Washington University
School of Medicine
Department of Neurology

Residents' Day Symposium

Friday, May 27, 2022
7:30am – 9:15am
Farrell Learning and Teaching Center ~ Atrium

Poster presentations will begin at 7:30am

Awards will be presented at 9:00am

We encourage everyone to attend this important event.

Amar, Jordan

Location-atypical lesions in non-ketotic hyperglycemic epilepsy: expansion of the clinico-radiographic phenotype

Jordan Y. Amar, MD, MSc; Anup K. Bhattacharya, MD; Adaku M. Uzo-Okereke, MD; Chris A. Chou, MD; Katie D. Vo, MD; Manu S. Goyal, MD, MSc, Robert C. Bucelli, MD, PhD

Objective: Non-ketotic hyperglycemia (NKH) produces a spectrum of symptoms and radiographic findings due to poorly-controlled diabetes mellitus. These lesions, which predominantly affect parieto-occipital cortex, are commonly missed by neurologists and neuroradiologists due to their subtle hypointense appearance on T2-based imaging. We report four atypical cases of this syndrome to highlight its subtle, protean presentation to aid in timely diagnosis.

Methods: Our institutional case series describes four cases of NKH with atypical presentation and lesion burden affecting anterior cortex. We review the clinical presentations, laboratory derangements, neuroimaging, and corresponding electroencephalography.

Results: Four patients with atypical NKH are characterized in our series. Presenting symptoms ranged from rhythmic hand-tapping to generalized tonic-clonic status epilepticus. Laboratory values were notable for marked hyperglycemia (range: 447 - 627 mg/dL), mild pseudo- hyponatremia (range: 127 - 136 mmol/L), and elevated hemoglobin A1C levels (range: 10.9 -16.1%). All patients were found to have the classically-described pattern of T2-based hypointensities, three with atypical distributions involving “anterior” cortex. These lesions corresponded to the electrographic nidus of seizure burden. Of the available follow-up, both seizures and T2-based hypointensities resolved within weeks of serum glucose normalization.

Significance: Our series of four patients with atypical findings of T2-based signal abnormalities in NKH expands the clinico-radiographic phenotype to a more protean distribution than previously described. Knowledge of these atypical imaging features will aid both the neurologist and radiologist in timely diagnosis and care of these patients.

Baer, Matthew

An atypical presentation of an atypical disease

Abstract:

A 35-year-old previously-healthy right-handed woman presented to a neurology resident clinic for a second opinion of right-sided carpal- and ulnar-tunnel syndromes. She described a two-year history of a chronic progressive pure-motor distal predominant right upper extremity syndrome with hyperreflexia and spasticity. She developed a new focal-to-generalized seizure with left occipital onset between the time of her initial evaluation and when her imaging was obtained. Head CT at the time of her seizure showed scattered left-sided subcortical encephalomalacia, left parieto-occipital hypodensity, and frontoparietooccipital atrophy. CT-angiogram head and neck showed no underlying vascular malformation (not shown). CT chest, abdomen, and pelvis with contrast revealed no peripheral malignancy or lesion. MRI brain revealed an infiltrating and destructive lesions with extensive edema and multifocal ring-enhancement in the left hemisphere. Serum studies were normal, and CSF was mildly inflammatory with 15 nucleated cells (100% monocytic). She had a positive serum cysticercosis antibody, which was deemed a false positive. Interval MRI performed two months later showed resolution of some ring-enhancing lesions with interval development of new lesions. Brain biopsy demonstrated areas of necrosis on gross section; histologically, there was chronic perivascular inflammation with a mixture of T-lymphocytes, plasma cells, and histiocytes affecting large and small vessels, with necrosed blood vessels and microinfarcts. The absence of systemic evidence of inflammation together with this collection of histologic findings is consistent with primary lymphocytic vasculitis of the central nervous system. The patient was started on high-dose steroids and is currently on a prolonged steroid taper awaiting imaging to determine the next step of immunomodulation.

Chopra, Ravi

Toward a motor network model of selective vulnerability in amyotrophic lateral sclerosis (ALS)

Ravi Chopra MD, PhD[1], Timothy M. Miller MD, PhD[1], Keith B. Hengen PhD[2]

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Amyotrophic lateral sclerosis (ALS) is a devastating paralytic neurodegenerative syndrome of progressive weakness and eventual death due to degeneration of corticospinal motor neurons (CSMNs) and anterior horn spinal motor neurons (SMNs) (Brown and Al-Chalabi, 2017; Saberi et al., 2015). While the pathobiology of ALS is complex (Al-Chalabi et al., 2014), network excitability is understood to be a key player in ALS pathogenesis. Paraclinical measurements of cortical and spinal network behavior in ALS patients indicate that vulnerable circuits show abnormal excitability early in ALS (Vucic et al., 2008; Geevasinga et al., 2015; Mogyoros et al., 1998), and that network dysfunction predicts disease onset in ALS patients (Kanai et al., 2012; Shibuya et al., 2016). One of the only available disease-modifying therapies for ALS (the small molecule Riluzole) is thought to slow disease progression by modifying network excitability (Bellingham, 2011), and there are ongoing efforts to develop additional disease-modifying therapies that target network function (Wainger et al., 2021).

Despite the consistent observations of network dysfunction in ALS patients, the pathophysiology of network dysfunction in ALS remains poorly-understood. Excitability at the network level is an emergent property of voltage-gated and synaptic activity across multiple cell types, but single-cell measures of excitability in ALS rodent and cell models have either been inconsistent between models (Wainger et al., 2012; Devlin et al., 2013; Gunes et al., 2020) or have been found to vary in a stage- and cell type-specific manner (Kim et al., 2017; Saba et al., 2016; Saxena et al., 2013). These findings suggest that rather than a disease of uniform neuronal hyperexcitability, ALS is a complex network disease where multiple cell types are affected, producing an abnormal network that does not readily localize to a single cell type or channel, and therefore may not respond in an intuitive fashion to channel-based therapy. There is a need for network-wide excitability markers that reliably correlate with disease progression in preclinical models, both as hypothesis-generating tools and as platforms for novel therapeutics.

Recent experiments performed by the Hengen lab demonstrate that high-order network properties measured *in vivo* may serve as reliable and biologically-relevant excitability markers of hippocampal neurodegeneration in a model of genetic tauopathy. We propose to extend this strategy to the corticospinal circuit in a model of ALS. Our proposed research strategy combines chronic cortical recordings in primary motor cortex (M1) along with subcutaneous implantable electromyography (EMG) to concurrently measure CSMN and SMN function in the hSOD1-G93A mouse model of ALS over weeks of disease progression. Using this platform, we will explore the central hypothesis that motor network instability reliably predicts ALS proteinopathy and CSMN/SMN degeneration. Future studies will then be focused on validating specific network biomarkers as disease markers, while also exploring the pathobiology of the observed network abnormalities.

Cole, Jordan

Development and Implementation of Institutional Guidelines for the Evaluation of Children with Global Developmental Delay/Intellectual Disability

Abstract:

Global developmental delay (GDD) and intellectual disability (ID) are common reasons for referral to child neurology clinic, with about 1-3% of the population affected by these disorders. The etiology is readily identifiable by history and physical exam alone in up to 45% of affected individuals, often less frequently by the time of referral to neurology. The appropriate diagnostic testing for children without a readily identifiable etiology of GDD/ID is not uniformly defined by national society guidelines, which can create confusion and uncertainty in practice, particularly for trainees. I sought to develop and implement evidence-based institutional guidelines for the evaluation of GDD/ID. Pre-implementation survey data indicated strong support for development, and post-implementation survey data indicated use of the guidelines at least 25% of the time by a majority of respondents, with most saying they plan to continue to use the guidelines going forward. No statistically significant differences in practice were identified when comparing pre- and post-data. Lessons learned included need for greater visibility, accessibility, and simplicity of guidelines and surveys to improve user-friendliness and response rates.

Farkas, Nathan

Cranial Auscultation as a Modality for Evaluation of Cerebral Vascular Lesions in Patients with Pulsatile Tinnitus

Abstract:

Pulsatile tinnitus (PT) has only recently been identified as a separate pathology from traditional ringing/buzzing tinnitus. This revelation was driven by movement of patients who created an online website (www.whooshers.com) to share their workups and etiologies. This group demonstrated that PT could be recorded objectively and uploaded several recorded waveforms allowing other patients to find an understanding community. In the physician world however, cranial auscultation as described by William Osler, has become a lost art.

We developed a novel cephalascope to optimize identification and characterization of objective pulsatile tinnitus caused by intracranial bruits and their associated underlying vascular pathologies. We recorded patients in the neuro-otology and neuro-interventional radiology clinics presenting with objectively appreciable pulsatile tinnitus on exam. 8 patients were recorded with detectable pulsatile tinnitus. 2 patients had sigmoid sinus dehiscence, 1 torcula dural arteriovenous fistula (dAVF), 1 arteriovenous malformation (AVM), 1 dAVF, 2 patients with idiopathic intracranial hypertension and associated venous sinus stenosis. Lastly, we identified 1 patient with a novel PT etiology caused by a variant occipital artery origin from the vertebral artery, who had cessation of PT when the occipital artery was compressed manually.

Gilbert, Laura

Top Ten Research Themes for Dystonia in Cerebral Palsy: A community-driven research agenda

Laura A Gilbert DO MBA[1], Darcy Fehlings MD MSc[2], Paul Gross BA[3], Michael Kruer MD[4], Wendy Kwan[3], Jonathan W Mink MD PhD FAAN[5], Michele Shusterman[6], Bhooma R Aravamuthan MD DPhil[1]

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OBJECTIVE: To develop a community-driven research agenda for dystonia in cerebral palsy (D-CP): a common, debilitating, but understudied condition. The CP community (people with CP and their caregivers) is uniquely equipped to help determine the research questions that best address their needs.

DESIGN/METHODS: We developed a community-driven D-CP research agenda using the well-established James Lind Alliance methodology. CP community members, researchers, and clinicians were recruited via multiple advocacy, research, and professional organizations. To ensure shared baseline knowledge, participants watched webinars on D-CP outlining current definitions, management, and research prepared by a Steering Group of field experts (https://cprn.org/research-cp-dystonia-edition). Participants next submitted their remaining uncertainties about D-CP and prioritized them between randomly generated serial pairs. The top uncertainties were consolidated into themes via iterative consensus-building discussions within the Steering Group. The themes were then ranked in order of the highest ranked uncertainty that contributed to the theme.

RESULTS: 166 webinar viewers generated 113 uncertainties yielding 67 unique uncertainties. 29 uncertainties (17 from community members) were prioritized higher than their randomly matched pairs. These coalesced into the following Top 10 D-CP Themes:

1) Develop new treatments;
2) Assess rehabilitation, psychological, and environmental management approaches;
3) Compare effectiveness of current treatments;
4) Improve diagnosis and severity assessments;
5) Assess the impact of mixed tone (spasticity and dystonia) in outcomes and approaches;
6) Assess predictors of treatment responsiveness;
7) Determine pathophysiologic mechanisms;
8) Describe the natural history;
9) Develop dystonia pain treatments;
10) Increase family awareness.

CONCLUSION: We have identified areas of research/clinical priority for D-CP. This agenda reflects the concerns most important to the community, both in perception and in practice. We encourage future D-CP research to center around these themes. Community members generated the majority of top-prioritized uncertainties, highlighting the important contributions community members can make to research agendas, even beyond D-CP.

Kerashvili, Nino and Soloveychik, Dina

Challenging Case of Dihydrolipoamide Dehydrogenase Deficiency (DLD), Resulting in Leigh syndrome.

Kerashvili N, Soloveychik D, Gooch C, Zempel J.

Washington University in St. Louis. St. Louis, MO. Section of Genetics,
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Abstract:

Dihydrolipoamide dehydrogenase deficiency (DLD) is a rare, mitochondrial disorder with a wide phenotype ranging from early-onset neurological manifestation to adult-onset live disease and rarely a myopathic presentation. DLD functions as the E3 subunit in three mitochondrial enzyme complexes (branched-chain alpha-ketoacid dehydrogenase (BCKDH) complex, α-ketoglutarate dehydrogenase (αKGDH) complex, and pyruvate dehydrogenase (PDH) complex) and the glycine cleavage process. DLD is encoded by nuclear DNA and inherited as an autosomal recessive disorder. DLD deficiency is affecting multiple metabolically active enzymes and enhances reactive oxygen species generation, which is thought to be the pathophysiology of the disease caused by DLD deficiency.

DLD is known to be associated with Leigh syndrome, which is thought to be mediated primarily through PDH Deficiency. Leigh syndrome is a subacute necrotizing encephalopathy, that can be a feature of multiple mitochondrial disorders, including DLD. This is a progressive disorder, characterized by irreversible decompensation during illness or as a result of medications, with a known association between volatile anesthesia, muscle relaxants, and propofol. It is a life-limiting condition, with death occurring due to respiratory or cardiac failure. Classically Leigh syndrome affects basal ganglia and/or brainstem, with characteristic symmetric T2/FLAIR changes in this distribution.

We present a case of a 3-year-old Hispanic female with global developmental delay, who presented with recurrent vomiting and encephalopathy for 10 months. She was found to be in liver failure of unknown etiology. Her course was improving, and her initial brain MRI was normal. After sedation with ketamine for lumbar puncture, she developed worsening encephalopathy. Shortly after, she developed ophthalmoplegia, myoclonus, ataxia, appendicular hypotonia, and intermittently eligible reflexes. She had repeated sedation with ketamine for line placement. In the setting of the second ketamine, she developed acute seizures. Her clinical picture deteriorated with dystonia, multiple seizures, and encephalopathy, requiring intubation. She had a repeated MRI brain imaging that revealed bilateral basal ganglia, caudate, thalamic, and dentate FLAIR abnormalities with diffusion restriction in the caudate, basal ganglia, and scattered areas in bilateral cortical-subcortical regions. Clinical picture, laboratory workup, and brain imaging diagnostic for Leigh syndrome.

Rapid exome sequencing revealed biallelic variants in *DLD*, a paternally inherited pathogenic variant c.685G>T; p.Gly229Cys and maternally inherited likely pathogenic variant c.548C>T; p.Thr183Met. We initiated therapy with IV Arginine, as this has been thought to optimize nitric oxide production, which can be aberrant in Leigh Syndrome. We also initiated a traditional mitochondrial cocktail with no improvements.

We considered the ketogenic diet, as poor carbohydrate oxidation can be seen in DLD but it was eventually declined by the family. Unfortunately, she had a progressively worsening clinical course, both from cardiorespiratory and neurologic standpoints, and the family elected comfort care. Our patient passed away within one month of her diagnosis.

Klinman, Eva

Using directly converted human neurons to study the contribution of mitochondrial dysfunction and cytoskeleton changes to Alzheimer's disease

Abstract:

Alzheimer's disease (AD) is a devastating illness which affects millions of patients. Despite formidable efforts, current animal models of AD do not adequately mimic human disease, and available in vitro AD neurons are stripped of their age-associated cellular characteristics. The Yoo lab has developed a novel method of directly converting human fibroblasts into neurons. Using this microRNA-based process, which retains the age-associated epigenetic signatures of the donor, I compare young and old neurons from healthy individuals and those with early and advanced AD. As the project advances, I will examine how cumulative abnormalities in mitochondrial structure and function with age predispose neurons to degenerative disease. I hypothesize that age reduces mitochondrial resiliency, leading to increased fragmentation and degradation. I predict that this process is amplified by decreased actin filament reorganization. To test this, I am using live-cell imaging to examine the age- and disease-associated behavior of mitochondria, and determine if reduced actin turnover with age contributes to disease susceptibility. Identifying age- associated changes that contribute to neuronal disease should allow testing of various drugs designed to improve neuronal survival. I expect that this work will ultimately guide medical advances targeting mitochondrial dysfunction in a broad range of neurodegenerative diseases.

Langton, Erin

2yo girl with pathogenic activating variant in mTOR presenting as Smith-Kingsmore Syndrome complicated by stroke due to vasculitis

Abstract:

Smith-Kingsmore syndrome (SKS) is a rare autosomal dominant neurodevelopmental disorder characterized by macrocephaly/megalencephaly, developmental delay, intellectual disability, hypotonia, facial dysmorphisms, and seizures. SKS is caused by heterozygous somatic or germline activating pathogenic variant in mammalian target of rapamycin (MTOR) on chromosome 1p36. The mTORC1 (mTOR Complex 1) pathway is also activated in in vitro studies of large and small vessel vasculitis, including ANCA. Here we report the first case of ANCA vasculitis in SKS, a two-year-old girl with macrocephaly, developmental delay, hypotonia, cutaneous vascular malformation, and facial dysmorphisms who presents with intrapulmonary hemorrhage and multifocal stroke, complicated by seizure and post-hemorrhagic hydrocephalus, due to systemic and central nervous system vasculitis. Somatic Overgrowth Gene Set in buccal swab and blood reveals a heterozygous pathogenic germline variant in the MTOR gene, denoted p.T1977I. Serum C-ANCA is positive. She is treated with sirolimus and seroconverts to ANCA negative. The clinical features observed in our patient further expand the phenotypic spectrum of SKS, allow the inclusion of activating mTOR variants among the myriad causes of in vivo vasculitides, and suggest that the use of mTOR inhibitors in such cases warrants further study.

Newman, Joshua

Vertical Nystagmus, Ataxia, Hypomagnesemia, and Cerebellar Nodulus Lesions: A Clinical-Radiologic Correlate Case Series

Abstract:

Hypomagnesemia is a known cause of vertical nystagmus. However, there is little known about the localization of CNS dysfunction in the context of hypomagnesemia that explains this physical finding. There have been few individual case reports of transient cerebellar findings in the context of patients presenting with neurologic symptoms due to severe hypomagnesemia. We have found 3 patients at Barnes-Jewish Hospital who presented with acute onset vertical nystagmus in the context of severe hypomagnesemia who had characteristic changes on MRI in the cerebellar nodulus providing further evidence of a radiologic correlate to the clinical phenomenology observed.

Okonkwo, Joshua

Benign Intracranial Hypertension and Cavernous Sinus Syndrome – Two Rare Complications of Multiple Myeloma Presenting Separately in the Same Patient

Abstract:

For decades, there has been an association between IIH and anemia though it is unclear if this is truly a causal relationship. Separately, intracranial multiple myeloma is rare with only a few cases series reported in the literature. We present a case of multiple myeloma initially presenting with a clinical phenotype consistent with IIH without evidence of direction CNS involvement or CVST but with biochemical evidence of hyper-viscosity and anemia which to our knowledge has not been previously reported. IIH resolved with Rx of her MM but despite bone marrow transplant, the patient had relapse this time presenting with cavernous sinus syndrome with radiographic evidence of skull base involvement, another rare manifestation of MM with only a few case reports described in the literature.

Perez-Martinez, Enmanuel

Focus on Equitable Delivery of Neurologic Care: from ED to Clinic

Enmanuel J. Perez, Mimi Giang, Lauren Langford

Abstract:

Introduction: Unequal access to and utilization of neurologic care has been shown for multiple neurologic diseases. Outpatient Neurology referrals can be unreliable with high degree of loss-to-follow-up. Our goal was to examine the impact of various demographic and socioeconomic variables on attendance at referral appointments after an ED visit. We hypothesized that specific sociodemographic variables would impact neurologic care after an ED visit.

Methods: We examined a retrospective cohort of adult patients evaluated in the ED over a 12-month period (2019). Patient demographics were collected from all (478) patients who were subsequently referred to the Neurology COH and CAM Clinics from the ED. Chart records were reviewed to examine the primary outcome of outpatient Neurology follow-up. Univariate and multivariate regression models were used to assess the impact of age, sex, race-ethnicity, insurance status, and social vulnerability index (SVI) on outpatient follow-up

Results: Out cohort had a significantly higher proportion of Black patients, whereas a similar proportion of female patients when compared to St. Louis City census data. Different insurance types were well-represented in our cohort. Most common referral diagnoses included: seizures, headache, neuropathy, and stroke. There was a high proportion of patients with poor outcomes (lost to follow-up or never followed-up). In univariate and multivariate logistic regression models, Black and uninsured patients are less likely to follow-up, respectively.

Conclusions: Disparities in neurological care exist in our institution. Identifying groups that may be at a higher risk of non-adherence can help clinicians identify at-risk individuals/groups. Our future goal is to work with the health-care system to implement structural changes, including more efficient and equitable resource allocation, to assure equal access to neurological care.

Ray, Christopher

When Platelets Get Stuck: Stroke Due to Hereditary Thrombotic Thrombocytopenic Purpura in a Nonpregnant Female

Christopher Ray MD, Talora Martin MD, Salah Keyrouz MD

Hereditary thrombotic thrombocytopenic purpura (hTTP, also known as Upshaw-Schulman syndrome) is a rare autosomal recessive condition in which lack of functional ADAMTS13 enzyme leads to dysregulated platelet aggregation. Patients present with symptomatic episodes of microangiopathic hemolytic anemia and thrombosis, including ischemic stroke, when exposed to physiologic stress, particularly in the neonatal and peripartum periods. We report the case of a 54-year old female with lupus and 3 prior ischemic strokes who presented with encephalopathy and was found to have a punctate infarct in the left parietal lobe on MRI. Laboratory workup was notable for mild thrombocytopenia (nadir 130) and undetectable ADAMTS13 activity without inhibiting antibodies. The patient was treated with plasma exchange and transitioned to scheduled plasma infusions to replace the deficient ADAMTS13 enzyme. Genetic testing is pending. This case is a rare occurrence of stroke occurring outside of pregnancy in an adult patient with hTTP and highlights the importance of considering rarer causes of stroke in atypical clinical contexts.

Roach, Drew

Immune-Mediated Polyradiculoneuropathy associated with Camidanlumab Tesarine

Camidanlumab tesirine (Cami-T) is an antibody-drug conjugate (ADC) targeting CD25 on lymphoma cells. In a Phase II trial (NCT04052997) of Cami-T in relapsed/refractory classical Hodgkin's Lymphoma (RRcHL), it demonstrated overall response rate of 81% and complete response rate of 38%. Data from Phase I/II clinical trials of this agent report that 6.4% of RRcHL patients experienced acute Guillain-Barre Syndrome (GBS) as a complication of treatment. We report a case of a woman with RRcHL who developed a treatment refractory, asymmetric polyradiculoneuropathy five weeks after starting Cami-T. She experienced slow recovery after treatment with high dose corticosteroids, plasmapheresis, and IVIg. More research is needed to characterize and treat this unique neurologic complication of Cami-T therapy.

Valtcheva, Manouela

Gluten Sensitivity-Associated Progressive Myoclonus Ataxia

Manouela V. Valtcheva, MD, PhD, Jie Chen, MD, PhD, Robert C. Bucelli, MD, PhD,
Gabriela de Bruin, MD, Richard J. Perrin, MD, PhD

Abstract:

Celiac disease is a gluten-triggered autoimmune disorder causing a chronic enteropathy within the small intestine in genetically predisposed individuals. It can also be associated with a number of extraintestinal neurologic complications most commonly including neuropathy and ataxia. In very rare cases, individuals with Celiac disease may develop a syndrome of progressive ataxia and myoclonus. Here we present a case of a 43-year-old man with initial presentation of facial and palatal myoclonus, and detail his clinical course of progressive ataxia and myoclonus in the setting of subclinical Celiac disease. Throughout his progressive course, he underwent extensive work-up including MRI Spectroscopy, electrodiagnostic studies, and whole exome sequencing. In the setting of poor diet compliance and progressive symptoms, he was treated with empiric immunosuppression without significant improvement, and ultimately died of complications of his disease and treatment. Autopsy evaluation of the brain and cervical spinal cord demonstrated selective Purkinje cell loss and high cervical spinal cord lesions, representing one of few cases of Celiac-related myoclonus ataxia with detailed neuropathologic and genetic characterization.