Current Literature
In Clinical Science

Consensus Over Individualism: Validation of the ILAE Definition for Drug Resistant Epilepsy

A Validation of the New Definition of Drug-Resistant Epilepsy by the International League Against Epilepsy.

Tellez-Zenteno JF, Hernandez-Ronquillo L, Buckley S, Zahagun R, Rizvi S. *Epilepsia* 2014;55:829–834.

OBJECTIVE: To establish applicability, the recently proposed International League Against Epilepsy (ILAE) consensus on drug-resistant epilepsy (DRE) requires testing in clinical and research settings. This study evaluates the reliability and validity of these criteria in a clinical population. METHODS: In phase I, two independent evaluators reviewed 97 randomly selected medical records of patients with epilepsy at two separate intervals. Both ILEA consensus and standard diagnostic criteria were employed. Kappa, weighted kappa, and intraclass correlation coefficient (ICC) were used to determine interobserver and intraobserver variability. In phase II, ILAE consensus criteria were applied to 250 patients with epilepsy to determine risk factors associated with development of DRE and to calculate point prevalence. RESULTS: The interobserver agreement of the four definitions was as follows: Berg (0.56), Kwan and Brodie (0.58), Camfield and Camfield (0.69), and ILAE (0.77). The intraobserver agreement of the four definition was as follows: Berg (0.81), Kwan and Brodie (0.82), Camfield and Camfield (0.72), and ILAE (0.82). The prevalence of DRE was the following: with the Berg's definition was 28.4%, Kwan and Brodie 34%, Camfield and Camfield 37%, and with ILAE was 33%. SIGNIFICANCE: This is first study to establish reliability and validity of ILAE criteria for the diagnosis of DRE. This new definition compares favorably with previously established constructs, which continue to retain clinical significance.

Commentary

Consensus in Merriam–Webster's dictionary is defined as "a general agreement about something." However, since the introduction of classifications of seizures, epilepsy syndromes, and surgical outcome scales, there seems to be an inability to reach agreement in the epilepsy community about details and wording. To alleviate some of the controversial items, the International League Against Epilepsy (ILAE) has called task forces and published statements to standardize classifications and definitions (1–3). One such statement is the definition for *drug-resistant epilepsy* (2). However, definitions are of value only if they are practical, usable, and generally accepted.

A possible way to assess whether a published medical definition is valid is to evaluate the definition for *repeatability*, *consistency*, and *practicability* in daily medical care. The above study by Tellez-Zenteno et al. attempts to validate the ILAE definition for drug-resistant epilepsy and compares the ILAE definition to previously published definitions by individual authors. In short, the ILAE defines *drug-resistant* as "failure of adequate trials of two tolerated and appropriately chosen AED schedules (whether as monotherapies or in combination) to achieve seizure freedom" (2). The authors find that the ILAE definition is consistent with other previously published definitions of *drug-resistant epilepsy*. Kappa statistics, a generally accepted measure of agreement, report substantial agreement between scales and nearly perfect inter-rater reliability. A kappa value of 0.6–0.8 between various definitions indicates substantial agreement, and values greater than 0.8 indicate nearly perfect agreement for inter-rater agreement. Assessing inter-rater reliability is important. It is just human nature to classify the same thing into a different category at a later time point. Another interesting finding in the study is that mesial temporal sclerosis seems to be significantly more drug-resistant than other epilepsy syndromes.

Words are important. Should the term *drug-resistant epilepsy* be universally accepted? Should it instead be called *pharmacoresistant epilepsy*, *intractable epilepsy*, or *refractory epilepsy*? Is the word really important if we all understand what is meant? If a disease and entity is defined, the term should not only be understandable by the specialist but also by general practitioners and other healthcare providers, and it seems intuitively easier to understand what is meant by *drug-resistant* as compared to the other terms.

Defining *drug-resistant epilepsy* is necessary to determine when more invasive interventions, such as surgery, are indicated. After having evaluated a patient several times, it is usually apparent whether the seizures responded to anti-epileptic medications and whether further intervention is necessary. It does not seem important what we call this disease, as long as there is consistency. It would greatly help literature searches

Epilepsy Currents, Vol. 15, No. 4 (July/August) 2015 pp. 172–173

and scientific collaboration if there were consensus about the terms.

The difficulties defining *drug-resistant epilepsy* come from the fact that it is difficult to define "what is a seizure-free outcome?" Do auras count? Does the seizure-free interval need to be three or six times the previous interseizure interval (4)? All those questions are valid and can be discussed in length. The ILAE definition does not allow for auras and requires 12 months of seizure freedom or three times the seizure-free interval, whichever is longer (2). Definitions such as the ILAE definition are necessary, but drug-resistant severe generalized tonic-clonic seizures certainly call for more treatment than drug-resistant focal seizures without objective manifestations. Epilepsy remains a dynamic disease with spontaneous fluctuations in seizure occurrence, which makes it so difficult to determine outcomes (5). The desire to consider just a one-time intervention and report the associated outcome may not fit the nature of the disease (6).

The authors applied the definition to an epilepsy clinic in Saskatchewan, a specialty clinic in Canada. It exclusively included adult patients. This population certainly is a select population, as it included only patients referred to the clinic and excluded patients treated by the primary care physician or non-epilepsy providers. They reported a prevalence of drug-resistant epilepsy between 28.4 to 37 percent in this population. This is consistent with previously reported data that is derived from epilepsy clinics, but lower numbers are reported when populations are derived from other data. A study in France that attempted to include all possible patients in a geographic area estimated the prevalence of drug-resistant epilepsy at 15.6% (7). The 2004 HealthStyles survey, thought to be representative of the general U.S. population, reports 25.5% of patients with seizures in the last three months (8). Statements about incidence and prevalence always have to be interpreted in light of the population that was examined, and there are substantial differences between healthcare systems and geographic locations.

Although the authors validated the latest ILAE definition of *drug-resistant epilepsy*, they used an outdated classification for their seizure etiology and classified the patients into cryptogenic, idiopathic, and symptomatic epilepsy (3). This seems to reflect the fact that the seizure syndrome classification is not universally accepted, and it would enhance communication if validation of previously suggested classifications as reported in this study would facilitate a final agreement about seizure and epilepsy syndrome classifications (9, 10). No definition will be perfect and include all possible individual cases. But consensus would trump individualism in that regard and enhance communication and research. The community could collaboratively focus on coming up with new innovative interventions to eliminate seizures instead of focusing on finding the right words for diseases, which we all know can be devastating.

by Barbara C. Jobst, MD

References

1. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J Jr, Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshé SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S. ILAE official report: A practical clinical definition of epilepsy. *Epilepsia* 2014;55:475–482.
2. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshé SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010;51:1069–1077.
3. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, 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.
4. Westover MB, Cormier J, Bianchi MT, Shafi M, Kilbride R, Cole AJ, Cash SS. Revising the "rule of three" for inferring seizure freedom. *Epilepsia* 2012;53:368–376.
5. Jobst BC, Cascino GD. Resective epilepsy surgery for drug-resistant focal epilepsy: A review. *JAMA* 2015;313:285–293.
6. Wang SP, Mintzer S, Skidmore CT, Zhan T, Stuckert E, Nei M, Sperling MR. Seizure recurrence and remission after switching antiepileptic drugs. *Epilepsia* 2013;54:187–193.
7. Picot MC, Baldy-Moulinier M, Daures JP, Dujols P, Crespel A. The prevalence of epilepsy and pharmacoresistant epilepsy in adults: A population-based study in a Western European country. *Epilepsia* 2008;49:1230–1238.
8. Kobau R, Gilliam F, Thurman DJ. Prevalence of self-reported epilepsy or seizure disorder and its associations with self-reported depression and anxiety: Results from the 2004 HealthStyles Survey. *Epilepsia* 2006;47:1915–1921.
9. Panayiotopoulos CP. The new ILAE report on terminology and concepts for the organization of epilepsies: Critical review and contribution. *Epilepsia* 2012;53:399–404.
10. Luders HO, Amina S, Baumgartner C, Benbadis S, Bermeo-Ovalle A, Devereaux M, Diehl B, Edwards J, Baca-Vaca GF, Hamer H, Ikeda A, Kaiboriboon K, Kellinghaus C, Koubeissi M, Lardizabal D, Lhatoo S, Lüders J, Mani J, Mayor LC, Miller J, Noachtar S, Pestana E, Rosenow F, Sakamoto A, Shahid A, Steinhoff BJ, Syed T, Tanner A, Tsuji S. Modern technology calls for a modern approach to classification of epileptic seizures and the epilepsies. *Epilepsia* 2012;53:405–411.