Restricted expression of transgene to astrocytes in the central nervous system following systemic injection with a novel self-complementary AAV9 vector

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Abstract: We previously demonstrated that expression of the $\epsilon_2$ allele of human apolipoprotein E via intraventricular injection of adeno-associated virus (AAV) serotype 4 can reduce pathological processes in transgenic mouse models of Alzheimer’s disease including slowing down the progression of amyloid deposition and alleviating neurotoxicity \textit{in vivo}. As an alternative preclinical approach to further enhance the safety and efficacy of this strategy, we engineered a novel self-complementary AAV serotype 9 (scAAV9-GFA') designed to drive expression of transgene specifically in astrocytes after peripheral intravascular infusion. Intravenous delivery of scAAV9-GFA’ encoding green fluorescent protein led to robust and long-lasting transduction of astrocytes throughout the entire central nervous system, in the absence of neuronal transduction or more than trivial levels of peripheral expression of the transgene. scAAV9-GFA’ led to transduction of approximately 10\% of cortical astrocytes, two orders of magnitude higher levels than the comparable traditional single-strand AAV9 serotype. Reporter gene was expressed in both GFAP activated and resting astrocytes. \textit{In vivo} expression of GFP in the CNS after peripheral intravenous delivery of scAAV9-GFA’ was demonstrated by 2-photon laser scanning microscopy. These data suggest the potential of scAAV9-GFA’ as a system to drive expression of therapeutic genes specifically in astrocytes of the CNS.
Presentation Title: One-year follow-up of a case of Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE) responding to transdermal nicotine.

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Abstract: ADNFLE is a hereditary form of epilepsy characterized by multiple seizures during stage 2 sleep. It is caused by different mutations involving the alpha-2, alpha-4 or beta-2 nicotinic acetylcholine receptor (nAchR) subunit genes. The net effect of these mutations, is increased activity of the nAchRs. Carbamazepine or oxcarbazepine are effective first-line agents. However, up to one third of patients have refractory seizures. Nicotine, which ultimately blocks nAchRs, is an effective and well-tolerated alternative treatment. In this abstract, we discuss the clinical, neurophysiological and pathophysiological aspects of a case of multi-drug refractory ADNFLE responding to transdermal nicotine, with a one-year follow-up.

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Assessing the Role of Cultural Perceptions and Knowledge of Epilepsy on Medication Adherence in a Multi-Ethnic Epilepsy Clinic: A Pilot Study

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Objective: The aim of this study is to investigate the influence of cultural perceptions and knowledge of epilepsy on medication adherence in a multi-ethnic epilepsy population.

Background: Anti-epileptic drugs (AEDs) offer seizure control for over 70% of patients with epilepsy. Despite the efficacy of AEDs, non-adherence has been reported in 33-67% of patients. There is considerable misinformation about epilepsy, which may account for the high prevalence of non-adherence amongst patients. At BMC there is much cultural diversity, which in itself may influence patient adherence.

Design: A pilot study was conducted over 6 weeks using a unique 40-item survey addressing beliefs, knowledge of epilepsy and medication adherence. It was administered in English, Spanish, Haitian Creole, and Portuguese versions to 148 patients of a diverse epilepsy clinic. Spanish, Haitian Creole and Portuguese survey responses were analyzed together due to a small sample size (n=30, n= 8 and n=8, respectively). English speakers’ responses (n=102) were compared to non-native English speakers (n=46) to assess for discrepancies in knowledge of epilepsy and medication adherence.

Results: We achieved a 70% survey response rate from 216 possible survey participants. There were lower rates of medication knowledge in Non-native English speakers compared to controls (M=0.58 vs. 0.70, p <0.05). Cultural perceptions of epilepsy differed significantly, with 33% of non-native English speakers incorrectly identifying false statements such as ‘epilepsy is caused by evil spirits’ (p <0.05). Patients with correct responses to epilepsy knowledge questions were more likely have higher adherence scores.

Conclusions: We found that adherence scores were lower in non-native English speakers than controls. This may be due to differences in cultural perceptions of epilepsy. This discrepancy affords us the opportunity to improve medication adherence by addressing misconceptions with educational interventions. This pilot study demonstrates the need for further investigations amongst the ethnic groups studied.
Presentation  Differential Blinking Rates as a Function of Handedness: Serendipitous Findings from a Study of the Evoked P300 Potentials Recordings

Title:  

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Abstract:  Electroencephalography (EEG) is a recording of the electrical activity of the brain using scalp electrodes, widely used clinically and in neurocognitive research. EEG signal is subject to eye blink artifacts. Eye blinks are protective to the eye, and their rate is known to be controlled by dopaminergic pathways in the brain. In this study, a number of different subject-specific and experimental factors were analyzed with a purpose of reducing the amount of eye blink artifacts during the recordings of P300 evoked potentials. Significantly lower blinking rates in left-handed individuals (N=16) compared to right-handed ones (N=30) were found during these recordings (p-value = 1.4e-7). This finding, previously unreported in literature, was also robust when study participants were grouped by gender (p-value for males = 7.3e-7 and p-value for females = 9.7e-3). Based on this finding, an epidemiologic study was performed using the Michael J. Fox Foundation’s PPMI database for the study of Parkinson’s disease (PD) to investigate whether there was a relationship between person’s handedness and the side of the body, in which they develop dominant PD symptoms. Based on the database’s data, no significant relationship was found (odds ratio 95% confidence interval 0.59-1.83). For the future work, it may be useful to attempt replicating blinking rate variation with handedness in a large sample of study participants. If confirmed, this variation will be an important factor in the design of the dopaminergic medications trials, in which blinking rates are used to quantify the medications effects.
Presentation Title: The UNITE Study: Understanding Chronic Traumatic Encephalopathy through Clinicopathological Correlation: Methods & Instructive Case.

Authors: LMurphy¹, JMez¹, M.D., TSolomon¹, Ph.D., DDaneshvar¹, M.S., PKiernan¹, PMontenigro¹, NKowallis¹, M.D., DKatz¹, M.D., RStern¹, Ph.D., RCantu¹, M.D., JKriegel¹, BAbdolmohammadi¹, TStein¹, M.D./Ph.D., VAlvarez¹, M.D, AMcKee¹, M.D. Boston University School of Medicine¹ & VA Boston², Boston MA.

Abstract: Background: The UNITE study examines the clinical and neuropathological features of brain donors “at risk” for chronic traumatic encephalopathy (CTE).

Methods: Clinical data was collected through retrospective family interviews and medical record review on 200 deceased subjects exposed to repetitive brain trauma through sports or military service. Neuropathological diagnoses were made using previously published criteria (McKee 2013). Clinicians and neuropathologists were blinded to pathological and clinical data respectively. An expert panel subsequently reviewed the clinical summary and came to a consensus diagnosis using the provisional clinical research criteria for CTE (Montenigro 2014). The pathological findings were presented and clinicopathological correlations were reconciled.

Results and Conclusions (Exemplary Case): An 82 y.o. man who played American football for sixteen years including nine years in the NFL had a progressive disease course that included memory, executive function and visuospatial deficits beginning in his mid-sixties, functional impairment beginning in his early seventies and severe dementia prior to death. While the clinical consensus diagnosis for the case was Alzheimer’s disease (AD), the case met pathological criteria for only CTE (Montine 2012). This case suggests that some cases of CTE can present with clinical features strikingly similar to AD.
Presentation Title: Expression of the FSHD-associated DUX4-FL protein alters proteostasis and leads to aggregation of TDP-43 and DUX4-FL itself.

Authors: Sachiko Homma¹, Mary Lou Beermann¹, Frederick M. Boyce², and Jeffrey Boone Miller¹. ¹ Department of Neurology, Boston University School of Medicine ² Massachusetts General Hospital

Abstract: OBJECTIVE: Our goal was to identify mechanisms of pathogenesis caused by expression of the FSHD (facioscapulohumeral muscular dystrophy) -associated DUX4-FL protein. BACKGROUND: Pathogenesis in FSHD appears to be due to aberrant expression, particularly in skeletal muscle nuclei, of the full length isoform of DUX4 (DUX4-FL). Expression of DUX4-FL is known to alter gene expression and to be cytotoxic, but cell responses to DUX4-FL are not fully understood. DESIGN/METHODS: We used human myogenic cell cultures to analyze the effects of DUX4-FL when it was expressed either from its endogenous promoter in FSHD cells or by exogenous expression using BacMam vectors. We focused on protein ubiquitination and turnover and on aggregation of TDP-43 and DUX4-FL itself. RESULTS: Human FSHD myotubes with endogenous DUX4-FL expression showed both altered nuclear and cytoplasmic distributions of ubiquitinated proteins and aggregation of TDP-43 in DUX4-FL-expressing nuclei. Similar changes were found upon exogenous expression of DUX4-FL, but were not seen upon expression of the nontoxic short isoform DUX4-S. DUX4-FL expression also inhibited protein turnover in a model system and increased the amounts of insoluble ubiquitinated proteins and insoluble TDP-43. Insoluble DUX4-FL also accumulated. Inhibition of the ubiquitin-proteasome system produced TDP-43 aggregation similar to DUX4-FL expression. CONCLUSIONS: Our results identify DUX4-FL-induced inhibition of protein turnover and aggregation of TDP-43, which are pathological changes also found in diseases such as amyotrophic lateral sclerosis and inclusion body myopathy, as potential pathological mechanisms in FSHD.
Presentation Title: Improving Resident Performance in Acute Stroke Management Through Simulation Based Training

Authors: Jami Johnsen MD, Luciana Catanese MD, Judith Clark RN BSN, Julie Grimes MD, Benjamin Saunders MD, Pamela Corey RN MSN and Hesham Masoud MD (1. Department of Neurology, Boston University; 2. Solomont Clinical Simulation and Nursing Education Center, Boston Medical Center)

Abstract:

OBJECTIVE: To improve Neurology resident knowledge and confidence in the early management of acute stroke.

BACKGROUND: While the American Stroke Association provides best practice guidelines for achieving door-to-needle (DTN) times under 60 minutes and emphasizes a team based approach, they do not delineate a strategy for educating Stroke team members on acute stroke management and interdisciplinary collaboration. To this end, we designed an innovative simulation-based acute stroke curriculum for Neurology residents, who are among the initial responders when a stroke code is activated.

DESIGN/METHODS: Prior to simulation training each resident completed an online NIHSS certification. Each individual resident completed a simulated stroke code, while others observed via a live video feed to facilitate group discussion. Debriefing sessions after each case included resident self-assessment, communication skills, Get With the Guideline targets, NIHSS performance, t-PA eligibility, stroke mimics, interpretation of imaging, blood pressure control, and intracerebral hemorrhage management. Residents completed surveys and multiple-choice exams before and after simulation to assess confidence and knowledge of acute stroke management.

RESULTS: After simulation training, residents felt more comfortable with their knowledge base and ability to manage acute strokes. Residents enjoyed the experience and wanted more simulation sessions. Medical knowledge as assessed by pre and post intervention multiple-choice test scores improved though it was not statistically significant.

CONCLUSIONS: Simulation training is a welcome addition to traditional lecture based education with subjective and objective improvements in resident knowledge and confidence. Further study is needed to see if gains are maintained throughout the year and if patient outcomes are improved. Interdisciplinary simulation training with ER physicians and nurses may enhance teamwork during acute stroke codes.
Poster Text:

Objective:
To improve resident medical knowledge and confidence in the early management of acute ischemic stroke, with a focus on compliance with the American Heart Association/ASA Get With The Guidelines-Stroke in-hospital program.

Background:
The American Stroke Association (ASA) advocates reducing door to needle (DTN) times in IV t-PA eligible acute stroke patients to under 60 minutes as shorter DTN times are associated with improved patient outcomes.

At Boston Medical Center in 2013-2014, we met the goal of DTN < 60 minutes in 56% of acute ischemic stroke cases in the ER. Performance improved over the academic year with 80% of ER patients achieving a DTN time of < 60 minutes between April and June 2014 compared to only 55.6% between July and September 2013. This improvement highlights the importance of experience by the Stroke team, which has a high turnover of members on an annual basis.

While the ASA provides best practice guidelines, they do not delineate a strategy to educate members of the Stroke team in regards to acute stroke management and interdisciplinary collaboration. To this end, we designed an innovative simulation-based acute stroke curriculum for Neurology residents, who are among the initial responders when a stroke code is activated.

Design/Methods:
• The Model for Improvement was used as guidance. The initial Plan-Do-Study-Act cycle focused on the content and quality of the curriculum as assessed by subjective and objective changes in resident knowledge and confidence in acute stroke management.
• Measures:
  • Resident scores on a survey assessing subjective competence and comfort in acute stroke management
  • Resident scores on a multiple-choice test assessing knowledge in acute stroke management
  • Change
  • Creation of a simulation-based curriculum for acute stroke management
•Simulation sessions occurred in August 2014 with residents divided by PGY level
•Sessions were facilitated by 2-4 senior Neurology residents, the Stroke nurse, and a Vascular Neurology attending, all of whom underwent simulation facilitation and debriefing training
•Prior to the Simulation session, residents:
  •Completed an online National Institutes of Health Stroke Scale (NIHSS) Certification
  •Reviewed the departmental acute stroke protocol
  •Completed pre-simulation survey and exam
•During the Simulation session:
  •Each resident completed a simulated trauma bay assessment of a potential acute stroke case while the other residents watched via live video feed. Senior neurology residents performed role of standardized patient and ER staff.
  •Debriefing sessions after each case covered resident self-assessment of performance, communication skills, Get With the Guideline targets, performance of NIHSS, assessing for t-PA eligibility, identifying stroke mimics, ordering and interpreting imaging, managing blood pressure, and managing intracerebral hemorrhage
•After the Simulation session, residents:
  •Completed post-simulation survey and exam
  •Reviewed answers of the multiple-choice exam

Results:
All surveys done on a 5 point Likert scale with 1-5 representing strongly disagree, disagree, neutral, agree and strongly agree, respectively.
•Survey:
  •Prior to Simulation training, PGY-2 residents more than PGY-3 residents felt that they lacked stroke knowledge, particularly for differential diagnosis of a focal neurological deficit, identification of stroke mimics, contraindication for administering t-PA, and interpretation of CT scans. PGY-2 residents also felt more uncomfortable responding to and leading a stroke code [FIGURE 1]
  •After Simulation training, all residents felt that their knowledge and comfort with acute stroke management increased but only PGY-2 residents felt more confident leading a stroke code. All residents enjoyed the experience and wanted more simulation sessions [FIGURE 2].
•Exam:
  •Median PGY-2 scores increased 4% (n=6) [FIGURE 3]
  •Median PGY-3 scores increased 11.4% (n=7) [FIGURE 3]
Conclusions
• Simulation training is a welcome addition to traditional lecture based education
• It improved subjective resident knowledge and confidence with the greatest benefit in more junior residents
• It increased residents knowledge although results were not statistically significant in the view of the very small population samples. Larger studies are needed to confirm findings.

Next Steps:
• At three months, residents will complete another survey and exam to assess impact of simulation training on their clinical practice as well as knowledge retention. DTN times will also be reviewed to see if the change in curriculum affected patient outcomes.
• The curriculum will be repeated later in the academic year with new patient scenarios including more challenging cases for more senior residents. The debriefing sessions will be modified to address deficiencies identified by the resident survey and exam. Additional metrics to assess improvement such as a survey of ER staff on neurology resident performance during strokes codes will be added.
• An interdisciplinary curriculum for acute stroke management to be used by Neurology and Emergency Medicine residents as well as nursing will be created to enhance teamwork in the trauma bay.
Body Weight and Survival after Stroke: Exploring the Obesity Paradox in the Framingham Study

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**Abstract:**

OBJECTIVE: We sought to characterize how body weight affects mortality after stroke; we compared these results to mortality in control participants without stroke.

BACKGROUND: Several studies have shown that increased body mass index (BMI) may improve, rather than worsen, survival after stroke, a finding termed the “obesity paradox”.

DESIGN: Framingham Study participants who had BMI measured at a study exam within five years preceding a stroke were analyzed, categorized as normal weight (BMI 18.5-25), overweight (BMI 25-30) or obese (BMI >30). Non-stroke control participants were 3:1 matched by age, sex, and BMI. A multivariable Cox proportional hazards model adjusted for age, sex, time between the study exam and event date, education, marital status, and smoking, with mortality as the outcome.

RESULTS: There were 677 participants with stroke and 2031 control participants. Compared to the normal weight group, overweight participants had significantly decreased mortality at 10 years of follow up (HR=0.70, 95% CI 0.54-0.89, p=0.004). Further subgrouping of BMI showed decreased mortality in the mildly obese with BMI 30-32.5 (HR=0.60, 95% CI 0.42-0.86, p=0.005), but not in the very obese, BMI>32.5. No effect was seen in controls. Stroke cases age <70 with BMI>25 had better survival than normal weight participants with stroke below that age (HR=0.52, 95% CI 0.34-0.80, p=0.003).

CONCLUSIONS: In the Framingham Study, overweight and obese participants (but not the very obese) had better 10-year survival after stroke than normal weight participants with stroke. Further research is needed to understand how unmeasured factors in the obesogenic environment, specifically at a younger age, influence mortality after stroke.
Background: Several cases of parkinsonism in association with basal ganglia calcifications and hypoparathyroidism have been described. Reports have demonstrated parkinsonism in association with primary and secondary hypoparathyroidism, pseudohypoparathyroidism, and even hyperparathyroidism. We add to this collection a case illustrating autonomic dysregulation as a prominent component in the clinical picture of parathyroid deficiency associated with parkinsonism.

CASE: An 82 year-old woman was referred to our neurology clinic after a syncopal episode. She described having fainting spells since childhood. Past medical history was significant for chronic idiopathic hypoparathyroidism and parkinsonism. She had evidence of orthostatic hypotension, decreased facial expression, mild resting tremor, and slow shuffling gait. A head CT scan revealed extensive white matter calcification in the basal ganglia and dentate nucleus of the cerebellum. Treatment with compression stockings and hydration was advocated and fludrocortisone was initiated for blood pressure stabilization. The patient reported symptom improvement.

DISCUSSION:
The underlying mechanism for this parkinsonism with autonomic dysfunction may be a disruption of the motor projections through the autonomic control centers. The disruption may be direct due to stress on the system from the calcium deposits themselves, or indirect due to the chemical impact of the changes on calcium
Presentation Title: Cefepime Induced Neurotoxicity: A Case Series and Review of the Literature

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Abstract: Cefepime is a broad-spectrum bactericidal. Neurotoxicity has been reported most commonly in patients with acute renal failure. The most frequently reported signs include: myoclonus, seizures, hallucinations and confusion.

We present 3 cases of cefepime induced neurotoxicity in whom diagnosis were made after excluding other common etiologies of altered mental status.

In one patient, neurotoxicity manifested by new onset of progressive expressive aphasia which was seen within 4 days of initiating treatment and was not reported at the time of initial presentation. Two patients demonstrated asynchronous myoclonic activity of the limbs. The symptoms were seen within 4 days of initiating the treatment. The symptoms resolved completely within three days of discontinuation of cefepime. Acute structural abnormalities were excluded by CT and MRI of the head. EEG showed diffuse slowing activity with triphasic waves consistent with encephalopathy. In one patient renal function was within normal limits, whereas it was abnormal in two patients.

Neurotoxicity is a known but probably an underreported side effect of cefepime especially in patients with normal renal function. To our knowledge, this is the first report of cefepime induced asynchronous myoclonus and expressive aphasia in a patient with normal kidney function. Recognizing cefepime induced neurotoxicity could be challenging given accompanied confounding causes of encephalopathies in acute care settings. We should maintain a heightened index of suspicion in patients with renal and hepatic impairments, even when cefepime is dosed appropriately. Cefepime neurotoxicity is almost always reversible after discontinuation of the medicine.
**Presentation Title:** Labyrinthine Hemorrhage: An Unusual Etiology of Peripheral Vertigo

**Authors:** Simy Parikh, MD and Samuel Frank, MD

Boston University School of Medicine, Department of Neurology, Boston University.

**Abstract:** Labyrinthine hemorrhage is a rare etiology of peripheral vertigo that is characterized by a combination of acute-onset sensorineural hearing loss and vestibular symptoms. A 65-year-old male presented with a two-week history of gradually worsening vertigo, associated with nausea, vomiting, and acute-on-chronic left-sided hearing impairment. The neurological exam was notable for spontaneous horizontal nystagmus with fast beats to the right regardless of gaze direction and no gait impairment. These features suggested a peripheral cause of vertigo. Pre-contrast, high-resolution MRI imaging, with dedicated images through the temporal bones, demonstrated an absence of CSF flow signal and an increased T1 signal in the left cochlea, vestibule, and semicircular canals. Audiogram testing showed profound mixed conductive and sensorineural pure tone loss. These findings were consistent with labyrinthine hemorrhage. The patient was treated with lorazepam as needed, with improvement of vertigo. He also completed a seven-day prednisone taper for management of sensorineural hearing loss. A two-month follow-up audiogram showed improvement in air and bone conduction responses, and the patient reported a subjective return to baseline hearing. This case illustrates that labyrinthine hemorrhage should be included in the differential diagnosis of peripheral vertigo, especially in the setting of dual sensorineural hearing loss and vestibular symptoms. Recognition of this uncommon syndrome is essential for implementing appropriate therapy.
**Presentation Title:** Comprehensive Opportunities for Research and Teaching Experience (CORTEX): A Mentorship Program

**Authors:** José Rafael P. Zuzuárregui, MD\(^1\) and Anna D. Hohler, MD\(^1\)

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**Abstract:**

**Objective:** We developed a program to promote medical student interest in pursuing a career in Neurology. This program focuses on medical student mentorship. It also provides opportunities in teaching and clinical research in order to provide students with marketable skills for an academic career in Neurology.

**Methods:** Through this program, students are provided with guidance in developing a fourth year clerkship schedule and an application package for residency programs. Students are involved and mentored in clinical research. Opportunities are also provided for students to teach their peers, with sessions focusing on examination preparation.

**Results:** Since the implementation of this program in 2010, the number of students entering into the field of Neurology from our institution significantly increased from fourteen students between 2006 and 2010, to thirty students between 2011 and 2014 (p < 0.05). Medical student research productivity increased from seven publications during 2006 to 2010, to twenty-two publications, fourteen poster presentations and a book chapter after implementation of this program in 2010 (p < 0.05).

**Conclusions:** In this mentoring program, students are prepared for residency application and provided with research and teaching opportunities. Students develop a highly desirable academic skill set for residency and have matched at top ranked institutions. This program has been successful in improving student productivity in clinical research and garnering student interest in Neurology.
Presentation Title: Ehlers-Danlos Syndrome and Postural Tachycardia Syndrome: a relationship study

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Affiliations: Boston University School of Medicine

Abstract: Objective: This study examines a possible relationship between Ehlers-Danlos Syndrome (EDS) and Postural Tachycardia Syndrome (POTS).

Design/Methods: We retrospectively reviewed 109 medical records of patients suffering from autonomic dysfunction exhibiting at least one POTS symptom from one urban clinic for EDS and POTS diagnoses between 2006 and 2013. The prevalence of EDS within the POTS and non-POTS populations were calculated and compared to that of the general population.

Results: The review revealed 39 (36F:3M) patients with POTS (mean±SD age, 32.5±11.8 years) with 7 cases of EDS yielding a prevalence of 18% (95% exact CI: 8%, 34%), a statistically significant difference from the suggested prevalence of EDS in the general population of, 0.02% (p<0.0001). 70 patients (53F:17M) without POTS (mean±SD age, 51.1±14.7 years) contained 3 cases of EDS, yielding a prevalence of 4% (95% exact CI: 1%, 12%), a statistically significant difference from the general population (p<0.0001). The prevalence of EDS was significantly higher in the POTS group compared to the non-POTS group (p=0.0329). The odds ratio comparing the odds of EDS for POTS versus non-POTS patients is 4.9 (95%CI: 1.2, 20.1).

Conclusion: The prevalence of EDS is significantly higher in patients with POTS than that of the general population and in autonomic patients without POTS. We suspect an additional underlying mechanism of POTS caused by EDS.
Presentation Title: Gastrointestinal complaints in postural orthostatic tachycardia syndrome

Authors: Karen Morgensthern¹, Collin J. Culbertson¹, Liz B. Wang¹, Anindita Deb MD², Anna DePold Hohler MD²

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Abstract: BACKGROUND: Postural orthostatic tachycardia syndrome (POTS) is a dysautonomia associated with systemic symptoms, including chronic gastrointestinal (GI) symptoms. Previous studies in POTS patients have identified common GI complaints and shown abnormal gastric electrical activity and gastric emptying, but the full spectrum of GI symptoms remains unclear.

METHODS AND RESULTS: Surveys were given to 28 patients with POTS at Boston Medical Center. This included 30 questions describing GI symptoms on a Likert scale. Symptoms were considered positive if answered “strongly agree” or “agree.” The most commonly reported GI symptoms were nausea (86%), irregular bowel movements (71%), abdominal pain (70%), constipation (70%), heartburn (64%), abdominal cramping (61%), and bloating (59%). 82% of patients reported symptoms more than once per week, and 71% of patients reported symptoms lasting for at least a few hours. The majority of patients (61%) had seen a GI specialist, but a minority reported a diagnosis of irritable bowel syndrome (32%) or inflammatory bowel disease (7%). Twelve patients reported undergoing a gastric emptying study, which was positive for gastroparesis in six patients.

CONCLUSIONS: Subjective GI disturbance is common in POTS patients, and these symptoms are not necessarily related to primary GI pathology. Symptoms are frequent and prolonged, likely decreasing quality of life. Given the importance of autonomic input to normal GI function, the same autonomic impairment that leads to postural tachycardia also affects the enteric nervous system, leading to gastroparesis, abnormal gut motility, and esophageal reflux. Further studies correlating subjective symptoms with objective abnormalities of GI autonomies are needed.
Presentation Title: Ultrasound simulation training for the identification of spinal anatomy and preparation for ultrasound-guided lumbar puncture.

Authors: Savino, Anthony MD., Hohler, Anna MD., Leo, Meghan MD., Genthon, Alissa MD., Pavlakis, Pantelis MD., Janakiraman, Venkatesh MD., Weinberg, Janice ScD.

Abstract:

Objective: Studies through multiple disciplines have shown benefit of ultrasound-guided lumbar puncture, particularly in identification of spinal landmarks and obese patients. Our simulation training sessions were designed to assess benefit of ultrasound guidance and introduce ultrasound techniques for use in further study.

Methods: 2 groups comprised of resident, fellow and attending physicians from varying disciplines. Pre-surveys and tests were completed. Then participants were asked to identify 2 interspaces and midline by palpation. Accuracy was compared with marks made by 2 physicians with ultrasound training. Participants were given a lecture about basic ultrasound technique and the lumbar puncture procedure. Participants then attempted identification using ultrasound. Procedural measures included: time and proximity to landmarks. Post-training measurements: comfort level, utility of ultrasound during lumbar puncture and future interest.

Results: 60% had performed more than 10 lumbar punctures. Less than half had used ultrasound before and in general participants were uncomfortable using ultrasound, 35%, and identifying spinal anatomy, 4%, before training with improvement to 91% and 96% respectively. Ultrasound knowledge testing increased from 52% to 82%. Largest time difference between landmark and ultrasound identification was 357 seconds with mean of 117. Overall, 96% of participants have interest in further ultrasound training and 91% believe ultrasound would be beneficial for patient care. All participants felt prepared to use ultrasound for lumbar puncture after training.

Conclusion: A brief, introductory, simulation-based training session on the use of ultrasound and identification of spinal anatomy can increase trainee comfortability and prepare participants for the use of ultrasound-guided lumbar puncture.
Presentation Title: Differing Demographic and Clinical Profiles in Men and Women with Parkinson’s Disease

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Boston University School of Medicine

Abstract: Research on sex differences in Parkinson’s disease (PD) often focuses on clinical differences, rather than socioeconomic differences. We studied a population of patients with idiopathic PD at an urban safety net hospital in Boston, Massachusetts to examine differences in demographic characteristics and disease features between affected men and women.

Our study included 445 idiopathic PD patients (41.3% female, aged 30-100 years, M = 68.3 years, SD = 11). Compared to men, a greater proportion of women were non-white, (p = 0.03) and a trend was observed in which women were older at diagnosis (p = 0.08), and more likely to be on public insurance than men (p = 0.067). After adjusting for age at diagnosis, insurance type, and race, women were found to experience motor fluctuations (Odds Ratio, OR = 2.07, p = 0.004) and dyskinesias (OR = 2.92, p < 0.0001) more frequently than men, but were less likely to be diagnosed with dementia (OR = 0.436), and less likely to experience autonomic dysfunctions (OR = 0.513, p = 0.038) than men. An uncontrolled analysis demonstrated women to have more severe disease off medication than men, on the Hoehn and Yahr scale (p = 0.0024). However, this difference did not hold when we controlled for age at diagnosis, insurance type, and race.

Our results further characterize how clinical features cluster differently in men and women with PD. In addition, we provide evidence that socioeconomic factors, such as race and insurance type, may modify clinical differences, such as disease severity.
Abstract: Background: Agenesis of the corpus callosum is a relatively common abnormality, occurring in 0.1-0.7% of the population. In rare cases, it is accompanied by recurrent hypothermia and hyperhidrosis, a constellation of findings called Shapiro's Syndrome. This condition was first identified in 1967 by Shapiro and Plum, with about 50 cases described since. During attacks, body temperature falls to 31-35°C and is often accompanied by chills and diaphoresis. Clonidine has been reported to induce remission of attacks in many cases. We present a patient with Shapiro's Syndrome who was successfully treated with Clonidine.

Case report: A 44-year-old Caucasian male with developmental delay and seizure disorder presented with hypothermia to 31.7°C. On exam, he had left-sided weakness and spasticity. CBC showed anemia, but electrolytes, blood glucose, thyroid function, and cortisol were normal. Brain MRI revealed partial agenesis of the corpus callosum, absence of the splenium, and encephalomalacia of both frontal lobes. Shapiro’s Syndrome was diagnosed and the patient was started on Clonidine 250 mcg BID based on reports of success in treating the disorder. Due to hypotension, Midodrine was added for blood pressure control and the patient’s condition stabilized thereafter.

Discussion: The mechanism underlying Shapiro’s Syndrome remains unclear, but may involve structural or chemical abnormalities that lower the thermoregulatory set-point. Clonidine is an α2-adrenergic agonist that appears to act centrally to stabilize body temperature in patients with Shapiro’s Syndrome.
Presentation Title: IMMUNE-MEDIATED MONOFOCAL MOTOR NEUROPATHY: Report of 2 cases with long-term follow up and review of 6 published cases.

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Abstract: Multifocal motor neuropathy (MMN) is an immune-mediated motor neuropathy associated with asymmetric progressive weakness, demyelinating features with motor conduction block, elevated IgM anti-GM1 antibodies, and a favorable response to intravenous immunoglobulin (IVIg). There have been scarce reports of MMN affecting a single nerve. The clinical and electrodiagnostic findings of 2 cases with long-term follow-up are discussed, and 6 cases published in the literature are reviewed. Both patients responded to IVIg. One developed conduction block later in the course of the disease, in the absence of muscle weakness. Monofocal motor neuropathy, a pure motor immune-mediated mononeuropathy, is a rare disorder, which responds to IVIg. Although it may resemble MMN, some of its features lead us to consider it as a distinct entity.

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Title: BETA-AMYLOID IN CHRONIC TRAUMATIC ENCEPHALOPATHY, ALZHEIMER’S DISEASE, AND NORMAL AGING: EVIDENCE FOR NON-OVERLAPPING ETIOLOGIES

Authors: Philip Montenigro¹, Victor Alvarez², Yorghos Tripodis³, Robert Stern⁴, Ann McKee², Ann McKee², Thor Stein²,³
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Abstract: Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease induced by repetitive traumatic brain injury (RTBI) and characterized by a distinct pattern of tau accumulation. Deposition of Aβ is also associated with trauma and CTE. However, the relation between Aβ and tau, and normal aging in CTE is unknown. In this study 114 neuropathologically diagnosed cases of CTE were compared to 319 cases of neuropathologically diagnosed AD and to a large non-selected cohort of 2,332 normal aging cases (Braak 2011). Aβ deposition occurred in 43% of CTE cases. Compared to the normal aging cohort, the odds of developing neuritic Aβ were 11.1 times higher in the CTE cohort ($r^2=0.97$, $p=0.025$), and a weighted two-sample chi-square test demonstrated that the distribution of Aβ plaques by age in CTE was distinct from the distribution in normal aging ($X^2=21.4$, $p=0.0015$). Age-adjusted multiple linear regression analysis demonstrated that the presence of Aβ pathology predicted significantly greater CTE tau-pathological stage at the time of death ($B=0.53$, $p=0.003$) whereas the contribution of age on stage was negligible ($B=0.026$, $p<0.001$). Furthermore, Aβ was significantly associated with co-morbid Lewy body disease (OR=6.77, $p=0.009$), APOE e4 allele (neuritic: $p=0.020$), clinical dementia (OR=4.50, $p=0.007$), and clinical parkinsonism (OR=14.32, $p=0.019$). Supporting the biomechanical injury hypothesis for CTE, it was found that Aβ1-40 plaque burden was significantly higher in the cortical sulcus ($p=0.029$) compared to the gyral crests. Overall, our findings suggest that Aβ pathology is associated with a more aggressive CTE-related tauopathy and worse clinical outcome in CTE.
Title: Striatopallidal neurons control motor activity through striatal collaterals

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Abstract: The indirect pathway is considered as the main modulatory locus for basal ganglia control of motor and learning activity and is responsible for inhibiting undesired motor and learning programs, potentially through motor learning/information processes. To further define the critical role of the indirect pathway in the control of motor activity, we have developed two new transgenic mouse lines expressing ChR2 or Arch-GFP selectively in the medium spiny neurons (MSNs) of the indirect pathway under the control of adenosine A2A receptor (Adora2a) gene promoter. We verified the specific expression pattern of ChR2/Arch in the indirect pathway: i) Green fluorescence protein (GFP, fused with ChR2 or Arch) express in the striatum was largely detected in cell bodies, and was specifically co-localized with the Adora2a but not with substance P+ cells. Consistent with a previous optogenetic study, we found that light activation of ChR2 in the striatopallidal neurons suppress motor activity while light activation of Arch in the striatopallidal neurons in the DLS produced the predicted motor stimulant effect. We further hypothesized that the presence of profuse projections and collaterization within the striatum may contribute to striatopallidal pathway control of motor activity. To test this hypothesis, we optogenetically stimulated and silenced the striatopallidal neurons in the dorsal striatum and examined immediate early gene expression in the striatum. We found that ChR2 activation in the striatopallidal neurons in the DLS induced c-Fos expression in the GFP-positive MSN while Arch activation in the striatopallidal neurons in the DLS induced c-Fos expression in the GFP-negative MSN surrounding the GFP-positive MSN immediately underneath the optogenetic cannula. This is consistent with the suppression of GABA release in GFP-positive cells in DLS, resulting in the induction of c-Fos in the GFP-
negative cells with likely the collateral connections with the GFP-positive cells. Our findings raise new questions regarding the complexity of the role of the indirect pathway and the net effect of the collaterals in control of motor activity under normal physiological conditions.
MIR-10B-5P EXPRESSION IN HUNTINGTON’S DISEASE BRAIN RELATES TO AGE OF ONSET AND THE EXTENT OF STRIATAL INVOLVEMENT

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Abstract: MicroRNAs (miRNAs) are small non-coding RNAs that recognize sites of complementarity of target messenger RNAs, resulting in transcriptional regulation and translational repression of target genes. In Huntington’s disease (HD), a neurodegenerative disease caused by a trinucleotide repeat expansion, miRNA dysregulation has been reported, which may impact gene expression and modify the progression and severity of HD. We performed next-generation miRNA sequence analysis in prefrontal cortex (Brodmann Area 9) from 26 HD, 2 asymptomatic HD, and 36 control brains. Neuropathological information was available for all HD brains, including age at disease onset, CAG-repeat size, Vonsattel grade, and Hadzi-Vonsattel striatal and cortical scores, a continuous measure of the extent of neurodegeneration. We identified 75 miRNAs differentially expressed in HD brain (FDR q-value <0.05). Among the HD brains, nine miRNAs were significantly associated with Vonsattel grade of neuropathological involvement and three of these, miR-10b-5p, miR-10b-3p, and miR-302a-3p, significantly related to the Hadzi-Vonsattel striatal score (a continuous measure of striatal involvement) after adjustment for CAG length. Five miRNAs (miR-10b-5p, miR-196a-5p, miR-196b-5p, miR-10b-3p, and miR-106a-5p) were identified as having a significant relationship to CAG length-adjusted age of onset including
miR-10b-5p, the mostly strongly over-expressed miRNA in HD cases. Although prefrontal cortex was the source of tissue profiled in these studies, the relationship of miR-10b-5p expression to striatal involvement in the disease was independent of cortical involvement. Correlation of miRNAs to the clinical features clustered by direction of effect and the gene targets of the observed miRNAs showed association to processes relating to nervous system development and transcriptional regulation.
**Presentation Title:** Neck Circumference, Brain Imaging Measures, and Neuropsychological Testing Measures

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**Abstract:**

**Background** Perivascular fat may have direct effects on local vascularity. We have previously shown that neck fat is associated with carotid intimal thickness, a predictor of brain aging and cognitive outcomes. Whether neck circumference is a predictor of brain aging outcomes is unknown. The goal of this study was to investigate the associations of neck circumference with brain imaging and cognitive function.

**Methods** The study sample (n=2082, 53.5% women, mean age 60.9 years) was derived from Framingham Heart Study participants who underwent an examination, brain MRI, and neuropsychological testing. Multivariable-adjusted regressions modeled the associations between neck circumference, brain MRI parameters, and neuropsychological testing. Models adjusted for standard covariates with separate adjustments for waist circumference and body mass index (BMI). Separate models used waist circumference and BMI as the exposure variables to examine consistency with previous findings.

**Results** Per one standard deviation (2.8 cm in women; 2.9 cm in men) increase in neck circumference, there was a decrement of 0.34 (p<0.0001) percent in total cerebral brain volume and a decrement of 0.63 (p<0.0001) percent in frontal brain volume. Results were similar for BMI and waist circumference. No additional associations were observed for neck circumference, BMI, waist circumference, and neuropsychological test measures.
**Conclusions** There were no unique significant associations between neck circumference and brain MRI measures or neuropsychological test measures. Consistent with prior Framingham Heart Study observations, all adiposity measures tested showed associations with more adverse brain MRI measures and neuropsychological testing measures suggesting a global association of generalized adiposity.
**Presentation**  
**Title:** Mon Chéri Haiti: Neurology Lessons Learned

**Authors:**  
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**Abstract:**  
The Global Burden of Disease study conducted by the World Health Organization highlighted the significant burden of disease related to neurological disorders. Haiti is the site of the worst health indicators including life expectancy, infant mortality, and maternal mortality in the Western Hemisphere. Our department collaborated with neurologists throughout the US to develop a multidisciplinary team including an attending, a fellow, a resident, and a nurse. We provided clinical neurological care and education to the staff and patients of a pediatric and an adult hospital in Port au Prince, Haiti. During the one week program, 37 adult and pediatric cases were evaluated. The most frequently encountered neurological disorders were seizures, strokes, CNS infection, tumors, and headaches. Strokes and seizures accounted for more death and disability than infection which supports the recent WHO data. We did a systematic analysis of each case, addressing potential lack of resources, the goals of individual patient care, and analyzing the advantages and disadvantages of the Haitian and US systems. Several of these cases have been used to highlight areas for improvement in educational sessions in Haiti and in the US. Our quality improvement analysis identified laboratory testing, imaging, medications, and supplies that may significantly reduce morbidity and mortality at low cost. In addition, we have identified educational programming on disease and rehabilitation which will also improve quality of life. These improvement plans are currently being implemented into our program which continues to maintain a US neurologic presence in Haiti for one week of each month.
Presentation

Title: Clinicopathological findings in 100 former NFL players

Authors: PKiernan, LMurphy, JMez, TSolomon, DDaneshvar, PMontenigro, CNowinski, JAdams, KBabcock, LGoldstein, RCantu, DKatz, NKowall, RStern, VALvarez, TStein, AMcKee.
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Abstract: The VA---BU---SLI Brain Bank was established in 2008 to better understand the long-term effects of repetitive brain trauma (RBT). To date, 255 brains have been harvested from individuals exposed to RBT through sports, military or civilian activities, including 100 National Football League (NFL) players. Of the 84 neuropathologically analyzed, 80 NFL players (95%) met criteria for CTE diagnosis with an average CTE stage of 3.0 (maximum 4). 50 (63%) were diagnosed with pure CTE, 37% had co-morbid neuro-degeneration. Of those with pure CTE, 2% had no symptoms (mean age at death 48 yrs). 20% presented with mixed behavioral/mood and cognitive changes (mean onset: 45 yrs, age at death: 57 yrs), 48% with behavior/mood changes (mean onset: 39 yrs, age at death: 63 yrs), 24% with cognitive changes (mean onset: 56 yrs, age at death: 71 yrs). Players with CTE played every position except kicker. The overwhelming majority of this sample of former NFL players had at least stage II CTE. Ascertainment bias is a recognized limitation of brain donor cohorts, even when inclusion criteria are based solely on exposure. Caution must be used in interpreting the high frequency of CTE in this sample. The precise clinicopathological characterization of this NFL cohort will provide valuable information to aid in the future detection, management, and treatment of CTE in living individuals.

Dermatological manifestations in postural orthostatic tachycardia syndrome are common and diverse

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Background:
Postural orthostatic tachycardia syndrome (POTS) is a syndrome of orthostatic intolerance in the setting of excessive tachycardia with orthostatic challenge, and relief of such symptoms with recumbence. Apart from symptoms of orthostatic intolerance, there are many other co-morbid conditions associated with POTS including chronic headache, fibromyalgia, gastrointestinal disorders, cognitive impairment, and sleep disturbances. Dermatological manifestations of POTS are also common and wide ranged, from livedo reticularis to Raynaud’s phenomenon.

Design/Methods:
Questionnaires were distributed to 28 patients with POTS who presented to neurology clinic. They were asked to report on various characteristics of dermatological symptoms and answers were recorded on a Likert rating scale. Symptoms were considered positive if patients answered “strongly agree” or “agree” and negative if they answered “strongly disagree” or “disagree.”

Results:
The most commonly reported symptom was rash (77%). About 48% of patients reported symptoms of Raynaud’s syndrome. Less commonly reported symptoms included hives (25%). Furthermore, the distribution of rash included face, arms, legs, and trunk. Some patients reported that rash may spread (23%) and is likely to be pruritic (54%) or painful (21%). Very few (4%) reported worsening of symptoms on standing.

Conclusion:
The results suggest that dermatological manifestations in POTS are varied but common. It is therefore crucial that physicians have a detailed understanding of the dermatological autonomic manifestations. Furthermore, treatment of autonomic dysfunction may improve the dermatological manifestations in some of our patients. Further research defining underlying pathophysiology, clarifying incidence and treatment strategies is necessary.
Presentation Title: A novel AFG3L2 mutation in a Somalian patient with spinocerebellar ataxia type 28

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Abstract: Spinocerebellar ataxia type 28 (SCA28) is an autosomal dominant disorder caused by missense mutations in the ATPase family gene 3-like 2 (AFG3L2) gene. The disorder is characterized primarily by slowly progressive gait and limb ataxia, dysarthria, and nystagmus while additional symptoms can include ptosis, ophthalmoparesis, and hyperreflexia of the lower limbs. Imaging has shown cerebellar atrophy of the superior vermis. Although more prevalent in early adulthood, age of onset may vary from 3 to 60. To date, current literature has only reported cases in Caucasian populations. We present a new AFG3L2 mutation (571:G>A) of SCA28 in the first known case of a patient of African descent and with a late age of onset. The patient began experiencing bilateral lower extremity weakness and blurred vision at the age of 68. Clinical findings included gait ataxia, dysarthria, nystagmus on horizontal gaze, decreased sensation of lower extremities distally, slight dysmetria, and slight dysdiadochokinesia. The patient also had markedly diminished reflexes of the distal lower extremities. MRI revealed cerebellar atrophy.
Prevalence of Restless Legs Syndrome in an Atypical Parkinson's Disease Patient Population

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Objective: The aim of this study was to determine the prevalence of Restless Legs Syndrome (RLS) in Multiple Systems Atrophy, Corticobasilar Degeneration, Progressive Supranuclear Palsy and/or Diffuse Lewy Body Dementia, collectively known as Atypical Parkinson’s Disease (APD), compared to a control group and Parkinson’s Disease (PD) group.

Background: A prevalence of RLS has been established in PD, up to 22% in some studies, when compared to the general population, quoted at 4-11%. Although some studies have evaluated RLS in APD, these have focused on a small number of subjects and prevalence figures are not well documented.

Design: Three study groups were assessed for prevalence and severity of RLS. Patients diagnosed with APD were compared to patients with PD and a control group. A survey was administered to determine the presence of symptoms consistent with RLS, as well as to assess severity.

Results: We surveyed 73 patients and compared their responses to 35 age matched controls. Of these patients, 52 were diagnosed with PD and 21 with APD. Twenty percent of patients with PD met the diagnostic criteria for RLS than while only ten percent of patients with APD, trending towards significance. There was no difference between the control group and patients with PD.

Conclusions: Restless leg syndrome is more prevalent in patients with PD than those with APD. This difference may be explained by the difference in pathophysiology between PD and APD disorders. Further investigation is needed to further define the prevalence of RLS in APD disorders.
Presentation Title: Spectrum of White Matter Hyperintensities in Young Adults with Stroke at Boston Medical Center

Authors: Catanese L. MD, Shoamanesh A. MD, Rayhill M. MD, Lau H. RN, Romero RJ. MD, Babikian V. MD, Kase CS. MD, Pikula A. MD

Abstract: Objective: To determine the prevalence and associated risk factors of white matter hyperintensities (WMH) in the young stroke population presenting to Boston Medical Center and compare findings with available data through a literature review.

Design/Methods: This retrospective observational cohort study reviewed the clinical and imaging data of 146 consecutive patients aged 18-49 years admitted to Boston Medical Center between 01/2006-02/2010 with a new diagnosis of ischemic or hemorrhagic stroke. Patients with interpretable MRI, admission serum creatinine, blood pressure and echocardiogram were eligible (n=107). WMH were graded per the Age-Related White Matter Changes and Fazekas Scales whereas cerebral volume was assessed using the Global Cortical Atrophy Scale. We defined silent lacunar infarcts (SLI) as hypointense subcortical lesions on FLAIR with diameters of 3 to 15 mm, left ventricular hypertrophy (LVH) as any degree of LVH per transthoracic echocardiogram using the modified Sympson’s method, admission hypertension (aHTN) as a blood pressure higher than 140/80 mmHg and elevated creatinine (eCr) as baseline creatinine higher than 1.1 mg/dl in females and 1.2 mg/dl in males. Using logistic regression, we compared the association of these indicators between patients with moderate-severe WMH to those without. A Pubmed/Cochrane search compared our data with the available literature.

Results: WMH were present in 57% of patients (mean age 41 years). WMH were graded as mild, moderate and severe in 31%, 16% and 10% patients, respectively and were mostly bilateral subcortical (56%), and frequently located in parieto-occipital (49%) regions. aHTN, a known history of HTN (kHTN), SLI, LVH and eCR were present in 78%, 54%, 44%, 30% and 21% of the population, respectively. In univariate analysis, all indicators of systemic HTN were overrepresented in patients with moderate-severe WMH. Therefore, this group was more likely to be black (63% vs. 42%, P<0.01), hypertensive (93% vs. 72%, p<0.0001), with higher systolic (175 vs. 145 mmHg, p<0.0001), diastolic (104.7 mmHg vs. 84.2 mmHg, p<0.0001) blood pressures and eCr (1.7 vs. 0.9 mg/dl, p<0.001) on presentation and kHTN (79% vs. 45%, p<0.01) and
LVH (48.3% vs. 23%, p<0.01). Additionally, they were more likely to have had at least 1 (30% vs. 8%, p<0.01) and >10 (13% vs. 0%, p=0.01) cerebral microbleeds (CMBs), SLI (92% vs. 25%, p<0.001) and moderate-severe cortical atrophy (27% vs. 7%, p<0.01) on MRI. In stepwise regression analysis only aHTN (OR6.1 [95%CI 1.2-32, p=0.03]) and a kHTN (OR3.3 [95%CI 1.1-9.7, p=0.02]) remained significant. Compared to available data from similarly aged populations, our cohort has a higher prevalence of WMH, which are not age dependent.

Conclusions: Our data suggests that WMH are prevalent in young stroke patients at our institution and largely driven by modifiable risk factors. The independent association between WMH and aHTN, after adjusting for kHTN, is novel and may be related to 24hr blood pressure variability, or possibly inadequate primary care access. Further research is required to confirm our findings and explore inherent predisposing factors for early aggressive forms of this condition in order to apply timely interventions that limit WMH-related disability in this young population.
**Presentation Title:** CSF 5-methyltetrahydrofolate serial monitoring to guide treatment of congenital folate malabsorption due to proton-coupled folate transporter (PCFT) deficiency

**Authors:** Torres A, Newton SA, Crompton B, Borzutzky A, Neufeld EJ, Notarangelo L, Berry GT.

**Abstract:** Hereditary folate malabsorption is characterized by folate deficiency with impaired folate transport into the central nervous system (CNS). This disease is characterized by megaloblastic anemia, combined immunodeficiency, seizures and cognitive impairment. The anemia and immunologic disease are responsive but neurological signs are refractory to folic acid treatment. We report a 7-year old girl who has congenital folate deficiency and SLC46A1 gene mutation who is unable to transport folate from her gut to the circulatory system and from blood to the cerebrospinal fluid (CSF). As a result she developed undetectable 5-methyltetrahydrofolate levels in her plasma and CSF and became immunocompromised and quite ill. Intramuscular treatment with 5-formyltetrahydrofolate (folinic acid) was therapeutic at her presentation and has been successful preventing other signs and symptoms of hereditary folate malabsorption even at relatively low CSF levels. Although difficult, early detection and diagnosis of cerebral folate deficiency are important because folinic acid at a pharmacologic dose may normalize outcome in PCFT gene defects, as well as bypass autoantibody-blocked folate receptors and enter the cerebrospinal fluid by way of the reduced folate carrier. This route elevates the 5-methyltetrahydrofolate level within the central nervous system and can prevent the neuropsychiatric disorder. CSF levels of 5-methyltetrahydrofolate between 18 nmol/L and 46 nmol/L may be sufficient to eradicate CNS disease.