The 68th American Epilepsy Society Annual Meeting Seattle (WA), USA, December 5-9, 2014

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The American Epilepsy Society's Annual Meeting is the premiere meeting for epilepsy and other seizure disorders. The Annual Meeting is an international forum for the exchange of current findings in epilepsy research. Information is communicated and disseminated through symposia, lectures, scientific exhibitions, poster, and platform presentations. The Annual Meeting attracts attendees from all over the world and provides educational and networking opportunities for the academic and practicing neurologist, epileptologist, neurophysiologist, neuroscientist, neurosurgeon, internist, pediatrician, pharmacist, nurse, social worker, and other professionals. In 2014, the American Epilepsy Society Annual Meeting was held on 5-9 December 2014 in Seattle (WA), USA. The following syllabus provides highlights from this meeting.

Meeting Highlights

Translational Research

How reliable are the high-frequency oscillations and delayed responses as epileptogenicity biomarkers? A study based on intracranial stimulation

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Intracranial single-pulse electrical stimulation (SPES) may evoke high-frequency oscillations (HFO) and delayed responses (DR), considered as biomarkers of the epileptogenic networks. A number of brain structures are known to exhibit such responses even when non-pathologic (Engel et al., 2009; Buzsaki & da Silva, 2012). In some patients, these responses are not present at all. These are limiting factors for the use of such biomarkers. We performed a retrospective analysis in 16 patients of the responses in various brain structures that have been explored with depth electrodes and calculated the probability for each structure to exhibit normal or pathological responses. It was concluded that the sensitivity of HFOs is significantly higher that the sensitivity of DRs. The positive predictive values of both biomarkers are highest for the mesial structures. There is little predictive value of biomarkers for the seizure onset zone, strictly speaking. Predictive value of the biomarkers is high for the irritative zone. The analysis we have performed provides an estimation of the stimulation-evoked pathological vs physiological HFO and DR frequency, which can help in taking decisions regarding the delineation of the resection area.

HIGHLIGHTS FROM INTERNATIONAL NEUROSCIENCE MEETINGS

Inhibitory effect of Cys-Lt receptor antagonist pranlukast on MES and PTZ induced convulsions

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Prior studies have shown that cysteinylleukotriene (CysLT1) production is increased during limbic seizures triggered by kainic acid. It is possible that LT and LT-R could be associated with mechanisms of seizure onset, and epileptogenesis. Lenz et al already reported montelukast (one of the potent LTRA) suppressed PTZ induced seizure and discuss that CysLT1 receptors may be a suitable target for anticonvulsant development. On the other hand, free radical generation also resulted in seizure onset of epilepsy. The aim of this study is to evaluate whether another CysLT1 receptor antagonist (LTRA), pranlukast (PL), might suppress PTZ kindling, maximum electrical shock (MES) or pentylenetetrazol (PTZ) induced convulsive seizures, and speculate its mechanism of pranlukast's effect on convulsion or epiileptogenesis from the view of free radical and LT generation. It was concluded that Montelukast sodium, a leukotriene D(4) receptor antagonist markedly and in a dose dependent fashion suppressed the development of kindled seizures as well as pilocarpine induced spontaneous recurrent seizures. PL, a blocker of LT-R suppressed convulsion induced by MES, PTZ, and kindling. The mechanism of suppression of 14-day PL diet of convulsions may be related to enhanced release of LT when rat brain is stimulated by MES or PTZ.

Antecollis and levodopa-responsive parkinsonism are late features of Dravet syndrome

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Dravet syndrome (DS), one of the most severe genetic epileptic encephalopathies, mainly caused by SCN1A mutations. Children usually develop febrile seizures in the first year of life and later afebrile, extremely frequent and pharmacoresistant seizures of several types. Besides a variable degree of cognitive delay, the neurological examination is usually normal early on but some patients later develop gait ataxia. The clinical manifestations of adults with DS have only recently received attention. In addition to cognitive disability and seizures, a "crouch gait" has been described in these cases. Given the poor knowledge of the clinical features of DS patients surviving until the adulthood, we prospectively investigated the motor abnormalities in a consecutive sample of adults with genetically proven DS. In this study, it was described for the first time that the majority of adult Dravet syndrome patients have features of parkinsonism and antecollis. Meaningful improvement after levodopa trial was seen. These findings expand the phenotype of a disease mainly known by its severe epilepsy and cognitive delay to include drug-responsive movement abnormalities. Knowledge of levodopa responsiveness may greatly diminish the burden of care of such complex patients.

HIGHLIGHTS FROM INTERNATIONAL NEUROSCIENCE MEETINGS

Neurophysiology

Change in neurotransmitter gene expression correlated with EEG stages during lithium/pilocarpine-induced experimental status epilepticus

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Five days after implantation of epidural screw electrodes, SE was induced in 250-280 gm male albino Sprague-Dawley rats by injection of 3 mmol/kg LiCl IP, followed 20 hours later by pilocarpine, 30 mg/kg SC. Control rats were given LiCl but saline rather than pilocarpine and did not develop SE. Experimental rats were sacrificed 5 min after onset of SE EEG stage I (discrete electrographic seizures), III (continuous spiking), stage V (continuous periodic epileptiform discharges) or 4 hrs after onset of stage V by rapid anesthetization with isoflurane and decapitation. Brains were rapidly removed for dissection of hippocampus and cortex samples, which were stored at -80°C until RNA isolation. Nine rats were studied for each condition, and RNA isolates were randomly pooled from 3 rats each to produce 3 RNA isolate pools to allow for statistical analysis. It was concluded that striking changes in gene expression occur during experimental Li/pilocarpine-induced experimental SE, using the EEG pattern as the marker of the severity and degree of progression of the episode of SE. The marked decrease in GABArg2 and GABAra6 expression could help explain the decreased responsiveness to benzodiazepines observed in late stages of SE both clinically and in experimental models. Furthermore, the decrease in expression of GABA transporter proteins may reflect a compensatory response in the brain to impaired GABAA receptor function in progressive SE by an attempt to increase synaptic GABA. The changes in gene expression we observed at specific EEG stages may help in understanding the underlying pathophysiology of dynamic changes during SE.

Spike-Wave discharges versus seizures after fluid percussion injury in sprague-dawley rats

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In this study quantified features of SWD episodes throughout the lifetime of normal "control" rats with the objective of distinguishing normal brain activity from that heralding the development of non-convulsive and convulsive seizures. These results were compared to the same timeline in brain-injured rats receiving moderate to severe LFPI. A support vector machine was trained on the fully developed SWD of each rat and used to detect and quantify subsequent episodes. It was concluded that these results suggest that the presence, duration, amplitude, and frequency of occurrence of SWD may not unambiguously reflect epileptogenesis in acquired epilepsy with moderate to severe LFPI. However, none of our LFPI rats developed convulsive seizures across 1-12 mo of video/EEG monitoring. Work is underway to examine LFPI animals undergoing more severe impact pressures to determine parameters of SWD that may be uniquely associated with epileptogenesis.

Clinical Epilepsy

Refractory partial seizures as manifestation of polymerase gamma (PoLG) mutation in pediatric patients

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A retrospective chart review of 2 patients with seizures later diagnosed with PoLG mutation was carried out. Then a PubMed search was made for reports from 1950-2014 using the following terms: EEG or Electroencephalography and PoLG and Alper's and PLEDS/EPC. It was concluded that epilepsia partialis continua and very frequent

lateralized epileptiform discharges particularly in absence of a structural lesion and other clinical features like hypotonia and developmental delay should raise the suspicion for this condition. Early diagnosis has important implications on treatment as Valproic Acid can induce fatal liver dysfunction and should be avoided.

Prolonged propofol infusion in pregnant women with refractory status epileptics

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Clinical presentation, electro-imaging finding, management and clinical course of the 31-year-old pregnant patient who presented to our hospital with RSE were described in this paper. Fetal ultrasound prior, during, and following Propofol infusion were unchanged and showed a 22-week viable fetus, with normal heart rate and movements. Patient remained seizure free and discharged home on AEDs+PHT (300mg/day). Post -discharge, she continued to have intermittent mild focal seizures in spite of out-patient AED adjustments. Her antenatal follow ups were unremarkable and she gave birth to a full term healthy baby. It was concluded that early recognition and treatment of RSE is the key for better outcome. Propofol may serve as an effective and relatively safer treatment option for RSE during pregnancy. Further studies and experience in managing RSE in such population would help outline the standard of care.

Comorbidity (somatic & psychiatry)

Analgesic opioid use in a health insured epilepsy population during 2012

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The primary objective was to compare the prevalence of analgesic opioid use in an epilepsy patient population to a matched non-epilepsy control population. In order to understand why opioids may have been used in an epilepsy patient population, and the second objective was to determine if the prevalence of different pain conditions was different in the epilepsy population than in the matched non-epilepsy control population. The incidence of analgesic opioid use in an epilepsy patient population was compared with the incidence in a matched nonepilepsy control population using health insurance claims and membership data from 9 United States health plans for the year 2012. It was concluded that individuals with epilepsy were significantly more likely to use opioid analgesics in 2012 than matched controls. All pain conditions examined were significantly more prevalent in the epilepsy group than in matched controls.

Association between depressive symptoms and seizure response among subjects with refractory partial-onset seizures in clinical trials of eslicarbazepine acetate (ESL)

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The objective of this study is to examine the association between seizure frequency reduction and baseline depressive symptoms in three Phase III trials of adjunctive ESL. The depressive symptoms at baseline for subjects in the pooled per-protocol population (N=1006) were assessed using the Emotional Well Being (EWB) domain of the Quality of Life in Epilepsy Inventory-31 (QOLIE-31). So, the conclusion in this post-hoc analysis of the pooled phase

III clinical trials for ESL, depressive symptoms at baseline, as assessed by the QOLIE-31 EWB domain, were not predictive of seizure response, and did not modify the association between ESL treatment and seizure frequency response.

Antiepileptic drugs

Ceftriaxone treatment in a rat post traumatic epilepsy model preserves cortical inhibitory interneuron function and parvalbumin expression

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The objective of this paper is to determine whether ceftriaxone treatment after TBI preserves cortical inhibition, as measured by ppTMS, and to assess the effect of ceftriaxone on inhibitory interneuron survival after TBI as measured by parvalbumin (PV) gene expression. So, an adult male rats (n=33) received moderate lateral fluid percussion injury (LFPI; 2.3 ± 0.1 atm) via a craniotomy over the motor cortex, and were divided into 2 groups: to receive Cef (200mg/kg/day IP, n=16 Cef-TBI) or saline (n=17), daily, for one week after TBI. A sham group (n=5) received all surgical procedures except LFPI, and did not receive IP injections. This data demonstrated for the first time that ceftriaxone treatment in the acute post-TBI period preserves the functional health of cortical inhibitory interneurons as measured by ppTMS and preserves PV gene expression in injured cortex compared to saline controls weeks after TBI. Ceftriaxone mediated upregulation of GLT-1 does not last beyond cessation of treatment one week after TBI, however the intervention seems adequate to mitigate post-traumatic loss of inhibition. Since ceftriaxone is a safe and widely used β-lactam antibiotic, It was cautiously concluded that the ceftriaxone neuroprotective effect can be tested in clinical trials.

Mifepristone treatment (MF) post-status epilepticus normalizes basal corticosterone levels, decreases the loss of hilar mossy cells and reduces hilar BrdU+ cells in mice

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In this study, it was explored whether blockade of glucocorticoid signaling might mitigate pathological changes normally present in the hippocampus after SE, such as reactive neurogenesis or ectopic granule cell accumulation. It was suggested that pilocarpine induced-SE leads to the short-term suppression of CORT release. A 24 hour following SE mice show elevated basal levels of CORT when compared to non- SE control mice. An increase in basal CORT can be normalized by a 4-day treatment with the glucocorticoid antagonist mifepristone. MF had no effect on cell proliferation as assessed by DG BrdU+. Mifepristone treatment in post-SE mice decreased the number of BrdU+ labeled cells in the dentate hilus, suggesting that it might mitigate the accumulation of ectopic granule cells in this region. Treatment with MF reduced mossy cell loss in the dentate hilus of post-SE mice. Overall, this data suggests that 7 day treatment with MF following SE may be beneficial to prevent some of the acute pathological changes associated with SE injury. Future studies are needed to determine the mechanisms and functional significance of these changes in cell proliferation, survival and integration.

HIGHLIGHTS FROM INTERNATIONAL NEUROSCIENCE MEETINGS

Non-antiepileptic drugs & non-surgical treatment of epilepsy

Efficacy of Ketogenic Diet: An Experience at King Fahd Specialist Hospital-Dammam (KFSHD)

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The aim of this study was to test the efficacy of the ketogenic diet at KFSH-D. **Methods:** 31 children aged between one and 14 years who had at least daily seizures, had failed to respond to at least 2 antiepileptic drugs, and had not been treated previously with the ketogenic diet participated in a retrospective study of its efficacy to control seizures between February, 2010, and July, 2012. Children were seen at KFSH-D. Early withdrawals were recorded, and seizure frequency on the diet was assessed after 18 months. Tolerability of the diet was assessed during clinic visits every 3 months. It was concluded that the results from this experience at KFSH-D of the ketogenic diet support its use in children with treatment-intractable epilepsy.

Outpatient Education Reduces Emergency Room Use by Epilepsy Patients

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The purpose of this study is to assess whether educating clinic patients on epilepsy self-management and seizure first aid would reduce ER visits related to their epilepsy in the 4 months following education. Self-management includes proper anti-epileptic drug (AED) use and compliance; awareness of potential AED side effects; awareness of common seizure triggers and harmful lifestyles, and ways to avoid these; compliance with clinic follow-up appointment. It was found that providing clinic patients with educational materials on epilepsy care, seizure first aid, and proper ER use is correlated with a significant decrease in ER use among patients with epilepsy. This finding supports patient education as a valuable tool to reduce ER use, which may in turn cut down on healthcare cost.

Surgery

To Coordinate or Not to Coordinate?

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A total of 42 patient charts were extracted from an epilepsy surgery database. The patient charts covered a span of 2 years and 5 months. (January 2011-May 2014) Out of the 42 charts, 32 patients were evaluated for epilepsy surgery prior to having an Epilepsy Care Coordinator and 10 patients were evaluated for epilepsy surgery after an Epilepsy Care Coordinator was in place. From these dates the median time lag was calculated (in days) and compared by using the date of the first surgical suggestion and the date of the actual surgery date. Establishing a point person such as an Epilepsy Care Coordinator can expedite the process from first consideration of a surgical option in clinic to surgery, resulting in a greater number of patients being able to move through the surgical process. It is anticipated that with patients going through the surgical evaluation in a timelier manner; better use of the surgical testing equipment and more epilepsy surgeries in a shorter timeframe can be achieved.

HIGHLIGHTS FROM INTERNATIONAL NEUROSCIENCE MEETINGS

What's in a Year? EEGs Encountered in an ACGME-Accredited Clinical Neurophysiology Fellowship

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The goal of this study was to provide a description of a clinical neurophysiology fellow's EEG experience after one year in the ACGME fellowship in order to serve as a basis for comparison for subsequent studies and to identify deficiencies so that future trainees may be better prepared for clinical practice. It was found that this clinical neurophysiology fellow was exposed to a wide variety of EEG findings mainly through video EEG. Neonatal EEGs and the presence of electroclinical syndromes comprised a small proportion of the encountered studies. Future investigations can evaluate parity in training by comparing this sample to EEGs encountered at other training institutions. Program directors should be aware of the deficiencies in clinical EEG exposure so learning can be supplemented by other mechanisms.

Genetics

Magnetoencephalography-guided surgery in MRI negative or ill-defined frontal lobe epilepsy using neuronavigation and intraoperative MR imaging

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In this retrospective study, we investigated the impact of MEG-guided localisation and resection of epileptic tissue with the aid of neuronavigation and intraoperative MR imaging (iopMRI) on seizure outcome of FLE patients. It was concluded in this analysis that invasive monitoring and MEG-guided resection using neuronavigation and iopMR imaging led to promising seizure control rates in patients with MRI negative or ill-defined refractory frontal lobe epilepsy. Achieving a complete resection rate of the defined epileptogenic zone of 75% and acceptable risks of postsurgical neurological deficits, we present one possible approach to resect epileptic tissue using multimodal imaging techniques.