Journal of Epilepsy and Clinical Neurophysiology

J Epilepsy Clin Neurophysiol 2012;18(1):21-25

Trabalho vencedor do *Prêmio Paulo Niemeyer* – XXXIV Congresso Brasileiro de Epilepsia – 2012

Pre-Surgical Mood Disorders Associated to Worse Post-Surgical Seizure Outcome in Patients with Refractory Temporal Lobe Epilepsy and Mesial Temporal Sclerosis

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SUMMARY

Objectives: This study aims at verifying the impact of pre-surgical PD on seizure outcome in patients with refractory temporal lobe epilepsy and mesial temporal sclerosis (TLE-MTS). **Methods:** After previous consent, retrospective data from 115 surgically treated (corticoamygdalohyppocampectomy) TLE-MTS patients (65 females; 56.5%) were analyzed. Psychiatric evaluations were performed through DSM-IV criteria. Engel IA was established as a favorable prognosis. **Results:** Forty-five patients (41.6%) were classified as Engel IA, while 47 (40.8%) presented pre-surgical PD. Depression (OR=5.11; p=0.004) appeared as a risk factor associated to a non-favorable seizure outcome. **Conclusion:** In patients with refractory TLE-MTS, the presence of depression predicts an unfavorable outcome.

Keywords: Temporal lobe epilepsy; mesial temporal sclerosis; epilepsy surgery; psychiatric disorders; seizure outcome.

RESUMO

Transtornos de humor pré-cirúrgicos associados ao prognóstico pós-cirúrgico desfavorável em pacientes com epilepsia do lobo temporal e esclerose mesial temporal

Objetivo: No presente trabalho avaliamos o impacto da presença de transtorno psiquiátrico pré-cirúrgico sobre o prognóstico cirúrgico em pacientes com epilepsia do lobo temporal e esclerose mesial temporal (ELT-EMT). **Metodologia:** Analisamos, retrospectivamente, os dados de 115 pacientes com ELT-EMT (65 mulheres, 56,5%) tratados cirurgicamente (corticoamigdalohipocampectomia). As avaliações psiquiátricas foram feitas de acordo com os critérios DSM-IV. O prognóstico favorável foi definido como ausência de crises desde a cirurgia (Engel IA). **Resultados:** Dos 115 pacientes tratados, 45 (42,6%) tiveram prognóstico favorável e 47 (40,8%) apresentavam transtorno psiquiátrico pré-operatório. A presença de depressão (OR=5,11; p=0,004) foi associada ao prognóstico cirúrgico desfavorável. **Conclusão:** A presença de depressão durante a avaliação psiquiátrica pré-operatória é um fator preditivo de prognóstico desfavorável em pacientes com ELT-EMT.

Unitermos: Epilepsia do lobo temporal, esclerose mesial temporal, cirurgia de epilepsia, transtorno psiquiátrico, resultado cirúrgico.

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Received Apr. 28, 2012; accepted Apr. 30, 2012.

1 INTRODUCTION

Anterior and mesial temporal lobectomy (ATL) is an important treatment option for 30 to 40% ofpatients with temporal lobe epilepsywhich present a medically intractable disease, with an approximately 70% chance of long-term seizure freedom.[1-5] Refractory temporal lobe epilepsy and mesial temporal sclerosis (TLE-MTS) is a condition that compromises the main structures of the limbic system,being also one of the most common surgically remediable epileptic syndromes.[1-5]

Studies have observed a comorbid psychiatric prevalence rate of 20-40% in TLE-MTS, rising to 70% in patients with refractory forms of epilepsy.[6-11] Mood disorders are the most common (24-74%), followed by anxiety (10-25%), psychotic (2-9%) and personality disorders (1-2%).[6-11] The association between pre-surgical PDand a worse post-surgical seizure outcome in patients with refractory epilepsy submitted to epilepsy surgery has been also increasingly recognized.[12-15] However,different types and etiologies of epilepsy have been analyzed together in such studies, precluding important insights regarding specific epilepsy syndromes.[16] The present study aims to verifytherisk of pre- and post-surgical PDin predisposing to a worse seizure outcome in a homogeneous series ofpatients with refractory TLE-MTS submitted to ATL.

2 METHODS

2.1 Subjects

All patients were followed-up in the Epilepsy Surgical Program of the Universidade Federal de São Paulo, Brazil, from 2003 to 2011. After previous consent, 115 TLE-MTS patients were included in the study. Inclusion criteria were patients older than 18 years of age, the presence of electroclinical diagnosis of TLE based on ILAE,[17] ATL as the surgical procedure and follow-up of at least one year. All participants hadclear MRI findings of unilateral MTS and concordant interictal and ictal EEG data.

2.2 Procedures

Patients underwent 2-6 days of continuous video-electroencephalographic(VEEG) MTS was defined if atrophy, an increased T2-weighted signal, a decreased T1-weighted signal, and disrupted internal structure of the hippocampus were present on visual inspection of MRI. Epilepsy was considered resistant to medical treatment when seizures persisted after the utilization of at least two first line medications for partial seizures at highest tolerated doses. The surgical procedure consisted of "en block" resection of superior, middle, inferior temporal and fusiform gyri, with 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 parahyppo-campal gyrus) were also resected "en block".[1,2,5] The most recent Engel's classification was utilized to measure the patients' seizure outcome,[18] and only the subcategory Engel IA (completely seizure-free since surgery) was considered as a favorable prognosis. Initial precipitant injury (IPI) was defined as the occurrence of severe cere-bral 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 as IPI.

2.3 Psychiatric evaluation

All patients were evaluated by the same psychiatrist (GMAF) through the Diagnostical and Statistical Manual of Mental Disorders (DSM-IV) axis I criteria.[19] The presence of other specific psychiatric diagnoses of epilepsy not covered by DSM-IV, such as the interictal dysphoric disorder (IDD), postictal psychosis (PIP) and interictal psychosis (IIP) were evaluated through ILAE criteria.[20] Information about lifetime history of psychiatric treatment, defined as any treatment with psychiatric drugs occurred in the past, was collected with patients in the first clinical interview, as well as family history of epilepsy and PD. Due to ethical issues, all patients underwent pre-surgical and at least one post-surgical psychiatric evaluation within the first year after surgery. In addition to surgical follow up, those patients with pre-surgical, post-surgical and/or *de novo* PD received psychiatric follow-up after surgery, and the most recent psychiatric evaluation was considered for analysis.

2.4 Statistics

Statistical analyses were performed with SPSS 10.0 software. Patients were divided into those with or without a favorable post-surgical outcome at the moment of the study. Bivariate statistical analyses were performed through the most adequate statistical test for each situation (chi-square, χ^2, Fisher's exact test or Student's t test for unequal variances). A multivariate statistical analysis (logistic regression model) was performed to identify predictors ofa non-favorable seizure outcome, and the *odds-ratio* (OR) was calculated for significant risk factors. P value of <0.05 was considered significant.

3 RESULTS

Data from 115 TLE-MTS (65 females; 56.5%) were analyzed. The mean age and epilepsy duration were of 36.9 ± 10.77 and 27.1 ± 12.14 years, respectively. All patients had been in use of association of two or more antiepileptic drugs (AED). Carbamazepine (CBZ) was

the most frequent, followed by clobazam (CLB) and phenobarbital (PB). The mean follow-up interval after surgery was of 4.7±1.66(one to eight) years.Forty-nine patients (42.6%) were seizure-free (Engel IA) at the moment of the study, whereas 31 patients (26.9%) were Engel IB/IC/ID, 23 (20%) were Engel II, ten (8.7%) were Engel III, and two (1.8%)were Engel IV. Pre-surgical PD occurred in 47 patients (40.8%), while post-surgical PD occurred in 31 (26.9%). Pre-surgical PD observed in both groups of patients are described in Figure 1.

We found no significant differences between the two groups was seen when all the others clinical and socio-demographic variables were analyzed, except for pre-surgical PD, which was associated to a non-favorable seizure outcome (p=0.002) in the initial model. See Table 1.

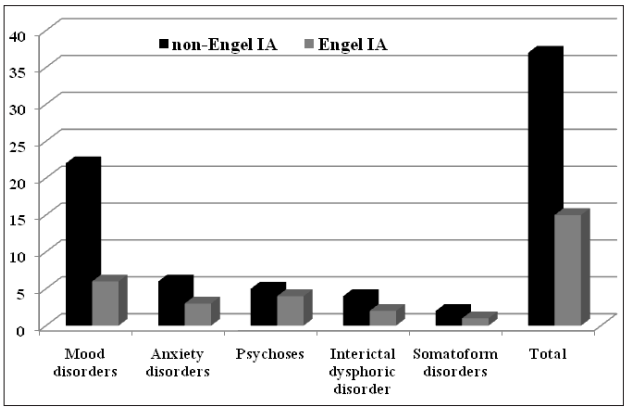

Figure 1. Number and types of pre-surgical psychiatric diagnoses in patients with temporal lobe epilepsy and mesial temporal sclerosis submitted to anterior temporal lobectomy.

Table 1. Clinical and demographic data from temporal lobe epilepsy and mesial temporal sclerosis patients submitted to anterior temporal lobectomy.

Clinical/demographic data	Engel IA	Non-Engel IA	*P*
Number of patients (%)	49 (42.6)	66 (57.4)	-
Age at surgery (mean ± SD)	36.7±10.9	37.0±10.7	0.85
Gender-females (%)	26 (53.1)	40 (60.6)	0.45
Age at epilepsy onset (mean ± SD)	10.5±9.0	8.8±7.3	0.28
Years of epilepsy at surgery (mean ± SD)	24.1±12.9	24.2±12.5	0.67
Lifetime psychiatric treatment (%)	12 (24.5)	19 (28.8)	0.67
Family history of epilepsy (%)	12 (24.5)	24 (36.4)	0.22
Family history of psychiatric disorders (%)	5 (10.2)	13 (19.7)	0.20
Presence of febrile seizures (%)	8 (16.3)	17 (25.8)	0.23
Presence of left-sided MTS (%)	29 (59.2)	46 (69.7)	0.32
Presence of pre-surgical PD (%)	13 (26.5)	37 (56.1)	0.002*
Presence of post-surgical PD (%)	11 (22.4)	20 (30.3)	0.40
Disorganized VEEG background activity (%)	9 (18.4)	14 (21.2)	0.81
Contralateral slow-waves on VEEG (%)	12 (24.5)	18 (27.3)	0.97
Contralateral epileptiform discharges on VEEG (%)	15 (30.6)	19 (28.8)	0.64
Years of follow-up (mean ± SD)	4.5±1.6	4.8±1.6	0.27

MTS: mesial temporal sclerosis; SD: standard deviation; PD: psychiatric disorders; VEEG: video-electroencephalographic monitoring.
* $p < 0.05$.

A multivariate logistic regression model was performed (sensivity 78.8%; specificity 71.2%; positive predictive value 73.2%; negative predictive value 68.1%; area under the curve 0.768) to identify possible clinical and socio-demographic risk factors associated to a non-favorable seizure outcome. The presence of any pre-surgical PD was associated to a worse surgical outcome (OR=3.53; p=0.002) at initial model.However, when psychiatric diagnoses were analyzed separately, onlymajor depressive disorderpersisted as statistically significant (OR=5.11; p=0.004), while other PD together (except depression) were not significant (OR=1.62; p=0.34).The presence of post-surgical PD wasnot associated with a worse seizure outcome (OR=1.50; p=0.35), as well as others clinical and socio-demographic variables. Table 2 shows the final adjusted model's results.

Table 2. Logistic regression results: final adjusted model.

Risk factors	Odds ratio	*p>z*
Family history of PD	2.49	0.14
Presence of febrile seizures	4.25	0.06
Lifetime psychiatric treatment	1.69	0.25
Pre-surgical PD (except depression)	1.62	0.34
Post-surgical PD	1.50	0.35
Pre-surgical depression	5.11	0.004*

PD: psychiatric disorders.
* $p<0.05$.

4 DISCUSSION

In the present paper we studied theimpact of pre-surgical PD on the seizure outcome in a homogeneous series of patients with a specific and prevalent epilepsy syndrome submitted to the same surgical procedure (ATL). Psychiatric evaluations were performed by the same diagnostic criteria based on the modern psychiatric nosography.

Surgery became an important treatment option for patients with refractory TLE-MTS and ATL has appeared as a safe and efficient surgical procedure,[1-5] althoughsome authors have highlighted the relative high risk of the appearance of PD in patients submitted to surgical procedure, while other studies do not support such hypothesis.[16,21-24]

Some recent studies consider pre-surgical PD as predictors of seizure outcome after surgery.[12-15] However, most reports consist of patients with heterogeneous epileptic syndromesand followed-upfor limited periods, precluding conclusionsin more specific populations, such as TLE-MTS.[16] Nevertheless, it has been increasingly recognized that a pre-surgical PD could be a significant predictor of seizure outcome after surgery. Literature data have observed that pre-surgical PD, as well as a lifetime history of depressionpredicts a worse post-surgical seizure outcome among patients with refractory TLE. The most discussed hypothesis in literature is that pre-surgical PD, and particularly depression, would be possible epiphenomena of a more diffuse cerebral disease and with a consequently worse seizure control.[13-15] Such observations could reinforce the bidirectionality of the association between depression and postoperative seizure status that could be explained by underlying common pathophysiological mechanisms in both depression and epilepsy.[13-15,25] Moreover, the majority of series reported an association between the absence of post-surgical PD and a better surgical outcome.[21-25] The present study observed a statistically significant association between the absence of pre-surgical PD and a favorable seizure outcome. In addition, pre-surgical major depressive disorder was associated to a worse seizure outcome at the multivariate logistic regression model. Such findings are in accordance with recent data and also support current hypothesis regarding pre-surgical PD and seizure outcome.[13-15]

Although performed in a relatively small number of patients, our observations are in line with recent literature data and strengthenthe importance of the pre-surgical PDin a specific population of TLE-MTS patients. The findings of the present paper are of great value and reinforce the importance of performing a detailed psychiatric pre-surgical evaluation of epilepsy patients,[4,5,13-16] once it showed anassociation between pre-surgical PD and non-favorable seizure outcome.[13-16]

ACKNOWLEDGMENTS

This work was supported by CAPES and FAPESP from Brazil.

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