



Society Proceedings

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1. Across all the seven seas: Fifty years in neurology, EEG and epilepsies—Paul Hwang MDCM FRCPC

Since the 1960s, major neuroscience advances have facilitated the development of new antiepilepsy drugs (AEDs) targeting specific neurotransmitter-receptor systems, particularly the GABAergic, the NMDA-receptors and voltage-gated ion channels. In addition to the classical AEDs, carbamazepine and cogeners act at the voltage-gates sodium channels, while ethosuximide acts at the calcium channel, improving the treatment of partial and generalized seizures. But approximately 30% of partial complex seizures remain refractory to AEDs, leading to novel AEDs: levetiracetam, tiagabine, lacosamide, perampanel and others. The pharmacoresistant epilepsies are typically dyscognitive partial-onset, arising from limbic structures of mesial temporal lobes, better visualised by improved neuroimaging methods eg. MRI and PET. Together with invasive intracranial monitoring in specialized units with long-term recording of multichannelled EEG and video-recording of behaviour, the localization of the seizure-onset zone has allowed targeted excision of the epileptogenic tissue for better outcome.

Functional neurosurgical methods include vagal nerve stimulation and deep brain stimulation of selected targets in affected circuits, mapped by new EEG criteria including gamma rhythm, HFOs, ripples and clusters. Novel intervention in refractory epilepsies include the ketogenic diet and variants, neurosteroids, hormones eg. progestins and ACTH. A number of genetic mutations and copy number variants have been linked to epilepsies. It remains to be seen how expanded knowledge of the genetic bases of the epilepsies and epileptic encephalopathies leads to new intervention improving long-term prognosis and quality of life in persons afflicted with this ancient curse of the human condition, 'The Falling Sickness' also known as 'The Sacred Disease' (Hippocrates).

In the words of Sir William Osler: 'He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all' ('Aequanimitas' by Osler), quoted in Herbert Ho Ping Kong, 'The Art of Medicine: Healing and the Limits of Technology' (ECW Press, 2014 Toronto).

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2. Do repeated limbic seizures induce depression-like behavior in rats?—W. McIntyre Burnham, Brian W. Scott (University of Toronto, Canada)

It has been reported that rapid kindling of the hippocampus produces lasting depression-like behavior in rats, as evidenced by increased immobility in the forced swim test and a loss of preference for sweetened water (Mazarati et al., 2007). This might suggest that repeated limbic seizure activity could be the cause of the depression often seen in patients with temporal lobe epilepsy.

Sixty-day old male Wistar rats were implanted with electrodes in the amygdala and ventral hippocampus and kindled (or sham kindled) daily to a criterion of 10 stage 5 seizures. Two weeks later subjects were tested in the forced swim and sweet taste preference tests. No differences were found between the kindled and sham kindled animals.

Subsequently, twenty-one day old male Wistar rat pups were implanted and quick kindled (or sham kindled) in the ventral hippocampus. Kindling was accomplished in a single day by stimulating every 5 min for 84 stimulations. Four days or two weeks later they were tested in the forced swim and sweet taste preference tests. No differences were found between the kindled and sham kindled animals.

The present data do not support the idea that repeated limbic seizures induce depression-like behavior in rats.

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3. Asymmetric hypersarrhythmia: An insight into the pathophysiology of infantile spasms. A retrospective cohort—B. Desnous, M. Arbour, H.S. Nguyen, A. Lortie, D. Chartrand, E. Rossignol, P. Diadori, P. Major, L. Carmant, A. Birca (Division of Neurology, Sainte Justine Hospital, University of Montreal, Canada)

Infantile spasms (IS) is a catastrophic epilepsy where treatment precocity improves outcome. Previous studies demonstrated an association between asymmetric hypersarrhythmia on EEG and ipsilateral hemispheric lesions on MRI, suggesting a possible role of cortical lesions in the initiation of IS. Epileptiform abnormalities appearing during early infancy have also been linked to IS emergence. We hypothesized that focal lateralized EEG abnormalities during the prehypersarrhythmic period will be associated with asymmetric hypersarrhythmia at IS onset.

We recruited a retrospective cohort of 80 infants, 7.4 ± 3.6 months old at the onset of hypsarrhythmia and IS, admitted to Sainte-Justine Hospital between 2007 and 2016. Seven infants showed an asymmetric hypsarrhythmia pattern and, as expected, all of them had lateralized lesions on MRI. Of the remaining 73, 42 had abnormal MRI, but only 3 infants had lateralized lesions (100% vs 7.1%, $p < 0.01$). Thirty-four patients had pre-hypsarrhythmic EEG recordings at the age of 4.6 ± 2.6 months, 3 ± 2 months before IS onset, including four infants with asymmetric hypsarrhythmia. Five infants had no pre-hypsarrhythmic epileptiform abnormalities.

Six had focal lateralized, while 23 multifocal abnormalities. The proportion of patients with focal abnormalities was higher in those who developed asymmetric compared to symmetric hypsarrhythmia (50% vs 13.3%, $p < 0.05$).

Our data confirm the link between asymmetric hypsarrhythmia and lateralized MRI lesions. Moreover, we show that focal lateralized EEG abnormalities precede asymmetric hypsarrhythmia, which supports the involvement of cerebral cortex in the IS genesis. More sensitive EEG biomarkers of high IS risk may help developing preventative treatments that will improve outcomes in IS.

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4. Prevention of trauma-induced epileptogenesis in mice via manipulation of the network excitability—S. Soltani, J. Seigneur, S. Chauvette, I. Timofeev (CRIUSMQ, Québec, Canada)

A large proportion of patients with severe brain damage become epileptic several months to years after the trauma. The mechanisms leading to the development of epilepsy (epileptogenesis) are unknown. We hypothesize that brain damage leads to partial deafferentation and a drop in excitability of the affected area. To compensate, the brain employs a variety of mechanisms to restore this drop of excitability and if not properly controlled, this leads to epilepsy. We performed undercut in the somatosensory area in adult C57/BL6 mice and implanted LFP and EMG electrodes for continuous electrographic recordings for at least two months. We proposed to manipulate (increase or decrease) network activities in order to prevent/enhance epileptogenesis applying DREADD technology. Target cortical regions were injected with AAV-hM3D(Gq) or AAV-hM4D(Gi). Activation of the designed receptor in infected neurons was achieved by clozapine-N-oxide continuously injected via an osmotic pump. Activation of hM3D(Gq) leads to depolarization and increased firing in infected neurons, while the activation of hM4D(Gi) induces a hyperpolarization of neurons. If our hypothesis is true, we expect to obtain epileptogenesis in adult mice without DREADD manipulations, either abolition or strong reduction of epileptogenesis in hM3D(Gq) mice, and increased epileptogenesis symptoms in hM4D

(Gi) mice. In the following weeks all adult mice without DREADD manipulations revealed recurrent seizure activities. Mice in which hM4D(Gi) was activated revealed earlier and more severe seizures. Mice with hM3D(Gq) activation did not reveal paroxysmal activities. These results will lead to the development of new preventive treatments of epileptogenesis induced by brain damage.

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5. Epilepsy and EEG activity in early-onset Alzheimer's disease—Ángela Milán-Tomás¹, Paul Hwang² (¹Clinical Research Fellow in Movement Disorders and Cognitive Neurology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; ²UTERP, EpLink-OBI, NYGH, University of Toronto, Toronto, ON, Canada)

Objective: The aim of this review was to evaluate and summarize the current literature regarding the incidence and features of epileptic seizures in early onset Alzheimer's disease (AD) as well as its epileptiform characteristics as described by electroencephalography (EEG).

Background: The incidence of epilepsy in AD is higher than in the general population, although the true prevalence of seizures has remained unclear due to methodological problems detecting these events in a cognitively impaired population.

Design/Methods: A literature search using Medline with PubMed and EMBASE was carried out identifying papers published focusing on EEG and epilepsy in early-onset Alzheimer's disease (EOAD). A total of 767 abstracts were obtained, 55 full publications were screened and references were checked for additional material where appropriate.

Results: Only 20 studies included EEG data regarding epilepsy in Alzheimer's disease of which 11 were animal models. AD due to amyloid precursor protein (APP) mutations has been described as one of the most common early-onset AD forms presenting with epileptic seizures. Neurodegeneration of the hippocampal region causing aberrant excitatory neuronal activity is the most accepted hypothesis for the occurrence of epilepsy in AD.

Conclusions: There is a need for better methodological studies addressing the role of EEG in the diagnosis and characterization of seizures in AD. Subclinical epileptiform activity may lead to a faster decline in cognition and they occur more often during sleep stages, therefore a prolonged sleep EEG can be an effective diagnostic tool for detecting this activity.

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