Neuroscience Day 2008 Abstracts

Amanda Hamilton
Continuous video EEG monitoring of comatose patients in the intensive care unit
We are planning to look at patient's in the ICU over the last one-two years who were comatose and underwent continuous video-EEG monitoring to see what the treatments and outcomes were. Questions of interest that may be answered include does aggressive treatment of such cases actually change the potentially poor outcome? Does the duration or number of seizures effect the patient's outcome? How long should monitoring be performed to assess for subclinical seizures? Could other comorbidities play a significant role in outcomes?

Angela Mark
A randomized crossover study of standard NIPPV and low expiratory pressure NIPPV in ALS patients
Angela Mark, MD‡, Brisa Sanchez Loya, PhD‡; Devin Brown MD, MS‡; Kirsten L. Gruis MD, MS‡;
‡ Department of Neurology, University of Michigan Health System, Ann Arbor, Michigan, USA
‡ Department of Biostatistics, University of Michigan Health System, Ann Arbor, Michigan, USA
Introduction: Tolerance to noninvasive positive pressure ventilation (NIPPV) prolongs survival and improves quality of life in ALS patients with respiratory muscle weakness. Yet, only a small proportion of ALS patients who meet American Academy of Neurology practice parameter guidelines for NIPPV treatment are actually using the therapy, in large part due to NIPPV intolerance. Methods for improving ALS patient NIPPV tolerance are desperately needed.

One reason for NIPPV intolerance may be the requirement to breathe out against expiratory positive airway pressure (EPAP), likely increasing dyspnea and respiratory fatigue. EPAP is used in standard bi-level NIPPV machines to prevent CO_2 re-breathing. However, portable lap-top ventilators eliminate the possibility of re-breathing expired CO_2 by having two separate circuits for inspiration and expiration. This allows NIPPV to be administered as IPAP (inspiratory positive airway pressure) only.

Objective: to conduct a randomized, crossover study comparing standard NIPPV with IPAP-only NIPPV, with respect to objective NIPPV use, quality of life, patient satisfaction, and side effects.

Methods: Study subjects: 18 patients with probable or definite ALS who have been using NIPPV for 2 months or more will be recruited from the University of Michigan, Motor Neuron Disease clinic. Patients must also have a maximal inspiratory force (MIF) < 60 cm/H_2O or forced vital capacity (FVC) < 50% predicted.

Study Design: The study is a randomized, crossover study of two different NIPPV settings. Subjects will be randomized on a 1:1 basis to one of two groups differing in the sequence of NIPPV settings ((a) standard followed by IPAP-only or (b) IPAP-only followed by standard). Subjects will then spend 6 weeks using the first NIPPV set-up before crossing over to the other NIPPV treatment for 6 weeks. Viasys Healthcare lap-top ventilators will be used to provide both the standard and IPAP-only treatments. For standard treatment, IPAP and EPAP will be set to the patient's current, bi-level IPAP and EPAP settings. For IPAP-only treatment, IPAP will be reduced by 4 cm H_2O and EPAP will be lowered to 0 cm H_2O to maintain the identical pressure support.

Study Outcomes: The primary outcome is NIPPV use, as summarized by weekly means and standard deviations of objective hours of use for the two NIPPV set-ups (standard and IPAP-only) over weeks 2-6 of each treatment period. Secondary outcomes measured at the end of each treatment period include quality of life, dyspnea, and patient satisfaction, measured with validated scales.

Statistical Methods: Sample Size: Eighteen subjects are required to detect a 2-hour difference in the primary outcome assuming the following: power of 80%, an alpha = 0.05, with 2-sided testing. This is based on the assumption that the within-patient standard deviation of the response variable is 2 hours, and there will be negligible carryover effects.

Analysis Plan: The primary analysis will be conducted using repeated measures analysis of variance. The treatment effect will be adjusted for time period to account for any increase in NIPPV through the study period due to, for example increased respiratory muscle weakness. This adjustment is conducted by including a main effect for period in the model. Treatment effect will be tested at the 0.05 significance level. Quality of life and dyspnea, secondary outcome measures, will also be analyzed in a similar fashion with a repeated measures analysis.

Conclusion: Funding (ALS Association, PI: Gruis) and IRBMED approval were secured. Enrollment has begun. We anticipate results in approximately one year.
Brian Abaluck

Changes in Cognition During Internship

Insufficient sleep during physician training is a primary contributor to medical error, adverse patient outcomes including death, and impaired mental health among trainees. Despite ACGME regulations that limit work hours, residents continue to work up to 80 hours per week in shifts as long as 30 hours. Several studies have demonstrated impaired performance, sometimes equivalent to that of moderate alcohol intoxication, associated with these work hours. However, the potentially cumulative cognitive effects during a full year of training remain largely unexplored. Acute effects of call schedules on cognitive performance are well studied. One meta-analysis found the greatest next-day cognitive impairments in clinical performance, followed by vigilance, memory, and finally verbal intelligence. Only two studies have examined potential subacute effects of call-induced sleep restriction, by comparing non-post-call resident performance during heavy in-house call months and non-call months: one study found no difference in verbal intelligence while the other found relative impairment in vigilance during call months. Thus, call-related impairment may differ by type of task, but tasks known to be most sensitive to sleep loss (i.e., vigilance) may demonstrate both acute and chronic impairment from sleep deprivation during medical training. No study has evaluated the residual cognitive impairment that may occur following repeated exposure to call across a year of medical training. In contrast, long-term exposure to sleep deprivation associated with call is known to be associated with mood disturbances. A cohort of interns at the University of Pennsylvania experienced depression, anger, and fatigue that worsened across the first five months of internship and then stabilized. A subsequent intern cohort demonstrated development of depression and burnout. Among interns in this cohort who were not chronically sleep-deprived or depressed at the onset of internship, chronic sleep deprivation (report of <42 hrs of sleep over prior 7 nights) moderated the development of depression during internship. Experimental studies of healthy non-physicians suggest that chronic partial sleep deprivation induces cognitive deficits that do not recover immediately. In one study, subjects restricted to 3, 5, and 7 hours of time in bed for seven consecutive days demonstrated dose-dependent declines in vigilance. Subjects restricted to 5 and 7 hours nightly did not demonstrate complete recovery of baseline vigilance after three days of 8-hour recovery sleep periods. Subjects restricted to 3 hours per night reached a level of vigilance equivalent to that seen in the 5-hour group after one night of recovery sleep, but showed no further recovery in vigilance after 2 more nights of recovery sleep. The degree or time course of recovery beyond three days remains unknown.

In short, several lines of evidence from subjects subjected to chronic partial sleep deprivation combine to suggest that interns may experience significant declines in cognition across spans of time longer than those previously tested. An empirical measure of the accrued effects of sleep deprivation, emotional challenges, and other features of internship on cognition would contribute valuable information to the ongoing discussion regarding medical work hour reform and medical error.

Therefore, we propose a prospective cohort study with the following aims:

Aim 1. To assess cognitive functioning before, during, and after frequent call nights that are required during one year of medical internship (n=25 interns) or absence of overnight call during one year of dental residency (n=25 residents). Medical interns and dental residents have similar levels of education. Hypothesis 1. Compared to dental residents, cognitive functioning in medical interns will show greater decline after several months (2nd time point) and one year (final time point) of training. Aim 2. At similar time points and in the same groups, assess subjective sleepiness and depression. Hypothesis 2a. After baseline measurement, medical interns in comparison to dental residents will show greater subjective sleepiness and depression. Hypothesis 2b. In statistical models, sleepiness and depression will each partially account for differences in cognitive performance observed between physician interns and dental trainees.

Dan Leventhal

The Role of the Basal Ganglia in Movement Initiation and Suppression

Dan Leventhal M.D., Ph.D., and Joshua Berke, Ph.D. (Department of Psychology, U of M)

Parkinson’s disease (PD) is a neurodegenerative condition characterized by resting tremor, bradykinesia, rigidity, and postural instability. We propose to use electrophysiologic methods in rats trained on a task known to be impaired in PD to 1) study BG circuits important in the pathophysiology and treatment of PD, and 2) establish a test system to study how dopamine depletion and PD treatments impact these circuits. Stop-signal tasks provide a measure of the ability to inhibit a planned action. In these tasks, the subject is trained to respond to a cue; in a subset of trials, the subject is presented with a second stimulus (the stop-signal) indicating that the planned movement should be arrested. We have chosen this task to for several reasons. First, it is not only impaired in patients with PD, but is also affected by DBS of the subthalamic nucleus (STN). As described below, there is mounting evidence that the BG circuits that mediate the stop-signal response are the same ones important in the pathophysiology and treatment of PD. Finally, rats have been successfully trained on stop-signal tasks, and stop-signal experiments can be performed in human subjects during implantation of DBS electrodes. Therefore, an opportunity exists to directly compare animal to human data. A horse-race model of action cancellation has been proposed where GO and STOP processes evolve independently, with the winner determining behavior. This model has been applied in human and animal studies of behavior inhibition, with generally good agreement with the data. While these studies suggest the existence of a subconscious race, the neural substrates of the GO and STOP processes remain unknown.

Several lines of evidence suggest that the direct BG pathway is critical for movement initiation, while the hyperdirect pathway is important for action cancellation. Lesioning or depleting dopamine from the striatum leads to slowed reaction times. Conversely, subthalamic nucleus lesions or stimulation improve reaction time, but may lead to unwanted movements and impulsivity. Recently, an fMRI study in humans suggested activation of the direct pathway with movement initiation, but activation of the inferior frontal gyrus and an area in the vicinity of the subthalamic nucleus upon presentation of a STOP signal. While the above studies suggest regions that are important in action initiation and suppression, they lack the spatial and temporal resolution necessary to determine which signals are driving decision-making and which are epiphenomena. We plan to test the hypothesis that separate basal ganglia pathways mediate the GO and STOP signals by simultaneously recording from multiple key regions in freely behaving rats.
In vitro: Data from split night PSGs for an 18-month period prior to November 2007 were reviewed. Studies were excluded if they were not initial studies, the patient refused Continuous Positive Airways Pressure (CPAP), did not meet split-night criteria, or had incomplete data. Subsequent titration PSGs were also reviewed for those whose split-night PSG was not successful, in order to obtain final CPAP pressures for all subjects.

Results: A total of 402 studies were initially identified and 209 subjects (71% male) fitted the above criteria. Thirty-seven subjects (21%) had unsuccessful split-night PSGs. Studies were excluded if they were not initial studies, the patient refused Continuous Positive Airways Pressure (CPAP), did not meet split-night criteria, or had incomplete data. Subsequent titration PSGs were also reviewed for those whose split-night PSG was not successful, in order to obtain final CPAP pressures for all subjects.

Conclusion: Disease severity was not found to play a significant role in determining which children should have EMG testing. There also is the potential for further statistical analysis of the data once it is obtained. I plan to present biopsy results (if it was completed), and the nerve conduction and EMG results. We hypothesize that EMG and nerve conduction studies are very helpful in the diagnosis of GBM cancer stem cells as well. Mechanisms that disrupt the N-CoR complex may lead to cell differentiation and/or apoptosis in GBM cells and provide the basis for an effective therapeutic strategy. In the current study, we introduce a novel synthetic inhibitor of protein phosphatase PP2A to target specific components of the N-CoR pathway. The serine-threonine protein phosphatase PP2A dephosphorylates Akt kinase, subsequently inactivating it. We show that LB1, a new inhibitor of PP2A, promotes the phosphorylation and activation of Akt kinase, and in turn, the phosphorylation of N-CoR. Phosphorylated N-CoR translocates to the cytoplasm, and gliogenic gene transcription can subsequently occur. Here, we use LB1 to inhibit the in vitro and in vivo growth of GBM cells and correlate its anti-tumor activity with changes in PP2A activity. Akt kinase expression, and N-CoR expression. Finally, the effects of LB1 in vivo and in vitro GMB models are directly visualized with immunostaining. Our findings suggest the potential utility of phosphatase inhibitors such as LB1 in the treatment of malignant gliomas through an N-CoR-mediated differentiation-based mechanism.
Jim Burke

**Background:** Wilson's disease is associated with a host of variable neurologic symptoms and physical findings. Yet, there is limited data correlating those symptoms with long-term outcomes and response to treatment.

**Methods:** A total of 143 patients with neurologic Wilson's disease have been enrolled in treatment trials at our institution over the last 18 years. Of those patients, a total of 87 had a standardized baseline neurologic examination and at least one year of follow-up. A linear regression was performed on both the raw and scaled individual symptom scores compared to the change in total patient score over time.

**Results:** There was a highly significant negative correlation between the presence of tremor on both raw (correlation coefficient -1.77, p < .00004) and scaled (correlation coefficient -2.34) p < .00001) subscores and outcomes, with the presence of tremor predicting improved long-term outcomes. None of the other raw symptoms scores - rigidity, dystonia, finger-nose-finger testing, gait, chorea, speech, cog-wheeling, finger tapping, facial expression, posture or pull testing - was significantly correlated with long-term outcomes. Similarly, there was no significant correlation between symptom duration, gender or age and outcomes. The initial summed symptom score was a better predictor of long-term outcomes than either the initial copper level or the copper clearance attained through the study.

**Conclusions:** The presence of tremor portends a relatively favorable long-term outcome in neurologic Wilson's disease. No specific symptoms were significantly correlated with negative long-term outcomes.

---

John Betsiennann

**Neurology Clinical Skills Builder**

Despite impressive advances in diagnostic testing, reliable histories and physical examinations are still the key to accurate diagnosis. This is true throughout medicine, but particularly in neurology. Medical students must learn the elements of the history and examination that are particularly helpful in narrowing the differential diagnosis, and they must learn how to interpret their findings. The goal of the Neurology Clinical Skills Builder is to create an interactive computer simulation that affords preclinical students, as well students in their neurology clerkship, an opportunity to refine these skills and be exposed to abnormal exam findings that they might otherwise not see. Building on a computer program that was developed in the Department of Medical Education at the University of Michigan, the Neurology Clinical Skills Builder presents various clinical scenarios for student to work through. At the beginning of each case the students are presented with a chief complaint such as, involuntary movements. They are then asked which areas of the history they would like to explore. This is followed by watching a video of a faculty member or resident interviewing an actual patient. In addition, they choose which areas of the physical exam are likely to produce pertinent positive or negative findings. They next see videos of neurologists performing these areas of the exam and demonstrating abnormal findings. These are contrasted with normal examinations. Students also work through review questions associated with the exam findings with various disease processes while stressing neuroanatomic localization. The program emphasizes the importance of performing a complete history and physical, but at the same time allows the students to hone in on the most relevant aspects of each.

---

John Cowan

**Seatbelt and Helmet Depiction on the Big Screen: Blockbuster Injury Prevention Messages?**

**Background:** Injuries from vehicle crashes are a major cause of death among American youth. Many of these injuries are worsened due to noncompliant safety practices. Messages delivered by mass media are omni-present in young peoples' lives and influence their behavior patterns. In this investigation, we analyzed seatbelt and helmet messages from a sample of top-grossing motion pictures with emphasis on scene context and character demographics.

**Methods:** Content analysis of 50 top-grossing motion pictures for years 2000 to 2004, with coding for seatbelt and helmet usage by trained media coders.

**Results:** In 48 of 50 movies (53% PG-13; 33% R; 10% PG; 4% G) with vehicle scenes, 518 scenes (82% car/truck; 7% taxi/limo; 7% motorcycle; 4% bicycle/skateboard) were coded. Overall, seatbelt and helmet usage rates were 15.4% and 33.3%, respectively, with verbal indications for seatbelt or helmet use found in 1.0% of scenes. Safety compliance rates varied by character race (18.3% white; 6.5% black; p<.036). No differences in compliance rates were noted for high-speed or unsafe vehicle operation. The injury rate for noncompliant characters involved in accidents was 10.7%. A regression model demonstrated black character race and escape scenes most predictive of noncompliant safety behavior.

**Conclusions:** Safety compliance messages and images are starkly absent in top-grossing motion pictures resulting in, at worst, a deleterious effect on all populations, especially vulnerable youth. Healthcare providers should call on the motion picture industry to improve safety compliance messages and images in their products delivered for mass consumption.

---

Khoi Than

**Increased risk of cerebral vasospasm in the Hispanic population: a systematic review of the literature**

Khoi D. Than, M.D., Alexandre E. Kejner, B.S., Anthony C. Wang, M.D., B. Gregory Thompson, M.D.

**OBJECTIVE:** While there have been multiple studies examining prognostic factors for post-aneurysmal cerebral vasospasm (CV) that evaluate the implications of lifestyle, accessibility of care, and time to treatment, there has been no definitive comparison of susceptibility in the Hispanic population to that of the Caucasian population. **METHODS:** Using PubMed, Scielo, LILACS, and Imbiomed databases, we performed a literature search for studies reporting incidence of CV in Latin American countries. Studies were also found that originated from homogeneously-populated European countries. Collected data was then separated by method of CV diagnosis (symptoms of delayed ischemic neurological deficit, computed tomographic evidence of ischemic infarct secondary to CV, and/or angiography) and the incidences were compared with a Pearson chi-squared test. From this information, relative risk was calculated for both ethnic groups. **RESULTS:** A total of 95 studies resulted from the search using the aforementioned resources as well as referenced manuscripts. This was pared down to 16 studies using numerous exclusion criteria. Comparing the incidence of vasospasm by the various diagnostic methods, Hispanic patients were significantly more likely to develop symptomatic (RR = 1.51, CI: 1.27-1.80, p < 0.05) as well as computed tomographic (RR = 1.97, CI: 1.53-2.55, p < 0.05) evidence of CV. **CONCLUSION:** Hispanic patients had significantly increased likelihood of developing CV based on symptomatology and radiography than European patients when comparing the two groups of studies. This may represent divergent genetic trends between the two groups, and may influence clinical decision making when caring for aneurysm patients of Hispanic descent.
Khoi Than
Postoperative Management of Incidental Durotomy in Minimally-Invasive Lumbar Spinal Surgery
Khoi D. Than, M.D., Anthony C. Wang, M.D., Arnold B. Etame, M.D., Frank La Marca, M.D., Paul Park, M.D.
Unintended durotomy is a relatively common complication in spine surgery, with a reported incidence up to 14%. Traditional management has been mandatory bed rest for at least 48 hours following repair, with or without placement of a drain. With the muscle-splitting approach and decreased potential (dead) space created during minimally-invasive spinal surgery (MISS), there is less potential likelihood of symptoms such as spinal headaches or cerebrospinal fluid fistulas. We reviewed the cases of 5 patients undergoing lumbar MISS complicated by an incidental dural tear. Surgical treatment consisted of primary repair and/or use of DuraGen followed by application of either DuraSeal or Tisseel. Although the duration of bed rest varied, postoperative management involved early mobilization less than 48 hours after surgery without the use of a drain. One patient was mobilized early on the second postoperative day, 2 patients were mobilized the morning after surgery, and 2 patients were mobilized immediately upon recovery from anesthesia. None of the patients developed symptoms related to durotomy. Although this represents a small series, early postoperative mobilization appears to be a reasonable option and results in shorter hospitalization.

Lisa Cook
Long term outcomes in social and cognitive function in extratemporal resection for refractory epilepsy in the pediatric population
It is a short case review looking at the surgical outcomes for extratemporal resection performed here at the University of Michigan.

Nadir Osman
MICRODIALYSIS DELIVERY OF MORPHINE SULFATE (MSO4) TO THE SUBSTANTIUM INOMINATA (SI) DECREASES ACETYLCOLINE (ACH) RELEASE IN THE PREFRONTAL CORTEX (PFC) OF RATN.J. Osman*, A. Hill, H.A. Baghdoyan, R. Lydic
Opioids are a mainstay of therapy in moderate to severe pain and unwanted side effects include diminished arousal, impaired cognition, and respiratory depression. Cortical ACh is essential for arousal and cognition, and SI cholinergic neurons are the main source of cortical ACh (Behav Brain Res 115: 251, 2000). This study tested the hypothesis that dialysis delivery of MSO4 to the SI region of the basal forebrain inhibits ACh release in the ipsilateral PFC. Adult male Sprague Dawley rats (n=12) were anesthetized with isoflurane and microdialysis probes were placed in the SI for drug delivery and in the PFC for ACh measurement by HPLC/EC. MSO4 was administered in concentrations of 10, 100, and 1000 µM. Compared to Ringer’s control, delivery of MSO4 to the SI caused a concentration dependent decrease in PFC ACh release (F= 26.993; df= 3,107; p < 0.0001). Mean ± S.D. ACh release as a percent of Ringer’s control caused by the different concentrations of MSO4 was: 10 µM = 83.90 ± 18.33, 100 µM = 80.47 ±9.11, and 1000 µM = 63.72 ±18.26. The decrease in ACh release caused by 1000 µM MSO4 was blocked by co-administration of naloxone. These data are the first to show that MSO4 administered to the SI causes a concentration dependent inhibition of ACh release in the PFC. The results are consistent with the possibility that MSO4-induced depression of cognition and arousal are caused, in part, by inhibiting cholinergic SI neurons that project to the PFC.

Neeraj Kaplish
*Central Sleep Apnea in Epilepsy. *Kaplish N1, Chervin RD1, Consens FB1, O’Brien LM1,2
Introduction: Obstructive sleep apnea (OSA) and epilepsy are common treatable disorders in the general population. Obstructive sleep apnea is present in up to 24% of men and 9% of women, and several reports now suggest that patients with epilepsy are at particular risk. In medically refractory epilepsy, the prevalence of OSA has been reported to be as high as 50% in men and 19% of women. In contrast, no reports have examined the frequency of central sleep apnea (CSA) in patients with epilepsy. Though less common than OSA, CSA could potentially pose a significant problem in the presence of pathology or medications that affect the central nervous system. Our objective, therefore, was to assess whether CSA may be more common in epileptics than in controls matched for age, sex and apnea-hypopnea index (AHI).Methods: Twenty five sleep laboratory referred patients with epilepsy and 26 referred controls were identified from a database. Each had undergone diagnostic polysomnography (PSG) that generated a CSA index (number of central apneas/hour), total duration of the central apneas (Td-CSA), and minimum SaO2% during sleep as well as sleep efficiency. Results: Subjects with epilepsy had a CSA index (1.39±3.14) that was no different from that of controls (1.33±2.50, T test p=0.921). The Td-CSA during sleep in subjects with epilepsy was marginally lower (49± 103.78 seconds) than that for controls (131± 249.10 seconds, p=0.079). Minimum SaO2% and sleep efficiency did not differ between groups (p=0.61 and p=0.94, respectively). Conclusions: Epilepsy patients referred for evaluation of OSA are not an increased risk of central sleep apnea, and their minimum oxygen saturation during sleep and sleep efficiency were similar to those of matched controls.
Sleep Architecture In Children with Down Syndrome

Nicole Phillips

Introduction: Children with Down Syndrome (DS) are reported to sleep poorly. It has been suggested that up to 60% of children with DS may have sleep-disordered breathing (SDB). However, children with DS may have altered sleep architecture and sleep fragmentation, only partly related to SDB. We sought to identify sleep architecture characteristics of children with DS in comparison to those of typically developing (TD) children from a general sleep clinic population.

Methods: We performed a retrospective case-control study, comparing sleep architectures and other variables on diagnostic polysomnography (PSG) between DS children and age-, gender-, and SDB-severity matched TD children. Data was reviewed and compared using paired t-tests.

Results: A total of 38 PSGs of DS children were identified and matched to those of 38 TD children. Mean ages of DS vs. TD children were 7.3±4.3 years vs. 7.4±4.3 years and mean apnea/hypopnea index was 11.3±11.9 vs. 9.0±9.4. Seventy five percent of subjects were male. As a group, DS children exhibited significantly increased wake after sleep onset (WASO; 61.4±51.0 vs. 49.2±48.0 minutes; p=0.013), despite matching for SDB severity. When subjects were further divided based on age (1-4, 5-9, and 10-16 years), differences in sleep architecture were prominent. Specifically, DS children in the 5-9 year group (n=17) exhibited lower sleep efficiency (SE; 82.1±11.7% vs. 87.1±10.9%; p=0.03), less total sleep time (TST; 380.6±71.1 vs. 425.2±50.7 minutes; p=0.007), increased WASO (65.7±63.7% vs. 36.5±45.3%; p=0.002), more stage 1 (14.5±7.3% vs. 7.9±4.8%; p=0.001), and less REM sleep (11.0±7.0% vs. 16.2±6.2%; p=0.012) compared to TD children. Slow wave sleep (SWS) showed an increasing trend across the DS age groups, and those in the 10-16 year group (n=11) exhibited significantly more SWS than matched TD children (31.5±12.3% vs. 22.9±6.3%; p=0.019). Also, REM sleep was reduced in DS children with increasing age, although this only reached significance in the 5-9 year age group.

Conclusions: Children with DS exhibit more sleep fragmentation and altered sleep architecture compared to TD children, independently of SDB severity. Of interest, decreased REM sleep and increased SWS has been previously reported in DS adults. Our findings suggest that this sleep architecture pattern may emerge during childhood and may reflect a developmental phenotype in this population.

Robert Keeton

An Aerobiological Analysis of CPAP Efflux

Robert Keeton1, Louise M. O’Brien1,2

Background: In patients undergoing treatment for obstructive sleep apnea (OSA) nasal symptoms - such as allergic rhinitis - frequently accompany continuous positive airway pressure (CPAP) use. Heat humidification is often used to improve CPAP compliance by alleviating nasal dryness and irritation. However, humidifiers have been previously identified as a potential source of bioaerosol production (1). Furthermore, patients with OSA who use CPAP have been reported to have a higher incidence of upper airway infections than patients with OSA who do not use CPAP (2). Objective: To determine whether there is an increased fungal spore count in CPAP humidifiers in active use at subject homes compared to ambient air in their homes. Methods: An Allergenco Sampair slit-style, volumetric, impaction air sampler was employed to assess for bioaerosols in subject homes and the efflux of their CPAP humidifier. Ambient air was sampled within 2ft of the CPAP humidifier. Slides were prepared for spore identification and quantification by a counter (RK) certified by the National Allergy Bureau and counts were expressed in particles per cubic meter (ppcm). Results: Data were obtained from 10 CPAP humidifiers. All of which were being used with REMstar M-series CPAP machines. Nine different spore types were identified: Basidiospores, Epipoccum, Cladosporium, Torula, Alternaria, Aspergillus/Penicillium, Pithomyces, Ascosporales, and Bipolaris. Overall, the mean spore count was 508.3 ± 414.0 ppcm in the ambient air compared to 83.3 ± 84.2 ppcm in CPAP humidifiers (p=0.008). In all cases, the number of each spore sampled in the ambient air was reduced by the filtration assembly of each CPAP unit sampled. There were no cases of mycelial, spore producing fungal contamination of CPAP humidifier units studied. Conclusions: In subjects using heated humidification with CPAP for the treatment of OSA, allergic bioaerosol exposure is an unlikely explanation for CPAP related nasal symptoms
Background: Patients with medically refractory epilepsy, about 40% of all individuals with epilepsy, may be successfully treated with surgical resection of seizure foci especially if the area can be precisely identified. For this purpose, a very careful comprehensive pre-surgical evaluation is completed at Epilepsy Monitoring Unit using scalp electroencephalography (EEG), video monitoring, and imaging (MRI) of the brain. Some patients may require further evaluation by utilizing functional imaging to precisely identify the seizure foci. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are important noninvasive functional imaging tools to accurately pinpoint the epileptogenic zone. To achieve optimal SPECT scan quality, tracer injection should be done as quickly as possible after seizure onset and under highest safety conditions. Prior studies at University of Michigan have shown average injection time to be 11 seconds for surgical patients.

METHODS: We performed a retrospective analysis of patient's epilepsy history. Patient records admitted to University of Michigan Epilepsy Monitoring Unit for ictal SPECT between January 2005 and December 2005 were analyzed utilizing inpatient charts, EEG, monitoring data, monitoring reports generated by physicians. Results: Between Jan 2005 and March 2006, 45 patients were admitted to University of Michigan Epilepsy Monitoring Unit for ictal SPECT. The average age was 36 years, 31 female and 14 male, 20 patients had MRIs with no focal or structural abnormality, the refractory epileptic patients were on average of 2 antiepileptic medications, and average age of onset of epilepsy was 16 years of age. The number of patients had epilepsy surgery was 23 (51%). The reason patient did not have surgery: 2 patients responded to medication, 1 patient did not have seizures during grid mapping, 6 patients decided not to have surgery, 7 patients were not candidates based on diagnostic testing, 6 patient postponed surgery or pending further investigation. The patients who had epilepsy surgery: 9 had non lesional MRIs, 1 patient had brain tumor (oligodendroglioma), 2 patient had AVM (1 had hemorrhage), 4 patient had mesial temporal sclerosis, 2 temporal lobe dysplasia, 1 increased signal in temporal lobes, 1 patient with porencephalic cyst with congenital hydrocephalus, 1 porencephalic cyst, 1 with cortical dysplasia. Second phase testing: 15 patients underwent grid mapping, and 3 patients had ECOG prior to surgery. The outcome of surgery was 18 (78%) of the patients became seizure free for up to 2 year after surgery. The patients with abnormal MRI and temporal lobe onset seizures showed seizure free outcome rate of (7/8) 88%. The five patients who did not become seizure free: 2 had normal MRIs, 1 had AVM with hemorrhage, 1 had oligodendroglioma, 1 had mesial temporal sclerosis. Four of the five patients showed 75% reduction in their seizure frequency.

Conclusion: When there is uncertainty about the lateralization or localization of the ictal onset zone in patients with refractory epilepsy, ictal SPECT can be very useful in identifying the site of seizure onset. In our series, 78% of patients who underwent this procedure were seizure free, and all but one of the patients who was not seizure free had a 75% reduction in seizure frequency. Our results are somewhat better than those previously reported (2,3). This excellent outcome may be the result of a rapid injection time, or careful selection of patients for this procedure. We advocate ictal SPECT strongly as a means for identifying ictal onset zone in patients with cortical MRI abnormalities, normal MRI or difficult lateralization of temporal lobe epilepsy.

Case Presentation: 55 yo RH M with Wilson’s disease (low serum ceruloplasmin 0.11 g/L; high 24 hour urine copper excretion 1.33 micromol/d; and bilateral K-F rings) with parkinsonian features was admitted due to complex partial seizures. Seizures began on week 4 of treatment with Tetrathiomolybdate (Phase III Study of Dose Regimen in Neurological Wilson’s Disease) Seizures were characterized by forced clonic eye and head deviation to the right followed by unresponsiveness, bilateral eye blinking and right hand automatism. EEG confirmed frequent clinical seizures arising from the left frontal region. He was started on Keppra 1000mg BID but he developed non-convulsive status epileptics with nonclinical seizures every 5-10 minutes as confirmed by Video-EEG. Seizures were lasting 1-2 minutes each. He was treated with Versed and Dilantin with successful control of the seizures. He remained seizure free and discharged home on Keppra. MRI of the brain showed diffuse brain atrophy, mineralization of the basal ganglia, and patchy FLAIR increase signal in the left frontal lobe. Review of the literature will be detailed in the poster.

Conclusion: Seizures in Wilson’s disease are a rare occurrence. A literature report from a center specialized in the care of these patients, documented a prevalence of seizures as high as 4-6%. There are no reports of the incidence and prevalence of seizures in patients with Wilson’s diseases from specialized Epilepsy Centers.
**Zahra Afshari**

**A Novel skeletal muscle alpha-actin gene (ACTA1) missense mutation in a patient with dilated cardiomyopathy**

Zahra S. Afshari, Mila Blaivas, James Dowling, and Kirsten Gruis

Introduction: Dilated cardiomyopathy is the most common form of cardiomyopathy, characterized by dilated cardiac chambers with impaired contractility. The potential of sudden death due to ventricular arrhythmia and refractory heart failure often necessitates heart transplantation. Proposed etiologies include idiopathic, genetic, viral, immune-mediated, alcohol/toxic, or cardiovascular disease. In an estimated 20-30% of cases, the condition appears to be familial with a predominant autosomal dominant mode of transmission. Alpha-cardiac actin (ACTC) missense mutations have recently been found in two small families with dilated cardiomyopathy. Alpha-skeletal actin (ACTA1) mutations have been found in patients with congenital myopathy including: central core myopathy, nemaline myopathy, and most recently fiber type disproportion (CFTD). Among all reported patients with congenital fiber type disproportion, there have been only two children with cardiac involvement.


Results: Forty-nine year old man with developmental motor delay without cognitive impairment. He achieved all motor milestones and worked as a technician. He has one unaffected daughter, and no other family members with similar symptoms. Motor examination demonstrated generally reduced muscle bulk, mild neck flexor weakness, and mild hip flexor and extensor weakness. Cranial nerve, sensory, coordination examinations and deep tendon reflexes were normal except for lower facial weakness, specifically in testing resistance to lip opening and facial pucker.

Electrocardiogram demonstrated severe left ventricular diastolic and systolic function with estimated ejection fraction of 5%, severe right ventricular systolic dysfunction, and dilated tricuspid and mitral valves with secondary severe regurgitation. Despite stable skeletal muscle strength when compared to previous examinations over the past five years, his non-ischemic dilated cardiomyopathy resulted in refractory heart failure, necessitating transplant.

Pulmonary function tests demonstrated a moderate restrictive ventilatory defect with impaired gas exchange. In addition to respiratory muscle weakness he had evidence of mild obstructive sleep apnea and began treatment with nocturnal positive pressure ventilation.

Nerve conduction studies and electromyography (EMG) suggested myopathic motor units and mild axonal polyneuropathy. Skeletal muscle biopsy was notable for type I muscle fiber predominance and atrophy, in the absence of inflammatory infiltrate, nemaline rods, inclusions, or cores, and was consistent with the diagnosis of congenital fiber type disproportion (CFTD) myopathy.

ACTA1 gene sequence analysis indicated a novel coding variant, E5K (Glu6Lys), a non-conservative amino acid substitution in a highly conserved portion of the gene. As there have been no benign amino acid substitutions observed in this gene in hundreds of normal controls (Sparrow 2003), this de novo missense mutation in the ACTA1 gene is pathogenic.

---

**Sean Lanigar**

Heart rate variability can be measured via spectral analysis and is a measure of autonomic cardiac function. Previous studies have shown reduced heart rate variability in patients with epilepsy, putting them at risk for Sudden Unexplained Death in Epilepsy (SUDEP). Most measurements of HRV are done with selected epochs over 24 hours. There have been limited studies which have looked at shorter epochs and have found measurable differences in sympathetic and parasympathetic tone. Having last year validated measurable differences in sympathetic tone from an isolated 5 minute epoch, I chose to retrospectively look at an isolated 5 minute epoch at the beginning of patient’s monitored under the status epilepticus protocol over the past two years. Not everyone under this protocol ends up being in status epilepticus (some just show slowing on EEG consistent with encephalopathy). The patient was divided into two groups, those that ended up having evidence of status epilepticus on monitoring, or abnormalities that were concerning for status epilepticus, and those who did not end up having a recording consistent with status epilepticus. There were a total of 55 patients evaluated over the past two years, with 29 (13/16) having abnormalities concerning for status epilepticus and 26 (12/14) not having abnormalities concerning for status. The goal is to see if there are statistically significant differences between these groups with measures or heart rate variability. If there are, then the question is if a 5 minute epoch of heart rate data could be used as a screening tool for subclinical status epilepticus.

---

**Seema Kumar**

**OUTCOME OF VAGAL NERVE STIMULATION FOR REFRACTORY EPILEPSY**

Kumar and D. Minecan

Only few studies are available reporting efficacy and outcome of vagus nerve stimulation (VNS). VNS is thought to have a cumulative effect in time on seizure frequency reduction. There also might be other variables than reduction of seizure frequency in order to determine VNS efficacy. In this retrospective study we describe the outcome of vagus nerve stimulation on medically refractory epilepsy patients of all age groups. We included all the patients underwent VNS implant for intractable epilepsy at the University of Michigan. We obtained information from the patient’s medical charts including age, sex, age of onset of epilepsy, characteristics of the seizures, EEG findings, MRI findings and age at VNS implantation. These patient’s were followed up in clinic and effect of VNS was studied on seizures control and also on adjustment to anticonvulsant therapy. Preliminary results will be presented.

---

**Shachie Aranke**

Shachie Aranke, M.D. and James Teener, M.D.

Transient neonatal myasthenia gravis occurs in about 10-30% of newborns born to mothers with acquired myasthenia gravis. This condition has been reported in mothers with Acetylcholine receptor antibodies and seronegative cases. There has not been any report of this condition in neonates who have mothers with MUSK antibody myasthenia gravis. We are reporting the first documented case of transient neonatal myasthenia gravis in a baby born to a mother with MUSK antibody myasthenia gravis. This neonate had a particularly severe course. It is conceivable that transient neonatal myasthenia gravis in babies born to mothers with MUSK antibody myasthenia gravis may have a more severe course. We wish to make clinicians aware of the potential for this more severe course in such neonates.
Shalini Paruthi
*Sleep-Disordered Breathing: Does It Play A Role In Anxiety?*Paruthi S, Felt BT, Hoban TF, Chervin RD, Ruzicka DL, O’Brien LM. University of Michigan, Ann Arbor, MI, USA

Introduction: Sleep-disordered breathing (SDB) is a common condition in children and is frequently associated with cognitive and behavioral morbidities, such as hyperactivity. Anxiety in children is often multifactorial and can be associated with other disorders including attention deficit hyperactivity disorder. However, no data exists on anxiety and its association with SDB. We investigated whether anxiety may be associated with SDB.

Methods: *Children in grades 2-5 of an urban public school system were surveyed about SDB symptoms as well as behavior. SDB symptoms were assessed using a validated instrument; the sleep-related breathing disorders (SRBD) subscale of the Pediatric Sleep Questionnaire, minus 6 of the 22 items that directly ask about behavior. Anxiety was assessed using the Conners' Parent Rating Scale (CPRS). A score of at least 0.33 on the SRBD subscale indicates risk for SDB and anxiety was identified by a score of at least 2SD above the mean on the domain T-score.* 

Results: A total of 341 families completed the questionnaires. Thirty three children (9.7%) were identified with anxiety and 66 children (19.4%) had risk for SDB. Children at risk for SDB, compared to those without, were more likely to have anxiety (19.7% vs. 7.3%; p=0.005). The SDB score correlated with both the anxiety score (r=0.33, p<0.001) and hyperactivity score (r=0.41, p<0.001). After controlling for hyperactivity score there remained a correlation between SDB score and anxiety score (r=0.2, p=0.001). In a linear regression, hyperactivity and SDB score were both independently associated with anxiety (p<0.01). Hyperactivity and SDB score together accounted for 19% of the variance in anxiety score.

Conclusion: Children with high risk for SDB are more likely to have anxiety. This relationship is independent of hyperactivity, which is known to be associated with both SDB and anxiety. *Support:* University of Michigan Medical School Clinical Research Initiatives Program: grant U014227

Sharon Poisson
Is experience overrated? Clerkship performance does not correlate with the number of patients a student sees or their diagnoses

Sharon N Poisson MD, Douglas Gelb MD, PhD, Mary Oh BS, and Larry Gruppen PhD

Objective: To determine whether educational outcomes correlate with how many patients students see (and/or their diagnoses).

Design/Methods: We reviewed patient logs maintained by students during the neurology clerkship in the 2005-2006 academic year, and determined the number of patients each student saw in 5 diagnostic categories (seizure, headache, stroke, acute mental status change, and dementia). We compared these numbers with the students' written exam scores (total and category-specific) and clinical evaluation scores using Pearson product-moment correlations.

Results: 212 students were analyzed. For each student, there were 5 data points (one for each diagnostic category), yielding 1060 data points in all: for each data point, the x-coordinate represented the number of patients the student saw in that category, and the y-coordinate represented the student's exam sub-score for that diagnostic category. The resulting correlation coefficient was -0.066 (p = 0.03). In separate analyses, the total number of patients seen by each student did not correlate significantly with the student's total exam score (r = -0.021, p = 0.77) or the student's overall clinical performance rating (r = 0.089, p = 0.23).

Conclusions/Relevance: The more patients that students saw in a given diagnostic category, the lower their exam sub-score was in that category. The total number of patients that students saw did not correlate with their performance on the exam, or the evaluation of their clinical performance by faculty and housestaff. Thus, patient census may not be a meaningful index of educational outcome. Considerable time, money, and effort are required to maintain an accurate log of trainees encounters with patients; based on the current study, this may not be an effective use of resources.

Sonalee Kulkarni
*Does Response to IVIG Therapy Define a Treatable Disorder of the Lower Motor Neuron?*Sonalee Kulkarni, MD and James Teener, MD

Objective: It is our clinical practice to treat most patients with progressive weakness with lower motor neuron dysfunction, but who do not meet formal criteria for ALS, with a trial of IVIG therapy. In this study, we reviewed our experience with such patients.

Methods: Retrospective case cohort analysis of 50 patients who had received IVIG therapy for weakness related to lower motor neuron dysfunction in the past 5 years.

Hypothesis: Multifocal motor neuropathy (MMN) is an autoimmune disorder which produces progressive weakness. In its purest form, MMN is defined electrodiagnostically by conduction block (CB) affecting only the motor fibers in peripheral nerves. Some patients have an antibody to a peripheral nerve ganglioside, most often GM-1. Many patients with MMN have one or both of these identifying features, but some have neither a measurable antibody nor CB on routine nerve conduction studies. Identification of MMN is of great importance because it is treatable. Most patients with MMN experience an improvement in strength following IVIG therapy. We frequently encounter patients with progressive weakness due to lower motor neuron dysfunction, without the classic electrodiagnostic finding of CB, and without a GM-1 antibody. In such patients, it is currently impossible to know whether they will progress to clearly have ALS, or whether an alternative diagnosis such as MMN is the cause of the weakness. We have observed that some of these patients experience improvement in strength following IVIG therapy. It is our clinical practice to treat most patients with progressive weakness with lower motor neuron dysfunction, but who do not meet formal criteria for ALS, with a trial of IVIG therapy. In this study, we reviewed our experience with such treatment. We anticipate that the results of this retrospective study will guide future prospective studies of this promising therapy.

Results: We reviewed their medical records for the following information: ultimate diagnosis, duration of IVIG treatment, degree of response to IVIG measured as improvement in strength in a muscle, presence of anti-GM-1 antibodies, presence of electrodiagnostic evidence of CB or demyelination.
Tiffany Braley

MS exacerbation risk in the 30 day postoperative period

Introduction: MS exacerbation in the post-operative period is a common concern amongst anesthesiologists and surgeons treating MS patients. The question of post-operative risk stratification is frequently posed to neurologists and MS specialists as part of the pre-operative workup, despite the fact that these concerns are based primarily on previous anecdotal evidence and case reports. To our knowledge, there are no large-scale studies addressing this issue. We propose to show that the incidence of MS exacerbation is not increased in the 30 day postoperative period.

Materials/Methods: - We will perform a retrospective review of postoperative data up to 30 days out from all surgical procedures, including same day outpatient procedures, in patients with a clinical diagnosis of MS as per MacDonald criteria, treated at < > - Data of interest will include baseline neurologic examinations and EDSS scores, intraoperative anesthesia records, post-anesthesia recovery unit (PACU) data, neurology consult notes (if present), discharge summaries, and any subsequent neurology clinic visit/phone notes or MRI done in the 30 day postoperative period. - Data will be obtained via anesthesia records maintained by the < > Database, as well as < > electronic charting system. - MS exacerbations will be defined as any acute neurologic change lasting > 24 hours leading to loss of neurologic function not present on baseline preoperative examination, with or without subsequent administration of steroids, presence of new gadolinium enhancing lesions (if MRI done) or worsening of the EDSS score. - We will then compare exacerbation incidence in the post-operative patients to the incidence in age matched, sex matched, and MS subtype matched controls.

Aaron Mammoser

Comparison of imaging modalities in evaluation of radiation necrosis versus tumor recurrence in CNS tumors

Radiation therapy is a mainstay of many treatment protocols for aggressive CNS tumors. Where possible, a gross total resection of the tumor is frequently followed by radiation therapy alone or in combination with chemotherapy. Newer chemotherapies are frequently used concurrently with administration of radiation with the intention of sensitizing the tumor to the effects of radiation. As treatment has improved, the average interval to tumor recurrence has lengthened. Given the toxic effects of radiation, alone or in combination with chemotherapy, it can be difficult to determine if changes on serial imaging represent necrosis due to radiation or recurrence of tumor. Radiation necrosis results in vascular changes (vessel wall hyalinization, thickening and fibrinoid necrosis, fibrinous exudates, vascular hemorrhage, and thrombosis affecting small arteries and arterioles.) Demyelination is also evident. Radiation necrosis imaging findings on CT include hypodensity and contrast enhancement, and on traditional MRI there can be associated T1 hypointensity, T2 hyperintensity, and gadolinium enhancement. Mass effect can be seen on both imaging modalities. The similar imaging characteristics make determination of radiation necrosis versus tumor recurrence unlikely based solely on these imaging methods.

New methods of imaging are constantly being designed and tested for clinical feasibility. Presently, studies of PET-methionine, FDG-PET, MR spectroscopy, MR diffusion tensor imaging, and MR perfusion are ongoing to determine their efficacy in delineating between radiation necrosis and tumor recurrence. We are proposing to compare PET-methionine directly to MR spect and diffusion tensor imaging. This is as an adjunct to an ongoing study within the departments of radiology, neurology, neurosurgery, radiation oncology, and pathology here at the University of Michigan. Patient selection is based on appearance of contrast enhancing lesion in the vicinity of previously excised and irradiated tumor. Imaging is obtained using multiple imaging methods, and based on imaging characteristics sites for biopsy and pre-biopsy diagnosis are determined. Prior to lesion resection, biopsies are performed at these predetermined sites and histopathology is evaluated for the presence of necrosis, tumor recurrence, or both. Total tissue specimen histopathology is then analyzed for overall tumor make-up.