Article

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Prevalence of psychiatric comorbidities in temporal lobe epilepsy in a Southern Brazilian population

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ABSTRACT

A great prevalence of psychiatric disorders in epilepsy is well demonstrated, although most studies have used unstructured psychiatric interviews for diagnosis. Here we present a study evaluating the prevalence of psychiatric comorbidities in a cohort of Southern Brazilian patients with temporal lobe epilepsy (TLE) using a structured clinical interview. We analyzed 166 patients with TLE regarding neuropsychiatric symptoms through the Structured Clinical Interview for DSM-IV. One hundred-six patients (63.9%) presented psychiatric comorbidities. Mood disorders were observed in 80 patients (48.2%), anxiety disorders in 51 patients (30.7%), psychotic disorders in 14 (8.4%), and substance abuse in 8 patients (4.8%) respectively. Our results agree with literature data where most authors detected mental disorders in 10 to 60% of epileptic patients. This wide variation is probably attributable to different patient groups investigated and to the great variety of diagnostic methods. Structured psychiatric interviews might contribute to a better evaluation of prevalence of psychiatric comorbidities in TLE.

Key words: seizures, epidemiology, behavioral neurology, chronic psychiatric illness, neurology.

Prevalência de comorbidades psiquiátricas na epilepsia do lobo temporal em uma população do sul do Brasil

RESUMO

Embora muitos estudos tenham demonstrado uma alta prevalência de transtornos psiquiátricos em pacientes com epilepsia, a maioria utilizou entrevistas psiquiátricas não-estruturadas para o diagnóstico. Este método pode levar a diferenças significativas nos resultados. Nós estudamos a prevalência de comorbidades psiquiátricas em pacientes com epilepsia do lobo temporal (ELT), utilizando uma entrevista clínica estruturada. Foram estudados 166 pacientes com ELT, aos quais foi aplicada a Entrevista Clínica Estruturada para o DSM-IV (SCID). Cento e seis pacientes (63,9%) apresentaram comorbidades psiquiátricas. Transtornos de humor, observados em 80 pacientes (48,2%), foram o transtorno neuropsiquiátrico mais comum. Transtornos de ansiedade, observados em 51 pacientes (30,7%), foram a segunda comorbidade psiquiátrica mais frequente. Transtornos psicóticos foram encontrados em 14 (8,4%), e abuso de substâncias foram observados em 8 pacientes (4,8%), respectivamente. Nossos resultados estão de acordo com os dados da literatura, que demonstra problemas psiquiátricos em 10-60% dos pacientes com epilepsia. A grande variação dos resultados pode ser atribuída aos diferentes grupos de pacientes estudados e à variabilidade de métodos diagnósticos empregados. Entrevistas psiquiátricas estruturadas podem contribuir para uma avaliação mais adequada da real prevalência de comorbidades psiquiátricas na ELT.

Palavras-chave: crises epilépticas, epidemiologia, neurologia comportamental, doença psiquiátrica crônica, neurologia.

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Epilepsy is a common neurological disease. The world prevalence of epilepsy is estimated to vary from 0.5 to 1.5%[1]. The term Epilepsy encompasses different neurological disorders characterized by a tendency to recurrent epileptic seizures. Epileptic seizures are the clinical correlates of paroxysmal events generated by an enduring condition of hyperexcitability and hypersynchrony of brain electrical activity. However, the clinical spectrum of epilepsy encompasses many neurobehavioral comorbidities[2]. Epilepsy and neurobehavioral conditions might share some physiopathologic, genetic, and environmental-mechanisms[3].

The association between epilepsy and psychiatric disorders has been known since ancient times, but the last two decades were marked by an explosion of studies about this issue[4]. Prevalence of psychiatric comorbidities fluctuates from 20 to 40% in patients with epilepsy. In selected populations, prevalences may reach two-fold higher values[5]. Different definitions of psychiatric comorbidities, different study populations, and different forms of psychiatric evaluation are factors that might explain this great variability. Indeed, studies with structured psychiatric interviews are still lacking.

The objective of the present study was to determine the prevalence of major psychiatric disorders in a cohort of patients with TLE living in Southern Brazil, using a structured psychiatric interview, and to compare the findings with similar worldwide data. Moreover, we believe that our study might contribute to a better view of the worldwide prevalence of psychiatric comorbidities in epilepsy.

METHOD

We performed a cross-sectional study of a cohort of 166 consecutive Caucasian patients (108 women and 58 men) with TLE, from march of 2007 to septrember of 2010. Patients were selected from the Epilepsy Ambulatory of Hospital de Clínicas de Porto Alegre, a tertiary hospital located in the Southern region of Brazil. Porto Alegre is the capital of Rio Grande do Sul state. Its economy is based on industry, commerce and services. In Brazil, health is responsibility of the State and its access is universal. As in the rest of the country, health, education and safety are provided by both public and private services. It is estimated that about 2/3 of the population uses the governmental services.

Inclusion criteria for the study were presence of electroclinical and neuroimaging features of TLE, according to the ILAE classification for epileptic seizures and syndromes[6]. Patients less than 18 years old of age, those with generalized epilepsies, extratemporal epilepsies, mental retardation (IQ scores below 70), brain tumor, systemic disease (eg.: systemic erythematous lupus, AIDS), or penetrating head trauma were excluded.

After giving written informed consent, all patients were submitted to the Structured Clinical Interview for DSM-IV (SCID)[7], divided into six modules, for the detection of one or more lifetime diagnoses of the Axis I Diagnostic and Statistical Manual, fourth edition (DSM-IV)[8]. Interictal spikes were independently reviewed by two board-certified electroencephalographers (J.A.B. and C.M.T.) that were blind to psychiatric evaluation. Whenever the results were discordant, EEGs were reviewed by the two examiners together to reach a consensus. When available, all MRI exams were reviewed to improve etiological diagnostic. Control of seizures was assessed by an events calendar filled by the patient. Seizures occurring more than once monthly were considered uncontrolled. Data regarding prior and current antiepileptic treatments, as well as the use of any psychotropic or sedative drug (eg.: antidepressants, antipsychotics) were registered in a database for posterior statistical analyses.

Results were displayed in a percentage form. We analyzed the impact of psychiatric diagnosis on main aspects of TLE (control of seizures, interictal EEG, MRI abnormalities, presence of aura). We compared results of patients with and without a positive SCID using Pearson's chi-square test. All results were expressed using O.R. (95% C.I.). A significant level was considered when $p<0.05$.

The study was approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre.

RESULTS

Mean age of the study population was 43.9 (±12.8) years (range: 19 to 79 years), with a mean age at first seizure of 18.7 (±14.4) years (range: 3 months to 67 years) and a mean duration of epilepsy of 25.3 (±14.0) years (range: 1 to 67 years). The main clinical characteristics of the study population are shown in Table 1. One hundred-six patients (63.9%) had a diagnosis of at least one lifetime psychiatric disorder. Eighty patients (48.2%) had a mood disorder; 51 (30.7%) had an anxiety disorder; 14 (8.4%) had a psychotic disorder, and 8 patients (4.8%) had alcohol or drug abuse (Table 2). An association between mood and anxiety disorders was the most common psychiatric comorbidity observed, being present in 34 patients (20.5%).

Major depression was the most frequent mood disorder observed in our series, being present in 56% of the patients with mood disorders and in 27% of all patients. Dysthymic disorder was observed in 15% of patients with mood disorders (7% of all patients). A past depressive episode was observed in 20% of patients with mood disorders and in 10% of the total patient series. Generalized anxiety disorder was present in 25 patients (49% of patients with anxiety disorders and 15% of all patients), and

Table 1. Clinical features of the patients studied.

Factor	Number of patients (%)
Gender	
Men	58 (34.9%)
Women	108 (65.1%)
Controlled seizures	
Yes	75 (45.2%)
No	90 (54.2%)
Aura	80 (48.2%)
Yes	
No	86 (51.8%)
Family history of epilepsy	
Yes	60 (36.2%)
No	106 (63.8%)
Family history of psychiatric disorders	
Yes	59 (35.5%)
No	107 (64.5%)
Initial precipitant insult	
Yes	42 (25.3%)
No	124 (74.7%)
EEG focus lateralization	
Right	58 (35%)
Left	98 (59%)
Not lateralized	10 (6%)
Neuroimaging	
Normal	53 (31.9%)
Abnormal	59 (35.5%)
Not available	54 (32.5%)
Antiepileptic drug	
Monotherapy	86 (51.8%)
Polytherapy	80 (48.2%)
Psychotropic drugs	
No drugs	136 (81.9%)
One drug	25 (15.1%)
Combined therapy	5 (3%)

Table 2. DSM-IV Axis I psychiatric diagnoses.

Diagnosis	N	%
Mood disorders	80	48.2
Major depression	24	24.5
Dysthymic disorder	8	8.1
Past depressive episode	6	6.1
Past manic episode	2	2.0
Bipolar disorder	1	1.0
Anxiety disorders	51	30.7
Generalized anxiety disorder	5	5.1
Panic disorder	4	4.1
Post-traumatic stress disorder	3	3.1
Panic with agoraphobia	2	2.0
Specific phobia	2	2.0
Obsessive compulsive disorder	2	2.0
Psychotic disorders	14	8.4
Substance abuse	8	4.8

panic disorder in 8 (3 with agoraphobia). Post-traumatic stress disorder was observed in 7 patients (Table 2).

In Table 3 we present our findings compared with other similar data around the world, with different methodologic characteristics. The overall prevalence of psychiatric disorders in our patients was 64%, with a pattern of dominant mood disorders occurring at almost two-fold higher rates than those for anxiety disorders. These values are high, but similar to those observed in other European or South American studies which used similar structured interviews in populations of epileptic patients attended at tertiary centers[9]. Moreover, we found a greater prevalence of psychiatric disorders in our patients when compared with the general population of Porto Alegre, data published in a previous study (Table 4)[10].

Although there was a tendency to patients with uncontrolled epilepsy present some lifelong psychiatric disorder (not significant), we did not have found any statistical difference between patients with and without lifetime psychiatric disorders, regarding presence of MRI abnormalities, interictal EEG features, control of seizures, or presence of aura (Table 5).

DISCUSSION

We observed a high prevalence of lifelong psychiatric disorders in our TLE patients. Psychiatric comorbidities were present in 63.9% of them. The main psychiatric diagnoses found in our series (Table 2) were mood disorders (found in 80 patients, 48.2% of the total), followed by anxiety disorders (51 patients, 30.7% of the total). Psychotic disorders and substance abuse were observed in 14 (8.4%) and 8 (4.8%) patients, respectively.

Our results agree with the literature. Most reports show that mood disorders are the most frequent psychiatric comorbidity in TLE patients[11]. According to previous reports, a higher prevalence of psychiatric comorbidities is observed in epileptic patients studied at tertiary centers (40-60%)[12], while population-based studies show an intermediate prevalence of about 20%[13]. Nevertheless, in all studies the frequencies of psychiatric disorders among epileptic patients were higher than in the general population (12.2-16.2%)[14].

Several authors have reported a wide variability of

Table 3. Geographical distribution of psychiatric comorbidities in epilepsy.

Continent	Country	Authors	N	Instrument	Population	Psychiatric disorders	Mood disorders	Anxiety disorders	Psychosis	Substancee abuse
North America	USA	Victoroff et al., 1994[31]	60	SCID - DSM-III-R	TLE - candidates for surgery	70%	58.3%	31.7%	13.3%	–
		Ettinger et al., 2004[32]	775	CES-D	Epilepsy - community-based	–	36.5%	–	–	–
		Strine et al., 2005[21]	427	Kessler 6 scale	Epilepsy - community-based	–	32.6%	14.4%	–	–
		Kobau et al., 2006[33]	131	Health Style Survey (self- reported depression and anxiety)	Epilepsy - community-based	–	39%	39%	–	–
	Canada	Tellez-Zenteno et al., 2007[27]	253	CIDI	Epilepsy - community-based	23.5%	17.4%	12.8%	–	–
Europe	UK	Pond and Bidwell, 1960[34]	245	Unstructured psychiatric interview	Children with epilepsy - community-based	29%	–	–	–	–
		Graham and Rutter, 1968[35]	63	Unstructured psychiatric interview	Children with epilepsy - community-based	28.6%	–	–	–	–
		Edeh and Toone, 1987[9]	88	CIS	Epilepsy - selected by general practitioners (GP)	48%	22%	15%	3.4%	–
		Davies et al., 2003[36]	67	SCID	Epilepsy - community-based	37%	–	–	–	–
		Gaitatzis et al., 2004[3]	5834	ICD-9	Epilepsy - selected from a database generated by GP	41%	18.2%	11.1%	9%	2.4%
		Mensah et al., 2006[13]	499	HADS	Epilepsy - from GP	–	11.2%	–	–	–
	Italia	Perini et al., 1996[37]	38	SADS, BDI, STAIX1, STAIX2	JME and TLE (selected) patients	80% (TLE), 22% (JME)	55% (TLE), 17% (JME)	15% (TLE), 11% (JME)	–	–
	Netherlands	Swinkels et al., 2001[38]	209	CIDI	Epilepsy - tertiary epilepsy center	–	24.9%	29.7%	0.5%	20.1%
	Czech Republic	Havlová, 1990[39]	225	Chart review (unstructured)	Cohort of epileptic children	6.7%	–	–	–	–
	Iceland	Gudmundsson, 1966[40]	654	Clinical interview (unstructured)	Epilepsy (community-based)	54.5%	–	–	9%	–
		Stefansson et al., 1998[15]	241	ICD-9	Epileptic patients receiving benefits	35.3%	–	–	6.2%	5%
	Sweden	Forsgren, 1992[41]	713	Chart review (unstructured)	Epilepsy - community-based	5.9%	–	–	0.7%	–
	Finland	Jalava and Sillanpaa, 1996[42]	94	Chart review and ICD-9	Epilepsy - selected from different sources	24%	–	–	3.1%	–
	Denmark	Bredkjaer et al., 1998[43]	67	ICD-8	Epilepsy - community-based	16.8%	–	–	–	–
Asia	India	Hackett et al., 1998[44]	26	ICD-10	Epilepsy - community-based	23.1%	–	–	–	–
Africa	Nigeria	Gureje et al., 1991[45]	204	CIS	Epilepsy - tertiary center	37%	–	–	30%	–
South America	Brazil	De Araújo Filho et al., 2008[46]	270	SCID	Refractory TLE and JME from a tertiary epilepsy center	50% (TLE), 49% (JME)	25.8% (TLE), 19% (JME)	14.1% (TLE), 23% (JME)	15.8% (TLE), 3% (JME)	2% (JME)
		Our study	166	SCID	TLE - selected from a tertiary epilepsy center	63.9%	48.2%	30.7%	8.4%	4.8%

BDI: Beck Depression Inventory; CES-D: Center for Epidemiological Studies Depression Scale; CIDI: Composite International Diagnostic Interview; CIS: Columbia Impairment Scale; HADS: Hospital Anxiety and Depression Scale; ICD-9: International Classification of Diseases-9; JME: juvenile myoclonic epilepsy; SADS: Schedule for Affective Disorders and Schizophrenia; SCID-DSM III-R: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders -III-Revised version; STAIX 1 and 2: State Trait Anxiety Inventory 1 and 2; TLE: temporal lobe epilepsy.

psychiatric comorbidities in epileptic patients. The prevalence of these comorbidities varies according to the type of patient studied, the type of psychiatric disorder studied, the duration of the study (last 12 months or lifelong), and the type of diagnostic procedure used (structured interview or self-applicable questionnaire). For example, community-based studies of epileptic patients with structured interviews have found prevalences of psychiatric comorbidities varying between 23.5% and 37.5%, always higher than in the general population (10-20%). In contrast, studies using ICD diagnoses and data from administrative registries have shown greater variation (16.8 to 60%)[5,15]. Larger prevalence was found in populations extracted from lists of individuals with some other associated disease, and therefore probably with a selection bias[5,15].

The prevalence of psychiatric disorders seems to increase according with the severity of neurological disorders (Figure), in the following sequence: patients with chronic non-neurological diseases, patients with non-epileptic neurological diseases, patients with generalized epilepsies, patients with extratemporal focal epilepsies, patients with non-surgically treatable TLE, and finally, patients eligible for surgery[16]. The prevalence of psychiatric disorders in TLE patients is, in general, two-fold greater than in the general population[17]. Our data are closely similar to those observed in other selected populations of epileptic patients. Indeed, more than half of our patients (54%) do not have appropriate seizure control (Table 1).

Another interesting aspect is the observation that studies conducted with structured interviews tend to point to higher frequencies of neuropsychiatric disorders in epilepsy (Table 3). Because the use of structured psychiatric interview is relatively more recent and limited to smaller populations, it is possible that larger epidemiological studies might underestimate the true prevalence of psychiatric disorders in epilepsy. Thus, further observations are necessary to clarify these matters.

We observed more than one type of lifelong psychiatric disorder in about 25% of our patients. Most frequently this association was between mood and anxiety disorders. This association has been recognized since ancient times, but its pathophysiologic mechanisms are still

Table 4. Prevalence of psychiatric comorbidities in Porto Alegre[13].

Psychiatric diagnosis	TLE patients (n=166)	General population (n=6471)
Overall	63.9%	42.5%
Mood disorders	48.2%	11.3%
Anxiety disorders	30.7%	9.6%
Psychotic disorders	8.4%	2.4%
Substance abuse	4.8%	9.2%

TLE: temporal lobe epilepsy.

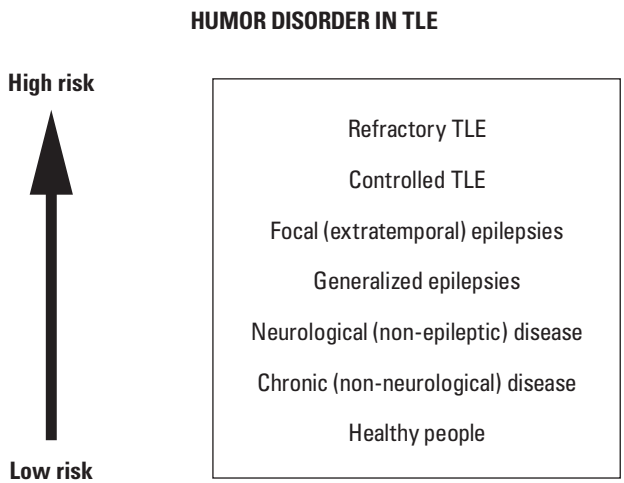

Figure. Risks for mood disorder by type of neurological disease.

Table 5. Association among psychiatric disorders and clinical features of TLE.

	SCID+	SCID–	Risk (95%CI)	p
Controlled epilepsy	45	30		
Uncontrolled epilepsy	60	30	0.5 (0.3-2.9)	0.51
Unilateral EEG spikes	63	35		
Bilateral EEG spikes	40	20	3.3 (0.5-5.4)	0.35
Abnormal neuroimaging	33	26		
Normal neuroimaging	36	17	2.5 (0.4-3.6)	0.29
Presence of aura	51	29		
Absence of aura	55	31	3.2 (0.6-4.4)	0.86

SCID: structural clinical interview for DSM-IV; CI: confidence interval.

poorly understood[18]. Studies with adults and children suffering from epilepsy have shown a high prevalence of this comorbidity in association with epilepsy, sometimes up to 70%[19]. Depression, anxiety and epilepsy seem to share some biological and structural mechanisms related to limbic system dysfunctions. This is an interesting topic which has been intensely investigated over the last few years.

Fear is a frequent type of aura, been observed in about 15% of TLE patients, and sometimes mimics panic attacks[20]. A previous study[21] found a high prevalence of post-ictal anxiety symptoms in epileptic patients. However, we could not observe this association because there were too few patients with anxiety symptoms in our sample (and just 6 patients with an aura of fear). Goldstein et al.[22] observed an inverse correlation between seizure frequency and post-ictal anxiety symptoms. The authors suggested that it might be caused by "habituation" of the anxiety generator circuits (mostly amygdala) due to high seizure frequency, processing them as ordinary events. Another possibility could be the "learned helplessness" phenomenon[23]. Further researches are needed to clarify these aspects.

There are many evidence suggesting that TLE and depression may share common pathogenic mechanisms[24]. For example, in both TLE and depression smaller volumes of frontal lobes have been found[25]. High-resolution MRI studies have shown that hippocampal volumes in depression are decreased bilaterally or in the left hippocampus only. In TLE, volumes may be reduced on the site of seizure origin or, when combined with depression, bilaterally[25].

A strong hypothesis derived from those data is that neuronal hyperexcitability can possibly be expressed either as impaired emotions or seizure activity.

One limitation of our study was its inability to identify mood disorders not yet classified by DSM-IV[26]. Another limitation of our study is its cross-sectional design which did not allow us to identify psychiatric disorders temporally related to seizures (peri-ictal and interictal symptoms). In these venues, mood disorders are different in epileptic patients when compared to subjects from the general population.

Mood changes preceding or following the epileptic event[27] are quite frequent. As ictal phenomena, however, depression[28], and mania[29], are much less frequent situations.

Although structured interviews are necessary for accurate determination of psychiatric diagnoses in epilepsy, their application in a busy clinical setting is not always feasible. Most rating scales and self-report questionnaires are developed to screen for psychopathology in nonepileptic patients. Nevertheless, validated screening instruments (such as The Mood Disorder Questionnaire and the Neurological Disorders Depression Inventory for Epilepsy - NDDI-E) were specifically developed for screening of psychiatric disorders (especially mood disorders) in patients with epilepsy. These instruments are self-rating, can be completed in a few minutes, and are confident, because they minimize the risk of overlap with adverse antiepileptic drugs effects or preexisting cognitive problems[30].

We found a high prevalence of psychiatric disorders in our TLE patients. The most frequent diagnoses found were mood and anxiety disorders. Both conditions occurred simultaneously in 20% of patients. Our data agree with the international literature. In fact, the prevalence observed was similar to those observed in European studies (Table 3). This is interesting because our population is basically composed by descendent of Europeans. Thus, in spite of living in a different world region, it seems that psychiatric comorbidities in epileptics might remain similar to that observed in ancestor populations. Our finding might suggest that genetic predisposing factors might be even more important than eventual environmental factors. This interesting aspect deserves further studies. Moreover, because of the high prevalence observed, our study agrees with growing evidence in literature indicating that TLE and psychiatric disorders share similar physiopathologic mechanisms.

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