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Patient historical risk factors associated with seizure outcome after surgery for drug-resistant nonlesional temporal lobe epilepsy.

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Abstract:

Objective: To investigate the possible influence of risk factors on seizure outcome after surgery for drug-resistant nonlesional temporal lobe epilepsy (TLE).

Methods: This retrospective study recruited patients with drug-resistant nonlesional TLE who underwent epilepsy surgery at Jefferson Comprehensive Epilepsy Center and were followed for a minimum of one year. Patients had been prospectively registered in a database from 1991 through 2014. Postsurgical outcome was classified into two groups; seizure free or relapsed. The possible risk factors influencing long-term seizure outcome after surgery were investigated.

Results: Ninety-five patients (42 males and 53 females) were studied. Fifty-four (56.8%) patients were seizure free. Only a history of febrile seizure in childhood affected the risk of post-operative seizure recurrence (odds ratio 0.22; 95% CI: 0.06-0.83; p = 0.02). Gender, race, family history of epilepsy, history of status epilepticus, duration of disease before surgery, aura symptoms, intelligence quotient, and seizure type or frequency were not predictors of outcome.

Conclusion: Many patients with drug-resistant nonlesional TLE responded favorably to surgery. The only factor predictive of seizure outcome after surgery was a history of febrile seizure in childhood. It is critical to distinguish among different types of TLE when assessing outcome after surgery.

Key words: Nonlesional; Outcome; Risk; Surgery; Temporal lobe epilepsy.

Introduction

Focal epilepsies account for about two-thirds of all adult patients with epilepsy, and temporal lobe epilepsy (TLE) is the most common type of focal epilepsy [1, 2]. Mesial temporal sclerosis (MTS) is the most common pathological substrate of TLE [3]. However, only about 70% of patients with drug-resistant TLE show signs of MTS on their MRI; about 16% of patients demonstrate no MRI abnormality [4]. Temporal lobe epilepsy is the most common type of drug-resistant epilepsy referred for epilepsy surgery; it often responds favorably to surgery [5, 6]. In drug-resistant TLE, resective brain surgery is superior to prolonged medical therapy [4]. However, there are still ambiguities about which patients will benefit most [7]. This is particularly true in the subgroup of patients with nonlesional TLE. Relatively little work has been done to identify the factors that characterize good or bad epilepsy surgery candidates within this group.

In order to obtain a clearer picture of the possible influence of risk factors on postoperative seizure outcome for patients with drug-resistant nonlesional TLE, we conducted a retrospective study of a large surgical cohort. We examined seizure outcome during long-term postsurgical follow-up in patients with normal magnetic resonance imaging (MRI) who had undergone epilepsy surgery for drug-resistant seizures. This may shed light on the significance of distinguishing specific types of TLE when predicting outcome after surgery.

Methods

In this retrospective study, we examined data from all patients with a clinical diagnosis of drug-resistant nonlesional TLE who underwent epilepsy surgery at Jefferson Comprehensive Epilepsy Center between 1991 and 2014 and had a minimum of 1-year postoperative follow-up.

Patients were prospectively registered in a database with historical data obtained by board certified neurologists. The diagnosis of TLE was made by epileptologists working at this institution and based on clinical grounds (history and semiology) and electroencephalographic (EEG) findings. There was no age limit to enter the study. For all patients, a comprehensive presurgical evaluation including a 1.5 Tesla (in 91 patients) or 3 Tesla (in 4 patients) brain MRI (epilepsy protocol; techniques changed with equipment modernization) and PET scan were performed. Magnetic resonance imaging and PET scan studies were analyzed (visual inspection only) by neuroradiologists, neurologists, and neurosurgeons with expertise in epilepsy. A normal brain MRI was required to confirm nonlesional TLE for entrance into the study. Patients with incomplete data with regard to pre- and postoperative seizure information (i.e., type and frequency) were excluded from this study. Pathology specimens were reviewed by pathologists, but most results were not sufficient to make a precise pathological classification.

All patients included in the analysis had an anterior temporal lobectomy including resection of the mesial temporal limbic structures. Early on, we performed lateral resections in the dominant hemisphere 4 cm from the pole; more recently these resections were performed 2-3 cm from the pole. In the nondominant hemisphere, early on we performed lateral resections 5 cm from the pole; more recently 3-4 cm from the pole. In mesial resections there was no difference in resection size between dominant and nondominant foci. The patients were followed for up to five years after surgery (in many patients the data was missing beyond five years of follow-up). Postsurgical outcome was classified into two groups; seizure free or relapsed. Aura was not considered as a relapse; only postoperative tonic-clonic seizures and complex partial seizures were considered as relapse.

Age, gender, race, epilepsy risk factors (e.g., history of perinatal problems, febrile seizures in childhood, head injury, CNS infections, family history of epilepsy, etc.), age at seizure onset (i.e., the first afebrile habitual seizure), seizure type(s) and history, date of surgery, date of the first relapse (if any) and date of the last contact with all patients were registered routinely. Auras were classified into seven groups as follows: epigastric, affective, cognitive, auditory, multiple, others, or none. The type and number of febrile seizures was not registered, so only their presence or absence based on history could be obtained.

Demographic variables and relevant clinical variables were summarized descriptively to characterize the study population. Outcome predictors, including gender, age at surgery, duration of epilepsy, race, history of status epilepticus before surgery, history of tonic-clonic seizures before surgery, history of febrile seizure in childhood, family history of epilepsy, full scale intelligence quotient (IQ), and seizure frequency were assessed comparing seizure free and non-seizure free patients, who had similar duration of postoperative follow-up (4.4 ± 1.1 *vs.* 4.3 ± 1.1 years, respectively). Initially, we performed univariate analyses using Pearson Chi-square, Mann-Whitney, Kolmogorov-Smirnov, and t-test. Variables that were significant or nearly so in univariate tests ($p < 0.1$) were assessed in a logistic regression. Time to event analysis was used to produce a Kaplan-Meier estimate of seizure recurrence. Cox-Mantel test was used. Odds ratio and 95% confidence interval (CI) were calculated. P value less than 0.05 was considered as significant. We used IBM SPSS Statistics 23 software. This study was conducted with approval by Thomas Jefferson University Institutional Review Board.

Results

During the study period, 685 patients had anterior temporal lobectomy at our center. Of these, 118 patients (17.2%) had normal MRIs; 95 patients (42 males and 53 females) in our database had drug-resistant nonlesional TLE with at least one year of postoperative follow-up and complete seizure data. Fifty-four (56.8%) patients had sustained seizure freedom and 41 (43.2%) patients experienced one or more seizures after surgery; of these, 13 patients (13.7% from total 95 patients) had some postoperative seizures, but were seizure free for one year or more in their last follow-up visit; therefore, 67 patients (70.5%) were seizure free for one year or more in their last visit. Three patients had early postoperative seizures (within the month after surgery); they continued to have seizures later on. For the statistical purposes, we first considered 54 patients as seizure free (those with sustained seizure freedom), as in this long-term postsurgical follow-up study patients were studied for different lengths of time. Risk factors for recurrence of the postoperative seizures in univariate analyses appear in Table 1. Seizure free patients were more likely to have had febrile seizures in their childhood and also a family history of epilepsy. Gender and having a history of status epilepticus showed a trend in univariate analyses (Table 1). We then performed a logistic regression analysis, assessing these four variables. Only a history of febrile seizures in childhood remained as a significant factor to predict postoperative seizure outcome (odds ratio 0.22; 95% CI: 0.06-0.83; $p = 0.02$); 69.3% of the cases were correctly predicted by the model. Gender ($p = 0.2$), a history of status epilepticus ($p = 0.1$) and a family history of epilepsy ($p = 0.1$) were not significant risk factors. Therefore, a history of febrile seizures in childhood was a strong predictor, and the only predictor, of good postoperative seizure outcome in patients with drug-resistant nonlesional TLE (Figure 1). We then performed the same analyses, while compared those who were seizure free for one year or

more in their last visit (67 patients) with the others (28 patients). The only significant factor in univariate analysis was a history of febrile seizure in childhood ($p = 0.02$).

In a subanalysis, we studied patients according to their positron emission tomography (PET) scan results. Twenty-eight patients did not have PET results available; 12 patients had a normal PET scan and 55 patients had abnormal PET results (e.g., hypometabolism). Among patients with a normal MRI and an abnormal PET scan (i.e., 55 patients), logistic regression analysis showed that only a history of febrile seizures in childhood was significant (odds ratio 0.036; 95% CI: 0.002-0.528; $p = 0.015$); 46.2% of the cases were correctly predicted by the model. Gender ($p = 0.1$), a history of status epilepticus ($p = 0.09$), a family history of epilepsy ($p = 1$), and a recent history of preoperative tonic-clonic seizures ($p = 0.5$) or any history of preoperative tonic-clonic seizures ($p = 0.1$) were not significant risk factors.

Discussion

Drug-resistant nonlesional temporal lobe epilepsy is a relatively common type of focal epilepsy that often responds favorably to surgery. In our study, 56.8% of the patients had sustained seizure freedom and 70.5% of the patients were seizure free for one year or more in their last follow-up visit, which is concordant with most previous studies [6-9]. This study aimed to resolve ambiguities regarding the prognostic value of historical risk factors in drug-resistant nonlesional TLE after surgery and found only one to be relevant to the seizure outcome.

A history of childhood febrile seizures predicted a better postoperative seizure outcome in patients with drug-resistant nonlesional TLE. This feature has never been examined in this population, as most previous reports have included patients with MRI-proven mesial temporal

sclerosis; such patients were excluded from our analysis. A previous meta-analysis of the predictors of temporal lobectomy outcome in a heterogeneous population of TLE patients found febrile seizures to be a strong prognostic indicator of seizure remission (odds ratio 0.48; 95% confidence interval 0.27–0.83) [7], which is similar to our findings. In some previous studies, which included patients with MTS, a history of febrile seizure in childhood did not predict the seizure outcome after surgery [10, 11]. Febrile seizures are strongly associated with MTS [12, 13], which itself is associated with a favorable prognosis. However, as an independent predictor, febrile seizure only predicts outcome when MTS is one of many underlying pathologies in patients with diverse etiologies for their epilepsy. It loses its predictive value when the subgroup of patients with MTS is examined [11]. Our finding that childhood febrile seizures were associated with favorable outcome in nonlesional TLE is probably due to the fact that many of these patients may have underlying MTS despite having normal MRI [6, 8]. We could not explore this in our study as we did not have adequate pathological examination of hippocampus in most of our patients.

In our study, occurrence or frequency of preoperative tonic-clonic seizures did not predict postoperative seizure outcome in patients with nonlesional TLE. Our findings contrast with a previous study of 64 patients with nonlesional TLE in whom a history of preoperative tonic-clonic seizure correlated with poor outcome [6]. When MRI or pathology clearly shows MTS, then preoperative tonic-clonic seizures reduce the chances of postoperative seizure freedom [10, 14]. In a previous study of patients with MRI-proven mesial temporal sclerosis, we observed that patients with a history of tonic-clonic seizures in the year preceding surgery were more likely to experience seizure recurrence (odds ratio 2.4; 95% CI: 1.19-4.80; p = 0.01). Another study of 339 patients followed for more than 2 years found that absence of generalized tonic-clonic

seizures and presence of hippocampal atrophy on MRI were significantly associated with remission in patients with medial temporal resection[15]. The relationship between seizures and outcome may be more complex, as there are multiple potential sites outside of mesial temporal lobe that may produce seizures. Seizures emanating from the temporal pole may differ from those from lateral neocortex, which may differ from basal foci. More careful anatomic definition may be needed to accurately assess this issue.

In our study, IQ did not predict postoperative seizure outcome in patients with nonlesional TLE. In one study, the authors examined the relationship between baseline IQ scores and seizure outcome in 1,034 temporal lobectomy patients from eight epilepsy surgery centers [16]. Those patients who continued to have seizures following surgery had statistically lower preoperative IQ scores than those who were seizure free ($p < 0.009$), but only by 2.3 points. There was considerable overlap between the two groups. However, relative risk analyses revealed no significant increase in risk of surgical failure among patients with low IQ scores who had no structural lesions other than mesial temporal sclerosis [16]. This is consistent with our findings. However, another study that included all resective epilepsy surgeries found a significant relation between IQ and seizure freedom, with higher IQ associated with better outcome [17]. Intelligence quotient may be relevant in epilepsy surgery when etiology is not considered, but appears to be of no importance in the subset of patients with nonlesional TLE. Similarly, our data suggests that the duration of epilepsy, frequency of preoperative habitual seizures, presence or absence of aura or the type of aura, a history of status epilepticus in the past, gender, race and a family history of epilepsy do not affect surgery outcome in patients with drug-resistant nonlesional TLE. However, as with other variables, better definition of location within the temporal lobe of the epileptogenic zone may provide other insights.

Previous studies have identified other risk factors associated with seizure outcome after surgery for drug-resistant nonlesional TLE. For example, in a previous study of 23 patients [18], the authors observed that the EEG findings were useful in predicting the postoperative seizure outcome. The best outcome occurred when seizure onsets and interictal epileptiform patterns were exclusive to one basal temporal region. Unfavorable outcome was more likely to occur when ictal origins were from mid-posterior temporal regions and when interictal discharges were bitemporal or multifocal in distribution [18]. Just one patient in their study had a history of febrile seizure in childhood. In another study of 40 patients with nonlesional drug-resistant TLE [19], preoperative factors associated with good outcome were absence of contralateral or extratemporal interictal epileptiform discharges and subtraction ictal single photon emission computed tomography (SPECT) Coregistered to MRI (SISCOM) abnormality localized to the resection site [19]. Eleven percent of their patients had a history of febrile seizure in childhood.

The limitations of our study include its retrospective design and single institution nature. In addition, imaging techniques have changed with equipment modernization and the general ability to detect abnormalities on MRI scans has improved. Other non-historical factors (e.g., resection size, EEG, etc.) are not taken into account in this study. Additionally, resections have evolved somewhat over the years, but there has been no difference in treatment strategy. Finally, pathology specimens were reviewed by pathologists, but most results were not sufficient to provide a precise pathological classification. Further studies should be designed to address these limitations (e.g., by looking at data from other institutions, performing a prospective study to improve the histology results, and looking at other types of TLE).

Conclusion

The historical risk factor associated with seizure outcome after surgery for drug-resistant nonlesional temporal lobe epilepsy in the current study (which was a history of febrile seizures in childhood) was different from such factor in mesial temporal lobe epilepsy patients (which was a history of tonic-clonic seizures in the year preceding surgery) in our previous study [14]. It is critical to distinguish among different types of TLE when assessing predictive factors for seizure outcome after surgery. This data will be combined with other data types to develop improved algorithms for predicting surgical outcome in patients with drug-resistant epilepsy.

Conflict of interest

Ali A. Asadi-Pooya, M.D., reports no disclosures.

Maromi Nei, M.D., Research: Upsher-Smith Laboratories, NINDS

Ashwini Sharan, M.D., Consulting, Clinical Trial Site – Medtronic; SJM, Clinical Trial Site – Grant, honorarium; ICVRX – ownership interest; ICP – ownership interest; Tiger labs – ownership interest; Saluda Medical – Clinical Trial Site.

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