Epilepsy Is Not Resolved

**A Practical Clinical Definition of Epilepsy.**


Epilepsy was defined conceptually in 2005 as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition is usually practically applied as having two unprovoked seizures >24 h apart. The International League Against Epilepsy (ILAE) accepted recommendations of a task force altering the practical definition for special circumstances that do not meet the two unprovoked seizures criteria. The task force proposed that epilepsy be considered to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome. Epilepsy is considered to be resolved for individuals who either had an age dependent epilepsy syndrome but are now past the applicable age or who have remained seizure-free for the last 10 years and off anti-seizure medicines for at least the last 5 years. “Resolved” is not necessarily identical to the conventional view of “remission or “cure.” Different practical definitions may be formed and used for various specific purposes. This revised definition of epilepsy brings the term in concordance with common use.

**Commentary**

The ILAE has re-defined epilepsy: epilepsy is a disease of the brain causing at least two unprovoked or reflex seizures occurring more than 24 hours apart or after one seizure if risks of recurrence are “high” (>60%). Conversely—and making a change that carries significant implications—they also now define epilepsy as “resolved” if an individual has outgrown their age-dependent syndrome or if they are seizure free for 10 years and off AEDs for 5 years.

Overall, the ILAE committee report is a useful and sophisticated practical definition of epilepsy that helps guide the clinical evaluation of patients with seizures: epilepsy implies a risk for seizure recurrence and may require treatment while clinical monitoring and safety restrictions can end when epilepsy is resolved. Their definition incorporates a number of points that are clearly reviewed and justified in the ILAE report. It is important, however, to note what this “practical clinical” definition of epilepsy “is” and “is not” and to note controversial aspects of the report.

First, unlike the 2005 conceptual definition of epilepsy, this is a clinical and not a neurobiological definition. The 2005 conceptual definition of epilepsy is “a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological and social consequences of this condition.” While the new “practical clinical” definition of epilepsy is not intended to replace the 2005 conceptual definition, its use may de-emphasize important links between brain disorders, epilepsy and associated emotional, cognitive and neurologic symptoms that are important to assess in patients with epilepsy (1, 2).

Secondly, the new definition of epilepsy incorporates several controversies: 1) Epilepsy is defined as a disease. Although epilepsy meets the broad definition of disease as any condition that impairs normal function, it is more precisely a “disorder” with seizures representing functional disturbances caused by multiple diseases. The practical elements of a broad definition for epilepsy won out; similar to “heart disease,” advocacy for epilepsy research funding and epilepsy awareness may be enhanced by terming epilepsy a disease. It may be less stigmatizing; however, to call epilepsy a “disorder” than a “disease” if this helps distinguish patients with benign and disabling etiologies for epilepsy; 2) patients diagnosed with an epilepsy syndrome are defined as having epilepsy, since “it makes little sense to say that someone has an epilepsy syndrome, but not epilepsy” (3, 4). This is a practical point, but may detract conceptually from emerging evidence that epilepsy is often a trait (e.g., genetic generalized epilepsy) with limited expression (3, 4) and that epilepsy may be only one of several phenotypes associated with single gene variants (e.g., recurrent copy number variants may be associated with multiple neuropsychiatric disorders and epilepsy [5]); 3) Epilepsy may be clinically defined as present following a single seizure if recurrence risks are high (>60%). This is reasonable in that most patients with single unprovoked seizures have low to intermediate risks for recurrence (20–50%); however, some pa-
tients, such as those with remote symptomatic etiologies and epileptiform discharges on EEG, are at high risk for multiple seizure recurrences (6). Only a small number of patients with single seizures would be currently defined as having epilepsy in this “practical” definition; this, however, may be an area of useful clinical research, e.g. is a patient with TSC1 mutation or other genetic disorders and a single seizure at high risk for seizure recurrence? 4) Although it is a reasonable concept, using a 10-year seizure-free period (with 5 years off medication) to define epilepsy as “resolved” is probably the least supported section of the new epilepsy definition. The ILAE report notes: “No adequate data are available on seizure recurrence risk after being seizure-free and off medication for extended periods of time.” The authors combined results from several 2- to 5-year outcome studies to support a 10-year standard. Most patients in these studies, however, were monitored for less than 3 years and the lowest risk that could be conclusively estimated was approximately 2% for seizure relapse. A study by Lossius et al. (7), for example, reported patients with >2 years of seizure freedom who withdrew from AEDs and were seizure free for another 3 years had an annual risk for seizure relapse of 3.6% (0.003 monthly risk) (7). Goellner et al. (8) reported that most patients with seizure recurrences after temporal lobectomy occurred within 6 months of surgery; only 1.9% of patients with relapses (2 patients) had seizures 4 to 5 years after surgery; however, most patients were monitored for <4 years (8). Lossius (7) also reported a patient who died of SUIDP during a relapse 4 years after discontinuing treatment. Risks over longer monitoring periods are not known.

Perhaps the “practical” definition of epilepsy should include a caveat that epilepsy can generally be considered “resolved” after long seizure-free intervals due to low recurrence risks (2%) but that special circumstances require more caution. The U.S. Federal Motor Carrier Safety Administration (FMCSA), for example, recently accepted recommendations from a medical expert panel that applicants might be licensed for interstate commercial driving licensure after 8 years of seizure freedom (either on or off AEDs)(9, 10). The panel members (including Dr. Fisher and me) felt that safety risks with an estimated risk of approximately 2% for seizure recurrence were acceptable (10). This is generally consistent with the new “practical” definition of epilepsy. Others might disagree, however, and it is reasonable to question whether epilepsy should be considered “resolved” in other situations in which a several percent risk of seizure recurrence may not be acceptable, e.g. scuba dive instruction or commercial piloting.

The new practical clinical definition for epilepsy has great practical and heuristic value and helps remind patients and clinicians of key issues when identifying and managing epilepsy. It should probably be viewed, though, as a broad guideline requiring individual assessments to determine when seizure recurrence risks are “high enough” to justify diagnosing epilepsy after single seizures or “low enough” to justify considering epilepsy “resolved” for safety judgments.

Representative recent patient: A 40-year-old male had epilepsy “resolved” for safety judgments. He remained seizure free for 16 years until age 12. He remained seizure free for 16 years until age 28, when he had a single car crash—it was unclear whether a seizure caused the crash; however, he subsequently developed frequent complex partial and secondary generalized seizures, up to 15 in one day. Seizure persisted on eight separate AEDs; MRI and PET were normal, and he had subdural grid guided right temporal lobectomy. This patient’s epilepsy was “resolved” for 16 years and then recurred. This case shows epilepsy is often a stochastic biologic process and that while the new definition is a practical framework for identifying individuals as having epilepsy, it does not replace previous physiological definitions.

by Gregory Krauss, MD

References
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