

IS EPILEPSY INTRACTABILITY PREDETERMINED OR ACQUIRED?

How Long Does it Take for Epilepsy to Become Intractable? A Prospective Investigation Berg AT, Vickrey BG, Testa FM, Levy SR, Shinnar S, DiMario F, Smith S. *Ann Neurol* 2006;60:73–79. **OBJECTIVE:** To determine prospectively when in the course of epilepsy intractability becomes apparent. **METHODS:** Data are from a prospective cohort of 613 children followed for a median of 9.7 years. Epilepsy syndromes were grouped as focal, idiopathic, catastrophic, and other. Intractability was defined in two ways: (a) two drugs failed, 1 seizure/month, on average, for 18 months (stringent), and (b) failure of two drugs. Delayed intractability was defined as 3 or more years after epilepsy diagnosis. **RESULTS:** Eighty-three children (13.8%) met the stringent and 142 (23.2%) met the two-drug definition. Intractability depended on syndrome ($p < 0.0001$): 26 (31.3%) children meeting stringent and 39 (27.5%) meeting the two-drug definition had delayed intractability. Intractability was delayed more often in focal than catastrophic epilepsy (stringent: 46.2 vs 14.3%, $p = 0.003$; two-drug: 40.3 vs 2.2%, $p = 0.0001$). Early remission periods preceded delayed intractability in 65.4–74.3% of cases. After becoming intractable, 20.5% subsequently entered remission and 13.3% were seizure free at last contact. **INTERPRETATION:** Intractable epilepsy may be delayed, especially in focal epilepsy. It often is preceded by a quiescent period, followed by further remissions. These findings help explain why surgically treatable epilepsies may take 20 years or longer before referral to surgery.

COMMENTARY

Epilepsy appears intractable in more than 35% of newly treated patients (1). As expected, the prevalence of intractability is higher in referral centers (2), and patients with partial epilepsy are more likely to be intractable. It has long been debated whether intractability is already present when the condition first expresses itself or develops over time. Some investigators have suggested that the longer uncontrolled seizures continue, the more difficult they will be to control, perhaps implying that a delay in effective treatment may contribute to the intractability (3). However, other studies have indicated that intractable epilepsy can often be detected early after onset of seizures (1,4). In one study of newly treated epilepsy, overall, 64% of patients became seizure free, while only 11% of those in whom the first drug was ineffective and only 4% of those who failed two drugs became seizure free (1). Thus, poor response

to the first and the second drug is a predictor of intractability. In addition, the pathology of hippocampal sclerosis was consistently predictive of intractability (2,5).

If the failure of two drugs predicts intractability, then one would expect that those patients who are candidates for epilepsy surgery could be identified and referred within 2–3 years, the time it would take to verify failure of at least two drugs. However, in a prior retrospective study examining the outcomes of resective epilepsy surgery, Berg and colleagues found that the mean duration of epilepsy before surgery was 22.1 years (6). Two factors for this delay were that as many as a quarter of patients reported variable periods of remission before deciding to pursue surgery and that the average time to failure of the second drug was 9 years. Early age at onset of epilepsy was the strongest predictor of delayed intractability. Because of these findings, it seemed appropriate to prospectively evaluate the latency to intractability in a cohort of children with epilepsy.

The prospective study by Berg and colleagues confirmed that delayed intractability is not uncommon, although early

intractability remained more likely. Approximately 30% of children with intractable epilepsy had delayed intractability. This phenomenon was more likely in focal than in other types of epilepsy. Temporal lobe epilepsy and hippocampal sclerosis were both associated with delayed intractability in the retrospective study (6). The current study found a greater likelihood of intractability in temporal lobe than in extratemporal epilepsy, which is in agreement with one referral center retrospective study (2). However, Berg et al. did not identify clear differences between temporal and extratemporal epilepsy with respect to delayed intractability. The study results did not include the prevalence of hippocampal sclerosis among patients with temporal lobe epilepsy, however, the authors indicated in the discussion that only one child had MRI evidence of hippocampal sclerosis at study entry. Although this finding may be a low estimate, it is nevertheless very likely that hippocampal sclerosis is much less prevalent in a population-based pediatric temporal lobe epilepsy group than it is in an adult temporal lobe epilepsy surgery group. Hippocampal sclerosis may still be specifically associated with delayed intractability.

Delayed intractability raises the possibility that epilepsy may be a progressive condition in some affected individuals. If accurate, the finding in turn may offer an opportunity for intervention, provided the underlying pathophysiology is understood. Assuming that the process of epileptogenesis is still ongoing in patients with delayed intractability, the development of antiepileptogenic drugs could be pursued to arrest this process. However, the mechanism of delayed medical intractability could be very different than progression of epileptogenesis. At the present time, two main mechanisms of drug resistance have been proposed: (a) increased expression of multidrug transporters (also called drug resistance proteins) that remove antiepileptic drugs from the epileptogenic zone and (b) reduced sensitivity of the drug target in the epileptogenic zone (7). Development of tolerance is another mechanism that now is receiving more attention (8).

Both drug transporter expression and certain drug targets can be modified by seizure activity in animal models. In particular, it has been demonstrated that some drug transporter proteins can be transiently overexpressed in rodent brain after experimentally induced seizures (7). It is not known what role the drug transporter proteins play in development of medically refractory human epilepsy. If human seizures can also induce drug resistance proteins, then induction of these proteins could potentially contribute to the occasional development of intractable epilepsy after antiepileptic drug withdrawal in previously seizure-free patients (9). With progress in the *in vivo* imaging of drug resistance proteins in the human brain, there is potential to learn if these proteins play a role in the delayed development of intractable epilepsy (10). If they do, strategies could be developed to reduce their impact, including the use of specific inhibitors.

Intractability is not always an irreversible phenomenon. Berg and colleagues reported that more than 20% of intractable patients went on to experience one or more remissions after meeting their stringent criteria of intractability and almost 50% had remissions following the less stringent criteria. Almost two-thirds of these patients were still in remission at the time of the last contact. The authors were not able to identify the factors responsible for late remissions and found no evidence that new antiepileptic drugs were responsible for better outcomes. However, that possibility cannot be excluded. The new antiepileptic drugs have been associated with seizure freedom for at least 6 months in up to 13% of previously highly refractory patients (11). A detailed analysis of the circumstances surrounding relapse and remission after apparent intractability would be of great interest. The prospective study of the current cohort is likely to continue to shed more light on the natural history of epilepsy intractability.

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References

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314–319.
2. Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, Cavalcanti D, Baulac M. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology* 1998;51:1256–1262.
3. Reynolds EH, Elwes RD, Shorvon SD. Why does epilepsy become intractable? Prevention of chronic epilepsy. *Lancet* 1983;2:952–954.
4. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B. Early development of intractable epilepsy in children: a prospective study. *Neurology* 2001;56:1445–1452.
5. Stephen LJ, Kwan P, Brodie MJ. Does the cause of localisation-related epilepsy influence the response to antiepileptic drug treatment? *Epilepsia* 2001;42:357–362.
6. Berg AT, Langfitt J, Shinnar S, Vickrey BG, Sperling MR, Walczak T, Bazil C, Pacia SV, Spencer SS. How long does it take for partial epilepsy to become intractable? *Neurology* 2003;60:186–190.
7. Schmidt D, Loscher W. Drug resistance in epilepsy: putative neurobiologic and clinical mechanisms. *Epilepsia* 2005;46:858–877.
8. Loscher W, Schmidt D. Experimental and clinical evidence for loss of effect (tolerance) during prolonged treatment with antiepileptic drugs. *Epilepsia* 2006;47:1253–1284.
9. Schmidt D, Loscher W. Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience. *Acta Neurol Scand* 2005;111:291–300.
10. Elsinga PH, Hendrikse NH, Bart J, Vaalburg W, van Waarde A. PET Studies on P-glycoprotein function in the blood-brain barrier: how it affects uptake and binding of drugs within the CNS. *Curr Pharm Des* 2004;10:1493–1503.
11. 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.