Residents' Day Symposium
Friday, May 23, 2014
7:30am – 9:15am
Farrell Learning and Teaching Center ~ Atrium

Poster presentations will begin at 7:30am

Awards will be presented at 9:00am

I encourage everyone to attend this important event.

Appu, Merveen

Novel familial pathogenic missense mutation in gap junction gamma 2 gene *(GJC2)* associated with hypomyelinating leukodystrophy in a female patient with Pelizaeus- Merzbacher- like disease (PMLD1)

Introduction: Hypomyelinating leukodystrophy is a rare group of progressive degenerative white matter disease . Classic Pelizaeus-Merzbacher disease (PMD) is inherited as an X-linked recessive pattern and is characterized by nystagmus, hypotonia, choreo athetoid abnormalities, seizures and developmental delays. In female patient, mutation in gap junction protein gamma 2 (*GJC2*) inherited as an autosomal recessive mutation, results in a similar presentation and is called Pelizaeus-Merzbacher-like disease (PMLD1).

Case: We report a 32 month old girl who presented with global developmental delays and abnormal eye movements who had a brain magnetic resonance imaging (MRI) study concerning for hypomyelinating leukodystrophy.

***Methods*:**
We did physical examination, radiological and genetic analysis on patient and biological parents.

Results: Based upon the clinical presentation of global developmental delays with nystagmus and a hypomyelination pattern on brain MRI, in a female patient, genetic testing for gap junction protein, gamma 2 gene (*GJC 2*) sequence analysis revealed two point mutations. One point mutation was a heterozygous mutation c298C>T resulting in amino acid change from proline to serine (p.P90S) on exon 2 of the gene which is a known pathogenic mutation. The second mutation was a novel missense mutation c 139T>C resulting in amino acid change from tyrosine to histidine (pY47H) on exon 2 of the gene which was of unclear significance. Tests designed to predict whether an amino acid change is a polymorphism or a pathogenic mutation including sorting intolerant from tolerant (SIFT- J. Craig Venter Institute) and Polymorphism phenotyping version 2 (Polyphen 2 – http://genetics.bwh.harvard.edu) revealed the novel amino acid change to be pathogenic.

Conclusion: We describe a novel familial pathogenic mutation in gap junction gamma 2 gene (*GJC2*) associated with autosomal recessive Pelizaeus-Merzbacher- like disease (PMLD1) in a female patient.

Buck, Joshua

Hyper-Acute MRI Protocol: Development and Preliminary Outcomes

Background:
While tPA has revolutionized the management of acute strokes, its narrow therapeutic window and inherent bleeding risk can limits its use. MRI offers many advantages over non-contrast CT in discriminating between acute strokes and mimics as well as allowing other research opportunities. Previous efforts to use MRI in the hyper-acute setting have been mixed in terms of success and efficiency. In 2013, a multidisciplinary group was formed to assess the current state of the hyper-acute MRI and to standardize the process for clinical use.

Process Changes:
Value stream analysis was preformed and a process was standardized. It involved coordinated changes involving the staff of Neurology, Emergency Medicine, Radiology, and MRI. A goal median "Door-to-MRI-begin" time and median "Door-to-Needle" time were set at less than 45 minutes and 55 minutes, respectively. Data was collected by manual review of electronic medical records on a monthly basis.

Results:
Data was collected on all hyper-acute MRIs between Aug 12, 2013 and Mar 10, 2014. Forty-eight hyper-acute MRIs—33 for possible mimics, 10 for “wake-up” strokes, and 5 for possible interventional treatments—were done during this time. The time from ED Arrival/Code Stroke page to MRI begin had a mean of 67.7 minutes with standard deviation of 43.1 minutes and a median of 57 minutes.

Conclusion:
The current hyper-acute MRI times exceed the target goals, but the changes in the process have made using the hyper-acute MRI clinically viable.

Cabaniss, Brian

Secondary Generalization and Disease Duration in TLE are Associated with Relative Decoupling of Resting State Functional Networks

Brian Cabaniss, MD, Antonello Baldassarre, PhD, Carl Hacker, BS, Emily Moseley, BS, Nicole Werner, PhD, Maurizio Corbetta, MD, Edward Hogan, MD, Luigi Maccotta, MD, PhD

Temporal lobe epilepsy (TLE) is associated with functional network remodeling. We have previously demonstrated decreased inter-hemispheric and increased intra-hemispheric connectivity in resting state BOLD fMRI in patients with unilateral TLE (Maccotta et al., 2013). Here we sought to determine whether secondary generalization is associated with more prominent connectivity changes, including the speculation that inter-hemispheric functional connectivity may be increased in such patients. As a secondary aim, we investigated whether the dominant ictal frequency range noted on scalp EEG has bearing on the likelihood of secondary generalization, with the hypothesis that seizures of slower frequency (suggesting a neocortical origin) would correlate with increased rates of secondary generalization (Wieser, 1983). 28 patients with unilateral TLE were divided into two groups on the basis of the presence or absence of secondary electrographic generalization and underwent resting-state fMRI.

Our principal findings were:
1) decoupling of specific functional resting state networks in patients with secondary electrographic generalization compared to patients who did not generalize
2) an association between duration of disease and the presence of secondary electrographic generalization

These observations provide further evidence of TLE as a disease of network dysfunction and suggest progressive functional decoupling and secondary generalization as a consequence of disease duration. This may be of therapeutic consequence as such changes may represent cumulative damage from chronic epilepsy and the presence of secondary generalization adds an increased risk of sudden death in epilepsy. Would heightened early efforts to abolish seizures in TLE lessen the risk of electrographic (and presumably clinical) secondary generalization in this population and preserve functional connectivity?

Cheung, Joseph

γ-Hydroxybutyric Acid-Induced Electrographic Seizures

We describe a case of absence-like electrographic seizures during NREM sleep in a patient who was taking sodium oxybate, a sodium salt of γ-hydroxybutyric acid (GHB). An overnight full montage electroencephalography (EEG) study revealed numerous frontally predominant rhythmic 1.5-2 Hz sharp waves and spike-wave activity during stage N2 and N3 sleep at the peak dose time for sodium oxybate, resembling atypical absence-like electrographic seizures. The patient was later weaned off sodium oxybate, and a repeat study did not show any such electrographic seizures. Absence-like seizures induced by GHB had previously been described in experimental animal models. We present the first reported human case of absence-like electrographic seizure associated with sodium oxybate.

Davis, Albert (Gus) and Kristin Gehrking

Genetic Variants Influence Parkinson Disease Risk and Age of Onset

Albert A. Davis[1*], Kristin M. Gehrking[1*], Bruno A. Benitez[2], Joel S. Perlmutter[1,3,4,5], and Carlos Cruchaga[2,6]

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Although multiple genetic variants have been linked with Parkinson disease (PD) risk, there remains a strong heritable component that is not accounted for by known mutations. PD is phenotypically diverse, and little is known about the genetic factors that may influence specific clinical manifestations and disease course. We used data from meta-analyses published in the PDGene database to select 24 common single nucleotide polymorphisms (SNPs) located on 8 genes (*ACMSD*, *STK39*, *MCCC1*, *GAK*, *SNCA*, *HLA-DRB5*, *LRRK2*, and *MAPT*) associated with PD. We then analyzed two populations of PD patients (from the Washington University Movement Disorders Center and the Parkinson's Progression Markers Initiative) to determine if these SNPs were associated with PD risk, age at onset, or disease progression. We found significant associations between PD risk and SNPs in several genes including *HLA-DRB5*, *MAPT*, *MCCC1*, and *SCNA*. We also report a novel association between PD age of onset and a SNP in the HLA-DRB5 gene as well as SNPs in MAPT. There were no significant associations between rate of motor function progression and any SNPs examined in these populations. These findings reinforce the complex genetic basis of PD and underscore the need for further investigation to identify additional genes implicated in disease modeling and targeted therapy development.

Ding, Ming-Chieh

A Case of a 29-year-old Man Presenting with Treatment Refractory Neurosarcoidosis

Neurosarcoidosis is a rare entity that is frequently difficult to diagnose and treat. Here we present a case of a patient who developed altered mental status and was initially thought to have meningitis due to abnormal cerebrospinal fluid findings. However, after not responding to multiple antibiotics and continued evidence of inflammation in his cerebrospinal fluid as well as his brain imaging, non-infectious etiologies were more strongly considered and he eventually required a brain biopsy showing granulomatous angiitis that was felt to be consistent with primary CNS vasculitis. He received high dose steroids with improvement in his symptoms and was then started on mycophenolate for chronic immunosuppression and weaned off of steroids as an outpatient. However, during subsequent follow-up appointments, he continued to have symptoms and progression on his serial imaging studies. He had rituximab added to his immunosuppressive regimen, but eventually developed new symptoms and repeat imaging showed even further progression of his disease. Given the constellation of his imaging findings and due to the presence of granulomas on his chest imaging, it was determined he more likely had neurosarcoidosis. He was placed back on high dose steroids and will be initiated on infliximab, which has demonstrated some efficacy in neurosarcoidosis in case reports. If he responds to the treatment, he will be one of only a handful of cases of neurosarcoidosis to report improvement to infliximab after failing treatment with other immunosuppresive agents.

Grover, Prateek

Contralesional and Bilateral Music Therapy as Therapeutic Interventions for Neglect in Stroke: Feasibility Study with a Test Subject

Grover, P *MD*, *PhD* [1,2], Soorya, A *MD* [1], Carter, A *MD/PhD* [1]
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Abstract

Neglect is a common, yet underdiagnosed manifestation of stroke. Recognition and management of this condition has significant potential for facilitating rehabilitation of other domains, hence improving QOL (Quality of Life) in this population. Cross-sensory benefit of auditory training on the visuospatial subtype of neglect has been documented [1-5]. There is, as yet, no consensus on the optimal dose, frequency and type of the auditory input.

The aim of this feasibility study was to contrast the effect of contralesional and bilateral ear music therapy on neglect in one test subject, and refine the methodology based upon the results. The test subject listened to self-selected music at home in both ears (BL, 1st week), and in the contralesional ear (CL, 2nd week), and completed the unstructured Mesulam at each outpatient visit. The results indicate that the magnitude of neglect increased significantly once bilateral music therapy was stopped. Fluctuating functional status may have contributed to the worsening neglect. Further study into the duration and dose of intervention is needed. Overall, the intervention is inexpensive, easy to perform, with no adverse effects, has high compliance.

References

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Hawasli, Ammar

Dissecting Human Cortical Oscillations with Surgical Transections

Ammar H. Hawasli[1], DoHyun Kim[2], Noah M Ledbetter[2], Dennis L. Barbour[2], Eric C. Leuthardt[1,2]

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Oscillating brain activity reflects changes in cortical potentials caused by activity in neuronal populations. Despite routine use of human cortical oscillations in neuroscience, the circuits and physiology underlying them remain largely unknown. Modulation of low-frequency oscillations tends to correlate across relatively large areas of cortex while the modulation of high-frequencies tends to be local. From this observation, we hypothesized that (1) low- and high-frequency oscillations preferentially reflect long- and short-range communications, respectively; and (2) Synchronization between low-frequency phase with high-frequency amplitude (i.e. phase/amplitude coupling) represents a mechanism that enables large-scale distributed brain-networks to coordinate with local cortical processing. We tested these hypotheses by selectively disrupting white or grey matter connections (i.e., long- or short-range) to cortex in humans undergoing neurosurgical resection and recording surface field potentials. We found that selective disruption of white matter connections reduced oscillation power in low-frequencies more than high-frequencies, as expected. Contrary to our hypotheses, white matter sectioning increased functional connectivity with adjacent cortical sites (predominantly at low-frequencies) and did not alter phase/amplitude coupling. Disruption of surrounding grey matter connections did not significantly alter oscillatory power but increased functional connectivity in higher-frequencies and substantively increased cross-frequency phase/amplitude coupling at a synchronized phase. When the lesions were combined at the same site, endogenous oscillations and complex oscillatory relationships were maintained or enhanced. Oscillations persisted even after cortical tissue was completely removed from the brain. These findings suggest that cortex consists of independent oscillatory-units (IOUs) that maintain their own complex endogenous rhythm structure. IOUs are differentially modulated by their white and grey matter connections, where long-range connections maintain topographical heterogeneity (i.e. separable processing along the cortical surface) and short-range connections segregate cortical synchronization patterns (i.e. separable processing in time). Modulation of these distinct oscillatory modules allows for functional diversity necessary for complex signal processing in the human brain.

Hsiao, Esther

De novo development of gliomas in a child with ?Neurofibromatosis Type 1, Fragile X, and a previously normal brain MRI??

A significant minority of children with Neurofibromatosis Type 1 will develop low-grade glial neoplasms. However, since neuroimaging is not routinely obtained until a child is symptomatic, little is known about pre-symptomatic radiographic characteristics of gliomas in this at-risk population. We describe here a child who was followed with neuroimaging for other reasons. The serial images provided demonstrate that brain tumors can arise *de novo* in these children, and that a normal baseline MRI is of limited prognosic value.

Karmarkar, Swati

Visual Estimation of Joint Angle: How accurate is Eyeballing?

Swati A Karmarkar MD, Janice E Brunstrom-Hernandez MD

Background: Assessment of patients with cerebral palsy (CP) includes measurement of joint angle to evaluate passive range of motion (ROM). The ROM in an extremity has great impact on its functional use. Accurate measurement of ROM is necessary for selection and monitoring response to therapies. Goniometer is considered the gold standard for evaluation of ROM. However, due to the time constraints of a busy outpatient practice, healthcare professionals need to rely on visual estimation (VE) of joint angles. There is a paucity of studies evaluating the accuracy of VE. We sought to determine the accuracy of VE of joint angles by residents in training and physical therapists (PT).

Methods: Neurology (adult and pediatric) and physiatry residents, and PTs were asked to look at photographs of popliteal and ankle angles in 5° increments in random order and provide a VE. The joint angles were measured by a goniometer in normal children and photographs of those were then used for this study. Error of > ±5° for ankle and > ±10° for knee joint was considered significant. One-way ANOVA test was used to compare groups.

Results: A total of 45 participants responded, including 20 adult and pediatric neurology, 10 physiatry residents and 15 PTs. Forty four (20/45) percent participants were male. Median (Interquartile range) years of experience was 4 (3-6). Only 4% (2/45) were able to estimate all ankle joint angles within ±5° and popliteal angles within ±10°. For ankle, 4% (2/45) were able to estimate all the angles within ±5°. For knee, 33% (15/45) were able to estimate all the angles within ±10°. No difference in accuracy was found with gender, type of training and experience ($p > 0.1$ for each comparison).

Conclusions: Accuracy of VE of joint angles is very limited in assessing ROM. We suggest more accurate tools such as a goniometer to assess ROM in a patient with CP.

Lal, Neeta

Two Instances of Stereotyped Fulminant Multiple Sclerosis Relapses after Cessation of Natalizumab: A Withdrawal Phenomenon?

Natalizumab remains a highly effective monotherapy for the treatment of aggressive relapsing-remitting multiple sclerosis. However, the risk of progressive multifocal leukoencephalopathy in JC virus positive patients limits its long term clinical utilization in practice. Recently, there have been several studies examining clinical and radiographic sequelae following cessation of natalizumab. Although a large scale meta-analysis of data from AFFIRM, SENTINEL and GLANCE studies did not show evidence of a rebound effect[1], the RESTORE study demonstrated such an effect, regardless of whether patients underwent a "drug holiday," "bridging" therapy, or switch to fingolimod or interferon.[2, 3] Rigau et al made note of a lethal multiple sclerosis relapse after cessation of natalizumab.[8] Other studies have suggested that there may be a subset of patients who may experience a rebound of MS activity after discontinuation.[4,7] Here we describe a case in which a patient presented in two separate instances several years apart with stereotyped fulminant multiple sclerosis relapses within six to eight months of discontinuation of natalizumab. We argue that this would support an actual withdrawal phenomenon associated with discontinuing natalizumab in this case, and not just disease relapse. Data for when and which treatment to initiate post-natalizumab remain inconclusive. This case strongly re-emphasizes the need for more prospective studies to further establish treatment strategies and guidelines after cessation of natalizumab.

Lin, Andrew

Codeletions at 1p and 19q Predict For a Lower Risk of Pseudoprogression in Oligodendrogliomas and Mixed Oligoastrocytomas

Background:
Pseudoprogression (PsP) occurs at a higher rate in glioblastoma multiforme (GBM) with a methylated *MGMT* promoter—a subset with increased sensitivity to chemoradiotherapy and better overall prognosis. In oligodendrogliomas (OG) and oligoastrocytomas (OA), presence of 1p/19q codeletions is highly predictive of response to treatment and is often associated with the methylated *MGMT* promoter; hence, this study queries whether the presence of 1p/19q codeletions in OG/OA correlates with a higher rate of PsP following therapy.

Methods:
A retrospective analysis was performed on all OG/OA in a database of patients with brain tumors that underwent resection of their tumor since 1998. Eight-eight cases (37 with and 51 without 1p/19q codeletions) met inclusion criteria, and their patient data was analyzed to determine whether the presence of 1p/19q codeletions is associated with PsP and survival.

Results:
OG/OA (WHO grade II and III) with 1p/19q codeletions had a significantly improved survival (p=0.041). Multivariate analysis found that PsP occurred less frequently in OG/OA with 1p/19q codeletions compared to tumors without codeletions (OR 0.047; 95% CI 0.005-0.426; p=0.0066). The rate of PsP was 19% for the entire cohort, 31% for tumors without codeletions, and 3% for tumors with codeletions.

Conclusion:
Codeletions of 1p/19q is a marker of good prognosis but is unexpectedly associated with a lower likelihood of PsP. PsP does not correlate with sensitivity to treatment and improved survival in OG/OA.

Ly, Cindy

Whole Exome Sequencing in Idiopathic Small Fiber Neuropathy

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Small-fiber neuropathy (SFN) refers to peripheral neuropathy selectively involving small, unmyelinated peripheral nerve fibers that subserve nociceptive, thermal, and autonomic function and clinically consists of dysesthesias, numbness, and autonomic dysfunction. Skin biopsy with evaluation of intraepidermal nerve fiber density (IENDF) has the highest diagnostic efficiency (88.4%)[1]. The prevalence of SFN has been estimated to be 53 cases / 100,000 patients[2] though this will likely increase with growing recognition of the condition.

Emerging evidence suggests that a number of congenital pain syndromes including SFN are channelopathies. Gain of function mutations in genes encoding ion channels including *SCN9A*, *SCN10A*, *SCN11A*, and *TRPA1* are causative in primary erythromelalgia and paroxysmal extreme pain disorder[3]. Recently, *SCN9A* mutations have been found to underlie disease in 10-25% of patients with SFN[4]. Moreover, a common *SCN9A* polymorphism (R1150W) that increases DRG neuron excitability has been linked to increased pain sensitivity in chronic pain patients and the general population[5]. Thus, investigating the genetic determinants of pain syndromes may help to identify novel mechanisms and potential therapeutic targets for treatment of chronic pain.

Whole exome sequencing was performed on a cohort of 20 patients with skin-biopsy proven, idiopathic SFN. Patients were selected based on absence of large fiber involvement, symptom severity, and a lack of clear etiology. Whole exome sequencing was performed such that the depth-of-read was >10x in over 90% of the exomic regions sequenced. We identified 6 of 20 patients (30%) with rare *SCN9A* variants- one variant (I739V) has been previously implicated in SFN[5]. Rare variants in other genes implicated in congenital pain syndromes including *SCN10A*, *SCN11A*, and *TRPA1* were also identified. Notably, expression of these ion channels is markedly elevated in sensory ganglia based on recent transcriptome data[6], a feature that can aid in determining additional candidate genes for analysis. An approach has been developed to facilitate discovery of novel genes involved in SFN that incorporates filters for familial inheritance and enriched expression in sensory ganglia.

References:

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Ong, Charlene

The Visible Brain: Computed Tomography's Impact on Neurological Practice

OBJECTIVE:
To qualitatively examine the impact that the introduction of Computed Tomography (CT) had on neurological practice through accounts of experienced neurologists.

BACKGROUND:
Throughout the 20th century neuroscientists strived to invent improved methods to visualize the neuroaxis in their patients. However it was not until the 1970s with the advent of CT that neurologists gained the ability to non-invasively 'see' inside the human head. The journey culminating in the immediate and widely accessible head CT scan is largely unstudied. This study aims to contribute first-hand accounts of neurologists who witnessed this tipping point in neurological practice.

DESIGN/METHODS:
In-depth semi-structured interviews were conducted with six senior neurologists, some of who were and continue to be leaders in the field such as Lewis Rowland and Michael Aminoff. Qualitative analysis was performed on the interview scripts and historical documents, leading to the identification of major themes through a grounded theory approach.

RESULTS:
All participants believed that there was a rapid shift from a practice in which clinical suspicion frequently remained unconfirmed to one in which imaging became as instrumental as the reflex hammer. An amalgamation of medical, political and cultural factors surrounding the genesis of CT led to its lasting success as a diagnostic tool. Its advent provided a quick and reliable adjunct to clinical acumen, becoming indispensible to emergent neurology and useful as a screening tool for more insidious or subacute processes.

CONCLUSIONS:
This analysis offers a means to gauge the current and future impact of other diagnostic technologies including functional MRI and the much-publicized intelligent diagnostic software, the "Watson" program. The advent of the head CT was a pivotal historical moment that stands as a model for modern medical revolutions.

Pathak, Sheel

Severe intractable epilepsy, psychomotor regression and death following Human Herpes Virus-6 Infection in two boys with mitochondrial depletion syndromes

Introduction:
Disorders of oxidative phosphorylation, specifically mitochondrial depletion syndromes, have a varied but characteristic phenotype of psychomotor regression, intractable epilepsy, and hepatic dysfunction. Multiple mitochondrial and nuclear encoded gene mutations have been implicated in these syndromes (the most severe phenotype being that of Alpers-Huttenlocher Syndrome). Patients with disorders of mitochondrial function may be at risk for more severe illness in the setting of common infectious illnesses, possibly due to the body's inability to maintain adequate ATP production during times of increased energy demand. There have been no prior studies evaluating the immune function of patients with mitochondrial disease in the setting of viral illness. We report two cases of previously healthy boys, later found to have mutations of the mitochondrial polymerase gamma gene, who developed progressive, refractory epilepsy, psychomotor regression and ultimately death from respiratory failure in the setting of Human Herpes Virus – 6 infections.

***Introduction*:**
Mitochondrial Depletion Syndromes, specifically Human Polymerase Gamma (POLG) gene mutations have a characteristic phenotype of psychomotor regression, epilepsy, and hepatic dysfunction. It is possible that patients with these disorders are at risk for poor outcome and more serious presentation in the face of febrile infectious illnesses which typically are benign and self-limited. We report on two cases of patients with underlying mitochondrial disease who had severe exacerbation of their illness following human herpes virus 6 infections.

***Methods*:**
We reviewed the hospital records of two boys, admitted to St. Louis Children's Hospital over a 2 year period.

***Results*:**
Laboratory testing in both patients revealed evidence of hepatic dysfunction, as well as heterozygous mutations of the polymerase gamma genes. CSF evaluations in both patients revealed evidence of concurrent human herpes virus 6 infections as well.

***Conclusion*:**
The mechanism of severe decompensation in the face of viral illness is not completely clear in patients with Alpers-Huttenlocher phenotype, but the recognition of this association is important for clinicians faced with patients who have severe or unusual presentations of infections which are typically benign and self-limited.

Tahsili-Fahadan, Pouya

Cerebrovascular complications of left ventricular assist devices

Authors: Pouya Tahsili-Fahadan[1], David Curfman[1], Albert (Gus) Davis[1], Noushin Yahyavi-Firouz-Abadi[2], Michael Nassif[3], Gregory Ewald[3], Allyson Zazulia[1]

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Abstract:
Left ventricular assist devices (LVADs) are mechanical circulatory support devices. LVADs are increasingly implanted in patients with advanced heart failure either as a temporary bridge to heart transplantation or even long-term destination therapy. Cerebrovascular events are common after LVAD implantation leading to significant morbidity and mortality. The optimal anti-thrombotic regimen to prevent ischemic events after LVAD placement is not well known. On the other hand, aggressive anticoagulation to prevent ischemic strokes increases the risk of systemic and intracerebral hemorrhagic events. Between May 2005 and December 2013, 392 patients underwent LVAD implantation at Barnes-Jewish Hospital/Washington University School of medicine. Neurology service was consulted on a quarter of the cases for various neurological complaints mostly consisted of cerebrovascular events. In this retrospective study, we reviewed both ischemic and hemorrhagic cerebrovascular events after LVAD placement. The incidence of events based on the goals of mechanical support, LVAD type and anti-thrombotic regimens, their anatomical location, risk factors, and associated morbidity and mortality were determined.