clinically, it is very challenging to differentiate particularly PD from MSA, especially at the early stage of the disease. Accumulating evidence suggests that αSyn aggregates associated to different synucleinopathies adopt distinct conformational strains. Our results also suggest the existence of distinct αSyn strains with the same disease (here called sub-strains). αSyn strains and sub-strains faithfully self-propagate and spread between cells. We propose that discrimination of these conformational αSyn strains and sub-strains hold promise for differential diagnosis and understanding the relationship between structures of αSyn strains and sub-strains and their pathologic functions.

Methods: We used protein misfolding cyclic amplification (PMCA) assay to detect αSyn oligomers in (cerebrospinal fluid) CSF referred to as αSyn-PMCA, which exploits the functional properties of these oligomers to seed soluble monomers used as substrates thus facilitating their detection. Further, we used a combination of biochemical, structural and biological methods to characterize the amplified products of αSyn-PMCA.

Results: αSyn-PMCA assay could readily discriminate between CSF samples from PD and MSA patients with high sensitivity. Moreover, the characteristics of amplified aggregates from the CSF of PD patients differed from aggregates amplified from CSF of MSA patients. We also found that the properties of aggregates that were amplified from CSF samples were similar to those amplified from the brain samples. Most importantly, we were able to subgroup PD and MSA patients based on αSyn-PMCA parameters and characteristics of amplified aggregates from CSF samples.

Conclusions: The findings obtained here will not only help to understand the relationship between the structure of αSyn strains and sub-strains and their pathologic function but may also help to discriminate diverse synucleinopathies, which will help in patients’ stratification, target enrollment for clinical trial and personalized treatment.

179. Pineal Tumor Precipitating Parkinson’s
Presentation: Case Report
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Objective: Describe an atypical presentation and resolution of Parkinsonism in the context of a pineal tumor.
Background: The clinical presentation of pineal tumors is typically associated with the size and location of the lesion. Identification following puberty is more common, but small lesions may be asymptomatic and escape detection during the lifetime of the individual. Lesions greater than 1cm in size, although rare, are typically associated with headache, symptoms of increased intracranial pressure, gaze irregularities, motor weakness or sensory change. Parkinsonian symptoms of tremor, rigidity and/or bradykinesia have rarely been reported in patients with pineal tumors presenting in the second through fourth decades. This Parkinsonian presentation raises suspicion of an atypical etiology, and leads to a more comprehensive workup. In contrast, Parkinson’s disease, with the identical triad of symptoms is more commonly associated with a presentation later in life, and therefore, individuals are not routinely suspected or frequently evaluated for other etiologies.

Case Presentation: A 59 year old right handed woman initially presented with a gradual onset of right-handed tremor at rest, which progressed with bradykinesia, poor balance and festinating gait, in December, 1980. This was associated with double vision on lateral gaze. CT of the head revealed a 2cm mass in the region of the pineal gland region of the posterior fossa, and hydrocephalus affecting the lateral ventricles. Since she had a prior history of pulmonary tuberculosis in 1943, with a recurrence in the left hip in 1960, the possibility of another recurrence as a tuberculoma was considered. Neither excision nor biopsy was considered feasible at that time and she received a right ventriculoperitoneal shunt. Residual double vision was addressed with prism glasses. She became and remained asymptomatic over the next 18 years, until the lesion further expanded, leading to death. Brain autopsy revealed a pineal gland neoplasm of intermediate differentiation (mixed pineocytoma/pineoblastoma) which infiltrated the midbrain down to the lateral third of the left substantia nigra and pontine tegmentum.

Conclusions: Although a common neurodegenerative diagnosis in older people, not all Parkinsonism is due to the same etiology. In this case, rapid reversal of symptoms occurred following early identification of a mass lesion, and treatment of associated hydrocephalus. It is believed that the initial pineocytoma was slow growing and transformed over time, ultimately causing death at age 77.

180. A Subtype-Specific Ablation Model of Parkinson’s Disease
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Parkinson’s disease (PD) is the second most common neurodegenerative disorder, causing severe disabilities in both motor and non-motor domains. PD symptoms are believed to be caused by the loss of dopamine (DA) neurons located in the substantia nigra pars compacta (SNC). It has long been known that DA neurons located ventrally within the SNC are more vulnerable to degeneration than those located dorsally, in both human PD patients and several mouse models. This phenomenon is likely a reflection of the molecular heterogeneity within midbrain DA neurons and their distinct properties. Despite this knowledge, the contributions of individual DA subpopulations to overall behavioral phenotypes and their roles in PD are not well established. Here, we investigate the subtype-specific contributions of Sox6+ DA neurons to motor deficits by utilizing intersectional genetic strategies to selectively ablate these neurons in mice. By ablating this individual DA subtype in isolation, we are able to observe its distinct functional role in motor behaviors, and thereby speculate its role in disease states. Through this work, we hope to further disentangle the functions and dysfunction of molecularly-defined DA neuron subtypes.
182. The Chicago Movement Coalition: Closing the Gap in Parkinson’s Disease

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Objective: To establish a community-partnered intervention for increasing knowledge of Parkinson’s Disease (PD) in underrepresented communities of the Chicagoland area. Here, we describe the development, structure, and preliminary outcomes of this program.

Background: Past studies suggest that underrepresented minorities are more likely to have delays in PD diagnosis compared to Caucasians and once diagnosed are less likely to receive specialized care. Inequitable care and delayed diagnosis lead to decreased quality of life and increased disability. Barriers to timely diagnosis and optimized treatment are multifaceted but include insufficient knowledge of PD in the community. Past research has described the use of community-based participatory research to increase sustainability and effectiveness of interventions and resources in underserved communities. We use this approach to develop an intervention to address disparities in PD education and awareness.

Design/Methods: We identified two Chicago communities with large underrepresented minority and low-income populations. The Chicago Movement Coalition (CMC), a community-academic partnership, was formed with advisory board leadership including people with PD, caregivers, and community leaders from the identified communities. Each of the two communities were paired with a local academic medical institution and movement disorders specialist. Two community focus groups were held to identify needs and inform the community-based intervention. Using the combined input from the CMC advisory council leadership and focus groups, four educational workshops were planned and executed to increase knowledge of PD symptoms, treatment, and available resources. Workshops included an informational presentation followed by small groups led by people with PD and their caregivers from the CMC. RESULTS: There were 162 participants across four community workshops, of which 97 completed pre- and post-workshops surveys. Ninety-five participants (98%) were satisfied or somewhat satisfied with the workshop structure and content. Ninety-one participants (94%) noted that they felt more comfortable with understanding the signs, symptoms, and treatment of PD with 81 participants (84%) reporting an increased knowledge of local PD resources after the workshop.

Conclusion: The CMC is a novel community-academic partnership established to address known inequities in PD. The coalition experience can be used to inform and structure future community-engaged education and research initiatives aiming to increase knowledge and decrease health and access disparities in PD across the country. The CMC has since expanded to include a third underserved Chicago community. Ongoing research is assessing how the CMC and its community-partnered events affect perceptions and attitudes toward clinical trials in underrepresented communities.

183. Deep Learning System for Labeling Neurology Text for Predictive Medicine

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Introduction: Labeling large neurology datasets for training Deep Learning (DL) systems is often prohibitive and expensive. Furthermore, using computational tools in a clinical setting requires an interpretable interface for safety. This study proposes a novel approach (ReGAL) that can interactively train labeling-rule-based DL systems that can classify clinical and scientific text in neurology fields. Such interpretable, automated labeling is critical for improving personalized medicine using unstructured text from medical records, articles, and clinical trials.

Methods: ReGAL is a DL framework that jointly generates declarative rules for discriminating textual classes and uses them in a classification model. ReGAL’s capacity to discriminate between similar neurodegenerative diseases with overlapping etiology is analyzed using a dataset of 30,000 PubMed abstracts on topics like Alzheimer’s Disease (AD), Huntington Disease (HD), and Parkinson’s Disease (PD). The ReGAL generated labeling rules are evaluated qualitatively by comparing them to those proposed by a subject matter expert. The performance improvement of a supervised classification model that incorporates the new rules is quantified using ground truth labels of each abstract to assess rule translation.

Results: ReGAL identified expressive keyword rules in the abstracts that can immediately help distinguish between the scientific text of the three diseases. For example, obvious top performing rules were “gait” and “kinesia” to discriminate PD; “older”, and “MCI” as more related to AD; and “HTT” and “protein” for HD. These example keywords represent the most basic discriminative characteristic aspects of each disease. Incorporating newly identified keyword rules into a noisy label classifier module resulted in an increase of 11.3% in the overall accuracy of the model compared to the label classifier trained using only the seed rules (41.2% to 52.5%).

Conclusion: The auto-generated labeling rules represent discriminative aspects of each disease as evidenced by the identification of words that relate to the characteristic movement in PD, the genetic expression of HTT in HD, and the later
onset of the disease for AD. Furthermore, due to the limited requirement of labeled data and the use of an interactive training workflow for the model, neurologists can use ReGAL to intuitively train a well-performing classifier for neurology text labeling without requiring a thorough understanding of DL or a major manual effort to create a suitable dataset.

184. Cardiovascular Safety and Pharmacokinetics of ATH434, a Novel Small Molecule Inhibitor of α-Synuclein Aggregation, in Adults and Older Adults

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Objective: Evaluate the cardiovascular safety, tolerability, and pharmacokinetics of ATH434

Background: ATH434 is a novel, brain penetrant small molecule inhibitor of α-synuclein aggregation. In transgenic mouse models of Parkinson disease (PD;A53T) and Multiple System Atrophy (MSA;PLP- α-Syn), ATH434 reduced α-synuclein aggregation and markers of oxidative stress, preserved neurons, and improved motor function. ATH434 reduced glial cell inclusions (PLP-α-Syn). ATH434 is thought to act by redistributing labile iron across neuronal membranes. The affinity of ATH434 for iron is lower than for iron trafficking proteins, such as transferrin and ferritin.

Design/Methods: In this randomized, double-blind, placebo-controlled study, adults received single oral doses of ATH434 (8/cohort) at 50, 100, 300 or 600 mg or 8 days dosing (10/cohort) at 100, 200 or 250 mg bid. Older adults (≥65 years) received 250 mg bid for 8 days. Serial blood samples were collected post-dose and CSF was sampled at 1.5 or 11 hours post-dose at 200-250 mg bid at steady state. Safety was assessed with postorthostatic vital signs, physical examination, adverse events (AEs), laboratory tests and 12-lead ECGs. A concentration-effect analysis was performed to estimate the effect of ATH434 on the QT interval using plasma levels and ECGs extracted from continuous Holter monitoring.

Results: ATH434 was readily absorbed with a Tmax of 0.5-2 hours and demonstrated dose-dependent pharmacokinetics after single and multiple doses. Mean elimination half-life up to 9.3 hours was observed. CSF concentrations of ATH434 correlated with free plasma concentrations ($r^2$=0.72). AE rates were similar for ATH434 and placebo. All AEs were mild to moderate in severity. There were no serious AEs or AEs leading to discontinuation. The AE profile was similar for adults and older adults. There was no evidence of drug-induced orthostasis after single- or repeated-dose administration and no clinically significant vital sign, laboratory, or 12-lead ECG findings. A linear mixed-effects model predicted the placebo-corrected, baseline-adjusted change in QTcF to be <2 ms (upper bound of 90%CI <4 ms) at the anticipated steady state Cmax.

Conclusions: CSF concentrations of ATH434 strongly correlated plasma levels and exceeded those associated with efficacy in animal models of PD and MSA. ATH434 was safe at all doses and did not promote orthostasis or QT prolongation. ATH434 is an orally bioavailable, brain penetrant, small molecule inhibitor of α-synuclein aggregation with potential to treat PD and MSA.

185. Electrophysiological Study of New Onset Tremor After SARS-CoV-2 Infection

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Background: In addition to a respiratory syndrome, SARS-CoV-2 infection, has been associated with neurological manifestations that can involve central, peripheral, and musculo-skeletal systems. Literature also includes cases when symptomatology can persist for weeks to months after the acute infection

Case: A 63-year-old, left-handed woman with history of obesity, Lyme disease, lumbar laminectomy and GIST resection was diagnosed with SARS-CoV-2 infection following a 2-week history of mild respiratory symptoms and low-grade fever. While these symptoms resolved, she developed alopecia, pruritic rash and, mild cognitive changes. Two months later, the patient developed an internal pulsating sensation in her chest that generalized to her entire body. Cardiac and endocrinological were etiologies excluded; empirical treatment with metoprolol was not beneficial. Subsequently, the patient reported intermittent involuntary bilateral hand tremor which was noticeable with action (pouring). We evaluated the patient 8 months after the tremor onset. Exam revealed impaired delayed recall, moderate microsmia, decreased sensation along the posterior aspect of left thigh and dorsum of left foot, mild decreased arm swing on the left and bilateral hand tremor. The Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS) score was 5 (1 for Activities of Daily Living, 4 for performance).

Results: EMG polygraphy setup included 4-channel surface EMG and 2-channel accelerometry. Electrodes were placed in a bipolar montage bilaterally over wrist extensors and flexors. Accelerometers were placed at the back of the hands. Recording conditions were 30 seconds each and involved rest, posture (outstretched-hands and arms supported) and posture plus the addition of 1, 1.5, and 2-pound weights bilaterally.
• Rest: bilateral 4-4.5 Hz component, without EMG correlate.
• Posture: bilateral 6 Hz component, with EMG correlate on the right side but not on the left.
• Weight loading: o 1-pound: bilateral, wide 3.5-5 Hz peak, without EMG correlate. o 1.5-pound: no clear peaks. o 2-pounds: 4 Hz peak on the right accelerometer, with possible EMG correlate. On the left, there were no peaks.
• Holding cup: o Right: 6 Hz component with EMG correlate. Left: there were no clear peaks.
• Other findings: 8-10 Hz peak on the EMGs that is present during posture (hand/finger). There was no accelerometer correlate at this frequency.

Discussion: The differential diagnoses of isolated tremor include enhanced physiologic tremor, isolated focal tremors and orthostatic tremors. Based on this electrophysiological study, the change in frequency with weight loading are indicative of an enhanced physiologic tremor.
186. Low-Frequency and Rare Variants in Parkinsonism-Related Genes Are Differentially Associated with Phenotypic Characteristics of Parkinson’s Disease at Presentation
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Introduction: Common genetic variants at more than 90 loci have been implicated as risk factors for Parkinson’s disease (PD) from case-control genome-wide association studies (GWAS) and pathogenic or likely pathogenic variants have been identified from studies of familial forms of parkinsonism (MDSgene.org). We asked whether variants at these loci uniformly or differentially contribute to the clinical phenotype of PD.

Methods: We used structured clinical documentation tools within the electronic medical record to obtain a standardized and detailed clinical phenotypic characterization at the point of care in a community-based PD patient cohort (N = 856). We obtained information on age at onset, disease duration, Unified Parkinson’s Disease Rating Scale I–VI scores, cognitive status, initial and presenting motor and non-motor symptoms, complications of levodopa therapy, co-morbidities and family history of neurological disease with one or more than one affected family members. We then used gene-level tests (SKAT, sequence kernel association tests) to assess whether low-frequency (<5% minor allele frequency) or rare (<1% minor allele frequency) variants that may affect gene expression or protein function of parkinsonism-related genes are associated with phenotypic characteristics and test scores at presentation in our cohort, using as covariates sex, age-at-onset, years-from-diagnosis, and, for cognitive measures, education-years. A Bonferroni-adjusted p<0.05 was considered significant.

Results: We find that low frequency and rare variants in parkinsonism-related genes are differentially associated with individual phenotypic characteristics at presentation. For example, rare-variant gene-level associations that retain significance after Bonferroni adjustment for the number of genes tested include GPNMG with the presence of bradykinesia at baseline [Bonferroni adjusted p = 1.2×10^-10], SCAF11 (p = 0.047), CHD9 (p = 0.047), and FAM49B (p = 0.0025) with bradykinesia as an initial motor symptom, LRRK2 with a clinical history of essential tremor (p = 0.0046), NUCKSI with scores on the UPDRS-III (p = 0.041) and UPDRS-V (H&Y stage) (p = 0.022), and TOX3 (p = 8.4×10^-5) and SULT1C2 (p = 6.0×10^-5) with UPDRS IV-total scores. Interestingly given the size of our cohort, some associations approach or exceed genome-wide significance. Protein-protein interaction network analysis of genes with significant associations suggest how this genetic variation could impact network function.

Conclusion: Low-frequency and rare variants in parkinsonism-related genes do not uniformly contribute to disease presentation. These findings support the hypothesis that genetic background has a significant impact on the neurodegenerative process that leads to different disease manifestations.

187. A Diagnostic Dilemma: Sialorrhea and Oromandibular Dystonia as a First Manifestation of Wilson’s Disease
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Background: Wilson’s disease (WD) is an autosomal recessive inherited disorder that leads to an impaired mechanism of copper excretion. Copper accumulation manifests as a combination of neurological, hepatic and psychiatric symptoms. Initial manifestations of WD in children are primarily of hepatic origin. Here we present a rare initial neurological presentation of WD resulting in a delayed diagnosis.

Case: A 14-year-old girl referred to pediatric neurology clinic with 3-year progressive history of drooling, articulation difficulty and inability to close her mouth. These symptoms were previously assessed by dentists and speech pathologist. Past medical and family history were unremarkable. Neurological examination revealed impaired horizontal saccades, spastic dysthria, constant sialorrhea and mild oromandibular dystonia. She had dysdiadochokinesia, dysmetria, dysrhythmia on the non-dominant upper extremity. Reflexes were normal with subtle antalgic gait. Her MRI-brain showed T2/Flair hyperintensities in bilateral putamen, caudate, substantia nigra, thalamus and pons. Her ophthalmological exam revealed Kayser-Fleischer rings. Cardiac, gastroenterological and psychiatric evaluations were normal. She screened negative for behavioral changes and deterioration of school performance. Laboratory investigations indicated a low ceruloplasmin level (0.13g/L) and elevated 24-hr urine copper (798.6 ug/d) confirming the diagnosis of WD. Patient was started on copper chelating agent.

Discussion: Neurological symptoms associated with WD are categorized as a movement disorder. Patients present with a myriad of symptoms including parkinsonism, dystonia, chorea and attherosclerosis. In children, isolated neurological manifestation of WD is rare and dystonia has been described as the most common neurological symptom. For any complaint of speech in children, a screening for WD is warranted. Cranial imaging in WD have signal abnormalities frequently in...
putamen, caudate nucleus followed by thalamus and pons as seen in this patient. Delayed treatment has been correlated with worsening brain imaging in patients.

**Conclusion:** This case broadens the initial neurological manifestation of WD in children in absence of psychiatric and hepatic involvement. Neurological manifestation associated with WD in conjunction with brain imaging findings can aid in early diagnosis and treatment initiation.


188. Extracellular Vesicle Biomarker Discovery for Dystonia Using Proteomics

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**Background:** Molecular biomarkers for most forms of dystonia have not yet been discovered. If identified, dystonia biomarkers could be used to assist diagnosis, predict disease course, stratify patients with shared etiologies, or monitor target engagement in clinical trials. Extracellular vesicles (EVs), which carry biomolecular cargo reflecting the physiological state of their parent cell, circulate in peripheral biofluids and are being studied as potential biomarkers in numerous neurological conditions. The Integrated Stress Response (ISR), a pathway regulating protein synthesis via phospho-eIF2α signaling, is impaired in DYT-TOR1A dystonia and other inherited and sporadic dystonias. We therefore hypothesized that EV-associated proteins derived from DYT1 samples would exhibit genotype- and ISR-dependent changes.

**Methods:** As proof-of-principle, we tested this hypothesis *in vitro* using murine embryonic fibroblasts (MEF) derived from a DYT1 knockout mouse model of dystonia (Tor1a+ΔCAGΔ). Wild-type and Tor1a+ΔCAGΔ cells were treated with phospho-eIF2α-modulating compounds and ritonavir, a candidate therapeutic drug that acts through ISR potentiation. EVs were then isolated by ultracentrifugation of the cell culture media and their protein contents were analyzed using unbiased mass spectrometry-based proteomics.

**Results:** We found that EV protein composition was substantially modified by DYT1 genotype. Strikingly, nearly 95% of proteins with significant genotype effects were also significantly modulated by ritonavir in the corrective direction. Over half of ritonavir-corrected EV proteins were also modulated by phospho-eIF2α signaling tool compounds in consistent directions.

**Conclusions:** Our results demonstrate that EVs derived from Tor1a+ΔCAGΔ MEF cultures contain differential protein cargo compared to EVs from wild-type control cells. We thus establish proof-of-principle that EVs have potential in dystonia for unbiased, high-throughput biomarker discovery. Our results further demonstrate that both DYT1 disease state and ISR signaling alter EV composition, and ritonavir treatment rescues these changes on a proteome-wide scale. Future research is needed to determine whether these specific EV changes are present in other preclinical models and clinical human biofluids.

189. Impact of COVID-19 Pandemic in Patients with Huntington’s Disease

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**Introduction:** The Covid-19 pandemic has significant health, social, and economic consequences internationally. Huntington’s disease (HD) is a rare, fully penetrant neurodegenerative disease, caused by a dominantly inherited CAG trinucleotide repeat expansion in the huntingtin gene on chromosome 4. It is a complex neuropsychiatric disease characterized by cognitive, motor, and psychiatric comorbidity. In this group of patients, COVID-19 may have serious direct implications and indirect consequences resulting from restrictive measures. The aim of our study was to examine the impact of the COVID-19 pandemic on a group of HD patients.

**Methods:** Between January and March 2021, we administered a telephone-based questionnaire interview to HD patients attending our dedicated clinic. Patients or caregivers were interviewed with a semi-structured questionnaire. The questionnaire was composed of two section. The first was dedicated to all patients and included: demographic and clinical data, development of new signs or symptoms, type of disability, psychiatric therapy, sleep disorders, discontinuation of physiotherapy. The second section was performed in HD patients with positive nasopharyngeal swab for Covid-19. It included information about infection related symptoms, need for hospitalization, access to emergency care, neurological status after Covid-19 disease resolution.

**Results:** We interview a total of 80 HD patients: 52.5% female, mean age 53.5 years (range 11-91), mean disease duration 8.3 years (range 1-20). Since the beginning of the pandemic, 70% of patients experienced new neurological and/or psychiatric symptoms, 27.5% changed their psychiatric therapy, 50% suffered from sleep disorders, 69.2% of subjects were forced to stop physical therapy, 71.3% skipped periodic neurological visits. Patients positive for Covid-19 nasopharyngeal swab were six (7.5%), three patients were asymptomatic, two had mild symptoms (fever, diarrhea, oxygen desaturation). One patient was hospitalized and experienced severe Delirium followed by post-covid encephalopathy.

**Conclusion:** This is the first study investigating the impact of Covid-19 on HD patients. HD patients showed similar infection rates as the general population. Non-infected HD patients suffered from limited access to HD center, limited availability of physical therapy, and showed an increased burden of psychiatric comorbidity.
Mutations in the gene glucosidase, beta acid 1 (GBA) are the strongest genetic risk factor for Parkinson’s Disease (PD), and are associated with a more aggressive decline in cognitive and motor symptoms. To date, most studies examining the role of GBA in neurodegeneration have been focused on neurons. However, recent data suggest that astrocytes may have a significant role in the uptake and degradation of extracellular proteins and extracellular vesicles (EVs). Our work using a Drosophila GBA deficient model manifests neurodegeneration, accelerated protein aggregation, and dysregulation of EVs that may promote accelerated spread of protein aggregates. We hypothesize that GBA may have a neuroprotective role in astrocytes in degrading pathogenic neuronal EVs that could seed and propagate Lewy pathology. To test this hypothesis, both astrocytes and neurons were differentiated from iPSCs generated from a PD patient carrying the pathogenic IVS2+1-G>A GBA mutation along with isogenic control wildtype GBA PD iPSCs and iPSCs from an unrelated age and sex-matched healthy control. Both cell types were confirmed with neuronal and astrocyte-specific markers via IHC, qPCR, Western Blot, and functionality via calcium uptake assays and electrophysiology. To examine astrocytic viability and uptake of neuronal-derived EVs is altered by GBA deficiency, we will isolate EVs from GBAIVS PD neurons expressing alpha-syn-GFP, a GFP-tagged human alpha-syn fusion protein, and add them to the media of GBAIVS PD, GBAWT PD or control astrocytes to examine whether EVs isolated from alpha-syn-GFP-expressing neurons are internalized by GBAIVS PD, GBAWT PD and/or control astrocytes. Internalization of exogenous neuronal exosomes containing alpha-syn-GFP will be analyzed by live-cell imaging and co-localization with markers for endolysosomal trafficking. We will also examine whether protein aggregation is induced in astrocytes using IHC markers for ubiquitinated proteins and alpha-syn. Finally, we will coculture GBAIVS PD or GBAWT PD neurons with control astrocytes, compared to GBAIVS PD or GBAWT PD neurons co-cultured with GBAIVS PD astrocytes, to test the hypothesis that GBA has a neuroprotective role in astrocytes to reduce non-cell-autonomous propagation of Lewy bodies in neurons. This work could reveal novel therapeutic strategies targeting previously unappreciated cell types to slow or halt the spread of pathogenic protein aggregates and provide the basis for preclinical studies for novel disease-modifying therapies.

Background and Objectives: Social media is being increasingly used for real-time information sharing and to improve patients’ and caregivers’ knowledge. This study aimed to analyze tweets related to COVID-19 in top Parkinson’s disease (PD) foundations and support group accounts on Twitter during the pandemic.

Methods: Top five professional Twitter accounts related to Parkinson’s disease with the highest number of followers were included in this study; Michael J. Fox Foundation (@MichaelJFoxOrg) 91128 followers (NY, USA), Parkinson’s UK (@ParkinsonsUK) with 71227 followers (UK), Parkinson’s Foundation (@ParkinsonDotOrg) with 69969 followers (FL, USA), Cure Parkinson’s (@CureParkinsonsT) 18292 followers (UK), and Parkinson Society British Columbia (@ParkinsonsBC) 2659 followers (Canada). We obtained original tweets in each professional account containing the keywords “COVID,” “COVID-19,” and the hashtags “#COVID19,” posted between Jan 1, 2020, and April 14, 2021. The data was obtained using twitter’s standard API (publicly available) and using Python tweepy library. Python Regex was used to search tweets containing the study keywords. Original tweets were extracted using pandas, numpy, and matplotlib libraries for further analysis.

Results: Parkinson’s Foundation account had the highest number of tweets related to COVID19 compared to the others (74 tweets out of total 1994 tweets), followed by Michael J. Fox Foundation (56 out of total 1407 tweets). Cure Parkinson’s account had the highest number of general tweets (total 2363), out of which 45 tweets mentioned COVID-19. Parkinson’s UK and Parkinson’s BC had 17 (out of 1185) and 15 (out of 302) tweets with “COVID” mention. Tweet contents were further classified as informative and raising awareness, the disease burden and treatments, advice seeking, and miscellaneous.

Conclusion: Social media, such as Twitter, has a critical role in the dissemination of health information for patients and caregivers via Parkinson’s Foundations and support communities. Social media content research can provide the opportunity to explore patients’ concerns, opinions, and individual experiences, globally.

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104. Investigating A Neuroprotective Role for GBA in Astrocytes
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Conclusion: Social media, such as Twitter, has a critical role in the dissemination of health information for patients and caregivers via Parkinson’s Foundations and support communities. Social media content research can provide the opportunity to explore patients’ concerns, opinions, and individual experiences, globally.

103. Satisfaction with Interdisciplinary Home Visits Among Individuals with Advanced Parkinson’s Disease and Their Caregivers
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University Medical Center, Chicago, IL, USA. 2Geriatric Medicine and Palliative Care, New York University Grossman School of Medicine, New York, NY, USA. 3VA New York Harbor Healthcare System, New York, NY, USA.

Objective: To compare satisfaction with care among people with advanced Parkinson’s Disease (PD) and their caregivers at baseline (best usual care in a tertiary referral center) and after one year of interdisciplinary home visits; to identify predictors of greater satisfaction.

Background: Patient and caregiver satisfaction are frequently used as metrics of patient-centered care; yet, satisfaction with care has only been minimally explored in PD. In cross-sectional studies in the US and Sweden, 57-59% of individuals with PD expressed high satisfaction with their medical care on study-specific scales. Using a validated assessment of client satisfaction with care, we sought to compare satisfaction with best usual PD care at baseline and after one year of quarterly home visits in individuals with advanced PD and their caregivers.

Methods: Among homebound individuals with advanced PD entering a trial of interdisciplinary home visits, we administered the Client Satisfaction Inventory-Short Form (CSI-SF, 9-item, 7-pt Likert scale survey, ranging 0 (low) to 100 (high)) at Visit 1, prompting patients and caregivers, individually, to reflect on their usual PD care at Rush University. After one year, we re-administered CSI-SF regarding home visit satisfaction. We used paired t-tests to assess differences over time and identify characteristics predicting ≥10-point improvement in satisfaction.

Results: Among patients (n = 48), CSI-SF improved from baseline mean 87.05/100 (SD 14.14) to 95.06 (SD 10.55) after one year of home visits (p = 0.002). Among caregivers (n = 47), satisfaction improved from 91.09 (SD 12.90) to 98.54 (SD 10.84) (p = 0.001). Younger age predicted ≥10-point improvement in patient CSI-SF: mean 74.80 years (SD 7.12) in 18 improvers vs. 79.96 (6.98) among <10-point improvers (n = 30), p = 0.02. Change in patient’s mobility predicted ≥10-point improvement in caregiver CSI-SF: mean improvement of 1.94 pts on PDQ-39 mobility domain (SD 17.05) among 16 ≥10-point improvers vs. mean worsening of 13.16 pts on PDQ-39 mobility (SD 26.01) among 31 <10-point improver caregivers.

Conclusions: People with advanced PD and their caregivers reported higher satisfaction with usual care than previously reported, and demonstrated even greater satisfaction with home visits. Younger patients were more likely to report significant gains in satisfaction. A marked ceiling effect was noted for all.

395. Sv2c is Required for Nicotine-mediated Rescue of Alpha-synuclein Toxicity
Sabrina Clemens, BS, Abby Olsen, MD PhD. Brigham and Women’s Hospital, Boston, MA, USA.

Objective: To develop a Drosophila model for testing gene-environment interactions in Parkinson’s disease.

Background: Parkinson’s disease (PD) is a neurodegenerative disease characterized by α-synuclein aggregation and the progressive loss of dopamine (DA) neurons in the substantia nigra. Risk of PD arises due to a combination of genetic and environmental factors, which may interact with one another, termed gene-environment (GxE) interactions. An inverse association between smoking cigarettes and risk of developing PD is well-established, but trials of nicotine as a therapeutic option for PD have yielded mixed results. A previous genome-wide GxE interaction study identified genetic variation in the synaptic-vesicle glycoprotein 2C (SV2C) locus as an important mediator of the degree to which smoking is inversely associated with PD. We sought to determine the mechanism of the smoking-SV2C interaction in a Drosophila model of PD.

Design/Methods: In this model, human α-synuclein is expressed in all neurons, and flies develop the hallmarks of PD, including motor dysfunction, loss of DA neurons, and formation of α-synuclein inclusions. We assessed the effects of increasing doses of nicotine on these parameters of neurodegeneration, in the presence or absence of SV2C knockdown.

Results: We demonstrate that α-synuclein-expressing flies treated with nicotine (the presumed active ingredient in
tobacco) have significant improvement in locomotion, in total number of brain cells and in DA neuron counts, and in α-synuclein aggregation. However, in α-synuclein-expressing flies in which Drosophila homologs of SV2C are knocked down, nicotine fails to rescue neurodegeneration and in fact further worsens motor behavior and loss of dopaminergic neurons.

**Conclusions:** This work confirms a GxE interaction between nicotine and SV2C, defines a role for this interaction in α-synuclein proteinostasis, and strengthens the idea that future clinical trials on nicotine should take genetic variation in SV2C into account. Further, this study provides proof of concept that our model can be used for mechanistic study of GxE, paving the way for investigation of additional known GxE interactions or identification of novel GxE.

396. **Clusters of Olfactory Performance Are Associated with Motor Decline in LRRK2 G2019S Variant Parkinson Disease**

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**Background:** Both idiopathic Parkinson disease (PD; IPD) and LRRK2-G2019S PD (LRRK2-PD) are associated with olfactory decline, although LRRK2-PD to a lesser degree. We previously demonstrated that olfactory scores may define subgroups of LRRK2-PD, supporting the notion of pathologic heterogeneity. We extend this work and evaluate the longitudinal course among olfactory subgroups.

**Methods:** 165 LRRK2-PD and 200 IPD from the LRRK2 Ashkenazi Jewish Consortium (Mount Sinai, Columbia University, Tel Aviv Sourasky) with follow-up for 93 LRRK2-PD and 75 IPD, had assessment of olfaction (University of Pennsylvania Smell Identification Test/UPSIT), motor function (Unified PD Rating Scale/UPDRS), and cognition (Montreal Cognitive Assessment/MoCA). Gaussian mixture models were performed on UPSIT percentile scores to determine clusters based on olfactory performance. To assess the relationship of mixture model subgroups, as well as hyposmic subgroups (defined as ≤15th percentile for age/gender, and based on new normative data from PARS/PPMI) to motor and cognitive change over time, both linear and logistic mixed effects models using PD duration as the time scale were applied respectively.

**Results:** Baseline olfactory performance was better in LRRK2-PD compared to IPD (mean UPSIT ± SD: 24.1 ± 8.8 vs 18.9 ± 7.6), with a higher mean percentile score (difference:10.3 ± 16.7) (p<0.001), and less frequent hyposmia (55.2% vs 85.5%; p<0.001). Gaussian mixture model analysis suggested three classes among LRRK2-PD: group1(mean UPSIT percentile ± SD: 4.8 ± 3.2), group2 (27.4 ± 10.0), and group3(75.0 ± 15.9). Age at onset in LRRK2-PD was earlier in the hyposmic group overall (55.0 ± 11.2 vs. 61.7 ± 9.1)(p<0.001) as well as in worst olfaction cluster compared with groups 2 and 3, (54.5 ± 11.1 vs. 61.7 ± 9.3)(p=0.012). The worst UPSIT performers had baseline increased UPDRS-III (22.6 ± 13.0 vs. 18.2 ± 10.7; p=0.029) as well as significantly faster motor deterioration than the best UPSIT performers (group 3 vs. group 1: B=0.24, SE=0.22 vs. B=0.80, SE=0.14)(rate difference=-0.56, SE=0.25)(p=0.03). However, group membership was not associated with worse cognitive decline.

**Discussion:** In this larger cohort with longitudinal analysis, we extend prior work demonstrating subgroups defined by olfaction in LRRK2-G2019S-PD, and show that the worst olfaction group has earlier age at PD onset, and more rapid motor decline. This supports a cohort that might show more rapid change in a clinical trial of LRRK2 related agents, and highlights the importance of further study in the presymptomatic subgroup of LRRK2 carriers with worse olfaction.

397. **Monogenic Hub of the Global Parkinson’s Genetics Program (GP2): The 500 Genomes Pilot Project**

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**Background:** The Global Parkinson’s Genetics Program (GP2, http://gp2.org/) is an international collaborative program that focuses on improving our understanding of the role that genetics plays in Parkinson’s disease (PD) and on making this knowledge globally available and actionable. The “Monogenic Hub” represents one of the two major arms of GP2 and aims to perform both short and long-read whole-genome sequencing (WGS) for a total of up to 10,000 PD patients starting with a 500-genomes pilot project, with the goal of identifying novel monogenic causes of PD.

**Methods:** We reached out to PD clinicians and researchers from around the globe and collected PD patients from multiplex families, or as singleton cases, when a monogenic cause was suspected. Clinical and pre-existing genetic data on
patients were obtained through online questionnaires and are further collected through the Monogenic Portal, an easy-to-use online application (https://monogenic.gp2.org). All submitted cases were evaluated and prioritized for pilot WGS based on the following criteria: number of affected family members and sample availability, pedigree structure, history of consanguinity, AAO, and availability of genetic pre-screening. Particular emphasis was placed on cases from populations underrepresented in currently available genetic studies.

**Results:** 16 research teams from 10 different countries submitted 757 PD index patients to the Monogenic Hub. We selected a total of 512 cases for our 500-genomes pilot; ~75% of them were familial cases (with up to nine affected members), and the remaining were singletons with AAO ≤ 40 years, 12 of whom were included as parent-offspring trios. The vast majority (~93%) had some negative genetic pre-screening and about 20% are from underrepresented populations.

**Conclusion:** Within the GP2 Monogenic Hub, we established a screening process and an online platform for case/family submission allowing us to perform WGS for the first 500 PD patients from 279 families with yet unknown but suspected genetic etiology. This study is expected to strongly contribute to the identification of novel monogenic causes of PD. Following the pilot project, we will focus our efforts on reaching out to a larger number of sites across the globe, in order to increase the diversity of our cohort.

398. ASN51, an Orally Bioavailable Small-Molecule O-GlcNAcase Inhibitor, Has Both Immediate and Disease-Modifying Benefits in Preclinical Models of Parkinson’s Disease and Epilepsy

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We report the development of ASN51, a potent, reversible, and substrate-competitive small molecule inhibitor of O-linked-ß-N-acetylglucosaminidase (OGA). Inhibition of OGA stabilizes a posttranslational carbohydrate modification, termed O-GlcNAcylation, on intracellular proteins by preventing its removal. O-GlcNAc has emerged as a post-translational modification of high interest in the context of neurodegenerative diseases because it is predominantly found within intrinsically disordered regions of proteins, including those that are prone to the formation of toxic intracellular aggregates. Emerging evidence is also showing that inhibition of OGA produces immediate and beneficial effects on synaptic function, in part by reducing neuronal excitability. The mechanism of action of ASN51 has been demonstrated in vitro and in vivo, where it has been shown to dose-dependently increase brain total protein and tau protein O-GlcNAcylation. In vivo, ASN51 has both immediate and disease-modifying effects in preclinical models of Parkinson’s Disease, potentially reflective of neuroprotection, and epilepsy, which may be the result of reducing neuronal excitability. Chronic administration of ASN51 in the Line61 transgenic mouse model of Parkinson’s disease significantly increased the O-GlcNAcylation of alpha synuclein and improved motor performance. In the in vivo pentyleneetetrazol model of epilepsy, a single dose of ASN51 had a therapeutic effect on tonic convulsions and improved survival, indicative of rapid effects on neuronal excitability. These data support the hypothesis that increased brain O-GlcNAcylation slows neurodegenerative pathology and improves the symptoms of neurodegeneration through multiple mechanisms. Taken together, our data support the clinical development of ASN51 for both disease-modifying and symptomatic indications in neurologic diseases including Parkinson’s Disease, Alzheimer’s Disease, and epilepsy. A first-in-human study of ASN51 is currently underway.

399. Effect of Hydrogen Sulfide on Alpha-Synuclein Aggregation

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Parkinson’s disease is characterized by abnormal accumulation of alpha-synuclein (α-syn) and neuronal cell death in many areas of brain and especially in the midbrain substantia nigra. The search for compounds that can prevent or reverse alpha-synuclein aggregation has become a recognized priority. Recent evidence suggests hydrogen sulfide (H2S), a neurotransmitter, has anti-inflammatory and anti-oxidant effects, and exerts a neuroprotective effect during neural injury. Here we investigate the effect of H2S on α-syn aggregation and accumulation.

**Methods:** We investigated the effect of H2S donor NaHS on polymorph (WT, A53T, A30P, H50Q and G51D) dependent α-syn aggregation *in vitro* utilizing a cyclic amplification paradigm, and also in HEK293T cell lines stably expressing α-syn (A53T)-YFP. We assessed cell viability and mitochondrial membrane potential upon seeded aggregation of α-syn.

**Results:** NaHS inhibited aggregation of A30P monomer but did not affect aggregation kinetics of H50Q, G51D, and A53T variants in an RT-QuIC assay. However, NaHS did demonstrate a protective effect by slowing the induced aggregation of α-syn in the presence of preformed fibrils (PFF). Analysis of the resultant fibrils demonstrated that mutations of α-syn greatly increased the average length of fibrils. Treatment with NaHS reduced fibril length as measured on TEM. Preformed fibrils of WT, H50Q, G51D and A53T α-syn but not A30P, induced α-syn aggregation in A53T-YFP overexpressing cells. NaHS reduced the production of α-syn phosphorylated at Ser-129 (pS129-α-syn). NaHS also attenuated α-syn seed-induced toxicity and improved mitochondrial integrity. PFF-seeded cells exhibited a reduction in concentration of Nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting enzyme in NAD+ biosynthesis. Treatment with NaHS increased NAMPT expression and restored the level of NAD.

**Conclusion:** This study suggests that H2S decreases α-syn fibrillation and potentially decreases fibril cytotoxicity. The mechanism may be through alteration of aggregate...
conformation as supported by structural data. Further studies are needed; however, the current findings suggest that H2S may offer a promising avenue of investigation in PD.

400. DYT-TOR1A Subcellular Proteomics Reveals Selective Vulnerability of the Nuclear Proteome to Cell Stress
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Background: The path to design novel therapeutic strategies for treatment of dystonia can be accelerated by a better understanding of dystonia pathogenesis; genetic variants that cause dystonia provide a key opportunity. Such a variant exists for TorsinA, a AAA+ ATPase that shuttles between the ER lumen and outer nuclear envelope and is functionally implicated in nucleocytoplasmic transport. We hypothesized that the DYT-TOR1A dystonia disease-causing variant, ΔE TorsinA (n. ΔGAG), may disrupt the normal subcellular distribution of proteins between the nuclear and cytosolic compartments.

Methods: We performed quantitative proteomic analysis on nuclear and cytosolic subcellular fractions from DYT-TOR1A (TOR1AΔΔGAG) and wild-type (TOR1A+/+) mouse embryonic fibroblasts (MEFs). We also examined the compartmental proteomes following six hours of exposure to thapsigargin, an endoplasmic reticulum stressor, because compartmental proteomics to reveal events that localize to discrete cellular compartments and refine thinking about the mechanisms and significance of cell stress in DYT-TOR1A pathogenesis. Future studies are needed to determine the interplay between TorsinA function and cell stress in the context of neural development; however, these results suggest that compartment-specific cellular stress response modulation may play a key role in the pathogenesis of dystonia.

402. CSF MicroRNA Analysis Reveals Angiogenesis and Autophagy Defects in Parkinson’s Disease Patients
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Background: MicroRNAs (miRNAs) are post-transcriptional regulators of gene expression, predominantly through silencing of target mRNA, although gene activation has also been reported.

Objectives: We investigated the effects of discoidin domain receptor (DDR)-1 inhibition on CSF miRNAs in Parkinson’s disease patients.

Methods: Cell-free total RNA was isolated from 200μl of CSF using the Qiagen miRNAeasy serum/plasma extraction kit (Qiagen, 217184). Quality control analysis to confirm RNA was performed on each sample using UV-VIS spectroscopy on a Nanodrop ND-1000 (ThermoFisher).

Results: We observed significant changes in the expression of microRNAs upstream of angiogenesis and autophagy pathways in placebo-treated patients, indicating impairment of brain vasculature and cellular transport in Parkinson’s progression. Interestingly, miRNAs associated with angiogenesis correlate with a decline in motor and non-motor symptoms in Parkinson’s patients. Furthermore, nilotinib, 300mg, a potent DDR1 inhibitor, significantly reverses miRNA changes versus nilotinib, 150mg or placebo; and these changes correlate with long-term motor and non-motor stability.

Conclusions: Collectively, this study demonstrates vascular and autophagy defects in Parkinson’s disease progression and DDR1 inhibition reverses these effects and improves clinical outcomes. Our findings suggest that CSF miRNA may serve as a biomarker for drug response and that DDR1 inhibition alters biological mechanisms that positively affect brain pathology.

426. Daytime Sleepiness in Parkinson’s Disease: Subjective and Objective Measures
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Background: Excessive daytime sleepiness (EDS) is one of the leading sleep complaints in the Parkinson’s Disease (PD) population. Potential causes are poor nocturnal sleep, neurodegeneration of the alerting brainstem regions, or dopaminergic medications. EDS can vary from mild daytime sleepiness, to frequent napping, or even sudden sleep onset without warning - increasing the risk of accidents.

Objective: In this observational, cross-sectional study, we aimed to investigate relationships between subjective and

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Objective measures of EDS in participants with PD, as well as the relationships between daytime napping and nocturnal sleep and dopaminergic medications.

**Methods:** We evaluated 52 PD participants, aged 45-78, with a mean disease duration of 5.8 years, mean levodopa equivalent dose (LED) of 679mg, and dopamine agonist (DA) LED of 125.7mg. EDS, quantified as duration and number of naps/day, was measured objectively with actigraphy over 14 days, while subjective EDS was measured with the Epworth Sleepiness Scale (ESS). The psychomotor vigilance task (PVT) was evaluated as a secondary objective measure of EDS. Nocturnal sleep was evaluated objectively with laboratory-based nocturnal polysomnography (PSG) and actigraphy. The recorded sleep parameters for both actigraphy and PSG were: total sleep time (TST), sleep efficiency (SE), sleep latency (SL), and wake after sleep onset (WASO).

**Results:** Forty-four participants had at least one nap/day, with a mean nap duration of 54 minutes. Subjective sleepiness (ESS) was not correlated with nap duration. However, more subjective sleepiness showed a trend toward correlation with the number of naps/day and correlated with more lapses as measured by the PVT. A higher number of naps/day was correlated with prolonged nocturnal SL and WASO, shorter TST, and worse SE. Duration and number of naps were not correlated with LED, but naps/day had a trend toward correlation with higher DA LED. There was agreement between actigraphy and PSG measurements.

**Conclusion:** The ESS, a subjective measure of EDS, fails to adequately capture propensity for daytime sleep (napping) in this sample of PD participants. In contrast, the number of naps per day is associated with longer latency to sleep onset at night, shorter nocturnal sleep duration, and lower nocturnal sleep efficiency. Thus, nocturnal sleep is associated with objective measures of EDS in PD. Focusing on improving nocturnal sleep in PD might help reduce EDS, lowering the risk of accidents. Further studies are needed to examine the factors involved in EDS in the PD population.

430. Patterns of Cortical Tau Pathology in LBD and PSP: A Multi-Center Digital Histology Study

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Tau is the primary pathology in progressive supranuclear palsy (PSP) and clinically-relevant levels are found in half of autopsied Lewy body dementia cases (Braak: >III/VI, LBD +tau). Detailed study of tau pathology patterns in grey and white matter (GM, WM) can inform models of disease progression and aid in the development of tau-directed imaging biomarkers in these parkinsonian disorders.

We studied 20 LBD+tau and 23 PSP autopsy cases from the University of Pennsylvania and validated our findings in 17 LBD+tau and 17 PSP cases from the University of California San Diego. Sections from middle frontal cortex (MFC), superior temporal cortex (STC), and angular gyrus (ANG) were immunostained for tau. Whole slide images were obtained and regional %area occupied (%AO) of pathological inclusions in GM and WM were calculated using QuPath image analysis software. Immunostaining conditions and detection algorithms were optimized at each site. Paired and independent t-tests compared tau%AO within and between PSP and LBD+tau respectively. Linear regression compared associations between GM and WM tau%AO between LBD+tau and PSP using pathology group as an interaction factor.

In both discovery and validation cohorts, LBD+tau had the highest GM tau%AO in the STC (p<0.04 versus MFC and ANG) which was higher than PSP in the discovery cohort PSP (p=0.02) but was at trend-level in the validation cohort (p=0.08). LBD+tau had the highest WM tau%AO in the STC (p=0.05 versus MFC) while PSP had similar levels throughout (p>0.3). In both cohorts, PSP had higher WM tau%AO than LBD+tau in the MFC, ANG, and overall (p=0.004 for all). The ratio of WM/GM tau%AO was also higher in PSP than LBD+tau in all regions in both cohorts (p<0.03 for all). GM and WM tau%AO were correlated in both LBD+tau and PSP (R>0.8, p<0.001 in both cohorts). For every unit increase of GM tau%AO, there was a larger increase in WM tau%AO in PSP than LBD+tau (t=2.9, p=0.006 for both cohorts).

In this multicenter autopsy study, we find divergent GM and WM tauopathy patterns in clinically similar parkinsonian disorders. The STC had the greatest GM and WM tau pathology in LBD+tau but PSP had greater degrees of WM tau pathology overall. These data suggest divergent patterns of tau propagation in atypical parkinsonian disorders which could improve antemortem diagnosis. Our discovery-validation approach demonstrates the capability of digital histological methods for use in multisite comparative studies.

431. Neuroimaging Associations with 4R Tauopathies in Progressive Apraxia of Speech

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**Background:** Progressive apraxia of speech (PAOS) is a neurodegenerative syndrome affecting spoken communication that is often associated with a 4R tauopathy, including corticobasal degeneration (CBD) and progressive supranuclear...
pa nary (PSP). PAOS is associated with atrophy and hypometabolism in premotor cortex with abnormal white matter diffusivity observed underlying these regions, although little is known about how patterns differ according to pathology. We aimed to investigate longitudinal imaging associations with pathology in a large cohort of autopsy-confirmed PAOS patients who were followed over 10-years.

**Methods:** Twenty-seven PAOS patients recruited by the Neurodegenerative Research Group at Mayo Clinic and followed longitudinally have died, and undergone autopsy with a diagnosis of CBD (n=17) or PSP (n=10). All patients underwent detailed clinical evaluations, structural MRI, diffusion tensor imaging, and [18F]fluorodeoxyglucose (FDG) PET during life, with 88 visits available for analysis. Voxel-level comparisons were assessed at baseline using SPM12. Bayesian hierarchical models were used to model longitudinal change in regional cortical FDG-PET metabolism, subcortical brain volume, and white matter diffusivity, with groups compared at baseline, 4-years from baseline, and in terms of rates of change.

**Results:** In voxel-level maps, PAOS-CBD and PAOS-PSP both showed hypometabolism in lateral and medial premotor cortex and reduced fractional anisotropy in body of the corpus callosum, cingulum, superior corona radiata, and superior frontal, precentral and postcentral white matter. Differences were observed between PAOS-CBD and PAOS-PSP in the longitudinal hierarchical models. While there was little evidence for difference at baseline in cortical metabolism, PAOS-CBD showed faster rates of decline and lower metabolism 4-years from baseline across most cortical regions compared to PAOS-PSP. PAOS-CBD showed smaller volumes and faster rates of atrophy in striatum and thalamus compared to PAOS-PSP, while PAOS-PSP showed smaller volumes and faster rates of atrophy in cerebellar dentate and midbrain compared to PAOS-CBD. Regional fractional anisotropy did not differ between groups at baseline, although PAOS-CBD showed lower fractional anisotropy in the superior and posterior corona radiata 4-years from baseline compared to PAOS-PSP.

**Conclusion:** These findings help define the neurobiology of PAOS and show that neuroimaging features differ according to pathology. Patients with CBD tend to show more rapid decline in corticostraital and thalamic networks, while those with PSP show more involvement of brainstem and cerebellar regions. These findings have implications for predicting pathology and the development of biomarkers for clinical treatment trials that target these 4R tauopathies.

473. Complexes of Soluble α-Synuclein and Amyloid-β with Their Cognate Antibodies Activate the NLRP3 Inflammasome in hiPSC-Derived Microglia

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Parkinson’s disease is characterized by accumulation of α-synuclein (αSyn). Release of oligomeric/fibrillar αSyn from damaged neurons may potentiate neuronal death in part via microglial activation. Herefore, it remained unknown if oligomeric/fibrillar αSyn could activate the NLRP3 inflammasome in human microglia and whether anti-αSyn antibodies could prevent this effect. Here, we show that αSyn activates NLRP3 inflammasome in human induced pluripotent stem cell (hiPSC)-derived microglia (hiMG) via dual-stimulation involving TLR2 engagement and mitochondrial damage. In vitro, hiMG can be activated by mutant (A53T) αSyn secreted from hiPSC-derived A9-dopaminergic neurons. Surprisingly, αSyn/antibody complexes enhanced rather than suppressed inflammasome-mediated IL-1β secretion, indicating these complexes are neuroinflammatory in a human context. A further increase in inflammation was observed with addition of oligomerized amyloid-β (Aβ) and its cognate antibody. In vivo, engraftment of hiMG with αSyn in humanized mouse brain resulted in caspase-1 activation and neurotoxicity, which was exacerbated by αSyn antibody. These findings may have important implications for antibody therapies aimed at depleting misfolded/aggregated proteins from the human brain, as they may paradoxically trigger inflammation in human microglia.

K-401. Stabilization of Overall Quality of Life via Interdisciplinary Home Visits Among Individuals with Advanced Parkinson’s Disease

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**Objective:** To examine overall and domain-specific quality of life (QoL) using the Parkinson’s Disease Questionnaire (PDQ-39) among homebound individuals with advanced Parkinson’s Disease (PD) prior to and after one year of interdisciplinary home visits to determine whether this model of care mitigates QoL decline.

**Background:** In cross-sectional studies validating the PD-specific PDQ-39, patients rated Hoehn and Yahr (HY) Stage 3 (moderate) scored a mean 36.5 (SD 19.6) on the PDQ-39 Summary Index (PDQ-SI), and individuals HY 4-5 (severe) scored a mean of 48.6 (15.1). In longitudinal studies, patients with advanced PD demonstrate worsening QoL over
time. In a small pilot of interdisciplinary home visits, we reported a stabilization of QoL despite progression of PD severity. This was limited by a non-PD-specific QoL scale. We now use the PDQ-39 to examine longitudinal change in overall and domain-specific QoL in advanced PD patients receiving home visits for one year.

**Methods:** Enrolled participants had a diagnosis of PD, HY 3-5, met Medicare homebound criteria, lived within 40 miles of Rush University, and consented to 4 home visits (nurse and social worker in-home, neurologist via telemedicine) over 12 months. Change from Visit 1 (V1) to Visit 4 (V4) in PDQ-SI and individual domains assessed via paired t-tests.

**Results:** Among 65 enrolled participants (68% male, mean age 78.9, 78% HY 4-5, median 15 years PD duration): 51 completed Visit 4 (9 died, 5 withdrew). We found no significant decline in PDQ-SI over one year (V1 mean 38.4 (SD 14.0); V4 37.7 (12.7), p = 0.72). We detected worsening mobility (V1 mean 65.0 (19.9) vs. V4 73.7 (20.3), p = 0.01) and worsening ADLs (V1 mean 55.8 (22.6) vs. V4 62.68 (24.7), p = 0.03). Bodily discomfort improved (V1 mean 43.8 (27.1) vs. V4 34.3 (24.4), p = 0.03). Improvements in stigma (23.6 (25.0) vs. 17.5 (21.8), p = 0.08) and communication (38.6 (23.8) vs. 33.3 (22.4) p = 0.09) approached clinical and statistical significance.

**Conclusions:** Contrary to the expectation that QoL will necessarily worsen with PD over time, we again found that an interdisciplinary home visit model of care may uncouple progression of disease severity from QoL, using a validated, PD-specific QoL measure. Additionally, we detected improvements in bodily discomfort, stigma, and communication. Interdisciplinary models of care offer promise for palliation of symptoms and QoL in people with advanced PD.

**K-503. Prefrontal Cortical Beta and Theta Encode Subjective Value and Reward Context Respectively**

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Uncovering how distributed prefrontal cortico-basal networks subserve reward evaluation towards optimal goal-orientated decision making is critical to understanding a wide range of neurological diseases characterized by aberrant reward processing. Here, we utilize chronic intracranial electrocorticography, paired with subcortical local field potential recordings in patients with Parkinson’s disease through sensory enabled deep brain stimulators. Patients performed a reward - effort discounting task during recordings from orbitofrontal cortex (OFC) and basal ganglia (BG; subthalamic nuclei and globus pallidus). This revealed multiplexed neural population signalling with OFC beta (13-30 Hz) signalling subjective value on the single trial basis and theta (3-7 Hz) signalling previous trial value. At movement initiation, this value signal was transferred to subcortical structures. Discovery of the neural population signals of subjective value in the OFC and BG promise to reveal network neurophysiology of reward evaluation and support future responsive neurostimulation therapies for reward deficit symptoms such as apathy and impulsivity.

**K-507. α4β2-Nicotinic Receptor Availability is Associated with Domain-Specific Cognitive Impairment in Parkinson’s Disease**

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**Background:** Substantial evidence exists for the role of cholinergic dysfunction in thalamic, striatal, and brainstem regions in cognitive impairment in Parkinson’s disease (PD). Elucidating the role of specific cortical and extra-thalamic nicotinic cholinergic receptors in PD has been challenging due to the relatively low affinity of the available radiotracers for imaging of cortical regions involved in cognition. [18F] XTRA was developed as a high affinity radioligand to better image cortical and extrathalamic α4β2-nicotinic cholinergic receptor availability.

**Objective:** To evaluate the association between cortical and hippocampal (extra-thalamic) α4β2-nicotinic cholinergic receptor availability and cognitive function status in patients with Parkinson’s disease (PD).

**Methods:** Twenty seven subjects with PD (Hoehn & Yahr 2.5-3, mean age 67.7 years) with mild cognitive impairment (PD-MCI level 1 criteria, N=9) or normal cognition (N=18) underwent neuropsychological testing and a 90 minute PET scan on the High Resolution Research Tomograph after injection of 10 mCi of [18F]XTRA. 10 healthy controls underwent PET imaging only. Tracer kinetic modeling used the Logan graphical method with metabolite-corrected arterial input function to calculate regional total distribution volumes (V T) of extra-thalamic regions of interest. Non-displaceable binding potential (BPND) was calculated using the corpus callosum as a reference region. Neuropsychological tests were age- and gender-calibrated and combined into cognitive domain composite T-scores. Hypothesized region of interest BPND’s were correlated with cognitive domain T-scores using multiple linear regression, adjusting for age.

**Results:** BPND in the extra-thalamic ROI’s was higher in PD patients than controls in the cerebellum, mesial temporal cortex, parietal cortex, posterior cingulate cortex, prefrontal cortex, and precuneus, and was different between PD-normal cognition and PD-MCI in those regions as well as the anterior cingulate cortex, hippocampus, occipital cortex, and striatum. In PD patients, Montreal Cognitive Assessment showed an inverse correlation with α4β2 availability in the mesial temporal (r = -.39), occipital (r = -.39), parietal (r = -.42), and precuneus (r=.44) regions, all p<0.05. A worse composite attention T-score was associated with higher α4β2 availability in many ROI’s and worse visuomotor composite cognitive T-score associated with higher α4β2 availability in the thalamus (β=-2.42), parietal cortex (β=-9.67), and precuneus (β=-10.62), all p<0.05 uncorrected.

**Discussion:** Increased α4β2 nicotinic receptor availability in the thalamus, striatum, and multiple cortical regions, presumably due to decreased cholinergic innervation, is associated with global cognitive impairment. Higher regional...
cortical receptor availability is associated with attentional and visuospatial dysfunction, which are commonly seen in Parkinson’s disease.

K-509. Combined Effects of GBA and STN-DBS Negatively Affect Cognition in Parkinson’s Disease

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Objective: To compare the rate of change in cognition between GBA mutation carriers and non-carriers with and without STN-DBS in Parkinson’s disease (PD).

Background: GBA mutation carriers with PD are at higher risk for more aggressive cognitive and motor decline compared with non-mutation carriers. Some studies have suggested that STN-DBS is also associated with cognitive decline. The interaction between GBA and STN-DBS has not been examined.

Methods: Clinical and genetic data from 12 datasets were pooled from University of Amsterdam, Columbia University, Hôpital Pitié-Salpêtrière, National Institutes of Health, Norwegian University of Science and Technology, Parkinson’s Progression Markers Initiative, Rush University, Mount Sinai University, University College London, LRRK2 Cohort Consortium, STEADY-PD, and the PD Biomarkers Program. The following data were collected: age, age of onset, sex, years before DBS, years since DBS, family history, Unified Parkinson’s Disease Rating Scale (UPDRS), Mini-Mental Status Exam (MMSE), Montreal Cognitive Assessment (MoCA), and Mattis Dementia Rating Scale (MDRS). MMSE and MoCA scores were converted to MDRS scores. All subjects were required to have a baseline MDRS score of 130 or greater to be included in the analysis. Subjects were examined for mutations in GBA and then categorized as GBA+DBS+, GBA+DBS-, GBA-DBS+, GBA-DBS-. GBA mutation carriers were further subcategorized according to mutation severity (risk variant, mild, severe). Subjects who carried both GBA and LRRK2 mutations were excluded. Linear mixed modeling was used to compare rate of change in MDRS scores over time comparing the groups according to GBA and DBS status and then according to GBA severity and DBS status. The model was adjusted for age, age of onset, sex, and study site (random factor).

Results: Data were available for 128 GBA-DBS-, 84 GBA+DBS-, 98 GBA-DBS+, and 59 GBA+DBS+ subjects. Mean age at baseline, age of onset, baseline MDRS scores, and median follow-up time are reported. MDRS scores decreased fastest in the GBA+DBS+ group compared with the other 3 groups. GBA+DBS+ with variant, mild, and severe mutations declined faster than GBA-DBS- with similar mutation severity.

Conclusions: This study suggests that there is an interaction between GBA and STN-DBS that negatively affects cognition. Genetic screening for GBA mutation status should be part of the DBS pre-operative evaluation. Whether pallidal DBS rather than STN-DBS would lead to better cognitive outcomes remains unknown.

K-512. Functional Changes in the Central Autonomic Network Contributes to Autonomic Dysfunction in Pre-manifest Huntington’s Disease

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Background: Patients with Huntington’s Disease (HD) have been found to have dysregulation of their autonomic nervous systems (ANS), with a predominance of sympathetic tone. Clinical manifestations consistent with ANS dysfunction occur in the premanifest phase of the disease.

Objective: The aim of this pilot study was to assess functional connectivity of central autonomic network (CAN) in pre-manifest patients with HD.

Methods: We recruited 10 male subjects with a known CAG ≥ 36 to the University of Iowa. To be eligible for this study, participants had to have a diagnostic confidence level of ≥ 4 at the time of their visit. We recruited nine male control subjects with no family history of HD. All participants underwent a resting-state, functional MRI study and an electrocardiogram to perform heart rate variability analyses. A single seed was placed in the right anterior insula (rAI) and a region-of-interest (ROI)-to-ROI analysis was conducted within brain regions of the CAN. Fisher R-to-Z transformations were performed to quantify functional connectivity between brain regions. ANCOVA analyses were performed to quantify differences in functional connectivity between the HD group and the controls, controlling for age and BMI. Functional connectivity measures were directly correlated to measures of heart rate variability.

Results: Participants in the HD group had significantly decreased functional connectivity relative to the control group between the rAI and 1) right (p=0.03) and left (p=0.009) rostral prefrontal cortex (RPFC), 2) left anterior insula (p=0.012), and 3) anterior cingulate cortex (ACC) (p=0.027). They also had significant decreases in the root mean square of successive RR interval differences (RMSSD) (p=0.037) and the percentage of successive RR intervals that differ by more than 50 milliseconds (pNN50) (p=0.044) compared to the control group. Lower values are indicative...
of decreased parasympathetic tone. There were significant correlations with pNN50 values are functional connectivity between the rAI and right and left RPFC (p=0.039 and p=0.011, respectively).

Conclusions: To the best of our knowledge, this is the first time that alterations in the functional connectivity of the CAN have been reported in pre-manifest HD. This pilot suggests that changes in functional connectivity within the CAN may mediate dysfunction of the ANS seen in HD.

LB-446. SAGE-324/BIB124, an Oral Neuroactive Steroid (NAS) GABA_A Receptor Positive Allosteric Modulator (PAM), in Patients with Essential Tremor: Results from the Phase 2 KINETIC Trial

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Objective: To present efficacy, safety, and tolerability from the phase 2, placebo-controlled KINETIC Study (NCT04305275) of SAGE-324/BIB124 60mg in patients with essential tremor (ET) aged 18 to 80 years.

Background: SAGE-324/BIB124 is an investigational, oral NAS GABA_A receptor PAM. GABA dysregulation has been implicated in the pathophysiology of ET.

Methods: Patients with ET (N=69), aged 18-80 years, with a score of ≥10 on item 4 (right and left upper limb tremor in the extended forward posture, the “wing” posture, and finger-nose-finger task) of The Essential Tremor Rating Assessment Scale (TETRAS) Performance Subscale at screening and baseline were randomized 1:1 to receive SAGE-324 60mg or placebo once daily for 28 days. SAGE-324 could be down-titrated to 45mg or 30mg based on clinical judgement and tolerability. The primary endpoint was change from baseline compared to placebo in TETRAS item 4 at Day 29 (1 day after last dose).

Results: Sixty-nine patients were randomized to receive SAGE-324 60mg (n=34) or placebo (n=35). Of the 34 patients randomized to SAGE-324, 23.5% (8/34) completed the treatment period on the 60mg dose; 55.9% (19/34) had their dose reduced to 45mg; 32.4% (11/34) had their dose further reduced from 45mg to 30mg, and 5.9% (2/34) had their dose reduced from 60mg directly to 30mg. Patients who received SAGE-324 experienced a statistically significant least-squared (LS) mean [SE] reduction from baseline at Day 29 in TETRAS item 4 (SAGE-324: -2.31 [0.401]; placebo: -1.24 [0.349]; p=0.049), corresponding to a 36% reduction from baseline in tremor amplitude compared to a 21% reduction in patients who received placebo. Patients with a baseline TETRAS item 4 score at or above the median score of 12 (SAGE-324: n=25; placebo: n=22) also experienced a significant LS mean reduction [SE] from baseline (SAGE-324: -2.75 [0.426]; placebo: -1.05 [0.412]; p=0.007), corresponding to a 41% reduction from baseline in tremor amplitude in patients who received SAGE-324 compared to an 18% reduction in patients who received placebo. The most common TEAEs occurring in ≥10% of patients in the SAGE-324 treatment group and at a rate at least twice that of placebo were somnolence 67.6%, dizziness 38.2%, balance disorder 14.7%, diplopia 11.8%, dysarthria 11.8%, and gait disturbance 11.8%.

Conclusions: SAGE-324 treatment led to a significant reduction in upper limb tremor at Day 29 compared with placebo.

LB-451. Online Patient Reporting of Postural Instability Symptoms as Outcomes for Parkinson Disease Clinical Trials

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Background: Postural instability is a therapeutically intractable feature of Parkinson disease (PD), associated with decreased quality of life, risk of falling, and adverse consequences on morbidity and mortality. Patient symptoms as precursors and predictors of falling have been relatively neglected as outcome measures in framing disease-modifying clinical trials for PD. Direct patient reporting may benefit earlier identification of research participants at risk of falls in clinical trials, particularly in the absence of in-person clinical examination.

Methods: Using the PD Patient Report of Problems (PD-PROP) module on the Fox Insight online research platform https://foxinsight.michaeljfox.org, participants replied in their own words to: (1) What is the most bothersome problem due to your PD? (2) In what way does this problem affect your ability to accomplish what needs to be done? Responses reported up to their 5th most bothersome problem at baseline and were reminded at about six-month intervals to update their PROPs. Verbatim replies were transcribed, examined by natural language processing, systematically categorized by a team of clinical curators, and classified into symptoms of gait disorder, balance, falling, and freezing.

Results: Among approximately 24,000 Fox Insight research participants, 13,892 provided two or more PD-PROP replies referable to the symptom domain of postural instability within an observation period up to 2.5 years. Cumulative falling occurrence was highest for participants whose duration of PD was greater than five years since diagnosis and falling prioritized as most bothersome problem. By 1.5 years, new-onset gait disorder among all participants occurred in ~42%, balance in ~28%, falling in ~23%, and freezing in ~8%. These survival data informed achievable sample size estimates for controlled clinical trials, assuming 1:1 allocation of placebo and experimental treatment with effect sizes of 20%, 30% and 50%.
Conclusions: Postural instability and symptoms referable to gait disorder, balance and falling developed anew in substantial proportions of PD patients over 1.5-2.5 years of observation. Online PD-PROP reporting in patients' own words can be analyzed and practically applied as clinically meaningful outcomes in trials aimed at forestalling the onset of intractable postural instability symptoms and thereby favorably altering the course of PD.

LB-466. Data Driven Exploration of Network Connectivity in Task-fMRI of Writer’s Cramp Dystonia
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Background: Dystonia is a brain disorder with limited understanding of the functional connectivity differences in the brain circuit. Prior fMRI studies have demonstrated abnormalities in the functional activation and connectivity in dystonia. However, these findings were based on a hypothesis driven region of interest analysis or by applying data driven approaches to understand connectivity differences in resting state (or ‘off’ disease state) fMRI. It remains unclear which functional networks are playing a role in the “on” disease state of dystonia.

Objective: The aim of this research study was to use independent component analysis (ICA) on patients with writer’s cramp (WC) dystonia, a task-specific dystonia, to understand functional network changes while subjects performed the dystonic task.

Methods: 12 WC and 12 age-matched healthy volunteers (HV) performed 3 motor tasks during fMRI acquisition: writing, sequence tapping and finger flexion-extension. Group ICA analysis was used to identify 11 functional networks. The functional networks were then correlated with the task time course to evaluate networks with the highest correlation to the dystonic task and identify any differences between the two groups. Lastly, differences in functional network connectivity were evaluated between the two groups.

Results: Our analysis showed that in WC there is significantly decreased correlation of the basal ganglia and increased correlation of the orbitofrontal network to the writing task time course. There is significantly decreased connectivity of the basal ganglia to the left sensorimotor network specifically during the writing task in WC patients. We also observed significantly increased correlation of the cerebellum to the orbitofrontal and parietal networks in dystonia.

Conclusions: Collectively, our analysis further suggests that dystonia is brain network disorder in which the basal ganglia and cerebellum play key roles. Based on our findings, we also propose a unifying mechanism of network changes that may distinguish primary disease from compensatory network changes. Our study is the first to apply a purely data-driven approach to understand network interactions in WC dystonia patients during task performance.

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Background: Access to and optimization of DBS therapy for Parkinson’s disease and essential tremor patients has been an ongoing challenge for patients, caregivers and clinicians. This was further aggravated during the COVID-19 pandemic. With the recent and first FDA approval of true remote programming in DBS, the Abbott NeuroSphere™ Virtual Clinic platform, we present first data on an efficient clinical workflow and our use of this platform with full as well as hybrid (mixed) systems.

Methods: Patients interested in enrolling for this technology upgrade signed written consent to Abbott or verbal consent to the Clinician. The patient’s DBS controller device (iPod Touch or iPhone) was upgraded with the new App and the patient’s IPG mapped to an authorized Clinician. Remote programming required session be initiated by patient and multi-factor authentication by the Clinician. The IPG itself didn’t require any upgrading. The platform synchronized stimulation changes with integrated video allowing real-time assessments. A protected recovery mechanism ensured fail safe continuity of therapy in case of network failure.

Results: In just over 5 weeks since the availability of this technology, we have set up 17 patients with the upgrade and conducted over 50 remote sessions producing multiple patient testimonials reflecting improved access and improved perceived quality of care. We report that the most efficient clinical workflow for software upgrade on patient controllers is during IPG implantation; whether during de novo placement (S2) or replacement (S3). During S2, 6/6 patients were set up. During S3, 1/1 patient was set up. The remaining 10 patients were set up in-clinic during their initial or follow-up programming sessions. Training was provided to all patients in-clinic. Remote programming was also set up in patients with hybrid/mixed systems (non-Abbott DBS leads with Abbott IPGs). This may be an important clinical consideration for patients likely to benefit more from remote programming than from diagnostic MRI or for those with impedance issues precluding them for an MRI.

Conclusions: This is the first report on an efficient clinical workflow and use cases of the recent FDA approved DBS remote programming platform. We hypothesize that using remote programming in the first 3 months of initial DBS programming in addition to the usual in-person appointments will make therapy optimization faster and more efficient. We are collecting measurements and data to that end.
Multiple Sclerosis

192. Serum Serotonin Levels Are Reduced in People with Multiple Sclerosis and Correlate with Depression and Anxiety Scales Scores

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Objective: To evaluate plasma serotonin levels in people with multiple sclerosis (PWMS) compared to controls and investigate its correlation with depression and anxiety scales scores.

Background: PWMS have a higher risk of developing psychiatric manifestations, including depression, than the general population. Serotonin could be involved in the biochemical mechanisms of depression in PWMS. Earlier studies also showed that serotonin levels can be reduced in PWMS. To our knowledge, the correlation between serotonin levels and depression and anxiety scales scores in PWMS was not studied.

Design/Methods: A cross-sectional design was used to study a cohort of PWMS and matched healthy controls. Clinical, demographic and laboratory data were collected at the same visit. Subjects with known use of antidepressants and/or a diagnosis of depression were excluded. The Hospital Anxiety Depression Scale (HADS) and the Beck Depression Inventory (BDI) were used to evaluate depressive and anxiety symptoms. The Expanded Disability Status Scale (EDSS) was used to evaluate disability. Serum levels of serotonin were measured in both groups. Pearson correlation coefficient (r) was conducted to test the relationships between serum serotonin levels and depressive and disability scales scores in PWMS. Partial correlation analysis was conducted to examine that correlation while controlling for the effects of confounding factors, including age, sex, and EDSS.

Results: Thirty-eight PWMS, mean (SD) age was 34.42 (10.97) years (29 females (76%)) and thirty matched healthy controls, mean (SD) age was 36.56 (11.44) (22 females (73%)), completed the study. HADS-anxiety, HADS-depression, and BDI scores were significantly different between PWMS and the control group (p<0.0001). Serum serotonin levels were significantly lower in PWMS compared to controls [182.14 (26.56) ng/ml vs. 198.9 (21.1) ng/ml, p=0.006]. Serum serotonin level correlated with scores of HADS-anxiety (r=-0.44, P=0.005), HADS-depression (r=-0.37, P=0.021) and BDI (r=-0.45, P=0.005). Correlations remained significant after adjusting for age, sex and EDSS scores.

Conclusions: Our study demonstrates that serum serotonin levels are reduced in PWMS, and these levels correlate with scores of depression and anxiety, independent of disability measured by the EDSS. These findings highlight the role of serotonergic pathways in the pathophysiology of neuropsychiatric manifestations of MS. Future studies are needed to replicate our findings and evaluate future therapeutic targets and perhaps following serum serotonin as a biomarker for treatment response in MS associated anxiety and depression.

193. Predictors of Multiple Sclerosis Prevalence Globally: Beyond Latitude and Vitamin D

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Introduction: Multiple sclerosis (MS) is a leading cause of disability among young adults. However, its reported prevalence varies widely by country and world region, variation that is often attributed to latitude and vitamin D exposure.

Objective: To evaluate the association between sociodemographic, health systems, and neurology-specific factors with MS prevalence on a national and regional level.

Methods: National and regional-level data regarding pre-specified sociodemographic (e.g. gross domestic product (GDP) per capita, gross national income (GNI) per capita), health systems (e.g. current health expenditure per capita and by percentage of GDP, universal health coverage (UHC) index, medical doctors per capita), and neurology-specific (e.g. MRI unit density, neurologists per capita) factors were obtained from multilateral organizations and scientific literature. Extracted data were utilized in univariable and multivariable stepwise regression analyses to evaluate associations between national and regional MS prevalence and individual factors of interest.

Results: Univariable regression analyses were significant at the national level for all investigated factors. When stratified by World Health Organization (WHO) region, MS prevalence in the European Region was positively associated with all investigated factors in univariable models, except neurologists and current health expenditure per capita. MRI unit density and UHC index were significant in four of six WHO world regions, making them the variables most frequently associated with MS prevalence. Analyses stratified by World Bank income group showed that MS prevalence was significantly associated with all investigated factors in high-income countries, while only neurologists, GDP, and GNI per capita were associated with MS prevalence in low-income countries. Latitude was associated with MS prevalence for all income strata except the low-income group. In a multivariable stepwise regression analysis, current health expenditure per capita ($10 USD) (β = 0.21; 95% CI = 0.15 - 0.27; p < 0.01) and latitude (β = 1.89; 95% CI = 1.14 - 2.64; p < 0.01) were the only variables significantly associated with MS prevalence.

Conclusion: We found that health expenditure per capita was strongly correlated with national MS prevalence, suggesting that current theories that attribute variations in MS prevalence primarily to latitude effects are likely incomplete. Access to adequate healthcare, including neurologists and MRI scanners, likely explain a substantial proportion of the variation in MS prevalence globally, especially since equatorial countries tend to be lower-income countries with less...
194. Restless Limbs Syndrome (RLS) Mimicking Multiple Sclerosis (MS): May Explain the Misdiagnosis of MS in Migraine

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Retrospective studies of referrals to academic MS specialty clinics reproducibly indicate a misdiagnosis rate of 20-25%. The most common diagnosis in all of these studies is migraine. Neurologists and radiologists are increasingly aware that migraine is associated with MRI changes in the deep, periventricular white matter that can include MS in the differential diagnosis. RLS may be an underappreciated but common mimicker of MS. We believe that these various clinical features of RLS associated with migraine headaches, taken in conjunction with the MRI changes in these patients, may help elucidate these misdiagnoses.

We conducted a retrospective study of 985 patients with IRLSSG criteria for RLS who completed a 33 question survey addressing demographics, symptoms, comorbidities, family history and response to therapy. 75% suffered from headaches with photophobia (86%), phonophobia (73%), nausea (66%) and vomiting (24%). Other neurological symptoms in our cohort included paresthesia (numbness and tingling in the limbs), coldness (13%), and dysesthetic pains such as burning (25%), electric shocks (15%) and coldness (13%). 60% had symptoms beginning in one or both legs, suggesting a myelopathic pattern. 13% had symptoms beginning in the arms and legs. We also found that 11% of RLS patients present with a hemisyndrome of paresthesia and dysesthesia involving ipsilateral arm and leg, suggesting a cerebral lesion. Increasing the clinical confusion with MS were demographic findings of a female predominance of over 2 to 1 and an average age of onset of 39 years. We will present cases to illustrate these clinical features.

We believe that these various clinical features of RLS associated with migraine headaches, taken in conjunction with the MRI features of migraine, lead to the misdiagnosis of MS. We hope this information will be useful in evaluating headache patients with abnormal MRI scans and improve diagnostic acumen. RLS may be an underappreciated but common mimicker of MS.

195. Fbxw7, an E3 Ligase Component, Functions in Oligodendrocytes to Control Development and Limit Myelin Production

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Background: In the central nervous system (CNS), myelin is formed by cellular projections of specialized glial cells called oligodendrocytes (OLs). Myelin is vital for proper CNS function as evidenced by the disability resulting from dysfunctional/absent myelin in leukodystrophies and myelin damage in multiple sclerosis. Unfortunately, there are currently no therapies that effectively restore absent, lost, or damaged myelin. There is a pressing need to understand the fundamental biology of OLs in the hopes of developing myelin restorative therapeutics. From a forward genetic screen in zebrafish, we previously discovered that mutations in fbxw7 increase CNS myelination. Fbxw7 is a highly conserved substrate recognition component of SKP1-Cullin-Fbox E3 ubiquitin ligase complexes. Homozygous fbxw7 mutants present with an increased number of myelinated axons and thicker myelin in the dorsal spinal cord of zebrafish. Loss of fbxw7 function in zebrafish also results in an early increase in spinal cord OL precursor cells (OPCs) and an increase in myelin sheath length. The goal of his work was to investigate the role of Fbxw7 in mammalian OL development and CNS myelination.

Methods: In this work, we used multiple rodent model systems to investigate the cell autonomous role of Fbxw7 in OL function. Specifically, we utilized primary OPC culture coupled with siRNA knockdown of Fbxw7 and Cre-lox mediated OL-specific Fbxw7 knockout in mice. Within these model systems we employed immunohistochemistry, western blot, proteomics, and electron microscopy to elucidate the role of Fbxw7 in mammalian OLs.

Results: The loss of Fbxw7 in differentiating primary OLs resulted in enhanced differentiation and accelerated production of myelin related proteins. Proteomic analysis of cultured OPCs following knockdown of Fbxw7 revealed upregulated and downregulated proteins and suggest a role for Fbxw7 in the regulation of cytoskeletal elements and cholesterol-lipid metabolism. Mice in which Fbxw7 was selectively knocked out in mature oligodendrocytes demonstrate a number of myelin abnormalities including excessive myelin production in the form of severe myelin outfoldings and an associated increase in axonal degeneration.

Conclusions: Our data suggest Fbxw7 plays a cell-autonomous and conserved role in mammalian OL biology and CNS myelination. This data is exciting given that understanding the role of Fbxw7 in OL function holds the potential to identify novel pathways leading to myelin restorative or protective therapies.

196. Developing a Better Model for MS: Delayed Oligodendroglia Recruitment and Maturation in Large Volume Demyelination of the Rabbit CNS

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Background: In the central nervous system (CNS), myelin is formed by cellular projections of specialized glial cells called oligodendrocytes (OLs). Myelin is vital for proper CNS function as evidenced by the disability resulting from dysfunctional/absent myelin in leukodystrophies and myelin damage in multiple sclerosis. Unfortunately, there are currently no therapies that effectively restore absent, lost, or damaged myelin. There is a pressing need to understand the fundamental biology of OLs in the hopes of developing myelin restorative therapeutics. From a forward genetic screen in zebrafish, we previously discovered that mutations in fbxw7 increase CNS myelination. Fbxw7 is a highly conserved substrate recognition component of SKP1-Cullin-Fbox E3 ubiquitin ligase complexes. Homozygous fbxw7 mutants present with an increased number of myelinated axons and thicker myelin in the dorsal spinal cord of zebrafish. Loss of fbxw7 function in zebrafish also results in an early increase in spinal cord OL precursor cells (OPCs) and an increase in myelin sheath length. The goal of his work was to investigate the role of Fbxw7 in mammalian OL development and CNS myelination.

Methods: In this work, we used multiple rodent model systems to investigate the cell autonomous role of Fbxw7 in OL function. Specifically, we utilized primary OPC culture coupled with siRNA knockdown of Fbxw7 and Cre-lox mediated OL-specific Fbxw7 knockout in mice. Within these model systems we employed immunohistochemistry, western blot, proteomics, and electron microscopy to elucidate the role of Fbxw7 in mammalian OLs.

Results: The loss of Fbxw7 in differentiating primary OLs resulted in enhanced differentiation and accelerated production of myelin related proteins. Proteomic analysis of cultured OPCs following knockdown of Fbxw7 revealed 200+ upregulated and downregulated proteins and suggest a role for Fbxw7 in the regulation of cytoskeletal elements and cholesterol-lipid metabolism. Mice in which Fbxw7 was selectively knocked out in mature oligodendrocytes demonstrate a number of myelin abnormalities including excessive myelin production in the form of severe myelin outfoldings and an associated increase in axonal degeneration.

Conclusions: Our data suggest Fbxw7 plays a cell-autonomous and conserved role in mammalian OL biology and CNS myelination. This data is exciting given that understanding the role of Fbxw7 in OL function holds the potential to identify novel pathways leading to myelin restorative or protective therapies.
Remyelination-promoting therapies have the potential to restore neurologic function and prevent progression in multiple sclerosis (MS). While pharmacologic, such as Clemastine, which drive differentiation of oligodendroglia have had measured success in clinical trials, they have yet to improve clinical outcomes despite inducing ample remyelination in rodent models. These discrepancies suggest that current rodent models are inadequate and may fail to recapitulate key features of MS lesions. Of note, rodent lesions display abundant oligodendrocyte progenitor cell (OPC) recruitment following injury, where OPC densities increase between 2 and 16 times that of normal appearing white matter (NAWM). In stark contrast, MS lesions display weak OPC recruitment with densities of OPCs rarely exceeding normal levels. Thus, therapies which drive the differentiation of OPCs into myelinating oligodendrocytes (OLs) may work well in lesions which have abundant OPCs, but struggle when OPCs are less abundant. Given the 100-fold difference in size between MS and rodent lesions we hypothesized that OPC recruitment becomes rate-limiting as lesion volume increases leading to failure of OL differentiation and remyelination. In this study, we utilized lysolecithin injections into the large white matter tracts of the rabbit to create demyelinated lesions that have cross-sectional areas 20-fold larger than those previously reported in mice, and volumes 8-fold larger. Intriguingly, these lesions displayed MS-like densities of OPC recruitment where densities of OPCs never exceeded that of NAWM (288.2 ±44.64 vs 149.5±15.16, NAWM (n=16) vs 56dpl (n=5) respectively, p = 0.4242). Importantly, while the percentage of differentiated OLs recovered by 56 dpl, the density of mature OLs remained 50% of that of NAWM at the same timepoint. This indicates that OPCs preserved their capacity for differentiation, but failed to recruit adequate numbers of OPCs. Additionally, similar to MS lesions, rabbit lesions displayed reduced axonal densities in the lesion core (making up ~15% of the total lesion area) with no difference in oligodendroglia density. The size of these lesions permits in-depth analysis of OPC and oligodendrocyte dynamics within distinct regions such as lesion core, border, and peri-lesion and allows for a more direct comparison to analogous regions in human lesions. Together, we show that lysolecithin-induced lesions in the white matter of the rabbit recapitulate key features of MS lesions, and regardless of the pathophysiology of these differences being species or volume dependent, could improve the development of remyelination therapies.

197. The Impact of Neighborhood-Level Socioeconomic Status on Mental Health and Health-Seeking Behavior in a Multi-Ethnic Multiple Sclerosis Cohort
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Objectives: To explore the associations between neighborhood-level socioeconomic status (nSES) and race/ethnicity as predictors of psychiatric symptoms, mental health attitudes, and health-seeking behavior in persons with multiple sclerosis (MS).

Background: Psychiatric symptoms are common in MS. Racial/ethnic inequalities are linked to differences in socioeconomic status (SES). Low SES is associated with a greater burden of comorbidities in MS and with symptom management inequalities. SES effects on health can also be observed at the neighborhood level. We hypothesized that persons with MS with lower nSES are more likely to experience symptoms of depression, anxiety, fatigue, and alcohol dependence compared to those with higher nSES.

Design/Methods: Persons with MS answered a national web-based survey including demographic characteristics, mental health attitudes, the Patient Health Questionnaire-9 (PHQ-9), the Generalized Anxiety Disorder 7-item (GAD-7) scale, the Modified Fatigue Impact Scale 5-item version (MFIS-5), and the Alcohol Use Disorders Identification Test (AUDIT). nSES was calculated using the Agency for Healthcare Research and Quality (AHRQ) Index. Analyses were performed using descriptive statistics and multivariable analyses.

Results: 2095 participants answered the survey (mean AHRQ index 54.6±5.4, age 51.3±12.2 years, 7% Black, 5.4% Hispanic/Latino, and 81.8% women). Those in the lowest quartile of nSES (most disadvantaged) had higher mean MFIS-5 (11.9±5.1; p=0.001), PHQ-9 (9.2±6.3; p=0.001), GAD-7 (7.1±5.9; p=0.006) scores, and were more likely to be either Black or Hispanic/Latino as compared to those in higher quartiles (least disadvantaged). Of those who consumed alcohol (n=1489), participants in the highest AHRQ quartile had higher mean AUDIT scores (2.9±4, p=0.01) compared to those in lower quartiles. SES, but not race/ethnicity, was predictive of moderate-to-severe depression and of self-reported improvement in symptoms after receiving mental health treatment. A higher proportion of Blacks (44.1% vs 30.2%, p=0.003) and Hispanic/Latinos (49.1% vs 30.6%, p=0.001) were more likely to report they would “definitely go” receive MH care if co-located with their MS care as compared to White and Non-Hispanic/Latino participants, respectively.

Conclusions: Although Blacks and Hispanic/Latinos were overrepresented in the low nSES group (most disadvantaged), SES but not racial/ethnic background, predicted symptoms of moderate-to-severe depression and likelihood of symptom recovery after receiving mental health treatment in this sample. Co-location of mental health services with MS care might represent an area of opportunity to reduce the gap between access and need of mental health care in MS.
To investigate the impact of slowly expanding lesions (SELs) on clinical disability measures on Multiple Sclerosis Functional Composite (MSFC) and Symbol-Digit Modalities Test (SDMT) scores in relapsing-remitting multiple sclerosis (RRMS) patients. SELs are demyelinating lesions with ongoing destruction at their borders due to the accumulation of macrophages/microglia. These SELs can be detected by magnetic resonance imaging (MRI). The Multiple Sclerosis Functional Composite measures walking speed, fine motor skills, and cognition. It includes two trials of the Timed 25 Foot Walk (T25FW), the 9-Hole Peg Test (9-HPT) on the dominant and non-dominant hands, and the Paced Auditory Serial Addition Test at 3 seconds (PASAT-3). The SDMT is another cognitive assessment assessing attention, visual tracking, and speed. We retrospectively analyzed 29 RRMS patients (mean age $\pm$ SD = 43.9 $\pm$ 10.3, mean DD $\pm$ SD = 5.6 $\pm$ 7.8, males: females = 8:21, African American:Caucasian:other = 15:13:1) and identified SELs from their phase MRI scans. MRI scans were performed on a SIEMENS 3T Verio scanner. The MRI protocol included 2D T2 fluid attenuated inversion recovery (FLAIR) sequence, pre and post contrast T1 weighted (T1W) sequence and susceptibility weighted imaging (SWI) sequences. SELs were identified when they were presented with a hypointense paramagnetic rim signal on filtered phase images in SWI sequences and were not presented as Gad-enhancing lesions on post contrast T1W images. The number of SELs was estimated on each scan using Jim software. The MSFC tasks and SDMT were performed and recorded for each patient at their clinic visit. Spearman’s correlations were performed to analyze the association between the number of SELs and clinical disability measures (MSFC and SDMT scores) in SPSS v26. The mean number of SEL is 4.4. Although there was a trend between higher numbers of SELs and lower scores on the SDMT, T25FW, 9-HPT (dominant hand), and PASAT-3; no statistical significance was reached. The area of research examining the impacts of SELs on different aspects of MS disease progression is still relatively new. Further investigations with larger number of patients may improve our understanding of the role of SELs for clinical disability monitoring.

199. Pediatric Onset Multiple Sclerosis: Neuro-Performance Testing, MRI Metrics, and Quality of Life Measures

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Background: QoL research in POMS patients is a topic of growing interest. QoL data in POMS patients is limited due to the rarity of the condition. Current POMS studies have investigated factors affecting components of quality of life such as depression, anxiety, and fatigue. In this study, we investigated the association between neuroimaging, MRI metrics, and neuro-performance measures with QoL in POMS patients.

Methods: Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS) data cut 12 (July 23, 2020) was evaluated. MS PATHS is a multi-center initiative sponsored by Biogen in which comorbidities, sociodemographics, NeuroQol, phenotype and MRI performance measures are collected. All patients with disease onset before the age of 18 were included. Spearman correlations were conducted to test associations between performance scores, neuroimaging measures, and NeuroQol. Quality of Life in Neurological Disorders scores. Neuroperformance tests included manual dexterity test (MDT), involving a nine-hole peg test, and walking speed test (WST), involving a 25 foot walk, all recorded electronically.

Results: 660 POMS patients were included. 63% had relapsing-remitting MS at the time of the analysis. Mean MDT duration was 26.54 seconds (SD 6.54) and mean WST duration was 6.42 seconds (SD 3.33). Mean T2 lesion volume was 15.25 mL (SD 14.43) and mean brain parenchymal fraction was 0.85 (SD 0.03). Significant correlations were found between MDT and NeuroQol fatigue score (r(206) = -0.269, p<0.001), MDT and NeuroQol social participation score (r(205) = -0.345, p<0.001), WST performance and NeuroQol social participation score (r(205) = -0.284, p<0.001), PST performance and NeuroQol social participation score (r(205) = -0.335, p<0.001), and T2 lesion volume and NeuroQol social participation score. (r(205) = -0.231, p<0.001).

Conclusions: These results suggest that upper and lower extremity performance measures and T2 lesion volume are associated with several NeuroQol domains in POMS patients. Poor physical performance and greater MRI lesion volume correlate with worsened quality of life. The strong observed relationship between disease status and QoL suggests that effective disease management may improve QoL in POMS patients.

200. Pregnancy Outcomes in Alemtuzumab Treated Women with Multiple Sclerosis: A Case Series

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Introduction: Alemtuzumab is an anti-CD52 humanized monoclonal antibody, approved for relapsing-remitting multiple sclerosis (RR-MS). Since IgGs cross the placental barrier, alemtuzumab may represent a risk for the developing fetus. Therefore, child-bearing women should use contraceptive measures during treatment and for 4 months after each Alemtuzumab course. Real-world data on pregnancy outcomes in alemtuzumab-treated women have never been reported.
Methods: We retrospectively collected data on pregnancies in MS patients conceived after Alemtuzumab treatment. We collected written informed consent from each patient and provided a descriptive

Results: We found eight pregnancies in seven patients during Alemtuzumab treatment. Mean disease duration of these patients was 10.1±4.3 years, EDSS score 2.4±1.0, age at conception 33.4±3.4 years, months from last Alemtuzumab infusion to conception 5.7±2.7. Interestingly two pregnancies occurred within 4 months from Alemtuzumab infusion, despite patients had been thoroughly informed on the importance of pregnancy prevention. We found no evidence of thyroid disease in their clinical history and during pregnancy follow-up. We found one congenital Cytomegalovirus (CMV) infection, one pre-term birth (32 weeks), one spontaneous miscarriage, one induced miscarriage. The latter was a forced decision based on an extraterine pregnancy. CMV infection occurred in a patient conceiving within one month after Alemtuzumab infusion. None of the patients had concomitant or medical conditions other than MS and did not receive concomitant medications. Second Alemtuzumab course was delayed from one to nine months. This did not result in clinical or radiological reactivation of the disease in any of our patients.

Conclusion: Family planning and contraception should be discussed carefully in everyday clinical practice, especially in women with childbearing potential. More attention should be paid to avoid pregnancy onset within 4 months after exposure to Alemtuzumab because it appears to be associated with poorer outcomes. CMV is a common cause of intrauterine infection and carries a high risk of mother-to-child transmission. In our case the alemtuzumab-induced immunodepression may have promoted the infection. Spontaneous abortion rate in alemtuzumab clinical trials was comparable with that of treatment-naive MS patients and general population and not related to time from treatment.

313. Functional Prioritization of Multiple Sclerosis-Associated Genetic Variants That Perturb Regulatory Element Activity in T Cells
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Genome wide association studies (GWAS) have identified hundreds of regions in the genome associated with risk of multiple sclerosis (MS) and other autoimmune disorders. However, the genetic variant that is functional and causally driving disease risk is not known at the vast majority of these associated regions. This is due to pervasive linkage disequilibrium in the human genome and because most associated variants are in non-coding regions, where the effects of variants are difficult to predict. To help identify disease-causal genetic variants, we performed a massively parallel reporter assay (MPRA) to systematically assess allelic differences in gene regulatory activity in this reporter assay. Since MS-associated variants are highly enriched in T cell non-coding regulatory regions, and because T cells are highly relevant to the pathophysiology of MS, we screened 18312 genetic variants across 578 regions of the genome (including 7725 variants across 290 regions associated with MS) in a cultured T cell line. We identified 313 putatively functional genetic variants with strong allelic effects on reporter activity in the MPRA. Combining data from allele-specific reporter expression with epigenetic profiling across lymphoid cell types, we prioritize 53 of these genetic variants for further mechanistic dissection, including genetic variants in regions with genes known to alter T cell function such as IRF5, RASGRP1, and BACH2. We highlight one MS-associated genetic variant (rs72928038) near the BACH2 gene. We found that this variant overlaps a regulatory region that is preferentially active in naïve CD4 T and CD8 T cells as compared to their effector cell populations. We used base editing to replace this variant in a cultured T cell line and validated its effects on BACH2 gene expression. We also engineered mice with a deletion of the orthologous regulatory region overlapping rs72928038. In mouse naïve CD8 T cells with the deletion, we observe a reduction in expression of Bach2 and genes that maintain naïve T cell stemness and suppress T cell activation. Our work highlights how MPRA can effectively prioritize disease-associated regulatory variants for more detailed mechanistic follow-up and identifies a functional role of an MS-associated genetic variant on expression of BACH2 and on modulating T cell stemness.

314. Psychosocial Impacts of COVID-19 in People Living with Multiple Sclerosis
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Background: The high prevalence of pre-pandemic depression and anxiety in people with multiple sclerosis (PwMS) may place them at increased risk for psychosocial distress during the coronavirus disease (COVID-19) pandemic. We aim to describe the mental health status and assess risk factors for depression and anxiety symptom burden among PwMS during the COVID-19 pandemic, prior to widespread vaccine rollout.

Methods: We developed and implemented a survey, distributed online through the iConquerMS platform from 12/18/2020 to 02/10/2021, to assess self-reported experiences during the COVID-19 pandemic. Depression and anxiety symptom burden were measured via the Patient-Health Questionnaire-9 (PHQ-9, range 0-27) and Generalized
315. Interrogation of Extracellular Vesicle miRNA Repertoire in Adult and Pediatric MS

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**Objectives:** 1. To characterize extracellular vesicle miRNA repertoires in adult and pediatric MS patients. 2. To perform functional annotation and pathway enrichment analysis of the dysregulated miRNAome in MS.

**Background:** MS is a chronic, inflammatory demyelinating disorder of the central nervous system (CNS) driven by a complex interplay of genetic and environmental factors. The etiology is unknown and there is no cure. Extracellular vesicles (EVs) have gained increased attention as novel orchestrators of intercellular communication and key mediators of CNS neuroimmune crosstalk within the CNS and between the CNS and periphery. Several laboratories have examined the role of EVs as conveyors of pathogenic microRNAs, in both MS and murine EAE. MicroRNAs (miRNAs) have garnered increasing recognition as novel epigenetic modifiers of gene expression in CNS neuroinflammation and in obesity, which is one of the established risk factors in MS. We hypothesized that patient-derived EVs would exhibit distinct miRNA repertoires that would provide hypothesis-generating insights into epigenetic pathomechanisms in both adult and pediatric MS.

**Methods:** Pediatric (active MS, n=7; stable MS, n=6; bariatric controls n=10) and adult (active MS, n=6; stable MS, n=5; healthy donors, n=5) study participants were included from two independent Neuroimmunology clinics. EVs from participant serum were isolated by differential ultracentrifugation. EV concentration and size distribution was determined by microfluidic resistive pulse sensing (MRPS). Exosome markers (CD63, CD9, CD81) were detected by Western Blot. EVs were confirmed by transmission electron microscopy. Total RNA was isolated and processed for miRNA analysis on the Affymetrix miRNA 4.0 Array. Differential analysis, *in silico* target prediction and functional gene enrichment were performed.

**Results:** EVs were successfully isolated from the serum of adult and pediatric MS patients and control groups. EVs exhibited typical exosome markers (CD63, CD9, CD81) and intriguingly also demonstrated the adipocyte marker adiponectin. Differential miRNA analysis demonstrated unique miRNA repertoires that distinguished not only MS patients (active vs. stable) from control subjects but also between pediatric and adult MS.

**Conclusions:** Our preliminary results demonstrate the feasibility of isolating various EV subpopulations from the serum of adult and pediatric MS and control participants. The observation that EVs contained the adipocyte marker adiponectin provides tantalizing evidence for the exploration of adipocyte-derived EVs in MS pathogenesis. Ongoing studies are aimed at validating these findings in a larger cohort and further characterizing the role of adipocyte-derived EVs in epigenetic pathomechanisms in both adult and pediatric MS.
Objective: B-cell depleting (anti-CD20) disease modifying therapies (DMT) for multiple sclerosis (MS) may increase the risk for COVID-19 and worsen clinical outcomes. How these patients respond to mRNA vaccines is not known since immunosuppressed patients were not included in clinical trials. Here we explore the humoral response in MS patients on B-cell depleting therapies to mRNA vaccination against COVID-19.

Methods: Immunoglobulin G antibodies to the SARS-CoV-2 spike protein receptor binding domain and nucleocapsid protein were measured in MS patients and compared to control participants 3-4 weeks after initial and 3-6 weeks after the second mRNA vaccination. Clinical responses to the vaccination were also collected and compared.

Results: After the 2nd vaccine dose, 10/10 controls developed antibodies to RBD, but only 2/10 MS patients on anti-CD20 DMTs (OR 0.014, 95% CI 0.0005 - 0.3328). After the 1st vaccine dose, 6/7 controls had seroconverted while 0/6 patients on anti-CD20 DMT seroconverted. One patient who had COVID-19 while on rituximab did not develop antibodies to the nucleocapsid protein but seroconverted to RBD protein after the 1st vaccination dose suggesting a benefit to immunizing previously infected COVID-19 patients on B-cell depleting therapies. Antibody titers were significantly reduced in the MS patients (p<0.001). No differences in symptomatic response to the vaccine were observed. This response contrasted with one patient on natalizumab and two on dimethyl fumarate who seroconverted after the second vaccination.

Conclusion: Patients with MS on anti-CD20 DMT are less likely to develop antibodies to SARS-CoV-2 RBD and had lower titers after mRNA vaccination. This highlights the importance of better understanding vaccine responsiveness with larger studies and developing better strategies for effective vaccination in MS patients on B-cell depleting therapies.

K-497. Changes in Excitatory Synapse Structural Integrity and Dynamics In Vivo in a Mouse Model of Multiple Sclerosis

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Background: In patients with multiple sclerosis (MS), chronic inflammation of the central nervous system leads to widespread neurodegeneration, which is a major contributor to the development of disability. Neurodegeneration begins early in the disease course, with the ultimate outcome of widespread synapse loss and dysfunction. We hypothesize that synapses under inflammatory neurodegenerative stress undergo a series of evolving changes in structural integrity and dynamics prior to eventual synapse loss. Objective: To dissect synaptic pathology under neurodegenerative stress in a MS mouse model by combining complementary techniques to observe the synapses (1) in living animals to interrogate changes in structural dynamics of synapses, and (2) in post-mortem tissue to interrogate the integrity of synaptic components at a super-resolution level.

Design/Methods: We utilized methods for sparse fluorescent labeling of neurons and their excitatory synapses in living adult mice. Following surgical placement of a cranial window, the dendritic arbor of cortical pyramidal neurons in layer 2/3 of the cortex were longitudinally imaged in living anesthetized mice subjected to the experimental autoimmune...
encephalomyelitis (EAE) model of MS using two-photon imaging. Afterwards, brains were extracted and processed using a method that allows for reversible expansion and super-resolution imaging of cellular architecture known as magnified analysis of proteome (MAP). In these processed tissue samples, neurons and synapses were identified and stained for important synaptic proteins and inflammatory factors.

**Results:** In preliminary experiments, we have successfully longitudinally imaged excitatory synapses in vivo in mice subjected EAE. Analysis is ongoing to define changes in turnover of excitatory synapses in pre-symptomatic and symptomatic EAE. We will define the different populations of excitatory synapses with different dynamic behavior in EAE, and whether they segregate to different parts of the dendritic tree. Postmortem neurons and synapses from mice subjected to EAE are imaged at super-resolution after staining of excitatory synaptic proteins to assess the structural integrity of excitatory synapses under inflammatory stress. We are also validating additional targets for MAP immunostaining for inflammatory factors that may be implicated in the synaptic pathology of MS.

**Conclusion:** Here we use methods combining the examination of synapses both in living mice with in vivo two-photon imaging and postmortem at an ultrastructural level as a platform for assessing synaptic dysfunction and loss in neurodegeneration in a mouse model of MS.

**K-504. Older Age is Associated with a First Clinical Demyelinating Event in Children with the Radiologically Isolated Syndrome**

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**Objective:** To determine whether age at index scan is associated with the subsequent development of a first clinical demyelinating event in children with the radiologically isolated syndrome (RIS).

**Background:** The typical MRI findings of multiple sclerosis (MS) may be detected incidentally in individuals who underwent MRI scans for unrelated reasons. This clinical scenario has been termed RIS. We previously reported that 42% of children with RIS developed a first clinical demyelinating event in a median of 2 years. Little is known about risk factors associated with the development of a first clinical demyelinating event.

**Methods:** We analyzed a historical cohort of children (<18 years) with RIS enrolled in an international longitudinal study. All children met 2010 MRI criteria for dissemination in space (DIS) on index scans (Ped-RIS). All scans also met 2017 DIS criteria on MRI. We created multivariable Cox proportional hazards models for time to a first clinical demyelinating event.

**Results:** We included 89 children with Ped-RIS (median follow-up time 2.8 years; interquartile range 1.7-5.1 years). Median age at index scan was 15.4 years (range 8.1-17.9 years) and 68% of children were girls. Older age at index scan was associated with increased risk of a first clinical demyelinating event even after adjustment for sex, ≥2 unique oligoclonal bands in spinal fluid, asymptomatic spinal cord lesions on MRI, and treatment with a disease-modifying agent for MS (hazard ratio [HR] 1.4 per one year increase, 95% CI 1.04-1.4, p=0.04). Children >13 years (n=72, 81%) were at increased risk compared to those <13 years (adjusted HR 2.9, 95% CI 1.01-9.2, p=0.04).

**Conclusion:** Older children with Ped-RIS, particularly those >13 years, are at increased risk for a first clinical demyelinating event. Whether this finding is related to the effects of puberty is an area for future investigation. This information is important for parental counseling, consideration of more frequent monitoring, and identifying children at highest risk who may benefit from enrollment in an intervention trial.
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Purpose: Multiple sclerosis (MS) is an inflammatory disorder characterized by progressive demyelination of central nervous system axons, leading to episodic neurological symptoms. Direct links between heat stress (e.g., increased core temperature after exercise) and MS symptom exacerbations have been established, while links between ambient meteorological conditions (temperature, relative humidity (RH)) and MS remain understudied. This study aimed to examine these relationships, testing our hypothesis that exposure to sudden temperature change is associated with elevated risk for MS clinic visit.

Methods: Data on MS visits to all Veteran Affairs clinics between Jan. 2010-Dec. 2013 were obtained. Climate data (hourly temperature and humidity) from the National Climatic Data Center were estimated by zip code. We used a case-crossover design in which cases served as their own controls by comparing to a random day (90 to 270) prior to diagnosis. Daily lagged exposure to four meteorological conditions (temperature, RH, standard deviation (SD) of temperature (temperature variation), and temperature-RH interaction (heat index)) were computed for up to 30 day lags. We first examined independent associations between meteorological conditions and clinic visit risk, followed by a multivariate logistic regression incorporating all variables concurrently. These analyses were conducted at the national level and across climate regions.

Results: 533,066 visits were diagnosed with MS during the study period. The Northeast (NE) and Upper Midwest (UMW) regions reported the highest visit rates, and visits were 8.9% more likely to occur from spring to fall (March-October) compared to winter (OR=1.089; p<0.01). Under univariate analyses, SD of temperature, temperature, and temperature-RH interaction were positively associated with clinic visit risk, while RH was negatively associated. Under multivariate analyses, the link with temperature became negatively associated, while the other variables retained their direction. Nationally, the strongest associated variable was SD of temperature, with a one SD increase in temperature being associated with 1.2% increased risk for clinic visit (OR=1.012; p<0.01). These links varied across climate zones, however SD of temperature was also the strongest variable at this level.

Conclusion: MS clinic visit risk was negatively associated with temperature and RH, and positively associated with SD of temperature (temperature variation) and temperature-RH interaction (heat index). While these associations varied across climate zones, temperature variation was the strongest predictor both nationally and regionally. Our findings have implications for the management of MS, especially considering the expected changes in daily temperature variation and intensity of heatwaves with global warming.

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201. Learned Motor Patterns Replayed in Human Motor Cortex During Sleep

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Consolidation of learning is believed to involve offline replay of neural activity. Though amply demonstrated in rodents, it is less well documented in humans, particularly regarding motor learning. Previous work has demonstrated evidence of replay during rest in human motor cortex immediately following a motor task, but no studies have explored this phenomenon during sleep. We recorded from human motor cortex as a research participant performed a novel motor task and subsequently slept overnight. A 36-year-old man with tetraplegia secondary to cervical spinal cord injury enrolled in the ongoing BrainGate brain-computer interface pilot clinical trial had two 96-channel intracortical microelectrode arrays placed chronically into left pre-central gyrus (PCG). Single- and multi-unit activity was recorded while he played a color/sound matching memory game. On each of 160 trials, the participant was cued to a sequence of four screen locations; his task was to quickly move a computer cursor to those locations in the same sequence. Seventy-five percent of trials were the target sequence; the other trials were randomly interspersed distractor sequences. On each trial, intended movements were decoded from motor cortex neuronal activity by a real-time steady-state Kalman filter that allowed the participant to control a neurally-driven cursor on the screen. Intracortical neural activity from PCG and surface EEG were subsequently recorded overnight as he slept. When decoded using the same steady-state Kalman filter parameters, intracortical neural signals recorded overnight replayed the target sequence from the memory game at intervals throughout sleep (confirmed by surface EEG) at a frequency significantly greater than expected by chance. Replay events occurred at speeds ranging from one to four times as fast as initial task execution and were most frequently observed during slow-wave sleep. These results demonstrate that recent visuomotor skill acquisition in humans may be accompanied by replay of the corresponding motor cortex neural activity during sleep.
202. Analysis of Neuroinfection with Nanopore 16S Amplicon Sequencing for Patients Who Had Neurosurgery

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Objective: Central nervous system infection after neurosurgery is critical for a patient’s prognosis. Generally, empirical antibiotic treatment is administered when the neuroinfection is suspected. The diagnostic method with microbial culture has a high false-negative rate, so for accurate treatment, we performed Nanopore 17S ribosomal RNA (rRNA) sequencing from the cerebrospinal fluid (CSF).

Methods: Among the patients who visited the neurosurgery department of Seoul National University Hospital (SNUH) between July 2017 and June 2020, those suspected of neuroinfection by clinicians were included. The 16S rRNA PCR was performed from the CSF and Nanopore sequencing was performed for up to 3 hours. The reads were aligned to the BLAST database, and the results were compared to conventional culture studies.

Results: Of the 285 samples obtained from 179 patients who had the test of 16S rRNA sequencing, forty-one samples (14.4 %) were diagnosed with the established infection. Among them, forty samples (97.6 %) were sequencing positive, and only one sample (2.4 %) had sequencing false-negative with the microbial culture positive. More than half (23/41, 56.1 %) of the samples with the established infection showed the false-negative microbial culture test. CNS foreign body and post-operative fever were meaningfully associated with the neuroinfection (p = 0.001, OR 4.320, 95% CI 1.886-9.992, p = 0.002, OR 6.989, CI 2.328-26.932, respectively). Among 40 cases diagnosed with established infection by 16S rRNA sequencing, twenty-three cases (23/40, 57.5%) had the false-negative result of the microbial culture. Especially, in cases with intraventricular hemorrhage, the false-negative rate was significantly high in the microbial culture (p = 0.013).

Conclusion: Nanopore 16S sequencing was more effective than conventional culture studies in neuroinfection and enables an accurate treatment for the bacterial target in the central nervous system.

203. Orolingual Angioedema with Tissue Plasminogen Activator: Does the Route of Administration Really Matter?

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Background: Orolingual angioedema is a rare but known complication of intravenous recombinant tissue plasminogen activator (IV-rtPA) occurring in about 1.3 - 5.1% of patients. Most cases of post-rtPA angioedema begin hemiinguously, usually contralateral to the area of infarct. A proposed theory for this phenomenon is that infarction of the contralateral insular cortex can lead to autonomic dysfunction and vasomotor changes in the hemiparetic side. It has also been postulated that patients with concomitant angiotensin converting enzyme (ACE) inhibitor use are at an increased risk of angioedema following rtPA as the angioedema is thought to be bradykinin mediated. Apart from the most common intravenous use during acute ischemic stroke, rtPA is also used intracereally for fibrinolysis in the setting of obstructive hydrocephalus due to an intraventricular hemorrhage (IVH), and recurrent external ventricular drain (EVD) dysfunction due to clot occlusion. Intrathecal tissue plasminogen activator, however, has been rarely reported to cause angioedema.

Objective: We aim to increase awareness of orolingual angioedema as a potentially lethal complication of IT-rtPA administration.

Case Description: A 45-year-old female with a past medical history of chronic hypertension and end stage renal disease presented with altered mental status and was intubated for airway protection. Head imaging showed a right frontal intracerebral hemorrhage (ICH) with intraventricular hemorrhage (IVH) extension. She subsequently developed obstructive hydrocephalus, requiring an EVD. She had persistent hypertension and lisinopril 10 mg daily was added on hospital day (HD) 2. A dosage of 2 mg of IT-rtPA was administered once on HD 6 after several occurrences of EVD dysfunction manifested as loss of wave form and absent drainage, likely due to recurrent occlusion. Few hours after IT-rtPA administration, the patient developed severe lingual angioedema. She then received 10mg IV dexamethasone and scheduled 12.5 mg IV of diphenhydramine every 6 hours. Lisinopril was discontinued. Tracheostomy and subsequent debulking glossectomy was done 2 weeks after.

Conclusion: Tissue plasminogen activator, irrespective of the route of administration (IV vs. IT) can potentially cause angioedema. Airway protection should be a priority for management. Treatment is supportive, and tracheostomy and glossectomy can be considered for refractory cases.

204. BrainClass: A Classification Model for Summarizing Brain Injuries from CT Reports After Text Extraction Using BrainNer

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Background: Natural language processing (NLP) can be used to extract important information from unstructured text. While there are some applications of single entity recognition within the scope of neurological radiology reports, there is limited exploration of general information extraction. We propose an expansion upon our prior work of BrainNER, a Named Entity Recognition (NER) model for evaluating head computerized tomography (CTH) reports of acute brain injury. We designed and evaluated a classification model which utilizes the entity output data from BrainNER to...
make conclusions about the presence or absence of injuries within a CTH report and their associated properties.

Objective: To programmatically characterize brain pathology within a CTH report. We also sought to facilitate search queries within a large dataset and provide summary statistics about brain pathologies within a set of report documents.

Design/Methods: We created a rule-based NLP classifier which uses the long data output from BrainNER as input. The training set consisted of long data from 100 CTH reports from the Yale Acute Brain Injury Biorepository, all of which had some abnormality related to trauma, infarct, or hemorrhage. We defined a list of 16 clinically relevant brain injury categories within the BrainNER dictionary. We manually analyzed the training documents in order to derive rules which effectively modeled whether each of the 16 injury terms was described as present, possible, or not present within a report. We validated the model against 171 manually classified reports and performance was evaluated by precision, recall, and F1 score.

Results: We modeled 16 injury terms each for 171 CTH reports, for a total of 2736 conclusions modeled. The performance metrics across the 2736 terms are: Precision=97.7, Recall=98.1, F1 Score=97.8. Once the injury conclusions were modeled, they were entered into a SQL relational database to enable search and aggregate data queries. These injuries can then serve as the basis for extracting properties of these injuries such as size, location and chronicity.

Conclusion: The BrainClass classifier allows for the development of a NER+Classifier pipeline (BrainNER+BrainClass) which accurately models the status of pertinent injury terms and their properties within CTH reports. Given the level of performance, the search and statistical functionality will be effective in enabling further research on these documents.

205. Neurologic Deterioration After Renal Replacement Therapy in Patients with Acute Intracranial Injury

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Introduction: End stage renal disease (ESRD) requiring renal replacement therapy (RRT) is not uncommon in neurocritically ill patients. Continuous veno-venous hemodialysis (CVVHD) is often preferred over intermittent hemodialysis (iHD) due to potential for neurologic deterioration secondary to rapid osmolar and fluid shifts during dialysis.

Methods: We performed a retrospective analysis of patients hospitalized at an academic medical center between January 2017 and December 2018 with acute neurologic injury who underwent RRT. The primary outcome was neurologic deterioration (ND), defined as a drop of 2 or more points in motor Glasgow Coma Score (GCS) or change in pupillary exam within 24-72 hours of RRT initiation. Secondary outcomes included radiographic brain herniation (RBH) and mortality at discharge.

Results: Of 112 patients, diagnoses included intracerebral hemorrhage (35.7%), ischemic stroke (20.6%), hypoxic ischemic encephalopathy (19.6%), and intracranial masses (8.9%). CVVHD was performed in 67/112 patients (59.8%), and iHD in 45/112 patients (40.2%). Patients who underwent CVVHD had higher SOFA scores (44 vs 30, p=0.009), lower baseline GCS (4 vs 11, p=0.005), more RBH before dialysis (10.8% vs 0%, p=0.03), higher pressor requirement (80.6% vs 46.7%, p=0.005), and higher withdrawal of life-sustaining therapy (WLST) (47.7% vs 27.3%, p=0.06). There was no difference in median GCS pre-RRT vs post-RRT in both groups at 24 hours (p=0.89). ND occurred in 71.4% of CVVHD patients and 18.2% of iHD patients (p=0.17). Patients with ND had worsening midline shift post-RRT compared to pre-RRT (4.1mm vs 0.02mm, p=0.008), and greater change in serum sodium in the first 24hrs post-RRT (4.9 vs 3.1 mEq/L, p=0.001). Post-RRT, 14.3% suffered new RBH in the CVVHD group vs 7.1% in the iHD group (p=0.36). In a multivariable model adjusting for confounders there was no significant association between ND and dialysis mode, however there was a significant interaction between SOFA and dialysis mode (p=0.04), suggesting that the degree of multiorgan dysfunction maybe a mediator for this association. In a multivariable model adjusting for confounders, mode of dialysis was not associated with mortality at discharge (p=0.28).

Conclusion: In patients with acute high severity neurological injury, cerebral herniation was not infrequent during CVVHD. However, mode of dialysis was not associated with neurologic deterioration or mortality at discharge in this population with high use of CVVHD.

206. Concomitant Arterial and Venous Thrombus in a Female with COVID-19: A Case Report

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Introduction: While reports of COVID-19 related hypercoagulability have become increasingly common, these events are typically venous thromboembolic events (VTEs), including deep vein thrombosis and pulmonary embolism, with 25% of COVID-19 ICU patients experiencing VTEs. Although these sequelae are typically seen in critically ill patients, there have also been thromboembolic events documented in people who have fully recovered from COVID-19, including those on direct oral anticoagulants. Simultaneous arterial and venous thrombosis is an extremely rare condition which has been documented in only a handful of cases, seen in myeloproliferative disorders, Factor V Leiden, acute leukemia and catastrophic antiphospholipid antibody syndrome. We report the first ever known case of simultaneous intracranial arterial occlusion and venous sinus thrombosis in a patient with COVID-19 infection.

Case Description: A 52-year-old COVID positive female was brought in to the emergency department after being...
found unresponsive at home after several days of mild COVID symptoms, including fever and cough. On presentation, her National Institutes of Health Stroke Scale was 29 and Glasgow Coma Scale was four with extensor posturing and pinpoint, minimally reactive pupils. Non-contrast CT head showed diffuse cerebral edema, acute left middle cerebral artery (MCA) infarction, right parietal cortical subarachnoid hemorrhage, and hyper-density in the superior sagittal sinus, bilateral transverse sinuses and straight sinus. CT venogram confirmed diffuse venous sinus thrombosis and CT angiogram showed a concomitant left proximal MCA occlusion. MR perfusion showed large area of acute cytotoxic edema in the left L MCA distribution and venous infarction in the right parietal lobe and deep grey nuclei. She was not an endovascular thrombectomy candidate due to extensive infarct core. She was started on intravenous heparin and hyperosmolar therapy for cerebral edema and her electroencephalogram showed isoelectric and non-reactive waveforms the following day, and she was subsequently declared brain dead.

Discussion: To the best of our knowledge, this is the first case of simultaneous intracranial arterial and venous thrombotic event, and first such case associated with COVID-19 infection. Our case highlights the risk of such complications in patients with mild COVID-19 infections, and suggests further epidemiological studies to identify risk factors for hypercoagulability in mild COVID-19 cases are warranted. In light of this new presentation of mixed hypercoagulability in a COVID positive patient, providers should be wary of more widespread hypercoagulability. Increasing awareness of this rare presentation might improve recognition and potential treatment protocols to prevent similar devastating cerebrovascular events.

207. Associations Between Fibrinogen and Immune Effector Cell-Associated Neurotoxicity Syndrome in CAR-T Patients

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Background: Chimeric antigen receptor T-cell (CAR-T) therapy's efficacy against hematologic malignancies is limited by a severe neurotoxicity called Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS). The mechanism of this neurotoxicity is poorly understood but it is known to associate with Cytokine Release Syndrome (CRS), a systemic inflammatory complication of CAR-T. The coagulation factor fibrinogen is known to decrease precipitously in CRS, but its behavior in ICANS has not been fully investigated. An isoform of fibrinogen, gamma-prime fibrinogen (γ′), is an emerging biomarker reflecting inflammation and thrombotic disease which is differentially upregulated from fibrinogen in the presence of IL-6.

Objective: To investigate the profile of γ′ and total fibrinogen obtained pre-CAR-T infusion, 48-72 hours post-infusion, and again if/when ICANS occurred. Blood was obtained at each timepoint, spun and aliquoted for plasma, and stored at -70°C for batch analysis. Fibrinogen was measured with the Stago viscoelastic assay. For patients who developed ICANS, changes in concentration of γ′, fibrinogen, and γ′/total fibrinogen (γ′/f) were calculated from baseline to post-infusion (BL->PI, n=10) and post-infusion to symptomatic (PI->Sx, n=6) timepoints and reported as mean change in mg/dL (95%CI) and compared by paired samples t-test. Concentration differences from BL->PI in ICANS/non-ICANS groups were compared by independent sample t-test. All analyses were conducted in R (R Core Team 2019).

Results: Seventeen patients were included (35% women, mean age 59±14 years) of whom 10 developed ICANS. Mean change in fibrinogen was -6.7 (-178-192, p=0.94) and -205 (-471-61, p=0.10) for BL->PI and PI->Sx, respectively. Mean change in γ′ was -1.23 (-20.8-23.3, p=0.90) and -6.83 (-31-17, p=0.50) for BL->PI and PI->Sx, respectively. Mean change in γ′/f was -0.01 (-0.04-0.06, p=0.57) and 0.06 (-0.13-0.01, p=0.07) for BL->PI and PI->Sx, respectively. Changes in γ′, fibrinogen, and γ′/f from BL->PI did not significantly differ between ICANS/non-ICANS groups.

Discussion: We observed no significant differences in this preliminary paired comparison of biomarkers across select timepoints for patients who developed ICANS. However, the pattern of decreasing fibrinogen and γ′ together with a rising γ′/f ratio may reflect an IL-6 driven inflammatory state underlying coagulopathy and/or capillary leak in ICANS patients which should be validated in a larger cohort.

208. Association of CT-Based Fronto-Temporal Contusion Volume with the Development of Post-Traumatic Epilepsy

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Post-traumatic epilepsy (PTE) is a common complication of traumatic brain injury (TBI), and TBI is one of the primary causes of acquired epilepsy. Thus far, TBI severity has been the leading risk factor for PTE development. However, aside from severity and its related characteristics (penetrating injury, skull fracture, etc.) few etiological risk factors for PTE have been firmly established. Tubi et al (2018) found that lesion location based on MRI is related to both a high incidence of early seizures and longitudinal development of PTE, but lesion volume was not investigated. The CT scan is highly accessible and more common in TBI evaluations, and thus evaluation of contusion location and volume could feasibly be used as a screening tool for PTE risk. Thus, in this study we sought to evaluate the effect of both CT-based contusion volume and location on the development of PTE.
We identified a retrospective cohort of 25 TBI patients admitted to a tertiary care center from 2011-2015 who developed PTE. Patients were matched by age and TBI severity (Glasgow Coma Scale score) with 25 TBI controls who did not develop PTE. Using OSIRIX MD software, two blinded raters evaluated contusion volume and location in all 50 patients. Volumes were manually compared and adjudicated by consensus in cases of disagreement >5cc; volume measurements were then averaged. Contusions were classified according to laterality and involvement of the frontal or temporal lobes. Prior research has shown that parietal and occipital contusions exhibit minimal association with the development of PTE, and thus contusions in these lobes were excluded from analysis. Using two-tailed T-tests, we compared overall fronto-temporal contusion volume, and regional contusion volume (left/right frontal and temporal lobes). We also compared the proportion of subjects with contusions in each anatomic region using Fisher’s Exact Test. We found that patients who developed PTE had significantly greater fronto-temporal contusion volume (29.0 vs 4.6 cc, P < 0.05). Patients with PTE were more likely to have a left frontal lobe contusion compared to non-PTE subjects (Fisher’s Exact Test, P < .05). We did not find a significant difference in lesion volume for any specific region between PTE and non-PTE patients. These data suggest that greater fronto-temporal contusion volume is associated with development of PTE. These findings also illustrate the possible utility of CT contusion volume measurement as a PTE risk screening tool.

209. Pseudo-Cerebral Silence
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Introduction: COVID-19 is a rapidly evolving disease process caused by the SAR-COV2 virus. It is most notable for attacking the respiratory, renal, and cardiac systems, which can lead to multisystem organ dysfunction and death. Less commonly documented complications include neurologic dysfunction in the setting of acute infection. Although the exact mechanism is still being studied, it is proposed that macro- and microthrombi with the concomitant inflammatory response can lead to brain damage in select populations.

Case Presentation: We present a 58-year-old COVID-19 positive African American female with progressively worsening respiratory function requiring endotracheal intubation. During her hospital course, the patient clinically deteriorated, losing all neurologic function including loss of reflexes and lack of responsiveness off sedation. A nuclear cerebral perfusion scan showed an absence blood flow, confirming brain death. Within 24 hours upon reexamination, the patient regained consciousness and was shortly extubated. She was eventually discharged in good health.

Discussion: COVID-19’s initial presentation consists of nonspecific signs and symptoms but can quickly progress to devastating multisystem complications. Recent studies suggest this is in relation to the body’s overwhelming immunologic response and hypercoagulable state. Direct impact on the central nervous system, although rare, has been reported with newly published studies observing an increased incidence of acute disseminated encephalomyelitis (ADEM), which leads to widespread inflammation of the brain and spinal cord. In the setting of brain injury, our detailed literature review did not come across instances of complete recovery of neurologic function after established brain death in COVID-19 patients. Here we examine, the prevalence of neurologic impairment from COVID-19 and the sensitivity of neurologic perfusion scans in determining brain death.

Conclusion: With continued scientific advances in the understanding and treatment of COVID-19, we begin to uncover the physiologic mechanisms responsible for rapidly progressive multisystem organ dysfunction. These include, but are not limited to, amplified immune mediated responses and hypercoagulable states with macro- and microcirculatory thrombi. Rare inflammatory central nervous system disorders have been documented; however complete recovery after the establishment of brain death presents a unique challenge that questions the utility of nuclear cerebral perfusion scans, especially in COVID-19 patients.

210. EEG Findings and Clinical Outcome in COVID-19 Patients with Acute Encephalopathy: A Large Healthcare System Retrospective Cohort Study in the United States
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Background: COVID-19 patients may present with CNS involvement and a variety of neurological manifestations. There are no predictable markers for clinical outcome of patients presenting with acute mental status change. This study aimed to evaluate the clinical features including EEG findings, neuroimage results, hospital course and outcome in COVID-19 patients presenting with acute encephalopathy.

Methods: This is retrospective multicenter study, approved by institutional review board at MedStar Health. All patients admitted with a confirmed diagnosis of COVID-19 with a positive high-throughput sequencing or real-time reverse-transcription polymerase chain reaction analysis will be included. Electronic medical records for these patients admitted from April 2020 to July 2020 were reviewed and those with EEG and neurological examination were including in this study. Statistical analysis was performed using SPSS 25.

Results: Total 22 patients (10 female, 12 male) admitted with COVID-19, who had EEG study for evaluation of acute mental status change, were enrolled in this study. Mean age of these patients was 57.8 +/- 13.3 (26-83) years. 59.1% were African American, 22.7% Hispanic. Mean WBC count was 7.9 +/- 3.1. ESR and CRP levels were elevated in all patients (mean ESR 76.3 +/-14.9, and CRP 129.5 +/-70).
Six patients (26.3%) of patients had known history of epilepsy of which 4 patients had breakthrough seizure during this admission. Clinical evaluation revealed metabolic abnormalities in 81.8% patients, acute ischemic stroke (4.5%), acute hemorrhagic stroke (4.5%), encephalitis (4.5%), and new onset seizure (9%). Eighteen patients (81.8%) were admitted in ICU, and 14 patients (63.6%) were intubated, and 7 patients (31.8%) were expired during this admission. Out of the EEG findings, 2 patients had interictal abnormalities including generalized periodic discharges and focal spikes. The rest all had slow background activity ranging from mild to severe. 7 patients had moderate to severe background slowing. In terms of clinical outcome, 7 patients improved back to baseline, 8 patients had residual neurological deficits and 7 patients expired during the hospital stay. Interestingly, all patients (n=7) improved back to baseline had mild background slowing, and all expired patients (n=7) had severe background slowing, which may indicate background change may be a marker of clinical outcome for covid-19 related encephalopathy.

**Conclusion:** Acute alteration in mental status and severe background slowing in EEG are suggestive of ICU admission and poor outcome in hospitalized patients COVID-19.

### 333. Natural Language Processing Model to Extract Acute Abnormalities from CT Head Reports

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**Background:** Natural language processing (NLP) can be used to extract information from Electronic Health Records. Yet, there is limited exploration of NLP applications to extracting information about neurologic injury from radiology reports. We propose using spaCy BrainNER, a novel approach combining deep learning and Named Entity Recognition (NER), to evaluate non-contrast head computerized tomography (CTH) reports of acute brain injury.

**Objective:** To automatically extract acute brain pathology from CTH reports to relate injury features, such as injury size and location, to outcomes of interest.

**Design/Methods:** We adapted an open source NLP model, spaCy NER, into our custom spaCy BrainNER model by training it to extract abnormalities from CTH reports. The training set consists of 3,361 adult CTH reports from 3330 patients in the Yale Acute Brain Injury Biorepository with traumatic, ischemic, or hemorrhagic injuries. We trained the spaCy BrainNER model to recognize and classify acute pathologies into 63 pre-defined Named Entity categories outlined by a custom dictionary of words/phrases (entities), including terms describing hemorrhage, ischemia, size and location. We performed a 10-fold cross-validation, using manually labelled folds (gold standard) to train and test the model’s performance. We used all 10-folds of training data to create our final model which was then evaluated based on our test dataset 12.5% of data to evaluate our final model. We used a test set of 500 CT reports from MGH as our external validation. Overall performance was evaluated by averaging the ten models to find: precision (positive predictive value), recall (sensitivity), and F1 scores. We then created a classifier for automated exportation of identified abnormalities for future analysis.

**Results:** The average performance metrics across 10-folds are: Precision= 98.09, Recall 98.12, F1 score= 98.10. Our performance metrics for the Yale test set are: Precision= 98.82, Recall 98.81, F1 score= 98.81. Our spaCy BrainNER model identified 183273 true positive entities, 1512 false positives and 1700 false negatives. The MGH external validation dataset performance metrics are: Precision= 98.51, Recall 98.40, F1 score= 98.62.

**Conclusion:** This model reliably extracts and compiles entities representing acute abnormalities in CTH reports. Our next steps include: cross-validation with multiple external datasets and evaluate if re-training on multi-institutional data improves performance.

### 334. Stroke as a Cause of Donor Brain Death and Prognostic Implication in Heart Transplantation

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**Background:** Stroke as the proximate cause of brain death were lowest (P<0.001) and constant (P=0.16) at 13.8% in 2005 and 15.2% in 2018. The cause of brain death had a strong interaction with the donor age (Pinteraction=0.004). When allografts...
were procured from donors younger than 35 years old, stroke as the cause of brain death was associated with increased risk of mortality (23% versus 19% at 5 years; hazard ratio [HR], 1.17; 95% confidence interval [CI], 1.00-1.37) and graft failure (HR, 1.31; 95% CI, 1.01-1.70). When donors were older than 35 years old, the cause of brain death had no association with outcomes.

**Conclusions:** Recipients of cardiac transplantation from donors younger than 35 years of age and stroke as the cause of brain death have an increased hazard of death and allograft failure. These findings suggest an opportunity to explore modifiable factors in donor candidate management in this particular young cohort to improve transplantation outcomes.


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**Background:** Blood-brain barrier (BBB) disruption is a known component of traumatic brain injury (TBI), and has been implicated in TBI-related disability. Recently, BBB dysfunction has been associated with early cognitive impairment, a feared long-term consequence of TBI. Here we analyzed the relationship of plasma biomarker levels and dynamic contrast-enhanced (DCE) MRI as a measure of TBI-related BBB dysfunction.

**Methods:** We examined blood-based biomarkers and neuroimaging from eleven adult patients (median age 29 years, 81.8% male) admitted to the hospital following non-penetrating TBI (54.5% motor vehicle accident, 18.2% falls, 27.2% blunt trauma). Blood was collected within 72 hours of injury. 3T DCE MRI was performed 2 weeks post-injury. DCE MRI was analyzed using the Patlak 2-compartment model to calculate total voxel-wise volume across whole brain in which the volume transfer coefficient (K\text{trans}) was elevated above the 95th percentile of controls. Spearman correlations were performed to examine the relationship between the plasma and neuroimaging biomarkers.

**Results:** In this mildly injured cohort (median GCS 15; IQR 14-15; 82% with positive head CT imaging), mean (SD) volume of voxel-wise K\text{trans} elevation across whole brain for the sample was 960.66 mm³ (258.30 mm³). Platelet-derived growth factor receptor beta (PDGFR-ß) was significantly correlated with the K\text{trans} (\(r = 0.77; p = 0.005\)) and the normalized permeability index (\(r = 0.87; p < 0.0005\)). Other known TBI biomarkers, including GFAP (\(r = 0.35; p = 0.28\)), NFL (\(r = 0.44; p = 0.18\)), and UCHL-1 (\(r = 0.29; p = 0.38\)) were not correlated with K\text{trans}.

None of the biomarkers tested were correlated with post-TBI symptoms (Rivermead Post-Concussion Questionnaire) or global outcome (Glasgow Outcome Score-extended) measured at >3 months post-injury.

**Conclusion:** Plasma PDGFR-ß was a significant predictor of voxel-wise K\text{trans} elevation, suggesting that this may serve as a circulating biomarker of TBI-related BBB dysfunction. This is consistent with recent studies indicating that CSF PDGFR-ß correlates with hippocampal BBB dysfunction and may be an early marker of neurocognitive impairment. Future work will examine the relationship of these imaging and blood-based biomarkers with detailed neurocognitive outcome measures collected longitudinally.

**LB-445. Use of Continuous EEG with Off-Sedation Protocol for Neurological Prognostication in Patients on ECMO Support**

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**Background:** Patients requiring extracorporeal membrane oxygenation (ECMO) support have high risks of morbidity and mortality. Thus, protocolized evaluation of ECMO patients is crucial for neurological prognostication. We conducted a study of patients monitored on continuous EEG (cEEG) after weaning off sedation that are known to significantly alter EEG patterns.

**Method:** Records of adult patients who initiated ECMO support between 7/2016 and 12/2020 were reviewed. Per protocol, cEEGs were performed on patients with Glasgow Coma Scale (GCS)<8 despite minimal/absent sedation, had clinical seizures, or were within the first 48-72 hours since cardiac arrest. Patients continuing to receive sedation that affect EEG reactivity at the start of cEEG recording, including propofol, ketamine, or benzodiazepines, were excluded from analysis. Dexmedetomidine and fentanyl were deemed acceptable, as they have fewer confounding effects. EEG features that were evaluated included frequency, amplitude, variability, reactivity, and state change. The results were analyzed with Fisher’s exact tests and calculations of sensitivities and specificities.

**Results:** Of 290 patients, 40 underwent cEEG off-sedation (median age: 60 years, interquartile range (IQR): 46-66.5 years, 55% women, 85% venoarterial-ECMO, 15% venovenous-ECMO). 27 underwent withdrawal of life sustaining therapies (WOLST) at the time of being supported by ECMO, 9 were weaned off ECMO support but underwent WOLST later on during the same hospitalization, and 4 were weaned off ECMO support and survived at the time of hospital discharge. Decisions of WOLST were made in setting of significant single or multi-organ failure, and were not influenced by the results of the analyzed cEEG variables. Median length of ECMO support was 143 hours (IQR: 81-254 hours). Median length of analyzable cEEG monitoring data was 24 hours (IQR: 17-35.5 hours). Proportions of absent reactivity, absent state changes, and absent/poor variability were significantly higher in patients who had deceased at the time of hospital discharge compared to those who survived (odds ratios infinity, infinity, 13.57 respectively; p-values <0.001, <0.001, 0.0299 respectively). Sensitivity and specificity for absent reactivity were 91.67% and 100% respectively, for absent state changes were 97.20% and 100% respectively.
respectively, and for absent/poor variability were 83.33% and 75% respectively.

Conclusions: We demonstrated that absent reactivity, absent state changes, and absent/poor variability in cEEG of patients receiving ECMO support are associated with death at the time of hospital discharge.

Neurogenetics

212. Systematic Analysis of Brain MRI Findings in Adaptor Protein Complex 4 - Associated Hereditary Spastic Paraplegia Reveals Patterns for Diagnosis and Disease Progression
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AP-4-associated hereditary spastic paraplegia (AP-4-HSP: SPG47, SPG50, SPG51, SPG52) is an emerging cause of childhood-onset hereditary spastic paraplegia and mimic of cerebral palsy. Here we performed a systematic qualitative and quantitative analysis of 107 brain MRI studies from 76 individuals with genetically confirmed AP-4-HSP and investigate correlations with clinical findings including surrogate of disease severity. Our results define AP-4-HSP as a disorder of gray and white matter, and demonstrate that hypomyelination is prominent but not always static and that several metrics of reduced white matter volume correlate with severity of motor symptoms. We identify a common diagnostic imaging signature consisting of (1) a thin splenium of the corpus callosum, (2) an absent or thin anterior commissure, (3) characteristic signal abnormalities of the forceps minor (“ears of the grizzly sign”), and (4) periventricular white matter abnormalities. The presence of two or more of these findings has a sensitivity of ~99% for detecting AP-4-HSP, while the combination of all four is found in ~45% of cases. Compared to other HSP with a thin corpus callosum, the absent anterior commissure appears to be specific to AP-4-HSP. Our analysis further identified a subset of AP-4-HSP patients with polymicrogyria, underscoring the role of AP-4 in early brain development. Of clinical importance, these patients displayed a higher prevalence of seizures and status epilepticus, many at a young age. Collectively, our findings define the MRI spectrum of AP-4-HSP providing opportunities for early diagnosis, identification of individuals at risk for complications, and a window into the role of the AP-4 complex in brain development and neurodegeneration.

213. Implementing a Pharmacogenomics Clinic: The Suny Upstate Neurology Experience
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Objective: To determine the prevalence of actionable pharmacogenomics results in vascular patients with a history of medication intolerance or efficacy concerns.

Background: Evidence-based, gene-drug clinical practice guidelines exist for many secondary stroke prevention medications. However, little is known about the prevalence of actionable pharmacogenomics results in vascular patients.

DESIGN/METHODS: Since its opening in January 2020, the Pharmacogenomics Clinic at SUNY Upstate Neurology has focused on identifying individual patient genetic polymorphisms, associated with medication intolerance or decreased efficacy (genetically actionable results). We performed a cross-sectional study evaluating the first 6 months.

Results: Twenty-eight patients were referred to our pharmacogenomics clinic in the first 6 months (mean age 58±16 years; 86% Caucasian/White, 7% African American/Black, 7% Asian; 50% women). 100% had vascular disease. 82% were followed by vascular neurology, 71% by cardiology, and 7% by vascular surgery (groups not mutually exclusive). 50% reported medication intolerance or decreased efficacy with antiplatelet agents, 11% with anticoagulants, and 75% with statins. Genetically actionable results were present in 93% of patients with antiplatelet concerns (CYP2C19 or CYP3A4), 100% with anticoagulant concerns (CYP2C9 or VKORC1), and 86% with statin concerns (SLCO1B1 or ABCB1). When all drug classes were considered, medication changes were recommended for all 28 patients. Examples of cases where pharmacogenomics findings resulted in medication change recommendations will be presented.

Conclusion: Actionable pharmacogenomics results are common among vascular patients. Pharmacogenomics guided prescribing may optimize medications for secondary stroke prevention, in individual patients. We are currently applying pharmacogenomics to other neurologic specialties, given these promising early results in vascular patients. A multi-therapeutic approach to pharmacogenomics guided drug management has the potential to produce a greater health and economic benefit to patients and providers.

214. A Novel Heterozygous Mutation in a Hispanic Patient with Hereditary Hemorrhagic Telangiectasia and Cerebral Infarction
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Introduction: Hereditary Hemorrhagic Telangiectasia (HHT) is a familial vascular dysplasia with multiorgan effects and 85% cases having a genetic mutation of ENG, ACVR1I, SMAD4, or GDF2. Our patient has an under-recognized
presentation of cerebral infarction with underlying novel genetic mutation.

**Methodology:** Case-report involving acute cerebral infarction and newly-diagnosed HHT. Genetics data pertaining to this case was reviewed from the Genome Aggregation Database, University of Utah and The Human Variome Project.

**Results:** A 56-year-old, right-handed Hispanic man with hypertension, coronary artery disease, personal and familial recurrent epistaxis with mucocutaneous telangiectasias was admitted for repair of an unrelated hip fracture, with perioperative cerebral infarction status post (s/p) successful mechanical thrombectomy, due to paradoxical embolus from newly-discovered large pulmonary arteriovenous malformation (AVM) and left leg deep vein thrombosis with otherwise unremarkable ischemic workup. Genetic testing revealed heterozygous ACVRL1 variant of unknown significance (VUS) mutation at c.236G>A in exon 3. This ACVRL1 variant has low frequency of 0.00089%, but impact in the Hispanic population is undetermined. In our case, this variant seems clinically pathogenic. He underwent pulmonary AVM embolization, s/p inferior vena cava filter placement and is prescribed daily aspirin for secondary prophylaxis with planned surveillance.

**Conclusion:** We present a novel mutation associated with HHT. Screening for this variant can help establish an early diagnosis allowing further screening for associated pathology potentially avoiding future complications such as AVM rupture, ischemic stroke, and pulmonary failure with earlier intervention.

**215. Development of a Severity Scale for Multiple Sulfatase Deficiency**

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Multiple sulfatase deficiency (MSD) is an ultra-rare, neurodegenerative disease of early childhood that results in a progressive systemic burden of disease and neurologic regression. The natural history of MSD suggests two distinct phenotypes: a severe form characterized by profound global impairment and an attenuated form characterized by acquisition of ambulation followed by neurologic regression. Based on our natural history data, we hypothesized that a MSD-specific scale could be designed to measure the increasing burden of disease over time. To create the MSD scale, we selected items from validated outcome assessments based on rate of acquisition across MSD. The neurologic subscale includes mobility and communication skills, while the systemic subscale quantitates total disease burden. Next, we applied the scale to the clinical encounters available in our retrospective natural history study (n=30). Individuals were categorized by genotype severity (severe vs. attenuated), and we compared the average MSD scale score between key periods of time, including 2-4 years of age. We found that neurologic outcomes are proportional to early score values. Using this approach, we were able to establish a clinically meaningful disease specific scale capable of quantitating the burden of disease over time. In future directions, the scale will be applied prospectively during research encounters. We anticipate that this novel MSD-specific scale will be capable of stratifying subjects during clinical trials into severity classes and to guide inclusion/exclusion criteria in upcoming clinical trials.

**216. Genetic Counseling Through Virtual Visits in Parkinson Disease (GET VIRTUAL-PD): A Clinical Trial to Evaluate Methods of Genetic Counseling**

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**Objective:** The primary objectives of this study are to determine the efficacy of (1) a web-based pre-test genetic counseling tool called the Interactive, Multimedia Approach to Genetic counseling to INform and Educate in Parkinson’s Disease (IMAGINE-PD) compared to virtual visits with the genetic counselor, and (2) virtual disclosure of genetic testing results compared to telephone disclosure.

**Background:** The current genetic counseling standard-of-care, which utilizes a two-visit, face-to-face counseling model, is limited by access to trained genetic counselors who can provide personalized genetic counseling before and/or after consideration of genetic testing. In the Parkinson’s Disease (PD) field, genetic testing has become increasingly more common due to the ongoing development of GBA and LRRK2-targeted therapies, however the number of patients with PD outnumbers the availability of genetic counselors who specialize in adult neurology. Alongside expansions in genetic testing, it is essential that we develop novel models for safe and effective communication of genetic information at scale. Alternative genetic counseling and disclosure models involving video or web-based tools may help to alleviate this limitation.

**Methods:** Every patient with PD at the UPenn Parkinson’s Disease and Movement Disorders Center (>2000 patients) is offered enrollment in the Molecular Integration in Neurologic Diagnosis (MIND) biobanking initiative. Research-based genetic screening for 22 variants in GBA and LRRK2 genes is performed for all enrolled participants.

CLIA-approved clinical confirmation genetic testing and counseling is offered through enrollment in the GEnetic counseling Through VIRTUAL visits in Parkinson’s Disease (GET VIRTUAL-PD) trial. Participants are randomized by factorial design to pre-test genetic counseling via videoconference visit with the genetic counselor or web-based IMAGINE-PD, and results disclosure via telephone or videoconference visit. The primary outcomes are patient knowledge, satisfaction, and test-related distress via survey responses at 3 and 6 months after results disclosure.
**Results:** Between January 2021 and March 26, 2021, 20 MIND participants were contacted about the GETVIRTUAL-PD study, with 7 unsuccessfully contacted. 13 participants (100% of those successfully contacted) chose to enroll, of which completed pre-test counseling and 1 was scheduled. Enrollment is ongoing for a target of 380 participants.

**Conclusion:** Novel virtual genetic counseling approaches will increase access to genetic counseling and testing. Identifying PD patients carrying variants in GBA and LRRK2 is important for identifying research-eligible patients and to give patients the opportunity to learn more about their genetic information.

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**217. Interactive Multimedia Approach to Genetic Counseling to Inform and Educate in Parkinson Disease:** IMAGINE-PD User and Usability Testing

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**Objectives:** To obtain feedback on the Interactive Multimedia Approach to Genetic counseling to INform and Educate in Parkinson’s Disease (IMAGINE-PD) website to optimize content and usability.

**Background:** Clinical research studies enrolling carriers of genetic variants in GBA and LRRK2, the two most common genetic risk factors for PD, have led to increases in genetic testing. As interest in genetic testing expands, so too does our need for scalable approaches to counseling that are effective and safe. Lack of access to specialized genetic counselors, travel and cost restrictions remain major barriers in the field. To address these, an interactive, web-based, audiovisual, self-guided, genetic counseling tool was developed called IMAGINE-PD.

**Methods:** IMAGINE-PD content was developed by a certified clinical genetic counselor according to national guidelines. Content was revised by neurogeneticists and PD specialists and presented in a web-based format, utilizing videos, text, pictures, and audio. Six subject matter experts also provided content feedback. Thirteen individuals with PD and eleven PD Neurologists at UPenn were enrolled in user testing for content review. Twelve individuals with PD were enrolled in usability testing for website interface, aesthetics, and functionality. At user and usability testing phases feedback was collected by Likert-like scale and open-ended response. Quantitative data are presented as summary scores. Qualitative analysis was conducted at both phases.

**Results:** User testing patient participants had a median age of 64 (IQR63-69), 77% were male and 23% female, and had a median disease duration of 10 years (IQR7-13). Usability testing patient participants had a median age of 63 (IQR 60 - 72.5), 58% were male and 42% female, and had a median disease duration of 8 years (4.75 - 13). In all cohorts, internet use was common; all participants reported electronic communication with medical professionals. All participants in user testing reported that information was useful; some suggested adding figures, animations, and concise language. In user testing, patients and physicians reported a 9 of our 10 (IQR 9-10) overall rating for IMAGINE-PD. Participants in usability testing reported ease of navigation, fast load time, and clarity of information provided, but suggested changes in aesthetics and functionality.

**Conclusion:** Content review and usability testing were completed to develop this PD genetic counseling tool. Comparison of IMAGINE-PD to personalized genetic counseling methods is ongoing.

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**218. Characterizing the CDG-SRD5A3 Clinical Spectrum**

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**Objective:** We aimed to characterize the clinical spectrum of children diagnosed with CDG-SRD5A3 through a medical history questionnaire and standardized measures of adaptive functioning and quality of life.

**Background:** N-glycosylation is an essential post-translational modification that is involved in protein folding with disorders falling under the overarching group Congenital Disorders of Glycosylation (CDG). This includes the CDG-SRD5A3 subtype due to variants in the steroid 5a-reductase type 3 (SRD5A3) gene. Patients present with multi-systemic involvement including neurological disability, dermatologic abnormalities, and ophthalmological defects.

**Methods:** We conducted a cross-sectional study of children (n=6, ages 4-16 years) with a confirmed diagnosis of CDG-SRD5A3 (c.57G>A/ pTrp19X). Families completed a detailed medical history questionnaire, two quality of life measures (PedsQL Family Impact Module, the QI Disability Form), and the Vineland Adaptive Behavior Scales, 3rd ed.

**Results:** Prevalent clinical features in our cohort included visual impairment (6/6), developmental delay (6/6), nystagmus (5/6), retinal dystrophy (4/6), and hypotonia (3/6). The Vineland Adaptive Behavior Scales demonstrated deficits across all functional domains (Composite Mean 36.17, SD 26.88), ranging from 1 to 5 standard deviations below the standardized mean (standardized mean 100, SD 15), although one child did not show significant deficits. The QI Disability Form demonstrated a mean total score of 64.8 (SD 12.7), approximately 2 SD below the standardized mean of 100. The PedsQL-FIM demonstrated a mean total score of 56.5 (SD 31.5). However, one family has three affected children and demonstrated increased disability on this measure. By parent report, one child showed regression of rolling over and babbling, one child did not achieve any language or motor milestones, and four children exhibited developmental delay but continued milestone achievement.

Distribution of Vineland raw scores by age demonstrates patients attain skills through early childhood, plateau in adolescence, and decline in the teens. However, this is a small sample size and may not be generalizable. Vineland composite scores did not correlate with levels of disability captured by the QI-Disability Form (Pearson Correlation range -0.63 to +0.69, p>0.05 on all subscales).
Conclusions: For clinicians encountering patients exhibiting visual impairment, developmental delay, nystagmus, retinal dystrophy, and hypotonia, CDG-SRD5A3 should be considered. Despite genotypic homogeneity, there is notable variability in adaptive functioning and quality of life among affected children that does not correlate with age in this small sample size. Additional studies of CDG-SRD5A3 with larger populations or longitudinal data collection are needed to improve understanding of this disorder and explore treatment opportunities.

219. Parotid Neoplasm in a Patient with Wilson Disease and Levodopa-Responsive Parkinsonism
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Background: Wilson Disease (WD) is a genetic disorder that compromises copper metabolism with multisystemic manifestations. Despite the toxicity of copper, it may be related to cancer (CA) induction, due to its role in angiogenesis, the occurrence of CA in DW is rare. Even hepatocarcinomas (HCA) and cholangiocarcinomas (CCA), more common in occurrence of CA in DW is rare. Even hepatocarcinomas. Despite the toxicity of copper, it may be related to multisystemic manifestations. Wilson Disease (WD) is a genetic disorder that compromises copper metabolism with multisystemic manifestations. Despite the toxicity of copper, it may be related to cancer (CA) induction, due to its role in angiogenesis, the occurrence of CA in DW is rare. Even hepatocarcinomas (HCA) and cholangiocarcinomas (CCA), more common in

Design/Methods: Survey of CA cases in patients with WD, case report and analysis of diagnosis and conduct based on the digitally published literature referring to WD and CA.

Clinical Case: AES, 38 years old, male, married, born in Hidrolândia, Ceará, Brazil. In 2006, he began to experience emotional lability with easy crying, depressive symptoms and a period of aggression towards her wife and children. He had 3 brothers affected by Wilson’s disease, 2 of whom died and one was in terminal stage. He was diagnosed with WD in 2006, with mobility and speech disorders, Kayser-Fleisher rings and auditory hallucinations. He had parkinsonism with an excellent response to Levodopa. In 2011, there was a change in bilateral base nuclei compatible with the accumulation of heavy metal. In 2014, a solid mass suggestive of a parotid tumor was found, with a biopsy confirming neoplastic cells from carcinoma. In a second biopsy, atypical squamous cell neoplasia and free margins were found. Metastasis in 1 of 10 lymphnodes collected. Malignant neoplasm of the parotid gland invading deep planes close to the skull base and staging IVa (T4aN1M0). In 2016, after radiotherapy and left parotidectomy, he died.

Discussion: Copper is also an extremely important cofactor for the of many mediators in the angiogenesis process. When deprived of vascular supply, solid tumors do not exceed a few millimeters in diameter, which is the theoretical basis for its antiangiogenic treatment. Currently, there are few reports of CA in WD, the most common involving HCA and CCA. There are publications in the DW literature associated with colon cancer, acute lymphoblastic leukemia, CD5 large B cell intravascular lymphoma, primary breast cancer, Glioblastoma and Seminoma, however they are rare.

Conclusion: After reviewing the literature, as far as we know, this is the first report of complicated WD with parotid CA, especially considering the wealth of associated neurological symptoms. Therefore, a case report is important for a better understanding of the spectrum of manifestations of WD.

220. An iPSC-Based Neural Model of Sialidosis Uncovers Glycolytic Impairment-Causing Presynaptic Dysfunction
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Sialidosis is a neuropathic lysosomal storage disease caused by a deficiency in the NEU1 gene-encoding lysosomal neuraminidase and characterized by abnormal accumulation of undigested sialyl-oligoconjugates in systemic organs including brain. Although patients exhibit neurological symptoms, the underlying neuropathological mechanism remains unclear. Here, we generated induced pluripotent stem cells (iPSCs) from skin fibroblasts with sialidosis and induced the differentiation into neural progenitor cells (NPCs) and neurons. Sialidosis NPCs and neurons mimicked the disease-like phenotypes including reduced neuraminidase activity, accumulation of sialyl-oligoconjugates and lysosomal expansions. Functional analysis also revealed that sialidosis neurons displayed two distinct abnormalities, defective exocytotic glutamate release and augmented α-amino-3-hydroxy-5- methyl-4-isoxazole-propionate receptor (AMPA)-mediated Ca2+ influx. These abnormalities were restored by overexpression of the wild-type NEU1 gene, demonstrating causative role of neuraminidase deficiency in functional impairments of disease neurons. Comprehensive proteomics analysis revealed the significant reduction of SNARE proteins and glycolytic enzymes in synaptosomal fraction, with downregulation of ATP production. Bypassing the glycolysis by treatment of pyruvate, which is final metabolite of glycolysis pathway, improved both the synaptosomal ATP production and the exocytotic function. We also found that upregulation of AMPAR and L-type voltage dependent Ca2+ channel (VDCC) subunits in disease neurons, with the restoration of AMPAR-mediated Ca2+ over-load by treatment of antagonists for the AMPAR and L-type VDCC. Our present study provides new insights into both the neuronal pathophysiology and potential therapeutic strategy for sialidosis.

221. CSF Protein Co-Expression Implicates PIK3/Akt Pathway Involvement in Alzheimer Disease
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Background: Late-onset Alzheimer disease (AD) is highly heterogeneous. Some risk factors and aspects of the neuropathology are known, though much remains to be explained. It
is thus critical to find new biomarkers and identify potentially involved pathways.

Methods: Cerebrospinal fluid samples from 199 AD case and 579 control samples were processed using the aptamer-based SOMAscan 1.3k panel. After quality control, expressions for 699 proteins were discretized. The joint distribution of case covariates was used to select 302 controls and divide the samples into discovery (nD=288) and validation (nV=213) datasets by stratifying sex, APOE genotype, and ADAR1 patterns. Co-expression patterns were found using a novel mixed-integer program solver, Sync. Sync maximizes pTau quantiles. A pool of near-optimal solutions was also obtained. Pattern significance was calculated with Barnard’s exact test, with p-value adjustment via the Benjamini-Hochberg procedure.

Results: Of 217 candidates, eight patterns of PS=1, nine patterns of PS=5, and five patterns of PS=7 were significant. The larger patterns were highly overlapped and composed primarily of proteins from the smaller patterns. With the exception of AP3B1;42, all proteins in these risk patterns were up-regulated. A PS=7 pattern of particular interest (padj=0.046) had an OR of 9.8 (3.67-26.1) when calculated on the entire dataset. The pattern is composed of several 14-3-3 family members, Integrin A1/B1 complex, GPI and MAPK3. Interestingly, these proteins are all involved in the PI3K/Akt pathway.

Conclusion: Our unique approach detects known DEGs and novel co-expression patterns associated with AD resulting in higher OR than any individual protein in the dataset. Importantly, the identified patterns were not associated with sex or APOE. Significant associations with Clinical Dementia Rating® (p=0.000001), and high levels of tau (p=0.0000001), and pTau (p=0.000007) were observed. Exploration of the identified proteins using STRING suggested triosephosphate isomerase (TPI). TPI closely follows the synchronized expression of all PS=7 and PS=5 patterns, except TPI levels fall for AD cases exhibiting high levels of the identified proteins. Nitrotyrosination of TPI is observed in AD and links oxidative stress to paired helical formation of tau. Taken together, this research suggests future exploration of interactions between nitrotyrosinated TPI and the PI3K/Akt pathway.

308. Reverse Transcriptase Inhibition as a Novel Therapeutic Approach for ADAR1-Related Aicardi Goutières Syndrome

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Aicardi Goutières Syndrome (AGS) is an autoinflammatory leukodystrophy that results in severe neurologic disability and systemic complications. AGS is caused by mutations in genes that regulate nucleic acid accumulation or sensing, which leads to increased interferon response. ADAR1, which encodes the RNA-editing adenosine deaminase, accounts for one-sixth of the total AGS population. Retroelements are known to be a driving source of the pathology in some AGS related genotypes, but it is unknown if mutations in ADAR1 are linked to accumulation of retroelements. A prior pilot study shows that administration of reverse transcriptase inhibitor (RTI) can inhibit retroelement accumulation, decreasing activation of IFN pathways in AGS patients with TREN1, SAMHD1, RNASEH2ABC mutations. A follow-up clinical trial is ongoing but ADARI patients will be excluded, as there is no evidence showing ADARI mutation leads to dysregulation of retroelements. To characterize the relationship between ADARI and endogenous retroelements, we used a human lung cell line with deletion of the ADARIp150 (ADARI KO). Treatment with IFN led to an increase in downstream IFN stimulated genes (ISG) and cell death in ADARI KO cells compared to control cells. To examine if the retroelements LINE-1 and Alu contribute to the ongoing nucleic acid accumulation, we measured the gene expression levels of Alu and LINE-1. A significant increase in these retroelements occur in ADARI KO cells compared to control cells upon IFN treatment starting at 24 hours. We then tested if treatment with RTI will rescue the production of ISGs and cell death. We pre-treated both control and ADARI KO cells for 48 hours with the RTI Emtricitabine (FTC) and Tenofovir (TFV) in a dose dependent, followed with IFN stimulation. Treatment with RTI resulted in a decrease in ISGs and rescued ADARI KO cells in a dose dependent manner compared to untreated cells. This work demonstrates that ADARI mutations result in the dysregulation and accumulation of LINE-1 and Alu retroelements, which contributes to IFN-mediated cellular pathology in AGS. Importantly, treatment with RTI may be beneficial as a potential therapy for ADARI patients. Ongoing research using human induced pluripotent stem cells (iPSC) derived from ADARI patients will test the role of retroelements in AGS pathology, as well as the relevance of treatment with RTI. This work is highly translational and immediately applicable to inclusion criteria for enrollment of AGS patients in the ongoing clinical trials.

354. Trio Exome Sequencing with In-Depth Phenotyping in Pediatric Epilepsy: A Prospective, Single-Centered Cohort Study with Return of Research Results to Patients

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We sought to demonstrate the yield of trio whole-exome sequencing (WES) in children with epilepsies, combining phenotypic and genomic expertise to analyze cases and deliver clinical results, as well as expand the phenotypes of known epilepsy-related genes and identify novel genes. Starting in
2018, we prospectively enrolled children with unexplained epilepsy at Boston Children’s Hospital. WES was conducted and processed using a standardized alignment and variant calling pipeline. In-depth clinical history, including seizure semiology, epilepsy according to the International League Against Epilepsy (ILAE) classification, age of seizure onset, family history, EEG, MRI, presence of intellectual disability (ID) and/or autism, and treatment response were characterized by epileptologists. De novo and inherited variants were classified according to the American College Medical Genetics (ACMG) criteria, with special attention to a recursive and detailed phenotyping approach that allowed us to return to the patients to obtain data relevant to a given gene. We evaluated sequencing data from 513 children: 311 trios and 202 proband-only, including 195 (38%) developmental epileptic encephalopathy (DEE), 143 (28%) generalized genetic epilepsy (GGE), 126 (25%) non-lesional focal epilepsy (NLFE), and combined epilepsy. We identified clinically explanatory variants for 89 (17%) cases and novel candidate genes in 104 (20%) cases. The yield of clinically explanatory variants was highest in those with seizure onset earlier than preschool age (odds ratio (OR)=2.49 [95% confidence interval (CI)= 1.54-4.01], vs. those with GGE or NLFE (OR=2.35 [95% CI 1.48-3.74], P=2.4X10-4) and those with ID (OR=3.16 [95% CI 1.89-5.28], P=9.1X10-6). Proband with DEE had a higher yield of clinically explanatory results vs. those with GGE or NLFE (OR=2.35 [95% CI 1.48-3.74], P=3.8X10-6). Even so, we identified explanatory variants in the non-DEE groups. We demonstrate a high yield of clinically explanatory results in children with unexplained epilepsy, especially in patients with early-onset epilepsy, ID, and/or DEE but also in other subgroups, phenotyped and sequenced with the return of clinical results through an institutional platform. Research into candidate genes, including further case identification and functional studies, are predicted to increase this yield in the future.

403. Comprehensive Analysis of PRKN in a Large Parkinson’s Disease Cohort Identifies Causative Mutations and Validates Population Scale Screening by Microarray

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Objective: To screen for PRKN mutations at the population scale.

Background: PRKN mutations are the most common recessive cause of Parkinson’s disease (PD) and are a promising target for gene replacement therapies. Identification of biallelic PRKN carriers at the population scale, however, remains a challenge, as half of mutations are copy number variants (CNVs) and many single nucleotide variants (SNVs) are of unknown significance.

Methods: Genotyping microarray (NeuroX or Neuro Consortium Array) data were evaluated as a screening tool for PRKN biallelic patients in a cohort of 732 PD patients. All patients also received whole genome sequencing (WGS), which served as the gold standard for evaluating microarray accuracy. Finally, an algorithm was developed to identify PRKN CNVs from microarray data and applied to participants in the UK Biobank.

Results: All PRKN CNVs (14/14) and roughly a third of pathogenic SNPs (6/19) in our cohort were identified by microarray. Microarray detected at least one mutation in 7/8 biallelic PRKN patients and 8/17 monoallelic PRKN patients. This yielded a negative predictive value of 99.8% and a positive predictive value (PPV) of 46.7% for identifying biallelic PRKN patients (sensitivity = 87.5% and specificity = 98.9%). Including cutoff values for age at onset (AAO), ≥ 40, and o/faction, UPSIT ≥ 20, increased the PPV to 75%. In cases where pathogenicity of a variant was uncertain, assaying skin fibroblasts reliably distinguished monoallelic (N=3) from biallelic (N=8) PRKN carriers and resolved a novel intronic variant identified by WGS as loss of function. Finally, an algorithm for calling PRKN CNVs from microarray data was developed and applied to approximately half a million participants in the UK Biobank, detecting 2,597 CNVs. Additionally, 3,975 alleles had a p.T240M or p.R275W pathogenic mutation. Altogether, 1.34% in the sampled population carried a pathogenic mutation. Those with one detected PRKN mutation were as likely as those without a mutation to have PD (OR = 1.38, p-value = 0.063) or a parent with PD (OR = 1.05, p-value = 0.41).

Conclusions: PRKN mutation screening by microarray is feasible at a population scale and is further improved by inclusion of clinical data, such as AAO and UPSIT. Additionally, in the largest cohort of PRKN carriers tested, having a PRKN heterozygous mutation did not increase the risk of PD.

404. Characterization of a Mouse Model of PDE10A-Related Autosomal-Dominant Movement Disorder

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Objective: To characterize a newly generated mouse model of the movement disorder caused by PDE10A pathogenic mutation F300L. Background: Phosphodiesterase 10A (PDE10A) is a striatal specific enzyme that regulates dopaminergic and adenosinergic signaling in striatal projecting neurons through modulation of the intracellular levels of cAMP and cGMP. Heterozygous missense mutations in the GAF-B regulatory domain of PDE10A, including the recurrent variant F300L, were recently identified in patients with childhood-onset chorea and bilateral striatal MRI abnormalities. However, the mechanisms whereby these mutations cause abnormal movement production and striatal abnormalities are not known.
Microgliosis. Importantly, homozygous mice showed significant astrogliosis in the striata of mutant mice but no significant change in heterozygous mice at 6 months of age. Finally, we observed severe and progressive vacuolar lesions within the striatum beginning at one month of age. Eosin and Nissl staining revealed prominent and progressive accumulation of cytosolic protein aggregates that stained positive for PDE10A. Histological analysis with Hematoxylin and Eosin and Nissl staining revealed prominent and progressive vacuolar lesions within the striata at one month of age. Finally, we observed severe and progressive astrogliosis in the striata of mutant mice but no significant microgliosis. Importantly, homozygous mice showed significantly more profound abnormalities than heterozygous mice, indicating a dosage effect of the mutation.

Conclusion: The motor abnormalities and profound striatal histopathological lesions of our mouse model suggest a parallel to that of MRI abnormalities and motor symptoms seen in patients harboring dominant PDE10A mutations. Insights revealing a reduction of PDE10A levels and protein aggregate formation in vivo, highlight the need to further characterize the pathophysiological mechanisms underlying PDE10A mutations in the GAF-B domain.

K-211. High-Throughput Imaging of ATG9A Distribution as a Diagnostic Functional Assay for Adaptor Protein Complex 4 - Associated Hereditary Spastic Paraplegia

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Adaptor protein complex 4 (AP-4)-associated hereditary spastic paraplegia (AP-4-HSP) is caused by biallelic loss-of-function variants in AP4B1, AP4M1, AP4E1 or AP4S1 which constitute the four subunits of this obligate complex. While the diagnosis of AP-4-HSP relies on molecular testing, the interpretation of novel missense variants remains challenging. Here we address this diagnostic gap by using patient-derived fibroblasts to establish a functional assay that measures the subcellular localization of ATG9A, a transmembrane protein that is sorted by AP-4. Using automated high-throughput microscopy, we determine the ratio of the ATG9A fluorescence in the trans-Golgi-network versus cytoplasm and ascertain that this metric meets standards for screening assays (Z-scores > 0.3, SSMD > 3). The ‘ATG9A ratio’ is increased in fibroblasts of 17 well-characterized AP-4-HSP patients (mean: 1.54 ± 0.13 vs. 1.21 ± 0.05 SD in controls) and receiver-operating-characteristic analysis demonstrates robust diagnostic power (AUC: 0.85, 95%CI: 0.849-0.852). Using fibroblasts from two individuals with atypical clinical features and novel biallelic missense variants of unknown significance in AP4B1, we show that our assay can reliably detect AP-4 function. Our findings establish the ‘ATG9A ratio’ as a diagnostic marker of AP-4-HSP.

K-491. Phenotype-Conscious Models of Cohesin and CTCF Loss of Function

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Background: Interphase human chromosomes exist in a structured but dynamic three-dimensional configuration, which facilitates gene expression programs throughout development. This 3D genome organization is governed by at least a dozen proteins, including the cohesin complex and CTCF. Mutations in cohesin genes cause Cornelia de Lange syndrome, and mutations in CTCF cause another neurodevelopmental disorder, autosomal dominant mental retardation 21 (MRD21). Thus, it is hypothesized that these diseases result from changes to genome organization and resultant alterations to gene expression. Previous efforts to model these syndromes have limitations, owing to the use of cell types, species, and zygosities not reflective of human phenotypes and inconsistent approaches across genes.

Methods: We developed a CRISPR/Cas9-based pipeline to model loss of gene function (LoF) at disease-relevant zygosities in an extensively characterized human induced pluripotent stem cell (hiPSC) line. Gene editing and cell sorting were optimized to recover mutant and unedited control clones for each targeted gene. We refined existing differentiation protocols to yield cell types relevant to neurodevelopment including neural stem cells (NSCs) and induced neurons (iNs).

Results: Using this approach, we modeled LoF of CTCF and three representative cohesin genes including a cohesin loader (NIPBL), unloader (WAPL), and core cohesin ring gene (RAD21) on an isogenic human iPSC background. All four genes were amenable to the introduction of early frameshift alleles, clonal isolation, and zygosity genotyping, yielding multiple (≥5) heterozygous mutant and control clones per gene. Differentiation is in-progress.

Conclusions: We have created a series of cellular models of cohesinopathies and CTCF deficiency on an isogenic
human iPSC background. This approach will allow interrogation of genome organization, transcription, and cellular phenotypes using the appropriate gene dosage and cell type to probe the molecular mechanisms of aberrant neurodevelopment across the Cornelia de Lange syndrome and MRD21 phenotypes.

K-495. Modeling Neurological Aspects of GALNT2-CDG in Mice
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Congenital disorders of glycosylation (CDG) are a group of neurogenetic disorders that disrupt cellular glycosylation machinery and exhibit multi-system dysfunction, including severe neurological deficits. These disorders emphasize that glycosylation is an essential post-translational modification, yet the pathophysiology of neurological dysfunction in CDG remains unclear. Most CDG disrupt N-glycosylation, however, eight patients from five families with biallelic loss-of-function mutations in GALNT2, which encodes a Golgi-localized glycosyltransferase that initiates mucin-type O-glycosylation, confirms O-glycosylation is also critical to neurologic function. GALNT2-CDG patients exhibit global developmental delay, epilepsy, autistic features, and white matter changes on brain MRI.

I have modeled neurological aspects of this neurogenetic disorder, GALNT2-CDG, in mice using a floxed Galnt2 allele and cell-type specific Cre drivers to illicit neurobehavioral phenotypes dependent on O-glycosylation. Pan-neuronal Galnt2 KO (nKO) mice generated using a Snap25-IRES-Cre driver, exhibit deficits across numerous behavioral and learning domains, including altered locomotor activity in Open Field Test, increased anxiety-like behavior in Elevated Zero Maze, decreased sociability, deficits in motor coordination and learning on Accelerating Rotarod, deficits in context-dependent memory formation in Fear Conditioning, and poor nest building. Approximately 1/3 of these mice also demonstrate behavioral seizures. Interestingly, Galnt2 nKO mice also exhibit excessive weight gain. These findings demonstrate the key role of O-glycosylation in neurons initiated by just one of 20 related enzymes and implicate a role of O-glycosylation in diverse neurological processes, including learning, memory, neurotransmission, and body weight homeostasis.

Ongoing studies seek to characterize the epilepsy phenotype using time-locked video EEG and determine whether excessive body weight is due to increased caloric intake or decreased caloric usage. Future plans include glycoproteomic characterization of affected glycoproteins and their disrupted glycosites to investigate underlying molecular mechanisms.

K-523. Diagnostic Yield of Exome Sequencing for Cryptogenic and Non-Cryptogenic Cerebral Palsy
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Introduction: Approximately 20% of individuals with CP have no clear etiological explanation (“cryptogenic CP”). There is growing evidence that cryptogenic CP may be due to single gene disorders, but data in this area is still limited. In order to evaluate the landscape of single gene disorders in CP, we performed comprehensive phenotyping and whole exome sequencing (WES) analysis on a prospective cohort of 49 individuals with cryptogenic CP, non-cryptogenic CP, and CP masqueraders.

Methods: We enrolled participants in a prospective study involving WES on individuals CP or CP masqueraders. We classified probands as cryptogenic CP (meets criteria for CP; no clear perinatal risk factors), non-cryptogenic CP (meets criteria for CP; at least one perinatal risk factor), or CP masquerader (meets criteria for CP except for regression). For each patient, we characterized primary motor phenotypes; ascertained medical comorbidities; and classified brain MRI into one of several patterns. We analyzed WES data using an institutional pipeline for variant interpretation.

Results: There were n=49 probands in this cohort (19 females, 30 males; average age 10.2 +/- 8.1 years). n=24 had cryptogenic CP, n=20 had non-cryptogenic CP, n=4 had a CP masquerader classification, and n=1 had an unknown classification (due to limited perinatal history details). The hypotonia-ataxic subtype showed a statistically significant difference across the three classification groups (p = 0.02). The non-cryptogenic CP category had a higher percentage of individuals with multiple medical comorbidities (n=15/20, 75%) compared to the cryptogenic CP category (n=9/24, 38%) or CP masquerader category (n=1/4, 25%) (p = 0.02). The MRI pattern of “normal” occurred more commonly in the cryptogenic CP category vs. the non-cryptogenic CP and CP masquerader category (p = 0.04). In the cohort, there were n=12 (24%) participants with a pathogenic or likely pathogenic variant in 12 different genes (ECHS1, SATB2, ZMYM2, ADAT3, COL4A1, THOC2, SLC16A2, GNAO1, SPAST, PDHX, AT1L, ACADM), including one patient with two genetic disorders (ACADM- and PDHX-related disorder), and two patients with SPAST related disorder. The CP masquerader category was associated with the highest diagnostic yield (n=3/4, 75%), followed by the cryptogenic CP category (n=5/24, 21%). Notably, there were n=3 participants in the non-cryptogenic CP category (n=3/20, 15%) who had a genetic diagnosis after WES.

Conclusions: Our work adds to the growing body of literature suggesting that CP may be due in part to genetic causes. Continued work is needed to better understand the genetic landscape of CP.

K-525. Developing Hindbrain Motor Neurons Show Spatial and Temporal Transcriptomic Diversity Mapping to Wiring Decisions
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The brainstem ocular motor neurons (OMNs) mediate eye movements and are differentially affected in some disorders, compared with other motor neurons (MNs). In congenital cranial dysinnervation disorders (CCDDs) such as Duane Syndrome, OMN subpopulations show disrupted or aberrant innervation, while in Amyotrophic Lateral Sclerosis (ALS), OMNs continue to function while other MNs degenerate. Here we define unique gene expression patterns among developing MNs, and generate a toolbox of protocols and genetic markers to help study these disorders. We combine various mouse genetic reporter lines with intersectional temporal and spatial transcriptomics (bulk-, single cell-, and single nuclei hybridization, antibodies, and genetic axonal labeling. We correlate gene expression differences with cell age by both EdU labeling and tamoxifen-mediated temporal CreER induction, and visualize iDISCO- and EyeDISCO-cleared whole embryos by light sheet microscopy. Each MN population shows a unique genetic fingerprint, including novel markers of spatially- and temporally-distinct OMN subpopulations. Some OMN nerve branches correspond with cell birthdate and selectively contribute to specific aberrant branches in the Mafb knockout mouse model of Duane Syndrome. Overall, this MN transcriptomic atlas uncovers distinct developmental gene expression patterns and markers of the various cranial motor neurons, and provides new tools to study their differential vulnerability in the CCDDs and other motor neuron disorders.

LB-443. Lessons Learned from Studying the Genomics of a Large Recesive Neurodevelopmental Disorder Cohort
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Objective: Neurodevelopmental disorders (NDDs) are common with a prevalence of >3% in the general population. NDDs are a group of disorders with clinical and genetic heterogeneity resulting from perturbations in brain development and nervous system function. We previously performed exome sequencing (ES) in a cohort of 128 Turkish families with an NDD phenotype (TBM1). Six out of nineteen cases initially classified as having phenotypic expansion (presence of additional clinical features that were not previously linked with the initially identified disease locus), were found to have additional deleterious variants in one or more loci beyond the primary molecular diagnostic locus/gene (i.e. multiplex pathogenic variation, MPV). We therefore hypothesized that the presence of MPV is much higher than initially described and contributes to intra- and inter-familial variability, especially in recessive disease trait populations.

Methods: Exome and genome sequencing (GS) with family-based rare variant analyses were implemented in 234 newly enrolled (TBM2) and 20 previously unsolved Turkish NDD kindreds from TBM1. Strict variant prioritization criteria were used to consistently identify potential deleterious variants. Moreover, we systematically employed novel bioinformatic tools for InDel variant calling (xAtlas), CNVs (copy number variants; HMZDelFinder), and loss-of-function (LoF) mutations (NMDEscPredictor) to extant ES data.

Results: Deleterious variants were identified in 177 out of 234 families (75%). Of the 177 ‘molecular diagnostic solved’ families, potentially causative genetic variants were detected in 213 distinct genes, including 82 (35% novel disease gene candidates. In 52 out of 177 families (29%), evidence for multiple molecular diagnoses resulting from MPV were observed. Importantly, families with MPV were found to have larger total absence of heterozygosity (AOH) blocks, a surrogate measure for runs of homozygosity (ROH), reflecting genomic intervals identical-by-state, and likely driven by identity-by-descent. Furthermore, with the use of additional bioinformatic tools and expansion to additional family members, we established a molecular diagnosis in 5 out of 20 (25%) previously undiagnosed TBM1 families.

Conclusion: This study highlights the significant contribution of MPV in recessive NDD families with resultant intra- and inter-familial variability. Furthermore, several novel candidate ‘causative NDD genes’ were identified, highlighting the tremendous genetic heterogeneity and functional neurobiology that underlie NDDs.

LB-447. NTNG1 Allele RS4132604 is Associated with Frontal Lobe Hypoconnectivity in Subjects with Poor Executive Function
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Previous work in our laboratory has found that variations in netrin isoforms is associated with psychosis in some individuals. This is a replicated finding. The discover has consistently found allele G to be significantly higher than allele T in rs4132604 among groups of people who were prone to behavioral disruption and auditory hallucinations. Moreover, the group with this isomorf variation were more likely to suffer from a variety of neuropsychiatric symptoms. In this recent work we report upon the association of this allelic variation with nuclear magnetic resonance imaging (MRI) consistent with decreased innervation of the prefrontal cortex. The
association of the variant isoform was highly correlated with psychotic symptoms of behavioral disturbance and hallucinations (R = .88, p < .001) and likelihood ratio approximation of chi square = 7.98, p<.0001). The current study is unique in that it links this allelic variation to an MRI finding of decreased density in the prefrontal cortex, another finding independently associated with psychotic symptoms. When compared to control subjects, the epigenetic link between decreased density and isoform variation is highly significant between cases and controls (t = 8.63, p<.00001). We present this unique association and discuss the potential clinical implications.

**LB-458. Genetic Variants Associated with Ischemic Stroke: Findings from the First-Ever Stroke Genome-Wide Association Study in Indigenous Africans**

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**Background:** The genetic diversity in Africa, which is greater than in any other region, has implications for genetic mapping of complex diseases especially stroke. However, the genetic architecture of stroke in indigenous African populations is largely unknown. The Stroke Investigative Research and Educational Network (SIREN) is a multicenter study involving 15 sites in West Africa. We conducted the first-ever genome-wide association study (GWAS) of stroke in indigenous Africans.

**Methods:** Cases were consecutively recruited consenting adults (aged ≥ 18 years) with neuroimaging-confirmed ischemic stroke. Stroke-free controls were ascertained using a locally-validated Questionnaire for Verifying Stroke-Free Status. DNA genotyping with the H3Africa array was performed locally. DNA genotyping with the H3Africa array was performed following initial quality control, GWAS datasets were imputed into 3 reference panels, namely H3Africa-BioNet, Sanger Institute African Genome Resource (AGR) and NIH Trans-Omics for Precision Medicine (TOPMed) release2 from BioData Catalyst. Furthermore, we performed fine-mapping, trans-ethnic meta-analysis, and in silico functional characterization to identify likely causal variants with functional interpretation.

**Results:** We had 1,683 ischemic stroke cases and 1,738 stroke-free controls for the GWAS. Based on the imputation quality cutoff of R ≥0.3 and minor-allele frequency (MAF) >0.01, the TOPMed showed the highest average imputation quality of 98.81% as compared to 90.55% for H3AR3b and 95.55% for AGR. We demonstrated for the first time, that TOPMed imputation panel is superior to other imputation panels for African data. We observed genome-wide significant (p-value<5.0E-8) SNPs associations near **AADACL2** and miRNA (**MIR5186**) genes in chromosome 3, after adjusting for hypertension, diabetes, dyslipidemia, and cardiac status in the base model as covariates. SNPs near the miRNA (**MIR4458**) gene in chromosome 5 were also associated with stroke (p-value<1.0E-6). The putative genes near **AADACL2**, **MIR5186** and **MIR4458** were protective and novel. SNPs associations with stroke in chromosome 2 were more than 77kb from the closest gene **LINC01854** and SNPs in chromosome 7 were more than 116kb to the closest gene **LINC01446** (p-value<1.0E-6). In addition, we observed SNPs in genes **STXBP5-AS1** (chromosome 6), **GALTN9** (Chromosome 12), **FANÇA** (Chromosome 16), and **DLGAP1** (chromosome 18) (p-value<1.0E-6). Both genomic regions near genes **AADACL2** and **MIR4458** remained significant following fine mapping.

**Conclusion:** These findings suggest emerging roles of regulatory miRNA, intergenic non-coding DNA and intronic non-coding RNA in the pathobiology of ischemic stroke among indigenous Africans. Downstream analysis involving multi-omics approaches and larger sample sizes are anticipated.

**LB-459. Estimating the X Chromosome-Mediated Risk for Developing Alzheimer’s Disease**

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**Background:** Parental lineage has been shown to increase the risk of Alzheimer’s disease (AD) in the offspring, with greater risk attributed to maternal lineage. While 40 genes/loci have been linked to the risk of developing AD, none has been found on the X chromosome. We sought to estimate the risk that might be mediated by the X chromosome using an epidemiological approach, drawing on Mendelian Randomization methods, by analyzing the numbers of patients we saw, with unilateral ancestral lineage of Alzheimer’s disease or dementia, according to the gender of the proband.

**Methods:** We reviewed retrospectively records of patients aged 55-80 years presenting to our memory disorders clinic with amnestic mild cognitive impairment (aMCI) or early AD between May 2015-September 2020. We estimated the risk for developing AD mediated by the X chromosome in a subgroup of late-onset patients with aMCI or early AD and unilateral ancestral history of AD or dementia by analyzing their numbers (a-d) defined as follows: a = Number of female probands with paternal lineage AD or dementia. Risk can be conferred by the 22 autosomal chromosomes or/and the X chromosome. b = Number of female probands with maternal lineage AD or dementia. Risk can be conferred by the 22 autosomal chromosomes or/and the X chromosome. c = Number of male probands with paternal lineage AD or dementia. Risk can be conferred by the 22 autosomal chromosomes or/and the X chromosome.
lineage AD or dementia. Risk can be conferred only by the 22 autosomal chromosomes. $d$ = Number of male probands with maternal lineage AD or dementia. Risk can be conferred by the 22 autosomal chromosomes or/and the X chromosome. The odds ratio $OR=(a/b)/(c/d)$ estimates the relative risk conferred by the X chromosome, controlling for confounders. The estimated proportion of risk mediated by the X chromosome is calculated as $(OR-1)/OR$.

**Results:** 40 women aged 66.1± 5.1 years (mean-standard deviation) and 31 men aged 68.1±6.5 were identified. The OR was $(18/22)/(6/25) = 3.4$, (95% confidence interval 1.1-10.1; p=0.027). The estimated proportion of genetic risk borne by the X chromosome in this population is 70%.

**Conclusion:** Our numbers are small and the findings preliminary, requiring replication. This approach may provide an estimate for the proportion of risk mediated by the X chromosome in individuals who develop AD with unilateral ancestral lineage, and is generalizable.

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**Neuromuscular Disease**

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**222. Upper Motor Neuron Influence on Blink Reflex Testing**

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**Introduction:** Transcranial Magnetic Stimulation (TMS) is safe, noninvasive brain stimulation used to diagnose cortical excitability states. The blink reflex test (BRT) is a neurophysiological test that involves stimulation and evaluation of a lower motor neuron (LMN) circuit in the midbrain. The blink reflex also has cortical connections. We investigated the relationship between BRT and results from TMS to discern the cortical input to results of BRT.

**Objective:** To evaluate if the BRT correlates with TMS-induced cortical excitability.

**Methods:** Retrospective study of patients seen in the Department of Neurology at HSS between 1/1/2019 and 12/31/2019 who underwent both blink reflex testing and TMS.

**Results:** 8 subjects met inclusion criteria. Diagnoses included ALS (3), primary lateral sclerosis (PLS) (1), cerebral palsy (CP) (1), multiple sclerosis (MS) (1), neuro-amyloidosis (1) and frontotemporal dementia (FTD) (1). 3 subjects had normal results of both tests (MS, neuro-amyloidosis and CP). 2 subjects had normal BRT with abnormal TMS results (FTD and ALS). The FTD patient had an abnormal monophasic resting motor threshold RMT and the ALS patient had no RMT on both sides. In the ALS case, the blink reflex was confounded by patient startle. 3 cases with ALS or PLS had abnormalities in both tests, with absent contralateral R2 response on BRT and no RMT on the affected side with TMS.

**Summary/Conclusion:** In our small sample size, the absence of a contralateral R2 component on BRT correlates with an unexcitable contralateral hemisphere on TMS. This suggests that the BRT receives inputs from the motor cortex.

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**223. A Rare Overlap Between Miller Fisher Syndrome and Pure Motor Guillain-Barre Syndrome**

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**Background:** Guillain-Barre syndrome (GBS) is associated with ascending motor and/or sensory impairment, areflexia, and albuminocytological dissociation on cerebrospinal fluid (CSF) analysis. Meanwhile, ophthalmoplegia, ataxia and areflexia with minimal or no sensory/motor involvement is pathognomonic for Miller Fisher syndrome (MFS). This case highlights a unique overlap between MFS and pure motor variant of GBS.

**Case Presentation:** A 22-year-old man with no significant past medical history presented with rapidly progressive, symmetric limb weakness of 5 weeks’ duration. Symptoms started with upper respiratory tract infection 2 weeks prior, followed by ascending paralysis involving bilateral lower extremities within a few days. A week later, he had involvement of bilateral hands which progressed to double vision the following week. Patient denied sensory changes, bulbar weakness, or bladder/bowel involvement. There was no history of recent travel, recreational drug abuse or occupational exposure. Neurological examination revealed right exotropia on primary gaze in addition to impaired adduction bilaterally. Motor exam revealed flaccid tone with symmetric proximal and distal weakness bilaterally. Reflexes were diminished or absent but symmetric. Sensation was intact to large and small fiber modalities. Gait was ataxic. CSF analysis revealed elevated proteins 80 mg/dl and cell count 76/uL (98% lymphocytes). Serological work up including GQ1b, Lyme, West Nile Virus, sarcoid, HIV, heavy metals, paraneoplastic panel, and other infectious and inflammatory etiologies were unremarkable. MRI brain and total spine was found to be unremarkable. Given the clinical diagnosis of Miller Fisher Syndrome, he was treated with intravenous immunoglobulin (IVIg) with remarkable improvement. Patient was able to ambulate independently at the time of discharge.

**Conclusion:** There are several features that make this case unique. Although the patient had clinical manifestation of GBS, there was no explanation for lymphocytic pleocytosis despite exhaustive infectious and inflammatory work up. He was noted to have pure motor syndrome on examination which is typically associated with axonal variants of GBS or post-infectious motor neuronopathy; both of which have a slow recovery. The remarkable response to IVIg in the setting of negative spinal imaging confirms the diagnosis of inflammatory polyradiculopathy. Several publications are reshaping the distinctive diagnostic criteria of GBS and its variants to emphasize the continuous spectrum of MFS-GBS. We would like to highlight that the rare occurrence of lymphocytic pleocytosis in a pure motor variant of GBS with features of MFS should not exclude the diagnosis of MFS-GBS overlap syndrome.
224. Thymoma Associated with Autoimmune Multifocal Cortical Encephalitis and Subsequent Myasthenia Gravis
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Background and Purpose: Thymomas are known to be associated with paraneoplastic syndromes; both myasthenia gravis and limbic encephalitis are amongst the most common complications. Most examples of paraneoplastic encephalitis involve the structures related to the limbic system. There is a dearth of literature on the correlation of thymoma with various paraneoplastic syndromes. We report the third case of multifocal cortical involvement associated with thymoma, which required a prolonged course in neurocritical intensive care unit.

Methods: Case Report.

Results: A 42-year-old female with a recent history of recovery from COVID-19 infection and GAD-65 seropositive multifocal encephalitis associated with a mediastinal mass presented to the emergency department with one week of shortness of breath. She had recently suffered generalized tonic-clonic seizures and was on Lacosamide and Levetiracetam. She also complained of recent intermittent hyperopia, diplopia, and neck weakness that increased throughout the day. Chest computed tomography was negative for Pulmonary Embolism but revealed an elevation of left hemi-diaphragm. EMG showed significant 21% decrement on repetitive stimulation of left accessory nerve post-exercise of the trapezius muscle. MRI of the chest revealed hyperintensity consistent with thymoma. MRI Brain when compared to previous studies showed evolution of the encephalitis with resolution of a left occipital lesion, a new right occipital lesion, and increased extent of left parietal abnormality. She was positive for AChR blocking, binding and modulating, anti-striated muscle and GAD-65. She developed hypercapnic respiratory failure requiring emergent intubation and subsequently underwent robotic assisted radical thymectomy. The cytology of the mediastinal mass was confirmatory for WHO Grade B1 thymoma with abundant CD3+ T-cells thymocytes. She showed partial improvement in response to immunotherapy with IVIG and steroids requiring tracheostomy and PEG placement. Ultimately, she received plasmapheresis, azathioprine for maintenance, and discharged to outpatient rehabilitation.

Conclusion: Our case report is only the third reported case of thymoma-associated multifocal cortical encephalitis, which shows that autoimmune encephalitis can extend to cortical regions outside the limbic system. We should consider autoimmune encephalitis in the differential diagnosis of patients with myasthenia gravis or thymoma who develop new cognitive symptoms.

225. New-Onset Dysesthesias Following COVID-19 Inoculation
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The global COVID-19 pandemic resulted in an unprecedented rapid development and authorization of novel vaccines. Local and systemic adverse effects were found to be relatively common after the second dose, but no excess risk for neurologic events was observed in phase III clinical trials. However, vaccine safety monitoring is an ongoing process and the Vaccine Adverse Event Reporting System (VAERS) has now received rare reports of new-onset neuropathies following inoculation against SARS-CoV-2. We describe one such case in a 57-year-old woman, who presented one week after receiving the second dose of Covid vaccination (Pfizer®) with subacute onset of intense burning dysesthesias involving her feet with gradual spread to her calves, and to a minimal extent in her hands. There was no associated low back/neck pain, weakness, unsteadiness, or bowel/bladder involvement. Bulbar, systemic, and constitutional symptoms were absent. There was no known COVID-19 exposure and the patient had negative COVID-19 reverse-transcriptase-polymerase-chain-reaction testing nine months before her presentation. Clinical examination was notable only for distal loss to pinprick and cold sensation in her feet, and electrodiagnostic testing performed on the day of presentation was normal. Exhaustive serologic studies were all normal/negative. The SARS-CoV-2 antibody profile was consistent with a post-vaccination state but ruled out previous asymptomatic COVID-19 exposure, which could have resulted in a robust immune response. Skin biopsy demonstrated reduced epidermal nerve fiber density involving the left foot, indicative of previously undiagnosed small fiber neuropathy. Despite the length-dependent clinical findings, skin biopsies showed multifocal involvement with a more prominent reduction of intraepidermal nerve fiber density in the thigh biopsy. No evidence of small vessel vasculitis or other histologic abnormalities were identified. Gabapentin provided symptomatic improvement and her clinical course remained stable over the following two weeks. Though rare, several case reports describing small fiber neuropathy following various vaccinations have been described in the literature. A proposed pathophysiologic mechanism for vaccine-associated polyneuropathy is an immune-mediated hypersensitivity to the solvent/adjuvant (polyethylene glycol). We have now identified a case of biopsy-proven small fiber neuropathy as a possible post-vaccination complication following inoculation against SARS-CoV-2 with the Pfizer vaccine. Despite the profoundly positive impact that vaccination programs have on global public health and the lack of adverse neurological events in pivotal COVID-19 vaccine trials, rare occurrences of neuromuscular complications including small fiber neuropathy have now been reported to the VAERS and are indeed plausible.
226. Chronic Inflammatory Demyelinating Polyneuropathy with Anti-Neurofascin-155 Antibodies

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Objective: In patients diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP), testing for antibodies to paranodal complex proteins can guide treatment planning.

Background: Neurofascin-155 is an L1 family adhesion molecule expressed at the paranodal junctions by terminal loops of myelin, where it functions to stabilize the region. It associates with other proteins in the paranodal complex (contactin-1, contactin-associated protein 1) to allow for propagation of nerve impulses down myelinated axons. Anti-neurofascin-155 antibodies have been identified in both central and peripheral nervous system demyelinating conditions. Patients diagnosed with CIDP with positive anti-neurofascin-155 antibodies are less responsive to IVIG but respond to rituximab.

Design/Methods: We report a patient diagnosed with CIDP, minimally responsive to Intravenous immunoglobulin (IVIG) and mycophenolate, who was then found to have anti-neurofascin-155 antibodies.

Results: A 45-year-old woman with diabetes presented with 5 months of lower extremity weakness, numbness, and painful paresthesia’s that progressed to her hands. Examination revealed proximal and distal weakness of the lower more than upper extremities, length-dependent sensory deficits, impaired gait, diffuse areflexia, and postural tremor of the bilateral hands. She underwent NCS/EMG, which demonstrated primary demyelinating features with secondary axonal loss. Lumbar puncture revealed WBC 0 cells/mL and protein 243mg/dL consistent with CIDP. She was started on IVIG and mycophenolate with minimal clinical improvement over the following year. Testing for paranodal protein antibodies returned positive for antibodies to neurofascin-155. She was switched from IVIG to rituximab, with subsequent improvement in her paresthesias and weakness, including an improved ability to rise from a seated position as well as improved ambulation.

Conclusions: Patients with CIDP associated with anti-neurofascin-155 antibodies often present with prominent sensory ataxia and tremor with poor treatment response to IVIG. Testing for anti-neurofascin-155 antibodies in patients with CIDP can guide management, particularly in treatment-refractory cases, as transition to rituximab commonly results in significant clinical improvement.

227. An Open Label Study of Poly-MVA® to Treat Fatigue in ALS

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Introduction: Fatigue is a common and debilitating symptom among ALS patients, which is characterized by reversible motor weakness and whole-body tiredness that is only partially relieved by rest. The effectiveness of pharmacological or non-pharmacological treatments for fatigue in ALS is not yet established. The objective of this study was to assess the safety of Poly-MVA a dietary supplement containing a proprietary blend of lipoic acid mineral complex.

Methods: This was an open label non-randomized, non-blinded study. We recruited nine ALS patients (clinically definite based on revised El-Escorial criteria) from October 2020 to December 2020. We excluded patients with PEG tube or allergy/hypersensitivity to any component of Poly-MVA. Poly-MVA was administered with the dose of two teaspoons twice a day (morning and afternoon) for six months. We measured ALS Quality of Life-50 (ALSQ-50), Modified Fatigue Impact Scale (MFIS), Montgomery-Asberg Depression Rating Scale (MADRS) at baseline and monthly for six months.

Results: Age range was 59-74 years (mean age: 63.6). There were 7 men, 2 women. 8 were limb onset and one was bulbar onset. There were six patients that are on eitherriluzole and edaravone and just one patient was not taking either. ALSQ-50 at baseline was 7.19 and at one month improved to 8.1 but did not sustain. MFIS at baseline was 39.6 and improved to 35.9 at the end of first month that sustained for six months. MADRS at baseline was 8.5 with a reduction in depression score to 5.2 at 3 months which sustained through 6 months. One patient reported transient diarrhea but was severe enough to stop treatment.

Conclusion: This pilot study shows that Poly-MVA is safe and well-tolerated among ALS patients. There was improvement in fatigue score and depression scale early after treatment which sustained through six months.

228. Autosomal Dominant Myotonia Congenita: Thomsen Disease - A Case Report

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Background: Myotonia is defined as delayed muscle relaxation following voluntary or induced contraction. Can present as either dystrophic or non-dystrophic, with the former as a result of mutations in DMPK and ZFN9 genes, while the latter is due to a mutation in voltage-gated sodium and chloride channels. CLCN-1 encodes the voltage-dependent chloride channel which maintains the high resting membrane conductance in muscle fibers. A mutation in CLCN-1 causes increased sarcolemma excitability leading to the recurrent firing of action potentials or myotonic discharges and delaying muscle relaxation resulting in a non-dystrophic entity - Myotonia congenita. It can present in both the dominant (Thomsen) and recessive (Becker) forms. Both are slowly progressive between the ages of 4 and 14, characterized by varying degrees of largely painless muscle stiffness in legs, arms, jaw, or eyelids which often eases with repeated contractions. Affected individuals may appear extremely muscular, yet, some may have a proximal weakness. Of the two phenotypes, Becker disease can additionally display transient weakness after rest.
Case Description: We present a 47-year-old female with diabetes mellitus who presented with left foot drop and chronic back pain with left leg paresthesia for which she underwent multiple lumbar spine surgeries. Initial Electromyography (EMG) was read as complex repetitive discharges (CRD), denervation changes in upper limbs and thoracic paraspinal muscles, and hence the referral for amyotrophic lateral sclerosis (ALS) evaluation. Examination was significant for minimal left knee flexion and moderate to severe left foot dorsiflexion and eversion weakness. MRI of the lumbar spine showed post-surgical changes at L3-5 and foot weakness attributed to lumbosacral radiculopathy. This was confirmed by repeat EMG that showed a moderate to severe L4-S1 polyradiculopathy on the left side but no generalized denervation changes in thoracic paraspinals or upper limb muscles making ALS unlikely. Interestingly, there were profound myotonic discharges in all extremities. Further history revealed that she had difficulty relaxing her muscles for several years which was historically attributed to her mononeuropathies, lumbosacral radiculopathy, and degenerative joint disease. Genetic testing pursued showed heterozygous CLCN1 mutation, hence confirming the diagnosis of autosomal dominant myotonia congenita, Thomsen disease.

Conclusion: This case illustrates the need to correctly identify myotonic discharges on an EMG to enable further genetic testing and correct diagnosis. Treatment with Mexiletine can help with the symptoms of myotonia congenita. Furthermore, these patients are at risk for malignant hyperthermia with some anesthetic agents and hence early diagnosis is important.

229. A Rare Case of Total Intestinal Aganglionosis in Coincidence with Congenital Central Hypoventilation Syndrome (CCHS)
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Background: Total Intestinal Aganglionosis (TIA) is an uncommon variant of Hirschsprung’s Disease (HD). It occurs in approximately 2-13% of cases where the absence of ganglionic innervation can occur from the anus to the duodenum in its most severe presentation. About 10% of those with TIA will have Congenital Central Hypoventilation Syndrome (CCHS).

Case Presentation: An eight-month-old female infant was a known case of CCHS, and HD presented after no improvement in feed intake despite undergoing surgical intervention. The infant had previously undergone exploratory laparotomy for presumed bowel obstruction accompanied by rectal suction biopsy. The biopsy revealed the absence of ganglion cells. Despite this intervention, the infant could not advance on her substantial feeds. This time, the exploratory laparotomy revealed a gradual transition in the small bowel’s caliber, and a biopsy was taken 40 cm distal to the ligament of Trietz. On further exploration, eight additional leveling biopsy specimens were taken from the distal ileum. On the whole, only a total of 40cm of the distal small bowel had ganglion cells. Subtotal colectomy and a functional end jejunostomy were performed. On further follow-ups, the patient improved significantly from NPO to normal feeds. With normal bowel sounds, abdominal wall, and a healthy gastrostomy placement site, she eventually did well with a consideration of ostomy takedown in the mere future.

Discussion: TIA causes the entire colon to become aganglionic and may also extend into the small bowel. It can be well defined as aganglionosis extending from the anus to at least the ileocecal valve but no more than 50cm small bowel proximal to the ileocecal valve. Due to the number of TIA cases being very low and no high suspicion index, many infants with this fatal condition can be missed as the symptomatology of TIA and various other causes of bowel obstruction look alike. Therefore, low suspicion indexes for TIA cause patients to undergo repeated laparotomies without relief from a bowel obstruction. However, our patient eventually responded well to the surgical interventions.

Conclusion: TIA is a rare condition. Even though it affects males predominantly, our case described a female infant. Better long-term surgical outcomes for this manifestation remain controversial to date. However, ample background knowledge of TIA can help evaluate and treat patients with bowel obstruction or perforation with an unknown etiology.

230. Treatment Resistant Case of Morvan Syndrome
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Case Report: 52 year old female with a history of hypothyroidism, idiopathic adrenal insufficiency, severe irritable bowel syndrome, cachexia with a BMI 11.78 Kg\textsuperscript{2}, foot drop and superior mesenteric artery syndrome presenting with a 4-5 year history of lower back pain and stiffness with additional painful attacks of stiffness that affect her lower back and legs. Her symptoms were most noticeable in the evenings when fatigued or triggered when eating. Her symptoms started 8 years prior with hypersomnia and prominent dysautonomia: Repeated syncopal and presyncopal episodes, loose stool, post prandial bloating, dry mouth, reduced sweating, hypersomnia, cold extremities with hyperemia and heat intolerance; later on she was diagnosed with adrenal insufficiency.

There was no response to any of the attempted treatments: onabotulinum A injections, baclofen, tizanidine, dantrolene, carbamazepine, oxcarbazepine, ketamine infusion, clonazepam, diazepam, alprazolam, carbidopa/levodopa, trihexphenidyl, benztrapine, gabapentin, bromocriptine.
intrathecal ziconotide, medical marijuana, azathioprine, low dose prednisone, IV immunoglobulin infusion and plasma exchange.

Studies: Positive: tilt table testing, VGKC ab (Voltage gated potassium channel antibody) - subtype LGI1 and CASPR2 and EMG/NCS with evidence of muscle hyperexcitability and neuromyotonia. Negative/Normal: CK, other paraneoplastic antibodies, MRI brain, MRI LS spine, whole body PET scans.

Discussion: Morvan Syndrome is a rare disorder with less than 100 cases reported in the literature. The syndrome consists of peripheral nerve hyperexcitability, autonomic dysfunction, CNS symptoms (most commonly encephalopathy and sleep disorder), arrhythmia, hyperpyrexia or anorexia, intestinal pseudo-obstruction, paramnesia and laryngeal myotonia. It is important to note that the diagnosis is solely clinical. We recognize this case is atypical since our patient has hypersonmia instead of insomnia (which still fulfills criteria of sleep disturbance) but the other findings are highly suggestive of Morvan Syndrome.

231. Dyspnea on Exertion: Looking Beyond the Heart and Lungs
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Background: Dyspnea is a common symptom that carries a broad differential, usually approached from a cardiopulmonary standpoint. Central nervous system dysfunction, phrenic nerve paralysis, myopathy, neuromuscular junction disorders, and neuropathy could also lead to dyspnea that oftentimes is challenging to diagnose. The phrenic nerve originates from the anterior rami of C3 through C5 nerve roots and provides complete motor innervation to the diaphragm and sensation to the central tendon of the diaphragm, mediastinal pleura, and the pericardium. Cervical stenosis affecting these roots can lead to isolated hemidiaphragm paralysis, which is a rare but documented complication of cervical stenosis.

Case Presentation: 81-year-old man with a past medical history of kyphosis, and spondylosis of lumbar spine with spinal fusion surgery, was evaluated for two years of progressive exertional dyspnea. He initially complained of disproportionate shortness of breath with altitude (10000 feet), followed by a syncopal episode associated with chest pain. He underwent a cardiac workup that showed non-ST-elevation myocardial infarction and non-obstructive coronary disease. Given persistent SOB in subsequent visits with cardiology, he was extensively evaluated with a myocardial perfusion scan, echocardiogram, CT chest looking for pulmonary emboli, which were all inconclusive. Pulmonology suspected an atypical presentation of asthma versus neuromuscular pathology as a source of dyspnea given decreased maximal voluntary ventilation, maximal expiratory and inspiratory pressures since 2018. On initial evaluation by neurology, exam and electromyography did not show signs of motor neuropathy, neuromuscular junction disorder, or acute inflammatory demyelinating polyneuropathy. Restrictive pulmonary disease secondary to kyphosis was at the top of the differential. However, X-ray and CT chest showed elevation of R hemidiaphragm in addition to MRI of the cervical spine with severe C3-C4 cervical spinal stenosis which rose concern for diaphragmatic paralysis as etiology of persistent dyspnea. Fluoroscopic sniff test confirmed right hemidiaphragm paralysis most notable with deep respiration.

Conclusion: Dysfunction of one or both hemidiaphragms is an underdiagnosed cause of dyspnea. Clinicians should be aware that C3-C4 foraminal stenosis can cause hemidiaphragm weakness, and plain chest radiographs on maximum inspiration and expiration may be useful for screening.

232. Answer ALS: A Large-Scale Resource for Sporadic and Familial ALS Combining Clinical Data with Multi-Omics Data from Induced Pluripotent Cell Lines
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Answer ALS was conceived and organized as a comprehensive multi-omics approach to ALS to ascertain, at a population level, the various clinical-molecular-biochemical subtypes of ALS. This national program enrolled a combined total of 1047 ALS, ALS/FTD patients and matched control subjects. Individuals were recruited at 8 national ALS centers and followed longitudinally over one year. A smartphone-based system was employed to collect deep clinical data including fine motor activity, speech, breathing and linguistics/cognition. In collaboration with IBM Research, analytics of speech patterns reveals a strong correlation between clinical progression indices and speech. In parallel, IPS motor neurons were blood-derived from each patient and these cells underwent multi-omic analytics including whole genome sequencing, RNA transcriptomics, ATAC-Seq and proteomics. HIPAA compliant cloud databases were employed to store all data. Open access to all clinical, biological and molecular data is central to the program as well as public release of all generated IPS cell lines. The intent of this data is for the generation of integrated clinical and biological signatures using bioinformatics, statistics and computational biology to establish patterns that may lead to a better understanding of the underlying mechanisms of disease including subgroup identification. A web portal for open source sharing of all data was developed for widespread community-based data analytics. This community-based clinical and science program provides for the identification of distinct reliably identifiable subgroups among the sporadic and familial patients and the great utility in IPS based approaches to disease pathophysiology and therapy discovery. Clinical Trial Registration ID #NCT02574390.
233. Para-Infectious versus Post-Traumatic Guillain-Barré Syndrome: The Diagnostic Conundrum!
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Objective: To describe a case of para-infectious Guillain-Barré syndrome in the setting of recent cervical trauma.

Background: Guillain-Barré syndrome (GBS) is an acute, monophasic polyradiculopathy with typical features of progressive ascending weakness accompanied by loss of deep tendon reflexes. It often is a result of an inappropriate immune response to a preceding infection. Post-traumatic GBS though rare has also been described. Here, we highlight a case of acute-onset neurologic deficits initially attributed to trauma (either spinal cord injury without radiographic abnormality (SCIWORA) or post-traumatic GBS). However, further work-up suggested GBS secondary to a West Nile Virus (WNV) infection.

Case Description: 51-year-old man presented to an outside hospital with a minimally displaced C1 fracture without spinal cord injury requiring C-collar. Within two weeks, he presented to the emergency department with progressive weakness and numbness in all four extremities, moderate bilateral weakness, global areflexia, and severe respiratory difficulty requiring intubation. CSF analysis demonstrated albumino-cytologic dissociation with protein 101mg/dL and WBC 3/mm3. MRI of the cervical spine showed diffuse nerve root enhancement. Five courses of plasma exchange (PLEX) followed by five courses of intravenous immunoglobulin (IVIG) 2 gm/kg resulted in some improvement in limb strength, but failure to extubate resulted in tracheostomy. Three weeks after admission, facial weakness worsened on the left side likely suggesting a treatment-related fluctuation. Repeat CSF analysis showed significantly elevated protein (> 600mg/dL), normal cells, but positive anti-WNV IgM antibody. Nerve conduction studies and electromyography suggested a severe ongoing acute motor and sensory axonal neuropathy variant of GBS. Repeat course of PLEX resulted in improved muscle strength in the face and extremities and return of some reflexes.

Conclusions: Acute-onset neurologic deficits in the setting of cervical trauma may be due to spinal cord injury or post-traumatic GBS, but a search for a para-infectious etiology is always warranted. Treatment-related fluctuations may be seen in up to 10% of cases in the first four weeks of presentation and usually improve with a repeat course of IVIG or PLEX.

234. Burden Among Caregivers of Patients with Amyotrophic Lateral Sclerosis in the United States
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Objective: To describe the humanistic and economic burden experienced by caregivers of patients with amyotrophic lateral sclerosis (ALS) in the United States (US).

Background: ALS is a multisystemic neurodegenerative disease, clinically presenting with motor and nonmotor symptoms. As the disease progresses, patient symptomatology contributes to loss of independence and greater need for caregiver support.

Design/Methods: De-identified data were drawn from the Adelphi ALS Disease Specific Programme¹, a point-in-time survey of neurologists and their consulting patients with ALS. Data were collected in the US between July 2020 and March 2021. Neurologists recorded patient demographics, whether patients received support from any caregiver(s), how long patients had required caregiver support, and the amount of hours of care received per week. Where present, non-professional caregivers of these same patients were invited to voluntarily complete a questionnaire. Caregivers recorded demographics, their own health state (EQ-5D-5L), and both the humanistic burden (12-Item Zarit Burden Interview [ZBI-12]) and economic burden (Work Productivity and Activity Index [WPAI]) associated with caring for a patient with ALS.

Results: Fifty-five neurologists reported data for 354 patients with ALS, of whom 73% received support from a caregiver; 46% of patients received assistance from a non-professional caregiver only. Nonprofessional caregivers provided a mean 33.1 hours of care per week. In 51% of cases, nonprofessional caregivers had changed their working habits to care for the patient, with 38% having either reduced their hours or stopped entirely. Nineteen caregivers of ALS patients submitted a self-completion questionnaire. Of those caregivers, 68% were female, and the average age was 62.7 years. In 83% of cases, the caregiver was the patient’s partner/spouse. Additionally, 78% of caregivers experienced burden, with 50% experiencing high burden, according to the ZBI-12, with an overall mean score of 19.1. The mean caregiver-reported health state (EQ-5D-5L) score was 0.79. Mean percent of activity impairment and percent of overall work impairment (WPAI) were 28.3 and 20.8, respectively.

Conclusions: The results of this study demonstrate that there is a significant burden of care associated with ALS in the US, with most responsibility falling primarily on patients’ close family members. Caregivers of patients with ALS experience both humanistic and economic strain, and these results may suggest that many require greater support from healthcare services.

Sponsorship: Mitsubishi Tanabe Pharma America, Inc.

235. Early Recognition of a Rare Dermatomyositis Subtype
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Introduction: Dermatomyositis is an idiopathic inflammatory myopathy characterized by proximal skeletal weakness, muscular inflammation, and a variety of skin manifestations. More commonly diagnosed subtypes include classical dermatomyositis and amyopathic dermatomyositis, while rarer subtypes include anti-melanoma differentiation-associated
236. A Unique Manifestation of GD1a Antibody Associated Acute Motor Sensory Axonal Neuropathy

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Guillain-Barre syndrome (GBS) is a post-infectious immune disorder typically characterized by symmetric ascending weakness and areflexia. Work-up often reveals elevated anti-ganglioside antibody levels in the acute phase of GBS. GD1a antibody has been shown to be associated with acute motor axonal neuropathy (AMAN) variant of GBS. Here we report a case with atypical manifestations of acute motor and sensory axonal neuropathy (AMSAN) variant of GBS associated with GD1a antibody.

A 63-year-old African American woman presented for evaluation of gradually progressive bilateral lower extremity weakness and sensory abnormalities of 2 years’ duration. Her symptoms began acutely with bilateral lower extremity motor weakness. Weakness was most notable in proximal distribution and persisted for several months before sensory symptoms ensued. Eventually patient presented to clinic with proximal weakness and distal sensory abnormalities, impairing activities of daily living and ambulation. She noted increased frequency in falls and subsequently used a walking stick before becoming wheelchair-bound. She also reported paresthesia and burning sensation involving distal bilateral extremities. She denied recent illness, bulbar symptoms, and distal hand involvement. On neurological examination, she was noted to have asymmetric (left >right) proximal lower extremity weakness and diminished sensation to pain and temperature in distal lower extremities. Reflexes were absent in bilateral lower extremities. Imaging of the brain and spine was unremarkable. Serological work-up for neuroopathy and myopathy was largely unrevealing. Electromyography and nerve conduction study demonstrated sensorimotor axonal neuropathy consistent with AMSAN. On further testing, she had significantly elevated IgG anti-GD1a titers. The patient received aggressive rehabilitation and Duloxetine for dysesthesias with remarkable improvement in strength and sensation. Subsequently, she was able to ambulate independently without falls.

This case illustrates atypical manifestation of the AMSAN variant of GBS with GD1a antibody. Our patient presented with proximal asymmetric lower extremity weakness which is an unusual phenotype for GBS and its variants. Although the axonal variants are known to be associated with poor prognosis and recovery, our patient had a remarkable improvement with symptomatic therapy. Most cases of GD1a antibodies are associated with AMAN and its link with AMSAN is unclear. This case highlights the atypical phenotype of GBS variants and its association with GD1a antibody.
fine motor impairment in his right hand, which rapidly progressed to quadriparesis over two weeks. On neurologic exam, he had poorly sustained attention with otherwise normal mental status. Motor exam showed profound muscle atrophy with fasciculations in the right limbs and right arm spasticity. He had proximal greater than distal quadriparesis, which was most pronounced in the right upper limb. Diffuse hyperreflexia with Hoffman signs, extensor plantar reflexes, and sustained right ankle clonus were present. Despite complaints of severe pain, objective sensory exam was non-contributory. MRI brain was unremarkable. MRI total spine revealed patchy non-contrast enhancing T2 hyperintensities in the thoracic cord and diffuse lumbar ventral root contrast enhancement. Nerve conduction studies showed severely reduced CMAPs in all limbs with preserved conduction velocities and SNAPs. EMG showed diffuse active denervation and chronic reinnervation. CSF analysis revealed few lymphocytes, absent RBCs, moderately elevated protein, normal glucose, oligoclonal bands, and increased IgG index. Infectious meningoencephalitis, autoimmune encephalitis, and paraneoplastic panels were negative. Elevated serum and CSF WNV IgM and IgG titers confirmed neuroinvasive WNV. He was transitioned to comfort care due to worsening quadriparesis, respiratory failure, and intractable pain. Autopsy revealed T-cell-mediated meningoencephalitis with diffuse inflammation in motor neurons and axonopathies of the spinal cord, motor nerve roots, and peripheral nerves.

Conclusions: Neuroinvasive WNV may present as rapidly progressive motor neuron disease. Intractable pain and paresis were the first manifestations in our patient. WNV infection should be considered in those with atypical presentations of motor neuron disease and associated epidemiological risk factors, including location and time of year.

238. Brody Myopathy: A Tale of Three Variants

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Background: Brody disease is a rare autosomal recessive myopathy that results in an impaired activity of the skeletal muscle sarcoplasmic reticulum calcium-ATPase1 (SERCA1), which is encoded by the ATP2A1 gene on chromosome 16p12.1-12.2 while Brody syndrome is without the associated ATP2A1 gene mutations. Brody disease manifests as exercise-induced muscle stiffness due to delayed relaxation. Symptoms usually are present since the 1st decade and can be worsened by cold. Knowledge about the disease is limited, and genetic testing has become an imperative tool in the diagnostic work up.

Case Report: Here we present two patients with different phenotype-genotype correlation. First case: 19-year-old male presented with brief episodic muscle tightness triggered by exertion and difficulty releasing handgrip since childhood. Neurological exam revealed bilateral handgrip myotonia and mild right thenar eminence percussion myotonia. Electromyography (EMG) did not show evidence of myotonia given the pathology at intracellular organelle rather than muscle membrane, thus called pseudomyotonia. Gene testing showed two heterozygous variants of the ATP2A1 gene (c.1184 + 1 G>A - pathogenic; c.2744 +1 G>A - likely pathogenic), consistent with an autosomal recessive Brody myopathy. The proband is a 28-year-old female presented with episodic muscle spasms in the trunk and extremities over last few years. She endorsed generalized weakness and inability to relax her right hand. Neurological exam was normal. Workup included EMG, MRI of brain, C-spine, and T-spine, which were unremarkable. Genetic testing showed a likely pathogenic single heterozygous variant of AT2PA1 (c. 2758 C>T, p. Q920X). Absence of a second detectable mutation currently precludes us from a diagnosis of Brody myopathy but possibility of a symptomatic carrier state with a Brody syndrome phenotype is likely.

Conclusions: Neurogenetics plays a big role in diagnosing this rare entity of Brody disease. Subjective description of muscle spasms and objective evidence of myotonia on clinical exam are often questioned when EMG doesn’t show myotonic discharges, a term called pseudomyotonia.

239. A Family with an Autosomally Dominantly Inherited CHRNA1 Mutation and Congenital Myasthenia Syndrome

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Background: Congenital myasthenic syndromes (CMS) are a rare group of inherited neuromuscular junction disorders clinically characterized by fatigueable and/or persistent muscle weakness throughout the body. A small subset of CMS cases are caused by mutations in the alpha-subunit of the nicotinic acetylcholine receptor (CHRNA1). Due to low disease prevalence and ambiguity of symptoms on presentation, phenotype-correlations can be challenging. Here, we present a family with three affected individuals in two generations with a CMS phenotype and a Gly94Cys mutation in CHRNA1.

Cases: The proband is a 39-year female who initially presented with a three-month history of progressive distal and proximal weakness in the right upper extremity, fatigue and cognitive decline without sensory loss, ocular or bulbar symptoms. Her exam showed 4/5 strength on the MRC scale in the right wrist and finger extendors, finger adduction and shoulder abduction which decreased to 2/5 with repetitive testing. She was also found to have fatiguable weakness in less symptomatic left deltoid and bilateral hip flexors. Electrodiagnostics including an ulnar repetitive stimulation and single fiber EMG were unremarkable. Neural axis imaging was unremarkable. The probands youngest (5 years old) and oldest daughters (17 years old) reported hypotonia since birth, intermittent fatiguable weakness and cognitive difficulties. A repetitive stimulation of the youngest daughter demonstrated...
a 9.6% decrement with post exercise facilitation. Targeted exome sequencing panel for common neuromuscular disorders revealed a CHRNA1 c. 280G>T, p. Gly94Cys mutation in all three affected and not in the unaffected middle daughter. Whole genome sequencing was performed in the youngest daughter which revealed only the maternal Gly94Cys mutation, suggesting this variant as the causal mutation. The proband and youngest daughter were treated with pyridostigmine with no improvement in strength or fatigue. However, the proband had a near full response in strength and cognition six weeks after starting Firdipase (amifampridine, 3,4-diaminopyridine phosphate, 3,4DAPP).

Conclusion: In summary, we present a multigenerational family with CMS and a dominantly inherited G94C mutation in CHRNA1. This mutation was previously reported in compound heterozygosity in a CMS cases however with careful phenotyping and whole genome sequencing we determined this mutant as likely causative in heterozygosity. Additionally we show clinical response to 3,4DAPP in this phenotype, suggestive of a slow-channel physiology. 

240. Amyotrophic Lateral Sclerosis Surveillance and Survival in Two Midwest Metropolitan Areas, 2009-2011, 2018 
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Objective: To describe the demographics, incidence, and survival of persons with ALS identified in the National ALS Registry’s from Detroit and Chicago Metropolitan Area ALS Surveillance project.

Introduction: Amyotrophic lateral sclerosis (ALS) is a difficult to diagnose, rare neurological disease with unknown etiology. The National ALS Registry, maintained by ATSDR, funded the state and metropolitan surveillance projects (SMSP) to better understand the surveillance and demographic characteristics of ALS in three states and eight metropolitan areas.

Methods: The cases used for this analysis were collected through the SMSP, in collaboration with the Detroit Department of Health and Wellness Promotion (DHWP) and the Metropolitan Chicago Healthcare Council (MCHC), from January 1, 2009 to December 31, 2011. The Chicago and Detroit areas were combined in this analysis for their demographic similarities and to over-represent the minority population. In addition to the demographic characteristics of cases in Chicago and Detroit, the crude incidence rates were calculated for 2009-2011 and stratified by race and ethnicity. Using data from the National Health Index through 2018, we modeled the effect of patient covariates on mortality using the Cox proportional hazard regression.

Results: Of the 574 combined cases in Chicago and Detroit, 372 (64.8%) were diagnosed from 2009-2011. Of the total cases, a large portion of cases were diagnosed between 50 to 79 years of age. The crude incidence rates for the combined Chicago and Detroit area for 2009, 2010 and 2011 were 1.44, 1.53, and 1.73 cases per 100,000 person-years, respectively. Of the 486 subjects with complete survival data, 81% were deceased at the end of follow-up. The overall median survival time of the cases was 2.2 years, with more than 20% of participants surviving at least 10 years. While there were no reported differences on survival for males and females, we found a worsening survival with increasing age at diagnosis. Similar to other studies, a longer time between symptom onset and diagnosis estimated a longer survival time. Finally, non-whites experienced longer survival than their white peers, except for those cases diagnosed in the younger age categories.

Conclusion: To our knowledge, this project is one of the first to provide incidence and survival estimates for the Chicago/Detroit area using death data from 2009 to 2018. Understanding the survival experiences of patients with ALS can aid in understanding mutable prognostic factors, which can potentially extend survival and improve disease management.

241. A Rare Presentation of Guillain-Barre Syndrome in a Patient with COVID-19 Infection
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Introduction: The novel coronavirus (COVID-19), although primarily of respiratory manifestation, exhibits many neurological symptoms such as headache, anosmia, and ageusia, suggesting its neuroinvasive potential. Guillain-Barre Syndrome (GBS) is an immune-mediated polyneuropathy characterized by symmetrical weakness of limbs and hyporeflexia or areflexia, that is associated with numerous viral conditions. Although case reports have emerged describing the association between COVID-19 and GBS, there is a paucity of information in the literature describing different presentations of GBS in this setting.

Case Presentation: We present a case of a 41-year-old male with a history of recent type two diabetes who presented with a chief complaint of ascending muscle weakness of the bilateral lower and upper extremities over 24 hours. He was unable to stand and had lost bladder control. He was found to be COVID positive on PCR and IgG on the day of presentation in the absence of common COVID-19 symptoms. Neurological exam displayed diminished muscle strength in the bilateral extremities; however, greater on the left with associated left facial droop. There were absent deep tendon and Babinski reflexes. CT brain and neck, EKG, Chest X-ray, and MRI of the cervical and thoracic spine were without significant abnormalities. IVIG 0.4 g/kg daily was initiated for five days; however, he developed a progressive peripheral left facial nerve palsy and was intubated for acute
respiratory failure on hospital day one. CSF revealed albuminocytologic dissociation with negative Anti- GQ1b and ACh-R antibodies. VDRL, HIV, homocysteine, myelin basic protein, and angiotensin-converting enzyme testing in the CSF was also negative. After completion of IVIG without significant improvement, he was transitioned to plasmapheresis for five treatments with minimal improvement. Subsequently, he underwent tracheostomy and percutaneous gastrostomy tube placement and was discharged to a long-term acute care respiratory hospital.

Discussion: Most GBS cases developed in COVID-19 patients with respiratory and/or systemic symptoms and had a good prognosis with IVIG treatment. Our case is unique because of the predominance of left-sided weakness and facial droop in the setting of COVID-19 infection, displaying a non-typical asymmetric presentation of COVID-19 associated GBS.

Conclusion: GBS can be the initial symptom or sequelae of COVID-19 infection, presenting with asymmetric weakness and facial droop. This highlights the need for clinical diligence for this rare presentation of GBS associated with COVID-19 infection.

242. A Rare Case of Isolated Facial Diplegia Variant of Guillain-barre Syndrome with Covid-19 Infection
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Background: Facial Diplegia with distal paresthesia is an unusual variant of Gullian Barre Syndrome (GBS). There have been reports of GBS associated with COVID-19 and some of those patients having facial nerve weakness in addition to distal weakness. We present a rare case of isolated Facial Diplegia with paresthesia’s without any focal distal weakness as a clinical manifestation of GBS with COVID-19 infection.

Case Presentation: 39yr old construction worker tested positive for COVID-19 after developing fever, fatigue, dysgeusia & anosmia. After self-quarantine he was back to his work after 2 weeks. 2 weeks from the initial infection the patient developed left sided facial droop, followed by right sided facial droop in the next 4 days. He was initially diagnosed and treated as idiopathic Bell’s palsy with no improvement. He presented to neurology clinic on 12th day from onset of his left facial weakness. Exam showed bilateral (LMN) facial nerve weakness, areflexia & subjective distal paresthesia’s in both hands & feet. Rest of the cranial nerve, motor, sensory & coordination exam was intact. He also reported of bilateral facial myokymia. MRI brain showed contrast enhancement of both facial nerves. CSF analysis showed albuminocytological dissociation (Protein 106, 0 nucleated cells). He was diagnosed with GBS secondary to COVID-19 infection given the temporal relation between the initial COVID-19 infection & onset of facial weakness. He was treated with 5 day course of IVIG. Other common causes of facial diplegia including Lyme’s, sarcoidosis, CMV, EBV, Multiple sclerosis were ruled out. His serum was negative for anti-ganglioside antibodies. EMG during the hospitalization showed absent blink reflex, absent left facial motor response, reduced recruitment without fibrillations or positive sharp waves in several facial nerve innervated muscles. Follow up after 10 days of discharge showed resolved paresthesia’s and minimal improvement of right facial palsy (House-Brackmann grade IV on the right, Grade VI on the left).

Discussion: Clinical Spectrum of neurological manifestations with COVID-19 infection is very varied and classic symptoms of GBS has been reported post COVID-19 infection and in some cases included facial nerve weakness (both unilateral and bilateral). These patients have had focal weakness in addition to facial nerve weakness and often required additional therapy.

Conclusion: Given the myriad of variable clinical presentations with COVID-19 infection, in patients presenting with isolated facial nerve weakness, GBS should be considered in their differential diagnosis early on during their evaluation.

243. The History of a Peculiar Form of Peripheral Neuropathy
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Introduction: The management of polyneuropathy associated with hereditary transthyretin amyloidosis (hATTR) has been revolutionized with the use of gene silencer therapies. The road traveled has been long, starting with the pathologic identification of amyloid and having a turning point with the clinical description by Corino Andrade.

Objective: To present a chronological account of the early pathologic and clinical descriptions of amyloidosis and hATTR.

Methods: Review of historical documents.

Results: Nicolas Fontanus was probably the first to report amyloidosis in an autopsy in 1639. The term “amyloidosis” was first used by Matthias Schleiden in 1838 to describe normal amylaceous components in plants. Rudolph Virchow is credited with coining the term “amyloidosis” for the group of diseases we now know by this name. In 1854 he used the term amyloid to describe the reaction of cerebral corpora amylacea, which he thought was identical to starch, with iodine. Most early clinical reports where cases of secondary amyloidosis associated with infections. Samuel Wilks reported the first case of primary amyloidosis in 1856 and Weber identified the first case of amyloidosis associated with multiple myeloma in 1867. Congo red, an aniline dye, was first synthesized in 1883. It was introduced as a textile dye in Berlin in 1885, shortly after the Berlin West Africa Conference. The name “Congo” was used for marketing purposes, presumably to evoke the exotic images of central Africa. In 1922 Bennhold recognized that Congo red avidly stained amyloid. Divry reported the apple-green birefringence 5 years later, in 1927. Corino Andrade published his seminal paper on “A Peculiar Form of Peripheral Neuropathy” in 1952. He encountered his first case in 1939 in Povoa de Varzim, near Porto. He soon noted the endemic nature of what the locals called “foot disease”. He accumulated 74 cases over more years.
244. Relationships Between Cognitive and Motor Endpoints in Myotonic Dystrophy Type 2 (DM2): Is the Brain Driving Motor Dysfunction?

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Background: Myotonic dystrophy type 2 (DM2) is a progressive multisystemic disease. Although proximal muscle weakness is the primary feature of DM2, cognitive impairments are also reported among the most disabling symptoms. Previous studies have described executive dysfunction, episodic memory loss, and impaired attention in DM2. However, relationships between these cognitive symptoms and motor dysfunction have not been established.

Objective: To characterize cognitive endpoints in DM2 and evaluate relationships between cognitive endpoints and motor dysfunction.

Methods: Ten patients with DM2 and ten age and gender-matched controls were enrolled. All participants completed the Comprehensive Clinical Assessment Battery (CAB), including 1) NIH Toolbox Cognitive Measures (executive function, attention, working memory, language, and processing speed domains); 2) disease-specific motor testing (gait speed, 6-minute walk test, Jamar grip dynamometer, and 9-Hole peg test); 3) the short physical performance battery (SPPB), and 4) patient-reported outcomes. Wisconsin 2-sample tests and Spearman’s correlation coefficient were used to determine group differences and relationships between cognitive and motor endpoints.

Results: There were no differences between age (61.4 vs. 61.6 years), years of education (16.0 vs. 17.6 years), and gender (4 males and 6 females in each group) between the DM2 and control groups. The average age of symptom onset for DM2 participants was 45.4 years, with an average disease duration of 13.5 years. It took an average of 11.4 years after symptom onset for DM2 participants to be correctly diagnosed. Compared to controls, DM2 adults had poorer performance on most cognitive and motor endpoints, with significant differences in the SPPB (p=0.05, effect size 2.11) and 9-Hole peg test (p=0.03, effect size 2.4). A moderately strong correlation was found between 1) disease duration and grip strength (rho=−0.65, p=0.04), 2) working memory and the 9-hole peg test (rho=−0.62, p=0.05), and 3) processing speed and grip strength (rho=0.49, p=0.15).

Conclusion: Compared to controls, the DM2 group demonstrated poorer performance in cognitive and motor function. This study identifies relationships between specific cognitive domains and disease-specific motor endpoints. The findings support the notion that motor deficits in DM2 may be a multimodal dysfunction involving both skeletal muscles and the central nervous system. Future studies are needed to validate these findings and determine disease progression and clinical trial readiness in DM2.

245. A Heterozygous Mutation in Mff Associated with a Mild Mitochondrial Phenotype

Ricardo Roda, MD/PhD. Johns Hopkins School of Medicine, Baltimore, MD, USA.

Mutations in mitochondrial fission factor (MFF) are associated with autosomal recessive mitochondrial disease. We present a case of late onset mitochondrial phenotype associated with a heterozygous c.937 G>A, p.Glu313Lys MFF mutation. The index case presented with ptosis, diffuse weakness and fatigability and was thought to suffer from double seronegative myasthenia gravis as a result of abnormal neuromuscular junction studies. He failed to improve despite prolonged appropriate immunosuppression. A muscle biopsy revealed an increased number of COX negative fibers suggestive of mitochondrial disease. Studies on fibroblasts collected from the patient revealed a defect in fission compared to age-appropriate controls. Despite stopping immunosuppression his symptoms persisted but did not worsen. We suggest that heterozygous mutations in MFF present with a mild mitochondrial disorder which may mimic myasthenia gravis.

246. Acute Heroin-Induced Brachial Plexitis

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Background: Non-traumatic brachial plexitis is a form of immune-mediated inflammation against the brachial plexus. Possible causes include idiopathic (Parsonage-Turner syndrome), hereditary, radiation-induced, viral (cytomegalovirus, Coxsackie, herpes zoster, HIV, Epstein-Barr virus, Parvovirus B19), immunologic or toxic (vaccines, antibiotics, recreational drugs, rheumatological diseases). It is more common in middle-aged males with an infectious or immunogenic trigger reported in more than half of cases. The average time between the triggering event and symptoms is 1-28 days. The symptoms are usually unilateral in 70-90% of cases. Peripheral nerve disorders are important complications of intravenous diacetylmorphine (heroin) exposure.

Case Report: A 26-year-old male with a history of multiple substance abuse and HIV infection (not on HAART therapy), presented to emergency due to opioid overdose. He was undergoing rehabilitation treatment for multiple drug dependence when he relapsed and self-injected heroin to his left arm the night before admission. He was found unresponsive in his bed without signs of trauma. After receiving emergent...
treatment and upon regaining consciousness patient noted an inability to move his left arm. He developed severe painless flaccid paresis of the left upper limb with loss of reflexes and sensory loss of medial forearm, dorsal and palmar aspects of the hand. Investigations also revealed acute kidney injury due to rhabdomyolysis (creatinine kinase was elevated to 7,451 U/L). His CD4 count was normal and there were no signs of infection. MRI of the brachial plexus with contrast showed thickening and T2-hyperintense signal of the trunks and divisions of the left brachial plexus. The patient received supportive treatment, creatine kinase level and kidney function gradually normalized. For acute brachial plexitis he received a short course of oral steroids on discharge with a plan for outpatient NCS/EMG and physical therapy.

**Conclusion:** Heroin-induced plexopathy is a very rare complication of intravenous injections that usually occurs ipsilaterally to the injection site and often associated with concurrent rhabdomyolysis. Combined nerve and muscle injury occur without apparent trauma. The exact pathophysiology of plexitis is unclear in these cases. Possible mechanisms include focal ischemia, compression, myotoxic muscle damage, and immune-mediated inflammatory response. Awareness of this neurological complication of heroin addiction is important for prompt recognition and treatment.

**247. Persistent Ophthalmoplegia, Asymmetric Weakness and Areflexia in a Patient with Myasthenia Gravis**

_Mauricio X. Perez, MD, Ahmed Hanazeen, MD, Xiang Fang, MD. Neurology, UTMB, Galveston, TX, USA._

**Introduction:** Fatigable ptosis, diplopia, dysphagia, and generalized weakness are common clinical manifestations of Myasthenia gravis (MG). Diagnosis of MG with atypical presentations could be very challenging, and here we report an atypical case of MG with persistent ophthalmoplegia, asymmetric weakness and areflexia.

**Case Presentation:** A 62-year-old African American man presented with progressive upper and lower extremity weakness, gait difficulty and falls for 2 months. He also complained of severe constipation and 30-pound weight loss during this time without dysphagia and changes in appetite. Examination revealed a cachectic man with significant generalized muscle atrophy, asymmetric upper extremity weakness and areflexia. He was able to stand up but required significant support for ambulation. Cranial nerve exam showed horizontal gaze paralysis on his left eye, as well as weakness on right eye adduction. He denies ptosis and diplopia. Work-up including TSH, CMP, CK, neuroimaging and CT chest/abdomen were unremarkable. Antiganglioside antibody for Miller-Fisher syndrome were also negative. Further work-up showed significant elevated AchR-binding antibodies. Nerve conduction studies were remarkable for decremental response with repetitive nerve stimulation at 3-Hz on the left median and spinal accessory nerve, supporting the diagnosis of MG. He was treated with five days of IVIG with marked improvement of strength and gait, but ophthalmoplegia persisted. He was discharged with pyridostigmine and reported overall improvement.

**Discussion:** As a disorder of the neuromuscular junction (NMJ), the clinical manifestations of MG are typically related to weakness and fatigability of the axial, bulbar or extraocular muscles. Although there are no specific patterns of weakness, generalized MG usually presents with symmetric, proximal involvement of the upper extremities. Ocular MG presents with fatigable ptosis or diplopia due to extraocular movement paralysis. Atypical clinical presentations that are not consistent with involvement of the NMJ can present a challenge to the clinician. Persistent ophthalmoplegia, areflexia and gait disturbance are typically presented in Miller-Fisher syndrome, a variant of Guillain-Barre Syndrome (GBS). Although there are case reports of MG and GBS presenting simultaneously, in our patient all antiganglioside antibodies including anti-GQ1b were negative. Therefore, our patient presented with a constellation of symptoms that are considered atypical of MG.

**248. Late Onset Myasthenia Gravis Mimicking Acute Stroke**

_Mauricio X. Perez, MD, Elena Shanina, MD. Neurology, UTMB, Galveston, TX, USA._

**Introduction:** Myasthenia Gravis exacerbations usually present with severe musculoskeletal, bulbar or ocular weakness. We present the case of a woman with sudden onset speech difficulty and weakness mimicking acute stroke who was later diagnosed with Myasthenia Gravis.

**Case Presentation:** A 72-year-old Hispanic woman was taken to the hospital for sudden onset of generalized weakness and anarthria. She was in church praying out loud when she noticed progressive tongue heaviness and difficulty articulating her words. After a few minutes, her speech became very slurred and incomprehensible. She also had significant difficulty walking because of lower extremity weakness, so her family drove her to a local hospital with concerns of acute stroke. A brain MRI was unremarkable, but neck angiography showed chronic stenosis of the left internal carotid artery. She was discharged home on anticoagulant medications and follow up with vascular surgery for carotid endarterectomy. Further questioning during clinic visit revealed that she had two other episodes of severe generalized weakness, speech difficulties, and bilateral eyelid heaviness during the same year. Physical exam was significant for fatigable proximal upper and lower extremity weakness and bilateral ptosis with upward gaze. Electrodiagnostic studies were supportive of a neuromuscular junction disease and high levels of anti-acetylcholine receptor binding antibody were diagnostic for Myasthenia Gravis. She has not had any more episodes since starting pyridostigmine and azathioprine.

**Discussion:** Myasthenia Gravis is a neuromuscular junction disorder with many different clinical presentations that can mimic other unrelated conditions, especially in the elderly population. Although the disease is more commonly seen in younger individuals, almost a third of cases are seen in the seventh decade of life, particularly in men and in association with thymic hyperplasia or thymoma. Late-onset Myasthenia Gravis can present with symptoms that can mask...
an underlying neuromuscular pathology. For instance, an initial presentation consisting of dysphagia, dysarthria, or dysphonia in a geriatric patient with generalized weakness due to other comorbidities can represent a diagnostic challenge for every clinician. Moreover, sudden onset of bulbar symptoms in someone who is at higher risk for cerebrovascular events dictates a work-up dedicated to rule out posterior fossa lesions. Oftentimes, these patients remain without a formal diagnosis and proper treatment for many years until they present with life-threatening symptoms.

Conclusion: After cerebrovascular events have been ruled out, late-onset Myasthenia Gravis should be in the differential diagnosis of sudden onset dysphonia in the elderly population.

249. Incidence and Prevalence of Immune-Mediated Necrotizing Myopathy in Olmsted County, Minnesota
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Objectives: To determine the incidence and prevalence of immune-mediated necrotizing myopathy (IMNM).

Methods: We identified adult patients with IMNM defined by the 2016 European Neuromuscular Centre diagnostic criteria among Olmsted County, Minnesota, residents over a 20-year time period.

Results: Seven patients fulfilled the inclusion criteria, six of whom underwent IMNM antibody evaluation (4 HMGCR-IgG, 1 SRP-IgG and 1 double seronegative). The incidence of IMNM during 2010-2019 was 8.3 per million person-years, which is 4 times higher than what previously estimated. The prevalence of IMNM in 2010 was 1.85 per 100,000 people ≥50 years, which is 10-time lower than the prevalence of inclusion body myositis (IBM) in Olmsted County. Median age at symptom onset was 66 years (range: 52-86 years) and median time from symptom onset to diagnosis was 3 months (range <1 to 122 months). Two patients developed cancers a year and 6 years from myopathy onset. The incidence of malignancy in IMNM was not higher than that of the general population (P=0.65). Treatment outcome was favorable in all, but 2 patients because of delayed treatment (n=1) or insufficient therapy (n=1). Among 3 deceased patients, 1 died from cancer while 2 died from IMNM-related cardiorespiratory complications. Median life expectancy in the IMNM group was 87 years versus 91 years in the control group (P=0.02) and 84 years in IBM patients (P=0.0028).

Conclusion: IMNM is rare disease, but more common than previously estimated. IMNM patients are not at higher risk for cancer, but slightly shorter life expectancy compared to population controls.

250. Rapidly Progressive Primary Lateral Sclerosis
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Introduction: Primary Lateral Sclerosis (PLS) is among the spectrum of progressive motor neuron diseases involving the upper motor neuron (UMN) system. PLS remains a diagnostic challenge due to its rare occurrence and overlap with other motor neuron diseases, especially amyotrophic lateral sclerosis (ALS).

Case: A 57-year-old African American male presented to the hospital with progressively worsening speech, gait, repetitive falls, and incontinence. His medical history was significant for laryngeal cancer in remission and episodes of alcohol abuse. Approximately one year prior he developed slowing of his speech, which progressively became indiscernible. Within this timespan he developed difficulty ambulating due to ataxic gait, ultimately becoming bedbound. Physical examination revealed an alert and fully oriented, cachectic-appearing male. He was unable to ambulate and his speech was garbled and incomprehensible. He had no sensory deficits but had notable hyperreflexia with decreased power (2/5) in bilateral upper and lower extremities. Magnetic resonance imaging (MRI) reported hyperintense subcortical signals in the precentral gyri with associated cortical susceptibility. Symmetric hyperintense signal was revealed in the cerebral peduncles at the expected regions of corticospinal tracts with extension on the right to the posterior limb of the internal capsule. Cumulatively, these findings were suggestive of ALS. As part of the workup, EMG was also performed. The EMG did not show any fasciculations, fibrillations, or other spontaneous activity to suggest lower motor neuron disease. Lab findings were notable for CPK 684IU/L, ESR>120 mm/hr, TSH 87mIU/L and T4 of 0.6 ug/dL, for which he received levothyroxine. Based on examination findings and the absence of lower motor neuron (LMN) disease he was diagnosed with PLS.

Discussion: PLS is a rare motor neuron disease, distinguished from ALS by the absence of LMN pathology. In a majority of PLS cases, symptoms follow an ascending progression and appear insidiously over three to five years. Symptoms commonly begin in the lower extremities and progress superiorly with asymmetric severity, culminating in spastic quadriplegia. Corticobulbar dysfunction typically occurs later in the disease course, resulting in permanent dysarthria and dysphagia. Our case is a rare presentation of PLS with rapid progression of symptoms over one year, and early onset of corticobulbar dysfunction. It is important to diagnose PLS as it has a favorable prognosis and slower progression compared to ALS.

251. Diffuse Gonococcal Infection in a Patient with Treatment Refractory Acetylcholine Receptor Antibody-Positive (AChR+) Generalized Myasthenia Gravis (gMG) Treated with Eculizumab

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Patients receiving complement inhibitor, Eculizumab are at high risk for infections with encapsulated organisms such as Neisseria due to impaired opsono-phagocytic activity. Impaired complement immunity may increase the risk for dissemination of asymptomatic Neisseria gonorrhoeae. Disseminated Gonococcal Infection (DGI) is a rare but potentially life threatening complication associated with Eculizumab. We described a case of DGI in a 32 year old African American female patient with Acetylcholine Receptor antibody-positive (AChR+) Generalized Myasthenia Gravis (gMG), receiving Eculizumab. Patients should be educated about the increased risk of gonococcal infection and DGI with eculizumab. Healthcare professionals should keep DGI in their differential diagnosis especially in a patient with skin or joint involvement. When prescribing Eculizumab, physicians should obtain adequate sexual histories from the patients and educate them on safe sexual practices.

252. A Case of Isaac Syndrome with Refractory Neuropathic Pain

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Introduction: Isaac syndrome is a peripheral nerve hyperexcitability state associated with voltage gated potassium channel (VGKC) complex antibodies. Major manifestations are muscle twitching, stiffness, hypertrophy and dysautonomic features like hyperhidrosis. Neuropathic pain is a rare manifestation.

Case Report: a 45-year-old male presented with a four-week history of muscle twitching, burning pain, stiffness and episodic sweating in the extremities. He had no history of weakness, dysphagia or dysarthria. On examination positive findings included persistent muscle fasciculations over the deltoids, triceps, forearm, thigh and calf muscles. No muscle atrophy or hypertrophy was noted and strength was grade 4+ in all muscles. Patient was started on a 5 day course of IVIg for presumed Isaac syndrome. Burning pain in the extremities required high doses of Dilaudid and later Morphine with only mild relief. After starting IVIg muscle fasciculations improved with only minor improvement in pain and patient was transitioned to oral Percocet and Gabapentin. At the time of discharge patient’s pain was only mildly reduced in intensity but muscle fasciculations and stiffness had significantly improved. Workup included VGKC antibodies which were elevated at 63pmol/L (Normal 0-31). CT scan of the chest, abdomen and pelvis were negative for neoplasm. EMG/NC revealed spontaneous activity in the form of grouped discharges as well as neuromyotonic discharges. Motor unit potentials were normal. Two weeks after discharge patient presented to ER complaining of increasing episodes of breakthrough pain. The dose of Percocet and Gabapentin was increased and patient was asked to follow-up in the neurology clinic.

Discussion: Common manifestations of Isaac syndrome are muscle twitching, stiffness hypertrophy and dysautonmia. Sensory manifestations such as neuropathic pain are rare but as illustrated by our patient can be the most distressing symptom. In our patient not only was neuropathic pain disabling but it also showed the least response to IVIg during follow-up.

253. Unilateral Persistent Ptosis and Ophthalmoplegia and Elevated Antiganglioside Antibodies in a Patient with Myasthenia Gravis

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Background: Myasthenia Gravis (MG) is an autoimmune neuromuscular junction (NMJ) disease characterized by fatigable muscle weakness. Antibodies against acetylcholine receptor (binding, blocking, modulating), LRP4, Muscle specific tyrosine kinase (MuSK) and striational antibodies are commonly associated with this disorder. Association of Antiganglioside antibodies related to MG is rare and still largely unknown. We report a case of Myasthenia Gravis’ associated with significantly elevated antiganglioside antibodies.

Aim/Objective: Retrospective review of an atypical MG patients with elevated antiganglioside antibodies.

Case Report: 46 year old right-handed male with past medical history of Graves’ disease, Hypertension, left sided Bell’s palsy presented with chronic persistent binocular diplopia and ptosis of left eye. The symptoms started 2 years ago which progressively worsened without the pattern of fatigability. He stated that his left eyelid stays half closed throughout the day without any diurnal variation. He also reported vertical diplopia in all gaze and present at all times. He also had generalized muscle weakness that started around same time. He was diagnosed with Grave’s disease in 2019 and was treated with Methimazole and propranolol which improved his muscle weakness partially. He continued to have weakness while chewing and walking after treatment for Graves’ disease. He denied any difficulty swallowing or breathing, and there are no prodromal symptoms. Neuro exam revealed impaired left eye abduction, adduction and left eye ptosis, and residual lower motor neuron type facial palsy and symmetric proximal limb girdle muscle weakness. Deep tendon reflexes were normal, and there was no ataxia. CT chest revealed thymic hyperplasia. MRI Brain and orbit with and without contrast were normal. Acetylcholine binding, blocking antibodies, anti-GM1, anti-GD1b antibodies were elevated. Treatment with Pyridostigmine results in significant symptoms improvement in proximal muscle weakness, diplopia and ptosis.
Discussion: There are several case reports of Antiganglioside antibodies and their association with GBS post SARS-coV2 infection, paraneoplastic NMJ disorder, acute motor axonal neuropathy, Miller Fisher syndrome, multifocal motor and sensory neuropathy. Our case is unique in the fact that our patient is Seropositive for both acetylcholine antibodies (blocking and binding antibodies) along with Ganglioside antibodies (anti GM1 and anti GD1b) which to our knowledge was never reported. Elevated anti-ganglioside antibodies in patients with NMJ may contribute to atypical manifestation of NMJ disease, in this case, persistent unilateral ophthalmoplegia and ptosis.

292. Neurotoxic Properties of Human Endogenous Retrovirus-K Envelope Protein and Detection in Cerebrospinal Fluid of Patients with Amyotrophic Lateral Sclerosis
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Expression of human endogenous retrovirus K (HERV-K) subtype HML-2 envelope (Env) in human neuronal cultures and in transgenic mice results in neurotoxicity and neurodegeneration. Mice expressing HML-2 Env display behavioral and neuromuscular characteristics resembling amyotrophic lateral sclerosis (ALS). Addressing the question of extracellular neurotoxicity of HML-2 Env, we found that HML-2 Env protein could be found in the cerebrospinal fluid (CSF) patients with sporadic ALS. Using recombinant HML-2 envelope protein, we observed a dose and time-dependent neurotoxicity using assays for neuronal cell death, retraction of neurites and neuronal electrical activity using microarray electrodes. Injection of the Env protein into the brains of mice also resulted in neuronal cell death. The neurotoxic properties of the Env and the CSF could be rescued with the anti-Env antibody. Using a panel of compounds to screen for their ability to block Env-induced neurotoxicity, we found that GSK-3β antagonists, retinoic acid receptor agonists and select flavonoids were protective. In conclusion, HERV-K (HML-2) Env is released extracellularly in ALS and causes neurotoxicity via a novel mechanism. Present results pave the way for new treatment strategies in sporadic ALS.

293. CK1ε-Dependent TDP-43 Phosphorylation in ALS
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Introduction: ALS is the most common incurable adult-onset motor neuron disease. Despite heterogeneity in familial versus sporadic ALS, over 90% of all patients exhibit the key pathological hallmark of TDP-43 (TAR DNA-binding protein 43) mislocalization from the nucleus to the cytoplasm where it forms hyperphosphorylated TDP-43 (pTDP-43) aggregates which are suggested to be toxic in neurons. The details underlying this pathologic phosphorylation mechanism are still unknown. Our study of whole transcriptome sequencing of motor neurons isolated from ALS patient lumbar spinal cord tissues identified CSNK1E to be highly correlated with TDP-43 pathology. CSNK1E encodes casein kinase 1 epsilon (CK1ε) protein which is a cytoplasmic serine/threonine specific phosphorylation kinase.

Methods: Using cellular models of TDP-43 proteinopathy, we examined the effect of modifying CK1ε activity on TDP-43 phosphorylation, aggregation, and cellular toxicity. Further, we extended our findings into a TDP-43 mouse model that expresses molecular neuropathology phenotypes as well as robust motor deficits that recapitulate clinically relevant symptoms of ALS.

Results: In U2OS and SH-SY5Y cellular models, reducing CK1ε kinase activity via siRNA or small molecule chemical inhibitor results in significant reduction of phosphorylated TDP-43. Interestingly, we also observe increased cellular survival when CK1ε-specific inhibitor is added. We are underway with genetic CK1ε knockout in vivo experiments and also a CK1ε inhibitor administration approach to test CK1ε as a potential therapeutic target in ALS.

Conclusions: Our results suggest that CK1ε is an upstream regulator that phosphorylates TDP-43 and thus promotes cytoplasmic TDP-43 aggregation and neurotoxicity in ALS pathogenesis. Understanding the details underlying this pathologic phosphorylation mechanism may reveal CK1ε as a novel target for therapeutic intervention which could be rapidly translated for clinical use with existing CNS-penetrant selective chemical inhibitors.

294. Nuclear Accumulation of Chmp7 Initiates Nuclear Pore Complex Damage and Subsequent TDP-43 Dysfunction in Sporadic and Familial ALS
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Alterations in the components (nucleoporins, Nups) and function of the nuclear pore complex (NPC) have been implicated as contributors to the pathogenesis of genetic forms of neurodegeneration including C9orf72 ALS/FTD. We hypothesize that Nup alterations and the consequential loss of NPC function may lie upstream of TDP-43 dysfunction and mislocalization widely observed in ALS, FTD, and related neurodegenerative diseases. We now provide evidence that CHMP7, a critical mediator of NPC quality control, is dramatically increased in nuclei of C9orf72 and sporadic ALS iPSNs and postmortem human motor cortex prior to the emergence of Nup alterations. Inhibiting the nuclear export of CHMP7, triggers Nup reduction and TDP-43 dysfunction and pathology in human neurons. Knockdown of
CHMP7 mitigates disease associated Nup alterations, deficits in Ran GTPase localization, defects in TDP-43 associated mRNA expression, and alleviates downstream glutamate induced neuronal death. Thus, our data support a role for altered CHMP7 mediated Nup homeostasis as a prominent pathomechanism underlying familial and sporadic ALS and highlights the potential for CHMP7 as a novel therapeutic target.

295. Sex and Age Impact the Role of the Immune System in Amyotrophic Lateral Sclerosis

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The immune system contributes to the progression of amyotrophic lateral sclerosis (ALS). Despite recent insights into ALS immune mechanisms, however, clinical trials using immunotherapy have failed to improve disease outcomes in human subjects. This may be due to the heterogeneous nature of ALS, as numerous factors contribute to ALS development and the rate of progression. Two of these factors are age and sex: the incidence of ALS increases with age, and men develop ALS at a higher rate than women, particularly among younger individuals. Given these age- and sex-base discrepancies, we hypothesized that immune factors may play a more critical role in ALS progression within specific demographic groups. To test this, we examined immune levels and cellular activation within ALS and control subjects using flow cytometry, correlated these metrics with survival or disease progression rates, and stratified these associations by age and sex. First, we examined whether peripheral neutrophil levels associate with ALS survival in a sex-specific manner. Consistent with previous reports, reduced neutrophil levels was associated with increased survival in ALS subjects. However, this association was driven primarily by female subjects, as females with low peripheral neutrophil levels had an expected median survival that was significantly greater than any other group. In parallel, we examined the activation state of peripheral natural killer (NK) cells in ALS subjects and their association with disease progression. Cytotoxicity markers were significantly upregulated on NK cells in ALS subjects compared to controls, and changes in these markers were significantly associated with disease progression as measured by the revised ALS functional rating scale (ALSFRS-R). However, the strength of this association was dependent on both age and sex: the association between cytotoxicity markers NKG2D or NKP46 and ALSFRS-R was significantly stronger in older subjects, and the association between cytotoxicity marker NKP30 and ALSFRS-R was significantly stronger in female subjects. Finally, we examined inflammation within the postmortem CNS tissue of ALS subjects using flow cytometry. We found that microglia levels were significantly higher in the spinal cord of female ALS subjects than males. Together, these data suggest that immune mechanisms contributing to ALS progression differ based on age and sex and that these factors should be taken into account when designing and interpreting clinical trials involving immunotherapy.

296. The Gut Microbiome: Modulator of Environmental Insults in Amyotrophic Lateral Sclerosis

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Background: ALS likely results from internal and external lifetime exposures superimposed on genetic predisposition. Homeostatic gut microbiota maintains health while dysbiosis (imbalance) occurs in disease, including ALS. The gut microbiome is dynamic and responds to environmental cues. We have previously identified high plasma persistent organic pollutants (POPs) levels, aberrant metal uptake, immune dysregulation, and altered metabolites in ALS patients. However, whether the gut microbiome links those parameters is unknown. The objective of this study is to define the temporal interplay between the gut microbiome and metabolic signatures, immunophenotypes, and exogenous exposures in ALS.

Methods: Longitudinal fecal samples (ALS, n=85; age- and gender-matching control, n=106 subjects) were collected for up to 18 months. We performed 16S sequencing with an Illumina MiSeq platform and the bioinformatics workflow analysis described in https://github.com/guokai8/microbial.

Results: Preliminary results reveal overall lower alpha diversity in ALS compared to controls with reduced Firmicutes (p<0.01) and increased Proteobacteria (p<0.01). The cases show biological enrichment increase of KEGG metabolic pathways associated with hydrocarbon degradation including fluorobenzoate, dioxin, and xylene. In contrast, pathways related to DNA repair and amino acid and nucleotide biosynthesis, are decreased. Ongoing analysis will determine longitudinal microbial signatures correlating with metabolites and immunophenotyping and with individual- or multi-POP pollutant/metals models associated with ALS development, risk, and survival.

Conclusions: This study will identify interactions between molecular mechanisms modifiable by the environment as potential preventive and/or therapeutic targets for neurodegeneration. Funded by a Diversity NIEHS Research Supplement (R01ES030049-01A1) and the Neuronetwork for Emerging Therapies at the University of Michigan.

297. Dynamic Network Stability Analysis for Prioritizing Experimental Combination Therapies for Amyotrophic Lateral Sclerosis

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**Background:** Superoxide dismutase 1 glycine 93 to alanine (SOD1 G93A) transgenic mice exhibit instabilities in regulatory mechanisms that may play a considerable role in ALS disease progression. However, it is difficult and resource-intensive to test combination treatments for ALS in-vivo due to the overall complexity of ALS. The study objective was to model combination therapy performance for ALS in-silico with experimental data from the SOD1 G93A mouse model.

**Methods:** Computational models of wild-type (WT) and SOD1 G93A (ALS) mouse physiological stability were developed using dynamic meta-analysis, mathematical optimization, and unsupervised learning. WT and ALS models were based on seven prominent regulatory mechanisms in ALS pathophysiology: apoptosis, bioenergetics, chemistry, excitotoxicity, inflammation, oxidative stress, and proteomics. Each ontology was divided into 2 aggregation schemes with opposite physiological functions. For both models, the (gain) values linking each aggregation scheme to the system of dynamical derivatives were optimized using a genetic algorithm and validated using a separate experimental dataset. To simulate ALS progression and treatment, different subsets of aggregation schemes were modulated at times corresponding to disease pre-onset, onset, and post-onset over the course of 200 days. Different modulation bounds were tested to determine the effect size necessary to re-stabilize the ALS system.

**Results:** Preliminary assessments of treatment combinations show potential for re-stabilization of the ALS system by targeting subsets of the 14 aggregation schemes. Some combination treatments allowed the system to stabilize and maintain steady state values for the aggregation schemes, yielding smaller fluctuations over the 200-day time period. Increased effect size on the aggregation schemes led to increased stability. Descriptive statistics for each combination treatment and overall pattern analysis quantify which treatment combinations and effect sizes produced greatest stability in the ALS system. Approximately 1% of the simulation combination treatments could re-stabilize the mouse model using a modulator effect size of 25%.

**Conclusion:** An in-silico ALS mathematical model was constructed to determine combination treatments for re-stabilization of a SOD1 G93A mouse model. Preliminary results indicate that stability can be used as a prognostic indicator of ALS disease progression and enable ALS physiological effects to be visualized over time. Furthermore, the effect sizes necessary for each aggregation scheme to re-stabilize the ALS system can be used for experimental development and testing of translational treatments.

**310. Geographical Variation in Proportion of Muskel Antibody Myasthenia Gravis Around the World - A Multicenter Study**

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Twenty years ago, muscle specific kinase (MuSK) antibodies were reported (Hoch et al Nat Med 2001) in 70% of the acetylcholine receptor (AChR)-antibody “seronegative” (SNMG) patients who had been studied in Oxford by the late Professor John Newsom-Davis. However, it became clear that this cohort was heavily biased towards more severe, generalized SNMG and many patients referred from outside the UK particular from Mediterranean countries. Over the following years, we received many cohorts of SNMG samples for testing from around the world. The proportion of AChR-antibody seronegative patients who had MuSK antibodies, and how they related to the geographical region from which they came, will be described.

A total of 1173 AChR-Ab negative samples were sent from 34 centers (10 European, n=255; 9 Americas and West Indies, n=283; 8 Asian, n=291; 4 Middle East, n=173). 237 MuSK-Ab positive patients (20%) were identified by radioimmunoprecipitation of 125I-MuSK extracellular domain. MuSK-Ab positivity ranged from 13% of AChR-antibody negative patients in Asian countries to 28% in the Middle East. However, when the results for each center were considered separately, there was a clear relationship (P<0.001) between MuSK-antibody positivity and latitude above the Equator with <5% MuSK-antibody positivity in Northern Europe and Northern Canada to 30-44% around the Mediterranean, Middle East and Southern States of the USA, decreasing to lower, although variable, values in countries nearer the equator (mainly Asian Pacific Rim). Within the USA there were significantly more positives among the Afro-Caribbean population (56%) compared to Caucasians (25%; p=0.0025), as suggested previously (Oh et al Muscle Nerve 2009). Overall, as in many previous studies, MuSK-Ab patients were younger, had more severe disease and required additional therapies to achieve good outcomes than those patients who were AChR/MuSK antibody negative.

There are limitations in the variable number of samples from each center, and less than perfect global distribution of the centers, but these intriguing and unexpected observations suggest that, although MuSK-antibodies are associated with similar disease around the world, environmental factors, including climate, as well as possible ethnic/genetic factors may predispose to this form of myasthenia gravis.

**408. Muscle Biopsy in an Era of Neurogenetics: A Novel Mutation Leading to Becker Muscular Dystrophy**

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**Background:** Dystrophin, encoded by DMD gene, links actin to the dystrophin-glycoprotein complex adding stability to the sarcolemma. An out of frame mutation leads to prematurity stop codons and disrupted transcription, often leading to a complete lack of protein function. This results in the severe phenotype of Duchenne Muscular Dystrophy. However, in frame mutations often lead to a partly functional dystrophin protein and thus a milder phenotype called Becker Muscular Dystrophy (BMD). Clinical presentation could range from isolated muscle cramps and mild hyperCKemia to severe weakness with cardiomyopathy. Wide availability of genetic testing increasingly challenges the utility of muscle biopsy. However, genetic testing sometimes leads to discovery of variants of uncertain significance or mutations not previously reported which leads to uncertainty in genotype-phenotype

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correlation. Our case highlights the importance and continued relevance of muscle biopsy in diagnosis of select cases of dystrophinopathies where genetic testing is inconclusive. We also report a novel mutation.

Case: A 39-year-old man presented with muscle cramps since childhood with progressive symmetric painless proximal lower limb weakness since teens and early 20s. He is unable to get up from chair without support and has a wide based gait. He recalls his maternal grandfather had some leg weakness. Neurology exam showed moderate hip flexion and abduction weakness (MRC 3/5). Creatine kinase was elevated to 3323 U/L and aldolase 26.4 U/L. Electromyography showed evidence of generalized proximal irritative myopathy. Echocardiogram showed concentric remodeling of left ventricle with ejection fraction of 65%. Genetic testing showed duplication of exons 21-24 with breakpoints in intron 20 to 24 corresponding to a minimum duplication boundary via microarray based comparative genome hybridization of chromosome X:34326666-3508758 (GRCh37/hg19). This is a novel mutation not previously reported and hence results suggested it to be of uncertain clinical significance, adding to our diagnostic dilemma. However, muscle biopsy of vastus lateralis showed active chronic dystrophic process with patchy loss of staining for dystrophin and concurrent overexpression of utrophin, a feature diagnostic of dystrophinopathy. A milder phenotype enabled us to then diagnose BMD.

Conclusion: Widespread availability of genetic tests may dwindle the utility of muscle biopsy. However, it remains a gold standard where a phenotype-genotype correlation is necessary to establish pathogenicity of a novel mutation.

409. Brain Structure and Cognitive Endpoints in Myotonic Dystrophy Type 2
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Background: Myotonic dystrophy type 2 (DM2) is a pleiotropic multisystemic disease. Although proximal muscle weakness is the main symptom in DM2, 60% of patients report cognitive changes as one of the most disabling symptoms, which markedly affects their quality of life. Previous studies suggest that cerebral white matter is primarily affected in DM2. However, brain imaging studies incorporate with cognitive and motor endpoints are extremely limited.

Objective: To evaluate quantitative magnetic resonance imaging (MRI) measures of brain structure with a focus on white matter integrity and their relationships with cognitive and motor endpoints in DM2.

Methods: Structural 3T brain MRIs were acquired in 6 participants with DM2 and 6 age and gender-matched controls. Brain morphometry and white matter integrity were assessed using T1 MP-RAGE and diffusion tensor imaging (DTI) sequences. DTI scalars, including fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD), were compared between the two groups. A battery of cognitive (selected from the NIH Toolbox) and motor measures was performed and correlated with MRI measures.

Results: Mean age (60.7 vs. 61.6 years) and education (17 vs. 18 years) were similar between the DM2 and control groups. Compared to controls, adults with DM2 showed a significant reduction in global measures of cerebral white matter volume ($p=0.004$) and gray matter volume ($p=0.009$). Although white matter volume (WMV) decreased to a greater extent than gray matter volume, the differences were not significant. Total CSF volume was also increased in the DM2 group ($p=0.037$), suggesting that this could be a neurodegenerative process. Abnormalities of DTI measures (FA and RD) were the most prominent findings and more ‘robust’ than WMV (larger effect sizes), indicating that the pathology is within white matter integrity. Participants with DM2 had lower scores than controls in most cognitive and motor endpoints. Measures of cerebral FA, a proxy of white matter integrity, revealed a moderate correlation with working memory and language domains ($r=0.62$), and a strong correlation with grip strength ($r=0.77$).

Conclusion: Our pilot data demonstrate robust differences in brain structure, explicitly cerebral FA and RD, between DM2 and healthy controls. Also, measures of cerebral FA correlated with specific cognitive deficits and grip strength, suggesting that CNS pathology in DM2 affects both cognitive and motor function. Cerebral FA may be used as an appropriate endpoint for studies of CNS disease progression and therapeutic response in DM2.

410. Germline and Therapeutic Suppression of Tubulin Alpha 4a Rescues H-ABC Leukodystrophy in Mice
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Hypomyelination and atrophy of basal ganglia and cerebellum (H-ABC) is a rare leukodystrophy associated with mutations in tubulin alpha 4A (TUBBA4A). The p.Asp249Asn (D249N) mutation is a recurring variant found in a majority of H-ABC affected individuals. H-ABC typically begins in infancy, and is characterized by dystonia, ataxia, altered gait and progressive motor dysfunction. We recently characterized a CRISPR knock-in mouse model harboring this variant recapitulating the clinical features of H-ABC. Homozygous variants in the Tubb4aD249N/D249N result in progressive motor dysfunction, ataxia, decreased survival (P32-P37), severe myelinization deficits and neuronal atrophy in striatum and cerebellum. When the variant is present only in the heterozygous state, Tubb4aD249N/+ mice express a reduced phenotype characterized by a myelin defect without impact on motor abilities or survival. Thus, Tubb4aD249N/D249N mouse model is a unique pre-clinical tool to test therapeutic strategy for H-ABC disease.

Here we show that mice with germline deletion of both copies of Tubb4a (Tubb4aKO/KO) develop normally, exhibit normal motor functions and show no myelination or
neuronal deficits. When these Tubb4aKO/KO mice are crossed with Tubb4aD249N/D249N, the resulting Tubb4aD249N/D249N mice have improved motor deficits, reduced myelination defects, decreased neuronal loss in the striatum and cerebellum, and increased survival (~P110) relative to Tubb4aD249N/D249N mice (n=14-15, p<0.001). Together, these results suggest that H-ABC is caused by toxic gain of function and correlates with overall expression of mutant Tubb4a and relative preservation of wild type tubulin. Thus, we propose to treat H-ABC by reducing overall Tubb4a expression using anti-sense oligonucleotides (ASO). To evaluate the therapeutic potential of Tubb4a suppression in postnatal Tubb4aD249N/D249N mice, we tested ASOs in wild-type mice to decrease Tubb4a mRNA expression in vivo. Administration of a single intracerebroventricular (ICV) dose of Tubb4a ASO in diseased Tubb4aD249N/D249N mice improved motor deficits and survival as compared to vehicle treated or scrambled ASO treated littermates (n=5, p<0.01). Collectively, these approaches provide preclinical proof-of-concept for the development of Tubb4a suppression as a disease-modifying therapy for H-ABC.

411. Loss of TDP-43 Function and Rimmed Vacuoles Persist After T Cell Depletion in a Xenograft Model of Sporadic Inclusion Body Myositis

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Objective: To determine the role of T cells in the pathogenesis of sporadic inclusion body myositis (IBM).

Methods: We generated a novel xenograft model by transplanting human IBM muscle into the hindlimb of immunodeficient mice. Depletion of human T cells within IBM xenografts was performed by intraperitoneal injection of anti-CD3 antibody (OKT3).

Results: Xenografts from IBM patients display robust regeneration of myofibers derived from resident satellite cells of the human muscle biopsy. Myofibers in IBM xenografts are invaded by human, oligoclonal CD8+ T cells and exhibit MHC-I upregulation, rimmed vacuoles, p62-positive aggregates, mitochondrial pathology, and nuclear clearance and cytoplasmic aggregation of TDP-43, resulting in expression of cryptic exons. Depletion of T cells in a xenograft model of IBM suppresses MHC-I upregulation and mitochondrial abnormalities, but not formation of rimmed vacuoles or loss of TDP-43 splicing repression.

Conclusions: These results suggest that myofiber degeneration occurs independent of T cells, and that muscle cell-intrinsic mechanisms, such as loss of TDP-43 splicing repression, drive IBM pathogenesis.

412. Mitochondrial Replisome Protein Changes in Aging Mice

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Background: Sarcopenia, or muscle aging represents a significant burden on the healthcare system. Sarcopenia is defined as the age-related progressive loss of muscle mass, strength and physical performance. The mechanistic causes of sarcopenia are multifactorial, but they include endocrine dysfunction, motor neuron degeneration, inadequate nutrition, disuse as well as primary cellular degeneration process such as mitochondrial dysfunction. Accumulation of mitochondrial DNA (mtDNA) deletions and mutations correlates with muscle aging in the central and the peripheral nervous system. The mechanism by which mtDNA deletions occur is not well defined. They are thought to occur either during the process of mtDNA replication or following mtDNA repair after damage.

Methods: We harvested and compared tissue from aged mice (>20 months old) and young mice (<2 months old). We used qPCR to measure the levels of POLG1, TWINKLE and the mtDNA control protein TFAM. We also performed analysis of mitochondrial energetics using Seahorse from harvested and cultured fibroblasts from mice. Total mtDNA content and distribution of mtDNA mutations was also carried out in muscle tissue specimens.

Results: RNA expression analysis showed that there was a 50% reduction in expression of POLG1 in aged muscle and fibroblasts, while levels of TFAM remained stable. Western blot analysis of tissue again demonstrated that there was a reduction of POLG1 protein levels in aged mice when compared to TFAM levels (POLG1/TFAM ratio), particularly in gastrocnemius muscle. Mitochondrial bioenergetics analysis using Seahorse machine showed a decrease in baseline oxygen consumption rate in fibroblasts harvested from aged mice.

Discussion: We find that there is reduction in the POLG1/TFAM ratio in aged mice. TFAM both functions as an enhancer of mitochondria DNA replication, but also coats the otherwise exposed circular mtDNA molecule. We propose that in aged tissue, a lower POLG1/TFAM ratio could reduce polymerase gamma processivity leading to less effective replication and a higher likelihood of mtDNA deletion generation.

413. Spectrum of Neuromuscular Complications Associated with COVID-19 Infection: A Case of Severe Rhabdomyolysis and Rapidly Progressive Myositis

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Background: Since the beginning of the coronavirus pandemic in early 2020, an array of neuromuscular complications has been increasingly described among patients with COVID-19 infection, with myalgia being one of the most common and early manifestations of the disease, with an estimated prevalence of 33.8%-44%. Elevated creatine kinase with a clinical picture of myositis occurs in 14% and rhabdomyolysis in 0.2% of all SARS-CoV-2 cases, respectively. These cases are usually associated with severe respiratory symptoms and higher mortality. We describe a case of rapidly progressive myositis with severe rhabdomyolysis in a COVID-19 infected patient who presented without respiratory symptoms.
Case Presentation: A 78-year-old female presented with generalized muscle tenderness, proximal more than distal weakness resulting in a bedridden state, acute kidney injury and no respiratory symptoms. She had elevated creatine kinase (CK) >90,000U/L (NL: 33-194U/L) and positive COVID-19 PCR, IgM and IgG. Myositis, antinuclear and HMGCR antibodies were negative. Muscle MRI showed extensive diffuse T2-hyperintensities with fluid tracks along fascial layers. Needle EMG showed myopathic units, rapid recruitment, and minimal irritability. Muscle biopsy showed scattered necrotic myofibers with few scattered endomyal and perimysial T-lymphocytes and perivascular B-lymphocytes. Patient received supportive treatment with careful fluid resuscitation and pulse doses of methylprednisolone. She responded with a significant improvement of strength, resolution of acute renal failure and reduction of CK to <300 U/L within 10 days.

Conclusion: Several neuromuscular manifestations can be the presenting symptoms of COVID-19. They are usually associated with severe respiratory symptoms and critical illness. The postulated pathophysiology includes direct virus invasion of skeletal muscle tissue due to expression of ACE-2 receptors, release of myotoxic cytokines, molecular mimicry, and infection-mediated systemic inflammatory response. There have been no case reports describing severe rhabdomyolysis with myositis in patients testing positive for COVID-19 without respiratory symptoms. Rapid recognition and treatment of these rare manifestations of COVID-19 disease is crucial to prevent complications and further clinical worsening.

414. Defects in Mitochondria-Lysosome Contact Site Dynamics in Charcot-Marie-Tooth-Type 2 Disease
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Charcot-Marie-Tooth disease is the most common group of genetically inherited peripheral neuropathies. Charcot-Marie-Tooth Type 2 represents a subgroup of these diseases involving autosomal dominant inheritance and axonal degeneration of lower motor and sensory neurons. As multiple genetic alterations associated with Charcot-Marie-Tooth Type 2 have been linked to mitochondrial or lysosomal dysfunction, both mitochondria and lysosomes may play important roles in Charcot-Marie-Tooth Type 2 pathogenesis. Recently, mitochondrial-lysosome contact sites were found to dynamically form between mitochondria and lysosomes, highlighting a novel pathway for these two organelles to communicate and crosstalk with each other. However, the role of mitochondrial-lysosome contact sites across multiple genetic forms of Charcot-Marie-Tooth Type 2 disease is still not well understood. Using confocal time-lapse microscopy at high spatial and temporal resolutions, we investigated how mitochondrial-lysosome contact site dynamics are disrupted in Charcot-Marie-Tooth Type 2 disease. We found that mitochondrial-lysosome contact dynamics are misregulated by multiple disease mutations linked to Charcot-Marie-Tooth Type 2 disease, suggesting that defects in this pathway may contribute to dysfunction of both mitochondria and lysosomes, and further drive disease pathogenesis. These findings highlight mitochondria-lysosome contact sites as an important mechanism to further study in the fields of axonal degeneration and Charcot-Marie-Tooth disease pathophysiology.

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Peripheral neuropathy (PN) is the most prevalent complication of diabetes affecting up to 60% of diabetic patients and 30% of prediabetic patients. Although there is no treatment for PN associated with T2D and prediabetes, dyslipidemia has emerged as a major risk factor for PN indicating that dietary fatty acids may contribute to PN progression. We recently showed that saturated fatty acids (SFAs) and monounsaturated fatty acids (MUFAs) differentially regulate nerve function in murine models of prediabetes. Mice fed an SFA-rich high fat diet (HFD) develop PN which is reversed by switching the mice to a MUFA-rich HFD. The molecular changes that underlie the beneficial effect of MUFAs on nerve function are unknown. Since dyslipidemia alters sphingolipid metabolism and contribute to nerve injury, the objective of this study was to evaluate the effect of dietary SFAs and MUFAs on sphingolipid levels within the sciatic nerve of murine models of prediabetes and PN. Four groups of mice were fed diets with varying fatty acid composition from 5-26 weeks of age including (1) a standard diet (SD), (2) a SFA-rich HFD (HFD-SFA), (3) a MUFA-rich HFD (HFD-MUFA), and (4) a dietary intervention group fed HFD-SFA from 5 to 16 weeks followed by HFD-MUFA from 16-26 weeks. At the termination of the study, mice received neuropathy phenotyping, metabolic measurements, and sciatic nerve sphingolipid levels were evaluated by targeted sphingolipid lipidomics. At 26 week, all HFD mice regardless of fatty acid composition had higher body weight, glucose intolerance, and increased body fat mass compared to SD mice. Neuropathy phenotyping showed significant decreases in sensory and motor nerve conduction velocity in HFD-SFA mice at both 16 and 26 weeks that was not observed in HFD-MUFA or SD mice. The HFD-SFA to HFD-MUFA dietary intervention group showed a significant improvement in nerve function by 26 weeks. Interestingly, this improvement was associated with significant increases in sphingosine-1-phosphate, very-long chain sphingomyelins, and cerebrosides (glucosylceramides and galactosylceramides) in the sciatic nerves from HFD-SFA to HFD-MUFA dietary intervention mice. In summary, these results indicate that HFD-MUFA is beneficial for nerve function while the
HFD-SFA diet results in nerve damage in prediabetes murine models. Additionally, increased levels of very-long chain sphingolipids in the sciatic nerve are associated with improvement in nerve function in prediabetic mice. Funding: 1K99DK119366 (AER), R24 DK082841 (ELF) and NeuroNetwork for Emerging Therapies

416. A Pilot Study on Hand Palmar and Digital Nerve Ultrasound in Peripheral Nerve Diseases
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Introduction: Palmar and digital nerves of the hand can be imaged easily and with high resolution using ultrasonography. Digital nerves represent the distal most portion of sensory nerves thus they are ideal for the evaluation of length-dependent sensory or sensorimotor neuropathies. However, no studies have systematically evaluated these nerves in polyneuropathies.

Objective: Measure the cross-sectional area (CSA) and echogenicity (represented as % black) of the palmar and digital nerves of the hand in chronic polyneuropathies.

Methods: In total, we studied 52 individuals: 26 with electrodagnostically confirmed chronic peripheral nerve diseases compared with 26 age and gender-matched controls. The chronic peripheral neuropathy group was composed of 16 demyelinating polyneuropathies (7 CMT1A, 6 CIDP, 3 HNPP) and 10 axonal polyneuropathies (8 non-diabetic idiopathic, 2 CMT2A). Ultrasonography was performed in the median and ulnar nerves at: digits 2 and 5 lateral and medial common palmar nerves at the distal palmar creases(D2/5-LCP), digital nerve to digit 2 and 5 at the metacarpophalangeal joints (D2/5-MP), distal wrist crease (DWC) and forearm (FA) with a 22mHz transducer (GE Logiq e R8). CSA and % black were calculated for all measurements in triplicate using ImageJ.

Results: In demyelinating polyneuropathies, regardless of underlying pathology, D2-LCP was significantly enlarged in CSA compared to axonal polyneuropathies (mean ± SD, 3.23 ± 0.399mm² versus 1.17 ± 0.582 mm², p<0.001) and healthy individuals (3.23 ± 0.399mm² versus 1.306±0.321, p<0.001). The % black of the D2-LCP, D2-MP and D5-MP was significantly reduced in axonal polyneuropathies compared to demyelinating polyneuropathies (35.4 ± 7.72%, 41.9 ± 6.97%, 46.6 ± 6.54% versus 53.0 ± 9.25%, 63.8 ± 7.11%, 62.9 ± 5.66% all p<0.01) and healthy individuals (35.3 ± 7.72%, 41.9 ± 6.97%, 46.59 ± 6.54% versus 51.36 ± 6.29%, 60.08 ± 8.71 59.4 ± 7.11%, all p<0.05). No statistically significant difference in % black was seen in the DWC or FA.

Conclusion: In this pilot study, we show digital and palmar nerves of the hand reproduces CSA enlargement of demyelinating polyneuropathies as is well described in other nerves and may detect axonal loss in the form of increased intraneural echogenicity.

417. NADPH Oxidase 5: A New Player in Peripheral Neuropathy
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Background: Peripheral neuropathy (PN) is a debilitating complication that affects over 30% of pre-diabetic and 60% of type 2 diabetic (T2D) patients. Beside hyperglycemia, dyslipidemia has emerged as an important mediator of pre-diabetic and T2D nerve injury. However, the mechanisms by which dyslipidemia leads to injury in murine and human PN are not fully defined. While dyslipidemia is associated with systemic and tissue-specific oxidative stress in complication-prone tissues, how dyslipidemia intersects with specific sources of reactive oxygen species (ROS) to contribute to nerve damage is unknown. NADPH oxidase (Nox) enzymes are specialized for ROS production, and of the 7 members (Nox1-5, Duox1 and 2), the Nox5 isoform is only expressed in humans, and not in rodents. In this study, we examined the role of Nox5 in human peripheral nerves and in in vitro models of PN.

Methods: Nox5 methylation status, gene and protein expression were assessed in sural nerve biopsies from patients with PN. At the cellular level, human Schwann cell (SC) and neuronal cultures were exposed to high concentrations of the saturated fatty acid palmitate to evaluate Nox5 gene and protein expression. Nox-derived ROS generation, redox sensitive transcription factor NF-E2-related factor-2 (Nrf2) nuclear translocation and caspase-3 dependent apoptosis. We also assessed the Nox4-Nox5 interaction by co-immunoprecipitation.

Results: Evaluation of sural nerve biopsy tissues of T2D patients with PN revealed Nox5 promoter hypomethylation in patients with worse PN that was associated with increased Nox5 gene and protein expression. In vitro, our results show that palmitate treatment increases Nox5 gene expression in cultured neurons with increased ROS generation at early and late time points. Although Nrf2 nuclear translocation was increased after 24 h of palmitate exposure, this effect was not sufficient to reduce dyslipidemia-induced injury determined by upregulated caspase 3 protein expression at early and late time points. Similar results were observed in SCs, with preliminary data pointing toward a potential Nox5-Nox4 interaction following palmitate treatment.

Conclusion: Our findings provide evidence of a previously unrecognized role of Nox5 as a critical target for dyslipidemic oxidative stress that may injure PN-relevant cell types and contribute to the development of PN. Funding: Milstein Emerging Scholar (SAE), R24 DK082841 (ELF) and NeuroNetwork for Emerging Therapies.

418. A Novel Pathologic Variant in MFN2
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Background: Mutations in the mitofusin-2 (MFN2) gene are the most common cause of axonal CMT, classified as
CMT2A. Substantial phenotypic variation exists within CMT2A, ranging from disabling motor predominant neuropathy in children to relatively mild sensorimotor neuropathy affecting older adults. Other associated features can include optic atrophy, dysautonomia, vocal cord palsy and diaphragmatic paralysis. Pathogenic mutations in MFN2 are typically missense mutations and inherited in an autosomal dominant fashion.

Case: We report a case of a 55-year-old male with a 12-year history of bilateral foot pain, and a 6-month history of exertional orthostasis with syncope. Bilateral lower extremity symptoms began in his late 40s as burning foot pain. Examination at onset was significant for reduced light touch and pinprick on the distal foot. EMG/NCS demonstrated a mild symmetric motor and sensory axonal polyneuropathy. Autonomic testing demonstrated mild orthostatic tachycardia during tilt table testing and abnormal QSART testing. Laboratory evaluation for common causes of neuropathy was negative. He first presented to our clinic at age 55 with worsening pain, numbness, orthostasis and syncope. Examination revealed a reduction in all sensory modalities in the hands and feet with preserved strength and reflexes. Repeat EMG/NCS showed mild progression in the axonal sensorimotor polyneuropathy. Detailed family history revealed nearly identical symptoms in his sister and his mother who also has bilateral diaphragmatic weakness of unknown etiology. A comprehensive neuropathies genetic panel was obtained, revealing 3 hereditary Variants of Unknown Significance (VUS): KIF1A (c.3584G>A; p.Arg1195His), MFN2 (c.1979C>A; p. Ala660Asp), and PLEKHG5 (c.823G>A; p.Gly275Ser). Subsequent testing of first-degree relatives revealed all three variants in his mother, and the MFN2 and PLEKHG5 variants in his sister. Based on the phenotypic presentation, we believe the shared MFN2 variant is likely pathogenic. The only other variant shared by all 3 family members is PLEKHG5. PLEKHG5 variants typically cause recessively-inherited intermediate CMT or lower motor neuron disease, and thus is an unlikely explanation of this hereditary neuropathy. The genetic testing company reports that this variant may be reclassified as pathogenic with additional data.

Conclusions: MFN2 missense mutations cause AD CMT2A. This novel variant in MFN2 (c.1979C>A; p. Ala660Asp) is a likely pathogenic. Further characterization of the probands’ family members is underway. This case underscores the importance of multigene testing panels in hereditary neuropathy. Follow-up familial variant testing is frequently offered for free and may be valuable. Further research is required to confirm this variant, and fully understand disease phenotypes and underlying mechanism.

485. Mapping of Critical Events in ALS Progression
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Background: The progression of many degenerative diseases is tracked using scales evaluating functionality in daily activities. Although estimating the timing of critical events (i.e., disease tollgates) during degenerative disease progression is desirable, the necessary data may not be available in scale records. Further, analysis of disease progression poses data challenges, including censoring and misclassification errors, which need to be addressed to provide meaningful research findings and inform patients.

Methods: We developed a novel binary classification approach to map scale scores into disease tollgates to describe disease progression leveraging standard/modified Kaplan-Meier analyses. The approach is demonstrated by estimating progression pathways in amyotrophic lateral sclerosis (ALS). Tollgate-based ALS Staging System (TASS) specifies the critical events (i.e., tollgates) in ALS progression. We first developed a binary classification predicting whether each TASS tollgate was passed given the itemized ALSFRS-R scores using 514 ALS patients’ data from Mayo Clinic-Rochester. Then, we utilized the binary classification to translate/map the ALSFRS-R data of 3,264 patients from the PRO-ACT database into TASS. We derived the time trajectories of ALS progression through tollgates derived from the augmented PRO-ACT data using Kaplan-Meier analyses. The effects of misclassification errors, condition-dependent dropouts, and censored data in trajectory estimations were evaluated with Interval Censored Kaplan Meier Analysis and Multistate Model for Panel Data.

Results: The approach using Mayo Clinic data accurately estimated tollgate-passed states of patients given their itemized ALSFRS-R scores (AUCs>0.90). The tollgate time trajectories derived from the augmented PRO-ACT dataset provide valuable insights; we predicted that the majority of the ALS patients would have modified arm function (67%) and require assistive devices for walking (53%) by the second year after ALS onset. By the third year, most (74%) ALS patients would occasionally use a wheelchair, while 48% of the ALS patients would be wheelchair-dependent by the fourth year. Assistive speech devices and feeding tubes were needed in 49% and 30% of the patients by the third year after ALS onset, respectively. Although the onset body region alters some late limb and bulbar tollgate passage time estimations (e.g., needing wheelchair, communication device, feeding tube) by 1-2 years, the time trajectories for passing early limb tollgates surprisingly look similar for both onset types.

Conclusions: Estimated tollgate-based time trajectories inform patients and clinicians about prospective assistive device needs and life changes. More research is needed to personalize these estimations according to prognostic factors. Further, the approach can be leveraged for other neurodegenerative diseases.

K-477. Childhood Amyotrophic Lateral Sclerosis Caused by Excess Sphingolipid Synthesis
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Amyotrophic lateral sclerosis (ALS) is a progressive, neurodegenerative disease of the lower and upper motor neurons with sporadic or hereditary occurrence. Age of onset, pattern of motor neuron degeneration, and disease progression vary widely among individuals with ALS. Various cellular processes may drive ALS pathomechanisms, but a monogenic disturbance has not been causally linked to ALS. Here, we show SPTLC1 variants that result in unrestrained sphingoid-base synthesis cause a monogenic form of ALS. We identified four specific, dominantly-acting SPTLC1 variants in seven families manifesting as childhood-onset ALS. These variants disrupt the normal homeostatic regulation of serine-palmitoyltransferase (SPT) by ORMDL proteins, resulting in unregulated SPT activity and elevated levels of canonical SPT products. Notably, this is in contrast with SPTLC1 variants that shift SPT amino acid usage from serine to alanine, resulting in elevated levels of deoxysphingolipids, and manifest with the alternate phenotype of hereditary sensory and autonomic neuropathy. We custom designed siRNAs that selectively target the SPTLC1 ALS allele for degradation, leave the normal allele intact, and normalize the sphingolipid levels in vitro. The role of primary metabolic disturbances in ALS has been elusive; this study defines excess sphingolipid biosynthesis as a fundamental metabolic mechanism for motor neuron disease.

K-489. Efficient Knockdown of ATXN2 in Motor Cortex and Anterior Horn Cells Using AAV-Mediated Delivery of RNAi

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Treatment of amyotrophic lateral sclerosis (ALS) is limited in part by difficulties in delivering therapeutic agents to both the motor cortex and the anterior horn cells of the spinal cord. A hallmark of ALS is the cytoplasmic mislocalization of the nuclear RNA processing factor TDP-43, and an early pathogenic event is the sequestration of TDP-43 in cytoplasmic stress granules. Inhibiting stress granule formation is therefore a promising approach for the treatment of sporadic ALS. Promisingly, Becker et al. developed antisense oligonucleotides (ASOs) targeting the mRNA encoding Ataxin-2, a protein necessary for stress granule formation, and found that intracerebroventricular ASO delivery extended lifespan and ameliorated disease pathology in a mouse model of ALS. To circumvent the translational difficulties of repeated injections to these hard-to-reach areas of the CNS, we developed an AAV expressing a microRNA targeting ATXN2 (miATXN2) with the goal of achieving long-term knockdown after a single, systemic injection. We found robust transduction of the motor cortex as well as of anterior horn cells throughout the cervical, thoracic and lumbar spinal cord. Four weeks after treatment, we measured ATXN2 levels in the motor cortex, brainstem, and spinal cord by quantitative PCR, and found a 50% reduction throughout these areas of the CNS. This is a promising approach for development of a single treatment that can provide sustained knockdown of Ataxin-2 for treatment of ALS.

K-500. Epidermal SIRT1 Modulates Diabetic Mechanical Alldynia

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Introduction: Diabetic neuropathy (DN) is a debilitating disorder characterized by sensory loss and pain. It has traditionally been considered a small-fiber neuropathy, defined by loss of epidermal free nerve endings. Free nerve endings, however, are nociceptors that are not directly responsible for the mechanical allodynia phenotype in DN. We herein investigated the role of mechanoceptors, specifically Meissner corpuscles, and their regulators in the development of diabetic mechanical allodynia.

Methods: Our investigation focused on a skin molecule SIRT1, an NAD+-dependent deacetylase. We hypothesized that in DN, low epidermal SIRT1 activity leads to decreased BDNF expression and Meissner corpuscle loss, resulting in mechanical allodynia. To test the hypothesis, we created a tamoxifen-inducible epidermal SIRT1 knockout (KO) and a doxycycline-inducible epidermal SIRT1 overexpression mouse model. KO and control mice were placed on high-fat diets (HFDs), and were subsequently assessed by behavioral,
ion channel function leads to rapid phosphorylation and a factor of mutant TRPV4 degenerative phenotypes. Furthermore, a repeat domain where most neuropathy mutations reside. In a rupt TRPV4-RhoA binding, leading to excessive RhoA activation and cytoskeletal changes. In a mouse model, we have also identified CaMKII as a potent mediator of mutant TRPV4 degenerative phenotypes. Together these results identify RhoA and CaMKII as critical mediators of TRPV4 neuropathy mutant toxicity in vivo, and suggest that disruption of TRPV4-RhoA binding in particular may be a key determinant of tissue-specific toxicity of TRPV4 neuropathy mutations.

LB-449. Phase 3, Open-Label, Multicenter Safety Study of Oral Edaravone Administered Over 48 Weeks in Subjects with Amyotrophic Lateral Sclerosis: Study Design and Baseline Characteristics (MT-1186-A01) Manabu Hirai, MS1, Takeshi Sakata, MS1, Bradley Bloom, MD2, Daniel Selnes, RN, BA, MBA3, Alejandro Salah, MD, PhD, MBA, BCMAS2, Stephen Apple, MD2. 1Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan, 2Mitsubishi Tanabe Pharma America, Inc., Jersey City, NJ, USA, 3Mitsubishi Tanabe Pharma Development America, Inc., Jersey City, NJ, USA.

Background: Radicava® (edaravone injection) was approved by the US Food and Drug Administration in 2017 for patients with amyotrophic lateral sclerosis (ALS). There is interest in non-IV formulations of edaravone and an ongoing, multicenter phase 3 study is currently assessing the safety of an oral formulation of edaravone (MT-1186).

Objectives: To describe the baseline characteristics and study design for the first global phase 3 clinical trial with oral edaravone.

Methods: This global, multicenter, open-label phase 3 study is evaluating the long-term safety and tolerability of oral edaravone in patients with ALS. The study includes a screening period of up to 3 weeks, an open-label treatment period of 48 weeks, and a safety follow-up period of 2 weeks after the last dose. Entry criteria include males and females aged ≥18 years to 75 years, with an ALS diagnosis of definite ALS, probable ALS, probable laboratory-supported ALS, or possible ALS, according to El Escorial criteria; baseline forced vital capacity ≥70% predicted; disease duration ≤3 years; and functioning independently. Patients are receiving a 105-mg dose of oral edaravone administered in treatment cycles that replicate the dosing of IV edaravone. This includes an initial treatment cycle with daily oral dosing for 14 days, followed by a 14-day drug-free period. Subsequent treatment cycles consist of daily oral dosing for 14 days of a 14-day period, followed by a 14-day drug-free period. Treatment cycles are every 4 weeks. In addition to the primary safety analysis, the study also includes exploratory end points, such as change from baseline in the revised ALS Functional Rating Scale score and time to death, tracheostomy, or permanent assisted mechanical ventilation.

Baseline Characteristics: A total of 213 subjects were screened in the MT-1186-A01 study, with a mean age of 60.3 years. Sixty-one percent of the patients are Caucasian and 32% are Japanese. The baseline mean score for the revised ALS Functional Rating Scale (ALSFRS-R) is 40. Additional baseline characteristics will be included in the late-breaking presentation.

Discussion: The first phase 3 trial of oral edaravone will provide important information on the long-term safety and tolerability of this new formulation of edaravone in patients with ALS.

K-505. Neuropathy-Causing TRPV4 Mutations Disrupt RhoA and CaMKII Signaling Resulting in Aberrant Cytoskeletal Remodeling Brett A. McCray, MD, PhD, Brian M. Woolams, PhD, Jeremy M. Sullivan, PhD, William H. Aisenberg, PhD, Thomas E. Lloyd, MD, PhD, Charlotte J. Sumner, MD. Johns Hopkins University, Baltimore, MD, USA.

TRPV4 (transient receptor potential vanilloid 4) is a calcium-permeable cation channel that responds to a variety of environmental stimuli, including shear stress and hypotonicity. Dominant mutations of TRPV4 cause forms of inherited neuropathy designated as Charcot-Marie-Tooth (CMT) disease type 2C and forms of distal spinal muscular atrophy. These conditions share features of variably severe arm and leg weakness and frequent vocal cord and diaphragmatic involvement. Distinct mutations in TRPV4 also cause a spectrum of disorders of bone and connective tissue known as skeletal dysplasia. Both neuropathy and skeletal dysplasia mutations cause gain of function ion channel function and increased intracellular calcium in vitro, but the pathogenic mechanisms and basis for tissue-specific disease are unknown. Mutations causing peripheral neuropathy localize to the intracellular N-terminal domain whereas skeletal dysplasia mutations are in multiple domains. Using an unbiased screen, we have identified the cytoskeletal remodeling GTPase RhoA as a TRPV4 interact. TRPV4-RhoA binding occurs via the ankyrin repeat domain where most neuropathy mutations reside. Notably, neuropathy but not skeletal dysplasia mutations disrupt TRPV4-RhoA binding, leading to excessive RhoA activation and cytoskeletal changes. In a fly model of TRPV4 neuropathy, inhibition of RhoA rescues axonal and dendritic degeneration phenotypes. Using a suppressor screen in this fly model, we have also identified CaMKII as a potent mediator of mutant TRPV4 degenerative phenotypes. Furthermore, we find that TRPV4 interacts with CaMKII, and TRPV4 ion channel function leads to rapid phosphorylation and activation of CaMKII. Together these results identify RhoA and CaMKII as critical mediators of TRPV4 neuropathy mutant toxicity in vivo, and suggest that disruption of TRPV4-RhoA binding in particular may be a key determinant of tissue-specific toxicity of TRPV4 neuropathy mutations.
LB-454. Hepatic Steatosis in Patients with Spinal Muscular Atrophy
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Objective: To study whether evidence of fatty liver in patients with spinal muscular atrophy (SMA) can be detected non-invasively by liver sonography.

Background: Innovative treatments for SMA have focused on Central Nervous System (CNS) augmentation of the deficient Survival Motor Neuron (SMN) protein as SMA is generally regarded by clinicians as a motor-neuron disease. However, data from animal studies and necropsies suggest that SMA is a systemic disease. Mouse models of SMA develop hepatic steatosis, and rare necropsies of pediatric patients with severe SMA have shown micro-vesicular steatosis. Since impaired function of the peripheral tissues and organs may become significant future comorbidities in SMA patients, finding non-invasive ways to detect and monitor peripheral organ pathology is important.

Design/Methods: This is a single-center retrospective cohort study. All pediatric and adult SMA patients without any past medical history of liver disease, who were seen physically in clinic from 2020-2021, and who had received hepatic sonography, were included in the study (N=4). The sonographic steatosis grade was determined by an ultrasonographer. Liver enzymes and serum markers of liver synthetic function were reviewed.

Results: Mild to moderate hepatic steatosis was present in 100% of SMA patients who received hepatic sonography, regardless of age and therapy regime. Three were adults aged 19, 24 and 52, and one was aged 3. The adults received nusinersen and/or nusinersen, and the child had received nusinersen, onasemnogene abeparvovec-xioi and rilisapl. Liver enzymes were raised in two adults. Serum albumin, protein and INR were normal in all.

Conclusion: SMA is a rare disease affecting only 1/10,000 live births. Although this is a small cohort study, limited in part by pandemic restrictions, the contribution to the literature is timely and relevant in the era of innovative therapies. Our small study suggests that sonographic evidence of hepatic steatosis may be frequent in SMA, may be a more sensitive measure of liver dysfunction as compared to liver enzymes or serum markers of liver synthetic function, and could be used as a clinical biomarker. It broadens the concept of managing SMA as a systemic disease with manifestations that should be monitored in pediatric and adult patients. Next steps will be to expand the study to more patients and understand how liver pathology contributes to the overall pathology of SMA, affects drug metabolism and clinical outcomes.

LB-457. A Randomized, Double-Blind, Placebo-Controlled Study of Arimoclomol in Patients with Inclusion Body Myositis
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Background: Inclusion body myositis (IBM) is the most common idiopathic inflammatory myopathy occurring in patients over the age of 45 years. Since immune suppression has not been effective, modulating the cytoprotective “heat shock response” (HSR) represents a candidate therapeutic approach targeting both inflammation and degeneration. In a pilot study, arimocлом, an amplifier of the HSR, was safe and well tolerated with some trends suggesting efficacy at 8 months in subjects with IBM.

Objectives: To present the efficacy and safety/tolerability data from a phase 2/3 randomized controlled trial of arimocлом in IBM (NCT02753530).

Methods: In this international multicenter, double-blind, placebo-controlled trial, subjects were randomized (1:1) to receive either arimocлом citrate 400 mg or matching placebo capsules three times a day (1.200 mg/day) for 20 months. The primary outcome measure was the change from baseline to Month 20 in the IBM Functional Rating Scale (IBMFRS) total score. Hierarchically ordered key secondary outcome measures included hand grip strength (strongest hand), Modified Time Up and Go, Manual Muscle Testing (24 muscles), 6-minute walk test distance, and the Short-Form 36 health survey. Other outcome measures included patient and clinician impressions, and other measures of muscle strength and function. Drug safety and tolerability were evaluated.

Results: One hundred fifty-two IBM subjects fulfilling ENMC 2011 criteria were randomized with mean age 67.2 years (SD 8.1), mostly men (76%), mean disease duration 98 months (SD 58), and mean baseline IBMFRS of 27.4 (SD 4.6). The IBMFRS declined by a mean of 3.25 points with arimocлом vs. 2.26 points with placebo over 20 months (p=0.11). Secondary efficacy outcome measures did not show any statistically significant treatment group differences. Most frequently reported AEs observed with higher incidence in arimocлом group were gastrointestinal disorders (54.8% vs. 39.7%). Patients receiving arimocлом were more likely to discontinue treatment due...
to AEs (17.8% vs. 5.1%). The relative frequency of serious AEs was comparable in the two treatment arms (arimoclomol 15.1% vs. placebo 23.1%). Elevated transaminases were reported in the first three months and were more frequently observed with arimoclomol than with placebo (15.4% vs. 6.4%).

Conclusions: This trial did not demonstrate a benefit of arimoclomol in IBM with respect to its primary and secondary efficacy endpoints.

LB-467. A COVID Crisis: Rhabdomyolysis
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Background: The Novel Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), lead to varying cases of skeletal muscle injury concerning for rhabdomyolysis, viral or necrotizing autoimmune myositis, and critical illness myopathy. We report two COVID-19 cases with rhabdomyolysis. Additionally, we performed a literature review of COVID-19 and skeletal muscle injury hoping to increase awareness of this potentially life-threatening condition.

Methods: We report two cases of rhabdomyolysis after COVID-19 infection at the University of Massachusetts Medical Center. We then reviewed literature on skeletal muscle injury and COVID-19 infection.

Results: A 47-year-old man was admitted for respiratory failure from COVID-19 and noted to have serum creatine kinase (CK) markedly elevated as well (>60,000 U/L). He ultimately required hemodialysis after CK remained elevated (41,730 U/L) despite treatment. The second case involved a 45-year-old woman admitted due to seven days of respiratory symptoms secondary to COVID-19 with progression to sepsis and acute kidney injury. CK, not checked until after her kidney injury developed, was found to be 52,338 U/L and peaked >60,000 U/L. Treatment required renal replacement therapy. An early clinical study from Wuhan, China (Mao, Jama Neurology, 2020) reported cases of muscle injury in about 11% of patients with COVID-19. One study reported six patients’ with COVID-19 that developed acute flaccid quadriplegia thought to be due to critical illness myopathy based on electromyography and CK levels (Mada, Neurology, 2020). Rhabdomyolysis with CK levels > 11,000 U/L have been reported in COVID-19 patients and an association of the SARS-CoV-2 through either viral or necrotizing autoimmune myositis remains elusive; two of these reported cases may indirectly suggest a viral triggered necrotizing autoimmune myositis (Gefen, Pediatric Nephrology, 2020; Jin, Emergency Infectious Disease, 2020; Suwanwongse, Cureus, 2020). Also, expression of ACE-2 has been noted in skeletal muscle (Cabello-Verrugio, Med Res Rev, 2015); questioning direct SARS-CoV-2 infection of skeletal muscle fibers.

Conclusions: Understanding of these observations noted with COVID-19 associated muscle injury necessitates further work-up such as muscle biopsies and antibody screening to help identify underlying mechanisms and develop potentially lifesaving treatment protocols.

Neuro-Oncology

254. What Was Learned and What is in the Pipeline with Regards to the Treatment of Primary Spinal Tumors and Spinal Metastases: A Scoping Review of Registered Clinical Studies Over the Past Two Decades
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Background: This scoping review was performed to synthesize and appraise what was learned and what will potentially be discovered from the recently completed and ongoing clinical studies related to the treatment of primary and secondary spinal neoplasms that were registered in the ClinicalTrials.gov website.

Methods: This scoping review included all clinical studies on the treatment of spinal neoplasms registered in the ClinicalTrials.gov website from February 2000 to December 2020. The terms “spinal cord tumor”, “spinal metastasis”, and “metastatic spinal cord compression” were used to identify the clinical studies focused on the treatment of spinal neoplasms.

Results: Of the 174 registered clinical studies, the vast majority of the clinical studies registered in this American registry were interventional studies led by single institutions in the North America (n=101), Europe (n=43), Asia (n=24) or other continents (n=6). The registered clinical studies mainly focused on treatment strategies for spinal neoplasms (90.2%) that included studies related to stereotactic radiosurgery (n=33), radiotherapy (n=21), chemotherapy (n=20), and surgical technique and instrumentation (n=11). There were also fewer clinical studies related to registries (3.4%) or to diagnosis (2.3%), prognosis (2.3%) and prevention (1.7%). Of the 69 completed clinical studies, the results from 44 studies were published in the medical literature including advances in surgical treatment (n=13), non-surgical interventions such as new radiotherapeutic techniques and chemotherapies (n=30), or a novel assessment tools in the field of spinal oncology (n=1).

Conclusion: The results of this scoping review highlight the key features of the 174 clinical studies on primary spinal tumors and spinal metastasis that were registered from 2000 to 2020. Most of those research initiatives have been interventional studies on stereotactic radiosurgery, chemotherapy, and external radiotherapy. Given that North American and European institutions led most of the clinical studies in this field, their applicability in Asian, African and Latin American countries may be limited due to the dissimilarities in the
epidemiology of spinal neoplasms, healthcare access and coverage among different populations. The rarity and heterogeneity of spinal neoplasms represent a major challenge in the recruitment of participants and affordability of clinical studies in spinal oncology that often require long-term sustainability.

255. A Rare Presentation of Medulloblastoma in an Adult Female Patient
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Introduction: Medulloblastoma is an aggressive CNS malignancy of embryonal origin, mostly located in the vermis of the cerebellum. It commonly affects children and accounts for approximately 30% of pediatric CNS neoplasms, whereas it is rare in adults, with an annual incidence rate of 0.05 per 100,000 per year. It occurs most frequently in men than women.

Case report: A 28-year-old female with no significant past medical history presented to the emergency department with a complaint of sudden onset frontal headache, different from her migraine headaches, not relieved with Tylenol, denied any associated nausea or vomiting. The physical exam was normal. Computed Tomography (CT) scan of the head without intravenous contrast showed a large right cerebellar mass measuring 2.6 x 4.1 x 2.5 cm, with midline shift in the posterior fossa. Magnetic Resonance Imaging (MRI) of the brain with and without contrast confirmed the findings. The neurosurgery team was on board and the patient underwent right sub-occipital craniotomy with resection of the tumor. Histopathology of the tumor was consistent with classic SHH-activated medulloblastoma (composed of blue cells with focal formation of Homer Wright rosettes) additional molecular was positive for wild type TP53 without any evidence of MYC amplification, positive for GFAP with reactive background astrocytes. The tumor cells showed expression of YAP1, GAB1, and cytoplasmic expression of beta-catenin. Given her suboptimal resection with her first surgery, she underwent repeat craniotomy and resection of the remaining tumor. Postoperative MRI showed no obvious evidence of residual disease, consistent with a gross total resection. Post-resection, the patient felt well except for some residual right-hand weakness. The cerebrospinal fluid analysis cytology was negative for malignant cells. According to NCCN guidelines, treatment protocol includes maximal safe resection, followed by adjuvant therapy involving chemotherapy and radiation. The plan was to start the patient on adjuvant craniospinal radiotherapy with concurrent vincristine for a period of eight weeks, followed by maintenance multi agent chemotherapy including cisplatin, lomustine, and vincristine for eight cycles.

Discussion: Medulloblastoma is found to be associated with multiple rare genetic disorders including Gorlin syndrome, Li-Fraumeni syndrome, APC-associated polyposis conditions, and Fanconi anemia. The exact sequence of treatment of adult medulloblastoma is unknown given the rarity of presentation.

Conclusion: Medulloblastoma is the most common brain tumor in children but is rare in adults. Here, we are reporting an adult female patient with medulloblastoma at the age of 28 years.

256. Awake Craniotomy for Excision of Brain Tumors: The First 200 Cases from Pakistan
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Objective: To review the first 200 cases of awake craniotomy performed at our center for excision of brain tumors, and assess clinical outcomes.

Methods: It was a retrospective review of awake craniotomies (AC) performed at our hospital for excision of brain tumors. Data was collected from patients’ medical records, and included demographics, tumor location/histology, clinical complaints, and functional status. We used Karnofsky performance scale (KPS) to assess function. Extent of resection was determined on post-operative MRI. Statistical analysis was done using SPSS version 22.

Results: Two hundred cases were reviewed. Mean age was 39.3 ± 11.9 years and 79% (158) were male. Seven attending surgeons performed these cases; however, 168 (84%) surgeries were performed by a single surgeon (SA Enam). Although 52% (104) patients had malignant neoplasms, seizures were the most common presenting symptom in 63% (126) cases followed by motor deficits in 29% (58). Left frontal lobe was the most common location for tumors (50; 25%). The most common tumors were low grade oligodendroglioma (58; 29%) followed by glioblastoma (42; 21%). Mean length of hospital stay was 3.15 days ± 1.7 days. Gross total resection was achieved in 82 (41%) patients. New intraoperative neurological complaints were seen in 31 (15.5%) patients, however, 22 (11%) of these had recovered by median follow-up of 1.4 months. KPS at last follow-up improved in 92 (46%), remained stable in 94 (47%) and deteriorated in 14 (7%) patients.

Conclusions: AC is a safe tool for excision of brain tumors, and offers a good chance of preserving patients’ functional status, along with adequate extent of resection.

Keywords: awake craniotomy, brain tumors, low- and middle-income countries

257. A Rare Case of Gliomatosis Cerebri Lurking Beneath the Shadows of a Stroke Mimic
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discharged to hospice and deceased few months later. To worsening clinical condition. Video EEG showed contin-

prefrontal gyrus. Patient could not undergo brain biopsy due to the left cerebral hemisphere and extending into the brainstem, bilateral cerebellum, corpus callosum, and right hemisphere. Etiology was presumed to be cardio-

extension of previously noted stroke. Six months later, the patient was transferred to tertiary facility for video EEG imaging sign of ischemic stroke. GC should be considered as a rare mimic of characteristic histologic and radiographic features, GC is a difficult diagnosis that is quite often delayed.

Design/Methods: Case Report Results: A 61-year-old gentleman was evaluated in the neurology clinic with right arm weakness for two weeks. Initial MRI brain was reported as subacute ischemic stroke in left pre-central gyrus extending into the thalamus. Etiology was presumed to be cardio-embolic due to history of atrial fibrillation and patient was started on apixaban. However, the patient rapidly declined. He progressively developed worsening right-sided weakness, uncontrollable spastic hand movements, aphasia, and dyspha-

gia. Serial MRI brain imaging was reported as acute/subacute extension of previously noted stroke. Six months later, the patient presented with acute encephalopathy and electroencephalogram (EEG) revealed lateralized periodic discharges and patient was transferred to tertiary facility for video EEG monitoring. MRI brain images showed interval expansion of infiltrating T2/FLAIR hyperintense signal involving much of the left cerebral hemisphere and extending into the brainstem, bilateral cerebellum, corpus callosum, and right prefrontal gyrus. Patient could not undergo brain biopsy due to worsening clinical condition. Video EEG showed continued persistent lateralized periodic discharges and patient was discharged to hospice and deceased few months later.

Conclusions: This case demonstrates the elusiveness of Gliomatosis Cerebri. Its prompt recognition is important due to the poor prognosis and limited therapeutic implications for patients diagnosed with this rare condition. Non-vascular causes though rare such as gliomatosis can cause false neuro-imaging sign of ischemic stroke. GC should be considered as one of the possible though rare mimickers for stroke.

258. Rare Metastatic Basal Cell Carcinoma with Spinal Cord Compression

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Introduction: Basal cell carcinoma (BCC) is a common skin cancer that arises from skin basal cell layer, most commonly from chronic solar ultraviolet radiation exposure. BCCs are common in the head and neck, in patients greater than 50 years old. It is usually a low-grade malignancy with extremely rare metastasis (0.55%) and low mortality rate. We present a rare case of a young gentleman who presented with BCC metastatic to cervical and thoracic vertebrae leading to cord compression syndrome.

Case Presentation: A 38-year-old Caucasian male crawfish boat worker was transferred from an outside hospital with complaint of mid-back pain over the past year, worsening over the past 2 weeks prior to admission. His medical history included smoking since the age of 17, asthma, primary epi-

dysphagia; and surgical excision of BCC over left cheek with no subsequent follow-ups. On admission, he reported paresthesia below the level of right shoulder with sensory loss below umbilicus extending to bilateral feet. There was no bowel/ bladder incontinence, but he had motor weakness in both lower limbs on exam. MRI demonstrated multi-level cervical and thoracic vertebral metastatic contrast-enhancing lesions with most severe involvement at T3 and T7-9 with T8 compression fracture with exaggerated kyphosis and compressive myelitis at T7-9 region. Patient refused surgery on initial admission and agreed for clinic follow up. He returned a month later with progressive symptoms and underwent surgical resection with posterior thoracic fusion of T1-L1 with bone allograft and autograft and T3/T4 and T7/T8/T9 lam-

inectomies. Pathology demonstrated a metastatic neoplasm morphologically consistent with BCC.

Discussion: Although BCC is a common cancer, it rarely causes gross disfigurement, disability, or death from metastases. Common metastatic sites are lung, bone, lymph nodes, the pleura, spleen or the brain. Rare metastases have been found in adrenal, kidney, pancreas, diaphragm, pericardium, dura, and skin. Our patient is a rare case of a young gentle-

man with metastatic BCC presenting with vertebral lesions causing spinal cord compression symptoms, after 10 years of initial surgical resection of the primary skin BCC.

259. A Blur During a Progesterone Peak

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Case Report: We present a rare case of a 40-year-old female (G4P1021) 31 weeks pregnant, with no significant medical history, who presented with rapidly declining vision loss in her left eye for one month. Visual acuity (VA) on initial exam outside was 20/20 bilaterally. Left eye VA dropped to 20/40 in three weeks. Neuro-ophthalmology exam in a week showed rapidly declining VA of 20/150 in the left eye (OS), a frank relative afferent pupillary defect (APD) and decreased color vision OS. Optic nerves were normal bilaterally with normal retinal nerve fiber layer (RNFL) bilaterally. Humphrey visual field showed severe inferonasal defect OS and an early temporal defect in the right eye (OD). She was started on IV Soli-Medrol for concerns of optic neuritis versus a compressive mass and urgently sent for MRI brain without contrast, avoiding contrast due to her pregnancy. MRI revealed a 9x13x11.5mm supra-sellar mass rising extrinsic to the pituitary gland, compressing and elevating the left optic nerve and chiasm. Aquaporin-4 receptor and
Myelin-oligodendrocyte (MOG) antibodies were negative. Infectious labs were unremarkable. Given high risk of visual loss, a multidisciplinary team approach including obstyn, endocrinology, neurosurgery, and neuro-ophthalmology was made, and with the patient’s consent, she underwent a successful cesarean section with no complications to the mother or baby. Subsequent MRI with and without contrast revealed a diffuse homogenous enhancement in the supra-sellar region consistent with a possible meningioma. She underwent a left cranial-orbital osteotomy for tumor resection successfully. Biopsy and pathology confirmed a WHO grade 1 transitional cell meningioma positive for progesterone receptor. Following resection, patient’s visual acuity returned to 20/20 OS immediately 5 days post operatively but with resolution of her APD and a small residual inferonasal defect on Humphrey visual field at one month.

Conclusions: Her initial presentation was very interesting since the differentials were broad, including retro-bulbar optic neuritis. However, her visual field defect was localizing to the left optic nerve and chiasm (likely prefixed) which was more suggestive of a rapidly progressive compressive mass, revealed on MRI brain. Supra-sellar meningiomas, although rare, can present with visual acuity and visual field deterioration during pregnancy. Presence of progesterone receptors (more common than estrogen receptors) can lead to altered hemodynamics and accelerated growth and hence heightened aggravation of symptomatic meningioma in pregnancy. Immediate surgical resection is advised when there is high risk for irreversible blindness.

260. Myositis and Myocarditis Associated with PD-1 Inhibitor
Shaweta Khosa, MBBS1, Joss Cohen, MD2, Shrityam Mishra, MD2, Bhavesh Trikamji, MD3, Robert Freundlich, MD4.

Objective: To describe a case of myositis and myocarditis secondary to immune checkpoint inhibitor-Pembrolizumab.

Background: Immune checkpoint inhibitors are often used to treat malignancies, but their use has been limited due to a spectrum of rare autoimmune side-effects including lifelong threatening neuromuscular disorders.

Methods: A 65-year-old man with metastatic gastric adenocarcinoma presented with four days of worsening shortness of breath, piosis, generalized weakness and myalgias after receiving two doses of palliative pembrolizumab five weeks prior to presentation. Initial examination was notable for dysarthria, bilateral piosis with intact extraocular muscles, and symmetric proximal muscle weakness greater than distal, and intact reflexes. Initial laboratory work-up was remarkable for creatine kinase of >7000 UI/L, aldolase 92, AST 352 UI/L, ALT 265 UI/L, troponin 7.8 ng/ml, and BNP 712 pg/ml. Patient was treated with 1gm intravenous methyl prednisone daily for 7 days and anti-thymocyte globulin without adequate benefit. Further laboratory work up revealed borderline positive acetylcholine receptor (AChR) binding antibody panel. Patient was trialed on empiric pyridostigmine 60 mg TID without improvement. Pembrolizumab was discontinued and patient was started on Intravenous immunoglobulin (IVIg), gonal oral prednisone taper, and mycophenolate mofetil with improvement in strength one month later.

Discussion: The patient showed extensive myositis and myocarditis after initiation of Pembrolizumab with oculor bulbar weakness and positive AChR antibody, resembling myasthenia gravis. Patient reported significant improvement in symptoms with steroids, IVIg, and mycophenolate.

Conclusion: This case is consistent with other reported cases of PD-1 inhibitor induced myositis and highlights the spectrum of neuromuscular side-effects that can be seen. As the use of immune check point inhibitors grows, continued awareness of immune related adverse events by neurologist will be key for early recognition and treatment.

261. Anaplastic Pleomorphic Xanthoastrocytoma in the Resection Bed of Previous Focal Cortical Dysplasia in a Young Man with Medically Controlled Epilepsy. Case Report and Literature Review
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Objective: Brain tumors and focal cortical dysplasia (FCD) are well-known causes of epilepsy, but these two entities’ coexistence is rare. We report the case of a young-adult patient with epilepsy secondary to recurrent right parietal lesion where first resection was consistent with FCD and second resection two year later revealed anaplastic pleomorphic xanthoastrocytoma (APXA).

Background: FCDs comprise a spectrum of focal developmental malformations characterized by disruption of the normal cytoarchitecture of the cerebral cortex, highly associated with epilepsy. On the other hand, pleomorphic xanthoastrocytoma (PXA) is a rare astrocytic tumor most often present in children or young adults. While most PXAs at presentation are WHO grade II tumors, a subset either presents or recurs with anaplastic features and is thus designated APXA, WHO grade III. In general, APXAs acquire features of a more aggressive astrocytic neoplasm that include increased proliferation, necrosis, microvascular proliferation and increased infiltrative growth. The activating BRAF p. V600E mutation is a common genetic alteration in both PXA and APXA, with significant therapeutic implications.

Methods: Case report with literature review. CASE: 26-year-old, right-handed man with history of migraine with sensory aura and right (R) parietal FCD status post resection 2 years ago with resultant focal to bilateral tonic-clonic seizures (controlled with levetiracetam 750 mg twice daily), presented with new focal aware seizures manifested by tingling in left (L) tongue, L face, L arm lasting for 1-2 minutes followed by L face and arm numbness. Normal general and neurologic exam. Brain MRI with and without contrast revealed new R frontoparietal brain mass in the resection bed s/p resection w/o complications and neither residual neurological deficits. Biopsy showed APXA, BRAF V600E mutant. Patient
completed a course of radiotherapy with the first post-radiotherapy MRI showing modest changes consistent with treatment effect w/o evidence of early tumor recurrence, with plan to start targeted therapy with the combination of BRAF inhibitor and MEK inhibitor (dabrafenib 150 mg twice per day and trametinib 2 mg daily).

**Conclusion:** The pathogenesis of APXA developed in long-standing FCD is uncertain. FCD is a developmental migration disorder of neuronal cells, and APXA might derive from pluripotential-primitive cells in long-standing cortical dysplasia through oncogenic transformation. This case also enhances the importance of advances in central nervous system neoplasms’ molecular characterization to improve tumor classification and therapeutic outcome.

262. An Incidental Finding? A Case of Bilateral Lateral Ventricle Choroid Plexus Xanthogranulomas

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**Background:** Intraventricular xanthogranulomas are rare, with an incidence of 1.6-7% on autopsy. Most are very small, measuring a few millimeters in diameter. However, occasionally some present as masses of significant size (>2 cm in diameter). When this happens, they are included in the differential diagnosis of choroid plexus tumors. They are composed of cholesterol clefts, lymphocytic infiltration, giant cells with multiple nucleoli, hemosiderin deposits, and foamy macrophages. Radiologically, they are often indistinguishable from choroid plexus cysts.

**Case Presentation:** A 42-year old female with a past medical history of fibromyalgia headaches, ulcerative colitis, and hypothyroidism presented to the emergency department (ED) for evaluation of headaches associated with left-sided falling. On physical examination, motor and sensory function were normal as were mood and affect. Considering her complaints of falling to the left, code stroke protocol was obtained with CT of the head, CTA of the neck and head, and CT perfusion, all of which returned normal. A head Magnetic Resonance Imaging Brain without contrast revealed thin-walled cystic lesions in the bilateral ventricular atria. The differential diagnosis given by radiology was choroid plexus cysts or choroid plexus xanthogranuloma. Referral to outpatient neurology determined the lesions to be choroid plexus xanthogranulomas, a benign and incidental finding. This determination was made due to plexus cysts being uncommon in the adult population. It was further determined that these lesions were non-contributory to her ED presentation. Reassurance was provided and no further work-up was ordered. The patient reported significant improvement of symptoms since her ED visit. She was sent home with education on complex migraine management, counsel to keep a headache diary, and sumatriptan as needed.

**Discussion:** Fortunately, choroid plexus xanthogranulomas are most often incidental findings and have a benign prognosis. They may result in symptomatic obstructive hydrocephalus when located near the foramen of Monroe or within the third ventricle. Surgery is indicated in symptomatic cases.

**Conclusion:** The differential diagnosis for choroid plexus tumors is not small. Our case highlights the importance of differentiating benign intraventricular masses from malignant or infectious ones, and whether intervention is required versus safe observation. In this case of bilateral lateral ventricular choroid plexus xanthogranulomas, the lesions represent an incidental finding that required no further workup.

K-316. Leukocyte Adhesion Causes Brain Capillary Obstruction During Neurotoxicity in a Mouse Model of Chimeric Antigen Receptor (CAR) T Cell Therapy

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**Background:** Neurotoxicity affects ~40% of patients receiving cancer immunotherapy with CAR-T cells, and fatal cerebral edema in <1%. It remains unclear what causes this brain dysfunction. We previously showed that mice treated with murine CD19-directed CAR-T cells develop systemic cytokine release syndrome, behavioral abnormalities, cerebral microhemorrhages, and brain capillary plugging during days 3-7 after treatment. Based on these findings, we hypothesized that increased leukocyte adhesion in microvessels causes alterations in the neurovascular unit and local tissue hypoxia.

**Methods:** We performed multicolor in vivo two-photon imaging through a thinned-skull window in wild-type BALB/c mice treated with 10 million murine CD19-directed CAR-T cells, which bind normal B cells and proliferate without a cancer target. Controls received mock transduced T cells. Primary sensory cortex was imaged under light anesthesia on day -1, 4 and 6 after CAR T cell treatment. We used i.v. fluorescent dextran to label the blood plasma, and fluorescently conjugated antibodies to label leukocytes. Presence of blood flow within capillary segments was determined by movement of red blood cells. Behavioral manifestations were measured by daily 20-item neurophenotyping exams.

**Results:** Mice developed severe acute brain capillary obstruction. On day 6 after CAR T cell treatment, a mean 11.9%±3.0% of brain capillaries were plugged (vs 1.1%±0.4% in controls, P<0.0072). The severity of plugging correlated with neurophenotype scores (P=0.0052, Pearson’s correlation), and was associated with focal brain hypoxia revealed by pimonidazole-adduct immunolabeling. Capillary stalls were caused by CD45.2-positive leukocytes. Of capillaries stalled on day 4, 66% had recanalized on day 6, 23% continued to be plugged, and 4% regressed. Capillary remodeling was also apparent on post-imaging immunolabeling for laminin (capillary basement membrane) and CD13 (pericytes). String capillaries, indicative of involuting capillary segments, were more common in CAR-T treated mice (249/mm3 cortex) compared to controls (47/mm3, P=0.0280). Capillaries of CAR T treated mice also lost pericyte coverage, and the
severity of this loss correlated with behavioral neurotoxicity ($P=0.0262$, Spearman’s $\rho$).

**Interpretation:** Our in-vivo two-photon studies during acute CAR-T cell neurotoxicity reveal obstruction of brain capillaries by leukocytes as a possible mechanism of brain dysfunction. Impairment of microvascular flow and neurovascular unit remodeling could explain cognitive changes seen in CAR-T patients. We will next test whether modulating endothelial adhesion of leukocytes can mitigate CAR-T neurotoxicity.

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**Neuro-Ophthalmology**

**263. Resolution of Vertigo with Extreme Eye Deviation - A Nascent Variant of the Epley Maneuver**

**Jack W. Hirsch, BA$^1$, Matthias Dunse, MD$^2$. $^1$Ross University School of Medicine, Bridgetown, Barbados; $^2$Neurology, Rutgers New Jersey Medical School, Newark, NJ, USA.**

**Objective:** To understand that minimal head movements may reduce vertigo.

**Background:** Treatment options described in benign paroxysmal positional vertigo (BPPV) include canalth repositioning maneuver (CRM) aiming to displace otolithic debris from the affected semicircular canal. Techniques to accomplish this include the Epley (Epley, 1992), Semont (Cohen, 2004), Gans (Califano, 2017), Gufoni (Gufoni, 1998) maneuvers, Lempert roll (Lempert, 1996) as well as forced prolonged positioning (Vannucchi, 1994). These require assistance from a therapist and mandate substantial positional changes of the patient, coincident with truncal deflection and head deviation, for extended periods. The resolution of the symptoms with eye movement and minimal turning of the neck, so slight as to not be recognized by the patient, has not heretofore been described.

**Methods:** Case Study: A 52-year-old right-handed woman, presented with 1½ years of clockwise vertigo, occurring up to 12 times a day, in epochs of minutes, often precipitated with a change in head position. The symptoms would be provoked by hyperextending her neck and hanging her head over the edge, while in a supine position. By forcing her eyes to the far right for 10 to 15 seconds, the symptoms would always resolve, and not recur for days to weeks. Associated with the dizziness was nausea.

**Results:** Abnormalities on Neurologic Examination: Motor: Drift testing: right pronator drift with right abductor digiti minimi sign. Cerbellar: bilateral endpoint dysmetria, left more than right. Reflexes: 3+ throughout. Hoffman’s reflex bilaterally positive. Other: as opposed to just deviating her eyes to the right, when demonstrating how to eliminate vertigo with gaze fixation to the far right, she additionally rotates her head approximately five degrees, unaware that she actually turns her head. Calibrated Finger Rub Test: 70 cm AU (normal) Brain Magnetic Resonance Imaging with and without contrast and Brain Magnetic Resonance Angiography: normal

**Conclusion:** Rotation of the neck eliminating the vertigo was so minuscule that the patient perceived it was just the eye deviation that led to the resolution of her symptoms. This is in contradistinction to the CRMs, which involves substantial turning of the head. Resolution with turning the head to the right might mimic the initial steps of the Dix-Hallpike Maneuver and the Epley Maneuver (Brevnen, 2015). Treatment for BPPV, requires excessive multidirectional deviation (Eggers, 2019). Resolution of symptoms with smaller need for mobility markedly simplifies canalth repositioning maneuvers.

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**264. Visual Hallucinations in the Blind: Browne Beats Bonnet**

**Frederick E. Lepore, MD. Neurology, Rutgers -Robert Wood Johnson Medical School, New Brunswick, NJ, USA.**

Based on Charles Bonnet’s (1720-1793) descriptions in 1760 of his visually-impaired grandfather’s variegated cinematic, silent, and unreal “visions” of people, his own doppelganger, carriages, pigeons, etc., (and possibly Bonnet’s own deathbed visions), the first scientific study of visual hallucinations in the blind (with $n=1$) - the so-called Charles Bonnet Syndrome (CBS) - was eponymously attributed to the French insect biologist and natural philosopher by de Morsier in 1936. Subsequently the mechanism of CBS has been variously imputed to “diseases affecting the retina, light transmission within the eye … or visual pathways or visual cortex” (ffytche) and old age (de Morsier).

Bonnet never used the term “hallucinations” in his original descriptions.

 remarkably with physiological optics, pupillary reactivity, double vision, cornea, “Chryllalline humour” (lens), retina, “optimc nerve”, and crucially that “all sense [was] proceeding from the brain,” Browne was well qualified to recognize patients with hallucinations - “visual percepts arising in the absence of external reality” (Sacks 2012) - in concert with disease of the visual pathways.

Just as we seek the basis of CBS with increased $\text{MRI}$ signals in V1-V4 during visual hallucinations (Hahamy 2020) today, the efforts of Charles Bonnet in 1760 to ground his “visions” in the neuroanatomy (or “that part of the brain which is connected with the organ of sight”) of his day, thought experiments with statues being endowed with senses one-by-one, and the “soul” (akin to today’s “mind”), though prescient may have been preceded 114 years earlier by Thomas Browne MD who speculated that “incurable hallucinations” might stem from perceptions “magnified, distorted, and ill placed in the Mathematicks of some brains.”
**265. Isolated Cranial Nerve Palsies in Multiple Sclerosis**

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**Case Report:** A 31-year-old woman who was diagnosed with multiple sclerosis (MS) two years ago when she initially presented to a neuro-ophthalmology clinic with binocular horizontal diplopia consistent with a left abducens nerve palsy. MRI brain was unremarkable but C-spine revealed demyelinating lesion. Lumbar puncture at that time showed 15 oligoclonal bands with normal opening pressure, consistent with MS. She was started on Tecfidera. Two years later, she again presented with new onset binocular oblique diplopia and ptosis of the left eye. MRI of the brain with and without contrast did not show acute intracranial abnormalities or FLAIR T2 hyperintensities. CT Angiogram of the head and neck did not show posterior communicating artery aneurysm. She received intravenous (IV) solu-medrol but changed to IV immune globulin due to concerns of worsening symptoms on steroids [concerns for Miller Fisher variant of Guillain Barre Syndrome (GBS)]. Neuro-ophthalmologic exam showed a 9mm, nonreactive left eye (OS) pupil, but no afferent pupillary defect (APD), complete ptosis OS, and a left eye exotropia and hypotropia in primary gaze consistent with a left third nerve palsy. Rest of her neurology exam was unremarkable with intact reflexes. GQ 1b antibody, Aquaporin-4 receptor, myelin oligodendrocyte glycoprotein antibody, VZV, Lyme, myasthenia gravis panel were all negative. She was later started on Rituximab, with resolution of diplopia in a month.

**Conclusion:** We present here a rare case of an MS relapse with isolated cranial nerve three palsy. Isolated cranial nerve palsies are rare presentations of MS and even rarer symptoms of relapse as compared to new onset internuclear ophthalmoplegia and optic neuritis which are more common ophthalmic presentations of MS. Zadro et al. found that isolated cranial nerve palsies were present in 10.4% as either the presenting symptom or as a relapse. The most common cranial nerve involved in MS is the trigeminal nerve. Third nerve palsies have been noted as a rare initial presentation of multiple sclerosis, but its presentation as a MS flare is even less common. Few case reports have shown the oculomotor cranial nerve palsy as an initial presentation of MS but so far there has been no reported case of oculomotor nerve involvement as a symptom of MS relapse. Our case here shows that multiple sclerosis should be considered on the list of differential diagnoses in young adults presenting with isolated cranial nerve palsies.

**Objective:** To compare current paper/pencil versions of the Mobile Universal Lexicon Evaluation System (MULES) and Staggered Uneven Number (SUN) tests of rapid automatized naming (RAN) with a new digitized format, the MICK App.

**Background:** Rapid automatized naming (RAN) tasks have been utilized for decades to assess traumatic brain injury and other neurological disorders. Data have shown that time scores for the MULES test of rapid picture naming and the SUN test of rapid number naming are prolonged (indicating worse performance) with concussion, mild cognitive impairment, multiple sclerosis and Parkinson’s disease. We present work demonstrating the validity of a new digitized version of the MULES and SUN tests for tablet devices, the Mobile Integrated Cognitive Kit (MICK). Advantages for a digitized version include portability, widespread access for research and clinical assessments, potential for data sharing, and integration into electronic medical records.

**Design/Methods:** The MICK app is a digitized version of the MULES and SUN tests, accessible on tablet devices. Participants, including healthy office-based volunteers and professional women’s hockey players completed two trials of the MULES and SUN tests on both platforms (tablet and paper/pencil). A random number generator was used to determine which platform would be performed first. Statistical analyses were done using Stata 16.0 (StataCorp, College Station, TX). Between-platform variability was calculated using the two-way random effect intraclass correlation coefficient (ICC); the ICC represents the proportion of variability that is between-participant, and thus not due to variability between tablet and paper/pencil versions of the MULES and SUN.

**Results:** Among 60 participants (median age 32, range 22-83) the ICCs for agreement between the digitized and paper/pencil tests were 0.92 (95% CI 0.86, 0.95) for the MULES and 0.94 (95% CI 0.89, 0.96) for the SUN; these ICCs represent excellent levels of agreement. Among study participants, 42% performed the tablet version first and 58% performed the paper/pencil version first; order testing format was not significantly associated with test performance.

**Conclusions:** The MICK app format for MULES and SUN testing demonstrates excellent agreement of time scores with paper/pencil testing among adult volunteers. The ability to perform these tests via computerized tablet allows for greater accessibility and scalability to assess patients with neurological disease, perhaps even remotely from the office setting. Sideline testing for sports-related concussion in athletes may also benefit from this technology.

**266. The MICK (Mobile Integrated Cognitive Kit) App: Digital Rapid Automated Naming for Visual Assessment in Neurological Disorders**


**Objective:** To compare current paper/pencil versions of the Mobile Universal Lexicon Evaluation System (MULES) and Staggered Uneven Number (SUN) tests of rapid automatized naming (RAN) with a new digitized format, the MICK App.

**Design/Methods:** The MICK app is a digitized version of the MULES and SUN tests, accessible on tablet devices. Participants, including healthy office-based volunteers and professional women’s hockey players completed two trials of the MULES and SUN tests on both platforms (tablet and paper/pencil). A random number generator was used to determine which platform would be performed first. Statistical analyses were done using Stata 16.0 (StataCorp, College Station, TX). Between-platform variability was calculated using the two-way random effect intraclass correlation coefficient (ICC); the ICC represents the proportion of variability that is between-participant, and thus not due to variability between tablet and paper/pencil versions of the MULES and SUN.

**Results:** Among 60 participants (median age 32, range 22-83) the ICCs for agreement between the digitized and paper/pencil tests were 0.92 (95% CI 0.86, 0.95) for the MULES and 0.94 (95% CI 0.89, 0.96) for the SUN; these ICCs represent excellent levels of agreement. Among study participants, 42% performed the tablet version first and 58% performed the paper/pencil version first; order testing format was not significantly associated with test performance.

**Conclusions:** The MICK app format for MULES and SUN testing demonstrates excellent agreement of time scores with paper/pencil testing among adult volunteers. The ability to perform these tests via computerized tablet allows for greater accessibility and scalability to assess patients with neurological disease, perhaps even remotely from the office setting. Sideline testing for sports-related concussion in athletes may also benefit from this technology.

**267. Deep Learning Model Detects Nystagmus from Video Recording**

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Background: Identification and interpretation of nystagmus is challenging for non-expert neuro-otologists and neuro-ophthalmologists. This challenge is magnified when this task must be performed via telemedicine. Deep learning models have not been heavily studied in video-based detection models of nystagmus.

Methods: We developed, trained, and validated a deep-learning system to classify 60 Hz recordings (n=435) as videos with nystagmus or video without nystagmus. The dataset was created from monocular video-oculography (VOG) recordings collected retrospectively used in the AVERT clinical trial. The AVERT clinical trial collected data from vertiginous patients in five emergency rooms across the US. The dataset was labelled by one expert provider. Nystagmus was defined as the presence of at least two consecutive beats - otherwise a label of "no nystagmus" was assigned. The performance of the model detecting nystagmus was calculated using the receiver-operating characteristic curve with sensitivity, specificity, negative (NPV) and positive (PPV) predictive values.

Results: The dataset included 50% with no nystagmus and 50% with nystagmus and was split into training and test sets in a ratio of approximately 3 to 2. Nine different variations of the model were tested. Using the test set, the best AUC, sensitivity, specificity, NPV, PPV and accuracy were 0.87, 0.88, 0.85, 0.82, 0.85 and 84% respectively.

Conclusion: Deep learning is useful in detecting nystagmus in 60Hz video recordings - making it a useful screening tool for the vertiginous patient, and potentially applicable for future automated smartphone ocular motor diagnosis.

Methods: Retrospective chart review for all patients seen in the neuro-ophthalmology clinic between 11/2019-5/2020 with ON from MS( group 1), MS without ON (group 2) and ON from other causes(group 3). Patients who had a full dilated eye exam, automated perimetry, and OCT were included. Eyes with acute ON, eyes with concomitant glaucoma, or other optic neuropathies were excluded.

Results: 38 patients were included in the study (Group 1: 11 patients/13 eyes, group 2: 13 patients/26 eyes, group 3: 14 patients/24 eyes). The age ranged between 18-82 years. 68.4% were females. In group 1, average RNFL thickness in the affected eyes was 67.75 u versus 86.75 u in the non-affected eyes (P= 0.028). In group 2, average RNFL thickness was 84.9 u in the right eye and 86.7 u in the left eye (insignificant inter-eye difference, P= 0.44). In group 3, average RNFL thickness of the affected eyes was 48.5 u versus 91 u in the unaffected eyes (P= 0.0006). Also, in group 3, the average RNFL thickness was 58.8 u in the right eye and 50.4 u in the left eye. 40% eyes in group 1 and 91% eyes in group 2 had temporal RNFL loss. 80% of eyes in group 3 showed global RNFL loss. GCIPL loss was seen in 36%(61.5% affected eyes) in group 1, 8% in group 2, and 79%(91.7% affected eyes) in group 3.

Conclusion: RNFL loss was more pronounced in ON from other etiologies compared to MS. But interestingly was also noted in MS without ON. Segmental RNFL loss was seen in MS with and without ON while global RNFL loss was seen in ON from other etiologies. Significant GCIPL loss was seen in ON from other etiologies compared to MS.

269. Syphilitic Intracranial Hypertension Presenting with Transient Visual Obscurations

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Objective: To present a case with demographics, symptomatology, and neuroimaging mimicking Idiopathic intracranial hypertension (IIH) but work up revealing intracranial hypertension from neurosyphilis.

Background: Syphilis is often referred to as "the great masquerader" as it may mimic many other conditions posing a diagnostic challenge. IIH commonly affects obese women of childbearing age presenting with chronically worsening positional headaches, pulsatile tinnitus, transient visual obscurations from chronic intracranial hypertension. IIH is a diagnosis of exclusion. Neuroimaging in IIH is normal but commonly has findings likely empty sella, transverse venous sinus stenosis, etc.

Case Description: A 33-year-old woman, BMI 40 kg/m2 with a six-month history of intermittent headaches, pulsatile tinnitus presented with worsening transient visual obscurations. Visual acuity was 20/40 in the right eye and 20/25 in the left eye. Slit-lamp examination was normal without any cell in the anterior chamber or vitreous. Fundoscopic exam revealed grade 4 papilledema. Cranial nerve exam revealed
bilateral abducens palsy. MRI brain revealed partial empty sella but otherwise unremarkable. MR venogram ruled out venous thrombosis but revealed focal tapering at the junction of transverse and sigmoid sinus bilaterally commonly seen in IIH. Serum HIV was negative. Serum rapid plasma reagin and Treponema Pallidum particle agglutination were positive. Cerebrospinal fluid opening pressure was 44 cm H2O with lymphocytic pleocytosis (20 WBC). CSF Venereal Disease Research Laboratory (VDRL) was negative. Other infectious work-up was negative on CSF including cultures. On further interrogation, she revealed a history of syphilis at age 8 with subsequent treatment and suspected re-infection at age 19 with partial treatment. The infectious Disease team recommended treatment for presumed neurosyphilis with intravenous penicillin G (4 million units every 4 hours) for 14 days.

**Conclusion:** Neurosyphilis can present with symptomatology and neuroimaging mimicking IIH. A diagnosis of IIH should be provided only after excluding alternative diagnoses even though clinical suspicion is high.

### 270. A Lesson on Diagnostic Perseverance: A Rare Case of Orbital Large B-cell Lymphoma

**Johanna Yun, MD, Julien Thomas, MD, Caroline Manos, MD, Andrew Elson, MD, Karima Benameur, MD, Hang Shi, MD, Emory University School of Medicine, Atlanta, GA, USA.**

An 88-year-old male with history of polyarteritis nodosa (PAN) and previously diagnosed left orbital pseudotumor presented to the hospital for new left ptosis, worsening of left facial pain with numbness, and inability to move his left eye. Two years ago, he developed left-sided proptosis, retro-orbital pain and diplopia. Imaging showed a small enhancing orbital mass, too small to biopsy, and he was diagnosed with orbital pseudotumor. He was treated for presumed inflammation with prednisone and mycophenolate mofetil (MMF). His ocular problems persisted and was referred to Emory mid-2020. Repeat MRI showed a slightly enlarged mass and orbital biopsy showed lymphohistiocytic infiltrate with chronic inflammation and scarring with continued suspicion for an orbital pseudotumor. In early 2021, he started to develop progressive left facial pain with numbness. Three weeks prior to his presentation, he woke up with complete ptosis of his left eye and was eventually seen at the Emory Eye Center. He was subsequently admitted for further work-up. MRI Brain/Orbits showed interval progression (October 2020 to February 2021) of his left orbital mass with new extension into the cavernous sinus, Meckel’s cave, temporal bone, extradurally along the left middle cranial fossa, and into the masticator space along V3. There was also extension into the left pterygopalatine fossa, with clival invasion and encasing of the internal carotid artery, and invasion into the sella with displacement of the infundibulum. Oculoplastic surgery performed orbital biopsy, which showed lymphohistiocytic infiltrate with chronic inflammation. Flow cytometry was negative for malignancy. Lumbar puncture was showed neutrophilic-predominant pleocytosis, elevated protein, and blood contamination. Infectious/vasculitic/inflammatory work-up was negative. CSF showed no abnormal hematolymphoid cells on flow cytometry. CSF was sent for cytology as well, but the sample was insufficient and was limited due to blood contamination. Six days later, a second CSF sample showed no pleocytosis, elevated protein, and negative flow cytometry and cytology for malignancy. After careful consideration, ENT performed a skull-based surgical biopsy. Histopathology and flow cytometry of the biopsy revealed large B-cell lymphoma. In conclusion, after repeatedly unremarkable work-up, including two orbital biopsies, our patient was diagnosed with large B-cell lymphoma through a skull-based biopsy. Due to the nature of his initial negative work-up, he was falsely suspected of having an orbital pseudotumor, which can initially present similarly and even have extension intracranially, although bone invasion would not be expected. Thorough diagnostic investigation is recommended.

### 271. Diagnostic Dilemma of Painful Bilateral Vision Loss: Vogt-Koyanagi-Harada Disease versus Ocular Tuberculosis

**Rogelio Garcia, BS, Dmitri Kovalen, MD, Xiangping Li, MD, MPA. Neurology, University of Texas Medical Branch, Galveston, TX, USA.**

**Background:** Vogt-Koyanagi-Harada (VKH) disease and Ocular tuberculosis (TB) share similar manifestations of uveitis, posing challenges in diagnosis and treatment. VKH was first described in the 1900’s and is an autoimmune inflammatory process mediated by CD4+ T cells that target melanocytes. It presents with early findings of choroid inflammation or retinal detachments due to targeting of melanin contained within the retina, leading to retinal degeneration seen in the later course of the disease. In addition, VKH manifests with headaches, meningismus, tinnitus, or CSF pleocytosis, and skin findings of alopecia, vitiligo or poliosis. Primary tuberculosis infects the conjunctiva, cornea, and sclera, followed by hematogenous spread into the choroid. The secondary immune reaction to mycobacterium causes uveitis and lacks a reliable rule out test.

**Case Presentation:** A 35-year-old Hispanic male presented with progressive bilateral vision loss, eye pain and redness over 1 month. He was initially seen in clinic for eye redness and photophobia in both eyes lasting for one week. Later, his vision deteriorated by 50-60% bilaterally and he presented to the hospital with visual acuity of 20/100 on the right eye and 20/400 on the left eye. Slit lamp examination revealed anterior uveitis. Fundus examination showed grade 1-2 optic disc edema and ocular ultrasound showed bilateral serous retinal detachments. MRI of the orbits showed contrast enhancement and diffusion restriction of the uveoscleral tracts bilaterally, suggestive of uveitis. Lumbar puncture showed normal opening pressure with CSF pleocytosis, low glucose, elevated protein. Infectious disease was consulted, suggesting investigation for extrapolmonary or ocular tuberculosis. Quantiferon gold test and CT chest were negative, along with extensive infectious workup, CSF cultures, cytology and viral meningitis panel. Since diagnostic criteria for VKH were...
clearly met, the patient was started on high dose IV methylprednisolone as well as empiric therapy for TB with Rifampin, Isoniazid, Pyrazinamide, Ethambutol (RIPE). Two days later, his visual acuity started to improve. He was discharged on a long-term taper of oral prednisone. After 3 months, ocular coherence tomography showed no intraretinal or subretinal fluid, however retinal pigment epithelium changes were seen.

Conclusions: Our case is unique in highlighting a treatment dilemma regarding timely initiation of IV steroids in the setting of suspected infection with ocular TB. We aim to review and provide guidance for clinicians encountering the notoriously difficult diagnoses of VKH and ocular TB.

272. Discontinuation and Non-Publication of Neuro-Ophthalmology-Related Intervventional Clinical Trials James Robbins, BA1, Tatiana Bakaeva, MD-PhD2, Taygan Yilmaz, MPH3, 1Warren Alpert Medical School of Brown University, Providence, RI, USA, 2Department of Neurology, Warren Alpert Medical School of Brown University, Providence, RI, USA, 3Division of Ophthalmology, Warren Alpert Medical School of Brown University, Providence, RI, USA.

Purpose: Although there are a variety of neuro-ophthalmology-based clinical trials that take place globally, a paucity of literature regarding the discontinuation and non-publication of such trials exists. We sought to evaluate the prevalence of non-publication in completed and discontinued interventional clinical trials as differentiated by both industry and academia.

Methods: A retrospective, cross-sectional analysis of neuro-ophthalmology-based clinical trials in ClinicalTrials.gov dating back to 1992 was conducted. Fisher’s exact test was used to determine any potential associations between trial characteristics and the likelihood of trial completion.

Results: A total of 69 trials were evaluated in this study, 34% U.S.-based. There was a 3-fold increase in the number of trials in the decade 2009-2018 compared to years prior. Of the included trials, 71% were not published and 78% were completed. Only 33% of trials published results of their study on ClinicalTrials.gov. Drugs accounted for 77% of the intervention types investigated. A total of 1,215 participants were enrolled in unpublished, completed trials; whereas 1,369 participants were enrolled in unpublished, discontinued trials. Only one principal investigator replied to our query of reasons for study discontinuation, but was bound by a confidentiality agreement to discuss further. We found no statistically significant differences in the odds of non-publication or discontinuation between industry and academia-sponsored trials (p=0.38, 0.77, respectively).

Conclusion: New policies and initiatives have helped usher in an era of improved methods for trial reporting. However, further action is needed to ensure that findings of all trials are shared in order to build a more comprehensive body of knowledge and decrease redundancy. Publication of inconclusive or negative results ensures that all research activities, regardless of outcome, contribute to a more robust, global medical literature.


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Objective: To describe a case of primary isolated optic nerve infiltrative mass lesion without the involvement of globe or optic nerve head in Essential Thrombocytosis (ET).

Background: ET is a myeloproliferative disorder most frequently associated with cerebrovascular events including non-fatal strokes and hemorrhages, thrombotic complications such as a transient ischemic attack, and migraine-like ischemic attacks. Neuro-Ophthalmic manifestations of ET are rare and include amaurosis fugax, scintillating scotoma, hemianopia, ischemic optic neuropathy, and even papilledema. The prevalence of orbital manifestation in ET is about 7.5 - 25%, however, leukemic transformation and optic nerve infiltration are very uncommon.

Case Presentation: A 47-years old female with ET, presented with a 3-month history of insidious onset of left eye proptosis, ocular pain, and discomfort. Visual acuity was 20/20 in both eyes, with normal optic nerve head and no evidence of disc edema or retinal hemorrhage. MRI of the orbit revealed evidence of an enhancing 3.4 cm x 1.9 cm X 1.7 cm lobulated intraconal mass surrounding the left optic nerve, which extended to the orbital apex in the superior orbital fissure. Optic nerve biopsy revealed lymphoid infiltrates, predominantly atypical B-cells, suggestive of extranodal marginal zone lymphoma. The patient was treated with radiation therapy with a favorable response. Follow up imaging after 2 months showed stable retinal nerve fiber layers and ganglion cell complex, without any disc edema.

Conclusion: Orbital infiltrative process affecting the retina, vitreous, or optic nerve head can be found in about 20% of patients with primary central nervous system lymphoma. On the contrary, optic nerve infiltration (ONI) is a very uncommon presentation where choroidal lymphoma can infrequently extend to the optic nerve and the orbit. We presented a rare case of primary isolated optic nerve infiltrative mass without involvement of the globe or optic nerve head in ET.


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Objective: To describe a case of optic neuropathy after prolonged Sirolimus therapy in the setting of cardiac transplant.

Background: Sirolimus is an immunosuppressant that inhibits Mechanistic Target of Rapamycin (mTOR) and blocks T-cell activation and B-cell differentiation by preventing response to Interleukin-2 (IL-2). Tacrolimus is another immunosuppressive agent, which is a calcineurin and IL-2 inhibitor, that blocks T-cell activation by preventing IL-2 transcription. One of the known but uncommon side effects of tacrolimus reported is bilateral optic neuropathy years after taking the medication in transplant patients. To the best of our knowledge, this is the first report of sequential optic neuropathy after several years of treatment with Sirolimus.

Case Presentation: A 69-years-old male with a history of cardiac transplantation presented with gradually progressive, sequential, painless, vision loss. Visual acuity was 20/150 in the right eye and 20/80 in the left eye, with impaired color vision in both eyes (Ishihara 0/10), bilateral disc pallor and mild optic disc edema in the left eye. Visual field was constricted in both eyes. The patient was on prolonged Sirolimus therapy for over 7 years. Orbital MRI revealed bilateral chiasmatic thickness and FLAIR hyperintensity, without optic nerve enhancement post gadolinium. After extensive workup, other etiologies such as infectious, inflammatory, and neoplastic lesions were ruled out. Subsequently, Sirolimus was substituted with Cyclosporin that led to gradual improvement of vision and visual fields bilaterally.

Conclusion: Optic neuropathy is a rare side effect of tacrolimus, which has been seen as sudden, painless, bilateral vision loss in post-transplant patients. Other concurrent medications influencing the cytochrome P4503A enzyme complexes may alter the pharmacokinetics of tacrolimus and increase the likelihood of toxicity. Discontinuation of the offending agent has been shown to improve visual defects. We presented a rare case of optic neuropathy in a patient on sirolimus, whose visual defects improved upon discontinuation of the current medication and switching to Cyclosporin.

Pain Mechanisms & Treatment

275. Patients with Osteoarthritis in North America, Europe and Japan Experiencing Clinically Important Improvement in Pain at Week 16 After Subcutaneous Tanezumab

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Background: Tanezumab, a monoclonal antibody that inhibits nerve growth factor, is under investigation for the treatment of moderate to severe osteoarthritis (OA) pain. As part of the phase 3 OA program, two randomized, placebo-controlled studies were recently completed and the data reported separately. Both studies showed early and sustained pain relief, following subcutaneous administration of tanezumab, at the time of the respective primary endpoints.

Objective: The objective of this pooled analysis of two studies was to evaluate the treatment response of tanezumab versus placebo as assessed by reductions in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC®) Pain subscale of ≥30%, ≥50%, ≥70% or ≥90% at Week 16. Reductions from baseline of ≥30% (moderate) or ≥50% (substantial) are often reported to be clinically important improvements.

Methods: Both studies were randomized, double-blind, and placebo-controlled (NCT02709486, NCT02697773) with placebo, tanezumab 2.5 mg or tanezumab 5 mg administered subcutaneously at baseline and Week 8 to patients with OA of the hip or knee. The proportions of patients with ≥30%, ≥50%, ≥70% or ≥90% reduction from baseline at Week 16 in WOMAC Pain were estimated by logistic regression.

Results: A total of 1545 patients were evaluated. The index joint was the knee for 84.1% of patients. Baseline WOMAC Pain scores were 6.9 ± 1.1 (mean ± standard deviation) in all three pooled groups. The proportion of patients achieving improvement from baseline in WOMAC Pain at Week 16 of ≥30% (55.6%, 68.0% and 69.4%) in the placebo, tanezumab 2.5 mg and tanezumab 5 mg groups, respectively), ≥50% (36.8%, 51.9% and 51.8%, respectively), or ≥70% (20.7%, 27.9% and 29.8%, respectively) was significantly greater in both tanezumab treatment groups compared with the placebo group (all P<0.05 versus placebo; Figure 1). The proportion of patients with ≥90% improvement was significantly greater in the tanezumab 2.5 mg group (10.7%; P<0.05), but not in the tanezumab 5 mg group (9.1%), compared with the placebo group (6.0%).

Conclusions: The pooled analysis of these studies showed that at Week 16, a significantly higher proportion of patients achieved a clinically important improvement in pain when treated with tanezumab (both treatment groups) than placebo, with little difference between the tanezumab treatment groups. Funded by Pfizer and Lilly. © 1996 Nicholas Bellamy. WOMAC® is a registered trademark of Nicholas Bellamy (CDN, EU, USA).

276. Peripheral Neurological Safety of Subcutaneous Tanezumab versus Placebo or Nsaids in Patients with Osteoarthritis

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Objective: To evaluate the peripheral nerve safety of subcutaneous (SC) tanezumab versus placebo or nonsteroidal anti-inflammatory drugs (NSAIDs).

Background: Tanezumab, an analgesic monoclonal antibody against nerve growth factor, has been associated with abnormal peripheral sensation (APS) in prior studies.

Design/Methods: Safety of SC tanezumab versus placebo was assessed using pooled data from 3 osteoarthritis trials (NCT01089725, NCT02697773 and NCT02709486). Treatments (every 8 weeks for 16-24 weeks with an 8-24 week follow-up) included placebo, tanezumab 2.5mg, 2.5mg at baseline and 5mg at week 8, 5mg and 10mg. Safety of SC tanezumab versus oral NSAIDs was evaluated in an osteoarthritis trial with a 56-week treatment period and a 24-week follow-up (NCT02528188). Patients received tanezumab 2.5mg or 5mg every 8 weeks, or twice-daily NSAIDs. Peripheral nerve safety assessments included use of a group of 27 adverse events (AEs) of APS.

Results: In the pooled SC placebo-controlled studies, AEs of APS were reported for 2.2%, 5.1%, 3.2%, 6.1% and 12.8% of patients during the treatment period in the placebo (n=586), tanezumab 2.5mg (n=602), 2.5/5mg (n=219), 5mg (n=347) and 10mg (n=86) groups, respectively. All AEs of APS were mild/moderate in severity. Up to an end of the studies, 1 patient (0.3%) in the tanezumab 5mg group discontinued due to an AE of APS (hypoesthesia). In the NSAID-controlled study, AEs of APS were reported for 6.2%, 9.0% and 4.6% of patients during the treatment period in the tanezumab 2.5mg (n=1002), 5mg (n=998) and NSAID (n=996) groups, respectively. Severe AEs of APS were reported for 0.1%, 0.3% and 0.1% of patients, respectively. Discontinuations due to AEs of APS up to end of study were reported for 0.4%, 1.5% and 0.4% of patients, respectively.

Conclusion: Compared with placebo or NSAID, a higher proportion of patients in tanezumab groups had AEs of APS; these were typically mild/moderate in severity and rarely resulted in discontinuation.

Disclosures: These studies were sponsored by Pfizer and Eli Lilly and Company. Medical writing support was provided by Steven Moore, PhD, of Engage Scientific Solutions and was funded by Pfizer and Eli Lilly and Company.

277. Use of Class IV Laser in Treating Complex Regional Pain Syndrome - A Case Report

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Objective: To report a new approach of treating Complex Regional Pain Syndrome (CRPS) Type I using Class IV Laser Therapy.

Background: CRPS is a broad term describing excess and prolonged pain and inflammation that follows an injury to an arm or leg. CRPS is categorized into Type I and Type II. The complex pathophysiology of CRPS-I is evidently due to a combination of genetic predisposition, exaggerated inflammatory response, sympathetic vasomotor disturbance, and maladaptive neuroplasticity. The treatment for CRPS involves a multidisciplinary approach involving psychotherapy, occupational and physiotherapy, medical and surgical interventions.

Case: A 15-year-old female patient presented to an outside clinic with pain, swelling, and loss of movement in the right forearm following an episode of blunt trauma. X-ray revealed a radio-ulnar dislocation. She was treated with immobilization and NSAIDs. A month later, she presented to our clinic with persistent pain and swelling of increasing intensity. Examination revealed hyperesthesia, swelling, and bluish discoloration of the affected area. Tremors were noticed in the Right hand. Her forearm was fixed in a pronated, semi-flexed position. X-Ray, Venous Doppler, and Nerve conduction studies revealed no abnormalities. Based on the clinical examination, history, and absence of peripheral nerve damage, the patient was diagnosed with CRPS type I using the Budapest criteria. She was started on steroids, Pregabalin and Nortripyline, nerve supplements, and 15 sessions of novel Class IV laser therapy over the next 4 weeks. Follow-up examinations over the course of treatment revealed drastic functional improvement along with significant reduction of pain, swelling, and discoloration.

Conclusion: Class IV laser therapy is a novel therapy whose potential is yet to be unraveled. This therapy is able to produce a biostimulative effect on deeper tissues and induces relief of aches, pain, and stiffness; relaxation of muscle spasms; increase in blood circulation. Given the complex pathophysiology of CRPS, various therapeutic approaches are essential. To our knowledge, this is the first reported case of CRPS that has shown drastic functional improvement within 4 weeks. We believe this approach to treating CRPS can bring forth a new treatment regimen.


278. Identifying Changes in the Gene Expression Profile of Sensory Neurons in Painful Diabetic Neuropathy

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Painful diabetic neuropathy (PDN) is a debilitating disease characterized by neuropathic pain and small-fiber degeneration. Given the prevalence, there is a dire need to identify new targets for the development of non-opioid and...
They included 15% of mitochondrial proteins which were disease-modifying therapeutics for PDN. In patients with PDN, nociceptors within the dorsal root ganglion (DRG) become hyperexcitable and degenerate, but the molecular mechanism underlying the phenomenon is unknown. Our overall aim is to identify the gene expression profile changes underlying this hyperexcitable phenotype of DRG neurons. We used a well-established mouse model of PDN, where mice are fed a high-fat diet (HFD) for 10 weeks. To facilitate an unbiased characterization, a single-cell RNA (scRNA-seq) sequencing approach was employed where DRG neurons were isolated from mice fed either a regular diet (RD) or an HFD. In addition to the expected neuronal and non-neuronal clusters, scRNA-seq revealed two closely related clusters expressing Mas-related G-protein coupled receptor (Mrgprd) which we refer to as non-peptidergic 1 type I (NP1T1) and non-peptidergic 1 type 2 (NP1T2) with the NP1T2 population showing a significant overexpression of Mrgprd in the HFD. To determine the functional relevance of the overexpression of Mrgprd, we used in vivo calcium imaging as a readout. Since Mrgprd is a subpopulation of the Na\textsubscript{v1.8} neurons, calcium transients were measured in real-time using the Na\textsubscript{v1.8}-Cre GCaMP6 animals in response to intradermal injections in the hind paw of animals with \(\beta\)-alanine (a known agonist of Mrgprd). We observed an increase in the percentage of neurons responding to \(\beta\)-alanine in HFD indicating the hyperexcitability of neurons that express Mrgprd. Mrgprd is an interesting target as the expression of this receptor influences the excitability of neurons and, this receptor is expressed by neurons that innervate the outermost layers of the skin. The overexpression and the hyperexcitability of these Mrgprd neurons suggest an important role of the Mrgprd receptor in the generation and maintenance of hyperexcitability in a mouse model of PDN.

419. Using a Highly Stringent Proteomic Analyses to Elucidate the Molecular Mechanisms That Underlie Neuropathic Pain in the High-Fat Diet (HFD) Mouse Model of PDN

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Painful diabetic neuropathy (PDN) is an intractable complication of diabetes that affects 25% of diabetic patients which is characterized by neuropathic pain and small fiber degeneration. Our hypothesis is that PDN is caused by dorsal root ganglion (DRG) nociceptor hyperexcitability and calcium overload. The molecular pathways linking hyperexcitability and calcium overload to neuropathic pain and axonal degeneration in PDN are unknown. This gap in knowledge represents a critical barrier to progress in developing effective and disease-modifying therapy for PDN. Using highly stringent quantitative proteomic analyses we found approximately 1000 proteins were differentially expressed in DRG neurons. They included 15% of mitochondrial proteins which were involved in mitochondrial fission in our High fat diet mouse model and that the mitochondria in DRG nociceptors of these mice displayed a fragmented morphology prior to the onset of mechanical allodynia and small-fiber degeneration. Using in vivo calcium imaging we observed increased calcium signals in Nav1.8 expressing DRG neurons from PDN mice. Interestingly we observed that preventing calcium entry into the mitochondria by selectively deleting the Mitochondrial Calcium Uniporter (MCU) from Nav1.8 expressing DRG neurons, restored normal mitochondria morphology and dynamics, prevented axonal degeneration and reversed mechanical allodynia in PDN mice. Hence, we propose that targeting calcium entry into nociceptor mitochondria may be a promising therapeutic approach towards realizing novel, effective and disease-modifying treatments for patients suffering from PDN.

420. Peripheral Neuropathic Changes in Prurigo Nodularis

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Prurigo nodularis (PN) is a chronic inflammatory skin disease characterized by hyperkeratotic nodules. Affected skin is intensely pruritic which can limit patient’s daily life. Little is known regarding the underlying mechanisms. In the current study, we compared patterns of intraepidermal nerve fibers (IENF), mechanoreceptors and blood vessels from affected and unaffected skin from patients with PN and control subjects. Punch skin biopsies from 10 prurigo nodularis patients were performed at the distal leg of both affected skin and adjacent unaffected areas and were compared to biopsies from distal leg site in 10 healthy control subjects. Tissue was processed to analyze the density of IENF (IENFD) labeled by neuronal marker (PGP9.5), Merkel cells (cytokeratin 20), blood vessels (CD31) and density of mast cells (tryptase). Subsets of IENF were further stained for CGRP, SP and NFH. Structures were quantified using stereology or validated quantification methods. We observed that PN-affected skin had significantly lower IENFD than PN-unaffected or anatomically matched control skin in the epidermis. In contrast, Merkel cell density, blood vessels and mast cell counts were higher in PN-affected skin compared to either control or PN-unaffected skin. These findings suggest that alterations in prurigo nodularis patients extend beyond keratinocytes and may provide strategies to study neuropathic itch in PN and the mechanisms of neuropathic pain in keratoderma disease.

421. Gq-Linked G-Protein Coupled Receptors Signaling in Keratinocytes Regulates Degeneration of Cutaneous Nerves

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Painful diabetic neuropathy (PDN) is one of the most common complications of diabetes, affecting 25% of diabetic patients. DPN is characterized by small-fiber degeneration, which can progress to complete loss of cutaneous innervation and is accompanied by neuropathic pain. Uncovering the mechanisms underlying degeneration of cutaneous nerves in PDN remains a major challenge to finding effective and disease-modifying therapy. Keratinocytes are closely juxtaposed to cutaneous nerve terminals potentially enabling communication between keratinocytes and cutaneous afferents. Our aim is to identify mechanisms by which keratinocytes communicate with cutaneous afferents and how this signaling regulates axonal degeneration underlying neuropathic pain in PDN. In this study, we utilized a chemogenetic approach using DREADD receptors, synthetic receptors based on the structure of human muscarinic receptors that can be activated by the synthetic ligands clozapine and clozapine N-oxide (CNO). We genetically expressed stimulatory DREADD (hM3Dq) into K14 basal keratinocytes (K-14) in mice as a tool for mimicking the activation of Gq-linked G protein-coupled receptors (GPCRs) in K14-expressing basal keratinocytes. Histological characterization of the skin from mice expressing hM3Dq in K-14 positive cells revealed a clear thickening of the epidermis (as shown by H&E staining) due to K-14 expressing cell hyperproliferation (as shown by BrdU incorporation). Additionally, we observed reduced innervation of the epidermis (as shown by PGP9.5 staining), indicating that activation of K-14 Gq-linked GPCRs drives nerve fibers degeneration in the epidermis. Furthermore, transcriptional profiling of activated K-14 from the skin of K14-hM3Dq mice revealed downregulation of genes involved in neuronal survival and neurite outgrowth, including Nerve Growth Factor (NGF), artemin, a member of the GDNF ligand family, and Semaphorin 3D. Our results suggest that basal keratinocyte Gq-linked GPCRs could represent highly “druggable” and easily accessible targets for the development of therapeutics that by reversing axonal degeneration of cutaneous nerves in a pathological conditions such as PDN and could ameliorate the associated neuropathic pain.

K-510. Transcriptional and Epigenomic Comparison of Human and Mouse Trigeminal Ganglia at Single-Cell Resolution
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Objective: Migraine involves the activation of trigeminal nociceptors, which are key substrates for the development of next-generation migraine therapeutics. However, the extraordinary cellular diversity within this structure has made it difficult to characterize molecular features of these neurons. Recent advances in single-cell genomics have enabled the massively parallel identification and molecular profiling of distinct cell types within a heterogeneous tissue. Here, we apply these tools to characterize gene expression patterns and chromatin accessibility within individual trigeminal ganglion cell types in both mouse and human, and describe evolutionarily conserved trigeminal nociceptor-specific features that have potential therapeutic relevance for migraine.

Methods: High throughput single-nucleus RNA sequencing was performed on samples of mouse and human trigeminal ganglia. Initially the sequencing data was analyzed individually by species. Nuclei were clustered based on their measured gene expression patterns, and cell types of each cluster were annotated by expression of canonical marker genes. Differential expression analysis was carried out to identify cell-type-specific genes. Mouse and human data were then computationally integrated and comparative analysis was conducted to compare gene expression patterns within each cell type across species. Single-nucleus assay for transposable-accessible chromatin (ATAC-seq) performed using the 10X Genomics platform for both mouse and human trigeminal ganglia. Cell type annotations were determined by co-clustering with gene expression using Seurat. Regions of accessible chromatin were identified using MACS2 and putative gene regulatory regions were identified using Cicero. Results: 22,158 mouse trigeminal cells and 17,452 human trigeminal cells were sequenced. Clusters of cells that represent neuronal, glial, vascular, and meningeal subtypes were identified. Individual cell types are clearly delineated based on their gene expression profiles, which enabled the interrogation of specific subtypes of neurons (e.g. CGRP+ nociceptors) or glia (e.g. satellite glia). Differential expression analysis was performed to determine the set of genes that were selectively enriched in each cell type. In particular, we have identified a set of genes that are highly enriched in distinct subtypes of both mouse and human trigeminal nociceptors. While human-specific gene expression and epigenomic features were observed, there was significant overlap of cell-type-specific genes between mouse and human trigeminal ganglia cell types. Conclusions: We found that mouse and human trigeminal ganglia contain similar transcriptionally-defined cell types. While there are human-specific genes expressed in distinct trigeminal neuron subtypes, the evolutionarily-conserved nociceptor-specific genes may have particular relevance to the mechanisms underlying head and facial pain and are likely to be amenable for study in animal models.

K-513. The Encoding of Peripheral Stimuli by Superficial Dorsal Horn Excitatory and Inhibitory Networks In Vivo
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The superficial dorsal horn (SDH) of the spinal cord is a region critical for somatosensation and the development of pain. The SDH contains heterogeneous populations of excitatory and inhibitory interneurons that process and modulate information from the periphery and shape outputs to higher brain centers. Despite the importance of the SDH, little is known about how excitatory and inhibitory circuits encode mechanical and thermal stimuli in naïve and pathological states. We implemented an in vivo imaging approach that allowed us to track the dynamics of molecularly labeled excitatory or inhibitory populations chronically over weeks. We find general fundamental differences in how excitatory and inhibitory neurons respond to peripherally applied thermal
and mechanical stimuli. Furthermore, the magnitude and direction of plasticity in these two populations differed considerably in a capsaicin model of pain sensitization. Our findings provide a novel understanding of how SDH networks encode peripheral stimuli and how they are modulated by inflammatory pain.

LB-456. Discovery of Hbw-3-80, a Potent, Bioavailable Sodium Channel Nav.1.8 Blocker for Pain
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Background: The tremendous therapeutic potential of voltage-gated sodium channels (Navs) has been the subject of many studies in the past and is of intense interest today. NaV1.8 is a voltage-gated sodium channel that plays a critical role in pain signaling in the peripheral nervous system. NaV1.8 is genetically validated as a novel target for the treatment of pain. Recently, a number of potent, selective and bioavailable small molecule NaV1.8 blockers, such as VX-150, have demonstrated clinical proof-of-concept with a bioavailable small molecule NaV 1.8 blockers targeting Nav.1.8 in multiple pain indications including acute pain, neuropathic pain and musculoskeletal pain.

Method: Novel NaV1.8 blockers were designed, synthesized and tested for NaV 1.8 blocking activities. Highly active compounds were assessed for microsomal stability and ADMET properties. Potent and bioavailable compounds were further evaluated for in vivo efficacy in rat complete Freund’s adjuvant (CFA) tactile allodynia model.

Result: As shown in the table, HBW-3-80 has greater potency, better hERG and pharmacokinetic profile (rats, 100mg/kg PO) than VX-150. In a rat complete Freund’s adjuvant (CFA) tactile allodynia model, HBW-3-80 and VX-150 were compared directly, all dosed at 10 mg/kg QD. The resulting Paw withdrawal threshold (PWT50%) data for HBW-3-80 was better than VX-150 at all three time points (2, 5 and 8 hours after dosing). Based on our data, HBW-3-80 is more efficacious than VX-150.

Conclusion: We have discovered a novel Sodium Channel NaV1.8 Blocker HBW-3-80 that has a superior potency, efficacy and safety profile than other known ones. HBW-3-80 provides a valuable clinical candidate for treating acute pain, neuropathic pain and musculoskeletal pain.

Regenerative Medicine

476. Neuronal Subtype-Specific Vulnerability to Demyelination in DRG Neurons
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Peripheral nervous system (PNS) myelin facilitates rapid nerve conduction velocities and provides trophic support to axons. Demyelination of the PNS is the hallmark of several human neuropathies. In addition, demyelination of the PNS is a debilitating result of chemotherapy treatment and diabetes. Demyelination of the PNS dramatically affects sensory neurons and leads to numbness of the limbs, loss of sensation and debilitating neuropathic pain. The consequences of mechanical damage of neurons, caused by either crush or axotomy, are well characterized. Strikingly, despite its clinical importance, the effect of PNS demyelination on neuronal gene expression is unknown. To determine the transcriptional response of DRG neurons to demyelination, we characterized the demyelination of the PNS in the PLP-CreERT; ROSA26-eGFP-DTA line. In this line, the expression of the diphertheria toxin A- subunit (DT-A) is prevented by an upstream "lox-stop-lox" (LSL) cassette, and upon PLP-CreERT mediated recombination, the stop sequence is removed, and the expression of DT-A is released, resulting in loss of oligodendrocytes and Schwann cells. We found that in this line the conduction velocity in the sciatic nerve is substantially reduced 21 days post tamoxifen administration (PID21), and full functional recovery of the PNS is achieved three weeks later. In parallel morphological studies we found that the peak of PNS demyelination at PID21 is characterized by appearance of demyelinated and remyelinated large caliper axons, aberrant morphology of Remak bundles, infiltration of phagocytic macrophages, and reduced myelin thickness (increased g-ratio), without axonal loss. To study the effect of this demyelination on neuronal gene expression, we harvested the cell bodies of the sensory neurons that project through the sciatic nerve (DRGs L3-L5) for Single Nucleus RNA-seq (snRNAseq) studies. We sequenced 14,710 nuclei and identified nine naive cell types including glial cells and six different subtypes of sensory neurons (14,096 nuclei). In DRGs derived from the peak of demyelination we identified an additional cluster of nuclei (614 nuclei, ~4% total) that expressed high levels of the known injury-induced genes Atf3, Sox11 and Spry1a. We therefore defined this cluster as "injured". Cell type annotation of the injured nuclei revealed that the injured nuclei derived specifically from proprioceptive neurons and Aβ rapidly-adapting low-threshold-mechanoreceptor (Aβ RA-LTMR) neurons. Our findings suggest that despite the vast morphological changes in the sciatic nerve upon PNS demyelination, the injury response among DRG neurons is neuronal subtype-specific to proprioceptive and Aβ RA-LTMR neurons, which have axons with the thickest myelin sheaths.
Sleep Disorders and Circadian Rhythm

279. Efficacy of FT218, a Once-Nightly Sodium Oxybate Formulation (ON-SXB), by Narcolepsy Subtype: Post Hoc Analysis from REST-ON
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Introduction: FT218 is an investigational, modified-release, once-nightly formulation of sodium oxybate (ON-SXB) for the treatment of narcolepsy. The purpose of this post hoc analysis of the REST-ON trial was to evaluate the effect of ON-SXB on measures of excessive daytime sleepiness (EDS) in patients with narcolepsy subtypes 1 (NT1) and 2 (NT2).

Methods: This was a randomized, double-blind, placebo-controlled, multicenter study in patients with narcolepsy ≥16 years old. Patients were stratified by narcolepsy subtypes and randomized 1:1 to receive ON-SXB or matching placebo: 4.5 g/night for 1 week, 6.0 g/night for 2 weeks, and 9.0 g/night for 5 weeks (maximum treatment duration, 13 weeks). Assessments included change from baseline in mean sleep latency on maintenance of wakefulness test (MWT); disturbed nocturnal sleep (DNS) on polysomnography measures of sleep fragmentation defined as shifts to Wake or N1 from N1, N2, N3 and REM; and Clinical Global Impression-Improvement (CGI-I) in the patient’s condition.

Results: A total of 190 patients were included in the modified intent-to-treat population (NT1: ON-SXB, n=72; placebo, n=73; NT2: ON-SXB, n=21; placebo, n=24). Patients with NT1 or NT2 receiving ON-SXB had significant improvement in MWT. Least-squares mean (LSM) difference in mean sleep latency (minutes) vs placebo for NT1 was: 9.0 g (week 13) = 5.97, 7.5 g (week 8) = 7.02, 6.0 g (week 3) = 4.89 (all P<0.001); and for NT2 was: 9.0 g = 6.27 (P<0.05), 7.5 g = 4.01 (P=0.005), 6.0 g = 5.33 (P<0.05). LSM difference in DNS vs placebo for NT1 was: 9.0 g = 22.03, 7.5 g = 17.29, 6.0 g = 11.19 (all P<0.001); and for NT2 was: 9.0 g = 25.00 (P<0.001), 7.5 g = 21.04 (P<0.05), 6.0 g = 11.80 (P<0.05). A higher proportion of NT1 patients receiving ON-SXB had significant improvement on CGI-I vs placebo (9.0 g = 75.5% vs 35.9%; 7.5 g = 66.9% vs 27.9%; 6.0 g = 39.9% vs 7.8%; all P<0.001). A higher number of NT2 patients receiving ON-SXB were consistently rated as much/very much improved vs placebo based on descriptive statistics. ON-SXB was generally well tolerated.

Conclusion: In post hoc subgroup analyses by narcolepsy subtype, ON-SXB had similar efficacy on EDS in NT1 and NT2 with improvement in MWT, DNS, and CGI-I greater than placebo. ON-SXB may provide effective treatment for EDS and DNS in patients with narcolepsy, with or without cataplexy.

280. Efficacy and Safety of Lower-Sodium Oxybate in Adults with Idiopathic Hypersomnia: With and without Long Sleep Time
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Introduction: Idiopathic hypersomnia (IH) is a central hypsomnolence disorder characterized by excessive daytime sleepiness. Long nocturnal sleep time (≥10 h) is a debilitating symptom common in IH. Currently, there is no approved treatment for IH. The efficacy and safety of lower-sodium oxybate (LXB; Xywav™) was evaluated in a phase 3 study in adults with IH (NCT03533114). This study evaluated the efficacy of LXB in participants with IH, based on the presence or absence of clinician-reported long sleep time (LST).

Methods: Eligible participants 18-75 years of age with IH began LXB treatment in an open-label titration and optimization period (10-14 weeks), followed by a 2-week, open-label, stable-dose period (SDP), and were then randomized to placebo or to continue LXB treatment during a 2-week, double-blind, randomized withdrawal period (DBRWP). The primary efficacy endpoint was change in Epworth Sleepiness Scale (ESS) score; key secondary endpoints were proportion of participants reporting worsening (minimally/much/very much worse) on the Patient Global Impression of Change (PGIC) and change in Idiopathic Hypersomnia Severity Scale (IHSS) score, all from end of SDP to end of DBRWP. This analysis was outside the statistical hierarchy; reported P values are nominal.

Results: The analysis population (n=116) included 25 participants with LST (mean ± SD age, 40 ± 16.2 years; 68% female; mean ± SD baseline ESS, 16.2 ± 4.4) and 91 participants without LST (mean ± SD age, 41.3 ± 13.3 years; 73% female; mean ± SD baseline ESS, 15.7 ± 3.6). ESS scores worsened with placebo but not with continuing LXB in participants with LST (modified intent-to-treat population; placebo, n=11; LXB, n=13; LS mean difference [95% CI]: −7.79 [−11.42, −4.15]; P=0.0002) and without LST (placebo, n=48; LXB, n=43; LS mean difference [95% CI]: −6.24 [−7.84, −4.64]; P=0.0001). Similarly, worsening was observed with placebo but not with continuing LXB in participants with LST (modified intent-to-treat population; placebo, n=11; LXB, n=13; LS mean difference [95% CI]: −7.79 [−11.42, −4.15]; P=0.0002) and without LST (placebo, n=48; LXB, n=43; LS mean difference [95% CI]: −6.24 [−7.84, −4.64]; P=0.0001). Common (>10% of participants)
treatment-emergent adverse events were nausea, headache, dizziness, anxiety, and vomiting.

Conclusion: In participants with IH with and without LST, LXB demonstrated clinically important treatment effects of similar magnitude.

281. Efficacy of Lower-Sodium Oxybate During Open-Label Treatment Optimization in a Placebo-Controlled, Double-Blind, Randomized Withdrawal Study in Adults with Idiopathic Hypersomnia

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Introduction: Idiopathic hypersomnia (IH) is a central hypersomnia disorder characterized by excessive daytime sleepiness (EDS), sleep inertia, and long nocturnal sleep time, with no currently approved treatments. The efficacy and safety of lower-sodium oxybate (LXB; Xywav™) was established in a double-blind randomized withdrawal study in adults with IH (NCT03533114). This analysis evaluated the efficacy of LXB during open-label treatment initiation in this study.

Methods: Eligible participants 18-75 years of age with IH per International Classification of Sleep Disorders, 2nd edition (ICSD-2) or 3rd edition (ICSD-3) criteria began LXB treatment in an open-label titration and optimization period (OLT; 10-14 weeks), followed by a 2-week, open-label, stable-dose period (SDP), and were then randomized to placebo or to continue LXB treatment during a 2-week, double-blind, randomized withdrawal period (DBRWP). The primary efficacy endpoint was change in Epworth Sleepiness Scale (ESS) score; secondary endpoints included change in Idiopathic Hypersomnia Severity Scale (IHSS) score and proportion of participants minimally/much/very much worsened on the Patient Global Impression of Change (PGiC) and Clinical Global Impression of Change (CGiC). Endpoints were collected at all site visits from OLT day 1 through end of DBRWP. Primary analyses were conducted on data from end of SDP to end of DBRWP.

Results: The study enrolled 154 participants (mean ± SD age, 40 ± 14 years; 68% female; mean ± SD baseline ESS, 16 ± 3.6). From start of OLT to week 4 and end of SDP, mean ± SD scores (n=115) decreased (improved) on ESS (15.7 ± 3.8 [day 1], 9.8 ± 4.5 [week 4], and 6.1 ± 4.0 [end of SDP]) and IHSS (31.6 ± 8.3 [day 1], 20.9 ± 8.9 [week 4], and 15.3 ± 8.5 [end of SDP]). From OLT week 1 to end of SDP, the proportion of participants minimally/much/very much improved increased on PGiC (from 79/151 [52.3%] to 115/123 [93.5%]) and CGiC (from 78/150 [52.0%] to 114/123 [92.7%]). Common treatment-emergent adverse events (reported by ≥10% of total participants across all study periods, excluding placebo data) were nausea, headache, dizziness, anxiety, and vomiting.

Conclusions: In adults with IH, daytime sleepiness, overall IH symptom severity, and self-reported patient- and clinician-rated global impression of change improved during open-label treatment with LXB.

282. Patient-Reported Symptoms and Health-Related Quality of Life Impacts of Idiopathic Hypersomnia

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Introduction: Idiopathic hypersomnia (IH) is a neurologic disorder characterized by excessive daytime sleepiness, sleep inertia, and prolonged sleep times. Patients with IH experience significantly reduced health-related quality of life (HRQoL) with associated cognitive impairment, higher incidence of psychiatric symptoms, work functioning and productivity impairment, and higher risk of driving impairment and accidents. The objectives of this study were to document the symptoms and HRQoL impacts of IH from the perspective of people with IH.

Methods: Qualitative interviews were conducted with adults with IH recruited from a patient advocacy group and a rare disease registry. Participants were asked a series of open-ended questions designed to elicit spontaneous descriptions of signs, symptoms, and HRQoL impacts related to IH. Interviews were audio-recorded, transcribed, coded, and analyzed.

Results: Interviews were conducted with 20 participants (mean age, 35.0 years; 70.0% female; 90.0% White/Caucasian). Saturation analysis demonstrated sufficient sample size, with most symptoms and all impact domains elicited in the first 75% of interviews. Participants reported 18 IH-related symptom concepts. The most frequently reported symptom concepts were excessive daytime sleepiness and sleep inertia, both of which were reported by all participants (n=20/20, 100.0%). Other symptom concepts frequently elicited were brain fog (n=16/20, 80.0%) and prolonged sleep of 10-11 hours (n=16/20, 80.0%). Excessive daytime sleepiness was reported as the most bothersome symptom and rated as the most important symptom to improve with treatment. Nearly all participants reported that IH had a negative impact on multiple life domains. Negatively impacted life domains frequently reported were emotional (n=20/20, 100.0%; n=15 concepts), cognitive (n=19/20, 95.0%; n=9 concepts), and work (n=18/20, 90.0%; n=12 concepts). Cognitive difficulty was rated as the most bothersome life domain and the most important life domain to improve with treatment. Results were further organized into a conceptual model that demonstrated the relationship among signs, symptoms, and HRQoL impact domains.

Conclusions: Findings from these interviews indicate that adults with IH experience a broad range of symptoms that negatively impact multiple domains of daily life, including emotions, cognition, and work, leading to a diminished
quality of life. These results highlight the unmet medical need for the treatment of patients with IH.

283. Content Validity of the Idiopathic Hypersomnia Severity Scale

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Introduction: Idiopathic hypersomnia (IH) is a rare neurologic disorder characterized by excessive daytime sleepiness, sleep inertia, and prolonged nighttime sleep. The Idiopathic Hypersomnia Severity Scale (IHSS) measures IH symptom severity, consequences, and responsiveness to treatment. This study evaluated the content validity of the IHSS by assessing participants’ ability to understand and respond to items as intended by developers.

Methods: Qualitative interviews were conducted in adults diagnosed with IH recruited from a patient advocacy group and a rare disease registry. Interviews had 2 parts: an open-ended concept-elicitation (CE) section (participants were asked questions designed to elicit spontaneous descriptions [results reported elsewhere]) and a scripted cognitive debrief (CD) section that assessed the content validity of the IHSS. In the CE, participants first completed the IHSS by “thinking aloud” to describe their process of arriving at answers to each item. Targeted CD questions were then asked to assess the readability, comprehensibility, relevance, and comprehensiveness of the IHSS. Participants were also asked what point changes (ie, 1- or 2-point change) they considered to represent clinical meaningfulness for items 2-14. Interviews were audio-recorded, transcribed, and analyzed.

Results: Interviews were conducted with 20 participants in the United States (mean age, 35.0 years; 70.0% female; 90.0% White/Caucasian). Most participants were able to read, comprehend, and interpret the instructions, recall period, and IHSS items; any difficulties were idiosyncratic and reported by single participants. Most participants (n=17/20, 85.0%) were able to read and comprehend the IHSS response options as intended by their developers. No major interpretation issues were reported. Participants articulated a range of changes that they considered necessary for a change to be meaningful, from a 1- to 2-point difference in a scale item to complete resolution of symptoms. No modifications were recommended to the IHSS questionnaire. Mapping of concepts elicited from the CE interviews onto items of the IHSS demonstrated that the IHSS comprehensively covers symptoms and functional impacts of IH; all 14 items of the IHSS were spontaneously elicited from patients during the CE.

Conclusions: The findings provide evidence of content validity of the IHSS, demonstrated as ease of completion, comprehensibility, and interpretability. Results also demonstrate that the IHSS assesses the symptoms and functional impacts that are most relevant and important to participants. These findings support the use of the IHSS to assess the signs, symptoms, and HRQoL in patients with IH.

284. Machine Learning vs Human-Scoring of Sleep EEG Data in Mice

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Sleep is a fundamental animal behavior and has been implicated in cellular mechanisms of plasticity, cortical network organization, memory consolidation and neurological disease. In mice, wakening and the various stages of sleep (NREM, REM) are subjectively scored by a human rater based on electroencephalogram (EEG) and electromyogram (EMG) recordings. This process consumes both time and energy and lacks inter- and intra-rater reliability. Machine learning algorithms have recently been developed to accurately and reliably score sleep in mice with the potential for significant time- and cost-saving measures. The purpose of this study was to compare sleep stage classification by a machine-learning algorithm and the corresponding human-scoring. We collected 3-hour recordings from 14 mice fitted with EEG/EMG electrodes. Recordings were manually scored in 10 second epochs by standard criteria and verified by two different expert scorers. AccuSleep, a machine learning program that utilizes convolution neural networks and mixture z-scoring to automatically characterize sleep stages, was applied to the EEG and EMG data of the 14 recordings (Barger et al). Sleep stage was classified with an accuracy of 0.92, misclassification of 0.081 and Cohen’s Kappa of 0.71. In conclusion, machine learning can reliably classify sleep states, provides a viable alternative to human scoring and will facilitate sleep-based studies on brain plasticity, cortical network organization, and neurological disease.

285. Efficacy of FT218, a Once-Nightly Sodium Oxybate Formulation (ON-SXB), by Stimulant Use: Post Hoc Analysis from REST-ON

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Introduction: FT218 is an investigational, modified-release, once-nightly formulation of sodium oxybate (ON-SXB) for the treatment of narcolepsy. The purpose of this post hoc analysis of the REST-ON trial was to evaluate the effect of ON-SXB on measures of excessive daytime sleepiness (EDS) in patients with narcolepsy with or without stimulant use.

Methods: This was a randomized, double-blind, placebo-controlled, multicenter study in patients with narcolepsy ≥16 years old. Patients were stratified by stimulant use and randomized 1:1 to receive ON-SXB or matching placebo: 4.5
Narcolepsy: Post Hoc Analysis from REST-ON Oxybate Formulation (ON-SXB), for the Treatment of comitant stimulant use.

EDS and DNS in patients with narcolepsy regardless of concomitant CGI-I. ON-SXB may provide effective treatment for comitant use, with improvement over placebo on MWT, DNS, and subjective sleepiness. ON-SXB was generally well tolerated.

Methods: A total of 190 patients were included in the modified intent-to-treat population (stimulants: ON-SXB, n=66; placebo, n=53; no stimulants: ON-SXB, n=31, placebo, n=40). Overall, 63% of participants received concomitant stimulants. Patients receiving ON-SXB had significant improvement vs placebo in MWT and DNS regardless of stimulant use. Least squares mean (LSM) difference in mean sleep latency versus placebo for stimulant use was: 9.0 g (week 13)=5.99, 7.5 g (week 8)=5.51, 6.0 g (week 3)=5.35 (all P<0.001). A total of 107 patients received ON-SXB and 105 received placebo. At baseline, mean (SD) and median weight were 81.2 (20.8) kg and 77.6 (range, 47.0 to 162.0; Q1-Q3, 67.5 to 89.7) with ON-SXB and 82.1 (22.5) kg and 79.0 (48.0 to 156.0; 65.0 to 95.3) kg with placebo. At end of study (week 13), mean (SD) and median weight were 80.9 (21.9) kg and 76.9 (range, 49.9 to 163.3; Q1-Q3, 64.9 to 89.2) kg with ON-SXB and 82.25 (21.6) and 79.4 (47.3 to 140.6; 65.3 to 94.3) kg with placebo. At week 13, mean (SD) and median change in weight from baseline were -1.29 (3.6) kg and -0.4 (range, -12.1 to 12.7) kg for ON-SXB and 0.19 (2.6) kg and 0.00 (-7.1 to 9.9) kg for placebo. The percentage of patients with ≥5% weight loss was 17.8% ON-SXB, 3.8% placebo. At baseline, mean (SD) BMI was 28.1 (7.8) kg/m^2 ON-SXB, 28.2 (6.6) kg/m^2 placebo. At study end (week 13), LSM (SE) change from baseline in BMI was -0.51 (0.13) kg/m^2 ON-SXB, 0.08 (0.13) kg/m^2 placebo (LSM difference [95% CI], -0.59 [-0.95 to -0.23]; P<0.001). ON-SXB was generally well tolerated.

Conclusion: Patients receiving ON-SXB experienced a significantly greater decrease in weight and BMI vs placebo. These results suggest that treatment with once-nightly ON-SXB may provide weight-related benefit for patients with narcolepsy and comorbid weight gain.

287. Chronic Nausea and Vomiting as a Risk Factor for Circadian Shift and Shortened Sleep

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Introduction: Chronic nausea and vomiting (CNV), characterized by symptoms lasting for at least 4 weeks, can be debilitating and associated with a diverse array of disorders (e.g., gastroparesis, cyclic vomiting syndrome [CVS]). Yet, little is known about how CNV may be related to circadian rhythms. Our aim was to examine the impact of CNV on circadian rhythms.

Methods: This longitudinal study had two waves: 12,218 subjects interviewed by phone during wave 1 (W1); 10,931 during wave 2 (W2) three years later. The sample was representative of the general population based on US Census. Analyses included subjects participating to both waves (N=10,931). CNV was defined as episodes of nausea and vomiting occurring 2+ times a month for at least one month (outside pregnancy). Logistic regression models were employed to determine whether CNV is a predictive variable for different indicators of sleep quality.
**Results:** Out of all W1 participants, 9.8% (95% CI: 9.2%-10.4%) reported nausea only while 3% (95% CI: 2.7%-3.3%) reported CNV. At W2, 7.7% (95% CI: 7.2%-8.2%) reported nausea only and 2.5% (95% CI: 2.2%-2.8%) reported having CNV. Of the subjects who participated in both W1 and W2, 25.7% of them reported CNV at both waves. Nearly 40% (39.5%) of subjects with persistent CNV (CNV[w1w2], i.e. reported at W1 and W2) reported a sleep duration of 30+ minutes shorter at W2 (vs. 27% in the no-CNV group). A shift in bedtime hours was observed for 47.7% of CNV[w1w2] subjects (vs. 29.1% of non-CNv). At W2, 44.1% of CNV[w1w2] subjects also have increased the number of meals per day. After controlling for age, sex, BMI, health status, alcohol intake and sleep disorders, shorter sleep duration was predicted by CNV[w1w2]: (RR: 1.8 [95% CI:1.1-2.9] p=0.02), increased number of meals (1 supplemental meal RR: 1.2 [95% CI:1.0-1.3] p=0.02; 2+ supplemental meals RR: 1.4 [95% CI:1.1-1.8] p=0.003) and a shift in bedtime (RR: 2.3 [95% CI:1.9-2.8] p=0.0001).

**Conclusion:** CNV[w1w2] showed to be related to changes in sleep duration as well as shift in bedtime habits. While circadian rhythms have not been previously investigated in CNV [w1w2], there has been literature showing that several GI disorders involving nausea and vomiting (e.g., gastroparesis or CVS) tend to have an increased intensity during late evening or early morning. This could partially explain why we observed modifications in circadian rhythms.

**288. Predictors for Chronic Sleep Paralysis in a Longitudinal Study of the American General Population**

**Maurice M. Ohayon, MD, DSc, PhD. Stanford University, Palo Alto, CA, USA.**

**Introduction:** Sleep paralysis refers to a sleep disorder characterized by an incapacity to move either a sleep onset or upon awakening from sleep. Sleep paralysis is a common symptom of narcolepsy, a disorder characterized by excessive sleepiness, cataplexy and disturbed sleep. It can also be observed in people with panic disorder or posttraumatic stress disorder. The evolution of the disorder remains seldomly investigated. There is no data regarding its incidence and its chronicity. This study examines the predictive factors for chronic sleep paralysis in the general population.

**Methods:** This longitudinal study had two waves: 12,218 subjects interviewed by phone during wave 1 (W1); 10,931 during wave 2 (W2) three years later. The sample was representative of the general population based on US Census. Analyses included subjects participating to both waves (N=10,931). Logistic regression models were employed to determine the predictive variables for chronic sleep paralysis in the general population.

**Results:** At W1, 9.7% (95% CI: 9.1%-10.3%) reported having at least 1 episode of sleep paralysis in the previous year. At W2, 15.1% (95% CI: 14.4%-15.8%) reported sleep paralysis. A total of 29.9% of subjects with sleep paralysis at W1 still reported episodes at W2 (2.9% of the sample). The 3-year incidence was 2.9% (95% CI: 2.6%-3.2%). After adjusting for age and sex, chronicity of sleep paralysis (i.e., present at both interviews) was predicted by the following factors present at W1: posttraumatic stress disorder (RR: 3.0 [95% CI:1.8-5.0] p<0.001); pain (RR: 2.5 [95% CI:1.6-3.8] p<0.001), excessive sleepiness (RR: 1.6 [95% CI:1.0-2.4] p=0.03); a sleep duration < 6 hours (RR: 1.6 [95% CI:1.0-2.4] p=0.034), insomnia symptoms (RR: 1.7 [95% CI:1.3-2.3] p<0.001) and cataplexy-like symptoms (RR: 2.8 [95% CI:1.8-4.3] p<0.001).

**Conclusion:** Episodes of sleep paralysis are frequent in the general population. Its chronicity is predicted by several factors associated with narcolepsy like excessive sleepiness and cataplexy but also by other factors like posttraumatic stress disorder or pain.

**423. New Insight Into REM Sleep Behavior Disorder Circuits in Living Humans**

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**Objective:** To investigate brainstem structural connectivity changes in REM-sleep-behavior disorder (RBD) patients using an in-vivo probabilistic brainstem nuclei atlas and 7 Tesla high angular resolution diffusion MR imaging.

**Background:** RBD is characterized by the absence of muscle-atonia during REM-sleep. RBD patients have up to 73.5% risk of developing a neurodegenerative synucleinopathy after 12 years from the RBD-diagnosis. Animal RBD models have described alterations within brainstem-nuclei, yet these changes remain uninvestigated in living humans due to the lack of an in-vivo brainstem nuclei atlas.

**Methods:** Data acquisition: We performed 7 Tesla MRI, under IRB-approval, in 12 RBD patients (age: 68±1.6yrs) and 12 controls (age: 66.3±1.6yrs): 0.75mm-isotropic T2-weighted MEMPRAGE and 1.7mm-isotropic spin-echo diffusion-weighted MRI were acquired. Data analysis: a) Preprocessing: We parcellated the root-mean-square MEMPRAGE image with Freesurfer. b) Definition of seed and target regions: We used as seeds the structural probabilistic atlas labels of 20 brainstem nuclei relevant for RBD and as targets 197 cortical/subcortical regions (Freesurfer parcellations, brainstem nuclei and spinal cord). c) DTI-structural connectivity analysis: We performed probabilistic tractography (iFOD2-MRtrix3) propagating 100,000 streamlines from each seed. We computed a “structural-connectivity-index” for each pair of seed-target masks (fraction of streamlines propagated from seed reaching target). d) Statistical analysis: We averaged the “structural-connectivity-index” across subjects and Wilcoxon test was used to compare the differences between groups.

**Results/Discussion:** The structural connectome of brainstem nuclei relevant for RBD showed connectivity changes in 14 brainstem seeds across groups mainly within brainstem nuclei. We found impaired connectivity in RBD between REM-on and REM-sleep muscle-atonia medullary
areas. This agrees with animal studies showing decreased excitatory connectivity between REM-on regions and ventromedullary nuclei, which generate muscle atonia during REM-sleep. Interestingly, ponto-medullary brainstem nuclei, known to be involved in REM-atonia, showed decreased structural interconnectivity, possibly related to an underlying neurodegeneration process. In contrast, meso-pontine regions showed overall increased inter-connectivity, possibly indicating compensatory mechanisms.

Conclusion: Decreased structural connectivity between REM-on and medullary brainstem nuclei underlies REM-sleep muscle-atonia in RBD patients.

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424. Sleep Disturbances in Two Progressive Supranuclear Palsy Variants

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Introduction: Sleep abnormalities have been described in the Richardson’s syndrome variant of progressive supranuclear palsy (PSP-RS). Recently, the Movement Disorders Society published criteria recognizing other variants of PSP. One such variant is characterized by progressive speech and language problems (PSP-SL). In this study, we aimed to investigate whether there is any sleep involvement in PSP-SL and whether sleep disturbance in PSP-SL is similar in degree to those observed in PSP-RS.

Methods: This study consisted of 161 prospectively recruited patients; 59 suggestive of PSP-SL (s.o. PSP-SL); 31 possible PSP-SL (poss. PSP-SL) and 71 probable PSP-RS (prob. PSP-RS). Four sleep-related screening questions were scored as present/absent by the caregiver: “screaming or talking during sleep”, “acting out dreams during sleep”, “unable to fall or stay asleep”, and “excessive daytime sleepiness”. All four were summed to create a sleep composite score. Each item and sleep composite were compared across groups with significance set at p<0.05.

Results: Of the 161 patients, 21 (35.6%) with s.o. PSP-SL, 12 (38.7%) with poss. PSP-SL and 48 (67.6%) with prob. PSP-RS exhibited at least one sleep-related disturbance. The most common sleep problem was “unable to fall or stay asleep” endorsed by 53 patients in total (32.9%). Both PSP-SL groups performed similarly on the sleep composite, and showed similar frequencies of “screaming or talking in sleep”(1.7% vs 0.0%), “acting out dreams” (0.0% vs 0.0%), and “unable to fall or stay asleep”(20.3% vs 19.4%), but these sleep problems were more common in prob. PSP-RS (11.3%, 8.5% and 49.3%, respectively ). The frequency of “excessive daytime sleepiness” was higher in prob. PSP-RS (39.4%) than s.o. PSP-SL (15.3%) but did not differ from poss. PSP-SL (29.0%).

Conclusion: Sleep abnormalities occur in PSP-SL and worsen with the development of core PSP features. The severity of sleep disturbance in PSP-SL is however less severe compared to prob. PSP-RS.

Support: This study is supported by NIH grant NS89757.

425. Global and Local Sleep Changes in Brain Oscillations After Stroke

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Introduction: After ischemic stroke there are global (brain-wide) changes in functional connectivity and brain oscillatory power over the course of stroke recovery. The role of brain states (sleep, wake, anesthesia, minimally conscious) in changing brain dynamics following stroke is unclear. Sleep, with its permissive role in neuroplasticity both globally and locally, may be a key process responsible for changing brain dynamics after stroke. Using wide-field optical fluorescence imaging combined with electroencephalography, we report sleep-specific changes in global and local functional connectivity and oscillatory power after stroke.

Methods: Three mice expressing the genetically encoded calcium indicator GCaMP in excitatory cortical neurons were fitted with plexiglass whole-cortex cranial windows for chronic optical fluorescence imaging (pixel resolution 78μm x 78μm) as well as EEG and EMG pins for sleep monitoring. Simultaneous wide-field optical imaging and sleep recordings were recorded at baseline and at 24 hours, 1 week, 4 weeks, and 10 weeks after photothrombotic stroke in the left forepaw somatosensory cortex. Brain behavioral states (wake, NREM, REM) were scored based off EEG and EMG in 10-second epochs. The GCaMP optical signal was subsequently processed in MATLAB to produce seed-based functional connectivity plots and spatial power topoplots separated by behavioral states.

Results: Independent of behavioral states, functional connectivity deficits induced by stroke recovered globally to pre-stroke levels over 10 weeks of recovery, except for connectivities within the infarct. When examined across states, functional connectivity deficits were more prominent in NREM compared to wake. Brain oscillatory power topoplots showed global increases in power that renormalized over the course of recovery. Locally, over the infarct, there were frequency-specific changes that renormalized over time: delta power (0.85-3Hz) acutely decreased at 24 hours post-stroke, while lower-delta power (0.02-0.1Hz) increased starting at 1 week. State-dependent topoplots revealed that the global power increase over 4 weeks was more pronounced during
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Hypersomnia
and Work Productivity in Participants with Idiopathic
427. Effects of Lower-Sodium Oxybate on Functioning
sleep manipulation to aid recovery.
fulness. Future studies will examine the role of global vs local
repair mechanisms during different stages of sleep and wake-
fulness.

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Introduction: Idiopathic hypersomnia (IH) is a central hyp-
somnolence disorder characterized by excessive daytime 
sleepiness (EDS). Most individuals with IH report difficulty 
with functioning and work due to EDS. No medication is 
currently approved to treat IH. The efficacy and safety of 
lower-sodium oxybate (LXB; Xywav™), containing 92% less 
sodium than sodium oxybate (Xyrem®), was established in a 
phase 3 study in adults with IH (NCT03533114). This anal-
ysis evaluated LXB effects on functioning and work produc-
tivity in participants with IH.

Methods: Eligible participants aged 18-75 years with IH 
based on ICSD-2/ICSD-3 criteria began LXB treatment in 
an open-label titration/optimization period (10-14 weeks), 
followed by a 2-week, open-label, stable-dose period (SDP), 
and then were randomized to placebo or to continue LXB 
treatment during a 2-week, double-blind, randomized with-
drawal period (DBRWP). The primary efficacy endpoint was 
change in Epworth Sleepiness Scale (ESS) score. Secondary 
endpoints included change in total score from the end of 
SDP to the end of DBRWP on the Functional Outcomes of 
Sleep Questionnaire, short version (FOSQ-10; normal score 
≈18). Exploratory endpoints included percent change from 
the end of SDP to the end of DBRWP in the Work Productiv-
ity and Activity Impairment Specific Health Problem 
(WPAI:SHP) questionnaire, with IH as the health problem 
for the following measures: work time missed (absenteeism), 
impairment while working (presenteeism), overall work 
impairment (absenteeism + presenteeism), and activity 
impairment. *P values for FOSQ-10 and WPAI:SHP were 
not adjusted for multiplicity and are nominal.

Results: The study enrolled 154 participants (mean±SD 
age, 40±14 years; 68% female). Mean±SD FOSQ-10 total 
score increased (improved) during titration/optimization 
(11.8±3.4 at study start and 16.7±3.0 at the end of SDP). 
FOSQ-10 total scores worsened in participants randomized 
to placebo; maintenance of improvement was observed in 
those continuing LXB (n=115; LS median difference [95%
CI] in change from SDP, 3.71 [2.50, 5.00]; *P<0.0001). 
WPAI:SHP measures decreased (improved) during titration/ 
optimization but worsened in participants randomized to pla-
cebo during DBRWP. Maintenance of improvement was 
observed in those continuing LXB during DBRWP (esti-
imated median difference [95% CI] regarding absenteeism: 
0.00 [−3.23, 0.00]; *P=0.0092; LS mean difference [95% 
CI], presenteeism: −27.51 [−37.1, −17.9]; *P=0.0001; absen-
teeism + presenteeism: −30.8 [−39.9, −21.7]; *P<0.0001; 
and activity impairment: −31.7 [−40.0, −23.5]; *P=0.0001)

Conclusions: In study participants with IH, LXB demon-
strated improvement in measures of functioning and work 
productivity.

Traumatic Brain Injury

289. Insufficient Sleep Following Pediatric Mild 
Traumatic Brain Injury Correlates with Neurocognitive 
Dysfunction
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Introduction: Sleep disturbance of any nature is reported in 
more than half of all mild traumatic brain injury (mTBI) 
patients. The pathophysiology of sleep disturbance following 
a mTBI is associated with structural and functional disrup-
tions of sleep circuitry and circadian rhythm. Specifically in 
the pediatric population, untreated sleep disturbance has 
been shown to delay mTBI recovery and compound other 
morbidities including neurocognitive dysfunction. Therefore, 
it was our goal to further analyze the impact sleep distur-
bance has on neurocognitive function in children recovering from a mTBI.

Methods: A retrospective chart review of 118 pediatric 
patients (mean age = 14.56 +/- 2.03 years) recovering from a 
mTBI between January 2010 and May 2019 was performed. 
Epworth Sleepiness Scale (SF-8) results were analyzed in rela-
tion to CNS Vital Signs (CNSVS) neurocognitive test out-
comes. SF-8 is a subjective estimation of a patient’s daytime 
sleepiness. CNSVS uses a multitude of domains to objectively 
evaluate the overall neurocognitive status of a patient. Pear-
son correlations were calculated using a type I error of p 
< 0.05 between variables.

Results: Epworth Sleepiness Scale (SF-8) results showed 
28.82% of participants were experiencing excessive daytime 
sleepiness sufficient enough to recommend medical attention. 
Upon further analysis, there was a significant negative corre-
lation between SF-8 and CNSVS neurocognitive test out-
comes including complex attention (r = −0.37; P = 0.0004), 
cognitive flexibility (r = −0.24; P = 0.0115), executive func-
tion (r = −0.21; P = 0.0350), and simple attention (r = −0.36; 
P = 0.0003) scores. This means as SF-8 scores increased (par-
ticipants defined as excessively sleepy), neurocognitive

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function scores in complex attention, cognitive flexibility, executive function, and simple attention decreased. There was not enough evidence to conclude a significant correlation between other CNSVS scores (composite memory, verbal memory, visual memory, processing speed, reasoning, working memory, and sustained attention) and SF-8 (all P > 0.05).

**Conclusion:** Our findings support the concern of neurocognitive dysfunction among pediatric mTBI patients with sleep disturbance. Further analysis is needed to determine if mTBI is the primary source or an exacerbating factor of sleep disturbance within this population. Nonetheless, these findings suggest a need for thorough evaluation when treating sleep concerns, irrespective of a history of childhood mTBI.

### 290. Human CTE Pathology in the Mouse: Systematic Review of the Literature and Spatiotemporal Evolution of the Histological Hallmarks in a Novel Murine Model

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**Background:** Traumatic brain injury (TBI) represents one of the strongest environmental risk factors for dementia associated with pathological accumulation of hyperphosphorylated tau (p-tau), including chronic traumatic encephalopathy (CTE) [1-4]. Although mice are frequently used to model TBI-associated pathology, concerns have been raised that mouse closed head injury models may not faithfully replicate TBI-associated pathology, concerns have been raised that mouse closed head injury models may not faithfully replicate the defining histopathological features of CTE [5]. Here we conducted a systematic review of reported CTE-like histopathology in mouse closed head TBI as well as characterized the spatiotemporal evolution of CTE-related pathology in a novel mouse repetitive TBI model.

**Methods:** Systematic review: We searched PubMed and Scopus on 2/21/2021 using search criteria that were established to be specific for mouse models of closed head injury and by focusing on studies referencing tau protein assessment, the pathological hallmark of CTE. We abstracted information on model characteristics, CTE-related pathological features according to published consensus criteria [1,2], non-specific histopathological outcomes that have been associated with CTE. Mouse study: Male C57BL/6J mice were subjected to repetitive concussive TBI (rTBI; once daily for 5 consecutive days) based on a previously described weight drop paradigm [6,7]. Histological analyses were conducted at 1 week (n=8, rTBI), 4 weeks (sham n=8, rTBI n=8), and 24 weeks (rTBI n=4).

**Results:** Systematic review: 3,756 articles were screened, 951 included for full text review, and 57 identified that investigated cerebral tau pathology. Three studies reported perivascular p-tau, a pathognomonic feature of CTE. An additional 22 studies reported p-tau in other cerebral locations and/or TDP-43 related pathology, supportive features of CTE. The most commonly reported non-specific CTE-associated histopathologies included neuroaxonal loss (53%), micro- and astrogliosis (51%, each), and beta amyloid deposition (28%).

**Mouse study:** Four and 24 weeks after rTBI there was notable accumulation of cerebral neuronal (NeuN) p-tau (AT8; perivascular, superficial cortical, subpial, subcortical nuclei) and cytoplasmic mislocalization of p-TDP-43. Astrocytic (GFAP) p-tau accumulation was restricted to the superficial layers of the cerebral cortex. Non-specific CTE-associated features included progressive neuroaxonal loss, astrogliosis, microglial activation, and microvascular injury.

**Conclusions:** Few studies reported presence of histopathological features that define CTE. Our novel mouse model replicated the defining and many associated pathologies of human CTE. Together, these observations highlight the mouse as a valid model organism to study the spatiotemporal associations between cellular pathologies as they relate to human CTE.

### 291. Focal Cooling of Concussions with Structured Recovery, Supports Best-Case Recovery After Traumatic Injury: The Brain-d’Aid™

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Focal cooling of concussions (within the first 5 minutes of injury, sustained for 24-72 hours), applied immediately and directly on focal site of injury 1. dramatically interrupts reactive inflammatory responses and 2. greatly attenuates long-term anti-inflammatory consequences, preventing anoxic necrosis (from inflammation). Application of focal cooling, combined with a structured recovery plan, can: 1. Minimize non-mechanical injuries normally found in traditional TBI treatment 2. Enhance and improve advanced development of non-injured brain areas, 3. Leading to a potentially stronger, smarter brain as 4. Cooled concussed areas regain functional dominance in overall neurocircuitries. Focal cooling of mild-moderate concussions has been routinely dismissed in the past as a suboptimal triage for concussions. The CDC website does not even mention cooling (Maguire, 2018, under review). After a concussion, an uncooled injury often deactivates both hemispheres of global brain function, leading to a wide array of debilitating symptoms lasting weeks, months, and even years. Sustained cooling should be accompanied by a structured recovery plan, based on the focal area of hit (avoid) and non-focal functional brain areas (engage). Improved function in non-injured areas of tissue serves as a recovery touchstone for damaged, promptly cooled tissue area/s. Curtailed by simplest focal cooling of 82-88 degree Fahrenheit, at the site of injury, “puts out the fire”, virtually stopping the anti-inflammatory response and cells’ memory of the injury. Cooling stabilizes injuries, allowing uninjured (un-cooled brain areas) to continue to function at relatively normal/normal levels. Sustained focal cooling after concussion leaves only mechanical damage (sheering, skin abrasions, etc) in the recovery paradigm - minimizing edema. Cooling enables the most expedient recovery and a potentially smarter, stronger brain, while empirically validated cognitive-behavioral neuroscience findings inform an individualized, structured recovery platform model, that improves in function while concussion is...
stabilized by cooling. The Brain-d’Aid™ is a simple, inexpensive, effective and convenient way to apply cooling to concussions. This product went through Business Model Development at Johns Hopkins Medical Institute and Yale SOM’s “Innovation to Impact” program in 2018. The Brain-d’Aid™ is a simple, inexpensive solution to non-hospitalized concussions (also cuts, burns, and fractures) that, similar to the common Band-d’Aid, belongs in every household, sports arena, and medicine cabinet. Focal cooling and precision structured recovery of concussive injuries represent a paradigm shift in the successful treatment of mild-moderate, non-hospitalized concussions.

434. Poor Cognitive Outcome One Year After Mild Traumatic Brain Injury: Results from the TRACK-TBI Study

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Objective: To create a clinically relevant definition of poor cognitive outcome at 1-year post-mild traumatic brain injury (mTBI) and to determine whether poor 1-year cognitive outcome can be predicted using routinely available baseline clinical variables.

Methods: We studied 672 adults (mean age 41 years) with acute mTBI (defined by Glasgow Coma Scale 13-15) enrolled in the prospective multisite trauma center-based TRACK-TBI Study. Participants underwent cognitive testing at 2-weeks, 6-months, and 1-year post-mTBI (Rey Auditory Verbal Learning Test, Trails A/B, Processing Speed Index, NIH-Toolbox). Poor cognitive outcome at 1-year was defined as cognitive impairment (1-year score <9th percentile on demographically-corrected norms on ≥2 two tests), cognitive decline (change score [best 2-week or 6-month score minus 1-year score] exceeding the 90% confidence interval of the reliable change index on ≥2 tests), or both. T-tests and chi-square tests were used to assess univariate associations of baseline factors and 1-year functional and symptom-related outcome data with poor cognitive outcome. Missing data was accounted for using propensity weighting. Backward stepwise logistic regression (alpha<0.05) was used to develop a prediction model for poor cognitive outcome.

Results: Overall, 17.3% of patients with mTBI had a poor 1-year cognitive outcome (8.9%, cognitive impairment only; 6.0%, cognitive decline with or without impairment; 2.4%, death). Compared to participants with good cognitive outcome, participants with poor cognitive outcome were older (44 years versus 40 years, p=0.034), more likely to be of black race (24% versus 16%, p=0.006), have less than high school education (16% versus 10%, p=0.002), be uninsured (30% versus 20%, p=0.001), have pre-injury depression (23% versus 13%, p=0.009), and have more severe injury on head CT (32% versus 16% with Rotterdam score≥3, p<0.001). Individuals with poor cognitive outcome reported lower rates of complete functional recovery, more post-concussive symptoms, greater psychological distress, and less satisfaction with life compared to individuals with good cognitive outcome (all p<0.05). The final prediction model included age, education, health insurance, depression, and Rotterdam score and achieved AUC=0.72 (95% CI=0.66-0.77) for discriminating patients with mTBI who had poor versus good 1-year cognitive outcome.

Conclusions: Poor cognitive outcome at 1-year post-mTBI is common, affecting nearly 1 in 5 patients. Routinely collected clinical variables predicted poor 1-year cognitive outcome with fair discrimination. These results highlight the need for better understanding of mechanisms underlying poor cognitive outcome after mTBI in order to inform precision medicine-based approaches to optimizing cognitive recovery.

435. Resilience of Arousal Mechanisms in Traumatic Coma

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Background: In patients with severe traumatic brain injury (TBI), coma is associated with impaired subcortical arousal mechanisms [1-5]. However, it is unknown which nuclei involved in arousal (“arousal nuclei”) are implicated in coma pathogenesis and are compatible with coma recovery.

Methods: We mapped a probabilistic atlas of arousal nuclei in the brainstem [6-8] (17 nuclei), thalamus [9], hypothalamus [10], and basal forebrain [9] onto 3 Tesla susceptibility-weighted images (SWI) in twelve patients with acute severe TBI who presented in coma and recovered consciousness within six months. We assessed the spatial distribution and volume of SWI microbleeds and evaluated the association of microbleed volume with the duration of unresponsiveness and functional recovery at six months.

Results: There was no single arousal nucleus affected by microbleeds in all patients. Rather, multiple combinations of microbleeds in brainstem, thalamic, and hypothalamic arousal nuclei were associated with coma and were compatible with recovery of consciousness. Microbleeds were frequently detected in the midbrain (100%), thalamus (83%) and pons (75%). Within the brainstem, the microbleed incidence was largest within the mesopontine tegmentum (e.g., pedunculotegmental nucleus, mesencephalic reticular formation) and ventral midbrain (e.g., substantia nigra, ventral tegmental area). Brainstem arousal nuclei were partially
affected by microbleeds, with microbleed volume not exceeding 35% of brainstem nucleus volume on average. Compared to microbleed volume within non-arousal brainstem regions, the microbleed volume within arousal brainstem nuclei accounted for a larger proportion of variance in the duration of unresponsiveness and 6-month Glasgow Outcome Scale-Extended scores.

**Conclusions:** These results suggest resilience of arousal mechanisms in the human brain after severe TBI.

**References:**

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436. **AMA Guides® to the Evaluation of Permanent Impairment: Achieving Equitable Impairment Ratings Through the Most Current Medicine**

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In 2019, following extensive industry feedback from physicians, state and specialty medicine societies, regulators and other industry stakeholders, the American Medical Association (AMA) initiated a program to update and modernize the AMA Guides® — the authoritative source for impairment rating information and tools.

The AMA is committed to serving stakeholders (e.g., patients, physicians, government) with fair and equitable permanent impairment ratings that can be completed promptly without undue administrative burden. By engaging the community of practice, the AMA Guides editorial process incorporates the best available science and evidence-based medicine, reflecting medical advances and new insights.

In this session, attendees will learn about the latest updates related to the AMA Guides, including the substantial modernization and simplified utilization of the new and improved AMA Guides, directly from the source. Panelists will address the importance of using the most current evidence-based medicine and how recent content updates impact impairment ratings and independent medical examinations. Topics that will be covered include mild traumatic brain injury, mental and behavioral health and more. Attendees will also be provided with more information on the educational resources available to them to help understand these changes.

437. **Mild Behavioral Impairment Domains Are Associated with Traumatic Brain Injury in All-Cause Dementia**

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**Introduction:** Traumatic brain injury (TBI) may exert lifelong neurological consequences, with growing evidence that history of TBI may increase risk of all-cause dementia (Li et al. PLOS ONE. 2017). In the context of dementia, prior TBI may play a role in the development of cognitive symptoms and neuropsychiatric symptoms (NPS), which account for substantial clinical morbidity and represent a management priority for patients and family members (Bray et al. Alzheimer’s & Dementia. 2021; Lobue et al. Neuropsychology. 2018). Despite their importance, NPS and their relation to TBI remain poorly characterized in this population. The International Society To Advance Alzheimer’s Research and Treatment (ISTAART) mild behavioral impairment (MBI) construct relates NPS based on underlying neural circuit disruptions, representing an important area of inquiry regarding TBI and dementia (Ismail et al. Journal of Alzheimer’s Disease. 2017). This construct comprises five domains: Abnormal Perception/Thought Content (delusions, hallucinations), Affective Dysregulation (depression/dysphoria, anxiety, elation/euphoria), Decreased Motivation (apathy/indifference), Impulse Dyscontrol (agitation/aggression, irritability/lability, aberrant motor behavior), and Social Inappropriateness (dissimulation).

**Methods:** Using National Alzheimer’s Coordinating Center data, individuals progressing from normal cognition to all-cause dementia over 7.6±3.0 years (range=1.0,13.4) were studied to estimate MBI incidence in 124 participants with prior TBI history compared to 822 without. Odds of MBI incidence prior to dementia diagnosis was assessed using logistic regression modeling. Looking across dementia progression (entire follow-up period), incidence of symptoms related by the MBI domains was estimated using survival analyses with Kaplan-Meier curves and Cox proportional hazard models.

**Results:** TBI was associated with greater odds of incident impulse dyscontrol (OR=1.614; p=0.037) and social inappropriateness (OR=2.374; p=0.041) prior to dementia onset. Across the time-course of dementia progression, TBI was associated with a higher incidence of MBI (any domain)
(HR=1.270; p=0.044) as well as the specific domains of decreased motivation (HR=1.734; p=0.001) and impulse dyscontrol (HR=1.372; p=0.025).

Discussion: TBI history appears to be associated with MBI during dementia progression, both prior to dementia diagnosis and throughout disease progression. Previously, the MBI construct has been used to evaluate related NPS prior to dementia onset; however, the present findings suggest the construct may have utility beyond this time-point with implications for researchers and clinicians. Understanding how TBI influences NPS development across different MBI domains may aid in elucidating underlying neuropathology in dementia progression with important clinical potential.

438. Associations of Pre-Injury Vascular Risk Factors with Traumatic Brain Injury Outcomes: A TRACK-TBI Study

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Objective: To evaluate associations of pre-injury vascular risk factor burden with traumatic brain injury (TBI) outcomes and to determine if these associations differ by age and injury severity.

Methods: Prospective study of 2,361 adults aged ≥18 years with acute TBI enrolled in the multisite trauma center-based Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) Study. Pre-injury vascular risk factors (hypertension, diabetes, hyperlipidemia, smoking) were assessed at baseline by self-report (cumulative burden categories: 0, 1, ≥2 vascular risk factors). TBI-related outcomes were assessed at 6-months post-injury. The primary outcome was the Glasgow Outcome Scale-Extended (GOSE). Secondary outcomes included the Rivermead Post-Concussion Symptoms Questionnaire (RPQ), the Satisfaction with Life Scale (SWLS), and the 18-item Brief Symptom Inventory (BSI-18). Logistic (GOSE score 1-6 versus 7-8) and linear (RPQ, SWLS, BSI-18) regression models were adjusted for demographic, socioeconomic, and injury-related factors. Formal testing for interaction by age and TBI severity was performed. Multiple imputation and propensity weighting were used to account for missing covariates and outcomes, respectively.

Results: Mean age of participants was 41 years, 31% were women, 16% were black, 77% sustained a mild TBI, 54% had 0 vascular risk factors, 35% had 1 vascular risk factor, and 11% had ≥2 vascular risk factors. Compared to individuals with 0 vascular risk factors, individuals with 1 or ≥2 vascular risk factors had worse global functional outcome on the GOSE overall, but in stratified analyses this association was only significant among individuals aged ≥40 years (OR=1.59 [95%CI=1.13-2.23] and OR=4.53 [95%CI=1.47-13.97] for 1 and ≥2 vascular risk factors, respectively) and not among individuals aged ≥40 years (OR=1.25 [95%CI=0.86-1.81] and OR=1.05 [95%CI=0.67-1.64] for 1 and ≥2 vascular risk factors, respectively, p-interaction-by-age=0.013). A higher burden of vascular risk factors was associated in a dose-dependent manner with more TBI-related symptoms (RPQ), lower satisfaction with life (SWLS), and greater psychological distress (BSI-18), all p-for-linear-trend<0.001. Associations with RPQ and BSI-18 scores were stronger among individuals with mild versus moderate/severe TBI (RPQ p-interaction-by-severity=0.006, BSI-18 p-interaction-by-severity=0.041). Associations with BSI-18 score were also stronger among younger (≤40 years) versus older (>40 years) individuals (p-interaction-by-age=0.004).

Conclusions: A higher burden of pre-existing vascular risk factors was associated with worse TBI outcomes in a dose-dependent manner and these associations were stronger among younger individuals and individuals with mild TBI. Aggressive treatment of vascular risk factors may be a promising strategy to improve TBI outcomes.


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Background: Concomitant traumatic brain injury (TBI) is relatively common among individuals with acute traumatic spinal cord injury (tSCI), but the potential effects of TBI on the outcomes post-tSCI remain understudied. This study examined the potential effects of concomitant TBI on clinical, neurological and functional outcomes at 1 year following acute tSCI.

Methods: This retrospective cohort study included all 499 individuals who were enrolled in the Third National Spinal Cord Injury Study (NASCIS-3). TBI was defined as a Glasgow coma score below 15 at admission. Individuals with dual diagnosis (tSCI+TBI) were compared with the individuals with tSCI alone regarding survival, and neurological and functional outcomes within the first year post-tSCI. Survival was analyzed using Kaplan-Meier curve and log-rank test. Data were analyzed using multiple regression models adjusted for the major potential confounders.

Results: There were 76 females and 423 males with mean age of 35.7 years (range age of 14 to 92 years) who were grouped into individuals with tSCI (n=413) and individuals with tSCI+TBI (n=86) who were admitted in an acute care facility with an initial GCS between 10 and 14. Both groups were comparable regarding age (p=0.7101) and sex distribution (p=0.6207). However, the dual-diagnosis group had higher proportion of complete (p=0.0059) and cervical tSCI (p=0.0031) and more often received 48-hour methylprednisolone treatment (p=0.0384) than tSCI-only group. There
was no significant difference between the groups regarding survival post-SCI (p=0.7676). Among the survivors, the dual-diagnosis group showed significantly lower neurological scores and functional scores at 1 year post-tSCI than the tSCI-only group. After adjusting for the major potential confounders, neurological outcomes (motor, sensory and pain scores) and functional outcome (total FIM score) at 1 year post-tSCI were not significantly affected by the concomitant TBI.

Conclusions: Individuals with tSCI+TBI had more severe tSCI and more often sustained cervical tSCI that resulted in less favorable neurological and functional outcomes than individuals with tSCI alone. Nevertheless, the coexistence of TBI and tSCI did not appear to intrinsically affect their survival, and neurological and functional recovery within the first year after trauma when data analyses were adjusted for major confounders.

440. Epigenetic Regulation of ABCC8 and TRPM4 is Associated with Intracranial Hypertension and Outcome After Severe TBI
Ruchira Jha, MD, MSc. Neurology, Barrow Neurological Institute, Phoenix, AZ, USA.

Introduction: SUR1-TRPM4 is a key channel that mediates secondary injury pathophysiology after traumatic brain injury (TBI). Genetic variation within ABCC8 (SUR1) and TRPM4 is associated with TBI intracranial hypertension, hemorrhage progression and outcome, with several significant polymorphisms influencing brain-specific expression of these genes. Epigenetic regulation of SUR1-TRPM4 remains unexplored and may alter gene expression in key pathways after TBI. We assessed associations between ABCC8 and TRPM4 DNA methylation, intracranial hypertension, and outcome in severe TBI.

Methods: 120 severe TBI (Glasgow Coma Scale [GCS] score ≤8) patients aged 16-80 were enrolled. Cerebrospinal fluid (CSF) was collected on days 1, 3, and 5 (368 samples) via external ventricular drain. DNA was extracted from CSF white blood cells and methylation was assessed (Illumina HumanMethylation450k bead chips), including DNA methylation at 29 sites in ABCC8 and TRPM4. 17 (4.6%) samples were removed after quality control. Multivariable linear regression models tested for associations between methylation and 3-month Glasgow Outcome Scale (GOS) score and proportion of hourly intracranial pressure (ICP) readings ≥25 mmHg for each patient (α=0.0009, Bonferroni). Models were adjusted for age, sex, GCS, and surrogate variables accounting for cell-type heterogeneity and batch effects (logFC calculated with M-values).

Results: Increased methylation on day 1 at two sites within the TRPM4 gene was associated with higher GOS score (improved outcome) at 3-months: cg16749456 (logFC=0.444, p=0.0001) and cg14325661 (logFC=0.250, p=0.0008). Increased methylation of one site within the 5’UTR of the ABCC8 on day 1 was associated with lower GOS score (worse outcome) at 3-months (cg13851843: logFC=-0.254, p=0.0006). Increased methylation on day 3 at an additional CpG site within TRPM4 was associated with a lower proportion of ICP measurements ≥25 mmHg (cg21520111: logFC= -1.214, p=0.0007).

Conclusions: In this exploratory study, DNA methylation of two sites in TRPM4 was associated with improved functional outcome, and methylation of a third site was associated with less intracranial hypertension. In our prior reports, protective variant TRPM4 polymorphisms decreased TRPM4 mRNA expression which is directionally consistent with these methylation data. In contrast, DNA methylation of a site in ABCC8 was associated with worse outcome. Epigenetic regulation may modulate expression of the SUR1-TRPM4 channel in the brain after severe TBI. Further studies validating these findings and investigating their molecular consequences are needed and might ultimately inform risk-stratification, prognostication, and precision management after severe TBI.

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Introduction: Early hypotension following moderate-severe traumatic brain injury is associated with increased mortality and worse long-term outcomes. Current guidelines support the use of intravenous vasopressors to maintain optimal blood pressure control and improve outcomes for patients; however, guidelines do not specify vasopressor type, resulting in variation in clinical practice. Existing studies comparing the utilization and efficacy of different vasopressors vary in their results. Therefore, we conducted a multicenter study to examine utilization patterns of different vasopressors in the management of early hypotension following TBI and their association with long-term clinical and functional outcomes.

Methods: In this retrospective cohort study of patients enrolled in the TRACK-TBI study, we examined adults with moderate-severe TBI (defined as Glasgow Coma Scale score <13) who were admitted to the ICU and received an intravenous vasopressor within 48 hours of admission. We excluded patients who received more than vasopressor in the first hour of admission. The exposure was initial vasopressor choice (phenylephrine versus norepinephrine) and the primary outcome was 6-month Glasgow Outcomes Scale Extended (GOSE), with secondary outcomes of length of hospital stay, length of ICU stay, in-hospital mortality, requirement of dialysis, and 6-month Disability Rating Scale (DRS). Regression analysis was used to assess differences in outcome between norepinephrine and phenylephrine, with propensity-weighting to address selection bias due to both the non-random allocation of the treatment groups and subject drop-out.

Results: The final study sample included 157 patients, of whom 79 (50%) received norepinephrine and 66 (42%) received phenylephrine as their initial vasopressor. 121 (77%) received an initial vasopressor other than norepinephrine and phenylephrine. Of all subjects, 73 (54%) received a second vasopressor after at least one hour following administration of the first vasopressor, most commonly phenylephrine. Choice of norepinephrine versus phenylephrine was not significantly associated with improved 6-month GOSE (weighted odds ratio 1.38, 95% CI 0.72-2.64, p=0.37) or any secondary outcome.

Conclusions: Most patients with moderate-severe TBI commonly receive either phenylephrine or norepinephrine as first-line agents for hypotension following brain injury, with significant variability among hospitals. Initial choice of norepinephrine, compared to phenylephrine, was not associated with improved clinical or functional outcomes.

LB-468. Alternatively Activated Neutrophils are Capable of Promoting Axon Regeneration
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Background: Axonopathy is an early and prominent pathological feature of optic neuritis, multiple sclerosis (MS), and traumatic central nervous system (CNS) injury. Although neuroinflammation is believed to be a driver of damage in traumatic CNS injury, MS and other neurological conditions, animal model studies have shown that certain immune cell subsets can have neuroprotective and reparative effects. The optic nerve crush (ONC) model is a well-established animal model of immune driven CNS repair after traumatic injury. Normally retinal ganglion cell (RGC) axons do not regrow following crush injury. However, robust axonal regeneration ensues in association with zymosan induced intravitreal inflammation consisting primarily of infiltrating myeloid cells.

Methods: Intravitreal inflammatory cells were harvested at serial time points following i.o. zymosan/ ONC for analysis by flow cytometry. Primary retinal ganglion cells (RGC) were co-cultured with immune cell subsets purified from the intraocular infiltrates, or with immune cell subset conditioned media (CM). After 24 hours, RGC neurite outgrowth was measured by staining with antibodies specific for TuJ-1. In separate experiments, purified immune cells were adoptively transferred into the eyes of mice after ONC injury. Optic nerves were collected 14 days later and axonal density was measured at serial distances from the crush site via anti-Growth Associated Protein (GAP)-43 immunohistochemistry.

Results: We found that Ly6G+ neutrophils are the predominant constituent of zymosan-elicited i.o. infiltrates. Furthermore, we identified a novel subset of Ly6Glow CD14+ neutrophils in the infiltrates that correlate with the extent of RGC axon regeneration. Ly6Glow neutrophils recruited arginase (Arg)+ CD206+ monocytes to the vitreous fluid and stimulated axon regeneration in vivo. We are able to selectively deplete these arg+ CD206+ monocytes in an Arg-DTR mouse which then prevents robust regeneration. Ly6GlowCD14+ neutrophils, Arg+ monocytes, or their CM, directly stimulated RGC neurite outgrowth in vivo. The pro-regenerative properties of the CM is at least partially mediated by production of neurotrophic factors.

Conclusion: A novel subset of Ly6Glow-CD14+ neutrophils is capable of driving the regeneration of transected CNS...
axons. These cells recruit Arg+ monocytes to the eye and work together to promote axon regeneration. These myeloid cells secrete pro-regenerative neurotrophic factors, and can be selectively depleted with an Arg-DTR mouse. Our findings may ultimately lead to the development of novel immunomodulatory drugs, or the repurposing of immunomodulatory drugs already in clinical use or development, to promote the differentiation and expansion of neuroregenerative neutrophils in patients with conditions characterized by axonopathy.
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