Epilepsy: A classification for all seasons?

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SUMMARY

Epilepsy classification is close to the heart of every clinician because it affects every consultation. Acceptance of change to fundamental concepts is difficult and implementation of new ideas requires considerable effort. It is therefore not surprising that the 2010 Organization of the epilepsies has evoked much passion and its fair share of criticism and controversy. Debate has been positive and has already led to modifications and gradual acceptance of the new framework. Although classification will never be perfect and continues to evolve with increasing knowledge, the time for updating our thinking to reflect current concepts and scientific understanding is well and truly here. Ongoing discussion will help to further mature the new organization.

KEY WORDS: Classification, Etiology, Focal, Generalized, Specificity, Treatment.

INTRODUCTION: THE EVOLUTION OF CLASSIFICATION IN EPILEPSY

In developing a classification of the epilepsies, it is essential to consider the primary aim of classification, which is to provide a common international language and terminology. Classification categorizes items in such a way as to define their key elements that describe fundamental similarities and differences. The primary focus of classification in epilepsy has been for clinical use and treatment, with a secondary purpose being its utility in research.

Since the introduction of classification in the epilepsies in the 1960s by Gastaut, classification has provided a framework for clinical practice (Gastaut, 1969, 1970). Historically, epilepsy classification has been largely based on clinical experience, developed by a group of eminent epileptologists with a lifetime of studying seizure disorders. There is no doubt that their work has been fruitful, as epilepsy classification has underpinned the immense progress that has occurred in clinical research and framed the interpretation of basic science studies of seizure disorders (ILAE, 1981, 1985, 1989; Engel, 2001, 2006). However, following its original inception, there has been limited development of the underlying concepts. In 2010, a substantial overhaul was published that reshaped the fundamental concepts of epilepsy classification in line with scientific advances (Berg et al., 2010).

A true classification should be scientifically based. Many well-accepted evidence-based classification systems exist such as the periodic table of the chemical elements and the phylogenetic tree of life. Despite much endeavor, our understanding of the epilepsies is not sufficiently developed to formulate a scientifically based classification system. For this reason, the International League Against Epilepsy (ILAE) Commission on Classification and Terminology elected to term the new classification system an “Organization” to reflect that we are not at the point of making a rigorous scientifically defensible classification system. The field can certainly move forward following the major advances in the last 30 years, especially in genetics and imaging, but in terms of a definitive classification, we “are not there yet.” By its very nature, classification will evolve and new changes will take time to be accepted and implemented. It is important that the Commission is reactive to commentaries, criticism, and evolving concepts and, following thought and discussion, modifies the Organization in a timely manner.

THE NEW ORGANIZATION OF THE EPILEPSIES

The new Organization and its modifications are worthy of careful scrutiny. Here I will outline the major changes,
but I refer the reader to the main documents for a more complete understanding of the concepts and thinking (Berg et al., 2010). In addition, we have welcomed the considerable debate regarding the new Organization in several issues of the “Gray Matters” section of Epilepsia. The structure of the Organization is based primarily on clinical semiology allowing division into focal and generalized seizures, supported by electroencephalography (EEG) findings, with the next level being etiologic classification that requires magnetic resonance imaging (MRI) and other investigations.

**Generalized and focal seizures**

First, the concepts underlying focal and generalized seizures have been redefined, in line with scientific insights. Although generalized seizures were thought to be generated by the entire cortex, it has been known for some time that specific networks are involved, but not the whole cortex. Generalized seizures are now defined as generating within and rapidly engaging bilateral networks that include both cortical and subcortical structures but not the entire cortex. In contrast, focal seizures originate within networks limited to one hemisphere that may be limited or widely distributed. They may spread to involve the other hemisphere and evolve to a bilateral convulsive seizure. It is recognized that there is overlap and it may not be possible to define every seizure into one or the other seizure type, but for the vast majority, seizures can be defined as focal or generalized. With more knowledge, the generalized network will become more clearly defined.

**Generalized and focal epilepsies**

Second, the inconsistencies that arise when attempting to define all patients as having either generalized epilepsy or focal epilepsy have been clearly enunciated. One of many examples is the use of the term generalized epilepsy for West syndrome in which in infants there may be a focal origin and sometimes be surgically amenable. The Organization states that not all patients have to be defined as either focal or generalized epilepsies, in recognition that features may overlap. It is, however, evident that the terms focal epilepsy and generalized epilepsy remain useful in daily practice, and they have been retained where appropriate, which is for the majority of patients.

**Etiologic categories**

Third, and perhaps the most important change, is the new terminology for etiology with the removal of the outdated terms idiopathic, symptomatic, and cryptogenic. Most areas of medicine left these terms behind many years ago because their meaning is not clear. The new terms have been expressly chosen to mean what they say. Idiopathic meant “no known cause except presumed hereditary factors.” The term “genetic” is now used to mean just that, where a genetic etiology exists based most commonly on well-designed, replicated family aggregation studies (Helbig et al., 2008). Less frequently, genetic refers to where a known molecular cause has been identified.

The second etiologic group was called “structural/metabolic,” perhaps an odd combination designed to match up with the old “symptomatic” category. I think it is time to separate these into distinct categories and consider the addition of a fourth “immune” etiologic group with the recent explosion in new immune causes of epilepsy (Vincent et al., 2011). This will require consultation with the Commission and discussion groups available to all on the ILAE website before being implemented (http://community.ilae-epilepsy.org/Home/).

The final group, previously referred to as “cryptogenic,” is now called unknown. This is a more transparent term reflecting the definition of cryptogenic, which was “presumed symptomatic.” As many say, all epilepsy is symptomatic of something!

**Diagnostic specificity**

In the Organization, a new level of thinking was introduced, one that recognizes the specificity of a diagnosis. This concept is important as not all diagnoses are equal. The electroclinical syndromes that are well established remain unchanged. Other diagnoses are less well defined. For example, a diagnosis of Dravet syndrome with a de novo SCN1A gene mutation could be considered a disease diagnosis and has greater depth in terms of etiologic understanding than one of nonlesional occipital lobe epilepsy. In the latter patient, the clinician needs to continue to search for the etiology, which may then inform treatment choices and prognostic counseling.

Within this discussion, we introduced the idea of “constellations,” or associations, to denote epilepsies that are associated with specific etiologies that may carry surgical implications. Key examples include mesial temporal lobe epilepsy with hippocampal sclerosis and gelastic seizures with hypothalamic hamartoma. Although Hauptman et al. (2012) suggest that these be considered “surgical syndromes,” the problems inherent with this approach are that not all patients with these associations warrant surgery and some may not be surgically amenable. For example, patients with hippocampal sclerosis and mesial temporal lobe epilepsy may not be refractory and may be controlled on one antiepileptic drug. The underlying message is important, however, that these patients deserve to be considered for surgery if they are refractory or do not tolerate medication.

**Treatment response**

Treatment response has also been mooted as a possible axis for classification in epilepsy. Although extremely important and an essential step in patient management once a specific diagnosis has been made, treatment
response is really another level after diagnosis and classification. Is management really a part of classification? Perhaps with greater inroads into understanding, such as teasing apart multiple genetic contributors to epilepsies with complex inheritance, treatment response may figure in this framework, but I do not think we are at that point.

**THE TARGET AUDIENCE—ONE SIZE FITS ALL VERSUS A FLEXIBLE, ADAPTABLE FRAMEWORK**

With epilepsy classification, there are many implicit tensions surrounding the utility of the classification that depends on the target audience. These are well illustrated in the accompanying discussion pieces that contrast issues such as what should be the minimum investigation battery to make an epilepsy diagnosis (specifically MRI and EEG), with a classification that is useful in resource poor countries where neither of these tools is available (Birbeck, 2012; Hauptman et al., 2012).

Epilepsy specialists in developed countries use a battery of investigations well proven to improve diagnostic yield and therapeutic outcomes. MRI is the mainstay of excluding or defining a structural cause and is taken as the minimum investigation for a structural etiology, acknowledging that it is not universally available. However, as alluded to by Hauptman et al., is MRI enough? As more sophisticated techniques are being developed, improved imaging methods such as tractography and diffusion tensor imaging can identify subtle structural abnormalities not visible on routine MRI. Moreover, combinations of functional and structural studies provide new insights into the localization of seizure origin with techniques such as ictal EEG and functional MRI studies, or coregistration of metabolic (positron emission tomography, PET) or perfusion (single photon emission computed tomography, SPECT) studies with structural imaging. These techniques are taking us forward in understanding epilepsy networks and their relationships to focal and generalized epilepsies. At present, although these findings are informing new concepts, they are not at a point to be employed in making an evidence-based epilepsy classification.

On the other hand, Gretchen Birbeck eloquently delineates the magnitude of the epilepsy problem in resource-poor countries, where 80% of the global epilepsy population resides. How can we make a classification that cannot be used where most of the patients live? This problem is certainly not unique to epilepsy and affects most discussions related to inequities in health, wealth, and education around the world. The design behind the flexible framework of the new Organization is intentionally to allow it to be used in a multitude of settings according to the user’s means. So in resource poor settings without EEG and MRI, semilogic classification would under-score diagnosis as it has in the past. This will lead to conclusions based on a specific level of diagnostic certainty that will be less refined than that achieved using EEG and MRI, but will nevertheless be useful for settings with similar resources to allow comparability and inform clinical and therapeutic outcomes.

Peter Camfield’s articulate discussion of population studies highlights the benefit derived from the previous classification framework in describing the impact of epilepsy as a global disorder (Camfield, 2012). We need to be mindful of the influence of classification in enabling global discussion and resource allocation for patients with epilepsy (Bergen et al., 2012). Despite Camfield’s concerns, the new framework of the Organization can relate to previous studies with similar “baskets” for classifying patients. For example, epilepsies may be focal, generalized, both, or unknown as before. Idiopathic epilepsies would now be broken down into genetic and unknown. Symptomatic epilepsies would be divided into structural, metabolic, immune, or unknown etiology. These would allow comparisons between datasets.

Peter Camfield suggests names for new entities. Although the ideas behind these names are of critical importance, many of the acronyms are somewhat complicated and confusing. Perhaps we need to add an additional axis to diagnoses regarding intellect separating patients based on clinical assessment into those with normal intellect and those with intellectual disability. There will always be debate about how to define these issues given that many children with epilepsy have learning difficulties, but Camfield (2012) is correct that these major subgroups deserve distinction. So one might consider that children with benign childhood epilepsy with centrotemporal spikes have focal epilepsy of unknown etiology with normal intellect. Similarly, childhood absence epilepsy could be considered a genetic generalized epilepsy with normal intellect.

Overall the views aired in the accompanying discussions are invaluable in taking epilepsy classification forward. All their points deserve consideration as we develop new means of classifying epilepsies to ensure we have a useful and integrated clinical tool to assist in optimizing patient care.

**ACKNOWLEDGMENTS**

Dr. Scheffer receives has received research support from the National Health and Medical Research Council of Australia, Health Research Council of New Zealand, The University of Melbourne, American Epilepsy Society, the Jack Brockhoff Foundation, the Shepherd Foundation, and the Perpetual Charitable Trustees.

**DISCLOSURE**

Dr. Scheffer has served on scientific advisory boards for UCB and Janssen-Cilag EMEA; may accrue future revenue on pending patent WO61/010176 (filed: 2008); Therapeutic Compound; has received
speaker honoraria from Athena Diagnostics, UCB, Biocodex, and Janssen-Cilag EMEA; and has received funding for travel from Athena Diagnostics, UCB, Biocodex, GlaxoSmithKline, and Janssen-Cilag EMEA. I confirm that I have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. No undisclosed groups or persons have had a primary role in the preparation of this manuscript.

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