The Timing of Surgical Intervention for Mesial Temporal Lobe Epilepsy

A Plan for a Randomized Clinical Trial

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It is estimated that 20% of patients with epilepsy have seizures that cannot be controlled by antiepileptic drug therapy. Approximately half of these patients are potential candidates for surgical treatment. Based on a prevalence of epilepsy in the United States of 0.5% to 1.0%, there should be more than 100,000 patients with poorly controlled epilepsy who might benefit from surgical intervention. Data obtained from an international conference on surgical treatment for the epilepsies held in 1992 indicated that only 1500 therapeutic surgical procedures were performed for epilepsy in the United States in 1990. With increasing interest in epilepsy surgery, this number may have doubled over the past 8 years. Nevertheless, there appears to be an extraordinary underutilization of this effective alternative treatment for a common and seriously disabling neurological disorder. Similar statistics can be found in every industrialized country, and surgical treatment for epilepsy is all but completely unavailable in the developing world.

THE PROBLEM

Major factors that account for continued underutilization of surgical treatment for epilepsy include concerns regarding expense and invasiveness and persistent questions about efficacy. However, tremendous recent advances, particularly in neuroimaging and surgical techniques, have greatly enhanced the safety and efficacy of epilepsy surgery, increased the numbers of patients who might be considered to be surgical candidates, and reduced costs by eliminating the need for intracranial electroencephalogram (EEG) recording in the majority of cases. Despite innumerable well-documented reports in the literature demonstrating that surgical intervention can completely eliminate disabling seizures and greatly improve quality of life in appropriately selected patients, physician referral and third-party coverage is undoubtedly negatively influenced by the fact that surgery as a treatment for epilepsy has never been evaluated with a randomized controlled trial (RCT). A primary problem in designing such an RCT is concern on the part of epilepsy surgery teams who would be performing the study that it would be unethical to deny patients what they believe to be a definitive treatment. Nevertheless, there is universal uncertainty regarding the question of when surgical treatment should be offered.

THE EQUIPOISE

There Are Inadequate Data to Determine the Timing of Surgical Intervention

Although it is the general experience of epileptologists that surgical outcome is better with early surgical intervention than when patients suffer intractable seizures for many years, there is a paucity of published data to support this contention and virtually no data from the clinical literature to indicate the best time to perform therapeutic surgery. Among patients with complex partial seizures, once carbamazepine and phenytoin therapy have failed, the chances that another drug or drug combinations will completely eliminate seizures appear to be extremely small. Furthermore, complex partial seizures typically become intractable during adolescence or
early adulthood, when disabling seizures can have an irreversibly negative effect on social and vocational development. If complex partial seizures in these patients continue to be disabling after a trial of high-dose monotherapy with the 2 or 3 most appropriate drugs, it is conceivable that seizures could still be brought under complete control with other drug regimens or spontaneously remit. However, the likelihood that this would occur and the effect of even rare continued seizures at this critical age on future quality of life are unknown. Success of pharmacotherapy is usually measured as seizure reduction, whereas surgical therapy is aimed at complete elimination of disabling seizures. On the other hand, there is always a risk of serious adverse effects from surgical intervention. Therefore, there is true clinical equipoise regarding whether surgical treatment at this time would yield better results than continued aggressive medical therapy. There are no published data to support either therapeutic strategy, and an RCT is ethically justified.

**Surgical Treatment Does Not Need to Be a “Last Resort”**

Physicians fail to refer patients for epilepsy surgery or refer them too late to reverse disabling psychosocial consequences of epilepsy because they consider this alternative treatment to be a “last resort” for medically intractable seizures. However, with so many antiepileptic drugs now available, the concept of “medical intractability” has no practical meaning; it would take more than a lifetime to carry out appropriate trials of every agent (as monotherapy in combination) on any given patient. If early (rather than late) surgical intervention provides the best opportunity not only to completely eliminate habitual seizures but also to prevent or reverse disabling psychosocial consequences, it is unlikely that the best medical practice in every case would be to prove absolute medical intractability before considering surgical intervention.9-11

Dogged persistence in pharmacotherapy is usually predicated on the belief that seizures must be amenable to medication and it is merely a matter of finding the right drug regimen. It is very common, if not the rule, to see patients go from one physician to another for many years before referral is eventually made to an epilepsy center. By this time, the patient may be well into the third decade of life or much older, and continuing severely disabling seizures may have compromised the acquisition of skills necessary to support a normal lifestyle. Surgery at this time is usually successful in eliminating seizures, but too often the patient does not then become gainfully employed, get married, or have children, but rather remains dependent on family and the welfare system.12 On the other hand, patients who were able to complete school, find work, and become socially involved with others prior to surgery do not become gainfully employed, get married, or have children, but rather remains dependent on family and the welfare system.12 On the other hand, patients who were able to complete school, find work, and become socially involved with others prior to surgery despite their seizures do extremely well postoperatively.10,12

**Criteria for Early Surgical Intervention**

**Could Be Developed for Specific Surgically Remediable Syndromes**

The development of referral criteria for optimal utilization of surgical treatment requires clear and convincing data on when to abandon pharmacotherapy in particular forms of disabling epilepsy. An important recent advance has been the identification of specific surgically remediable epileptic syndromes: conditions with relatively well-known pathophysiologies and natural histories, and seizures that are typically medically refractory but can be cured by surgery.1,6 It is now possible to recognize many of these disorders very early in their course using noninvasive diagnostic techniques. One can then legitimately question, for specific conditions, when to stop trials of medications and offer surgical treatment. Waiting too long could risk irreversible psychosocial consequences and even reduce chances for complete elimination of disabling seizures,13,14 while operating too early might introduce unnecessary risks of surgery for patients whose seizures would eventually come under medical control.

**THE STUDY POPULATION**

Mesial Temporal Lobe Epilepsy Is the Ideal Syndrome for an RCT to Determine the Timing of Surgical Intervention

The appropriate epileptic syndrome for an RCT of early surgical intervention is mesial temporal lobe epilepsy (MTLE), that form of temporal lobe epilepsy associated with hippocampal sclerosis.15,16 Characteristic history, ictal behavior, and results of electrophysiological and neuroimaging studies permit reasonably accurate early diagnosis in most patients, and according to literature reports, 70% to 90% of patients can expect to become seizure-free following anteromesial temporal lobectomy.10,11,17 Mesial temporal lobe epilepsy is also the most common difficult-to-treat epileptic syndrome18,19 and therefore provides the best opportunity for achieving a sufficient number of subjects to obtain statistically significant differences in an RCT.

There is now an accumulation of data supporting the current concept that MTLE is a discrete syndrome with characteristic clinical features. A history of onset before puberty, often preceded by febrile convulsions20 or other initial injury, such as intracranial infection or head trauma, within the first 4 or 5 years of life,21 may also be combined with a family history of epilepsy of various types.20 Habitual seizures typically begin with vegetative auras, such as epigastric rising, or affective symptoms (most commonly fear), but occasionally consist of complex delusional experiences or hallucinations or olfactory or gustatory sensations, all indicating involvement of mesial temporal limbic structures.22 The impaired consciousness of the complex partial seizure is usually heralded by arrest and stare, followed by oroalimentary, gestural, and reactive automatisms lasting 1 to 2 minutes for which the patient is amnestic. Afterwards, there is confusion for varying periods and the patient may have some postictal aphasia if the seizures begin in the language-dominant hemisphere. Given all or part of this history and typical ictal events, the diagnosis can be confirmed and the epileptogenic hippocampus lateralized with a high degree of confidence when the patient also has anterior temporal ictal interictal EEG spikes; a characteristic unilateral sphenoidal ictal EEG onset pattern23; and hippo-
campal atrophy on T1-weighted magnetic resonance imaging (MRI), increased mesial temporal signal on T2-weighted MRI, or localized temporal lobe hypometabolism on positron emission tomography with fluorodeoxyglucose ipsilateral to the site of ictal onset. Diagnosis is further aided by demonstration on neurocognitive testing of a memory deficit that is material-specific for the suspected temporal lobe and by characteristic findings on magnetic resonance spectroscopy and ictal or post-ictal single photon emission computed tomography. In patients with refractory seizures who have a concordance of these findings all pointing to the same temporal lobe, anteromesial resection can be recommended without invasive evaluation.

**Early Surgical Treatment of MTLE Might Prevent Irreversible Disabling Consequences**

For patients with MTLE who have seizures that do not respond to first-line antiepileptic drugs and who come to the attention of epilepsy surgery centers, the natural history of the disorder is relatively well documented. The first afebrile complex partial or generalized seizure usually begins before puberty, although it can occur later. Seizures initially appear to be well controlled with antiepileptic drugs but recur in adolescence or early adulthood and then persist despite treatment with appropriate antiepileptic medication at the highest tolerable dosages as monotherapy and in combination. When monotherapy fails, the chance of achieving a seizure-free state with polytherapy appears to be very small. Patients are typically disabled by complex partial seizures throughout a critical period of social and vocational development. There is also evidence from both human and animal experimentation to suggest that recurrent epileptic seizures in limbic structures can cause enduring neurological disturbances in neuronal function, leading to interictal behavioral disorders, particularly depression. Because seizures are initially controlled by medication but later become medically refractory and therefore more prone to sampling errors and biased interpretation than an RCT.

A striking finding of the studies by both Sperling et al and Agostini et al was that patients who continued to have seizures, whether caused by failed surgery or no surgery, had a much higher mortality rate than those who became seizure-free. Patients with intractable epilepsy are known to be at a higher-than-average risk of death, not only because of accidents related to seizures and status epilepticus, but also from suicide and sudden unexplained death. On the other hand, the mortality rate for patients who have undergone anterior temporal lobe resection for MTLE is close to 0. It is not generally appreciated that the risk of death from continued seizures is much greater than it is from a standard anteromesial temporal lobectomy. It is likely, therefore, that early surgery for MTLE would not only improve quality of life, but actually save lives.

**THE STUDY DESIGN**

The National Institute of Neurological Disorders and Stroke, Bethesda, Md, has approved a planning grant for a multicenter RCT of early surgical intervention for MTLE. Twelve epilepsy surgery centers are currently involved (Barrow Neurological Institute, St Joseph’s Hospital and Medical Center, Phoenix, Ariz; Columbia Presbyterian Medical Center, New York, NY; Emory University School of Medicine, Atlanta, Ga; Massachusetts General Hospital, Boston; Southern California Permanente Medical Group, Los Angeles; Stanford University Medical Center, Stanford, Calif; Thomas Jefferson University Hospital, Philadelphia, Pa; University of California, Los Angeles, Medical Center, Los Angeles; University of Michigan, Ann Arbor; University of North Carolina, Chapel Hill; University of Rochester, Rochester, NY; and University of Texas Southwestern Medical Center, Dallas) and have already made progress in developing a common protocol. Patients aged 12 years or older who have had complex partial seizures for less than 2 years that have not responded to adequate trials of 2 antiepileptic drugs, one of which must be either carbamazepine or phenytoin, will
undergo a standardized noninvasive presurgical evaluation. This will include inpatient video EEG monitoring to capture habitual seizures, MRI, positron emission tomography, and neurocognitive testing. Those patients diagnosed as having MTLE and considered to be surgical candidates will then be randomized to either a standardized anteromesial temporal resection or 2 additional years of pharmacotherapy. Detailed drug treatment protocols will be adhered to for patients in both the surgical therapy and pharmacotherapy arms. At the end of 2 years, the primary outcome measure will be a quantitative assessment of health-related quality of life. Secondary outcome measures will be seizure recurrence; objective indicators of social function, such as employment or school status, living conditions, and possession of a driver’s license; cognitive function; psychiatric evaluation; mortality and morbidity; evidence of pathophysiological progression assessed with EEG and MRI hippocampal volumetry; and a cost-effectiveness analysis.

The fact that there has never been a multicenter RCT of epilepsy surgery, which would clearly be an obvious and important step in justifying the use of surgical treatment for epilepsy, is testament to what must have been seen as overwhelming problems in organizing such a study. The recognition of MTLE as a surgically remediable syndrome, recent advances in EEG and neuroimaging technology and interpretation that permit early noninvasive diagnosis of this syndrome, and increasing evidence that outcome is better with early surgical intervention all contribute to making the proposed RCT timely and feasible. Furthermore, with the addition of a large number of new antiepileptic drugs to the pharmacotherapeutic armamentarium, an RCT designed to determine when to offer surgical treatment for epilepsy is needed now more than ever before. The greatest hurdle to be overcome, if such an RCT is to be funded, will be sufficient recruitment of appropriate patients. This will require the cooperation and perhaps collaboration of a large number of practicing neurologists. Those interested in learning more about the study and how to become involved are welcome to visit our home page at http://www.neurology.ucla.edu.

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