



Are We Too Pessimistic About Drug-Resistant Epilepsy?

Is Incident Drug-Resistance of Childhood-Onset Epilepsy Reversible? A Long-Term Follow-Up Study.

Sillanpää M, Schmidt D. *Brain* 2012;135:2256–2262.

Given the grave morbidity and mortality of drug-resistant epilepsy, it is of great clinical interest to determine how often prior proven drug-resistant epilepsy is reversible without surgery and whether remission can be predicted by clinical features in children with incident drug-resistant epilepsy. We determined the likelihood of 1-, 2- and 5-year seizure remission and terminal 5-year seizure remission after the first adequate drug regimen in a population-based cohort of 102 medically treated patients with incident, i.e. first-ever occurrence of drug-resistant epilepsy, as defined by the International League against Epilepsy. Among the 102 patients, 98 had focal seizures (68 symptomatic and 30 idiopathic/cryptogenic), one had generalized convulsive seizures and three had unclassified seizures. At the end of the 40.5-year median follow-up from the onset of adequate medication before the age of 16 years, 84 (82%) of 102 patients with incident drug-resistant epilepsy eventually entered one or more 1-year remissions, 81 (79%) one or more 2-year remissions, 70 (69%) one or more 5-year remissions and 52 (51%) of 102 5-year terminal remissions. In contrast, 18 (18%) of 102 patients with incident drug-resistant epilepsy never entered any 1-year remission, 21 (21%) 2-year remission, 32 (31%) 5-year remission and 50 (49%) of 102 any 5-year terminal remission. On multivariate analysis of clinical features, in every remission category, idiopathic or cryptogenic aetiology was the only significant predictor of entering remission. Incident drug-resistant epilepsy is eventually reversible in 49–79% of patients with mostly focal epilepsy, resulting in long-term remission of variable duration. Idiopathic or cryptogenic aetiology is a clinical predictor of reversible drug-resistant epilepsy.

Commentary

Drug-resistant epilepsy has been defined by an International League Against Epilepsy (ILAE) task force as failure of two tolerated, appropriately chosen and used antiepileptic medications to achieve sustained seizure freedom (1). How well does this definition predict long-term medical intractability, and can it be used for clinical decisions, such as determining candidacy for epilepsy surgery? Although a number of authors have suggested a variable but often low chance of achieving seizure control without surgery in drug-resistant epilepsy, all these studies have different limitations, such as use of other definitions of drug-resistant epilepsy, retrospective design, use of hospital-based referral populations, or inadequate follow-up for demonstration of sustained epilepsy remission (2–7). In the current study, Sillanpää and Schmidt address these concerns with a prospective, population-based investigation over decades, of outcomes to medical treatment without surgery, after new onset of drug resistance.

This study was possible because of unique data, derived from 245 patients, consisting of all children younger than age 16 living in the vicinity of Turku University Hospital in Finland who were seen for epilepsy from 1961 to 1964. These patients

had an initial inpatient hospital evaluation, and information on epilepsy type and seizure control was also collected, with follow-up examinations every 5 years. Because this dataset is population based and prospectively collected, with carefully collected outcomes into the year 2000 and beyond, it has already dramatically changed our understanding of the natural history of epilepsy and its mortality (8, 9). Patients from this group were included in the current study when they first met criteria for drug-resistant epilepsy (1). In addition, only patients with focal epilepsy, or epilepsy with convulsive seizures were included, and at least 10 years follow-up from diagnosis was required.

Although remissions for 1, 2, or 5 years were identified, the most important outcome was a 5-year terminal remission (that is, seizure freedom sustained for at least 5 years, but often much longer). It is remarkable not only that 50.1% of these patients with drug-resistant epilepsy did achieve a 5-year terminal remission but that this was achieved progressively over the course of 40 years—although more than 40% of the patients achieved these remissions within 25 years. Further, earlier 2- or 5-year periods of remission were a predictor of a 5-year terminal remission, meaning that the process of achieving sustained seizure freedom may evolve over many years. A 5-year terminal remission occurred in 41% of symptomatic epilepsies, but in 71% of cryptogenic/idiopathic epilepsies, and this was the only significant predictor of this type of remission on multivariate analysis. However, because this study began in



the 1960s, MRI was not systematically performed and is not reported. Other studies have reported even larger differences in outcome between patients with MRI lesions and cryptogenic/idiopathic cases (10), and it is likely that this study by Sillanpää and Schmidt underestimates this difference in outcome.

Another inherent limitation of this study is that in the era in which the study began, antiepileptic drug (AED) therapy largely consisted of hydantoins and barbiturates. Alternate agents began to slowly appear, with a novel AED every decade or so, until the accelerated release of new agents in the 1990s. While it is commonly said that new AEDs “haven’t made a dent in the problem of intractability,” nonetheless, in one study of 265 introductions of previously unused AEDs in 155 adults with drug-resistant epilepsy, 16% of these introductions led to seizure freedom, with a higher percentage in patients with fewer prior drug trials or idiopathic epilepsy (4). Although that study did include some patients who had only had one prior medication trial and also did not specify the reason for prior medication failure, seizure freedom was achieved in 11% of patients who had five or more prior drug trials (4). This, at least, raises the possibility that if more AED options were available in Finland 50 years ago, there could have been more rapid achievement of sustained seizure remission in this cohort.

The difficulty with relating these results to clinical practice is that there is no way to know why many of these patients became seizure free after so many years of treatment. In addition to the possibility that some became controlled because of the introduction of AEDs such as carbamazepine and valproate, there is the possibility of lifestyle changes, with some patients taking medication more faithfully, getting enough sleep, and avoiding alcohol and other substance abuse as they matured. There is also the possibility of remission reflecting the natural history of particular epilepsy syndromes, with individual patients “outgrowing” their seizures. While it may be quite difficult to determine the relative role of these different possibilities, nevertheless, they have quite different implications for applying the results of the current study to treatment decisions.

While these results cannot be translated into global recommendations, they imply that a more nuanced approach is needed when judging that further medication trials are futile and that it is time to consider epilepsy surgery. Many studies, including this one, demonstrate that lesional epilepsy has a lower chance of responding to medication trials. Since mesial temporal sclerosis and other types of epilepsy with discrete, resectable lesions, have a good response to neuro-

surgical treatment, the standard definition of drug-resistant epilepsy—failure of two AEDs—seems appropriate for judging surgical candidacy in this situation. However, patients with MRI-negative, cryptogenic focal epilepsy are difficult surgical candidates, as it is challenging to identify the seizure-onset zone, and the chance of a seizure-free surgical outcome is substantially less. For this reason, these individuals are typically subjected to many more than two AED trials. This study of Sillanpää and Schmidt demonstrates that longer periods of treatment may sometimes result in seizure freedom, particularly in cryptogenic epilepsy. Therefore, it is rational to implement a larger number of medication trials in cryptogenic/idiopathic epilepsy patients, although pessimism is still warranted.

by John W. Miller, MD, PhD

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