Epilepsy Currents
2019, Vol. 19(5) 299-301

DOI: 10.1177/1535759719868466
journals.sagepub.com/home/epi
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Predicting Response to Treatment of Epileptic Seizures: How Much Time and How Many AEDs Do We Need to Try?

Identification of Patients Who Will Not Achieve Seizure Remission Within 5 Years on AEDs

Hughes DM, Bonnett LJ, Czanner G, Komárek A, Marson AG, García Fiñana M. *Neurology*. 2018;91(22):e2035-e2044. doi:10.1212/WNL.0000000000006564. Epub 2018 Nov 2. PMID: 30389894.

Objective: To identify people with epilepsy who will not achieve a 12-month seizure remission within 5 years of starting treatment. Methods: The Standard and New Antiepileptic Drug (SANAD) study is the largest prospective study in patients with epilepsy to date. We applied a recently developed multivariable approach to the SANAD data set that takes into account not only baseline covariates describing a patient's history before diagnosis but also follow-up data as predictor variables. Results: Changes in number of seizures and treatment history were the most informative time-dependent predictors and were associated with history of neurologic insult, epilepsy type, age at start of treatment, sex, and having a first-degree relative with epilepsy. Our model classified 95% of patients. Of those classified, 95% of patients observed not to achieve remission at 5 years were correctly classified (95% confidence interval [CI]: 89.5%-100%), with 51% identified by 3 years and 90% within 4 years of follow-up. Ninety-seven percent (95% CI: 93.3%-98.8%) of patients observed to achieve a remission within 5 years were correctly classified. Of those predicted not to achieve remission, 76% (95% CI: 58.5%-88.2%) truly did not achieve remission (positive predictive value). The predictive model achieved similar accuracy levels via external validation in 2 independent United Kingdom-based data sets. Conclusion: Our approach generates up-to-date predictions of the patient's risk of not achieving seizure remission whenever new clinical information becomes available that could influence patient counseling and management decisions.

Commentary

There are many potentially helpful avenues for both diagnosis and treatment of epileptic seizures, which fortunately result in excellent outcomes for the majority of patients. However, despite treatment successes, many patients have an unknown etiology of epilepsy,[1] highlighting shortcomings in diagnostic testing to determine the underlying etiology of seizures, and some patients remain "drug-resistant" despite treatment with multiple appropriate antiepileptic mediations.[2] The likelihood of good outcome for most patients with epilepsy is an important clinical fact we should be sure to communicate to patients. However, the uncertainty of long-term outcome in epilepsy, especially during the initial stages of diagnosis and treatment, remains a justified concern for patients. While there are factors that predict outcome in epilepsy, the multifactorial etiologies of epileptic seizures overall often make prognostication difficult for individual patients. Therefore, there is a need for better measures for prognosis for patients with epilepsy.

Categories for etiologies of epileptic seizures are structural, genetic, infectious, metabolic, immune, and unknown,[1] highlighting the multifactorial causes for epilepsy. Looking to factors in these categories, and therefore using underlying etiology to determine long-term prognosis, provides a potential objective pathway to predict response to treatment. However, closely examining specific structural and genetic etiologies highlights difficulties for this approach and serves as an illustration of the complexity of establishing prognosis.

Hippocampal atrophy and signal changes on structural neuroimaging represent a valid biomarker for mesial temporal sclerosis (MTS), which is a cause of epileptic seizures.[3] Initial early studies, especially those from epilepsy surgery series in refractory temporal lobe epilepsy (TLE), posited MTS as a marker of refractory epilepsy. However, in a study of 101 patients with mild or benign TLE,[3] 39 (38.6%) had evidence of MTS on magnetic resonance imaging, indicating the variability of long-term prognosis associated with MTS in TLE. The differences in prognosis of TLE related to MTS between studies likely reflects the differences in associated patient cohorts, with those presenting for epilepsy surgery representing a refractory subgroup of all patients presenting with TLE.

Given the genetic etiology of seizures, genetic testing also holds promise to help determine outcomes in epilepsy.

However, variability of epilepsy phenotype associated with genetic factors often confounds their use as a reliable stand-alone test for prognosis. The gene for the alpha1-sodium channel subunit (SCN1A) plays a major role in the etiology of severe myoclonic epilepsy of infancy or Dravet syndrome. However, SCN1A mutations are also associated with a number of other milder phenotypes. Interestingly, even intragenetic deletion of the SCN1A gene within a single family shows marked variability in associated phenotype, with some family members showing severe cognitive impairment and medically refractory epilepsy, while others have normal cognition and complete seizure freedom after presenting with childhood seizures.[4]

While tests defining etiology of epileptic seizures play an important role in many aspects of clinical care, they unfortunately often fall short in predicting the natural history of epileptic seizures and response to treatment. Therefore, frequently our best option in clinical practice is to use response to antiepileptic drug (AED) treatment itself as a guide to define refractory, or drug-resistant, epilepsy.[2] In this context, it is very important to use the clinical response to treatment with adequate doses of AEDs, rather than AED plasma levels, to guide treatment. Much like factors of hippocampal atrophy and SCN1A genetic abnormalities, there is wide variability in clinical outcome related to AED plasma levels. Schmidt and Haenel[5] prospectively followed 84 patients taking monotherapy phenytoin, phenobarbital, and carbamazepine, titrating medication doses until patients were seizure free for 1 year. The average therapeutic plasma concentration of phenytoin in 53 patients was 17.9 μg/mL (range, 3 to 50 μg/mL). Using the typical "therapeutic" range of 10 to 20 μg/mL for phenytoin, 21% of patients achieved controlled with "low" levels, and 30% of patients achieved control with "high" levels. Given the variability in AED levels for adequate seizure control, titrating medication to the either seizure control or the highest clinically tolerated dose, rather than a specific AED level, remains an important criterion for defining drug resistant epilepsy.[2]

Within the context of our dependence on therapeutic outcomes of AED therapy to make appropriate treatment decisions for patients, the study by Hughes et al provides important information for patient care. Using data from the Standard and New Antiepileptic Drug (SANAD) study of new-onset epilepsy in the United Kingdom,[6,7] Hughes et al found 1577 patients who achieved at least 1 year of continuous remission within 5 years of starting treatment, and 175 patients who did not. Using the idea that prognosis changes over time, and evaluating variables to assess treatment failure during ongoing visits during the study, they define a paradigm that includes (1) the number of AEDs failed; (2) the occurrence of a seizure since the last clinic visit; and (3) whether a change in AED occurred during the last clinic visit. Applying these parameters at each clinic visit allowed independent prognostication of outcome at each time point, and correlated with other static factors to assess prognosis which included age of onset, type of epilepsy, family history, and number of seizures before treatment.

A major strength of the study includes external validation of the predictive model in 2 additional United Kingdom-based study data sets, the Multicentre Study of Early Epilepsy and Single Seizures (MESS) and the National General Practice Study of Epilepsy (NGPSE) studies. Application of the predictive model showed similar results in both the MESS and NGPSE cohorts.

For classification of no remission and remission groups, the predictive model required an average of 3.9 AEDs and mean time of approximately 3 years. Therefore, the results of this study indicate a greater number of AED trials are necessary to confirm drug-resistance than indicated in previous criteria, which defined drug resistance after failure of 2 adequate AED trials.[2] This definition strongly relied on a study of a large cohort of patients from Glasgow, Scotland, which showed that after failure of 2 monotherapy AEDs, the chance of the use of a third drug to produce seizure freedom was $<10\%$.[8] However, other studies show that patients respond favorably to >2 AED trials,[9,10] so the current study gives further evidence that persistence in treatment with AEDs, typically working with at least 4 AEDs over approximately 3 years, will yield positive results for patients.

Treatment of patients with epilepsy is often complex. The study by Hughes et al provides pertinent information about the typical number of AEDs and amount of time needed to work through adequate initial AED treatment before considering other treatment options, such as epilepsy surgery. Given the difficulty of establishing prognosis for epileptic seizures, these findings will be especially helpful in guiding treatments for our patients.

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