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Short Communication

Are psychogenic nonepileptic seizures risk factors for a worse outcome in patients with refractory mesial temporal epilepsy submitted to surgery? Results of a retrospective cohort study

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ABSTRACT

Objective: The objective of this study was to verify if the presence of psychogenic nonepileptic seizures (PNES) could be a risk factor precluding corticoamygdalohippocampectomy (CAH) in patients with refractory temporal lobe epilepsy (TLE) and mesial temporal sclerosis (MTS) (TLE-MTS).
Methods: This retrospective cohort study analyzed medical data of patients with refractory TLE-MTS accompanied in a Brazilian epilepsy surgery center. Presurgical psychiatric evaluations were performed using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. Engel's I classification two years after surgery was considered as a favorable outcome.
Results: Of the 81 patients initially included (65 females; 56.5%), 49 (60.5%) had TLE-MTS without PNES, 24 (29.7%) with TLE-MTS and PNES, and eight (9.8%) with PNES only, who were excluded from further statistical comparisons. Nine patients with PNES (37.5%) underwent CAH versus 35 (71.4%) without PNES ($p = 0.005$). Five patients (55.5%) with PNES versus 26 (74.3%) without PNES presented Engel I ($p = 0.54$). The relative risk (RR) was of 1.90 for patients without PNES to undergo CAH and of 1.33 to be at Engel I.
Conclusions: In this study, PNES were associated with less CAH. There were no differences, however, regarding favorable postsurgical outcomes. These results highlight that the sole presence of PNES should not preclude CAH in patients with TLE-MTS, despite the necessity of careful presurgical psychiatric evaluation.

1. Introduction

Recent data have demonstrated that 30–40% of patients with epilepsy present with medically intractable disease despite treatment with antiepileptic drugs (AEDs), and that corticoamygdalohippocampectomy (CAH) is a safe and efficient surgical procedure for patients with refractory epilepsy [1]. Refractory temporal lobe epilepsy (TLE) is one of the most frequent epilepsy syndromes followed up in tertiary epilepsy centers, and mesial temporal sclerosis (MTS) have been the most frequent etiology of TLE observed among these patients, compromising the primary structures of the limbic system, particularly the hippocampus and amygdala. Temporal lobe epilepsy and MTS (TLE-MTS) also have been associated with cognitive deficits, psychiatric disorders (PD) and lower quality of life [2]. Moreover, TLE-MTS is also one of the most common types of surgically remediable epilepsy syndromes [1,2]. Although CAH has become an important treatment option for patients with TLE-MTS in tertiary epilepsy centers, authors have highlighted that 20–40% of those patients have PD, which can rise to 70% in patients with refractory forms [2,3]. Additional evidence has suggested that the presence of presurgical PD has been possibly associated with worse postsurgical seizure outcomes [4,5].

Psychogenic nonepileptic seizures (PNES) are paroxysmal episodes superficially resembling epileptic seizures but are not associated with any electrical abnormalities [6,7]. Most patients with PNES, although their clinical heterogeneity, fulfill the diagnostic criteria of a functional neurological symptom disorder (FNSD) (Diagnostic and Statistical Manual of Mental Disorders [DSM-5]) or of dissociative convulsions (International Classification of Diseases 10th revision [ICD-10]) [8,9]. There is a scarcity of studies investigating such outcomes on specific subgroups of patients with dual diagnoses of TLE-MTS and PNES [10,11]. Apart from the severity of the comorbid TLE-MTS and/or the possibility to achieve seizure freedom, the presence of PNES has been considered a relative contraindication for CAH due to the possibility of pre- and postsurgical behavioral complications [11,12]. The present study aimed to investigate if the presence of PNES could be a risk factor to preclude CAH in a homogeneous group of patients with TLE-MTS treated in a tertiary epilepsy center,

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as well as to provide evidence of this therapeutic approach for this specific subgroup.

2. Methods

2.1. Subjects

At the time this study was conducted, 385 patients were treated in a tertiary epilepsy center (outpatient epilepsy clinic of Faculdade de Medicina de São José do Rio Preto — FAMERP) from 2003 to 2016. Included criteria for this retrospective cohort study were patients who were 18 years or older with a possible electroclinical diagnosis of TLE based on the International League Against Epilepsy (ILAE) classification [13]. After careful presurgical neurological, psychiatric and video-electroencephalographic (VEEG) investigation, some patients were submitted to CAH [1] on our unit and were followed for two years after surgery. Exclusion criteria were clinical or other neurological illnesses besides epilepsy, cognitive impairments precluding psychiatric and clinical evaluations, bilateral MTS, other epilepsy syndromes, and expressed reasons present in medical files to not undergo CAH.

2.2. Procedures

All patients underwent 2–6 days of continuous VEEG monitoring with 32-channel electroencephalogram (EEG) recording, with electrodes placed according to the 10–10 system on the temporal lobe. Mesial temporal sclerosis 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 magnetic resonance imaging (MRI) pictures. Refractoriness to AED treatment was defined 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.

As a routine procedure of the service, caregivers of patients with PNES were oriented by team professionals to distinguish between seizures and PNES, through the observation of patient's own seizures filmed during the presurgical monitoring period. After this training period, they were considered fit to distinguish between the two types of crisis if they obtained a hit rate higher than 80%, which was also considered an inclusion criterion. These caregivers, who were very close to patients, were responsible to verify the occurrence of PNES in postsurgical period.

Surgical procedures were already described in literature [1,2,5]. Engel's classification was utilized to measure seizure outcome and was determined through the verification, at clinical encounters, of daily seizure diaries. Only the subcategory Engel I was considered as a favorable prognosis [14]. Since this research was beased on retrospective data analyses, the informed consent term signature was dispensed after local ethics committee consultation and approval.

2.3. Psychiatric evaluation

A single psychiatrist (AERF) conducted the clinical interviews using the DSM-5 criteria [8]. All comorbid PD diagnosed were considered for statistical comparisons. The presence of other specific psychiatric diagnoses not covered by the DSM-5 but well-described in the literature, such as, interictal dysphoric disorder (IDD) and the psychoses of epilepsy, were evaluated using the ILAE criteria [15]. Data concerning lifetime history of psychiatric treatment (defined as any past psychiatric drug treatment) and family history of epilepsy and PD were also obtained from patients' files. All patients were submitted to at least one presurgical psychiatric evaluation. Psychiatric follow-up was offered to all patients with diagnosed PD.

2.4. Statistics

Statistical analyses were performed using SPSS 24.0 software (IBM, 2014). Patients were divided in two groups according to the presence of PNES in presurgical evaluation. Statistical analyses were performed using analysis of variance (ANOVA), Student's *t*-test or Fisher's exact test, and the Bonferroni adjustment for multiple tests was applied as a posthoc test for statistically significant differences. The relative risk (RR) indices were calculated for the possibility to underwent CAH and to reach Engel I classification two years after surgery. A p value of <0.05 was considered significant.

3. Results

Data from 81 patients were included. The VEEG investigation disclosed that 49 (60.5%) had TLE-MTS without PNES, 24 (29.7%) with TLE-MTS and PNES, and eight (9.8%) with PNES only, who were excluded from further statistical comparisons. The psychiatric diagnoses and statistical differences between groups are exposed in Table 1 and Fig. 1.

It was observed that a significantly higher number of patients with TLE-MTS without PNES underwent CAH (35; 71.42%) versus nine (37.5%) with TLE-MTS and PNES ($p = 0.005$). Nevertheless, five patients (55.5%) of the group with TLE-MTS with PNES and 26 (74.3%) from the group without PNES presented Engel I outcome two years after CAH ($p = 0.54$). The RR calculated was 90% higher for patients without PNES to undergo CAH ($RR = 1.90$), and 33% higher for the same group to be at Engel I two years after surgery ($RR = 1.33$).

Table 1
Clinical and demographic data of patients with TLE-MTS with and without PNES submitted to corticoamygdalohippocampectomy.

Clinical/demographic data	Patients with PNES	Patients without PNES	p
Number of patients	24	49	–
Number of females (%)	15 (62.5)	23 (46.3)	0.15[a]
Age	38.6 ± 12.4	38.4 ± 13.7	0.90[b]
Age at epilepsy onset (mean ± SD)	17.1 ± 13.9	12.4 ± 11.7	0.19[b]
Years of epilepsy duration (mean ± SD)	20.1 ± 14.4	25.4 ± 14.1	0.34[b]
Previous psychiatric treatment (%)	15 (62.5)	13 (26.5)	**0.02**[*,a]
Family history of epilepsy (%)	9 (37.5)	13 (26.5)	0.78[a]
Family history of psychiatric disorders (%)	10 (41.6)	7 (14.3)	**0.02**[*,a]
MTS lateralization			
Left	16 (66.7)	20 (40.8)	0.07[a]
Right	8 (33.3)	29 (59.2)	0.07[a]
Most frequently used AEDs (%)			
Carbamazepine	17 (70.8)	30 (61.2)	0.64[a]
Phenytoin	10 (41.6)	20 (40.8)	0.88[a]
Phenobarbital	8 (33.3)	15 (30.6)	0.84[a]
Topiramate	6 (25.0)	13 (26.5)	0.74[a]
Oxcarbazepine	4 (16.6)	10 (20.4)	0.64[a]
Benzodiazepines	13 (54.1)	21 (42.8)	0.53[a]
Presence of PD (%)	24 (100.0)	15 (30.6)	<**0.001**[*,a]
Major depressive disorder	8 (33.3)	7 (14.3)	0.22
Anxiety disorders	9 (37.5)	2 (4.1)	**0.002**[*,c]
Psychotic disorders	0 (0.0)	4 (8.1)	0.24[c]
Somatoform disorders	24 (100.0)	2 (4.1)	<**0.001**[*,c]
Dissociative disorders	6 (25.0)	1 (2.0)	**0.008**[*,c]
Interictal dysphoric disorder	5 (20.8)	3 (6.1)	0.16[c]
Two or more PD	17 (70.8)	5 (10.2)	<**0.001**[*,a]

AED: antiepileptic drug; IPI: initial precipitant injury; MTS: mesial temporal sclerosis; PD: psychiatric disorders; PNES: psychogenic nonepileptic seizures; SD: standard deviation; TLE: temporal lobe epilepsy ;.

[a] Analysis of variance (ANOVA).
[b] Student's *t*-test.
[c] Fisher's exact test.
[*] $p < 0.05$.

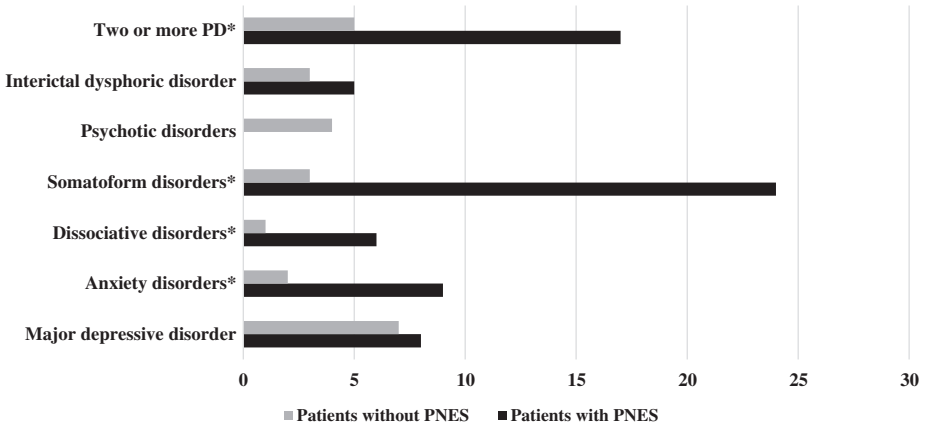

Fig. 1. Psychiatric diagnoses of patients with TLE-MTS with and without psychogenic nonepileptic seizures submitted to corticoamygdalohippocampectomy. PD: psychiatric disorders; PNES: psychogenic nonepileptic seizures; *$p < 0.05$.

4. Discussion

The main objective of this retrospective cohort study was to verify if the presence of PNES could be a risk factor precluding CAH in patients with refractory TLE-MTS treated in a tertiary center. Compared to patients without PNES, the group with TLE-MTS and PNES presented a significantly higher PD and less patients submitted to CAH. There were no differences, however, regarding favorable postsurgical outcomes.

There was an elevated frequency of PD among patients with TLE-MTS, corroborating the frequency and types of psychiatric comorbidities disclosed in other studies involving populations with TLE-MTS with and without PNES [2,5,11]. All patients with PNES presented at least one PD beyond FNSD, and more than half of them presented two or more PD, corroborating prior studies [6,7,11,12]. Therefore, a comprehensive psychiatric assessment undertaken by professionals with the skills required to handle such disorders is highly necessary [6,7,11,12].

Regardless of the variety of methodological concerns, evidence has suggested that the presence of presurgical PD has been possibly associated with worse postsurgical seizure outcomes [2–5]. Despite the scarcity of data in literature discussing the impact of PNES in epilepsy surgery, studies have observed that PNES have not been associated with a worse seizure outcome, also disclosing postsurgical behavioral and psychiatric improvements [12]. The present study reinforces such previous data, since there were no significant differences regarding favorable clinical outcomes when both groups were compared. To our knowledge, this is the first study that disclosed the impact of PNES in postsurgical outcomes in a homogeneous series of TLE-MTS. It was observed, however, significant differences of the proportion of patients who were submitted to CAH. In addition, there was a RR of 1.90 for patients without PNES to undergo CAH. These findings highlight that, despite opposing evidence, the presence of PNES possibly still has been considered a risk factor to preclude CAH [12].

There are, however, important limitations of the present study. Since the data were obtained in a retrospective manner, we were unable to assess the postsurgical status of patients. The results observed should not be generalized to all patients with a dual diagnosis of PNES and epilepsy, since a specific population of TLE-MTS with comorbid PNES was studied. However, this could also be considered an important strength of the present study, which has found psychiatric, clinical, and sociodemographic characteristics of this specific subgroup. Although based upon a relatively small number of patients, present findings are concordant with the extant literature and address a relatively homogeneous population of patients with dual diagnoses of TLE-MTS and PNES.

This study did not disclose statistical difference in favorable (Engel I) outcomes between both cohorts. However, since a relatively wide difference between Engel I outcomes (around 20%) was observed, this result need to be carefully interpreted. The numbers may have been within the limit of the statistical confidence interval and possibly would have clinical significance. To the present date, and despite the scarcity of data, studies have not observed worse seizure outcome in patients with epilepsy and PNES [12]. Therefore, we believe that such issue needs to be confirmed through manuscripts with a larger sample size and a prospective methodology.

To conclude, this study had disclosed that, although PNES were associated with an elevated frequency of PD and to a lower frequency of CAH, there were no differences regarding favorable postsurgical outcomes. Despite limitations, it was observed that the sole presence of PNES should not preclude epilepsy surgery in a homogeneous series of patients with TLE-MTS, even though they require a careful presurgical psychiatric evaluation [6,7,11,12].

Conflicts of interest

Authors report no conflict of interest.

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