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Psychiatric comorbidity in patients with two prototypes of focal *versus* generalized epilepsy syndromes

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ABSTRACT

The frequency of psychiatric disorders (PD) in a homogeneous series of patients with temporal lobe epilepsy with mesial temporal sclerosis (TLE-MTS) compared to patients with juvenile myoclonic epilepsy (JME) was evaluated, aiming to determine the frequency of PD and possible differences in psychiatric diagnoses between these two epileptic syndromes. Data from 248 patients with refractory TLE-MTS and from 124 JME patients were reviewed and compared. There was a high prevalence of PD in both groups of epilepsy patients, present in 100 TLE-MTS (41%) and in 58 JME patients (46.7%). Mood (23.7%), anxiety (13.7%) and psychotic (11.6%) disorders were the most frequent diagnoses in TLE-MTS group, while mood and anxiety disorders (25% and 21%, respectively) were the most common PD among JME. Psychoses were significantly associated with TLE-MTS ($p = 0.01$). These observations are concordant with our previous study, reforcing the existence of a possible anatomic correlation of PD and brain structures involved in both epilepsy syndromes.

1. Introduction

The association between epilepsy and psychiatric disorders (PD) has been recognized for centuries and has become a matter of interest, with important studies emphasizing these aspects.[1–8] Available data support an increased risk for psychiatric comorbidity in epilepsy patients, indicating that it occurs in 20–40% of this population, being even more frequent in patients with refractory seizures, in which this prevalence can be as high as 70%.[2] Although studies have highlighted temporal lobe epilepsy (TLE) patients to be at an increased risk for PD when compared to those with extratemporal or primary generalized epilepsies, this was not confirmed by other studies.[9–13] There is also a lack of data regarding the frequency of PD in specific etiologies of TLE such as mesial temporal sclerosis (TLE-MTS), a condition that compromises mainly structures of the limbic system, particularly the hippocampus and the amygdala. In addition, few studies had performed adequate controlled analyses using well-established diagnostic instruments for PD.[2,8,13] Besides, they have concentrated mainly in patients with TLE,[5–8] and a lack of data regarding the prevalence of PD in other epileptic syndromes still exists.[8,13]

Several investigators have reported a high prevalence of PD among patients with primary generalized epilepsies (PGE).[14–19] Recent studies have observed that up to one-third of patients with adult-onset PGE are diagnosed and treated for PD,[16–19] and a high frequency of mood and anxiety disorders, as well as mild to moderate personality disorders have been reported.[16–18] Juvenile myoclonic epilepsy (JME) is a well defined primary generalized epileptic syndrome that comprises 5–11% of patients with epilepsy, characterized by myoclonic jerks and generalized tonic-clonic seizures (GTCS) and typical findings of generalized 4–6 Hz spike and wave or poly-spike and wave activity maximum in frontocentral regions in electroencefalogram (EEG).[2] In this syndrome high rates of PD, particularly anxiety, mood and mild to moderate personality disorders have been described[14–18] as well as frontal lobe dysfunctions.[2,20,21]

The frequency of PD in a group of 170 TLE-MTS and 100 JME was performed in a previous study,[19] and no significant differences in the frequency and number of psychiatric diagnoses were observed when both groups were compared. In order to confirm those previous findings, we evaluated the frequency of axis I disorders in a homogeneous series of 248 patients with refractory TLE-MTS and in 124 with JME, aiming to investigate differences in types of PD in each group and possible correlations to clinical and physiopathological variables, such as duration of the disease, family history of epilepsy, and laterality of MTS. We focused our attention on the analysis of the importance of the type of epileptic syndrome (focal

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versus generalized epilepsies) for the development of PD, discussing possible anatomic correlations between the epileptic syndrome and its psychiatric comorbidity.[1,14]

2. Methods

2.1. Subjects

All patients were followed-up in the outpatient's clinic of a tertiary center (Epilepsy Section of the Universidade Federal de São Paulo, São Paulo, Brazil), from July 2005 to July 2010. After previous consent, 248 with refractory TLE-MTS and 124 patients with JME were included. The inclusion criteria were the presence of electroclinical diagnosis of JME or TLE based on ILAE classification[22] and having been treated in our unit for at least 6 months. All TLE patients also had clear MRI findings consistent with unilateral or bilateral MTS and concordant interictal and ictal EEG data. JME patients had typical EEG showing generalized 3–6 Hz spike and wave or poly-spike and wave activity maximum in frontocentral regions. Exclusion criteria were clinical illnesses besides epilepsy and antihistamine administration or alcohol consumption within 72 h prior to the evaluation. Caffeine or nicotine use on the day of testing, different from that usually taken, was also considered exclusion criteria.

2.2. Procedures

Patients with TLE underwent 2–6 days of continuous video-EEG monitoring with 32-channel EEG recording, with electrodes placed according to 10-10 system on the temporal lobe, including sphenoidal electrodes. MTS was defined if atrophy, an increased T2-weighted signal, a decreased T1-weighted signal, and disrupted internal structure of the hippocampus were present accompanied by atrophy of the amygdala and/or temporal pole signal alteration on visual inspection of MRI pictures. The epileptogenic zone was determined by predominantly ipsilateral interictal epileptiform abnormalities (80% cutoff) and seizure onset recorded during prolonged video-EEG monitoring. TLE 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.

Since most of JME patients continued presenting occasional absences and myoclonic seizures, making seizure counting difficult, a good response to treatment was considered the control of GTCS for at least 1 year. For statistical analisys, JME patients were divided into three groups, according to the presence of seizures: myoclonic plus GTCS, myoclonic plus absence and myoclonic plus absence plus GTCS.

2.3. Psychiatric evaluation

Clinical and socio-demographic data from patients were reviewed. All patients were evaluated by the same psychiatrist (GMAF) through the structured questionnaire Schedule Clinical Interview for DSM-IV, axis I (SCID I), which is a diagnostic instrument based on DSM-IV (Diagnostical and Statistical Manual of Mental Disorders),[23] having been internationally used to evaluate the prevalence of PD. For statistical comparisons, since each patient could have had more than one axis I psychiatric diagnosis, the number of patients diagnosed and all comorbid PD found in each group were both considered and were analysed separately. The temporality between epileptic seizures and psychotic symptomatology was the utilized criteria to differentiate postictal psychosis (PIP) from interictal psychosis (IIP).[24]

2.4. Statistics

Statistical analyses were performed with SPSS 10.0 software. Some socio-demographic characteristics were presented as one-sample proportions and with confidence intervals. The chi-square (χ^2) was used to calculate the majority of differences between both groups. Fisher's exact test, the generalization of Fisher's exact test, Z test and Student's t test for unequal variances were applied both to calculate the differences between the groups and the relationship between the group of patients and socio-demographic and epilepsy characteristic variables. p value of <0.05 was considered significant.

3. Results

The TLE-MTS and JME groups were paired according to age, gender, duration of epilepsy and age at epilepsy onset. MTS occurred more frequently on left side (146 patients; 58.8%), followed by right (86; 34.6%) and by 16 in which this lesion was seen bilaterally (6.6%). Seventy-nine patients had a history of initial precipitant injury (IPI), febrile seizures being the most frequent (45 cases; 56.9%). There were also 24 cases of head trauma, 7 of meningoencephalitis and 3 of perinatal hypoxia. The majority of MTS patients (191; 77%) had been in use of association of two or more AED. Carbamazepine (CBZ), in monotherapy or in association with other drugs, was the most frequent AED (162 patients; 65.3%), followed by phenobarbital (PB) (74; 29.8%). Benzodiazepines were the most frequently associated drugs, being prescribed in 111 patients (44.7%).

The majority of JME patients had presented myoclonic and GTCS at the moment of evaluation (63%), while 35 (28.2%) presented with myoclonic, absences and GTCS and 11 (8.8%) with myoclonic and absence seizures. Ninety-one patients (73.3%) were taking only one AED at the time of the study, and the most common was valproate (VPA) in 62 patients, followed by topiramate (TPM) in 19 and phenobarbital (PB) in 10. Of the 33 patients using more than one AED, 19 were taking VPA and clonazepam (CNZ); 8 TPM and CNZ and, finally, 6 VPA and TPM. Sixty-eight had been free of GTCS for more than 1 year, and 58 had been treated with their present medications for more than 2 years. Clinical and demographic data are summarized in Table 1.

PD were found in 100 patients (41%) with MTS. Mood disorders were the most frequent, being diagnosed in 59 (23.7%). Among

Table 1
Clinical and demographic data of patients with mesial temporal sclerosis and juvenile myoclonic epilepsy.

Clinical/demographic data	Mesial temporal sclerosis	Juvenile myoclonic epilepsy	Statistical test	p value
Age (mean ± SD)	37.4 ± 11.0	29.8 ± 13.2	$Z = 1.1$	0.26
Gender (% females)	138 (55.6)	72 (58)	$\chi^2 = 0.1$	0.35
Age at epilepsy onset (mean ± SD)	11.6 ± 10.2	12.4 ± 6.5	$Z = 1.7$	0.31
Duration of epilepsy (mean ± SD)	25.7 ± 11.1	22.5 ± 9.5	$Z = 1.4$	0.19
Family history of epilepsy (%)	71 (28.6)	73 (58.8)	$\chi^2 = 32.8$	0.006*
Patients with psychiatric disorders (axis I) (%)	100 (41)	58 (46.7)	$\chi^2 = 0.1$	0.22
Total of psychiatric comorbidities (axis I)	134	72	$\chi^2 = 1.8$	0.12

* $p < 0.05$.

these, there were 53 with major depression disorder, 4 with dysthymia and 2 with type I bipolar disorder. Thirty-four patients (13.7%) presented anxiety disorders. Among them, 31 patients presented generalized anxiety disorder (GAD), 2 social phobia and 1 obsessive-compulsive disorder. Psychotic disorders were seen in 29 patients (11.6%), being IIP in 16 (6.4%) and PIP in 13 (5.2%). There were also 12 patients (9.6%) with somatoform disorders, all of them being conversive disorders (non-epileptic events). Thirty-four patients fulfilled criteria for two axis I disorders, 18 of them presenting major depression and GAD, 9 major depression and somatoform disorders and 7 major depression and PIP.

Fifty-eight JME patients had presented a PD (46.7%). Mood and anxiety disorders, present in 31 (25%) and 26 (21%), respectively, were the most frequently observed. Among mood disorders we found 26 cases of major depression and 5 of dysthymia, while among anxiety disorders, 22 presented GAD, 3 specific phobias and 1 obsessive-compulsive disorder, while among. There were also 7 cases of somatoform disorders, 6 of them conversive disorders (non-epileptic events) and 1 of somatization, 6 of psychotic disorders and 2 of alcohol abuse. Fourteen patients fulfilled criteria for two axis I diagnoses. Comparing the two groups, we did not find any statistically significant difference in the number of patients with PD, as well as in the total number of psychiatric diagnoses. There were also no significant differences between the groups when the number of patients with mood, anxiety or somatoform disorders was compared. Psychotic disorders, as a group and separately, were significantly related to TLE-MTS group ($p = 0.01$). The psychiatric diagnoses are described in Fig. 1.

A comparison of clinical data regarding the presence of PD and clinical and socio-demographical characteristics was also performed. This was done analyzing the presence of PD (as a group and individually) and the clinical and socio-demographical variables. All comparisons were made through an application of an adequate statistical test (chi-square, *Z* test or Fisher's exact test). In TLE-MTS group, the lateralization of MTS was not related to any psychiatric diagnose. In addition, no correlation was observed between seizure frequency, secondary generalization, the presence of an IPI, or number and type of AED and the PD. In JME, mood disorders and GAD were related to inadequate seizure control ($p = 0.02$). The presence of treatment with VPA for more than 2 years appeared as a protecting factor against PD ($p = 0.01$). There was no association between duration of epilepsy, type of seizures or time without treatment to any specific PD or to a higher frequency of PD in JME group.

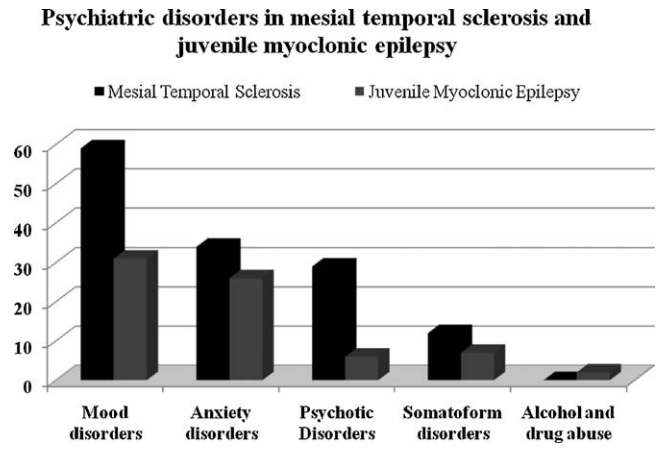

Fig. 1. Psychiatric disorders in mesial temporal sclerosis and in juvenile myoclonic epilepsy.

4. Discussion

The aim of this study was to conduct an evaluation of the frequency and types of axis I PD in two homogeneous series of specific epilepsy syndromes with different pathophysiology and clinical manifestations: a focal (TLE-MTS) and a primary generalized (JME) type. We also aimed to verify possible differences in the prevalence of PD between these groups and confirm the results of our previous study which was performed with a smaller number of patients.[19] Statistical correlations of PD and socio-demographical and clinical variables such as seizure frequency, type and number of AED and duration of epilepsy in each group, as well as the laterality of MTS in TLE, were performed.

Accurate estimates of psychiatric comorbidity in patients with epilepsy are not easy to find, because of the large variety of factors involved in this type of research, such as type of the study, severity and chronicity of epilepsy, the methodology applied, the population setting and the psychosocial aspects involved in this very stigmatized disease.[1,2,14] This variability could be in part responsible for the difficulty to find truly homogeneous patient groups and adequate controls in literature.[25] Although carried out in a tertiary center, where more patients with refractory epilepsies are treated, in this study we present two homogeneous groups paired according to age, gender, duration of epilepsy and age at epilepsy onset, evaluated through the use of standardized instruments based on the modern psychiatric nosography.

About 6% of epileptic patients in general appear to suffer from a PD. This number can rise to 20–40% in populations with TLE and to 70% in populations of refractory epilepsy.[1,2] Among these, mood disorders, particularly depression, are the most common (24–74%), followed by anxiety disorders (10–25%), psychoses (2–9%) and personality disorders (1–2%). Although the importance of the localization of epileptic discharges and the anatomical lesions provoked by the disease in the development of PD remains unclear, there is strong evidence that epilepsy places the patient at an increased risk of developing PD, and adequate controlled studies existing in literature show a higher risk compared to healthy control groups.[13,25–27] In this study, we found high rates of PD in both groups and mainly of mood and anxiety disorders, confirming the high comorbidity of these PD in epilepsy.[3,13–18,28] We could not evaluate the prevalence of attention-deficit disorder (ADD), an entity possibly frequent among epilepsy patients but not covered by the diagnostic instrument used (SCID-I); this was a limitation of our study.[29]

There was no statistically significant difference between the two groups regarding the number of patients diagnosed with PD or the total number of psychiatric diagnoses performed. Previous studies have traditionally highlighted the association between TLE and PD.[6–9,24,28] Limbic involvement has been suggested as a possible explanation for its high frequency given the role of these structures in the regulation of emotions and behavior.[1–3,6] Other studies, however, failed to document this association, referring that TLE per se can not be considered a risk factor in developing more psychopathology among epilepsy patients and highlighting the importance of other concomitant factors, such as duration of epilepsy, seizure frequency and particularly frontal lobe dysfunctions.[11–13,25] These results confirm our observations in a previous study, in which we did not observe such differences.[19]

A significant statistical association of MTS to psychotic disorders ($p < 0.01$) was observed in this study. Previous reports of psychosis have already pointed out a close relation between those disorders and TLE,[30–33] but since psychoses associated to epilepsy cannot be defined as a single or simple condition but as a complex entity with several possible subcategories, probably the disease contributes in different ways to the development of psychotic states.[28,29,33–35] The laterality of the epileptogenic zone

has also been considered as a potential risk factor for psychosis in TLE,[25] and the majority of the studies implicates the left hemisphere[12,33–35] or report no effect of lateralization.[10] Although frequently observed among TLE patients, psychotic disorders have rarely been mentioned in studies of JME using non-subjective modern rating scales.[15–18]

In our previous study, a significant association was observed between left-sided MTS and psychosis ($p < 0.01$), as well as JME and anxiety disorders ($p < 0.05$).[19] These statistical associations were not significant in the present study, in which the same statistical methodology was performed. This difference could be possibly attributed to the number of patients enrolled in this more recent and expanded version, in which more TLE-MTS and JME patients were evaluated. Nevertheless, other observations still remain statistically significant and concordant with data in current literature.[15–20]

Mood and anxiety disorders were associated to a higher seizure frequency in JME group ($p = 0.02$). Seizure control and compliance to the treatment are well recognized as very important for the mental health of these patients,[36–38] and some studies have already suggested a positive correlation between high seizure frequency and occurrence of psychiatric symptoms in generalized epilepsies[37,38] and in JME, in which such PD and other behavioral abnormalities could be a constituent of JME or be present in more serious forms of this syndrome.[15–20] Although JME has been considered a benign condition with good response to antiepileptic treatment,[37,38] there was a high proportion of JME patients who were not free of GTCS for at least 1 year (45.1%) at the time of the study, and this could possibly lead to a higher frequency of PD in this group. Previous treatment with VPA for more than 2 years appeared as a protecting factor against PD ($p = 0.01$). This finding could be due to a more efficacious seizure control or because of the well-known therapeutic effects of VPA in psychiatry, as this drug has been largely used for treatment of a high number of PD.[36]

We conclude that there was a high prevalence of PD in patients with TLE-MTS (41%). A high prevalence was also observed in patients with JME (46.7%), a form of idiopathic generalized epilepsy. Psychosis was significantly associated to TLE-MTS ($p = 0.01$). These findings are concordant with data in current literature regarding the prevalence of PD in both epilepsy syndromes and confirm our previous observations,[19] suggesting the existence of possible anatomic substrates for the developing of specific PD that could correspond to brain dysfunctions provided by each epileptic syndrome.[16,19–21] Once this question is yet to be properly answered, continued investigation of the psychiatric comorbidity in epileptic syndromes is certainly recommended.[19,24]

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