The Changing Landscape of Epilepsy

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When patients seek the help of a physician, they ask 3 universal questions:

- Why did this happen to me?
- Can you help me?
- What does my future hold?

Yet, for patients with epilepsy, typically all 3 of these questions remain mostly unanswered, despite advances in the field in recent decades, according to Daniel H. Lowenstein, MD, University of California, San Francisco Medical Center, San Francisco, California, USA. He noted that, although treatments are available for epilepsy, treatment selection and whether it will be effective in a patient too often remain an "educated guess." And for most patients, both the cause of epilepsy and their prognosis remain unknown.

THERAPEUTIC ADVANCES

Dr Lowenstein noted that at least 15 new agents have entered the market with FDA approval since the mid-1970s, but the overall evidence suggests that these new therapies have not significantly impacted patient care [Schmidt D, Sillanpää M. *Neurology*. 2012; Löscher W, Schmidt D. *Epilepsia*. 2011; Shorvon SD. *Epilepsia*. 2009]. Although drug regimens have simplified over the years for patients with epilepsy (which has led to the appearance that more patients may tolerate these drugs and do better on them), the evidence to support these observations is very weak. This was demonstrated by the SANAD trial, one of the largest studies to evaluate drug treatment of new onset epilepsy [Marson AG et al. *Health Technol Assess.* 2007]. SANAD compared the efficacy and tolerability of new drugs with carbamazepine and valproate in >2400 patients and demonstrated no significant difference between the newer and second generation agents.

Peer-Reviewed Highlights From the

American Academy of Neurology 2015 Annual Meeting

April 18–25, 2015
Washington, DC, USA

TRANSLATIONAL ADVANCES

In contrast, however, Dr Lowenstein emphasized that significant translational advances have occurred in the past 50 years, with a direct impact on patient care in epilepsy. These have been in the areas of

- neuronal physiology during seizures, in particular with respect to demonstration of the paroxysmal depolarization shift that occurs in neurons in epilepsy;
- understanding the molecular, cellular, and network characteristics of absence epilepsy;
- neuronal injury caused by prolonged seizures;
- video electroencephalogram (EEG) telemetry, which has advanced the diagnostic capabilities in epilepsy and the ability to identify effective therapies;
- discovery of epilepsy and drug toxicity genes;
- autoimmune epilepsy, which lends itself, in some cases, to immune modulation therapy; and
- neuroimaging, which has significantly impacted the ability to diagnose and treat the focus causing a seizure disorder.

SCIENTIFIC ADVANCES

Dr Lowenstein also discussed some major scientific advances that, in time, may also significantly impact patient care in epilepsy, including

- optogenetics as a novel way of treating epilepsy by modifying neuronal networks involved in seizures;
- the use of flexible arrays that conform to the brain's surface to investigate brain activity;
- inducible pluripotential stem cell use that might enable investigation of cells from patients with epilepsy who have defined gene mutations, ultimately facilitating identification of specific treatments; and
- high throughput screening, a technique that has been used in zebrafish for screening of antiepileptic drug candidates.

Dr Lowenstein highlighted 2 important large-scale projects involving patients with epilepsy. The Epilepsy Phenome/Genome Project (EPGP) [The EPGP Collaborative. *Clin Trials*. 2013] began in 2006 and aimed to develop a database of detailed phenotype information for patients with specific forms of epilepsy; create a repository of DNA and cell lines on all project participants; assess the phenotypic characteristics of different cohorts for evidence of relationships between phenotype and genotype; and apply cutting edge technologies to the data collected.

The largest cohort comprised patients with idiopathic generalized epilepsy with a first-degree relative who also had epilepsy, as well as patients with localization-related epilepsy with a first-degree relative with epilepsy. Another major cohort comprised patients with infantile spasms (IS), Lennox-Gastaut syndrome (LGS), or malformations of cortical development, and for whom both parents were triads.

The Epi 4K collaborative [The Epi4K Consortium. *Epilepsia*. 2012] involves a phenotyping and clinical informatics core and a sequencing, biostatistics, and bioinformatics core, both of which converge on 4 different projects that particularly focus on epileptic encephalopathies (EEs), multiplex families and pairs, prognosis, and copy number variant (CNV) detection.

Dr Lowenstein discussed the EEs project from the Epi4K collaborative that comprised 2 main groups—patients with either IS or LGS [Epi4K Consortium, Epilepsy Phenome/Genome Project. *Nature*. 2013]. Most EEs do not show transgenerational transmission, and most families do not have sibling recurrence. Therefore, it was hypothesized that many patients with IS and LGS have *de novo* causative mutations that arise in the germline and are therefore inherited only in a particular individual. The group thus aimed to target families that would highlight the increased chance of finding *de novo* mutations. This required the availability of both biological parents to compare the genome of the proband with that of each parent. In addition, it was required that the parents did not have epilepsy and that there was no familial recurrence.

This project showed that, in EEs, there is an overrepresentation of variants for mutations in genes that are intolerant, suggesting that they are causative.

Numerous other causative genes were also identified [Epi4K Consortium, Epilepsy Phenome/Genome Project. *Nature*. 2013]. According to Dr Lowenstein, research to date has determined approximately 20% of the genetic basis of all EEs. Mutations in one of the causative genes, *KCNT1,* are associated with a severe form of autosomal dominant frontal lobe epilepsy and another severe condition known as 'epilepsy of infancy with migrating focal seizures.' He shared the results of one study, demonstrating a significant increase in potassium channel current flow that correlated with disease severity associated with these gain-of-function mutations [Milligan CJ et al. *Ann Neurol*. 2014]. That study also showed that exposure to quinidine can modify these currents by decreasing the mutation effect. Quinidine also had a variable effect on additional mutations that were studied, and the effect was somewhat correlated with disease severity.

This research then led to the first attempt at targeted treatment using quinidine in a patient with *KCNT1* mutation [Bearden D et al. *Ann Neurol*. 2014]. Following administration of quinidine, improved psychomotor development and a marked reduction in seizure frequency was evident.

Dr Lowenstein proposed that these findings constitute a proof-of-principle demonstration of the identification of a genetic basis of epilepsy, discovering a potential therapy for the specific mutation *in vitro*, and then introducing the treatment into a patient to ameliorate the disease. Importantly, it also provides answers to the first 2 of the universal patient questions, although the prognosis for such patients remains unknown. Nevertheless, these findings mark the beginning of a new era in epilepsy care, he concluded.