Residents' Day Symposium
Friday, May 18, 2012
7:30am – 9:15am
Farrell Learning and Teaching Center ~ Atrium

Poster presentations will begin at 7:30am

Awards will be presented at 9:00am

Arsenault, Shawna and Mahathy Goli

Trial of Continuous Apomorphine in a Patient in a Chronic Minimally Conscious State after TBI

Background: Deficiency of dopamine after severe traumatic brain injury (TBI) may contribute to disorders of consciousness. Administration of apomorphine, as a dopamine agonist, may accelerate emergence from minimally conscious state (MCS) or vegetative state (VS).

Objective: To determine if continuous subcutaneous apomorphine may aid in emergence from a chronic MCS in a patient with penetrating brain injury.

Methods: In a prospective clinical study, a patient with penetrating TBI in a MCS for over six months was administered continuous, subcutaneous apomorphine for 60 days. The outcome measure was the Western Neuro Sensory Stimulation Profile (WNSSP).

Results: The patient tolerated the trial of subcutaneous apomorphine without any significant adverse effects. Subjectively, the patient appeared to have increased eye movements but did not show any other evidence of increased awareness. There was no change on his WNSSP.

Conclusion: Continuous subcutaneous apomorphine was ineffective in recovery of consciousness in a patient in chronic MCS after penetrating brain injury.

Arsenault, Shawna and Shawn Furst

Embolic Stroke Associated with Thoracic Outlet Syndrome in a Young Woman with Cervical Ribs: A Case Report

Shawn Furst, DO and Shawna Arsenault, MD

Thoracic outlet syndrome (TOS) is a condition characterized by compression of neurovascular structures as they traverse the thoracic outlet above the first rib, behind the clavicle, and between the anterior and median scalene muscles. Rarely TOS can cause ischemia in an extremity or in the brain.

A 20 year old female with history of presumed left upper extremity radiculopathy presented to the hospital with nausea, vomiting, blurred vision, dysphagia, and angioedema. The patient then became progressively somnolent and developed hemiplegia. Brain MRI revealed an acute infarct in the distribution of the right posterior cerebral artery and superior cerebellar artery, and cerebral angiogram showed occlusive distal basilar artery embolus at the superior cerebellar artery level. Chest CT demonstrated bilateral cervical ribs with left cervical rib causing narrowing of the subclavian artery. Ultrasound revealed subclavian artery post-stenosis dilatation and decreased arterial flow. She was diagnosed with TOS with retrograde cerebral embolism. The patient was anticoagulated with IV Heparin and underwent left cervical rib resection and thoracic outlet decompression four days after the initial presentation. She then completed six weeks of acute inpatient rehabilitation and made improvement in her functional impairments, but significant neurologic deficits remained.

This case illustrates the potential for severe cerebral ischemia with thoracic outlet syndrome. Although retrograde cerebral embolism is rare, it is a known possibility with TOS. Recognition of TOS is critical to institution of appropriate treatment and prevention of cerebral ischemia.

Bali, Taha

Clinical Characterization of the Washington University Amyotrophic Lateral Sclerosis Patient Cohort

BACKGROUND Amyotrophic lateral sclerosis is a fatal disorder characterized by progressive degeneration of brain and spinal cord motor neurons. ALS is familial (FALS) in 5-10% of cases. Recent discovery of *C9ORF72* hexanucleotide repeats in ALS has explained an additional 20-30% of all FALS cases and genotype-phenotype correlations are emerging. Sporadic ALS (SALS) should technically be called "simplex," and accounts for 90-95% of cases. A minority of cases show mutations in the same genes causing FALS.

OBJECTIVES 1) Clinically characterize the WUNM Center's ALS cohort 2) Characterize the distribution of gene mutations in this ALS cohort 3) Identify gaps in current data collection to improve data collection in the future.

METHODS All WUNM center patients >18 years of age at time of enrollment diagnosed with motor neuron disease were enrolled. 13 known ALS genes were sequenced by pooled-sample sequencing in all SALS patients and in those FALS pedigrees without known genetic cause. C9ORF72 repeat expansions were assayed by repeat-primed CPR. Data was compared to clinic-based FALS and SALS cohorts from other centers. Kaplan-Meier (log-rank) was used to compare age at onset and survival. Independent t-tests compared mean age of onset and survival. Fisher's exact test was used to compare frequencies.

RESULTS The WUNM cohort is enriched for FALS cases, accounting for 25% of samples. The WUNM SALS cohort shows trends consistent with the literature in mean age of onset (59), male-to-female ratio (1.2:1) and site of onset (26% bulbar-onset). Compared to a similar US clinic-based cohort (Mayo), WUNM FALS shows similar frequencies of mutations in *SOD1*, *FUS*, and *TARDBP* but a higher percentage of families with *C9ORF72* repeat expansions (41% vs. 23%). Completed retrospective chart review made the comparison of *C9ORF72* carriers to non-carriers possible, revealing, among other things, earlier age of onset. Availability of some clinical characteristics by chart review was inconsistent.

CONCLUSIONS The first 5 years of the Washington University Neuromuscular Genetics Project (2006-2011) successfully recruited a large cohort of FALS and SALS patients, many with paired fibroblast cell lines available for future studies. The basic clinical and demographic features of the WUNM cohort are similar to those published in the literature. Exceptions include a higher than expected frequency of FALS probands, which likely reflects referral bias to our center and a higher than expected frequency of *c9ORF72* repeat expansions that more closely resembles Irish (41% in 49 subjects) and Finnish (46.4% in 164 subjects) cohorts than a southern US cohort (23% of 34 families). This may reflect referral bias or historical migration patterns to the area. The retrospective chart review utilized in this study helped identify systematic gaps in available clinical data and helped guide the design of standardized data collection for participants.

Baweja, Anu

Bithalamic edema in a patient presenting with acute onset confusion: a case of tentorial Dural arteriovenous fistula

A 61 year old Caucasian male presented as a transfer from a referring hospital after approximately four days of confusion and memory impairment. On neurological exam he was somnolent, disoriented and had decreased attention and concentration. Metabolic, infectious, vasculitic and paraneoplastic work up was negative. Brain Magnetic Resonance Imaging (MRI) showed bithalamic enhancing lesions. PET scan was concerning for high grade glioma or lymphoma. Thalamic biopsy ruled out tumor and was felt to be consistent with Wernicke's encephalopathy. A repeat brain MRI / MRA done at a return office visit was suggestive of a posterior fossa arteriorvenous fistula (AVF) in the region of the vein of Galen. Carotid angiography showed a Type III tentorial dural AVF and an occluded / thrombosed straight sinus. Given the above, the bithalamic edema was felt to be likely related to venous hypertension / venous ischemia secondary to the dural AVF. The patient underwent endovascular embolization of the fistula followed by an open craniotomy procedure. Postoperatively, dural AVF in angiography was resolved and a marked improvement in memory and cognition was observed in the patient at a follow up visit after two months. This case illustrates the frequently considered but rarely confirmed pathophysiological mechanism of venous hypertension and ischemia in the bilateral thalamus to cause reversible neurological dysfunction.

Boellert, Karl and Angela Tripp

A Case Report of Transthyretin Familial Amyloid Polyneuropathy Mistaken for CIDP

Boellert K,Tripp A, Ruvinskaya R

Physical Medicine and Rehabilitation, Division of Neurorehabilitation
Washington University, St. Louis, MO 63109

Abstract:

Transthyretin (TTR) amyloidosis is a life-threatening form of familial amyloid polyneuropathy (FAP) transmitted as an autosomal dominant trait. Lesions are induced by amyloid deposits caused by mutated TTR (mTTR) gene. This typically causes a nerve length-dependent polyneuropathy and starts in the feet with loss of temperature and pain sensations, and results in death within 10 years on average. In the literature, there are several reports of amyloid neuropathies mimicking chronic inflammatory demyelinating polyneuropathy (CIDP).

This is a case report of a patient with a several year history of a progressive polyneuropathy later misdiagnosed as chronic inflammatory demyelinating polyneuropathy. Subsequent muscle/nerve biopsies and genetic analysis lead to correct diagnosis of a transthyretin familial amyloid polyneuropathy. This report describes his admission to an acute inpatient rehabilitation facility and subsequent functional improvement.

Bravo, Pablo

Title: Steroid responsive febrile infection-related epilepsy syndrome, a case report.

Abstract: Febrile infection-related epilepsy syndrome (FIRES) is a catastrophic epileptic encephalopathy with a yet undefined etiology. FIRES is encountered both in adults and children. The mechanism underlying this prolonged state is not clear, and an immunologic source, a genetic predisposition and an inflammation-mediated process have been hypothesized. Treatment modalities include antiepileptic drugs, burst-suppression coma, intravenous immunoglobulin, steroids and other less conventional agents. Despite multiple treatment modalities, the outcome of FIRES is poor. We reported the case of a previously healthy twenty year old woman presenting with fever and headaches, followed by intermittent complex partial seizures and subsequent development of prolonged status epilepticus. The etiology of her presumed meningoencephalitis was unclear. Despite multiple antibiotics and antiepileptic drugs, induced hypothermia and burst suppression coma, she remained on status epilepticus for 4 weeks. At this point, intravenous steroids were started. On day 3, her status epilepticus broke and a few days later she recovered consciousness. Although with moderate cognitive impairment, she was discharged to rehab with an otherwise nonfocal exam, including being oriented to self, place and time. No further status epilepticus episodes have been reported by her family on subsequent outpatient follow up visits. She remains on multiple antiepileptic drugs to control her intractable epilepsy.

Deline, Christopher

Severe Multi-focal Polyradiculoneuropathy After Administration Of Ipilimumab

George Manustakis[1], Alan Pestronk[1], Christopher J. Deline[1], Muhammad T. Al-Lozi[1], Matthew Harms[1], R. Brian Sommerville[1], Robert Schmidt[2]
[1] Department of Neurology, [2] Department of Pathology & Immunology,
Washington University in St. Louis

Abstract

Introduction: Ipilimumab is a monoclonal antibody against CTLA-4, recently approved by the FDA for treatment of metastatic melanoma. Immune-related adverse events have been previously reported, including neuromuscular complications.

Methods: Case Report.

Results: A 31-year old Caucasian male who developed rapidly progressive cranial neuropathies, severe asymmetric distal weakness of all limbs, and respiratory failure after 4 doses of ipilimumab. EMG/NCS showed an axonal polyradiculoneuropathy with transient conduction block in three motor nerves. Pathology showed microvasculopathy with isolated endoneurial inflammation. Other etiologies of neuropathy were excluded.

Conclusion: We report a rare and unusual case of ipilimumab drug-toxicity manifesting as a rapidly progressive severe multifocal polyradiculoneuropathy, with clinical-pathologic evidence of endoneurial inflammatory microvasculopathy or disruption of blood-nerve barrier. Further evaluation of the management of such a severe side effect is warranted.

Galindo, Rafael

Endogenous Nmnat1 protein expression in a mouse model of neonatal hypoxia-ischemia (H-I): implications for the role of NMNAT proteins in neuroprotection from neonatal H-I

Rafael Galindo., M.D., Ph.D – Dr. David Holtzman's Laboratory

Hypoxic ischemic encephalopathy is one of the most common neurological complications encountered in the neonatal period and its neurological consequences often lead to the development of chronic conditions including cognitive impairment, cerebral palsy and epilepsy. Recent published data demonstrates that increases in the expression of cytoplasmic NAD synthesizing enzyme Nmnat1 (nicotinamide mononucleotide adenylyl transferase 1) produces very strong neuroprotection against cerebral neuronal necrosis but not apoptosis from hypoxia-ischemia (H-I) via blocking NMDA-dependent glutamatergic cell death. Compared to adult brains, the control non-operated neonatal brain expresses relatively low levels of Nmnat1 protein. In these animals, Nmnat1 immunoreactivity is primarily localized to the neuronal nucleus and it is predominantly found in the cerebral cortex and the CA1 layer of the hippocampus as compared to other regions such as the dentate gyrus. Animals exposed to H-I consistently showed a time-dependent increase in Nmnat1 immunoreactivity in neurons of the hippocampus and cortex contralateral to the ischemic hemisphere (areas that are resistant to injury – contralateral to carotid ligation). In the ipsilateral brain regions, we also observed increases in Nmnat1 immunoreactivity in the cerebral at 24 and 72 hrs post H-I. In the ipsilateral hippocampus and primarily in the CA1 region, changes in CA1 immunoreactivity were also observed but were dependent on the extent of injury; animals with relatively mild injury showed increases in Nmnat1 immunoreactivity whereas animals with more severe injury demonstrated decreases in neuronal Nmnat1 immunoreactivity. In contrast, mouse cortices and hippocampi at 7 days following hypoxia-ischemia demonstrated consistent decreases in Nmnat1 neuronal immunoreactivity in both ipsilateral and contralateral sides as compared to 24 and 72 hrs post H-I. These data suggest that the expression of endogenous Nmnat1 changes in a time-dependent and region-specific manner in response to neonatal hypoxia-ischemia. While Nmnat itself may or may not be an enzyme that can be targeted for therapy, further understanding of the endogenous role of Nmnat1 and its homologues (Nmnat2 and Nmnat3) as well as the pathway by which it can be neuroprotective may provide new insights into both the pathogenesis and treatment of neonates exposed to hypoxia-ischemia.

Haydon, Devon H.

Predictors of Ganglioglioma Recurrence in Children

Mentor: Jeffrey R. Leonard, MD

Objective: Gangliogliomas are "benign" neuroepithelial tumors but can recur/progress with varying frequency. We reviewed our institution's series of gangliogliomas in children in order to identify features that predict event-free survival.

Methods: Clinical charts were retrospectively reviewed from St. Louis Children's Hospital and Barnes-Jewish Hospital. Fifty-three consecutive patients treated between 1990 and 2011 were identified who had been diagnosed with a WHO grade I ganglioglioma before age 21 and for whom complete follow-up data was available. Demographic, radiologic, treatment, histologic, and outcomes data were collected.

Results: Mean age at diagnosis was 11.2 years (range 10 months to 20 yrs) with a male to female ratio of 1.65:1. Cortical location predominated with 42 cases (79%). Six tumors were infratentorial. Twenty-eight lesions were cystic, and 79% of tumors demonstrated gadolinium enhancement on T1-weighted MRI. Thirty-seven patients presented with seizure (70%). Gross total resection was achieved in 34 cases (64%). Sixteen specimens showed evidence of microvascular proliferation (31%). Six cases revealed Ki-67 labelling ≥ 1.5%. Seventy percent of tumors showed mild inflammatory infiltrates, while moderate and severe infiltrates were present in 24% and 6%, respectively. Fifteen children (28%) experienced an event during the study period. Mean follow-up was 4.2 years. Kaplan-Meier analysis revealed a 5-year-event-free survival of 72%. In univariate analysis, age at diagnosis ($p=0.019$), gadolinium enhancement ($p=0.034$), seizure history ($p<0.001$), tumor location ($p<0.001$), extent of resection ($p<0.001$), microvascular proliferation ($p=0.017$), Ki-67 labelling (0.008), and presence of inflammatory infiltrates ($p<0.001$) were all associated with event-free survival. A multivariate Cox regression model of clinical features identified seizure history ($p=0.014$), tumor location ($p=0.004$), and extent of resection ($p=0.005$) as independent predictors of event-free survival. Multivariate regression also identified Ki-67 labelling ≥ 1.5% ($p=0.003$) and presence of inflammatory infiltrates ($p=0.02$) as independent histologic predictors of event-free survival.

Conclusion: Pediatric gangliogliomas are potentially curable neoplasms when complete resection is achieved. However, many subtotally resected and even some completely resected lesions progress/recur requiring additional therapy. Seizure history, tumor location, and extent of resection are independently associated with event-free survival. The histologic features of Ki-67 labelling and presence of inflammatory infiltrates identified a clinically more aggressive subset of WHO grade I gangliogliomas as well. Confirmation of these associations requires additional prospective studies.

Kafaie, Jafar
Jafar Kafaie MD, PhD, Mathews Harms MD, [1] Robert Baloh MD, PhD.[1,2]
[1]Washington University School of Medicine, Department of Neurology.
[2] Cedars-Sinai Medical Center's Neuromuscular Division, CA

CSF RNA-Seq pilot study in ALS: Diagnostic and biomarker

Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder of undetermined etiology that primarily affects motor neurons in the cortex, brainstem, and spinal cord. ALS is relentlessly progressive, with most patients succumbing to respiratory failure a median of 3 years after onset. Its incidence and prevalence in USA is about 2 per 100,000 and 3-8 per 100,000 respectively. The biologic basis of the disease is still not understood. Recently however, mutations in the transactive response DNA-binding protein (TDP-43) and fused in sarcoma/translocated in liposarcoma (FUS/TLS) were discoverand to cause ALS, pointing toward abnormal RNA processing as a potential mechanism of pathophysiology. The majority of current biomarker research focuses on brain and spine imaging, CSF proteomics and electrophysiological based markers, but CSF RNA expression studies remain under-explored and have not taken advantage of emerging next-generation sequencing technology. Next-gen sequencing approaches, such as RNA-seq, offer the opportunity to characterize RNA expression profiles while permitting the discovery of previously unannotated exons, identification of alternative splicing events (including exon skipping or intron inclusion), and the detection of non-human transcripts (i.e. from potential virus). We tested the feasibility of RNA-seq analysis of human CSF.

Methods: Whole-RNA was purified from CSF obtained from three patients with sporadic ALS using a Qiagen kit with minor modifications of the manufacturer's protocol. RNA quality and quantity was checked before preparing a stardard RNA library for sequencing. Next-generation sequencing was performed at the Washington University GTAC. Results were analyzed by Parteck software.

Results: An average of 20 ng of total RNA was purified from each 1 ml of CSF, and showed sufficient quality and quantity for RNAseq. An average of 27,000,000 reads identified per sample, identifying an average of 7000 transcripts originating from 4000 genes. A substantial fraction of reads could not be aligned to the human genome and represent a pool of potential novel transcripts or viral sequences. Further analysis is ongoing.

Interpretation: This pilot project provides a proof-of-feasability for RNASeq analysis of ALS CSF. Further study of a larger group of patients may reveal important changes in RNA processing that my shed light on ALS pathogenesis or identify potential biomarkers.

Mitike, Mesfin

Disseminated Blastomycosis: A case report

Mesfin T. Mitike, MD Washington University School of Medicine

Abstract:

Blastomycosis is a chronic systemic fungal infection characteristically affecting the skin and lungs. Involvement of the central nervous system (CNS) is unusual. We presented a 75 year-old immunocompetent man initially presented to outside hospital (OSH) with fever of unknown origin (FUO). He was found to have subcutaneous abscess which was surgically drained and culture and sensitivity grew Pseudomonas aerogenosa. He was treated appropriately with antibiotics and site of infection healed.

He latter presented with progressive neurologic deficits and altered mental status requiring prolonged hospitalization. His brain biopsy from OSH was non-diagnostic and slide reviewed at our pathology department. His work up included multiple biopsies based on PET positive scans and multiple CSF studies. He got biopsy to the masses seen on the muscle and cauda equina area which were non diagnostic. While being prepared for second brain biopsy, urine and CSF Histoplasmosis tests were positive leading to confirmatory skin biopsy and DNA probe test on the old scar tissue confirming the diagnosis of disseminated Blastomycosis.

He was treated with IV Ambisome with marked clinical improvement. He was discharged to rehabilitation with continued anti-fungal treatment for 12 months. He improved clinically and follow-up MRI of brain showed near complete resolution of the lesions in the brain. High index of suspicion and checking fungal serologic tests remained the diagnostic tool to reach to final diagnosis and avoid unnecessary surgical procedures.

Norris, Scott

Post-Surgical Brain Shift Following STN targeted DBS Electrode Placement in Patients with Parkinson Disease.

Norris SA, Campbell MC, Harring SD, Lugar HM, Hershey T, Karimi M, Tabbal SD, Videen TO, Perlmutter JS

Background: Deep Brain Stimulation (DBS) is frequently targeted at sub-thalamic nucleus (STN) for symptomatic therapy in patients with advanced Parkinson disease. A number of studies have demonstrated occurrence of brain shift during sterotactic surgery (Gerdes FU et al. 1975, Hariz MI et al. 1993, Halpern CH et al. 2008) and anterior curvature with displacement of DBS electrodes in the weeks following electrode placement (van den Munckhof et al. 2011). Active contact locations may differ with respect to the subthalamic nucleus, and thus may account for variability in motor, psychiatric and cognitive responses to DBS (Hershey et al. 2004). Thus, it is critically important to accurately locate and monitor active contact location in relation to structural targets following surgical implantation.

Methods: We retrospectively studied twenty-nine patients with bilateral implantation of STN DBS stimulators who underwent pre-operative MRI (1.5T Siemens Vision), immediate post-operative head CT (Siemens Somaton Plus 4), and delayed high resolution head CT (Siemens Somatom Definition). CT images were co-registered to pre-operative MR images with pre-identified anatomic fiducials. We utilized a validated fiducial-based atlas localization method (Videen et al. 2007) to identify active contacts on post-operative CT images in atlas space with respect to registered fiducial-based anatomical landmarks. We then compared active contact localization in the immediate post-operative head CT with the delayed head CT to assess for shift.

Results: Mean active contact localization was significantly displaced between the immediate post-operative head CT and the delayed CT in all three measured Cartesian planes (t-test, $p<0.05$) such that displacement occurred in the rostral-dorso-lateral direction. Mean vector magnitude of displacement on the right was 1.55mm, SD 0.74, and on the left was 1.63mm, SD 0.80. Mean displacement magnitude on the side operated first (left) did not significantly differ from the side operated second (right) (t-test, $p = 0.47$). Magnitude of displacement was independent of elapsed time between head CTs (range 6-84 months; mean: 21.8 months; SD: 19.4- $r = 0.075$, $p = 0.40$), and surgeon ($N = 2$, t-test, $p = 0.36$).

Conclusions: Following DBS electrode implantation targeted at STN, there is displacement of electrodes from the area of initial placement. While displacement is consistently in the rostral-dorso-lateral direction (along the entry tract), the overall vector magnitude is within the error of the test and less than the 2mm error accounted for in electrode placement. Thus, post-operative DBS electrode displacement in the current patient population likely does not contribute to a clinically significant effect. Furthermore, electrode displacement is independent of time duration from surgery, further supporting accumulating evidence that resolution of intraoperative brain shift likely accounts for observed electrode displacement post-operatively.

Peche, Shubhangi

The Spectrum of Diagnosis and Management of Headaches in a Pediatric Emergency Department

Shubhangi S Peche M.D., Sara Isbell MS, Jason Lenox MS, Soe Mar M.D., Arthur Prensky M.D.,

Department of Pediatric and Developmental Neurology, Washington University School of Medicine, St. Louis, MO.

Background: Headaches in Children and adolescents are common presenting complaints in emergency department. The prevalence of headache ranges from 37-51% during the elementary school years and gradually rises to 57-82% by the high school years .Headaches have a significant impact on the lives of children and adolescents, resulting in school absence, decreased extracurricular activities, and poor academic achievement. There is wide variation among acute treatments and their effectiveness

Objective: To analyze the diagnoses and management of children presenting with Headaches as a chief complaint.

Methods and Materials: Retrospective chart review of patients presenting with headache to St. Louis Children's Hospital ER between 2007 to 2010. **1499** charts with presenting diagnosis of Headache according to ICD 9 code were reviewed. Headaches were classified in to Primary, Secondary and non classifiable. Migraine patients were further analyzed to review Pre medication pain score (PRPS), Post medication pain score (POPS), and type of medication used (Oral, IV or combination). Patients with PRPS, POPS and Medications data available were included in final analysis. Kruskal-wallis test, Rank Analysis of Covariance tests were used for statistical analysis.

Results: Oral medications has statistically significant lower mean pre-pain score ($p=0.01$). Triptans and combination of triptans and Ibuprofen were given to patients with higher PRPS ($p<0.01$) than Ibuprofen alone. There was no significant difference among Ibuprofen, Triptans and combination of ibuprofen and triptans on the change in pain score ($p=0.06$) or post pain score ($p=0.22$). IV medicines and Combination of oral and IV medicines were given to patients with higher PRPS than oral medicines alone ($p=0.01$). There was no statistical difference between oral, IV or combination of oral and IV on post pain score ($P=0.53$). Oral meds alone had a significant lower change in pain score (PRPS minus POPS) ($p<0.01$), But when taken in to account that oral medications alone were prescribed to patients with lower PRPS, there was no statistically significant difference among the three medications strategies on the change in the pain score ($p=0.19$ by Rank Analysis of covariance)

Conclusion: Majority of ER visits were due to migraine or other minor illnesses that required outpatient analgesic treatment. Cost of healthcare and use of ER resources could be significantly reduced if they could be treated in Non ER setting. Prospective, controlled trials are needed.

Peche, Shubhangi

IPMS criteria in Children with CNS Demyelination: A Long Term Follow-up Study

Shubhangi S Peche M.D.[1],Amer Alshekhlee M.D.MS[3], Jason Lenox MS[1], Sara Isbell MS[1], James Kelly M.D.[2] ,Soe Mar M.D.[1]

1. Department of Pediatric and Developmental Neurology, 2. Mallinckrodt Institute of Radiology , Washington University School of Medicine, St. Louis, 3. Department of Neurology, Saint Louis University, St. Louis.

Background: Diagnoses of various childhood demyelinating diseases can be challenging. Historically they were commonly mislabeled. IPMS published consensus statement to standardize the definitions for the ease of diagnosis. We attempt to validate the use of those definitions for the correct diagnosis and routine use in clinical practice in this large cohort in which patients were followed up to 25 yrs.

Objective: To evaluate the practical application of international pediatrics multiple sclerosis (IPMS) definitions in children with inflammatory demyelination of the CNS. We also attempt identifying the possible predictor of multiple sclerosis (MS).

Methods and Materials: Data were collected on 123 children with acute first demyelination of the central nervous system for the period between 1985 and 2010. Information on the basic demographics as well as the initial diagnoses of different demyelinating condition according to the IPMS was recorded. These children were retrospectively and prospectively followed and the changes in the diagnoses were corroborated with the initial diagnoses. Multivariate logistic regression analysis was performed to assess the predictors for future development of MS.

Results: The mean age of this cohort was 10.8 ± 4.97; with the majority of female (56.1%). Using IPMS definitions, 47 (38.2 %) patients had met criteria for ADEM, 67 (54.4%) had clinically isolated syndrome (CIS). Information on clinical follow-up was available on 118/123 children (95.9%), with the mean follow-up of 79.2 ± 69.9 months. The rate of conversion from CIS to MS occurred in 26/67 (38.8%); whereas the rate of conversion from ADEM to MS occurred in 4/47 (8.5%). Adjusted analysis for an outcome of future development of MS showed the following **predictors**: **female gender** (Odds ratio 'OR' 12.44; 95%CI 1.03, 149.3); **initial diagnosis of brain stem or hemispheric dysfunction** (OR 24.57; 95%CI 3.06, 196.78); and **Callen MRI criteria** if met (OR 122.45; 95%CI 16.57, 904.57).

Conclusion: IPMS criteria affirm that children with initial CIS are more likely to develop future MS compared to those with initial diagnosis of ADEM in this large cohort .In addition, female gender, brain stem or hemispheric involvement and Callen MRI criteria predict the diagnosis of MS.

Ryman, Davis

Heritabilty of age of onset in autosomal dominant Alzheimer's disease mutations: a meta-analysis

The Dominantly Inherited Alzheimer's Network (DIAN) is a multicenter study which collects multiple forms of clinical and biomarker data in a large set of families carrying mutations causative for autosomal dominant Alzheimer's disease (ADAD). Although ADAD represents a small minority of total AD cases, the identification and study of ADAD mutations in the genes for amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) has been of central importance in elucidating the broader mechanisms of disease. If sufficiently powerful predictors of age at onset can be developed and validated, the DIAN study will enable highly informative evaluations of clinical and biomarker variables with respect to each individual's relative point in the disease process, prior to observing a clinical transition to dementia for all study participants based on existing diagnostic criteria.

ADAD mutations are highly penetrant and result in early onset of AD, often decades earlier than typical for the more common sporadic late-onset AD. The lack of a comprehensive meta-analysis comparing parent-child correlations at the individual level across multiple ADAD pedigrees has made it difficult to compare variability between families of different sizes, or to calculate heritability of age of onset by observing parent-child correlations within extended families. Evidence to date suggests that age of onset for ADAD affected individuals within a given family may vary by as little as plus or minus 2% to as much as +/- 35%, and the factors influencing age of onset in patients with ADAD mutations remain incompletely understood. By compiling a relational database recording parent-child relationships and age of symptom onset at the individual level for ADAD pedigrees from the published literature and from DIAN participant families, I aim to calculate estimates for the heritability of age of onset for specific ADAD mutations within extended families, and further investigate the effects of potential modifiers such as gender, years of education, and ApoE genotype within a subset of these patients.

Schindler, Suzanne

Treatment of Childhood Hydrocephalus in Haiti

Suzanne E. Schindler[1], David Limbrick[2], Keith Rich[2]
Department of Neurology[1] and Neurological Surgery[2]

Severe childhood hydrocephalus is relatively common in Haiti. The high prevalence of neural tube defects, meningitis, and decreased prenatal care likely contribute to high rates of the disorder. Neurosurgical care has often been unavailable, resulting in untreated hydrocephalus. When shunts have been placed by native surgeons, the infection rate has been unacceptably high (>50%). Endoscopic third ventriculostomy (ETV), which creates an artificial communication between the floor of the third ventricle and the subarachnoid space, is an alternative to shunting. Neurosurgeons from Washington University have performed the ETV procedure on >70 children with hydrocephalus. The rates of post-operative infection have been low. The most common complications have been fevers and seizures. Follow-up data is lacking; however, a number of children who have undergone the procedure have returned with good clinical outcomes.

Shah, Manish

"Early Readmissions on a Neurosurgical Service Can Reflect Excellent Care"

Mentor: Ralph G. Dacey, Jr., MD

ABSTRACT:

Objective:
To examine the reasons for early readmissions within 30 days of discharge to a major academic neurosurgical service.

Methods:
A database of readmissions within 30 days of discharge from April 2009 to September 2010 was retrospectively reviewed. Clinical and administrative variables associated with readmission were examined including age, gender, race, days between discharge and readmission and insurance type. The readmissions were then assigned by 2 independent neurosurgeons into one of 3 categories: scheduled, adverse event, and unrelated. The adverse event readmissions were further subcategorized into patients readmitted though best practices were followed, those readmitted due to progression of their underlying disease and those readmitted for preventable causes. These variables were compared descriptively.

Results:
A total of 348 patients with 407 readmissions were identified comprising 11.5% of the total 3552 admissions ranging from age 16 to 96 (mean age 54.8). The proportion of patients 65 or older (31.3%) was not significant ($p = 0.19$). There were 113 readmissions for electively scheduled operative cases (27.8%). There were 266 adverse events requiring readmission (65.4%), of which 118 patients (29.0%) were readmitted for preventable causes, 99 patients (24.3%) were readmitted although best practice was followed and 49 patients (12.0%) were readmitted due to progression of their underlying disease. Finally, 28 patients (6.88%) were readmitted due to unrelated causes from primary admission. There was no significant difference in the reason for readmission between privately insured patients and those with public or no insurance ($p = 0.09$).

Conclusion:
The majority of early readmissions within 30 days of discharge to the neurosurgical service were unavoidable adverse events. Many of these readmissions were for complications that occurred though best practices were followed or from progression of the natural history of neurosurgical disease requiring expected but unpredictably timed subsequent treatment. Overall, judicious care often requires readmission to prevent further morbidity and mortality in neurosurgical patients.

Thangarajh, Mathula

Magnetic resonance angiography-defined intracranial vasculopathy is associated with silent cerebral infarcts, and glucose-6-phosphate dehydrogenase mutation in children with sickle cell anemia.

Mathula Thangarajh,1 Genyan Yang2, Dana Fuchs,3 Robert C. McKinstry,3 Bruce Vendt,4 Mark Rodeghier,5 Michael J. Noetzel,1 James F. Casella,6 Michael R. DeBaun7

1Departments of Neurology and Pediatrics, Washington University School of Medicine, Saint Louis, MO; 2Clinical and Molecular Hemostasis Laboratory Branch, Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA; 3Pediatric Radiology and Neuroradiology Sections, Washington University School of Medicine, Saint Louis, MO; 4Electronic Radiology Laboratory, Mallinckrodt Institute of Radiology, Washington University School of Medicine, Saint Louis, MO; 5Statistical Collaborator, Chicago, IL; 6Department of Pediatrics, Division of Hematology, Johns Hopkins University School of Medicine, Baltimore, MD; 7Department of Pediatrics, Vanderbilt Meharry Sickle Cell Disease Center of Excellence, Vanderbilt University, Nashville, TN.

Abstract

We tested the hypothesis that silent cerebral infarcts (SCI) are associated with magnetic resonance angiography (MRA)-defined intracranial vasculopathy. Magnetic resonance imaging and MRA were available in 516 children between 5 and 15 years of age, with hemoglobin SS and S beta0 thalassemia enrolled in the Silent Infarct Transfusion Trial. SCI were present in 41.5% (214 of 516) of children, whereas, vasculopathy was present in 10.3% (53 of 516) of children. The prevalence of intracranial vasculopathy among children with and without SCI was 15.9% (34 of 214) and 6.3% (19 of 302), respectively ($p < 0.001$). Intracranial vasculopathy occurs in a minority of children with SCA, but when present, is associated with SCI. We further tested in male patients (n=209) whether genetic variation in glucose-6-phosphate dehydrogenase (G6PD)—alone or in the context of α-globin gene deletions—is a risk factor for vasculopathy, and abnormal cerebral velocity as measured by transcranial Doppler (TCD). G6PD gene status was associated with vasculopathy (OR 2.95, 95% CI (1.09-8.04), $p = 0.03$). Two α-globin deletions, age, and hemoglobin level were predictive factors for abnormal TCD ($p \leq 0.05$).

Acknowledgements

The Silent Infarct Transfusion (SIT) trial is supported by the National Institute of Neurological Disorders and Stroke (NINDS), Rockville, Maryland, #U01 NS042804 (ClinicalTrials.gov). The authors thank the children and their families for participation in the study, and the SIT Trial study coordinators.

Tripp, Angela and J. Kronberg

A Case Report of Epidural Gout and Paraplegia

Tripp A, Kronberg J, Juknis N, Boellert K.

Physical Medicine and Rehabilitation, Division of Neurology, Washington University, St. Louis, MO 63110

Abstract

OBJECTIVE AND IMPORTANCE:
Tophaceous gout of the spine is well documented in the literature in cases of myelopathy and cord compression. Nevertheless, relatively speaking, it is still a rare and interesting occurrence. We present a patient with the clinical manifestations of spinal cord compression initially, followed by peripheral joint inflammation, and finally, histologically proven peripheral and epidural gout. Interestingly, imaging also revealed a Chiari I malformation and extensive syringomyelia.

CLINICAL PRESENTATION:
A morbidly obese 34 y/o Male presented with sensory changes from T4 level down and lower extremity paralysis after his legs became weak and a subsequent fall. At initial presentation, there was no evidence of peripheral gout. However, 3 days into his hospitalization, he complained of elbow and wrist pain.

INTERVENTION:
Magnetic resonance imaging (MRI) demonstrated an epidural fluid collection from C7-T6. Additional findings included a Chiari I malformation, syringomyelia, and T12-L1 disc extrusion causing severe canal stenosis. Intravenous antibiotics were empirically initiated for epidural abscess. The patient underwent multi-level laminectomies and removal of a cheesy white material on the dura. An aspiration of his elbow was performed 3 days later. The joint aspirate was positive for negatively birefringent crystals, and the pathological examination of the intraoperative specimen revealed findings consistent with tophaceous gout. The patient received a course of oral Prednisone, steroid joint injection, and oral Colchicine was initiated.

CONCLUSION:
Spinal gout should be considered in patients presenting with back pain, radiculopathy, or myelopathy, especially in patients with risk factors or a history of gout. In this case, the patient's clinical presentation was consistent with the location of the epidural tophaceous deposits, but of additional interest were the aforementioned MRI findings. Despite medical and operative intervention, this patient remained neurologically compromised. His rehabilitation was severely limited by his size, upper extremity joint gouty arthritis, and persistent paraplegia.

Washington, Chad

A Novel Technique in Controlling for Severity of Subarachnoid Hemorrhage in Analysis of the Nationwide Inpatient Sample: The NIS-SAH Severity Score

Chad W. Washington, M.D. [1], Colin P. Derdeyn, M.D. [1,2,3],
Ralph G. Dacey, Jr. [1], Michael N. Diringer, M.D. [2], Gregory J. Zipfel, M.D. [1,2]

Departments of Neurological Surgery[1], Neurology[2], and Radiology[3]
Washington University Center for Stroke and Cerebrovascular Disease
Washington University School of Medicine
Saint Louis, Missouri, USA, 63110

Introduction

Studies utilizing the Nationwide Inpatient Sample (NIS) analyzing aneurysmal subarachnoid hemorrhage (SAH) outcomes have been limited by an inability to control for initial hemorrhage severity, a factor known to be predictive of patient outcome. To address this, we sought to develop and validate a novel NIS-SAH Severity Score (NIS-SSS).

Methods

Patients from the 1998-2009 NIS (N=296,353) with aneurysmal SAH, were randomly divided into Populations-I and II. Population-III (N= 716) was derived from our institutional database, cross-matching ICD-9 codes with admission Hunt & Hess (HH) grade and discharge modified Rankin score (mRS). Population-I was used to develop the NIS-SSS; Populations-II and III were for validation. Population-I was classified by diagnosis codes likely to predict SAH severity. Diagnoses were entered into a multivariate-logistical regression model predicting patient outcome. By summing model-generated coefficients of significant predictors, a NIS-SSS was calculated for each patient. In Population-III, the ability of the NIS-SSS to predict patient outcome and HH grade was analyzed using logistic regression and ANOVA. In Population-II, using logistical regression, NIS-SSS was compared to APR-DRG Mortality, APR-DRG Severity, APS-DRG Mortality, and DRG in predicting outcome.

Results

Significant predictors of outcome were: mechanical ventilation, coma, hydrocephalus, paresis/plegia, aphasia, and cranial nerve deficit. In all populations, NIS-SSS was a significant predictor of outcome. In Population-III, there was a significant correlation between NIS-SSS and HH grade (Figure-1A); and NIS-SSS and HH grade strongly predicted poor outcome (Figure-1B and 1C). In Population-II, NIS-SSS outperformed all other NIS measures in predicting outcome (Figure-2).

Conclusion

These results demonstrate that the NIS-SSS - which correlates with HH grade, predicts outcome after SAH, and outperforms established measures of disease severity - can be derived from the NIS database. From this we believe that the NIS-SSS should be included in future NIS analyses.