WORKSHOP REPORT

Workshop on Idiopathic Generalized Epilepsies: Bridging basic science and clinical research (October 3–6, 2007; Antalya, Turkey)

This Workshop considered a category of epilepsies that has been defined using the two main dichotomies on which the current ILAE classification is based—"idiopathic vs. symptomatic" and "partial vs. generalized." The Workshop provided geneticists, neurobiologists, and clinicians who study idiopathic generalized epilepsies (IGEs) with an interactive forum in which to discuss the data and concepts arising from recent research. Because the term "generalized" is better applied to the classification of seizures than syndromes (because both focal and generalized seizures may occur in some syndromes), the Workshop discussion of pathophysiologic mechanisms concentrated on seizures rather than epilepsy syndromes.

MECHANISMS OF GENERALIZED SEIZURES: EVIDENCE AND PERSPECTIVES

Although all brains are capable of supporting a seizure under extreme conditions, such as hypoglycemia or significant alterations in electrolyte concentrations, epileptic brains will generate seizures under otherwise normal conditions. To understand how these "spontaneous" seizures arise, basic research must develop a better understanding of the circuitry underlying seizures. Although there was a broad consensus among Workshop participants that the primary circuit for spike-and-wave discharges centers around the reciprocal connections between the thalamus and cortex, it was also agreed that many of the key details regarding the interactions between these regions that lead to seizures, are still unknown.

The most challenging discussion concerned recent evidence indicating that there is a focal origin of the spike-and-wave discharges underlying the absences that are considered prototypes of generalized seizures. This evidence has been obtained using two rodent models of absences—the Genetic Absence Epilepsy Rat from Strasbourg (GAERS) and the Wistar Albino Glaxo Rats from Rijswik (WAG/Rij)—and identifies the somatosensory cortex as the site of origin of these discharges, which subsequently generalize to involve the thalamo–cortico–thalamic circuitry. These new experimental data are consistent with clinical observations of a regional prevalence of the electroencephalographic (EEG) discharges associated with generalized seizures, and their lateralized onset from a leading hemisphere that can be demonstrated by means of signal analysis. There was a general consensus: (1) that the use of the term "focal" to describe such a regional onset can be misleading, as it may create confusion with "true" focal seizures; (2) that the available data support the idea of a trigger zone within a given thalamocortical system that has a particular genetically determined epileptogenic susceptibility; and (3) that during the absence seizures, the trigger area becomes a part of the oscillating network; and (4) that the oscillations constitute an emerging property of the whole system, (as in dynamic, nonlinear systems). Basic scientists and clinicians agreed upon the concept of "system epilepsy" to designate epilepsies caused by the oscillating thalamocortical system. The development of computational models will be necessary to obtain insights into this kind of oscillatory process.

Genetics-based information concerning human and rodent generalized epilepsies has provided new insights into epileptogenic mechanisms by showing that genetically determined dysfunctions in voltage-gated ion channels and receptors can result in epileptic activity. Voltage-gated sodium and potassium channels control the depolarizing and repolarizing phases of action potentials; calcium channels are key players at presynaptic nerve terminals during transmitter release; ligand-gated channels associated with acetylcholine, glutamate, and γ-aminobutyric acid (GABA) receptors integrate presynaptic signals at postsynaptic neurons; and other channels that are important for ionic equilibrium. It is very likely that not all epilepsy-producing mutations or variants in rats have an equivalent in humans, and that the opposite is also true. However, epilepsy-associated mutations in rats will probably give us insights into the many ways that mutations can lead to IGE-like disorders. Perhaps even more interesting is the common observation that a given gene mutation leads to epilepsy in one strain of mouse but not another, an observation that underscores the very important role the genetic environment can play in determining whether a given mutation will give rise to epilepsy. This observation may explain the variable penetrance seen in families with a clear epilepsy lineage.

In addition to the need to define the specific thalamocortical components of the primary absence seizure circuit, there is also a need to understand the other regions of the brain that have a significant input to the thalamus or cortex and that can influence or cause the system to generate a seizure. Because these seizures are greatly influenced by age and the presumed maturation of the brain, there is also a fundamental need to understand how the involved circuits mature and what aspect of the maturational process leads to a seizure-prone system. With the exception of a few major channel types, the molecular components of neurons in the defined thalamocortical circuits—such as the channels and receptors responsible for the initiation, maintenance, and ultimate suppression of spike-and-wave discharges—remain poorly explored. Once these molecular features have been determined, we will still need to learn what changes in these structures make a system epileptic. Understanding the multiple components underlying spike-and-wave discharges is not only necessary for determining how the system has been made epileptic, but also for understanding how individual seizures are generated. It is likely that nonreceptor mechanisms, such as the blood–brain barrier, glia, and gap junctions, play important roles and should, therefore, be examined.

Another key area that should be explored to enhance our understanding of this group of epilepsies is the effect of age on the circuit components that ultimately lead to the development of the epilepsy phenotype. A number of factors could contribute to the appearance of seizures at a particular age or developmental stage, including a shift in the isoform expression of selected key channels, receptors, or other molecular components; the effect of hormones on the circuits and their components; the state of myelination; and changes in the glia. One issue that is not clearly understood is whether the epileptic condition is caused by the gradual developmental appearance of sufficient numbers of abnormal components to allow seizures to occur, or whether there is a series of epileptogenic events unrelated to the normal maturational sequence. The former implies that the development of epilepsy is an inevitable result of development, whereas the latter suggests that the development of epilepsy could theoretically be prevented by timely and appropriate intervention.

One of the potential problems concerning the effect of age is the difficulty in relating age between rodent models and humans. Although many of the human syndrome variants are restricted to a certain period of life, rats often show a delayed onset of these phenotypes (e.g., spike-and-wave discharge) and then have the disorder for life. This difference in age-specific expression may indicate a specific pathophysiologic difference between the two species. However, another potential explanation could be that the rats have a simpler circuitry that may only mature to a state equivalent to the circuitry of a young human. If that is the case, the failure of the seizures to remit as a rodent matures may reflect the fact that the thalamocortical circuits in rodent brain do not mature beyond the circuit equivalent of a child.

The Concept of Idiopathic Epilepsies

The term ‘‘idiopathic epilepsy’’ (from the Greek *idios* = self or proper) was coined by Galen in the second century to designate an epilepsy caused by a disorder of the brain itself—in contrast to symptomatic epilepsy, where the brain is only secondarily affected by a disorder located elsewhere. According to the ILAE Commission Report of 2001, an idiopathic epilepsy syndrome is one that is ‘‘only’’ epilepsy, with no underlying structural brain lesion or any other neurologic sign or symptom. It is presumed that idiopathic epilepsies are genetic and usually age-dependent. The Workshop, therefore. discussed whether recent advances in the genetics of epilepsies have had any impact on this definition of IGE phenotypes.

Novel gene mutations have been identified using two main approaches: genome-wide linkage analyses or association studies, and candidate gene studies. Over the last 15 years, a number of large families with IGE have been described, and most of these familial traits show an autosomal dominant mode of inheritance with a high (although incomplete) level of penetrance. However, pedigrees with autosomal recessive idiopathic generalized epilepsy have also recently been reported.

In many instances, the IGE phenotype segregating in a family does not differ substantially from the classical phenotypes found in the general population, and pedigrees with autosomal dominant childhood absence epilepsy or juvenile myoclonic epilepsy were described. Genetic analyses have demonstrated that mutations segregating in these families are not involved in the more common sporadic forms, thereby confirming the complex and heterogeneous nature of IGE.

There was a general consensus on the identification of the following IGE syndromes: benign myoclonic epilepsy in infancy (BMEI), childhood and juvenile absence epilepsies (CAE and JAE), juvenile myoclonic epilepsy (JME), and idiopathic epilepsy with generalized tonic–clonic seizures only (IGE-GTCS). The merging of JAE, JME, and IGE-GTCS under the common heading of ‘‘idiopathic generalized epilepsies with variable phenotypes’’ is still open to discussion, as is merging the absence/myoclonic syndromes of eyelid myoclonia with absences (ELMA) and absences with perioral myoclonia (PMA). ELMA is a reflex IGE that shows onset in the first decade of life and is characterized by bilateral regional eyelid/eyebrow myoclonus with or without associated absences, photosensitivity, and eye closure–induced EEG abnormalities or seizures. PMA could be another distinct phenotype of absence/myoclonic IGE, with onset in the first decade of life. The effort to identify separate IGE syndromes is

justified by the need to define pure phenotypes for genetic studies, the results of which could validate the clinical criteria on which clinical classification is based. Some monogenic epilepsies, such as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) and benign neonatal familial convulsions (BNFC), have already been validated in this way. Moreover, the accurate phenotypic description of familial traits has led to the identification of previously unrecognized syndromes such as generalized epilepsies with febrile seizures plus ($GEFS^+$) and benign adult familial myoclonic epilepsy (BAFME). However, although genetic studies can contribute to solving some taxonomic controversies, it is clear that they have not yet provided the main criterion on which a general classification of IGEs could be based. The genotype associated with most IGEs is still unknown, and the possibility of a monogenic inheritance, which has been demonstrated in the case of ADNFLE, BNFC, and $GEFS^+$, seems to be the exception rather than the rule. Among the genetic traits that could contribute to determining IGEs, there has been special interest in photosensitivity as a potential endophenotype that may be useful in dissecting the complexity of the underlying genetic basis.

The relevance of genetics to IGE classification was also discussed with reference to the concept of an idiopathic condition, which is one of the pillars of the current classification system. Mendelian inheritance is rare among IGEs and has limited clinical implications, but it has provided a direct demonstration that mutations in genes encoding ion channel or receptor subunits can lead to epilepsies that are ''only epilepsies,'' and, therefore, fulfill the definition of idiopathic epilepsies.

Major advances have been made using techniques of expressing mutations that can cause epilepsy in simple preparations suitable for characterizing their functional consequences by means of electrophysiologic recordings. This investigative process has made it possible to trace the chain of pathophysiologic events linking mutations to their phenotypical expression, thereby clarifying some puzzling observations. One important example is provided by BNFC that had for some time been known to be linked to two different loci, located on different chromosomes. A combination of biomolecular and electrophysiologic analyses has now demonstrated that such genetic heterogeneity corresponds to pathogenetic homogeneity, as both genes code synergistic subunits of a K^+ channel (KCNQ2 and KCNQ3). Similar observations have been made in the case of other epilepsies caused by channel gene mutations (e.g., ADNFLE).

Another puzzling observation concerned gene mutations, leading to deletions of the encoded protein, which were unexpectedly associated with increased excitability; this apparent contradiction, which is exemplified by severe myoclonic epilepsy of infancy (SMEI), was solved by experimental evidence showing the selective expression of the mutation in inhibitory neurons, thus leading to the disinhibition of the principal neurons.

Conclusions

The impressive advances in the neurophysiology and molecular biology of the epilepsies are having a major impact on our understanding of mechanisms of the generalized epilepsies and our approach to their clinical management. The multidisciplinary discussion of the pathophysiology and clinical picture of the IGEs during this Workshop provided the participants with updated information concerning the genetics, molecular and cellular mechanisms, and phenotypes of the IGEs. The results of this discussion gave rise to a recommendation to revise the two concepts (''idiopathic'' and ''generalized'') on which the definition of IGE is based, and to propose the concept of ''system epilepsy.'' Clinical and experimental results concur in showing that the spike-and-wave discharges underlying absences have a local origin from a trigger cortical area, and, therefore, challenge the view of absences as prototypes of generalized seizures. Moreover, evidence showing that mutated Na^+ channels can be associated with a wide spectrum of epileptic phenotypes (including epileptic encephalopathies) prompted reconsideration of the concept of idiopathic epilepsy as a disorder ''that is only epilepsy, with no underlying structural brain lesion or any other neurologic sign or symptom'' and which is ''presumed to be genetic.'' If we accept the principle that a classification should reflect the state-of-the-art in a given field, the new information presented at the Antalya Workshop should have a significant impact on the ongoing discussion of the classification of IGEs.

Acknowledgment

The Antalya Workshop on ''Idiopathic generalized epilepsies: Bridging basic science and clinical research'' was supported by ILAE Commission of European Affairs (CEA) and The Scientific and Technological Research Council of Turkey (TUBITAK).

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

None of the authors has any conflict of interest to disclose.

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LETTERS/COMMENTARY

Epilepsy and respiratory chain defects in children with mitochondrial encephalopathies

To the Editors:

We read with interest the recent article on mitochondrial respiratory chain defects in children with epilepsy in the April issue of *Epilepsia* (Lee et al., 2008). The authors address an important and so-far poorly studied topic in the field of pediatric epilepsy. We would like to share our group's clinical experience with mitochondrial encephalopathies in children with epilepsy, recently published in *Neuropediatrics* (Khurana et al., 2008), which has striking similarities with the findings of Lee et al.

In the report of Lee et al., the authors described their study of 48 children with epilepsy and mitochondrial respiratory chain defects, and found deficiencies more frequently in complex I (73%), but also in complex IV (23%), complex II (2%), and in a combination of complexes I and IV (2%). In our study of 38 children with mitochondrial encephalopathy and mitochondrial respiratory chain defects, 61% had epilepsy, with 70% of them having refractory epilepsy. Complex II was the single most common defect seen overall in 57% of patients; however, children with epilepsy, and particularly those with refractory epilepsy, had a significantly higher incidence of complex I defects than children without epilepsy. The high incidence of complex I defects in children with epilepsy observed both by Lee et al. and our group indicates that some mitochondrial respiratory chain abnormalities are more frequent in patients with epilepsy, suggesting a possible relationship between mitochondrial oxidative stress dysfunction and the epileptogenic process.

In both studies, the majority of patients had a nonspecific encephalopathy, with only a few patients fitting into the clearly defined clinical syndromes of MELAS, MERRF, Kearn Sayre disease, or Leigh disease. The diagnosis was made on the basis of the biochemical findings on muscle biopsy. We would, therefore, concur with the conclusion of Lee et al. that mitochondrial respiratory chain defects are an important cause of symptomatic childhood epilepsy. Therefore, this group of disorders should be considered and investigated in any child with an underlying encephalopathy and epilepsy.

Acknowledgments

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure: None of the authors has any conflict of interest to disclose.

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