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CRITICAL REVIEW AND INVITED COMMENTARY

New concepts in classification of the epilepsies: Entering the 21st century

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Summary

Concepts and terminology for classifying seizures and epilepsies have, until recently, rested on ideas developed nearly a century ago. In order for clinical epilepsy and practice to benefit fully from the major technological and scientific advances of the last several years, advances that are revolutionizing our understanding and treatment of the epilepsies, it is necessary to break with the older vocabulary and approaches to classifying epilepsies and seizures. The Commission on Classification and Terminology made specific recommendations to move this process along and ensure that classification will reflect the best knowledge, will not be arbitrary, and will ultimately serve the purpose of improving clinical practice as well as research on many levels. The recommendations include new terms and concepts for etiology and seizure types as well as abandoning the 1989 classification structure and replacing it instead with a flexible multidimensional approach in which the most relevant features for a specific purpose can be emphasized. This is not a finished product and will take yet more time to achieve. Waiting any longer, however, would be a disservice to patient care and will continue the longstanding frustrations with the earlier system which, at this point in time, can be viewed as both antiquated and arbitrary.

KEY WORDS: Classification, Etiology, Seizure semiology.

The ILAE's classifications of seizures (Commission on Classification and Terminology of the International League Against Epilepsy, 1981) and epilepsies (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) were formally proposed in the middle of the last century (Gastaut, 1969a,b) and were based on concepts that had arisen and developed over the previous several decades. Since then, the human genome has been sequenced and genomic technologies for interrogating the genome have continued to develop at a dizzying pace. Concepts in molecular cell biology and genetics have revolutionized our understanding of what a gene is, how errors may occur in a gene, how they affect its expression, and the ultimate impact of those errors on function. Neuroimaging, structural and functional, is allowing unprecedented understanding of the organization and workings of the brain. Neurophysiologic techniques beyond the scalp electroencephalography (EEG) and digitizing of the EEG signal provide new tools for studying brain function and seizure generation and propagation. We are talking about epilepsy and studying epilepsy using a whole new set of tools and concepts. Although the ILAE classifications of seizures and epilepsies are familiar and comfortable to most of us, they are not able to incorporate in a useful, transparent manner the vast amount of new information that is accumulating and which is, on a daily basis, being incorporated into the understanding and care of people with epilepsy. This fact has not escaped the attention of others. For example, one author commented that ''Recent insights into the molecular genetics and pathophysiology of idiopathic epilepsies have threatened to make the term 'idiopathic' obsolete (Wong, 2010).'' Another group commented ''Moving away from the old classification of symptomatic, cryptogenic, and idiopathic to a better defined and more systematic classification, including specific diagnoses and subgroupings, will allow better understanding and analysis of the results of trials and of cohort studies'' (Osborne et al., 2010). Regarding terms used to describe seizures, ''… traditional seizure nomenclature does not adequately represent the current state of knowledge of the anatomy and physiology of generalized seizures'' (Miller, 2010).

For these reasons the Commission on Classification and Terminology of the ILAE made the bold if not entirely popular step to break with the nearly century-old concepts and

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language of the ILAE classification systems and propose some new, alternative concepts and terminology (Berg et al., 2010), which are summarized briefly below and in Table 1. These proposals are not meant to be permanent, but form part of a transition to a system that will ultimately allow for meaningful translation of scientific understanding to the classification of the epilepsies for clinical and other purposes.

1 The concepts of generalized and focal when used to characterize seizures now explicitly reference networks, an increasingly accepted construct in neuroscience where networks are studied directly through the use of techniques such as functional magnetic resonance imaging (MRI). For epilepsies, we recommended abandoning these terms as *overall* classification categories into which all epilepsies *must* fit (i.e., where all epilepsies are either generalized or focal), as there are many cases for which this dichotomy is not meaningful. ''Generalized'' and ''focal'' may well be useful in characterizing some forms of epilepsy, especially as the networks involved in those epilepsies become better understood. In fact, we explicitly acknowledged the group called ''idiopathic generalized'' epilepsies, although with a different name (see below). Generalized and focal were poor terms, however, for characterizing many of the encephalopathic conditions that occur in infants and young children and for some of the neurodegenerative disorders of later life.

2 For etiology, the terms idiopathic, symptomatic, and cryptogenic had become unworkable as descriptors of etiology and had, over time, taken on connotations of ''good'' and ''bad'' outcome. Let's consider some examples. Childhood absence epilepsy (CAE) was ''idiopathic.'' Glucose transporter 1 (GLUT-1) deficiency disease would have been considered ''symptomatic.'' That leaves one hard-pressed to classify early-onset CAE secondary to a GLUT-1 gene mutation (Suls et al., 2009). Dravet

Table 1. Comparison of major changes between the 1989 and 1981 Classification and Terminology and the newly proposed Terminology and Concepts (Commission 1981, 1989; Berg et al., 2010)

Old terminology and concepts	Recommended new terminology and concepts
Focal and generalized	
For seizures	
Focal (previously ''partial''): the first clinical and electroencephalographic changes indicate initial activation of a system of neurons limited to a part of one cerebral hemisphere	Focal seizures are conceptualized as originating at some point within networks limited to one hemisphere
Generalized: the first clinical changes indicate initial involvement of both hemispheres	Generalized seizures are conceptualized as originating at some point within and rapidly engaging bilaterally distributed networks
For epilepsies	
Localization-related (focal, partial): epilepsies with focal seizures	These terms were abandoned as overarching categories for classifying epilepsies per se, as many syndromes include both seizure types; they may still apply in some but not all instances
Generalized: epilepsies with generalized seizures	
Etiology	
Idiopathic: there is no underlying cause other than a possible hereditary predisposition	Genetic: the epilepsy is, as best as understood, the direct result of a known or presumed genetic defect(s) in which seizures are the core symptom of the disorder. This attribution must be supported by specific forms of evidence
Symptomatic: the epilepsy is the consequence of a known or suspected disorder of the central nervous system	Structural/metabolic: there is a distinct other structural or metabolic condition or disease that has been demonstrated to be associated with a substantially increased risk of developing epilepsy. These disorders may be of acquired or genetic origin. When of genetic origin, there is a separate disorder interposed between the gene defect and the epilepsy
Cryptogenic: this refers to a disorder whose cause is hidden or occult. Cryptogenic epilepsies are presumed to be symptomatic	Unknown: the nature of the underlying cause is unknown; it may have a fundamental genetic basis (e.g., a previously unrecognized channelopathy) or it may be the consequence of an unrecognized structural or metabolic disorder not yet identified
Focal seizure types	
Complex partial: with impairment of consciousness	No specific classification is recommended. Seizures should be described accurately according to their semiologic features without trying to fit them into artificial categories
Simple partial: consciousness not impaired	
secondarily generalized (note: this was not the terminology used in the 1981 document but has come into common use)	
Organizational structure for epilepsies	
Hierarchically organized by localization-related, generalized, and undetermined. Within those groups, by etiology (idiopathic, symptomatic, cryptogenic)	No specific organization is proposed. Instead a flexible approach depending on needs is advocated

syndrome, perhaps the premier example of a genetic epilepsy, has been called ''symptomatic generalized.'' Epilepsies that later were recognized as monogenic syndromes such as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) were classified as ''cryptogenic'' meaning ''presumed symptomatic,'' as in secondary to a brain lesion. Current developments in molecular genetics and neuroimaging and other areas will, we predict, lead to a rational system for characterizing and classifying causes based on mechanisms. In moving forward to the next phase, we suggested the following terms and concepts:

Genetic: The epilepsy is a direct result of a genetic cause. Ideally, a gene and the mechanisms should be identified; however, this term would also apply to electroclinical syndromes for which twin or family segregation studies reproducibly show clinical evidence of a genetic basis (e.g., in the case of the *genetic* generalized epilepsies). At this time, channelopathies are the best example of genetic epilepsies. Ultimately, we expect causes of epilepsies to be identified by the mechanisms involved (i.e., channelopathies, mitochondrial respiratory chain defects, etc.).

Structural-Metabolic: The epilepsy is the secondary result of a separate structural or metabolic condition. Structural and metabolic were combined to separate the concept from genetic and also because the two are often inseparable. Note that structural brain lesions, including many malformations of cortical development, often have genetic causes (Barkovich et al., 2005) and most metabolic disorders are also of genetic origin. The distinction between ''genetic epilepsy'' and epilepsy due to a structural/metabolic cause is far from perfect, but we anticipate more specific characterizations of cause in the upcoming years.

Unknown: Plain and direct, this label simply and accurately indicates ignorance and that further investigation is needed to identify the cause of the epilepsy. Unlike cryptogenic (presumed symptomatic), it makes no presumptions and requires no explanation or reinterpretation.

These recommendations are admittedly imperfect and follow perhaps too closely the old idiopathic-symptomatic-cryptogenic distinctions. As per above, they were intended as part of a transition phase toward the goal of developing a rational, scientifically justifiable approach for a true classification of causes based on scientific understanding of how they are related. This approach must be constructed in such a way as to allow updating and revision as knowledge grows. Of note, the classification of causes versus epilepsy is perhaps at the heart of some of the confusion and murkiness in prevalent thinking about epilepsy. Patients with the same electroclinical syndrome do not always share the same underlying cause [e.g., for West syndrome (Osborne et al., 2010)], and the same etiologic factor may be associated with a range of epilepsy phenotype expressions [e.g., *SLC2A1* mutations (Mullen et al., 2010) and *SCN1A* mutations (Zuberi et al., 2011)] which, along with other considerations, lead to the next change.

3 The rigid classification structure of 1989 was abandoned (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). Although a classification of the epilepsies in the sense of classifications such as the tree of life (for living organisms) or the periodic table of the elements is our vision, it was felt prudent to wait until our knowledge afforded by the new technologies and discoveries had sufficiently matured. These are matters for the scientific community to work out and not for an appointed group to dictate without a basis or adequate evidence. *No* specific alternative was established in its place. Instead we advocated for open-mindedness and flexibility and suggested that epilepsies (as well as their causes) might profitably be organized according to multiple dimensions or features. One could choose the features according to one's needs and purposes. As an example, and we emphasize it was only an example, we suggested one might organize epilepsies according to the specificity of the epilepsy diagnosis: ranging from most to least specific, that is, from electroclinical syndromes (further categorized by age at onset) and constellations (perhaps better construed as surgical syndromes), to nonsyndromic epilepsies with specific underlying causes (organized by specific cause), and finally to nonsyndromic epilepsies of unknown cause. In reality, one could organize epilepsies and their causes according to any relevant feature that is useful for a particular purpose. For example, one might group epilepsies by the presence or absence of specific seizure types [e.g., myoclonic (Table 2), tonic seizures, and so on]; by characteristic EEG patterns [e.g., generalized spike and wave (Table 2), electrodecremental response]; by known gene associations (e.g., *SLC2A1* mutations, *SCN1A* mutations); by involvement of the mTOR pathway, and so forth. These and many other features are becoming so central to diagnosis and treatment of epilepsy, as well as to counseling of families, that they should be considered in future attempts to organize our knowledge of the epilepsies and facilitate translation of improvements in scientific understanding into clinical practice. This approach is currently the backbone of efforts to create a diagnostic manual, although the utility does not stop there.

4 *Electroclinical diagnoses*: Although many changes were made, the list of specific electroclinical syndromes and epilepsy diseases was *not* affected. The clinical value of these diagnoses does not depend on how they are classified, labeled, or arranged, and the utility of these diagnoses remains unchanged. For example, one can still diagnose West syndrome (WS). Further characterizing WS, however, as a ''generalized epilepsy with

Table 2. Two examples illustrating different ways that information could be organized about specific forms of epilepsy (electroclinical syndromes)

(A) Myoclonic seizures

Mandatory or typical	May occur but are not distinctive of syndrome	Unusual or exclusionary
Myoclonic epilepsy in infancy	Epilepsy with myoclonic-atonic seizures	CAE
JME	Epilepsy with myoclonic absence	JAE
Progressive myoclonus epilepsy	Dravet	Epilepsy with GTC only
Early myoclonic encephalopathy		Lennox-Gastaut
		Ohtahara
		Benign familial neonatal epilepsy
		Epilepsy with malignant migrating focal seizures
		West syndrome
		BECTS
		ADNFLE
		Early-onset occipital epilepsy (Panayiotopoulos)
		Late-onset occipital epilepsy (Gastaut)
		LKS-CSWS
		Autosomal focal epilepsy with auditory features
		Familial temporal lobe epilepsy
		Familial epilepsy with variable foci

(B) Interictal EEG: generalized spike wave

Mandatory or typical	Unusual or exclusionary
Myoclonic epilepsy in infancy (Irreg)	Early myoclonic encephalopathy (BS)
JME (>3 Hz)	Ohtahara (BS)
Progressive myoclonus epilepsies (Irreg)	Benign familial neonatal epilepsy (MF)
Epilepsy with myoclonic-atonic seizures (>3 Hz)	Epilepsy with malignant migrating focal seizures (MF)
Epilepsy with myoclonic absence (Reg 3Hz)	West syndrome (Hyp)
Dravet (>3 Hz)	BECTS (CTS)
CAE (Reg 3 Hz)	ADNFLE (focal)
JAE (>3 Hz)	Early-onset occipital epilepsy (Panayiotopoulos) (focal)
Epilepsy with GTC only (>3 Hz)	Late-onset occipital epilepsy (Gastaut) (focal)
Lennox-Gastaut (<2.5 Hz)	LKS-CSWS (CSWS)
	Autosomal focal epilepsy with auditory features (focal)
	Familial temporal lobe epilepsy (focal)
	Familial epilepsy with variable foci (focal)

The syndromes are identified according to (A) the occurrence of myoclonic seizures or (B) generalized spike wave abnormality on the EEG. (B) Syndromes organized according to the presence of generalized spike wave (GSW) on EEG studies. Where syndromes do have GSW, the frequency and regularity of the GSW is written in brackets. In the unusual category, the most typical EEG finding for each syndrome is noted.

ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; BECTS, benign epilepsy with centrotemporal spikes; CAE, childhood absence epilepsy; GTC, generalized tonic–clonic seizures; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; LKS-CSWS, Landau-Kleffner syndrome—continuous spike wave in sleep; Irreg, irregular; Reg, regular; BS, burst suppression; MF, multifocal; Hyp, hypsarrhythmia; CTS, centrotemporal spikes; CSWS, continuous spike wave during slow wave sleep.

cryptogenic or symptomatic etiology'' does nothing to enhance diagnosis, evaluation, treatment, or management of the condition. Indeed it has been the source of considerable confusion over many years, potentially preventing appropriate treatment approaches being considered (e.g., where West syndrome occurs secondary to a surgically amenable brain lesion). On the other hand, identifying West syndrome secondary to tuberous sclerosis versus an *ARX* mutation versus an intraventricular hemorrhage, has potential therapeutic and counseling implications.

5 Terminology for focal seizures was revised to abandon the artificial and inconsistently used terms, simple and complex partial. Instead, use of clearly defined and transparent terminology was suggested. The Glossary of Ictal Semiology (Blume et al., 2001) provides an initial vocabulary which, while in need of revision and expansion, is an example of the type of ''dictionary'' needed for discussing seizure semiology. This not only allows but requires greater precision in seizure description. Terms such as hypermotor, akinetic, versive, hemiconvulsion,

and retained responsiveness or awareness communicate much more information about a patient's seizure manifestations than do the terms complex and simple partial.

6 Additional concepts and terms were offered to provide clearer ways to express qualities for which the etiologic label ''idiopathic'' had been inappropriately substituted. Suggested terms were self-limited (the epilepsy resolves completely on its own with time) and pharmacoresponsive (the epilepsy has a high probability of responding to treatment). Practically speaking, it would be more informative and direct to tell a patient that he has a self-limited, and easily treatable epilepsy than that his epilepsy is ''idiopathic'' and then have to explain that means presumed genetic, and then explain the prognosis, which actually varies considerably among the ''idiopathic'' epilepsies. The concept of epileptic encephalopathy was also emphasized. This has considerable implications for encouraging seizure control as early as possible and for recognizing the cognitive impact of seizures and epileptic activity regardless of age of the patient.

There is understandable discomfort with the loss of the older terms. Keeping them for the sake of convenience and comfort will lead to a situation in which clinicians are left behind speaking an archaic language while the scientific community making the inroads into advancing our knowledge moves on and adopts a language more suited for its purposes. That would create an unfortunate barrier between new breakthroughs and practice. We will have to go through a growing phase, and that will require some maturity and patience on everyone's part. Getting it right will require yet some time. Putting this off longer for convenience or comfort is simply not an option.

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