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Long-term Outcome of Nonsurgical Candidates with Medically Refractory Localization-related Epilepsy

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Summary: *Purpose:* Epilepsy surgery can result in complete seizure remission rates of upto 80% in patients with mesial temporal sclerosis and unilateral seizures. The seizure-free rate after surgery for patients with extratemporal nonlesional epilepsy has ranged between 30% and 40%. Some patients with medically refractory localization-related epilepsy cannot be offered surgical resection because of inadequate localization of the epileptogenic zone, documentation of bilateral ictal onsets, or functionally important areas of cortex that prohibit resection. The short-term rate of complete remission with medications in temporal lobe epilepsy is poor. Less is known about remission rates in patients who are not surgical candidates. In this study, we evaluated the outcome of medical treatment in patients with medically refractory partial epilepsy who were evaluated for possible epilepsy surgery but deemed to be inadequate surgical candidates.

Methods: A retrospective chart review and telephone survey with a self-rating questionnaire were completed for all patients who underwent epilepsy surgery evaluation but were not ultimately offered surgical treatment at the University of Michigan from 1990 through 1998. We assessed changes in seizure frequency and type, imaging characteristics, ictal recordings, interim medication history, and subjective changes in quality of life.

Results: Thirty-four subjects were available for follow-up study, at an average of >4 years after surgical evaluation. A significant reduction in seizure frequency was noted at the time of follow-up compared with that at the time of surgical evaluation. Of patients, 21% achieved seizure remission and remained seizure free for an average of 2.5 years. Four of the seven seizure-free patients attributed their remission to new antiepileptic drugs (AEDs). On a global self-rating item, 15 of 34, or 44%, felt more or much more satisfied with their lives, and 41% felt their quality of life was stable.

Conclusions: A surprisingly large number of patients we surveyed, with refractory partial epilepsy not eligible for surgical management, reported reduced seizure frequency at follow-up, and 21% were seizure free. Our findings suggest that the long-term prognosis in patients with refractory partial epilepsy who are not surgical candidates may be more positive than might be generally expected. **Key Words:** Epilepsy—Partial—Temporal lobe—Efficacy—Quality of life.

Although the natural history of localization-related epilepsy is incompletely understood, recent data indicate that treatment response is likely to correlate with the etiology of the epilepsy. Temporal lobe epilepsy (TLE) with mesial temporal sclerosis (MTS) seems to be the most refractory to medical treatment (1), with the likelihood of complete remission ranging from 11% (2) to 42% (3). A better prognosis with medical management has been associated with other types of partial epilepsies. For instance, cryptogenic partial epilepsy remitted at a rate of 45% (2), and patients with lesional epilepsy secondary to arteriovenous malformations had a 78% chance of becoming seizure free (3). Other prognostic variables include age at seizure onset, number of generalized seizures, duration of epilepsy, and severity of associated cognitive or psychiatric disturbances (4–7). Secondary epileptogenesis is thought to be most relevant to cases of bilateral temporal epilepsy and secondary bilateral synchrony (8), and some concern is expressed that partial epilepsy may be a progressive disease in these cases.

For patients with MTS, surgical removal of the epileptogenic zone is associated with seizure remission in 70–80% (9). In the only controlled trial (10), surgical management was shown to be clearly superior to medical management in a group of patients with TLE. In this carefully selected mesial temporal epilepsy group, only 8% had seizure control at 1 year with aggressive medication trials. However, surgical management does not yet deliver as much of an advantage in other types of localization-related epilepsy. For instance, only 32% (11) to 36% (12) of patients with independent bilateral temporal ictal

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onsets achieved seizure freedom after unilateral palliative resections of the more active side. Comparable estimates of seizure freedom after surgery were reported for patients with nonlesional extratemporal epilepsy, with a range between 42 and 45% (13,14).

We undertook this study to evaluate the outcome of medical treatment in a group of patients with medically refractory localization-related epilepsy who were evaluated for possible epilepsy surgery but deemed to be inadequate surgical candidates. This type of group has not previously been evaluated. We specifically analyzed changes in seizure frequency, as well as the patients' own perceptions of their overall quality of life. We also tried to identify predictive factors that could help discriminate between those with the best and the poorest outcomes.

METHODS

Selection of patients

Study candidates were identified by using the Epilepsy Surgery Database from the Department of Neurology at the University of Michigan. The database includes all patients with medically refractory localization-related epilepsy being considered for surgical intervention. The target population for this study consisted of patients evaluated for possible epilepsy surgery between 1990 and 1998 and deemed to be inappropriate surgical candidates. Patients who declined surgery on the basis of the likelihood of remission quoted, or on the basis of improvement in their condition were not included. At our center, the decision about surgical management is based on a consensus decision at a refractory epilepsy conference. Some patients with unilaterally predominant (usually $\sim \geq 70\%$) bilateral TLE have been offered palliative resections.

Study design

This study was approved by the University of Michigan Institutional Research Review Board. For each patient, we collected the variables of interest by reviewing the medical records, and after informed consent, we conducted a follow-up telephone interview.

The data collected from the medical records included demographic variables, risk factors for epilepsy, and results of the diagnostic workup. Specifically, we collected the age at seizure onset, age at enrollment into the study, and the time since evaluation for epilepsy surgery. Risk factors for epilepsy, including febrile seizures, closed head injury, or CNS infections were ascertained. In addition, we evaluated the monthly seizure frequency, epilepsy treatment regimen, employment, and driving status at or near the time of their first admission for the inpatient CCTV-EEG monitoring. We also recorded the results of diagnostic tests, including neuropsychometric testing, ictal and interictal CCTV-EEG, magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT; if performed), and positron emission tomography (PET; if performed). Based on those data, we noted the reason those patients were not deemed to be appropriate surgical candidates.

We conducted a telephone interview with patients and family members to assess their situation at the time of follow-up. We specifically inquired about their current monthly seizure frequency, changes in seizure semiology, current treatment regimen for epilepsy, and whether a vagus nerve stimulator (VNS) was implanted. We defined seizure freedom as ≥ 1 year without any seizures recognized by the patient or family. We also assessed quality of life including driving status, current employment status, and asked the patients to rate on a 5-point global categorical scale their current level of satisfaction with life since their evaluation for possible epilepsy surgery. In addition, we inquired about psychiatric intervention and availability of psychosocial support.

Analysis

We analyzed the change in seizure frequency at the time of follow-up compared with those at the time of presurgical evaluation with paired *t* tests. Correlations between specific variables and likelihood of remission were analyzed with one-way analysis of variance (ANOVA). Statistical significance was set at p values of <0.05. We used a Pearson's test to analyze the possible significance of sex to outcome, and used the Mann–Whitney test to evaluate the correlation of seizure frequency with outcome.

RESULTS

Demographics

A total of 47 patients identified through our surgical database qualified for participation in the study. At the time of follow-up, four patients could not be located, seven refused or were unable to participate in the phone survey, and two patients were deceased.

The remaining 34 patients (19 women, 15 men) were the subjects of this study. The reasons for rejection of surgical candidacy included diffuse or inadequately localizing ictal onsets, often associated with uninformative SPECT or PET studies (18 of 34; 53%), bilateral independent temporal ictal onset, (usually very close to 50% onset in each hemisphere with invasive monitoring), with normal or bilaterally abnormal neuroimaging studies (13 of 34; 38%), epileptogenic zones involving primary language cortex (two of 34; 6%), and one (3%) with evidence for bilateral temporal dysfunction who failed Wada testing even after a repeated superselective injection. Twenty-three (68%) of the 34 patients underwent invasive intracranial monitoring in unfruitful attempts to localize the epileptogenic zone. Eight of the invasive monitoring procedures involved grid or strip electrodes in the frontal (four), occipital (one), lateral temporal (two), and insular (one) regions. Fifteen of the intracranially studied patients had bilateral temporal depth electrodes.

The risk factors for epilepsy included a history of febrile seizures in 23%, head trauma in 33%, family history of epilepsy in 38%, and history of CNS infection in 12%.

The number and types of medications for the two groups were evaluated. The average number of medications at time of seizure evaluation was 1.4 and 2.0 at presentation and follow-up for the group who become seizure free, and 1.9 and 2.3 at presentation and follow-up in the group that was refractory. In the group with remission, the number taking new medications (introduced after 1990) increased from 57% to 86%. In the refractory group, the number taking new medications increased from 56% to 74%.

Seizure frequency

The mean interval between the presurgical evaluation and the follow-up phone interview was 4.4 years (range, 1.2–9.6 years). Compared with the time of the surgical evaluation, 26 (76%) patients reported an improvement in seizure frequency, three (9%) had no change in seizure frequency, and five (15%) had an increased in seizure frequency. Overall, a significant improvement in seizure frequency was seen at the time of follow-up ($p < 0.0001$). The median baseline seizure frequency in the whole group of 34 decreased from eight seizures per month (range, 1–195 seizures/month) to two seizures per month (range, 0–150 seizures/month).

Seven (21%) of the 34 patients [95% confidence interval (CI) + 14%] were seizure free at the time of follow-up, with a mean remission time of 2.5 years (range, 1–5.5 years). The demographic data for this group are summarized in Table 1 and compared with those of the group that did not achieve seizure remission. No statistical differences could be identified. Although women were more likely to achieve seizure remission, the gender difference did not reach statistical significance (Fisher's exact test; $p = 0.05$). No significant correlation was found between age at seizure onset, age at evaluation, or monthly seizure frequency and seizure outcome. In addition, no significant correlation was noted between remission rate and MRI abnormalities, VNS implantation, or reason for rejection of surgical candidacy. A worst-case scenario analysis, in which the 13 eligible patients who could not be interviewed are considered not to have achieved seizure remission, would have resulted in a seizure-free rate of seven of 47 or 15% (95% CI ± 10%).

Four patients with complete seizure remission had bilateral mesial temporal onsets; one had seizures originating from language cortex; and in the remaining two patients, the ictal-onset zone could not be localized. Four of the seven with remission had added topiramate (TPM) to their regimen, whereas one patient had stopped TPM. Four of the patients in the refractory group had also added this medication. No other medication changes suggested any trend.

Quality-of-life self-assessment

On global self-assessment rating, 44% of the patients felt they were more or much more satisfied with their quality of life compared with that at the time of their surgical evaluation, 15% felt their quality of life had declined, and 41% felt their quality of life was unchanged. A significant correlation was seen between remission of seizures and scores achieved on the self-assessment rating. The satisfaction rating scores for patients with complete seizure remission averaged 4.7 (SD ± 0.5) compared with 3.2 (SD ± 1.0) for those with persistent seizures ($p < 0.0001$).

DISCUSSION

In this study, we evaluated the long-term outcome in a cohort of patients with medically refractory localization-related epilepsy who were deemed not to be appropriate candidates for epilepsy surgery. We found that 21% of patients became seizure free, with a mean seizure remission of 2.5 years. If all patients lost to follow-up were considered not to have achieved seizure remission, the remission rate would still be 15%.

It is important to remember that these data apply only to a small subset of refractory patients who could not be offered surgical treatment. For patients with surgically remediable epilepsy, especially those with TLE, surgical resection is by far the most appropriate course of action for eligible candidates and is currently the standard of care (15). For those patients, epilepsy surgery can be associated with remission rates of ≤80%, results that cannot be approached with long-term medical treatment with

TABLE 1. *Demographics comparing seizure-remission versus continued-seizure patients*

	Seizure remission Mean (±SD)	Continued seizures Mean (±SD)	Significance
Number	7	27	
Females/Males	6:1	13:14	NS (Fisher's test)
Age (yr)			
At seizure onset	9.3 (±6.9)	10.0 (±6.5)	NS
At enrollment in study	32.7 (±12.1)	36.9 (±10.3)	NS
Time since surgical evaluation (mo)	60 (±31.2)	50 (±28.7)	NS
Seizure frequency at surgical evaluation (per mo.)	33.2 (±71.6) {median, 8.5}	18.1 (±30.4) {median, 4.0}	NS (Mann–Whitney test)
Time since last seizure (yr)	2.5-yr mean (range, 12–65 mo)		

drugs available on the market today. In addition, our results should not distract from the fact that evaluation for possible epilepsy surgery should be considered early, because refractoriness to medical therapy can usually be determined after failure of one AED administered at appropriate dosages and certainly after failure of two drugs (16). The clinical relevance of our findings is that they offer some hope and a quantitative assessment of seizure remission for those patients who are inappropriate candidates for epilepsy surgery. Before this study, we would have offered those patients, who were averaging 20 seizures per month and for whom treatment with multiple AEDs had failed, a very low likelihood of achieving seizure freedom with long-term medical therapy. However, our data suggest that those patients can expect a 15–21% remission rate with long-term medical therapy with the available AEDs.

We did not find any demographic variable that correlated with outcome, specifically neither age at seizure onset, age at evaluation, nor seizure frequency at the time of the surgical evaluation was a significant predictor. Although women were more likely to achieve seizure remission, the gender difference did not reach statistical significance (Table 1). We have investigated the outcome of medical management in patients with bilateral temporal epileptogenic zones. In studies of palliative surgical treatment, these patients have a much lower remission rate than that for unilateral TLE (11,12,17). Four of our 14 bitemporal-onset patients stopped having seizures (29%), some in association with trials of new medications. In the extratemporal group, three of 20 in our nonlocalizing, presumed extratemporal patients became seizure free with medications (15%). This is somewhat lower than previous reports (2,17), probably because of the severity of the epilepsy in this series (other series were not reporting surgical candidates). We also evaluated specifically patients who had completely normal MRI studies because of recent interest in prognosticating for this group (17). Three of the seven patients with normal MRI studies in our series achieved seizure remission with medical treatment. None of the seven seizure-free patients had MTS on MRI, whereas seven of 27 patients with continued seizures had unilateral or bilateral MTS. Finally, we evaluated the number of medications before and after surgical evaluation. No significant differences were found in the number of medications being taken or in the number of new medications during evaluation or at follow-up.

Two patients in this refractory group died before follow-up. The cause of death in one patient was likely related to sudden unexpected death with epilepsy (SUDEP), whereas in the other, the proximate cause was deemed to be severe hypokalemia and arrhythmia in a patient during a long battle with hepatic carcinoma. Both these patients had been classified as extratemporal, with nonlocalizing epileptogenic zones. Both were still actively having seizures at the time of their deaths, consistent with a number of reports describing increased mortality in refractory epilepsy from both SUDEP and other causes (18–20).

We evaluated the response to VNS in this group of refractory patients who were rejected as surgical candidates. In general, VNS provides substantial improvement in 28% of refractory partial epilepsy patients (21) and may exert its effect, at least partially, through changes in thalamic perfusion (22). In our group, 10 of the 34 most refractory patients went on to VNS implantation. None of these patients became seizure free: five had a significant improvement in seizure frequency, and seizures worsened slightly in three patients. We also looked at the possible influence of experimental drug trials. Five of our patients had been entered into experimental drug trails at the time of follow-up, and none of these was seizure free.

We were surprised by the substantial improvement in the quality-of-life assessment. Unfortunately, we did not have baseline validated QOLIE (quality of life in epilepsy) or other similar scores. The most dramatic changes were evident in the group with seizure remission, but even in those with continued seizures, quality of life was often considered improved compared with the time of evaluation. In an open-ended question about what the patients felt affected seizure frequency, seven of 26 patients with improved seizure control attributed their improvement to less-stressful life situations. More detailed quality-of-life assessments have been performed in patients with epilepsy and generally show quality of life in those still having seizures to be poorer than that measured in diabetics or hypertensive patients (23–25). In one such study, Vickrey (26) found that overall quality of life did not differ substantially in the surgical versus the nonsurgical group. In that study, the number of patients employed at follow-up increased dramatically in both the surgical and the nonsurgical group. Several authors investigating the predictors for quality of life described employability as a major predictor of satisfaction (27,28) and also indicated that social norms for vocational training and transportation may strongly influence quality of life. In our group, 11 patients were employed at the time of surgical evaluation, and 16 were employed at follow-up. Only one of the five incrementally employed patients was seizure free. Social supports did not seem to have dramatically changed. The reason 44% of our patients rated their overall quality of life improved remains elusive, particularly as not all of the patients with better quality of life were among those with reduced seizure frequency. It is certainly possible that patients investigate the possibility of epilepsy surgery at particularly stressful periods, emotionally or vocationally, and that this improvement represents a regression toward the mean. In the future, we plan to add a validated psychological scale to our epilepsy surgery evaluation so that we can objectively measure these changes at follow-up.

Finally, we plan to continue to investigate the variables that might predict a better outcome in these patients. Given

the surprising proportion of remissions, one would hope that studies conducted in larger groups might have the power to identify elements of the predisposition, semiology, or imaging that could predict a stronger likelihood of remission in some difficult to localize refractory partial epilepsy patients without unilateral mesial TLE.

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