A Greater Role for Surgical Treatment of Epilepsy: Why and When?

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Surgical Treatment for Epilepsy Is Underutilized

Surgical treatment for epilepsy is arguably the most underutilized of all proven effective therapeutic interventions in the field of medicine. Our failure, worldwide, to make optimal use of surgical treatment for epilepsy is all the more unacceptable, given the magnitude of the global health burden represented by epilepsy (1). The annual direct and indirect cost attributable to epilepsy in the United States is $12.5 billion, and 80% of this is accounted for by patients whose seizures are not adequately controlled by antiepileptic drugs (AEDs) (2). More than half a million people in the United States have epileptic seizures that continue despite appropriate pharmacotherapy (3), and it has been estimated that 100,000 to 200,000 of these are potential surgical candidates (4). Yet, in 1985, only 500 therapeutic surgical procedures were performed in the United States for epilepsy, which increased to 1,500 in 1990 (5), and, at most, may have doubled since then. Thus only a very small fraction of people with epilepsy who might benefit from surgical intervention receive it.

Surgical Treatment for Epilepsy Need Not Be a Last Resort

When a surgical referral *is* considered for a patient with AED-resistant epileptic seizures, it is usually viewed as a last resort. The average interval between onset of epilepsy and surgical intervention for more than 300 patients operated on in the last 5 years as part of a large multicenter study was 24

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years (S. Spencer, personal communication), and for 29 patients operated on for mesial temporal lobe epilepsy (MTLE) in 2000 and 2001, at an epilepsy center in Florida, was 18 years (6). Often successful surgery is too late to reverse the crippling psychological and social consequences of repeated epileptic seizures during ages critical for acquisition of interpersonal and vocational skills, and seizure-free patients remain disabled indefinitely. Despite tremendous improvements in the efficacy and safety of surgical treatment for epilepsy over the period of the past 2 decades, our own data indicate a progressive increase in the interval to surgery from $12^1/_2$ years from 1961 to 1970 to 18 years from 1996 to 2000 (G. Mathern, unpublished data).

Undoubtedly the doubling of available AEDs in recent years has contributed to a greater delay in surgical referrals. Because it would now literally take a lifetime to prove that epileptic seizures are unresponsive to every AED, in every possible combination, medical refractoriness can no longer be a necessary criterion for surgical referral. Therefore, the concept of surgically remediable epileptic syndromes was introduced to promote early surgical intervention for certain forms of epilepsy with well-defined pathophysiologic substrates that are known to have a poor prognosis after failure of a few AEDs and an excellent surgical prognosis (7). Epilepsies of infants and small children that can be treated with hemispherectomy are in this category, as are partial epilepsies due to discrete resectable structural lesions, but the prototype of a surgically remediable syndrome is MTLE (7). MTLE with hippocampal sclerosis is the most common form of human epilepsy, the most refractory to AEDs (8,9), and the easiest to treat surgically (5). MTLE also is easily diagnosed noninvasively, so why is it that patients with this disorder, as well as with other surgically remediable syndromes, are not referred to epilepsy surgery centers more often and sooner?

Factors That Commonly Discourage Consideration of Surgical Treatment

Fear of surgery is often cited by patients and their physicians as a reason for continuing pharmacotherapy despite repeated AED failures (10). However, it has been well documented that the morbidity and mortality of continued disabling seizures is much greater than the morbidity and mortality of surgery (11). New AEDs and vagus nerve stimulation (VNS) appear to be more attractive alternatives to a surgical

procedure. However, clinical trials in patients with the same types of epileptic seizures experienced by surgical candidates, at best, result in a 50% reduction of seizures in 50% of patients, and rarely render patients seizure free (12–14). Primary care physicians and general neurologists who doggedly pursue pharmacotherapy, or elect to try VNS, may not be aware of advances in the safety and efficacy of surgical intervention. However, hundreds of articles and more than 20 textbooks have been published on this topic in the last 15 years. Some have suggested that reluctance to consider surgical treatment for epilepsy stems from the fact that it had never been proven effective by the gold standard method for evaluating therapeutic interventions: the randomized controlled trial (RCT). This concern now has been addressed, at least for MTLE, by the landmark RCT carried out at the University of Western Ontario and published by Wiebe et al. (15) in 2001.

The First and Only Randomized Controlled Trial of Epilepsy Surgery

Although epilepsy has been treated surgically for almost 125 years (16,17), an RCT had never been performed until the Western Ontario study. At least since the advent of EEG greatly improved localization of the epileptogenic region (18,19), neurologists and neurosurgeons in epilepsy surgery centers have generally believed that surgical intervention was clearly superior to continued pharmacotherapy in patients for whom many AEDs have failed. Consequently, they have considered it unethical to design an RCT in which half of the patients referred to them with disabling AED-resistant seizures would be assigned to more medical treatment.

It was possible to design an ethical RCT of epilepsy surgery for MTLE at the University of Western Ontario because their waiting list for surgery was more than a year long, and patients could be randomized to *immediate* surgery or the usual 1-year wait. With an intention-to-treat paradigm, 80 patients were randomized to either presurgical evaluation, or continued pharmacotherapy while they remained on the waiting list. At the end of 1 year, 58% of patients in the surgical arm were free of disabling seizures compared with 8% in the medical arm, and patients in the surgical arm had a significantly better health-related quality of life (HRQOL) score, as measured by the Epilepsy Surgery Inventory–55, than did patients in the medical arm. In this short follow-up period, patients in the surgical arm also showed a trend toward improved social function. Because patients were randomized to the surgical arm before presurgical evaluation, four did not receive surgery. Of those who underwent surgical resection, 64% were free of disabling seizures, which is almost identical to the results for anterior temporal surgery for MTLE obtained in a large survey of epilepsy centers in 1991 (5). The only death occurred in the medical arm.

Evidence-based Practice Parameters for Epilepsy Surgery

In 1997, the American Epilepsy Society, in collaboration with the American Academy of Neurology (AAN), and the American Association of Neurological Surgeons, appointed a committee to prepare evidence-based practice parameters for surgical treatment of epilepsy. The committee decided that there was sufficient literature to assess the efficacy of anterior temporal lobe and localized neocortical resections, and reviewed data reported between 1990 and 1999. Although articles from 24 centers reporting on 1,952 anterior temporal resections, and from eight centers reporting on 298 localized neocortical resections, met rigid criteria for inclusion in this review, all were considered to be only class IV evidence by the AAN Quality Standards Subcommittee (QSS), because none had a masked outcome assessment. Evidence-based recommendations require class I or II evidence. With the addition of the Western Ontario study, however, which the QSS deemed class I evidence, the practice parameters were accepted in 2002, and published in *Neurology* and *Epilepsia* in 2003 (20,21).

The evidence-based practice parameters concluded that in the RCT, and also in the 24 class IV series of surgery for MTLE, two thirds of patients became free of disabling seizures (in some, auras remained), and 10% to 15% were unimproved after surgery; these outcomes did not change when class IV studies were stratified by geographic region, longer follow-up, or surgery after the advent of magnetic resonance imaging (MRI). Half of patients in eight class IV series of localized neocortical resections were free of disabling seizures, and 15% were unimproved. When combining temporal lobe and neocortical series, there was a positive correlation between degree of seizure improvement and HRQOL scores; there was a trend toward better social function, decreased mortality, and reduced medication regimens after surgery; neuropsychological and psychosocial function could improve or worsen, but worsening was related to persistence of seizures; and surgical morbidity and mortality were small (3% permanent neurologic deficits and no surgically related deaths). When the findings for the temporal lobe series were compared with results from pharmacotherapy trials (13,14), it could be recommended that patients with disabling complex partial seizures for whom appropriate treatment with first-line AEDs has failed, and who meet established criteria for antero-mesial temporal resection, should be offered surgical therapy. Despite the similarity between published temporal lobe and neocortical series, a definitive recommendation could not be made concerning localized neocortical resections because of the absence of class I evidence for this type of surgical intervention.

These practice parameters did not address the efficacy of surgical intervention for specific types of epilepsy or underlying pathologic substrates, the prognostic value of presurgical diagnostic tests or strategies, or the efficacy of a number of other commonly performed surgical interventions, including multilobar resections, hemispherectomies, corpus callosotomies, lesionectomies, and multiple subpial transections; nor did it address the cost-effectiveness of surgical intervention. Although these practice parameters now clearly recommend surgical treatment for AED-resistant MTLE, no recommendation could be made concerning the timing of surgery. In view of persuasive data suggesting that medical refractoriness can be reliably predicted after failure of only two drugs (22), the next important question is *when* in the course of MTLE is it appropriate to abandon further pharmacotherapy trials and refer a patient to an epilepsy surgery center? This question is now being addressed by the National Institute of Neurological Disorders and Stroke (NINDS)-funded multicenter RCT titled Early Randomized Surgical Epilepsy Trial (ERSET).

Early Randomized Surgical Epilepsy Trial

ERSET is based on evidence that early effective treatment of MTLE can prevent the development of irreversible adverse psychological and social consequences and rescue individuals from a lifetime of disability. This RCT addresses the question whether medication or surgery produces the best outcome early in the course of MTLE, after failure of two AEDs. Patients with MTLE who are 12 years or older, for whom at least two drugs have failed, one of which must be either brand-name carbamazepine (Tegretol, Carbatrol), phenytoin (Dilantin), or oxcarbazepine (Trileptal), who have not had disabling seizures for more than 2 consecutive years (for those who have experienced remission of 6 months or longer, the 2-year period would begin with seizure recurrence), and who are willing to participate in this study, will undergo a standardized presurgical evaluation. Those meeting criteria for anteromesial temporal resection will be randomized to surgery, or an additional 2 years of an optimal pharmacotherapy protocol designed by experts in clinical pharmacology of AEDs. Patients randomized to surgery will need to pass an intracarotid amobarbital procedure before surgery can be performed. Outcome assessment at the end of 2 years will include seizure recurrence, HRQOL, ancillary psychological and social measures, morbidity and mortality, and evidence of progressive mesial temporal disturbances on MRI and positron emission tomography (PET). It is anticipated that recruitment will be a challenge for successful completion of ERSET because most potential study candidates are still under the care of primary care physicians and general neurologists. We hope the publicity engendered by ERSET will stimulate earlier referral of patients with persistent epileptic seizures to epilepsy specialists.

Acknowledgments

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