

Refractory Epilepsy: One Size Does Not Fit All

Jacqueline A. French, MD

Professor of Neurology, Director, Penn Epilepsy Center, Assistant Dean for Clinical Trials, Hospital of the University of Pennsylvania, Philadelphia, PA

A unifying definition of refractory epilepsy has been hotly debated but, to date, has not been agreed upon. Evidence from clinical trials indicates that some patients actually are not refractory, as many will partially respond to add-on treatment or will worsen when antiepileptic drugs (AEDs) are removed. There are several important issues relating to the assessment of AED response that routinely have not been addressed in the determination of treatment responsiveness, such as incorporating baseline seizure severity, including partial response rather than solely an all-or-none response, and the consideration of variability in response over time.

At the time of diagnosis of epilepsy, there are few clues other than basic epilepsy syndrome categorization that identify the relatively “lucky” individuals, who will have few seizures in their life and may eventually be able to discontinue therapy, from the unfortunate patients, who will have to struggle with recurrent seizures despite interminable medication changes and additions. While a great deal is known about seizures and epilepsy, surprisingly little is known about the identification and causes of refractory epilepsy. Fortunately, many investigators now are studying this critical issue, both at the basic science level as well as the clinical level. Current investigations include attempts to determine the underlying pathophysiology involved in failure of drug treatment as well as to identify genetic underpinnings of treatment resistance.

In order for the studies to succeed, it will be essential to separate out refractory or treatment-resistant patients from those who are responders. To this end, a very important question

must be asked: do clinicians know a treatment nonresponder when they see one? Unfortunately, the answer may not be as straightforward as initially appears, because the definition of responder varies enormously among both clinicians and investigators. Even the name for this group of patients cannot be agreed upon. Many terms have been used, including “treatment nonresponder,” “refractory,” “intractable,” and “drug resistant.” One might imagine that each of these terms would confer a slightly different definition, but indeed all are used interchangeably, perhaps exemplifying the confusion.

The epidemiology of refractory epilepsy is complicated by several issues: (i) There is no unifying definition of refractory epilepsy. (ii) Patients do not necessarily become refractory immediately at the time of diagnosis, nor do they inevitably remain refractory throughout the course of their illness. Therefore, the same patient might be identified as refractory at one time, but treatment responsive at another. (iii) Response to medication is assessed without a pretreatment baseline, as most patients are treated rapidly after diagnosis. Therefore, it is unclear whether or not so-called refractory patients have had a substantial response to treatment. (iv) There is reasonable evidence from clinical trials that patients that are defined as refractory will respond readily, although not completely to therapy. Each of these thorny issues will be addressed in this article.

Defining Refractory Epilepsy

The relative frequency of refractory epilepsy varies from study to study but typically comprises approximately a third of newly treated patients. The definition used to distinguish responders from nonresponders is variable and, indeed, can differ substantially. Because of the impact of even a single seizure on physical, social, and psychological function, the clinical goal of therapy has been complete elimination of seizures. This clinical goal has been translated by many into a research definition. For example, in several landmark studies evaluating incidence of refractory epilepsy from the time of diagnosis, treatment nonresponse is defined as the occurrence of even a single seizure breakthrough, within some period of follow-up (1–3). Using this definition, patients can fall into only two categories: remission or resistance. Presumably, patients then may be identified as treatment resistant if they are rarely noncompliant or have an intercurrent illness. In contrast, other studies have defined treatment resistance as the occurrence of one seizure a month for some specified period of time or have included the number of drug failures into the definition (4–6). Some enlightened studies have recognized that two categories of outcome may not be sufficient

Address correspondence to Jacqueline A. French, MD, Professor of Neurology, Director, Penn Epilepsy Center, Assistant Dean for Clinical Trials, Hospital of the University of Pennsylvania, 3 West Gates, 3400 Spruce Street, Philadelphia, PA 19104-4283; E-mail: frenchj@mail.med.upenn.edu.

Epilepsy Currents, Vol. 6, No. 6 (November/December) 2006 pp. 177–180
Blackwell Publishing, Inc.

© American Epilepsy Society

and have added a third, such as one that subdivided epilepsy outcome into “good, bad, and in between” (7). Not surprisingly, the variability in definition leads to variability in results. A recent report investigated how many children from a cohort of newly diagnosed epilepsy patients would be considered refractory, if the definitions of treatment resistance from six different studies were applied (8). Even though the definitions were reasonably similar, each led to different determinations of the frequency of refractoriness in this population, ranging from 9% to 24%.

It could be argued that the variability in definitions might be expected, since studies with different purposes might need to approach the problem in different ways. Surely, then, at least studies with a common objective would use a common definition. Unfortunately, this supposition has not proven to be correct. For example, recent studies looking for genetic susceptibility to refractory epilepsy searched for polymorphisms of *ABCB1*, a gene associated with expression of drug transporters. Two studies found that the polymorphism 3435C-T, which is associated with higher level of P-glycoprotein (Pgp) expression, was more common in patients with refractory epilepsy. However, two subsequent studies failed to confirm the findings. One possible explanation for the lack of confirmation may be the definition of treatment resistance that was selected, which ranged from as low as four seizures a year to as high as six seizures a month (9,10). Thus, very different populations were examined.

Once Refractory, Always Refractory?

If a common definition of refractory epilepsy were agreed upon, the next task would be to separate patients into categories of refractory and nonrefractory, as was done in the studies described in the previous section. In order to do so, one must make the fundamental assumption that a patient will fall into one of the two categories and stay there. Unfortunately, for many patients, the assumption may be faulty. Several longitudinal studies of the natural history of epilepsy have found that a large number of patients may fit each category for periods of time. This finding is particularly true with children (11). In a unique study in Finland (please see the commentary by Dr. John Miller in this issue of *Epilepsy Currents*, which reviews the study), 144 patients presenting with epilepsy in childhood were followed from the time of diagnosis for an average of 37 years (11). Only 16% of the patients were immediately seizure free and remained so, uninterrupted by relapse, and only 19% were treatment resistant throughout, without ever experiencing a remission. The remaining patients had some periods of seizures and some periods of remission.

It is particularly common for children with a history of febrile seizures to present with treatment-responsive epilepsy in childhood, followed by development of refractory epilepsy associated with mesial temporal sclerosis in adulthood (12,13).

A recent study of 333 patients presenting for surgical resection revealed that 26% reported a remission prior to surgery of 1 to 28 years (14). Patients also move in the opposite direction, that is, from refractory to responsive. One study performed at an epilepsy center separated seizure-free patients into those who had been “easy to control” (i.e., easily became seizure free with low doses of medication) and those who had been “difficult to control” (i.e., required high doses or multiple treatment regimens to attain seizure freedom) (15). Twenty percent of the patients fell into the “difficult to control” category. Presumably, these patients would have been designated treatment resistant early in their course, but treatment responsive later. Patients also may change categories following surgical manipulation. After temporal lobectomy, many patients will become seizure free but will require continuation of antiepileptic medication to prevent seizure recurrence (16,17). In a sense, these individuals have shifted from being treatment resistant to being treatment sensitive, which implies that drug-response failure is localized, at least in some patients.

All-or-None Drug Response: Is There a Better Way to Define Treatment Outcome?

Epilepsy differs from other conditions that have been examined for treatment resistance in that symptoms are intermittent, and it often is necessary to begin treatment before frequency of seizures and severity of disease can be ascertained. When seizures are not completely controlled, the conclusion is that the administered drug is not effective and that the patient therefore is resistant. However, without a baseline severity rate, it is impossible to know whether there has been no response or a partial response to treatment: a patient having one seizure a month after initiation of treatment actually may have experienced no reduction or may have had a 90% reduction in seizures. It may be an erroneous presumption that going from one seizure a year to none is a more significant indicator of drug effect than dropping from 20 seizures a year to one. Yet, in most schemes, the first patient would be deemed drug responsive and the second drug resistant.

In many other conditions, pharmacogenetic studies benefit from either an understanding of the severity of disease at baseline or the ability to obtain a relative, rather than a dichotomous, response as outcome. For example, it is difficult to imagine a pharmacogenetic study of breast cancer that includes patients with an isolated breast lump along with patients with metastatic disease and uses remission as the *only* measure of response to chemotherapy. Similarly, in a recent study of the impact of cyclooxygenase (Cox) inhibitors on postsurgical pain, the presence of a polymorphism in the *Cox-2* gene was associated with a “significantly lower pain score on a visual analogue scale” (18). It is unlikely that the study would have been

successful if the only outcome assessed were pain versus no pain. In the assessment of newly diagnosed epilepsy, neither baseline severity nor graded outcome is taken into consideration. Some evidence supports the concept that baseline seizure rate has an impact on determination of treatment resistance. In several studies, patients with high baseline seizure rates prior to treatment were more likely to be drug resistant (19–21). This fact would be hard to explain by any theory of drug resistance based on genetic susceptibility but would fit in nicely with the theory that it is harder to eradicate many seizures than a few.

Are Treatment-Resistant Patients Truly Treatment Resistant?

It is a strange irony that the only patients for whom clinicians actually can repeatedly measure treatment response are the so-called treatment-resistant patients. Studies of newly diagnosed patients cannot measure treatment response, because the natural history of any selected population is unknown, and there is no placebo control group for comparison. This concept may be much debated, but it stands as the reason why the U.S. Federal Drug Administration will not grant a monotherapy license based on an active control trial that compares new AEDs to standard ones, such as phenytoin or carbamazepine (22). It is their contention that the percentage of remission seen both in the active control group and the experimental group, which are typically not different, may not result from a response to treatment but rather may represent natural history. In contrast, because the use of placebo is possible in randomized, placebo-controlled add-on trials for patients with refractory epilepsy, drug response is demonstrated in essentially every study. While the response rarely is complete, leading to lasting seizure freedom, it often is substantial. In studies of pregabalin, the most recently approved AED, 14% to 51% of patients experienced a 50% or greater reduction at doses between 50 mg and 300 mg (23). It also repeatedly has been demonstrated that removal of AEDs in refractory patients produces seizure worsening, again, implying a treatment response. In several recent withdrawal to monotherapy studies performed to gain approval of new AEDs, the percentage of patients randomized to a “pseudo-placebo” arm who worsened when their background medication was removed was between 80% and 100% (24).

Conclusion

There are still many challenges to identifying which patients are truly treatment unresponsive and to what degree. If progress is to be made in this area, much more thought needs to go into patient categorization. It is time to acknowledge that when it comes to defining treatment response, one size does not fit all. Different definitions will be needed for different purposes. If

possible, definitions of treatment response should include information about pretreatment seizure rate and severity as well as about prior AED response. More information is needed regarding the natural history of drug response. Finally, studies that are investigating similar areas of epilepsy should, if at all possible, use the same definitions of refractory epilepsy.

References

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314–319.
2. Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. *Epilepsia* 1979;20:729–737.
3. Mattson RH, Cramer JA, Collins JF. Prognosis for total control of complex partial and secondarily generalized tonic clonic seizures. Department of Veterans Affairs Epilepsy Cooperative Studies No. 118 and No. 264 Group. *Neurology* 1996;47:68–76.
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. Dlugos DJ, Sammel MD, Strom BL, Farrar JT. Response to first drug trial predicts outcome in childhood temporal lobe epilepsy. *Neurology* 2001;57:2259–2264.
6. Arts WF, Brouwer OF, Peters AC, Stroink H, Peeters EA, Schmitz PI, van Donselaar CA, Geerts AT. Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood. *Brain* 2004;127(Pt 8):1774–1784.
7. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B, Ebrahimi N. Defining early seizure outcomes in pediatric epilepsy: The good, the bad and the in-between. *Epilepsy Res* 2001;43:75–84.
8. Berg AT, Kelly MM. Defining intractability: Comparisons among published definitions. *Epilepsia* 2006;47:431–436.
9. Siddiqui A, Kerb R, Weale ME, Brinkmann U, Smith A, Goldstein DB, Wood NW, Sisodiva SM. Association of multidrug resistance in epilepsy with a polymorphism in the drug-transporter gene ABCB1. *N Engl J Med* 2003;348:1442–1448.
10. Zimprich F, Sunder-Plassmann R, Stogmann E, Gleiss A, Dal-Bianco A, Zimprich A, Plumer S, Baumgartner C, Mannhalter C. Association of an ABCB1 gene haplotype with pharmacoresistance in temporal lobe epilepsy. *Neurology* 2004;63:1087–1089.
11. Sillanpaa M, Schmidt D. Natural history of treated childhood-onset epilepsy: Prospective, long-term population-based study. *Brain* 2006;129(Pt 3):617–624.
12. French JA, Williamson PD, Thadani VM, Darcey TM, Mattson RH, Spenser SS, Spenser DD. Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination. *Ann Neurol* 1993;34:774–780.
13. Holmes GL, Engel J, Jr. Predicting medical intractability of epilepsy in children: How certain can we be? *Neurology* 2001;56:1430–1431.
14. Berg AT, Langfitt J, Shinnar S, Vickrey BG, Sperling MR, Walczak T, Bazil C, Pacia SV, Spenser SS. How long does it take for partial epilepsy to become intractable? *Neurology* 2003;60:186–190.
15. Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, Calvalcanti D, Baulac M. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology* 1998;51:1256–1262.
16. Kim YD, Heo K, Park SC, Huh K, Chang JW, Choi JU, Chung SS,

- Lee BI. Antiepileptic drug withdrawal after successful surgery for intractable temporal lobe epilepsy. *Epilepsia* 2005;46:251–257.
17. Sirven JI, Sperling M, Wingerchuk DM. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. *Cochrane Database Syst Rev* 2001;3:CD001902.
 18. Lee YS, Kim H, Wu TX, Wang XM, Dionne RA. Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. *Clin Pharmacol Ther* 2006;79:407–418.
 19. Mohanraj R, Brodie MJ. Diagnosing refractory epilepsy: Response to sequential treatment schedules. *Eur J Neurol* 2006;13:277–282.
 20. Elwes RD, Johnson AL, Shorvon SD, Reynolds EH. The prognosis for seizure control in newly diagnosed epilepsy. *N Engl J Med* 1984;311:944–947.
 21. Collaborative Group for the Study of Epilepsy. Prognosis of epilepsy in newly referred patients: A multicenter prospective study of the effects of monotherapy on the long-term course of epilepsy. *Epilepsia* 1992;33:45–51.
 22. Baulac M. Historical data in the design and interpretation of trials with newly diagnosed patients. *Epilepsy Res* 2006;68:77–81.
 23. Ryvlin P. Defining success in clinical trials—profiling pregabalin, the newest AED. *Eur J Neurol* 2005;12(suppl 4):12–21.
 24. French J. Historical control withdrawal to monotherapy. *Epilepsy Res* 2006;68:74–77.