

The Early Identification of Candidates for Epilepsy Surgery

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The effectiveness of resective surgery for the treatment of carefully selected patients with medically intractable, localization-related epilepsy is clear. Seizure-free rates following temporal lobectomy are consistently 65% to 70% in adults^{1,2} and 68% to 78% in children.^{3,4} Extratemporal resections less commonly lead to a seizure-free outcome, although one recent childhood series reported a seizure-free rate of 62% following extratemporal epilepsy surgery.⁵ With both temporal and extratemporal resections, additional patients have a reduction in seizures following surgery but are not completely seizure free. The identification of favorable surgical candidates has been the subject of extensive research, and many investigators have examined predictors of outcome following epilepsy surgery. However, the early identification of the potential epilepsy surgery candidate and the optimal timing of surgery have only occasionally been addressed in the literature. This issue is methodologically challenging to study since studies require large numbers of patients with new-onset partial epilepsy who are followed over time. The purpose of this article is to review the current ability for early prediction of medical intractability in patients with surgically remediable epilepsy. Emphasis will be placed on the early prediction of intractable temporal lobe epilepsy in children and adolescents, since temporal lobectomy remains the prototype epilepsy surgery, and early surgery may improve psychosocial outcome in younger patients.^{6,7}

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THE PROGNOSIS OF EPILEPSY IN ADULTS AND CHILDREN

Population-based studies of epilepsy patients of all ages have shown a mixed prognosis with 70% to 80% of patients becoming seizure free for 3 to 5 years,^{8,9} although adults with complex partial seizures have the poorest prognosis for complete seizure control.¹⁰ Studies of pediatric patients with various seizure types (not limited to partial epilepsy) indicate a 90% chance of achieving a 1-year remission¹¹ and a 76% chance of being seizure free for 5 years.¹² Such data are helpful to provide a broad overview but have limited applicability to individual patients. Studies on the prognosis of particular epilepsy syndromes (such as temporal lobe epilepsy

[TLE]) would be more clinically useful but are limited. The best available evidence on the prognosis of adult TLE is found in a hospital-based cohort study from France¹³ in which 80% of 500 adults with TLE had ongoing seizures with medical therapy, making TLE the most refractory form of adult partial epilepsy.

The prognosis of childhood TLE is more uncertain. Older hospital-based studies of childhood TLE suggest a poor prognosis. Lindsay et al¹⁴ studied a series of 100 children with TLE, beginning in 1948. When followed into adulthood, only 33% were seizure-free and living independently. Another series found only 10% of 63 children with TLE to be seizure free after 6 years of medical treatment.¹⁵ Patients in these studies were diagnosed before the use of magnetic resonance imaging (MRI) scans and video electroencephalogram (EEG), and some of the patients had

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evidence of brain disease outside of the temporal lobe,¹⁶ so the contemporary relevance of these studies is uncertain. Childhood TLE is almost certainly a more heterogeneous entity than these studies suggest, and small series have proposed benign variants of TLE in childhood.¹⁷ Studies limited to children with newly diagnosed complex partial seizures (many of whom have TLE) indicate remission rates of 59% to 63%.^{18,19} It has been suggested that children with cryptogenic TLE likely have a more favorable prognosis than children with temporal lobe lesions on MRI,²⁰ but this important point has not been demonstrated in a prospective study.

MEDICAL INTRACTABILITY

An issue inextricably linked to prognosis is medical intractability, where additional medical therapy is unlikely to completely control seizures and alternate treatment is considered. Hospital-based studies of adults with partial seizures indicate that patients who have persistent seizures despite an initial antiepileptic drug (AED) trial have only a 12% to 14% chance of complete seizure control with alternate AED monotherapy^{21,22} and a 3% to 11% chance with AED polytherapy.^{21,23} Consequently, many adult epilepsy centers define medical intractability as persistent seizures despite 2 years and 2 maximally tolerated AED trials.²⁴

Medical intractability is more challenging to define in children because of the tendency of many forms of pediatric epilepsy to remit with time. For example, a population-based study in Nova Scotia of children with generalized tonic-clonic, partial, and secondarily generalized seizures found that remission of seizures occurred in 42% of children who failed their first AED trial,²⁵ a vastly different conclusion than from hospital-based data in adults. The Nova Scotia study, however, was not limited to TLE, and no specific information is available on the impact of initial AED failure in children with TLE.

DELAY IN EPILEPSY SURGERY

Because of the irreversible nature of surgery and uncertainties surrounding prognosis (especially in children), it is not surprising that patient referral for epilepsy surgery is delayed. A recent adult temporal lobectomy series of 89 patients reported a mean age of epilepsy onset of 13.1 years but a mean age at surgery of 31.9 years, resulting in a mean duration of epilepsy of 18.8 years prior to surgery.¹ The delay occurred despite a median seizure frequency of 8 per month. In a childhood series, patients were referred for temporal lobectomy after receiving an average of 7 to 8 AED trials and 9 years after the onset of epilepsy.²⁶ Causes for such delay include lack of timely referral to epilepsy surgery centers from primary care physicians and community neurologists, multiple AED trials in patients with little chance of remission, lack of appreciation that even occasional complex partial seizures can be disabling, and patient reluctance to undergo irreversible surgery. Although surgery must clearly be avoided in patients destined to enter remission within a reasonable period of time, excessive delay in pursuing effective surgical therapy may risk serious psychosocial and physical disability.

BENEFITS AND RISKS OF EARLY SURGERY

It has been postulated that the early use of successful epilepsy surgery, especially in children and adolescents, could minimize the long-term physical and psychosocial consequences of intractable epilepsy.^{6,7} Children and adolescents with epilepsy are clearly at increased risk for considerable psychosocial, vocational, and cognitive dysfunction, which persists into adulthood.²⁷ A population-based study of 337 children and young adults with normal intelligence and epilepsy found the following: school failure in 34% of patients, special education utilization in 34%, mental health consultation in 22%, unemployment in 20%, social isolation in 27%, and inadvertent pregnancy in 12%.²⁸ Causes of such dysfunction are complex and difficult to study but may include underlying brain abnormalities, effects of recurrent seizures, AED toxicity, and psychosocial factors such as excessive dependency and overprotection.²⁸ If ongoing seizures or the psychosocial consequences of the seizures are largely responsible for this dysfunction, then earlier use of effective surgical therapy could reduce these long-term problems.

However, the ability of early surgery to actually improve long-term outcome has not been demonstrated and is particularly challenging to study. One series that supports this contention included 50 adolescents who underwent temporal lobectomy at a mean age of 15.8 years.⁶ Mean age at epilepsy onset was 7.5 years, with the time between epilepsy onset and surgery averaging 8.3 years. Postoperatively, 78% were seizure free or experienced auras only. No changes were seen in Wechsler Intelligence Scale scores after surgery, but there was a greater likelihood of improvement in verbal and perceptual intelligence quotients with a shorter time between seizure onset and surgery.

The obvious risk of early surgery is performing an invasive and irreversible procedure in a patient who ultimately would have become seizure free within a reasonable period of time, before irreversible psychosocial consequences ensued. The elusive goal of optimizing the timing of epilepsy surgery can be summarized and oversimplified as this: Not too early, but not too late. The current rule of thumb regarding timing of epilepsy surgery—at least 2 years and 2 AED trials—is likely not adequate for all types of surgically remediable epilepsy, especially in children. Regardless, the available evidence clearly suggests that most patients undergo epilepsy surgery well beyond 2 years and 2 AED trials.

A randomized clinical trial of early surgical intervention for mesial TLE has been proposed in the United States but has not yet begun.²⁹ Patients aged 12 years and older with refractory TLE of less than 2 years' duration would be randomized to surgery or an additional 2 years of medication. The challenges of successfully completing such a study are huge. Recruiting adequate numbers of patients willing to agree to randomization will be difficult. Another complex issue is whether patients willing to agree to such a randomization are generalizable.³⁰ The only randomized trial comparing epilepsy surgery to medical therapy was recently completed in Ontario, Canada,³¹ but randomization was accommodated via an

existing 1-year waiting list for epilepsy surgical evaluations, and the study did not address the issue of early surgical intervention. The proposed US trial will not be able to rely on a long waiting list to make randomization more attractive to potential study subjects. If randomized trials are not practical, other study designs such as cohort studies (retrospective or prospective) should be considered to answer questions regarding early surgery.

PREDICTING OUTCOME IN CHILDHOOD EPILEPSY

Because of the uniquely complicated issues surrounding prognosis in childhood epilepsy, several cohort studies have attempted to identify predictors of outcome for childhood epilepsy, although not necessarily with an eye on early surgery. One study looked at predictors of remission, and 3 studies examined predictors of intractability. A population study of 504 patients in Nova Scotia found that age younger than 12 years at onset, normal intelligence, no prior neonatal seizures, and fewer than 21 seizures before treatment were “reasonably accurate” predictors of remission.³² A population study of 178 patients in Finland found that poor short-term outcome of AED therapy, occurrence of status epilepticus, high initial seizure frequency, and remote cause were independent predictors of intractability.³³ A hospital-based study of 172 patients in the United States found a history of infantile spasms, early age of onset, remote symptomatic cause, and history of status epilepticus were independent predictors of intractability.³⁴ Lastly, a hospital-based study of 466 children in the Netherlands developed a regression model to predict outcome in newly diagnosed epilepsy. Variables such as number of seizures prior to treatment, seizure type, cause, and initial response to therapy were used in the model. The predictive model was correct in 66% of children in whom a “poor” outcome was predicted and 79% of children in whom a “not poor” outcome was predicted. Sensitivity of the model was only 47% and specificity 89%.³⁵ It is important to note that none of these studies were “syndrome specific” and thus were limited by the great heterogeneity of childhood epilepsy.

SYNDROME-SPECIFIC CLINICAL PREDICTION MODELS

A potential solution to the unanswered questions regarding optimal timing of epilepsy surgery lies in the development of clinical prediction models tailored to specific epilepsy syndromes. A clinical prediction model³⁶⁻³⁸ is a decision-making tool that includes a set of variables obtained from the history, physical examination, or simple diagnostic tests and provides the probability of an outcome or suggests a diagnostic or therapeutic course of action.³⁷ Predictor variables must be well specified, clinically appropriate, reliably measured between observers, reproducible between centers, and dependably available via medical record review; outcomes must be clearly defined and clinically important. Prediction models have been developed for several acute and chronic medical conditions, such as myocardial infarction, pneumonia, men-

ingitis, chronic renal disease, lymphoma, and prostate cancer.^{37,38} Prediction models are usually constructed using retrospective cohort data and then subsequently validated in a prospective cohort study.

A clinical prediction model designed to predict outcome in patients with TLE could include variables such as age of epilepsy onset, presence of early risk factors for epilepsy (such as a history of febrile seizures, central nervous infection, or serious head trauma), MRI results, family history of epilepsy, and response to the initial AED trial. Other variables such as suspected cause of epilepsy, number of seizures prior to treatment, presence of developmental delay or mental retardation, abnormalities in the neurological examination, and EEG findings could also be included if the information is available, accurate, and reproducible between examiners and centers. A reasonable outcome variable could be as simple as a dichotomous seizure frequency classification (seizure free: yes/no), a continuous variable such as number of seizures per month, or a score on a health-related quality of life instrument. For models initially developed using retrospective data, the available data in the medical records may limit the choice of the outcome variable to a dichotomous seizure frequency classification.

At The Children's Hospital of Philadelphia, we are constructing a clinical prediction model designed for the early identification of children with TLE destined to have refractory seizures at 2 years after epilepsy onset. The accuracy of a 2-year outcome in identifying longer-term outcomes will also be examined. Preliminary data³⁹ have suggested that the presence of an early risk factor for epilepsy or a temporal lobe MRI abnormality is linked to a poor response to initial AED trials, with only 16% of children becoming seizure free. Conversely, absence of early risk factors and normal findings on MRI scan were linked to a better outcome, with 62% of children becoming seizure free. These and other variables are being studied to identify accurate predictors of outcome at 2 years after epilepsy onset. If the 2-year outcome can be predicted early, and if the 2-year outcome reflects the longer-term outcome, then perhaps temporal lobectomy could be considered even earlier than 2 years after epilepsy onset in some patients.

Prediction models can be evaluated like diagnostic tests, using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). For example, the PPV of a model to identify patients destined to develop refractory TLE is the percentage of patients predicted to develop refractory TLE who actually do so ($PPV = \text{true positives} / [\text{true positives} + \text{false positives}]$). In contrast, the NPV is the percentage of patients predicted to be seizure free who actually are ($NPV = \text{true negatives} / [\text{true negatives} + \text{false negatives}]$). Clearly, any prediction model with the intent of identifying candidates for epilepsy surgery must have a high PPV (ie, very few false positives) so that patients are not unnecessarily subjected to surgery.

Another considerable challenge in the construction of a prediction model is the inclusion of patients with an appropriate mixture of disease severity. Models constructed based on data from epilepsy surgery referral centers will clearly be biased toward patients with poor out-

comes and thus will have limited generalizability. It is easy to imagine an epilepsy surgery referral center constructing a model which demonstrates that the presence of a temporal lobe lesion on MRI scan and failure of the first AED trial predicts a poor outcome with a very high PPV. Of course, missing from such a study are an unknown number of patients with abnormalities on MRI and first AED trial failures who became seizure free while receiving alternative AED therapy and thus were never referred to the tertiary care center. Multicenter data from epilepsy surgery centers would not address this potentially serious bias.

As challenging as it is to obtain, there is no substitute for population-based data in the study of epilepsy prognosis. As epilepsy surgery (especially temporal lobectomy) becomes more readily available, investigators who promulgate treatment recommendations must work diligently to ensure that recommendations generated at tertiary care centers are generalizable to the broader population. The effectiveness of epilepsy surgery is clear, but challenging work remains to be done to clarify and optimize the timing of epilepsy surgery, especially in children and adolescents.

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