By Steven Karceski, MD

When to Refer Someone to an Epilepsy Center

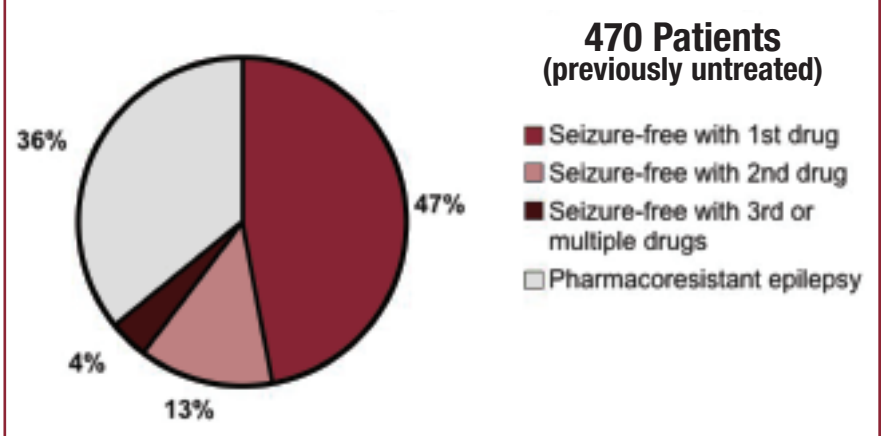
At what point is a case "refractory"? What can a tertiary care center offer that a general practice cannot? Here, an epileptologist explains.

There is no universal agreement as to when it is best for a general neurologist or other physician to refer a challenging case to a comprehensive epilepsy center. Some are referred after their first or second event in order to confirm the diagnosis or to continue the evaluation with more specialized diagnostic techniques that may be unavailable in a general practice.

At times, an early referral is made largely for counseling purposes or for medicolegal clarification. For instance, several states require physicians to report individuals who experience recurrent episodes of loss of awareness. Even one syncopal event may trigger a state's mandatory reporting requirement, particularly if the patient may endanger the lives of others (*e.g.*, a bus driver). However, the laws are not always clear, so a referral can better define the legal implications of the person's illness.

The majority of referrals, however, occur after a patient has already tried (and typically failed) several medications. This means that the person has continued to have seizures despite adequate trials of the antiepileptic drugs. Less often, 20 years may pass before a person is referred to an epilepsy center. At that point, they may have tried nearly all available AEDs, and the neurologist's goal in making the referral is to ask whether the person would be a candidate for epilepsy surgery. The question that we should ask ourselves is: at what point should non-medical options be considered?

Figure 1. Patient Response to AED Treatment



Source: Kwan P, Brodie MJ. Early identification of refractory epilepsy. New England Journal of Medicine 2000;342(5):314-9.

The point at which a general neurologist decides specialized care is necessary depends on his or her own definition of "refractory." The term *refractory* simply means that the seizures do not respond to medication(s). Although a simple idea, there is no universal agreement on how many medicines (or combinations) should be tried before applying this term. This has become a much more contentious issue over the last decade as many new AEDs have become available. As this list continues to grow, the number of possible combinations grows exponentially. In other words, a person could literally spend a lifetime trying different medicines in their multifarious combinations.

There is a certain morbidity (fractures, falls) and mortality (sudden unexplained death in epilepsy patients, or SUDEP) with uncontrolled seizures. During the often lengthy period or medication trial and error, the patient is at risk for both. Here again, the question becomes: when is enough enough? How many trials of medications should one attempt before non-medical options should be considered? When should a referral to an epilepsy center be made?

What the Data Show

Surprisingly, only a few trials have attempted to answer these important questions. The one most quoted was performed by Kwan and Brodie in 2000 and published in the *New England Journal of Medicine*.[1] This study, performed in the United Kingdom, included 525 patients (470 previously untreated) with newly diagnosed seizures who were then followed for an average of five years. Their results showed that the response that a person had to the first (or second) AED strongly predicted whether or not that

person would ever respond to medication (see Figure 1).

In this study, 47 percent responded to the first AED, 13 percent were seizure-free on the second agent and only one percent achieved success with the third monotherapy. Three percent became seizure free on a combination of two medications. In other words, about two-thirds of people with epilepsy will respond to a reasonable number of medication trials, and one-third will not. Further, this information indicates that the determination of refractoriness can be made early in the treatment of the illness.

A nearly identical finding occurred in a 2001 survey of epilepsy experts.[2] In this survey, a group of experts in the United States agreed that after the initial (two or three) trials of seizure medications a person with partial seizures should at least be considered for epilepsy surgery (see Figure 2). In other words, they agreed that once the person's seizures failed to respond to the initial trials of medication their seizures were refractory, and therefore should be considered for epilepsy surgery.

Here again, we encounter the term refractory. These studies suggest that we can make the determination of refractoriness early in the course of a person's illness. In other words, "refractory" does not have to mean that everything imaginable has already been tried. Instead, the term can simply refer to the point at which further medication trials are unlikely to help. It seems reasonable to assume that this would be a good point to refer someone to an epilepsy center.

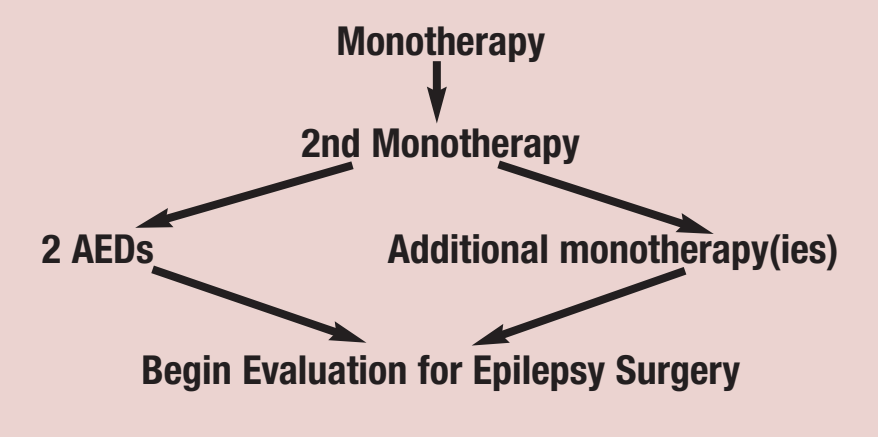
Making the Referral

The first step toward treatment is identifying the type of epilepsy. The diagnosis alone can present its own challenges—an epilepsy center can help in diagnosis, especially if the episodes are vaguely characterized or sound "atypical" for seizures. Once the diagnosis is made, the staff of the epilepsy center can select an appropriate medication. With the long list of possibilities today, this can also be a challenge. Certain medicines may work well for some epilepsies, but may worsen other types of epilepsy.

If it is unclear which medicine(s) to select, a referral can be helpful. A comprehensive epilepsy center, by definition, will have staff well-versed in the nuances of all AEDs, even the newest options. When two or three medications, or a combination of two medicines fails to produce seizure freedom, the seizures should be considered refractory. It is at this point that a referral, or re-referral, to an epilepsy center should be considered much more strongly. In this instance, one should also consider other treatment options such as epilepsy surgery, devices for epilepsy, the ketogenic diet and experimental medications.

A referral to an epilepsy center can accomplish several things. First, if there is any question as to the type of epilepsy (or there is concern about another diagnosis such as nonepileptic seizures), this can be addressed with a reassessment of the history and physical examination, video-EEG and/or newer neuroimaging techniques. For a person with refractory partial seizures, epilepsy surgery may be offered as a treatment option. Finally, the epilepsy center may be involved in clinical trials for investigational medications or newer devices for the treatment of epilepsy; this expands the list of treatment options that a person with refractor epilepsy might consider.

Figure 2. How to Approach Treatment of Partial Epilepsy



Conclusions

The treatment of epilepsy has changed dramatically over the past decade, thanks mostly to the development of new medications, devices for epilepsy and new surgical approaches.

The growing list of treatments offers patients more options; however, it presents the neurologist with greater challenges. The best way to select the optimal therapy or a combination of therapies is not always clear. However, it has become clear that one-third of patients will not respond well to medications alone. This determination can be made early after diagnosis: if the first few medication trials do not produce seizure freedom and a tolerable side effect profile, the person's seizures can be said to be refractory. It is at this point that a person should be referred to an epilepsy center. **PN**

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. New England Journal of Medicine 2000;342(5):314-9.

2. Karceski SC, Morrell MJ, Carpenter D. "The Expert Guideline Series: Treatment of Epilepsy." Epilepsy & Behavior 2001: 2(6): A1-A50