

When Medications Fail To Control Seizures:

A Case for Nonpharmacologic Options

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Introduction

With a prevalence of 1% to 2%, epilepsy is a common neurologic disorder.¹ Not only is it one of the most common conditions seen in neurology practices, but it also affects young people in their prime working and reproductive years. While about 70% of patients with seizures are controlled with medications, approximately 30% are not.^{1,2} Thus, a standard general neurology practice inevitably includes a sizable number of patients with refractory seizures.

A growing concern is that neurologists fail to identify and refer these patients, or do so too late. This is vividly illustrated by 2 facts: 1) the average delay from onset to correct diagnosis of psychogenic nonepileptic seizure (PNES) is 7 years³; 2) for patients who ultimately become seizure-free after surgery, the average delay from seizure onset to referral to an epilepsy surgery center is >15 years.⁴

There are basically 3 reasons why drugs may not work, which will all be discussed in this review:

1. The seizure-like episodes are not epileptic;
2. The medications chosen are not effective for the given epilepsy type; or
3. The epilepsy is medically intractable.

The Misdiagnosis of Epilepsy

The erroneous diagnosis of epilepsy is not rare and represents a significant problem.^{5,6} About one quarter of patients previously diagnosed with epilepsy are eventually found to be misdiagnosed, both in a referral epilepsy clinic and in epilepsy monitoring units.^{5,6} Many patients misdiagnosed as having epilepsy are eventually shown to have PNES⁷ or syncope.^{8,9} Occasionally, other paroxysmal conditions can be misdiagnosed as epilepsy, including complicated migraines, paroxysmal movement disorders, and sleep disorders. However, PNES and syncope are by far the most common conditions mistaken for epilepsy. Very often, electroencephalograms (EEGs) interpreted as providing evidence for epilepsy contribute to this misdiagnosis.^{4,5,10}

Whenever an erroneous diagnosis of epilepsy is made, it is notoriously difficult to “undo.” Subsequent normal EEGs, of course, never exclude the possibility of epilepsy, and it is necessary for the specialist (epileptologist, electroencephalographer) to obtain the actual EEG previously read as abnormal. Surprisingly, the majority of these records show “nameless variants,” ie, fluctuations

Table. Goals That Can Be Achieved Through the Use of EEG Monitoring

- Confirm the diagnosis of epilepsy. This is critical, since a sizable 15% to 30% of patients referred for refractory seizures do not have epilepsy, but have psychogenic nonepileptic seizures.
- Determine whether the epilepsy is localization-related or generalized, as defined by the International League Against Epilepsy.
- Distinguish, among generalized epilepsies, between the idiopathic (formerly called “primary,” now better termed *genetic*) type, and the symptomatic (cause known) and cryptogenic (cause unknown), formerly called “secondary” type.
- Differentiate, among localization-related epilepsies, between mesiotemporal and extratemporal/neocortical epilepsy.

of normal rhythms that do not fit into a well-described EEG waveform.¹⁰ Variants of alpha activity are by far the main offender, especially the widespread, unusually sharply contoured variants, as well as during early periods of drowsiness, when alpha waves become fragmented and isolated.^{10,11}

Psychogenic nonepileptic seizures are by far the most common condition misdiagnosed as epilepsy. The estimated prevalence in the general population is 2 to 33 per 100,000, making this problem nearly as common as multiple sclerosis or trigeminal neuralgia.¹² A number of “red flags,” in addition to the lack of response to antiepileptic drugs (AEDs), are useful in clinical practice, and should raise the suspicion that “seizures” may be psychogenic rather than epileptic. Certain characteristics of the motor (“convulsive”) phenomena are associated with PNES: slow or very gradual onset or termination; discontinuous, interrupted, irregular, or asynchronous (out-of-phase) movements; other specific types of movements (side-to-side head shaking, pelvic thrusting, opisthotonic posturing, bilateral movements with preserved awareness); and weeping.

Electroencephalogram video monitoring allows the diagnosis of PNES to be made with near certainty. In some instances, it is helpful to use provocative techniques or “inductions”—many epilepsy centers use such techniques to aid in the diagnosis. When correctly performed and interpreted (paying specific attention to confirming that the habitual episode was induced), specificity of provocative techniques for diagnosis of PNES approaches 100%, a rare luxury in medicine. Inductions have many advantages, but are somewhat controversial.^{13,14} However, many ethical objections are circumvented by the fact that activations can be performed without the use of placebos.¹³

Despite the availability of EEG video monitoring, which allows PNES to be diagnosed with nearly 100% certainty, the average delay in diagnosis of PNES remains long,³ indicating that the index of suspicion for PNES may not be high enough.

Syncope is the second most common condition

misdiagnosed as epilepsy, largely because syncopal attacks are quite often associated with abnormal movements. This issue has been studied by deliberately inducing syncope in patients, either to test automatic implantable defibrillators,¹⁵ during tilt-table testing,⁹ or in healthy volunteers.¹⁶ In these situations, motor manifestations, either tonic-like or clonic-like, are present in 45% to 90% of attacks,^{9,15,16} explaining why they could easily be described as “convulsions.” Because syncopal episodes are usually not frequent (unlike PNES), and cannot be induced by suggestion, EEG video monitoring is of less value in the diagnosis of the condition. Occasionally, tilt-table testing can trigger a typical attack and lead to the correct diagnosis, but usually the clinician has to rely on patient history alone (precipitating circumstances, prodromes, etc).

Epilepsy With Incorrect Syndromic Diagnosis

The treatment of a “seizure disorder” without any attempt at a more precise syndromic diagnosis can result in ineffective treatment.^{17,18} The most common situation encountered in practice is the use of a narrow-spectrum AED in a patient with an idiopathic generalized epilepsy (IGE) syndrome, such as juvenile myoclonic epilepsy.¹⁹ Narrow-spectrum AEDs include phenytoin (Dilantin, Pfizer; Phenytek, Bertek; others), carbamazepine (Carbatrol, Shire US; Tegretol, Novartis; others), oxcarbazepine (Trileptal, Novartis), gabapentin (Neurontin, Pfizer), and tiagabine (Gabitril, Cephalon). While the choice of AED is of little consequence when treating a localization-related epilepsy, the use of these narrow-spectrum agents in IGE typically fails to control seizures, and in fact may worsen seizure types other than generalized tonic-clonic, such as absence and myoclonic seizures.^{19,20} Since phenytoin and carbamazepine are the 2 most commonly used first-line agents in the United States, this situation arises quite often. Other AEDs (eg, phenobarbital, valproic

acid [Depakene/Depakote, Abbott; others], lamotrigine [Lamictal, GlaxoSmithKline], topiramate [Topamax, Ortho-McNeil], levetiracetam [Keppra, UCB Pharma], and zonisamide [Zonegran, Elan]) are considered “broad-spectrum,” in the sense that they work in all types of epilepsies—localization-related and generalized.

A clear syndromic diagnosis can usually be established with an abnormal EEG, together with the history and examination, but if the routine EEG is normal, the diagnosis may require EEG video monitoring.

Medically Intractable Epilepsy

Definition of intractability. Exactly how many AEDs should be tried, in what combination, and for how long, before deeming epilepsy “intractable” is no longer debated. It is now well known that the likelihood of achieving seizure control declines rapidly after the first few unsuccessful trials, and clinical practice supports the view that when the first few regimens fail, the probability of future control with an AED drops precipitously. Several recent studies have documented this important concept,^{2,21,22} and there is now convincing evidence that *intractability reveals itself early*. While the chances of success with new medications are probably never zero (ie, a new drug may prove to be effective in a given patient), these data would support the idea that nonpharmacologic options should be examined early, as is generally recommended.^{21,23,24} It is also important to recognize that drug failure should be defined as *either* persistent seizures, *or* seizure control obtained only at the expense of causing unacceptable side effects (ie, being seizure-free but unable to walk, think, and/or see because of side effects constitutes a drug failure). Finally, it should be emphasized that in addition to seizure severity and frequency, psychosocial morbidity may be important in the indication for nonpharmacologic treatments, including surgery. For example, a seizure frequency of 3 per year is

enough to prevent driving and can certainly affect employment. Thus, due to these multiple variables, drug failure should be ultimately decided on an individual basis and in conjunction with patients and their families. In general, referral to an epilepsy center is appropriate after the failure of 2 drug regimens.

Nonpharmacologic options for medically intractable epilepsy. The nonpharmacologic options for patients whose epilepsy has been found to be medically intractable include the ketogenic diet, vagus nerve stimulation (VNS, Cyberonics), and resective surgery. The exact role of each of these therapies is beyond the scope of this review but has been discussed elsewhere.²¹ An illustrative point is that for patients who are eventually rendered seizure-free with a temporal lobectomy, the average delay is >15 years.⁴ This may be related to misconceptions about efficacy and safety of epilepsy surgery.

A recently published expert opinion consensus on the treatment of epilepsy also recommends that referral for nonpharmacologic treatments should be made early, rather than as a last resort.²⁵ A relatively common situation is that acceptable seizure control is obtained at the expense of severe side effects that impair quality of life (eg, patients report extreme fatigue, clouded thinking, dizziness, etc). This, in fact, constitutes drug failure, but this concept is often overlooked, and patients are often taught that no alternatives exist outside of “more medications.” A possible reason may be the desire of physicians to “keep their patients” for a variety of reasons, including to enroll some in industry-sponsored clinical trials.

The consequences of years of ongoing seizures are well known, and include severe psychosocial effects^{26,27} that may not resolve if seizure-free status is achieved too late. Postoperative outcome also appears to be adversely affected by a longer duration of chronic seizures. In addition, mesial temporal lobe epilepsy may well be a progressive disorder,²⁷ and is particularly likely to become intractable.²⁸ Finally, it has been argued that the risk of death from ongoing seizures is higher than that from a typical temporal lobectomy.^{27,29,30}

Whatever the reasons for the poor referral pattern, epilepsy surgery is the standard of care when medications fail, and thus it can be argued that not referring patients with intractable seizures to the epilepsy center may raise issues of *ethics*. Failing to offer the possibility of (and evaluation for) nonpharmacologic treatments (eg, surgery, VNS, ketogenic diet) amounts to withholding information, and as such violates the principle of autonomy (letting patients decide if they are interested in these options). It also violates the principle of beneficence (providing the best available treatment). Specifically, it is probably unethical to enroll patients for investigational treatments (eg, drug studies) before at least *offering* an evaluation at a comprehensive (surgical) epilepsy center.



First Things First: An Accurate Diagnosis With EEG Video Monitoring

When 2 AEDs fail and seizures continue, EEG video monitoring should be performed. Some guidelines have stated that referral to a specialized epilepsy center is appropriate if seizure control is not achieved within 9 months by the general neurologist. Certainly, if seizures occur often (ie, weekly or more frequently than that), EEG video monitoring is indicated. In the vast majority of situations, the clinical data, EEG video monitoring, and high-quality magnetic resonance imaging with dedicated epilepsy protocols allow the neurologist to achieve the goals outlined in the Table (page 37). Based on the precise classification of the epilepsy syndrome (and not just the seizure type), the options can then be examined and presented to the patient.

Conclusion

The general tendency not to refer or to refer too late is a serious problem. Epilepsy is one area of neurology in which patients can actually be cured and have their lives radically changed. Perhaps general neurologists believe that these patients are rare. Every general neurology practice is likely to see such patients, and one that never refers them to the epilepsy center is in all likelihood failing to identify them. A recent randomized trial of surgery in patients with poorly controlled temporal lobe epilepsy³⁰ strongly argues for the superiority of surgery over medical therapy in terms of seizure control, quality of life, rates of employment, and school attendance. Another upcoming randomized, controlled US trial may help further,²⁷ and many patients could certainly testify that their lives have been enhanced as a result of surgery.³¹ Education about epilepsy surgery is seriously needed, both for the public and for healthcare professionals, including neurologists, as epilepsy surgery continues to be underutilized.

One third of patients with seizures do not respond to drugs. Most of them can be helped by the specialized epilepsy center, by rectifying an erroneous diagnosis of epilepsy, precisely defining the type of epilepsy and which drug should be used, or by determining which nonpharmacologic treatment is most appropriate. While there may be variability in this general approach, what is clearly inappropriate is to indefinitely perpetuate trials of AEDs in endless combinations.

References

- Cockerell OC, Johnson AL, Sander JW, Hart YM, Shorvon SD. Remission of epilepsy: results from the National General Practice Study of Epilepsy. Epilepsy Research Group, National Hospital for Neurology and Neurosurgery, London, UK. *Lancet*. 1995;346:140-144.
- Kwan P, Brodie M. Early identification of refractory epilepsy. *N Engl J Med*. 2000;342:314-319.
- Reuber M, Fernandez G, Bauer J, Helmstaedter C, Elger CE. Diagnostic delay in psychogenic nonepileptic seizures. *Neurology*. 2002;58:493-495.

- Benbadis SR, Heriaud L, Tatum WO, Vale F. Epilepsy surgery, delays, and referral patterns. *Seizure*. In press.
- Smith D, Defalla BA, Chadwick DW. The misdiagnosis of epilepsy and the management of refractory epilepsy in a specialist clinic. *QJM*. 1999;92:15-23.
- Scheepers B, Clough P, Pickles C. The misdiagnosis of epilepsy: findings of a population study. *Seizure*. 1998;7:403-406.
- Benbadis SR. Psychogenic seizures. *eMedicine Journal* [serial online]. 2002. Available at: <http://www.emedicine.com/neuro/topic403.htm>.
- Eiris-Punal J, Rodriguez-Nuñez A, Fernandez-Martinez N, et al. Usefulness of the head-upright tilt test for distinguishing syncope and epilepsy in children. *Epilepsia*. 2001;42:709-713.
- Zaidi A, Clough P, Cooper P, Scheepers B, Fitzpatrick AP. Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. *J Am Coll Cardiol*. 2000;36:181-184.
- Benbadis SR, Tatum WO. The overinterpretation of EEGs: a common cause for the misdiagnosis of epilepsy? In preparation.
- Benbadis SR, Rielo D. EEG atlas: normal awake EEG. *eMedicine Journal* [serial online]. 2002. Available at: <http://www.emedicine.com/neuro/topic674.htm>.
- Benbadis SR, Hauser WA. An estimate of the prevalence of psychogenic non-epileptic seizures. *Seizure*. 2000;9:280-281.
- Benbadis SR. Provocative techniques should be used for the diagnosis of psychogenic nonepileptic seizures. *Arch Neurol*. 2001;58:2063-2065.
- Gates JR. Provocative testing should not be used for nonepileptic seizures. *Arch Neurol*. 2001;58:2065-2066.
- Aminoff MJ, Scheinman MM, Griffin JC, Herre JM. Electrocardiac accompaniments of syncope associated with malignant ventricular arrhythmias. *Ann Intern Med*. 1988;108:791-796.
- Lempert T, Bauer M, Schmidt D. Syncope: a videometric analysis of 56 episodes of transient cerebral hypoxia. *Ann Neurol*. 1994;36:233-237.
- Benbadis SR. Observations on the misdiagnosis of generalized epilepsy as partial epilepsy: causes and consequences. *Seizure*. 1999;8:140-145.
- Benbadis SR, Lüders HO. Epileptic syndromes: an underutilized concept. *Epilepsia*. 1996;37:1029-1034.
- Lancman ME, Asconapé JJ, Penry JK. Juvenile myoclonic epilepsy: an underdiagnosed syndrome. *J Epilepsy*. 1995;8:215-218.
- Snead OC 3rd, Hosey LC. Exacerbation of seizures in children by carbamazepine. *N Engl J Med*. 1985;313:916-921.
- Benbadis SR, Tatum WO IV, Vale FL. When drugs don't work: an algorithmic approach to medically intractable epilepsy. *Neurology*. 2000;55:1780-1784.
- Kwan P, Brodie MJ. Effectiveness of first antiepileptic drug. *Epilepsia*. 2001;42:1255-1260.
- Anonymous. Patient referral to specialty epilepsy care. *Epilepsia*. 1990;31:S10-S11.
- Engel J Jr. Surgery for seizures. *N Engl J Med*. 1996;334:647-656.
- Karceski S, Morrell M. The expert consensus guideline series: treatment of epilepsy. *Epilepsy & Behavior*. 2001;2(6 suppl):A1-A50.
- Engel J Jr, Bandler R, Griffin NC, Caldecott-Hazard S. Neurobiological evidence for epilepsy-induced interictal disturbances. *Adv Neurol*. 1991;55:97-111.
- Engel J Jr. The timing of surgical intervention for mesial temporal lobe epilepsy: a plan for a randomized clinical trial. *Arch Neurol*. 1999;56:1338-1341.
- Semah F, Picot MC, Adam C, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology*. 1998;51:1256-1262.
- Sperling MR, O'Connor MJ, Saykin AJ, Plummer C. Temporal lobectomy for refractory epilepsy. *JAMA*. 1996;276:470-475.
- Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized, controlled trial of surgery for temporal lobe epilepsy. *N Engl J Med*. 2001;345:311-318.
- University of South Florida/Tampa General Hospital Comprehensive Epilepsy Program Surgery Book. Available at <http://epilepsy.usf.html>.