

RESULTS OF EPILEPSY SURGERY: STILL SO MUCH TO LEARN

Predicting Long-Term Seizure Outcome after Resective Epilepsy Surgery: The Multicenter Study

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BACKGROUND: In a seven-center prospective observational study of resective epilepsy surgery, the authors examined probability and predictors of entering 2-year remission and the risk of subsequent relapse.

METHODS: Patients aged 12 years and over were enrolled at time of referral for epilepsy surgery, and underwent standardized evaluation, treatment, and follow-up procedures. The authors defined seizure remission as 2 years completely seizure-free after hospital discharge with or without auras, and relapse as any seizures after 2-year remission. The authors examined type of surgery, seizure, clinical and demographic variables, and localization study results with respect to prediction of seizure remission or relapse, using χ^2 and proportional hazards analysis.

RESULTS: Of 396 operated patients, 339 were followed over 2 years, and 223 (66%) experienced 2-year remission, not significantly different between medial temporal (68%) and neocortical (50%) resections. In multivariable models, only absence of generalized tonic-clonic seizures and presence of hippocampal atrophy were significantly and independently associated with remission, and only in the medial temporal resection group. Fifty-five patients relapsed after 2-year remission, again not significantly different between medial temporal (25%) and neocortical (19%) resections. Only delay to remission predicted relapse, and only in medial temporal patients.

CONCLUSION: Hippocampal atrophy and a history of absence of generalized tonic clonic seizures were the sole predictors of 2-year remission, and only for medial temporal resections.

Antiepileptic Drug Withdrawal after Successful Surgery for Intractable Temporal Lobe Epilepsy

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PURPOSE: To investigate the prognosis related to antiepileptic drug (AED) discontinuation after successful surgery for intractable temporal lobe epilepsy.

METHODS: The clinical courses after temporal lobectomies (TLs) were retrospectively analyzed in 88 consecutive patients. All the patients had TLs as the only surgical procedure, and they had been followed up for longer than 3 years. AED discontinuation was attempted if the patient had been seizure free without aura for ≥ 1 year during the follow-up period.

RESULTS: Sixty-six (75%) patients achieved complete seizure freedom for ≥ 1 year; 28 patients were seizure free immediately after surgery (immediate success); and 38 patients became seizure free after some period of recurrent seizures (delayed success). AED discontinuation was attempted in 60 (91%) of 66 patients with a successful out-

come. In 13 (22%) patients, seizure relapse developed during AED reduction ($n = 60$), and in 7 (12%) patients after discontinuation of AEDs ($n = 38$). The seizure recurrence rate was not different between the immediate- and delayed-success groups. Among 20 patients with seizure relapse related to AED tapering, 9 (45%) of them regained seizure freedom after reinstatement of AED treatment, and AEDs were eventually discontinued in 6 of them. Seizures that recurred after complete AED discontinuation had a better prognosis than did the seizures that recurred during AED reduction (seizure freedom in 86% vs 23%). At the final assessment, 54 (61%) patients had been seizure free ≥ 1 year; 37 without AEDs and 17 with AEDs. The successful discontinuation of AEDs was more frequent for patients with a younger age at the time of surgery and for those patients with shorter disease duration.

CONCLUSIONS: Our results suggest that seizure freedom without aura at ≥ 1 year is a reasonable indication for the attempt at AED discontinuation. The subsequent control of recurrent seizures was excellent, especially if

seizures relapsed after the complete discontinuation of AEDs. Younger age at the time of surgery and a shorter disease duration seem to affect successful AED discontinuation for a long-term period.

COMMENTARY

Since the beginning of surgery for intractable epilepsy, failure to eradicate or even to ameliorate seizures in some patients has been a persistent problem. Most patients are dismayed when told that although their seizures could completely disappear after surgery, they still may need to continue taking antiepileptic drugs (AEDs) to remain seizure-free. Decades of thoughtful experience, careful collection of data, and dramatic technological advances have done little to improve the likelihood of a cure for epilepsy (even following a straightforward temporal lobectomy) or to increase the number of patients who can successfully stop taking AEDs. The studies under review were designed to reduce the numbers of disappointed patients (and therapists) by identifying factors that can reliably predict successful epilepsy surgery as well as successful postoperative AED withdrawal. The findings from both studies offer some guidance for clinical decision making but also highlight the stubborn uncertainties surrounding these treatment issues and the difficulty of designing meaningful, informative studies in this area.

Successful determination of accurate predictors of surgical success has foundered because of sample sizes that were too small, heterogeneous subject groups, variability of surgical procedures, differing follow-up times, and varying definitions of success or failure. Comparisons between patients with and without surgical intervention, but who otherwise have similar characteristics, are rare. Randomized, prospective surgical studies have not been attempted, nor would they be ethical at this point. It was only as a result of the “natural experiment,” which transpired because of unavoidable surgical delays inherent to the Canadian health care system, that the only prospective, randomized study to demonstrate the superiority of surgical versus medical treatment of temporal lobe epilepsy occurred (1).

Various studies have identified preoperative findings that are correlated with increased odds of a successful outcome following temporal lobectomy, including a history of febrile seizures, younger age at the time of surgery, absence of tonic-clonic seizures, medial temporal rather than neotemporal resection, hippocampal sclerosis, and normal contralateral chemical shift spectroscopy imaging. Successful resections in unselected nontemporal as well as in temporal lobe cases are more likely

to be associated preoperatively with unifocal interictal EEG spikes, concordance of three or more presurgical test modalities, EEG/MRI concordance, focal lesions on MR, abnormal MRI, neoplasms, focal subtraction peri-ictal single photon emission computed tomography (SPECT) [SISCOM] abnormalities, absence of intracranial monitoring, or extensive surgical resections; and in children, with better memory scores on ipsilateral Wada testing and freedom from seizures during the first postoperative week. None of these findings, however, have proven to be robust or even consistent enough to guide clinical decision making in individual cases. The surgical odds quoted to most patients are often the same ones used 25 years ago.

The study by Spencer et al. is remarkable for merging data from seven surgical centers, using identical protocols for patient evaluation and selection of surgical approach—quite an accomplishment in a field in which protocols, and even some surgical recommendations, may be decisively influenced by local clinical practice or habits, range of experience of the surgical team, or the availability of testing modalities. The results add to the gathering consensus that the absence of tonic-clonic seizures and the presence of hippocampal atrophy are most consistently found to increase the chances of successful surgery for seizures.

Even as the consensus grows, however, with the individual patient, clinicians faced with making a recommendation for or against surgery would do well to recall the actual findings, not just the statistical differences, among the patients in the study by Spencer et al. Patients who had a history of tonic-clonic seizures still had a 64.6% chance of achieving a 2-year seizure remission, as opposed to a 79.4% chance for those with no such history. Similarly, patients without the favorable indicator, hippocampal atrophy, still had a 54.7% chance of a remission, as opposed to a 74.9% chance in those with such atrophy. The authors themselves admit that no surgical center is likely to withhold surgery from all patients who lack these favorable indicators.

Some studies with prolonged follow-up periods have revealed an even more uncertain and unsettling postsurgical prognosis for epilepsy. Although studies have repeatedly found that outcomes at 2 years after surgery reliably predict the chances of long-term surgical success, exceptions to this pattern are regularly seen. Some patients who seem to have been cured by surgery, suffer from recurrent epilepsy many years later.

McIntosh et al. found that 25% of patients who were rendered seizure-free for 2 years following temporal lobectomy had some seizure recurrence within 10 years, whether or not AEDs were discontinued (2). Although the study of Spencer et al. found that such late relapses were much less likely in patients who had experienced swift resolution of seizures after surgery, another large, single-center study found seizure recurrence in almost half of the patients who had no seizures during the first postoperative year (3). Such relapses were more common for patients with normal resected tissue or with a longer preoperative illness.

Conversely, some apparently unsuccessful surgeries eventually end in gradual cessation of seizures, also known as the “running down” phenomenon. The frequency of such cases is unclear; many long-term studies simply observe group success rates over time but do not identify how many patients slip out of the failed group into the successful one, or vice versa. The Montreal group reported in detail on 100 such patients, who became seizure-free after months to many years following temporal lobectomy (4).

Interpretation of such late surgical outcomes is hampered by a general lack of control groups of patients who did not receive surgical therapy. One retrospective study of patients with focal epilepsy who were deemed ineligible for epilepsy surgery found that a surprising 21% were seizure-free an average of 4 years later (5). In contrast, the prospective study of surgical versus medical treatment of intractable temporal lobe epilepsy found that only 8% of patients treated medically were free from seizures 1 year after randomization (1). The true added gain of surgical treatment compared with best medical therapy is still to be discovered.

The patient who is initially seizure-free postoperatively and who wishes to discontinue AEDs, will find the clinician surprisingly unable to offer a reliable prediction of whether the seizure-free state can be maintained without AEDs. Furthermore, there is no certainty as to whether the length of the postoperative seizure-free period makes any difference to the final outcome. Most studies have found that about one out of three patients have seizures during or after AED withdrawal, 1 to 2 years postoperatively. Attempts to identify the patients at highest risk have not been altogether successful: as mentioned, an older age at the time of surgery and a longer duration of epilepsy prior to surgery have been reported to increase the risk of relapse; however, Kim et al. were unable to identify any significant predictors of successful AED withdrawal, even in their relatively homogeneous series of 88 patients with temporal lobe epilepsy. Even more disquieting are the observations that some patients who fail postsurgical AED withdrawal may revert to a medically intractable seizure pattern. It is not known how many of these patients would have resumed having severe seizures, even

if AEDs had continued to be administered uninterruptedly. Of 20 patients in the study of Kim et al. who tapered AEDs, 6 (30%) resumed having disabling seizures.

Of considerable practical benefit is the finding by Kim et al. that the duration of AED treatment from the onset of a postoperative seizure-free state to the time of AED discontinuation did not affect the rate of seizure recurrence. This finding has also been reported by other investigators and supports the practice of early (i.e., 1 year) rather than delayed discontinuation of AEDs in seizure-free patients. For many patients, the milestone of discontinuation of AEDs is an important enhancement of psychological well-being and quality of life. But, as all clinicians have found, the main determinant of whether or not to stop AED administration is if the patient has resumed driving. Until there is a better guarantee that drug withdrawal can be successful, most epileptologists are reluctant to jeopardize the privilege of driving for their patients.

That the questions addressed in these papers are still being asked many years after seizure surgery first began to be widely used, emphasizes the need for further studies. The obstacles are formidable. Spencer et al. point out that their multicenter study of over 800 patients, which used the same protocol for patient evaluation, selection, and surgical approach, was underpowered to detect less than a 250% difference in outcome rates between mesial temporal and neocortical resections—consequently, the study found no statistically significant difference. Considering the dozens of historical, semiological, pharmacological, and pathological elements that characterize the population of patients receiving surgery for epilepsy, no easy answers to these questions seem imminent.

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