Response to Early AED Therapy and Its Prognostic Implications

Jacqueline A. French, M. D.

Department of Neurology, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

Determining the prognosis of patients when they first present with epilepsy is a difficult task. Several clinical studies have shed light on this very important topic. Potential predictors of the refractory state, including seizure etiology, duration of epilepsy before treatment, and epilepsy type, have not been successful indicators of long-term outcome. One predictor of the refractory state appears to be early response to AED therapy. Inadequate seizure control after initial treatment is a poor prognostic sign. Recent research into genetic causes of the refractory state has included investigation of the multiple drug resistance gene, and polymorphisms at drug targets. More work is needed to determine the causes and predictors of drug resistance.

Introduction

When patients are initially evaluated and the diagnosis of epilepsy is made, it is impossible to distinguish those who will have a few seizures, but will respond immediately to treatment, from those who will have a lifelong disabling condition, with frequent seizures despite therapeutic trials of numerous antiepileptic drugs (AEDs). Patients with good and bad prognoses may have identical seizure types, etiologies, and demographics. However, it may not take long to identify refractory patients. One factor that is identified repeatedly as a predictor across studies is the critical importance of response to the first AED. In both children and adults, response to the first AED (or seizure recurrence within the first year of treatment) is a powerful predictor of long-term seizure remission (1,2). Recently the cohort of newly diagnosed epilepsy patients accumulated by Kwan and Brodie (3) and analyzed in two publications, one reviewed in this edition of *Epilepsy Currents*, highlighted and confirmed these observations. In this study, 47% of patients became seizure free with their first AED. Failure of the first drug because of an idiosyncratic side effect or intolerance did not substantially reduce the chance of responding to a second AED, as long as it was tolerated. However, the 113 patients who experienced recurrent seizures despite adequate treatment with the first AED had only an 11% chance of remitting on any treatment over up to a median of 5 years of follow-up. This stark differentiation of prognosis after the failure of the first drug has not been reported in other large cohort studies. For example, in a study of children with two or more seizures, those whose first drug failed still had a 42% chance of long-term seizure remission (4). However, the critical distinction between failure due to side effects and failure due to continued seizures was not made. If the study of Kwan and Brodie is a true representation of outcome in newly diagnosed patients, these results represent a profound change in the way we may need to think about refractory epilepsy. Essentially, with few exceptions, failure to respond to an AED seems to predict failure of response to all AEDs. This simple factor identifies the majority of refractory patients. In all, of the original 470-person cohort described by Kwan and Brodie, 300 became seizure free, and 170 did not; the first drug failed in 100 (59%) because of lack of response. As the authors of the study correctly noted, this implies that refractoriness does not develop over time, due to recurrent seizures or neuronal loss. Rather, refractoriness appears to be an intrinsic property of patients when the epilepsy develops.

Timing of Initial Treatment

The refractory state was not always presumed to be present at the outset of epilepsy. Many studies, including that of Kwan and Brodie, identified a higher number of seizures before treatment as a risk factor for refractory epilepsy (5–9). This finding was frequently hypothesized to be a demonstration of a "kindling" phenomenon in humans. In other words, there was a feeling that immediate treatment was critical to prevent the refractory state. This hypothesis has largely been abandoned, based on data from developing countries, where treatment is often delayed because of inadequate access to health care. Yet when AEDs are introduced, even years after epilepsy onset, remission rates are similar to those reported in newly diagnosed cohorts (10). In addition, a well-designed study failed to deter-

Address correspondence to: Jacqueline A. French, M. D., Department of Neurology, University of Pennsylvania Medical Center, 3400 Spruce Street, Philadelphia, PA 19104. E-mail: frenchj@mail.med.upenn.edu.

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mine that treatment after the first seizure altered prognosis for the development of refractory epilepsy, although such treatment reduced the risk of subsequent seizures (11). Most likely, occurrence of multiple seizures before treatment initiation is a surrogate marker for other factors, such as presence of partial epilepsy with unrecognized subtle complex partial seizures, or frequent seizures at epilepsy onset, both of which may indeed be linked to poor prognosis.

What Is the Cause of Refractory Epilepsy?

The predictive value of failure of the first AED does not answer the question of the cause of refractory epilepsy. In the Kwan and Brodie study, the initial drug-failure cohort was not characterized in terms of age, epilepsy type, or etiology. It is unknown whether AED failure relates to the cause of the epilepsy or to an underlying patient-specific genetic characteristic. Semah et al. (12) evaluated outcome in 2,200 adult outpatients who were seen at an epilepsy clinic. They identified several prognostic factors that they believed were important predictors of poor outcome. Etiology seemed to be critical in determining outcome; for example, 54% of patients with poststroke seizures were seizure free, versus only 11% of patients with hippocampal sclerosis and 3% of patients with hippocampal sclerosis combined with a second pathology. However, this study had potential bias because of its methodologic approach, which consisted of evaluating patients who attended a university epilepsy clinic. Only 8% were followed up from the time of diagnosis. This is clearly a selected sample and may not represent the universe of epilepsy patients. Many seizure-free or "easy to control" patients might never seek out specialized care. In a study by Stephen (13), using a cohort overlapping with that described by Kwan and Brodie, mesial temporal sclerosis was associated with a 42% seizure-free rate, which was slightly but not drastically different from the overall 57% seizure-free rate in the larger cohort. In other words, although the prognosis was worse than that seen in patients with other etiologies, many patients with this etiology fared well. Clearly, etiology, although important, is not the whole story behind drug-refractory epilepsy. With this in mind, there has been a recent explosion in research activity searching for other explanations of drug insensitivity. Areas of great interest include the multiple drug resistance gene (MDR-1). MDR-1 expresses a p-glycoprotein pump that is capable of exporting hydrophobic drugs out of cells, and ultimately back across the blood–brain barrier. If drugs cannot reach their target, they cannot produce an effect. MDR-1 has been demonstrated to be overexpressed in seizure foci of some drug-resistant patients (14–16). Overexpression of MDR-1 would be a reasonable explanation for repeated failure of drug response in certain patients, yet it is unlikely that all AEDs are substrates for the pump. Other possible explanations for drug resistance might be genetic polymorphisms in drug targets. This has been found to be an explanation for drug resistance in other conditions, such as asthma and psychosis (17). Further investigation of these mechanisms is clearly warranted, in both humans and animal models.

The New AEDs

The study of Kwan and Brodie was performed between 1984 and 1987. Many patients were treated with established drugs, although new AEDs were used in 71. It may be that new AEDs will be more effective in treating the refractory epilepsies. The presence of novel mechanisms and structures may overcome whatever mechanism explains lack of response. To date, all AEDs tested in randomized comparative trials have produced similar or lower percentages of seizure-free patients than have the established AEDs (18–23), yet there are a few hints that treatment response is not absolute. For example, the new AED vigabatrin (VGB) is exceptionally effective in eliminating seizures in patients with refractory seizures, but was less effective than carbamazepine (CBZ) in eliminating seizures in newly diagnosed patients (19,24). This might reflect less efficacy in the more common "responsive" patients but better results in the drug-resistant subset. The only way to explore this further would be to analyze the outcome with the second drug for patients in each group for whom the initial therapy failed.

Conclusion

What are the treatment implications of the study of Kwan and Brodie? The first is that knowing that initial therapy has failed for a patient is not sufficient to label the epilepsy as treatment refractory; the cause of failure must be known. Patients for whom treatment failed for reasons other than lack of efficacy ultimately did as well as early drug responders. It also is important to keep in mind that the study used only complete seizure freedom as an outcome. Some patients may have been experiencing only rare breakthrough seizures. Moreover, it is quite likely that many patients for whom the first drug fails may experience a seizure reduction with alternate therapy. However, for most patients, complete seizure freedom is the goal. These findings certainly support early referral for surgical evaluation. They also may support the use of one of the newest AEDs as a second therapeutic trial, although more data are needed to direct second therapy.

In summary, we have a long way to go in defining the drug-refractory state and determining its cause. We need to learn a great deal more if we hope to predict accurately and ultimately to treat these individuals, whose lack of treatment response is one of the most frustrating puzzles in the management of epilepsy.

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