Epileptologists in quest for the Holy Grail

Thierry Grisar

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The epilepsies affect around 50 million people worldwide and constitute in 2012 the second neurological group of diseases. Anyone can suffer one type of epilepsy with more or less severe repeated seizures independently of age, race, or of socioeconomic or geographic situation. In Europe, the prevalence of epilepsy is of 8.2 per 1,000 corresponding to 6 million individuals with active epilepsy and around 15 million having experienced epilepsy during their lives (see [1]).

Since almost two or even three decades now, the epileptologists repeatedly claim that in spite of the scientific progress in the field of basic neurosciences on the one hand and in clinical and neuropharmacological research on the other hand, 30–40 % of their patients remain incurable or at least drug-resistant.

It took a long time to recognize the extreme diversity of the epileptic syndromes and to remain concentrated on the treatment of the seizures themselves. One of the symptoms of this is the ongoing use of the term “Epilepsy” in the singular form. For years, this attitude was clearly justified, since the antiepileptic drugs were efficient in at least half of the patients.

Therefore, from the clinical point of view, considerable efforts have been developed to better identify and classify new epileptic syndromes and sometimes diseases.

Truly, the principal symptom that links the different epileptic diseases is the seizure itself, a phenomenon due to the sudden occurrence in a particular area of the cerebral cortex of an epileptogenic circuit probably starting by hypersynchronous bioelectrical discharges in a set of cortical

neurons then propagating in specific parts of the brain through synaptic connections. Therefore, for years, the therapeutic efforts tended to limit excitation and/or to favour inhibition considering epilepsy (i.e. “in singular”) as a clear imbalance between these two phenomena. Although several experimental evidences illustrated that one can produce huge epileptogenic circuits by favouring GABAergic inhibitory inputs in some circumstances, one has to observe that this “old thought” is still hard to tackle among the clinical and also the pharmacological world.

Since 1995, positional cloning strategies in multigenerational families with autosomal dominant transmission have revealed several genes (KCNQ2, KCNQ3, CHRNA4, CHRNA2, CHRNA2, CHRNA2, SCN1B, SCN1A, SCN2A, GABRG2, GABRA1...) and numerous loci for febrile seizures and epilepsies. Most of these genes encode neuronal ion channel or neurotransmitter receptor subunits creating a first enthusiastic hypothesis that at least idiopathic generalized epilepsies could be considered as a new group of *channelopathies*.

However, molecular approaches have revealed great genetic heterogeneity, with most genes remaining to be identified. One of the major challenges is now to understand phenotype–genotype correlations.

Following these advances, it became more and more popular to think of the antiepileptic treatment in terms of their basic mechanisms of action, i.e. acting on Na⁺ or K⁺ channels or GABA transmission, etc..., as if a specific and precise molecular mechanism of action in given epileptic syndromes (childhood absence epilepsy, medial temporal lobe epilepsy, or the Dravet syndrome, etc...) were completely elucidated. We have to admit that this probably still constitutes an illusion. Today, the effort to clarify the effectiveness of a rationale of antiepileptic treatment on a (somewhat empirical) clinical basis and multidisciplinary

T. Grisar (✉)
CHU, Department of Neurology, GIGA Neurosciences Research
Centre, University of Liège, Liège, Belgium
e-mail: tgrisar@ulg.ac.be

approach remains the second best standard for epileptologists.

Recently, an alternative conceptual view to the classical “channelopathies” emerged from studies of the Idiopathic (or “Genetic”) Generalized Epilepsies (IGE or GGE).

GGE was initially considered as a group of epileptic disorders that were very early believed to have a strong underlying genetic basis. Classically, they tend to begin during childhood or adolescence, although they may not be diagnosed until adulthood.

Patients with GGE have one or more of three types of primary generalized seizures: generalized tonic-clonic seizures, absence seizures, or myoclonic seizure. People with GGE have normal intelligence, normal neurological examination, and reputed “normal” MRIs. This means that, up to now, the brain was considered as anatomically normal.

The electroencephalogram (EEG) remains the only definitive test to confirm the diagnosis with various combinations of generalized spike-wave complexes, spikes, or polyspikes. Patients also often have a family history of epilepsy and were often considered to have a genetically predisposed risk of attack. Since several decades, the genetic cause of GGEs was suspected on a clinical basis though inheritance does not always follow a simple monogenic mechanism. GGEs include common disorders with a complex mode of inheritance and rare Mendelian traits suggesting the occurrence of several alleles with variable penetrance.

During the last decade, molecular genetic analyses have led to important breakthroughs in the identification of candidate genes and loci; genetic heterogeneity is common. As a result, the International League Against Epilepsy (ILAE) Commission on Classification and Terminology has revised concepts, terminology, and approaches for classifying seizures and forms of epilepsy. “Generalized” is redefined for seizures occurring in and rapidly engaging bilaterally distributed networks. Classification of generalized seizures is simplified. The concept of “generalized” does not apply to electro-clinical syndromes. “Genetic” illustrates the modified concept and replaces idiopathic.

More recently, however, different investigators published data illustrating a possible role of genes implicated in neuronal migration, brain development, or early corticogenesis as responsible for the occurrence of particular GGE syndromes.

For instance, we identified for the first time that a gene responsible for GGE (juvenile myoclonic epilepsy): Myoclonin 1 (or EFHC1) encodes a new microtubule associated protein (MAP) utilizing an unusual microtubule binding domain and not an ionic channel [2]. Thus, besides the

classical theory of *channelopathies* causing GGE, our work opens new perspectives in the identification of the precise molecular and cellular mechanisms of GGE, including subtle pathologies of early neuronal migration (“microdysgenesis”). We hypothesize that the mutations of Myoclonin 1 could induce subtle neuronal migration defects that may lead to abnormal epileptogenic circuitry during cortical maturation at the onset of adolescence. Eventually, the elucidation of such mechanisms will provide new targets for better, or at least different and probably more complex pharmacological treatments of a particular epileptic syndrome.

In the preface of the last edition of Basic Mechanisms of the Epilepsies, one can read:

In line with the enormous expansion in the understanding of basic epilepsy mechanisms over the past four decades, the fourth edition of Jasper’s Basic Mechanisms of the Epilepsies is the most ambitious yet. In 90 chapters, the book considers the role of interactions between neurons, synapses, and glia in the initiation, spread, and arrest of seizures. It examines mechanisms that underlie excitability, synchronization, seizure susceptibility, and ultimately epileptogenesis. It provides a Framework for expanding the epilepsy genome and understanding the complex heredity responsible for common epilepsies as it explores disease mechanisms of ion channelopathies and developmental epilepsy genes. It considers the mechanisms of conditions that are comorbid with epilepsy. And, for the first time, fulfilling the original Merritt and Jasper goals of “seeking rational methods of prevention and treatment,” this fourth edition describes the current efforts to translate the discoveries in epilepsy disease mechanisms into new therapeutic strategies.

Yet, at the end, we still do not have a new antiepileptic drug for a particular epileptic syndrome, and the only approach to cure epilepsy, when appropriate, in 2012 remains surgery.

Conflict of interest None.

References

1. WHO (2009) Epilepsy in the WHO European region. <http://www.ilae.org/visitors/.../euroreport160510.pdf>
2. de Nijs L, Leon C, Nguyen L, LoTurco JJ, Delgado-Escueta AV, Grisar T, Lakaye B (2009) EFHC1 interacts with microtubules to regulate cell division and cortical development. *Nat Neurosci* 12:1266–1274