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Major depressive disorder as a predictor of a worse seizure outcome one year after surgery in patients with temporal lobe epilepsy and mesial temporal sclerosis

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ABSTRACT

Purpose: The association between pre-surgical psychiatric disorders (PDs) and worse seizure outcome in patients with refractory epilepsy submitted to surgery has been increasingly recognized in the literature. The present study aimed to verify the impact of pre- and post-surgical PD on seizure outcome in a series of patients with refractory temporal lobe epilepsy and mesial temporal sclerosis (TLE–MTS).
Method: Data from 115 TLE–MTS patients (65 females; 56.5%) who underwent cortico-amygdalohippocampectomy (CAH) were analyzed. Pre- and post-surgical psychiatric evaluations were performed using DSM-IV and ILAE criteria. The outcome subcategory Engel IA was considered as corresponding to a favorable prognosis. A multivariate logistic regression model was applied to identify possible risk factors associated with a worse seizure outcome.
Results: Pre-surgical PDs, particularly major depressive disorder (MDD), anxiety and psychotic disorders, were common, being found in 47 patients (40.8%). Fifty-six patients (48.7%) were classified as having achieved an Engel IA one year after CAH. According to the logistic regression model, the presence of pre-surgical MDD (OR = 5.23; $p = 0.003$) appeared as the most important risk factor associated with a non-favorable seizure outcome.
Conclusion: Although epilepsy surgery may be the best treatment option for patients with refractory TLE–MTS, our findings emphasize the importance of performing a detailed psychiatric examination as part of the pre-surgical evaluation protocol.

1. Introduction

Epilepsy surgery has become an important treatment option for patients with refractory temporal lobe epilepsy (TLE), and 30–40% of patients with TLE are surgical candidates. Current evidence suggests that epilepsy surgery is associated with a 60–70% remission rate for long-term epileptic symptoms and significant improvements in quality of life (QOL).[1,2] Data from previous studies have demonstrated that cortico-amygdalohippocampectomy (CAH) is a safe, efficient surgical procedure for patients with refractory TLE and mesial temporal sclerosis (TLE–MTS), one of the commonest types of surgically remediable epileptic syndromes. TLE–MTS compromises the primary structures of the limbic system, particularly the hippocampus and amygdala.[3–7]

Previous research has demonstrated a prevalence rate of psychiatric comorbidity of 20–40% in TLE–MTS patients, rising to 70% in patients with refractory forms of this seizure disorder.[8–13] Mood disorders are the most common (24–74%), followed by anxiety (10–25%), psychotic disorders (2–9%) and personality disorders (1–2%).[6–11] Given the high prevalence of pre-surgical PDs in this population, the psychiatric outcomes of such patients after epilepsy surgery have attracted the particular interest of researchers.[6,7] Moreover, the association between pre-surgical PDs and a worse post-surgical seizure outcome in patients has been increasingly recognized.[14–17]

A number of risk factors for a poor post-surgical seizure outcome have been recognized. These include a lifetime psychiatric history, a history of secondarily tonic–clonic seizures, a long duration of the seizure disorder, larger resections of mesial temporal structures and the presence of neuropathologic abnormalities.[14–17] However, there are a number of methodological

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concerns about these studies: different types and etiologies of epilepsy have been analyzed together, patients submitted to different surgical procedures were analyzed together, different pre- and post-surgical psychiatric evaluations have been used, the psychiatric assessments were solely based on dimensional instruments, analyses have only included a limited number of clinical and sociodemographic variables and studies have included different follow-up periods after surgery.[18] These methodological problems have limited our understanding of the risk of surgical procedures with respect to post-surgical PD so far.[18] The present study aimed to verify the risk of pre- and post-surgical PD and other clinical and sociodemographic characteristics in predisposing individuals to a worse seizure outcome one year after surgery in a homogeneous series of patients with refractory TLE–MTS who were submitted to CAH.

2. Methods

2.1. Subjects

All TLE–MTS patients were followed in the outpatient clinic of a tertiary center (Epilepsy Section of the Universidade Federal de São Paulo, Brazil) from January 2003 to December 2011 and underwent video-electroencephalographic (VEEG) monitoring and a psychiatric evaluation. Inclusion criteria were patients who were above 18 years old, had an electroclinical diagnosis of TLE based on ILAE criteria,[19] had been submitted to CAH and had been subjected to follow-up for one year. All participants presented clear MRI findings of unilateral MTS and concordant interictal and ictal electroencephalographic (EEG) data. Exclusion criteria were the presence of other clinical or neurological diseases besides epilepsy, cognitive impairments precluding evaluations, bilateral MTS and/or age younger than 18 years old. All patients gave written informed consent to review their medical records.

Data from 115 TLE–MTS patients (65 females; 56.5%) were included in the study. The mean patient age, mean duration of epilepsy and mean age at epilepsy onset were 36.9 ± 10.77, 27.1 ± 12.14 and 9.5 ± 8.1 years, respectively. MTS occurred more frequently on the left side (75 patients; 65.2%). Background asymmetry on pre-surgical EEG was observed in 31 patients (26.9%) and was due to a slowing of the affected temporal regions (19 patients; 61.3%), a slowing of the affected cerebral hemispheres (9 patients; 29.0%) or to absence of physiological alpha and/or beta rhythms in the affected cerebral hemispheres (3 patients; 9.7%). Twenty-nine patients (25.2%) had a history of a potentially causative brain injury, with febrile seizures being the most frequent (25 cases; 86.2%). All patients had used at least two or more antiepileptic drugs (AEDs) prior to surgery. carbamazepine (CBZ) was the most frequently used AED, prescribed to 75 patients (65.3%), followed by phenytoin (PHT) (49 patients; 42.6%), phenobarbital (PB) (34; 29.5%), topiramate (TPM) (24; 21.2%) and oxcarbazepine (OXC) (12; 10.4%). Benzodiazepines (BZDs), particularly clobazam (CLB), were the most common adjunctive drugs and were prescribed to 49 patients (42.6%).

2.2. Procedures

Patients underwent 2–6 days of continuous VEEG monitoring with 32-channel EEG recording, with electrodes, including sphenoidal electrodes, placed according to the 10–10 system on the temporal lobe. MTS was determined to be present if atrophy, an increased T2-weighted signal, a decreased T1-weighted signal and a disrupted internal structure of the hippocampus were present, accompanied by atrophy of the amygdala and/or temporal pole signal alteration on visual inspection of the MRI pictures. The epileptogenic zone was determined by predominantly ipsilateral interictal epileptiform discharges (80% cutoff) and seizure onset recorded during prolonged VEEG monitoring. The association between MTS side and the frequency of interictal sharp waves on pre-surgical EEG was also analyzed, and a cutoff of >80% was considered for predominantly ipsilateral activity. Asymmetric background activity was defined by the presence of slowing or absence of physiological alpha and/or beta rhythms in the affected temporal lobes or cerebral hemispheres of background activity on pre-surgical EEG. Refractoriness to medical treatment was considered present if seizures persisted after the utilization of at least two first-line medications for partial seizures at the highest tolerated doses for at least 6 months. The potentially causative brain injuries were defined as the occurrence of severe cerebral events in the first year of life before the appearance of epilepsy that required medical intervention and/or hospitalization. Febrile seizures, meningoencephalitis, head trauma or severe perinatal hypoxia were considered potentially causes of brain injury.

The surgical procedure consisted of an en bloc resection of the superior, middle, inferior temporal and fusiform gyri, with a posterior limit of 4.5 cm from the tip of the temporal lobe. After opening the temporal horn, the mesial temporal structures (hippocampus, amygdala and parahippocampal gyrus) were also resected.[3–5] Engel's classification was utilized to measure the patients' seizure outcomes one year after CAH. Only the subcategory Engel IA (completely seizure-free) was defined as a favorable prognosis.[20] All of the Engel subcategories are described in Table 1.

2.3. Psychiatric evaluation

A single psychiatrist (GMAF) conducted the clinical interviews for this study using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) Axis I criteria.[21] Because each patient could have more than one Axis I psychiatric diagnosis, the number of patients diagnosed and all comorbid PDs diagnosed were both considered in the analysis. The presence of other specific psychiatric diagnoses commonly associated with epilepsy, not covered by the DSM-IV but well-described in the literature, such as interictal dysphoric disorder (IDD) and the psychoses of epilepsy, were evaluated using the ILAE criteria. These criteria were also

Table 1
Engel's classification of post-surgical outcome.

Class I: Free of disabling seizures[a]
A. Completely seizure-free since surgery
B. Nondisabling simple partial seizures only since surgery
C. Some disabling seizures after surgery, but free of disabling seizures for at least two years
D. Generalized convulsions with AED* discontinuation only
Class II: Rare disabling seizures (''almost seizure-free'')
A. Initially free of disabling seizures but has rare seizures now
B. Rare disabling seizures since surgery
C. More than rare disabling seizures since surgery, but rare seizures for the last two years
D. Nocturnal seizures only
Class III: Worthwhile improvement[b]
A. Worthwhile seizure reduction
B. Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not <2 years
Class IV: No worthwhile improvement
A. Significant seizure reduction
B. No appreciable change
C. Seizures worse

[a] Excludes early post-surgical seizures (first few weeks).
[b] determination of ''worthwhile improvement'' requires quantitative analysis of additional data, such as the percent seizure reduction, cognitive function and quality of life.
* AED: antiepileptic drugs.