A Lesson from "The Brodie Ultimatum": The Locus of Control for Epilepsy is Outside the Therapeutic Alliance

Patterns of treatment response in newly diagnosed epilepsy.

Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. *Neurology* 2012;78:1548–1554.

OBJECTIVE: To delineate the temporal patterns of outcome and to determine the probability of seizure freedom with successive antiepileptic drug regimens in newly diagnosed epilepsy. METHODS: Patients in whom epilepsy was diagnosed and the first antiepileptic drug prescribed between July 1, 1982, and April 1, 2006, were followed up until March 31, 2008. Outcomes were categorized into 4 patterns: (A) early and sustained seizure freedom; (B) delayed but sustained seizure freedom; (C) fluctuation between periods of seizure freedom and relapse; and (D) seizure freedom never attained. Probability of seizure freedom with successive drug regimens was compared. Seizure freedom was defined as no seizures for ≥ 1 year. RESULTS: A total of 1,098 patients were included (median age 32 years, range 9–93). At the last clinic visit, 749 (68%) patients were seizure-free, 678 (62%) on monotherapy. Outcome pattern A was observed in 408 (37%), pattern B in 246 (22%), pattern C in 172 (16%), and pattern D in 272 (25%) patients. There was a higher probability of seizure freedom in patients receiving 1 compared to 2 drug regimens, and 2 compared to 3 regimens ($p < 0.001$). The difference was greater among patients with symptomatic or cryptogenic than with idiopathic epilepsy. Less than 2% of patients became seizure-free on subsequent regimens but a few did so on their sixth or seventh regimen. CONCLUSIONS: Most patients with newly diagnosed epilepsy had a constant course which could usually be predicted early. The chance of seizure freedom declined with successive drug regimens, most markedly from the first to the third and among patients with localization-related epilepsies.

Commentary

Some stories are so intriguing, they must have a sequel. Some cliffhangers even need a second sequel. Professor Brodie's recent update of his ongoing prospective observational study (1) was perhaps not as eagerly anticipated as the Jason Bourne psycho-bio-über-dramas. For epilepsy watchers though, in another landmark paper, this third update (1–3) presents an ever-sharpening snapshot of the long-term course of persons diagnosed with epilepsy. And the picture is not so pretty.

In the authors' epilepsy clinic, new-onset patients were treated (usually after two seizures) according to a sensible protocol of trying one antiepileptic drug (AED) followed by substitution monotherapy if the first AED was not effective or not tolerated, or by add-on therapy in the case of incomplete response to the first AED. After this initial strategy, the clinicians treated refractory patients by aiming for monotherapy but also trying polytherapy. Patients with poor adherence were excluded from the study. The outcome at last follow-up was categorized into one of four mutually exclusive groups:

1. Seizure-free within 6 months of therapy and remaining so during follow-up.
2. Not seizure-free in the first 6 months but later achieving seizure-freedom and remaining so during follow-up.
3. Fluctuating course between seizure relapse and seizure-free periods that last more than one year.
4. Never seizure-free for more than one year.

With a mean of 7.5 years of follow-up on 1,098 patients enrolled between 1982 and 2006, 37% were continuously seizure free beginning within the first 6 months of initial treatment, 22% were continuously seizure free sometime after the first 6 months of initial treatment, and 25% were never seizure free. Given the demonstrated insightfulness of the clinical investigators, it is quite possible that other centers are not even doing this well. One caveat deserves consideration: The number of patients lost to follow-up throughout the study is not provided, and the results are basically the last observation carried forward. This methodology may bias the results, likely in the direction of painting a rosier picture of the outcomes since some patients had perhaps not relapsed by the time of last follow-up.

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There were 360 patients with at least 10 years of follow-up, however, and only 52% remained seizure-free during this time; consistent with the results evaluated by categorical outcomes. Of the total cohort, 25% (88/350) of patients who were initially seizure-free relapsed. Sixteen percent (28/174) of patients who achieved seizure freedom after the first initial 6 months also relapsed. Contrary to the authors' statement that most patients had a constant course that could be predicted early, they reported that patients who became seizure-free (for at least one year) immediately or within 6 months were just as likely to relapse as those who became seizure free after more than 6 months—basically, 20% relapsed in each category. The course is constant in that there is a high rate of seizure recurrence no matter when "seizure-freedom" is achieved. The longer the observation, the higher the rate of relapse: 31% at 2 years of continuous observation, 38% at 5 years, and 48% at 10 years. So, one clear answer to our patient's questions about how they will do over the long term is informed by this study. Even if a patient is readily seizure-free with AED treatment, he or she has about a 50% chance of a seizure recurrence within 10 years.

This report is interpreted as supportive evidence that epilepsy surgery should be considered early in the course, after the patient has continued seizures after two AED trials, instead of waiting longer for many more AEDs to fail. This is reasonable, as epilepsy surgery seems to be the only intervention that resets the seizure threshold; the patient's seizures may become responsive to AEDs after surgery whereas they were resistant before surgery.

However, as demonstrated in this study, many patients experience prolonged periods of seizure-freedom but still have a high risk of recurrence. Why is this? The patients in this study were treated by research physicians using a standard treatment protocol and were excluded if they did not take their medications. It is frustratingly obvious that long-term seizure control cannot be achieved by this approach in half of the seemingly lucky AED-responsive patients. The locus of control for epilepsy is outside the careful and sincere strategies worked out between the caregiver and patient, which usually involve the use of an AED.

Why do AEDs fail even after they are seemingly working so well? One theory is the complexity of the seizure-producing "network" that has a plasticity based on both formation of malignant circuitry and neuronal death, provoked by ongoing aberrant neurophysiology originating in a seizure focus (4). This idea is particularly applicable for the concept of late failure of resective epilepsy surgery (5): The entire network cannot be resected or even identified and, therefore, the seizure circuitry is eventually rerouted. Another possibility is AED resistance, the mechanisms of which remain to be established (6). But if a patient develops resistance to an AED after several years of exposure, this again suggests a dynamic process. Presuming that there are specific AED resistance mechanisms associated with AED mechanisms of action, perhaps a way to prevent the sequential recurrence of AED resistance is not by using initial or sequential monotherapy. A radical idea is to start with several medications at the onset of diagnosis using mechanistically varied AED polytherapy to reduce the open avenues for development of AED resistance. This, of course, is in contrast to the hallowed tenet of aiming for monotherapy (7).

Viewed from another angle, one can couch these relapses after a long dormancy into an infectious reactivation scenario. The classic viral reactivation that is illness-producing—the herpes simplex virus—has been found as human herpesvirus 6B in epilepsy surgical specimens of temporal lobe epilepsy (TLE) patients with mesial temporal sclerosis, and not in non-mesial TLE specimens (8). A recent paper clearly demonstrated an association between febrile status epilepticus and HHSV-6 and -7 infections. It is not a stretch therefore, to postulate that viral reactivation contributes to the often-described course of temporal lobe epilepsy occurring after years of seizure freedom in a patient with a history of febrile seizures. (9). A prolonged epileptic process that becomes clinically apparent after a threshold is reached, in the same manner as a neurodegenerative disease, has even raised the question of prion-like mechanism for epileptogenesis (10). A sister concept, brain inflammation, has jump-started an exploratory treatment approach (11). Sleep deprivation and stress are associated with susceptibility to viral and other illnesses; these are triggers for seizure relapse as well.

This update reveals our limitations with AED treatment, and this is reinforced by the result that there is no greater fraction of readily seizure-free patients in the current report compared to the initial report 12 years ago, in fact there are less—63% in the first report (2)—indicating a failure of new AEDs to have a major impact.

This commentary is also meant to give homage to a remarkable clinician–scientist, Professor Brodie, who has given us so much to think about. These simple words may not increase his stature, but it is an honor to try to do so. Still to come: "The Brodie Legacy"!

by Cynthia Harden, MD

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