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Classification and Epilepsy: The Future Awaits

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By now, most are aware that changes are afoot in the concepts and terminology used for discussing and "classifying" epilepsy (1). The changes have been met with scorn and derision by some (2, 3). In balance, they seem to be appreciated, not for being a final product but for finally moving the field from out of an archaic past in which it was stuck and into the present and, may we hope, the future. As it stands, the report, and its recommendations likely elicit feelings of dissatisfaction for not being complete, final, and carved in stone. The report did not even presume to present a new classification. The authors of the report share that frustration, with the caveat that little should ever be carved in stone in a field that is moving as rapidly as the life sciences.

The 2010 report represents the best efforts of a diverse group. In part, we built on the work of the previous Commission (4). Mostly, we tried to break away from what had become an inadequate, misleading, and extraordinarily confusing set of terms and concepts and to offer some alternatives to reflect changing understandings and knowledge afforded by the last 2 decades of scientific breakthroughs in genomics, neuroimaging, and neurophysiology. To that end, we advocated for more transparent language, so that the words we use help us to say what we mean and mean what we say without hand-waving or convoluted explanations. This is perhaps most pressing in the language used to discuss "causes" of epilepsy. The old "idiopathic" (meaning "presumed" genetic) sounds silly in the post-genomic world. "Symptomatic" itself isn't such a bad word, but isn't all epilepsy due to some underlying cause, whatever the nature of that cause might be? What does saying that epilepsy is "symptomatic" add? The worst term was "cryptogenic" meaning presumed symptomatic, but symptomatic of what, perhaps a mutation in *CHRNA2*, or *CHRNA4*, or *CHRN2* as in the case of autosomal dominant nocturnal frontal lobe epilepsy? The aligning of the term "idiopathic" with "benign" and "easily treated" is especially problematic in light of disorders such as Dravet syndrome, as genetic an epilepsy as we have yet to see, or epilepsies secondary to *SLC2A1* mutations, the gene that codes for the GLUT-1 transporter. Is severe GLUT-1 deficiency syndrome symptomatic (because it has a bad outcome) (5); and early-onset absence epilepsy secondary to mutations in the same gene "idiopathic" because it looks like childhood absence epilepsy (6)? Cause should not be confused with natural history or outcome; many genetic disorders are lethal. How does one handle the possibility that the some of the "idio-

pathic" epilepsies may be the result of subtle malformations of cortical development (7). Given the extraordinary advances in knowledge and understanding, is it not now time to start calling a spade a spade, and a channelopathy a channelopathy?

Another change was in simplification of seizure types. Most notably, we continued a process initiated in the previous Commission of decommissioning the terms "simple partial" and "complex partial" in reference to focal-onset seizures. Many lament the loss of these "useful" and "clearly understood" terms, but are they useful and clearly understood? Certainly in pediatric epilepsy, their use tends toward the wild guess and leaves one hard-pressed to classify events in preverbal or severely impaired children, or to classify hemi-convulsions or hypermotor seizures. The arguments offered for retaining them are often two-fold: first, the distinction between simple and complex partial is useful for deciding whether someone can drive. If that is the case, perhaps the decision should be made on an individual basis, based upon the actual seizure manifestations not an artificial classification of them. For example, hemi-convulsions, even if consciousness is preserved, may not be compatible with maintaining adequate control of a vehicle (or riding a bicycle), nor are some "generalized" seizures that do not necessarily involve impaired consciousness (e.g., atonic or massive myoclonic seizures). The other argument is that they are time-honored distinctions used in randomized trials. So, how well is that working for us? Researchers in the field constantly lament that, despite all of the new drugs, treatment of epilepsy, at least for control of seizures, is no better than it was 20 or 30 years ago. Randomized trial data do not provide evidence of a compelling difference among drugs used for these nonsyndromic epilepsies (8). At the same time, we see an almost stochastic response to sequential new drugs (9); just keep trying and one will eventually work. But is it stochastic? Without studying the differences between responders and nonresponders to individual drugs, and instead just lumping everyone together as having "partial epilepsy" with "complex

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partial” seizures, how can we possibly know? Might a more precise characterization of seizures and epilepsies provide key information that, as is clearly the case in pediatric epilepsy syndromes, just might help improve use of the large and growing number of antiepileptic drugs (AEDs)? For the time being, the 2010 Commission report incorporated an approach advocated in an earlier Commission report from 2001 on ictal semiology (10), although the content of the 2001 report needs expanding.

Another common concern (complaint!) is that this is all too complicated; classification must be kept simple for physicians. This is the most disingenuous argument of all. Physicians who are expected to master the basics of molecular cell biology, neurophysiology, neuroimaging, and a host of other basic sciences and clinical disciplines can’t come to grips with and understand terms such as “channelopathy” or “focal cortical dysplasia” for what they are, and therefore must be encouraged to use terms instead such as idiopathic and symptomatic! The axiom “keep it as simple as possible but no simpler” comes to mind. Idiopathic and symptomatic are inadequate simplifications. If one thinks about it, their use renders classification of epilepsy complex by virtue of the tortuous, inconsistent reasoning these terms impose.

The suppression of the terms “generalized” and “focal” for classifying epilepsies has also raised a stir. There were good reasons for their suppression, as reviewed previously (1, 11). In the end, the Commission tried to encourage a distinction between the underlying process and the outward manifestations. This can be of crucial importance especially in the developing brain. Of note, some bemoaned the loss of the useful and clinically relevant distinction between generalized and focal epilepsies (3). It is unclear what value is gained in teaching medical students and physicians that West syndrome and Childhood Absence Epilepsy are generalized epilepsies and should be grouped as such. There are few if any shared implications for evaluations (use of MRI, genetic testing), treatment, or prognosis. The same is true of benign epilepsy with central-temporal spikes versus gelastic seizures with hypothalamic hamartoma. The 2010 report emphasized the importance of recognizing the specific epilepsy diagnosis when one can be identified and de-emphasized the practice of artificially grouping epilepsies based on the focal–generalized dichotomy. The continued use of “generalized” and “focal” for describing seizure types was felt to be more justified; however, the fact remains that this distinction is not hard and fast, and perhaps it will be abandoned in the future or at least modified. We are certainly getting to the point with functional imaging where a more mechanistic–anatomic basis for classifying seizures may be near at hand.

At the center of some of the bitterest misunderstandings is the meaning of the term “classification,” which is understood and misunderstood in many ways. For our purposes in epilepsy, it is used in two ways. The first is to refer to the list of individual diagnoses that can be made in epilepsy (e.g., Childhood Absence Epilepsy, Epilepsy in Females with Mental Retardation). For specific diagnoses, the committee adopted the view that a method based on evidence, and not simply experts sitting around a table and voting, was needed. In the meantime, the genetics world has forged ahead and created its own

criteria, which are rapidly being accepted and the results put to clinical use. That is a far more efficient and likely more valid approach than the one previously in place. It is more transparent, merit-driven, and is subject to verification or refutation—a corner stone of the scientific method. Some may still see this emerging approach as imperfect, but to paraphrase very loosely Churchill’s quip about democracy: it may not be a great system, but we don’t have a better one. The second meaning of classification is the concepts by which and structures into which elements (diagnoses) are organized (e.g., sodium, calcium, and magnesium are elements classified within a classification scheme; the classification scheme is the periodic table of the elements). In the 1989 classification scheme (12), those concepts created categories such as idiopathic–localization related and symptomatic–generalized. Classifications, in this sense of the word, should teach (13). Their structure and categories should reflect quintessential elements that are key to understanding the items that are classified and how those items are related to each other. One can recognize the items without having to arrange them in a classification. Thus, the diagnostic and clinical value of the various electro-clinical syndromes remains untarnished. Classifying epilepsies along specific (and arbitrary) lines, however, implies knowledge that may not exist or may be misleading or is just simply wrong.

The biggest shortcoming of the 2010 classification report is that it does not provide a new classification scheme; it does not provide closure. This is admittedly frustrating. Some would argue we should stay with the old one until a new one can be formed. The clinical value and the other benefits of keeping the 1989 classification scheme are essentially nil, despite some who vociferously oppose this move. One could actually argue that retaining the 1989 approach would be worse than nil and that having nothing would be better than the older approach, which defies modern concepts and understanding of epilepsy. It will take a while still before we have a new “classification,” and it will require everyone in the field to come to grips with the fact that a new one is long overdue. Suggestions were made in the report that epilepsy diagnoses might be meaningfully organized according to specificity of diagnosis of the epilepsy presentation and underlying cause. In fact, a flexible approach was advocated that would allow each of us to organize epilepsies according to features that were most important for a given purpose (age at onset, EEG features, associated seizure types, associated genes, and so forth). In terms of clinical utility, however, no classification system per se is needed to diagnose a patient with a nonsyndromic epilepsy associated with focal seizures and secondary to focal cortical dysplasia or to diagnose another patient with West syndrome secondary to the same pathology. The specificity provides important, clinically relevant information. Further “classifying” these entities using the 1989 approach does not.

If the 2010 report leads to fruitful discussions, it will have been more than worthwhile. Answers to these issues are not simple, and it would have been a stroke of sheer arrogance for a group of appointed individuals, even with input solicited from around the world (as was the case with the 2010 report), to establish a new classification in one fell swoop. A little patience, imagination, and perspicacity is now what is needed as colleagues from around the world begin to pay at-



tention to this problem and, we hope, work together to move the classification of the epilepsies forward, not drag it back into the past.

References

1. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde BW, Engel J, French J, Glauser TA, Mathern GW, Moshé SL, Nordli D, Plouin P, Scheffer IE. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia* 2010;51:676–685.
2. Wolf P. Much ado about nothing? *Epilepsia* 2010;51:717–718.
3. Ferrie CD. Terminology and organization of seizures and epilepsies: Radical changes not justified by new evidence. *Epilepsia* 2010;51:713–714.
4. Engel J. Report of the ILAE Classification Core Group. *Epilepsia* 2006;47:1558–1568.
5. Klepper J, Leiendecker B. GLUT1 deficiency syndrome – 2007 update. *Dev Med Child Neurol* 2007;49:707–716.
6. Suls A, Mullen SA, Weber YG, Verhaert K, Ceulemans B, Guerrini R, Wuttke TV, Salvo-Vargas A, Deprez L, Claes LRF, Jordanova A, Berkovic SF, Lerche H, De JP, Scheffer IE. Early-onset absence epilepsy caused by mutations in the glucose transporter GLUT1. *Ann Neurol* 2009;66:415–419.
7. de Nijs L, Léon C, Nguyen L, Loturco JJ, Delgado-Escueta AV, Grisar T, Lakaye B. EFHC1 interacts with microtubules to regulate cell division and cortical development. *Nat Neurosci* 2009;12:1266–1274.
8. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B, Gamble C, Goulding PJ, Howell SJ, Hughes A, Jackson MJ, Jacoby A, Kellett M, Lawson GR, Leach JP, Nicolaides P, Roberts R, Shackley P, Shen J, Smith DF, Smith PE, Smith CT, Vanoli A, Williamson PR; SANAD Study group. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: An unblinded randomised controlled trial. *Lancet* 2007;369:1000–1015.
9. Schiller Y, Najjar Y. Quantifying the response to antiepileptic drugs: Effect of past treatment history. *Neurology* 2008;70:54–65.
10. Blume WT, Luders HO, Mizrahi E, Tassinari C, van Emde Boas W, Engel J. Glossary of descriptive terminology for ictal semiology. *Epilepsia* 2001;42:1212–1218.
11. Berg AT, Scheffer IE. New concepts in classification of the epilepsies: Entering the 21st century. *Epilepsia* 2011;52:1058–1062.
12. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;30:389–399.
13. Jackson GD. Classification of Epilepsies 2011. *Epilepsia*. 2011;52:1203–1204.



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