

SEIZURE REMISSION IN ADULTS WITH INTRACTABLE EPILEPSY: NOT JUST A PIPE DREAM

Likelihood of Seizure Remission in an Adult Population with Refractory Epilepsy. Callaghan BC, Anand K, Hesdorffer D, Hauser WA, French JA. *Ann Neurol* 2007;62(4):382–389. **OBJECTIVE:** We aimed to determine the likelihood of remission and its clinical predictors in adult patients meeting a strict definition of refractory epilepsy. We also wanted to investigate the influence of treatment regimen on remission. **METHODS:** A total of 246 patients with treatment refractory epilepsy (having at least 1 seizure per month and having not responded positively to at least 2 antiepileptic drugs) were identified in 2000 and followed for 3 years. We used Kaplan-Meier methods to estimate the rate of achieving a 6-month terminal seizure remission and Cox regression analysis to evaluate clinical predictors for seizure remission. **RESULTS:** The estimated 6-month terminal seizure remission rate was 19% (95% confidence interval, 14–26%) for all cases and 14% (95% confidence interval, 10–21%) when limited to those treated only with medication. Negative predictors for remission included a history of status epilepticus, younger age at intractability, number of failed drug therapies, and presence of mental retardation. No specific drug was significantly associated with remission, and frequently, no clear intervention led to terminal remission. **INTERPRETATION:** Fifteen percent (approximately 5% per year) of a drug refractory epilepsy population obtained a 6-month terminal seizure remission. Our results signify that no matter how many antiepileptic drug therapies have failed, there is always hope of a meaningful seizure remission in this population. Furthermore, we have elucidated four clinical predictors that can aid the epileptologist in prognostication.

COMMENTARY

Although an abundance of new anticonvulsants have been developed over the past decade, roughly a third of people with epilepsy still have medically intractable seizures (1). Poorly controlled seizures are associated with increased mortality and significant physical and psychosocial morbidity (2). While individuals occasionally demonstrate an exceptional response to the addition of one of the newer medications, there is little evidence that these agents have had a significant impact on seizure control for newly diagnosed patients (1) or patients who have not responded to other medications (3). In 2000, Kwan and Brodie reported that medical intractability often may be predicted early in treatment. In their study of newly diagnosed epilepsy, patients failing to respond to the first medication only had an 11 percent chance of responding to a second medication (1). Thus, clinicians have inferred that aggressive medication changes are likely to be futile in patients who have continued to have seizures despite several anticonvulsant trials.

Based on a series of patients with previously uncontrolled seizures, Callaghan and colleagues report that nearly 5 percent of patients per year will enter seizure remission, usually as a result of medication changes. While this finding is clearly less than optimal, the authors note that their data provide realistic hope that persistent medical attention may eventually improve a patient's seizure control. Their assertion is particularly important since most of these patients are not candidates for improving seizure control with surgery.

The authors contrast their findings with those of Kwan and Brodie; however, it is helpful to remember that the studies differ significantly in design and intent. The current study included patients who met strict criteria for poor seizure control (i.e., more than one seizure per month for 3 months, after trying at least two medications). Patients were treated aggressively, followed for roughly 3 years, and were considered in remission if they experienced a 6-month period without seizures. In contrast, Kwan and Brodie studied patients with newly diagnosed epilepsy, following them for as long as 16 years, and considered seizure free if they had not had seizures during the year prior to their last follow-up visit (1). Thus, Callaghan et al. scrutinized previously intractable cases for improvement, while Kwan and Brodie emphasized imperfect seizure control in patients who

started treatment with a clean slate. These studies should be regarded as complimentary rather than discordant.

Callaghan and colleagues used Kaplan–Meier methods to estimate the cumulative seizure remission rate. They wisely performed a separate analysis censoring surgery, since many patients became seizure free as a result of their operations. The estimated remission rates are likely to be accurate for the population studied, although it is not clear whether the results would apply to patients who were not in long-term care at an institution. Furthermore, a prospective study of patients with refractory epilepsy might yield less favorable results than were found in the retrospective study by Callaghan et al.

A modest proportion of the patients entering seizure-free intervals did so without an obvious temporal relationship to anticonvulsant manipulation. This outcome suggests that the natural history of refractory epilepsy for some patients may include good periods rather than relentless seizures. Berg and colleagues have shown that children with refractory epilepsy often have periods of remission before becoming refractory and that a significant subset enter remission again later (4). Taken together, these observations support a concept of seizure control as a moving target, necessitating careful consideration of methods for analysis. The methods used in the Callaghan et al. study distinguish patients who sometimes do well from those who do not.

The authors also attempt to define predictors of intractability; however, none of the factors analyzed remained significant in multivariate analysis. They make the point that the factors that were significant in their univariate analysis are likely to be true predictors, given that they have been replicated in other studies (5,6) or make intuitive sense. These factors include mental retardation, status epilepticus, number of medications failed, and duration of intractability. MRI and EEG abnormalities did not predict intractability. Given the uncertainty of the independent predictive value of the defined risk factors, they cannot be used at this time to confidently stratify risk in individuals, though they may still be useful as rough indicators of intractability.

The most important consequence of this study is to serve as a reminder that counseling patients on seizure control prognosis is a tricky business that necessitates more than cursory explanations. Pertinent to the discussion is the fact that a large number of patients will have variable seizure control throughout life and that treatment success (both medical and surgical) will be superimposed on that background. Indeed, a recent long-term study of seizure surgery outcomes indicates that freedom from seizures may vary significantly over time. While some patients who were seizure-free at 2 years, developed recurrent seizures, 20 percent of the people who were still having seizures 2 years after surgery were seizure-free 8 years later (7). Callaghan and colleagues' study is a reminder that no matter how things are going, improvement may be just around the corner for those patients with seemingly persistent seizures.

by Paul Garcia, MD

References

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314–319.
2. Devinsky O. Patients with refractory seizures. *N Engl J Med* 1999;340:1565–1570.
3. Zaccara G, Messori A, Cincotta M, Burchini G. Comparison of the efficacy and tolerability of new antiepileptic drugs: what can we learn from long-term studies? *Acta Neurol Scand* 2006;114:157–168.
4. Berg AT, Vickrey BG, Testa FM, Levy SR, Shinnar S, DiMario F, Smith S. How long does it take for epilepsy to become intractable? A prospective investigation. *Ann Neurol* 2006;60:73–79.
5. Huttenlocher PR, Hapke RJ. A follow-up study of intractable seizures in childhood. *Ann Neurol* 1990;28:699–705.
6. Sillanpaa M. Remission of seizures and predictors of intractability in long-term follow-up. *Epilepsia* 1993;34:930–936.
7. Asztely F, Ekstedt G, Rydenhag B, Malmgren K. Long term follow-up of the first 70 operated adults in the Goteborg Epilepsy Surgery Series with respect to seizures, psychosocial outcome and use of antiepileptic drugs. *J Neurol Neurosurg Psychiatry* 2007;78:605–609.