

## Original Article

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# Psychiatric Comorbidities in Epilepsy

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**Background and Purpose:** Psychiatric comorbidities (PC) occur more frequently in patients with epilepsy than in the general population. To determine the main PC associated with epilepsy and its association with demographic data and clinical features of epilepsy.

**Methods:** A retrospective study was carried out on patients with epilepsy at the Medical Specialties Center of the Municipal Health Department. Demographic data, crisis onset, time range of seizures evolution, type of epileptic seizures, types of epilepsy, etiology, brain injury, topographic location, hemispheric location, type of antiepileptic drugs (AEDs), use of monotherapy or polytherapy, control of epileptic seizures and the PC were recorded.

**Results:** One hundred forty adult patients were studied 51.4% male, mean age 44.9 years, time of evolution of the crises was 14 years, focal crisis 88.6%, mesial temporal sclerosis 42%, controlled 92.4%, monotherapy 66.1%, and the most used AEDs were carbamazepine (33.1%), valproic acid (28.2%), and phenobarbital (10.4%). The PC present in 67.1% of the patients was depression (22.8%), anxiety disorder (AD) (17.8%), psychosis (10%), dementia (9.2%) and bipolar affective disorder (BAD) (8.5%). The relationship between PC and crisis control was significant ( $p < 0.009$ ).

**Conclusions:** Schooling was lower than that reported in the general population in Brazil, and we found a low rate of unemployment or retirement. Epilepsy is associated with PC, the most frequent being depression, AD, psychosis, dementia and BAD. The absence of a relationship between depression and brain damage; anxiety disorder with education, types of epilepsy and etiology; psychosis with sex and time of epilepsy evolution were significant. (2022;11:21-26)

**Key words:** Depression, Epilepsy, Mental health, Psychiatric comorbidities, Seizures

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## Introduction

Psychiatric comorbidities are more frequent in people with epilepsy than in the general population and individuals with other chronic diseases, such as cancer and diabetes mellitus, both in children and in adults. In practice, this association is underestimated, underdiagnosed, and not properly evaluated.<sup>1,2</sup> According to Sadock et al.<sup>3</sup> 30-50% of people with epilepsy have psychiatric comorbidities during the lifetime of illness. Other authors report a frequency of 25-50% of psychiatric comorbidities of epilepsy, which is two to three times more frequent than in the general population: among these, mood, anxiety disorder, psychosis, cognitive impairment, and social cognition disorders are the most common.<sup>4-6</sup>

Psychiatric comorbidities and epilepsy have a bidirectional

interaction. Psychiatric conditions are more common among patients whose epilepsy is incompletely responsive to treatment with anti-epileptic drugs (AEDs) and the presence of psychiatric comorbidities hinders the therapeutic control of seizures. Additionally, the presence of psychiatric comorbidities affects the quality of life and social functionality of people with epilepsy.<sup>5-7</sup> There is a need to more fully define psychiatric comorbidities of epilepsy, particularly among persons with epilepsy receiving treatment in primary care settings. This is the primary aim of the present study, which also sought to identify association between psychiatric comorbidities of epilepsy and seizures types, the duration of epilepsy, etiology, use of AEDs, and degree of seizures control.

## Methods

We conducted a retrospective, descriptive, and cross-sectional

study of patients with epilepsy from Primary Health Care who were over 18 years of age and seen at the outpatient clinic of the Municipal Health Department from 2015 to 2019. The medical re-

**Table 1.** Relationship between psychiatric comorbidities with clinical characteristics of epilepsy

Psychiatric comorbidity	Yes	No	<i>p</i> -value
Time of evolution of the epileptic seizures (yr)			0.609
0-10	51 (63.7)	29 (36.2)	
11-20	16 (72.7)	6 (27.3)	
>20	27 (71.1)	11 (28.9)	
Epileptic seizures			0.370
Focal	82 (66.1)	42 (33.9)	
Focal+generalized	5 (100.0)	0 (0.0)	
Generalized	7 (63.6)	4 (36.4)	
Focal			0.799
Disperceptive	16 (66.7)	8 (33.3)	
Focal evolving to bilateral tonic-clonic	56 (67.5)	27 (32.5)	
Perceptive	7 (53.8)	6 (46.2)	
Perceptive+disperceptive	3 (75.0)	1 (25.0)	
Generalized			1
Motor	5 (55.6)	4 (44.4)	
Motor+non-motor (absence)	1 (100.0)	0 (0.0)	
Non-motor (absence)	1 (100.0)	0 (0.0)	
MRI finding			0.381
Hippocampus asymmetry	9 (75.0)	3 (25.0)	
Cerebral atrophy	6 (54.5)	5 (45.5)	
Calcifications	1 (50.0)	1 (50.0)	
Encephalomalaceae/gliosis	1 (100.0)	0 (0.0)	
Mesial temporal sclerosis	22 (78.6)	6 (21.4)	
Ischemia	4 (66.7)	2 (33.3)	
Malformation	1 (100.0)	0 (0.0)	
Sequel encephalitis	0 (0.0)	1 (100.0)	
Tumor	5 (100.0)	0 (0.0)	
Epilepsy syndrome			0.245
Unknown	2 (40.0)	3 (60.0)	
Focal	80 (67.2)	39 (32.8)	
Combined focal and generalizated	5 (100.0)	0 (0.0)	
Generalized	7 (63.6)	4 (36.4)	
Seizures control			0.009
Controlled	74 (62.7)	35 (32.1)	
Inactive	13 (100.0)	0 (0.0)	
Not controlled	16 (88.9)	2 (11.1)	
Therapy with AEDs			0.392
Monotherapy	51 (65.4)	27 (34.6)	
Politherapy	30 (75.0)	10 (25.0)	
Without AED	13 (59.1)	9 (40.9)	

Values are presented as number (%).

MRI, magnetic resonance imaging; AED, antiepileptic drug.

cords included demographic data; ages of seizure epileptic onset; the duration of epilepsy; types of seizures and epilepsy; results of cranial tomography (CT) and nuclear magnetic resonance imaging (MRI); result of video-electroencephalography (EEG); brain injury; topographic location; hemispheric localization of seizure foci; epilepsy etiology; type of AED; use of monotherapy or polytherapy; degree control of epileptic seizures and psychiatric comorbidities.

The types of seizures, epilepsy, and etiology were defined according to the criteria of the Classification of International League Against Epilepsy.<sup>8</sup> Drug-resistant epilepsy was defined by recurrent epileptic seizures despite the use of at least two clinically appropriate AEDs and used for an adequate period of time and at adequate doses.<sup>9</sup> Psychiatric comorbidities were defined by the medical interview using Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.<sup>10</sup> Patients with dementia were excluded. The data recorded in the clinical histories and diagnoses were reviewed and confirmed by the main author, a physician who teaches neurology and responsible for the outpatient clinic, during the interview of patients and family members. In addition, psychiatric conditions were considered comorbidities when the symptoms defining them were not better attributed to epileptic seizures (i.e., ictal or post-ictal events). Then, the data were transcribed to an electronic form in a flat file format according to the following variables: categorical (sex, education, profession, retirement, types of seizures and epilepsy, complementary exams, etiology, drugs, and psychiatric comorbidities) and continuous (age, age of onset, and duration of epilepsy). Data analysis was performed using the statistical software R version 3.6.3 (R Core Team, Vienna, Austria; 2019).

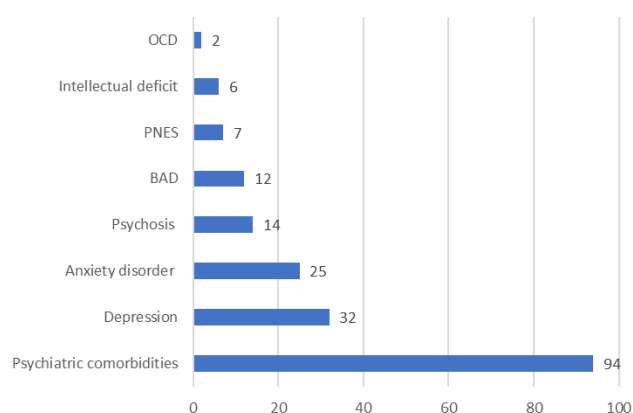
Descriptive evaluation was performed by verifying quantities and percentages for categorical variables and descriptive measures (minimum, maximum, quartiles, mean, and standard deviation) for continuous variables. The chi-square test and Fisher's exact test were used to compare demographic data, clinical features of seizures, type of epilepsy, results of complementary tests, etiology, AED, and associated psychiatric comorbidities. The same procedure was applied for the most frequent psychiatric comorbidities. A statistically significant difference was considered when  $p < 0.05$ . The research was approved by Plataforma Brasil and Ethics Committee (Certificate of Presentation for Ethical Appreciation-CAAE No. 09049719.1.0000.8040), the patients give informed consent, and was their anonymity preserve.

## Results

A total of 140 adult patients (51.4% men and 48.5% women) with a mean age of 44.9 years (standard deviation [SD],  $\pm 17.8$ ) were studied. The average age in men was 45.2 years (SD,  $\pm 16.1$ ) and in women 44.8 years (SD,  $\pm 20.9$ ). The number of years in school was distributed as follows: 8.6% uneducated; 9.3% of 1-4 years; 32.9% of 5-8 years; 43.6% 9-12 years and 5.7% with complete higher education. One hundred patients (71.4%) were working, and 33 (23.6%) were retirees, of which eight (5.7%) were due to epilepsy.

The age of onset of epileptic seizures was 29.9 years on average (SD,  $\pm 22.9$ ) and 21.4% of patients had started seizures at less than 10 years of age, 25.7% between 11 and 20 years and 52.9% after 20 years of age. The duration of epilepsy was 14 years on average (SD,  $\pm 15.4$ ). The most frequent type of epileptic seizures was focal, which occurred in 124 patients (88.6%). Of the focal ones, 45 (32.1%) were impaired awareness and 56 (45.2%) evolved to bilateral generalized seizures of the tonic-clonic type. Among the generalized seizures, 10 were motor and one was an absence seizure. The types of epilepsy were: focal 85%, generalized 8%, most generalized focal 4%, and unknown 3%. The etiology was distributed in: 47.2% unknown, 43.6% structural, 5% genetics, 2.1% metabolic, and 2.1% infectious.

CT was performed in 52.1% of patients, showing abnormality in 47.9%: central nervous system calcifications (31.40%), cerebral atrophy (28.6%), encephalomalacia (8.60%), and ischemia (8.6%). MRI performed in 61.4% of patients, was abnormal in 77.9% (Table 1). The cerebral topographic location of the seizures was distributed as



**Figure 1.** Frequency distribution of psychiatric comorbidities. Some patients had two or more psychiatric comorbidities. OCD, obsessive compulsive disorder; PNES, psychogenic non-epileptic seizures; BAD, bipolar affective disorder.

follows: temporal 47.1% (left 53%; direct 22.7%), frontal 12.8% (left 44.4%; right 11.1%), parietal 3.5%, multifocal 4.5%, and indeterminate 32.1%. Therapeutic control was achieved in 92.4% of the patients, of which 66.1% were in monotherapy regimen. The most used AEDs were carbamazepine (33.1%), valproic acid (28.2%), and phenobarbital (10.4%).

Psychiatric comorbidities were present in 94 patients (67.1%) and 30 patients (21.4%) had more than one psychiatric comorbidity (Fig. 1). We relate psychiatric comorbidities with the following categories with significant results: sex, age range, schooling, epileptic seizures onset, the duration of epilepsy, type of epileptic seizures, types of epilepsy, cerebral lesions, topographical location, hemispheric location, etiology, and use of monotherapy or polytherapy. A statistically significant association between psychiatric comorbidities and control of epileptic seizures ( $p < 0.009$ ) was observed (Table 1).

The most frequent disorders found were depression (22.8%), anxiety disorder (17.8%), psychosis (10%), bipolar affective disorder (8.5%), and psychogenic nonepileptic seizures (5%). These comorbidities were related to sex, age range, schooling, epileptic seizures onset, time range of seizures evolution, type of epileptic seizures, lesions cerebral, types of epilepsy, topographic location, hemispheric location, etiology, use of monotherapy or polytherapy and control of epileptic seizures without statistical significance. We found significant results for the absence of a relationship between: depression and brain injury ( $p < 0.006$ ); anxiety disorder and education ( $p < 0.046$ ), types of epilepsy ( $p < 0.007$ ) and etiology ( $p < 0.020$ ); psychosis and sex ( $p < 0.046$ ) and duration of epilepsy ( $p < 0.048$ ).

## Discussion

Among the limitations of this study are the relatively small sample size, its retrospective character, including only adult patients from a metropolitan region and the fact of comparing results between populations with epilepsy from different cultures, in addition to the complexity of psychiatric comorbidities in epilepsy. However, this bias in this area of research in epileptology is present in a non-depreciating proportion of studies. Nevertheless, we could contribute to the knowledge of psychiatric comorbidities in patients with epilepsy and its possible mechanisms, considering that it is a sample of patients in primary health care.

In the present study, the education level of patients with epilepsy was lower than that of the Brazilian population. According to Brazilian institute of geography and statistics<sup>11</sup> in Brazil in 2019, illiteracy was

6.6% and the upper level at 17.4%, which is in contrast to our results, where uneducated reached 8.6% and the upper level at only 5.7%. The low level of education in patients with epilepsy has been related to a high rate of school dropout, learning difficulties, psychosocial factors, and low income, which are conditions aggravated by the onset of epilepsy in childhood.<sup>12,13</sup> The low educational level found in the present study suggests a high rate of school dropout and/or difficulty in learning. We did not find a statistically significant relationship between the educational level with the age of onset, time of evolution and types of epileptic seizures, nor with the type of epilepsy, brain injury, hemispheric topography, etiology, use of monotherapy or polytherapy and degree of control of seizures. These findings suggest that school performance in people with epilepsy is multifactorial, possibly associated with greater relevance to social aspects than with epilepsy itself.

A high rate of unemployment and retirement has been reported in patients with epilepsy, but these data are contradictory, and recent publications have found less interference.<sup>14,15</sup> In Germany, Korchounov et al.<sup>15</sup> reported a slight increase in the employment rate from 1994 to 2009, which related to the approval of the use of lamotrigine in 1993, employment support legislation in 1996, and approval of levetiracetam in 2000. Accordingly, we found high numbers of employees (71.4%), and of the 23.6% of retired patients, only 5.7% were due to epilepsy. It is considered that the good control of epileptic seizures, improvement of public policies, increase in the offer of employment, and the greater demands on the criteria for retirement could explain these findings.

Persons with epilepsy have an increased incidence of psychiatric comorbidities (25-50%), which is two or three times more than in persons without epilepsy.<sup>3-6</sup> Dalmagro et al.<sup>16</sup> found 40.4% of psychiatric comorbidities in 490 patients with refractory focal epilepsy, concluding that clinical variables and structural abnormalities of the central nervous system contribute to this comorbidity in focal epilepsy. Josephson and Jetté<sup>4</sup> reported 60% and 45% risk of psychiatric comorbidities in focal temporal and extratemporal epilepsy, respectively. Lastly, Gaitatzis et al.<sup>17</sup> reported up to 41% of psychiatric comorbidities cases.

Our study determined a frequency of psychiatric comorbidities of 67.1%, and we estimate that this increase accompanies the global trend of mental disorders in recent years, in addition to the low level of schooling found in our casuistry, or that it represents a risk factor for or development of mental disorders. Unlike the reports in the literature,<sup>5,18</sup> we found a higher statistically significant number of psychiatric comorbidities in controlled patients. This result could represent

the bias due to the predominance of controlled patients in our series, and forced normalization, which is characterized by the appearance of psychiatric symptoms after controlling for epileptic seizures, cannot be ruled out.<sup>19</sup>

In different studies, it has been reported that the most frequent psychiatric comorbidities in epilepsy are depression (23%), anxiety disorder (18%), intellectual deficit (16%), psychosis (7%), and personality disorders (4-38%).<sup>3,20-22</sup> Similarly, the main psychiatric comorbidities found were depression (22.8%), anxiety disorder (17.8%), and psychosis (10%). On the other hand, they contrast the values we found intellectual deficit (4.2%) and personality disorders that was not detected. We tried to relate depression to demographic data and the clinical aspects of epilepsy without statistical significance. Depression has been associated with mesial temporal epilepsy, based on the similar circuitry of both processes.<sup>16,23</sup> Recent studies associate depression and anxiety with the loss of neurons, astrogliosis of the mesial regions of the hippocampus, atrophy of the hippocampus and frontal regions, as well as hyperactivity of the hypothalamic-pituitary-adrenal axis common in epilepsy and depression.<sup>24,25</sup> However, we found no significant association between depression and mesial temporal epilepsy. There was a significant absence of a relationship between: depression and brain injury; anxiety and brain injury, education, types of epilepsy and etiology; psychosis and sex and duration of epilepsy.

It is considered that epilepsy represents a risk of developing psychosis, with a prevalence that is seven times higher than primary schizophreniform disorders in the general population.<sup>26</sup> Psychoses in epilepsy, according to their temporal relationship with epileptic discharge, are classified as ictal, postictal, and interictal, with the latter being the most common.<sup>27</sup> It is estimated a prevalence of psychosis in epilepsy of 6% and is higher in temporal lobe epilepsy (TLE) (7%).<sup>25</sup> We found 10% of patients with psychosis interictal and the majority in patients with TLE, similar data to other authors.<sup>26-28</sup>

The association between bipolar affective disorder and epilepsy has been reported, highlighting similar characteristics between both diseases such as its episodic character, chronic evolution, kindling phenomenon, and responses to the use of AEDs.<sup>29,30</sup> The presence of bipolar affective disorder as an interictal comorbidity in our series was 8.5%, value greater than 1-2% of the population without epilepsy.<sup>30</sup> We did not find a significant statistical relationship between bipolar affective disorder with demographic data and clinical characteristics of epilepsy. There is an association between bipolar affective disorder and TLE, not found by us.

Psychogenic nonepileptic seizures are paroxysmal brain events that

resemble epileptic seizures, which cause diagnostic and therapeutic errors and are present at any age; however, they predominate in the age group of 20 to 40 years old and in females and have no clinical correlation with the electroencephalogram during the critical event, which allows them to be differentiated from epilepsies.<sup>31,32</sup> The prevalence of psychogenic nonepileptic seizures is variable between 5% to 33% in outpatients and 10% to 58% in inpatients for the treatment of refractory epilepsy.<sup>33</sup> We found seven patients (5%) with psychogenic nonepileptic seizures of which four were women between 24 to 58 years old (mean of 44 years), diagnosed during video-EEG of 24-hour. Seventy one percent of patients with psychogenic nonepileptic seizures were uncontrolled and all had another psychiatric comorbidities (five with mood disorders, one with AD and psychoses).

This research suggests an important relationship between lower schooling and psychiatric comorbidities with epilepsy. The presence of psychiatric comorbidities was statistically significant in the controlled patients. The high number of controlled patients and the forced normalization explains this result. The psychiatric comorbidities found in decreasing order were depression, anxiety disorder, psychosis and bipolar affective disorder without statistically significant relationship with the demographic data and clinical characteristics of epilepsy. There was a significant absence of a relationship between depression and brain injury; anxiety disorder with education, types of epilepsy and etiology; psychosis with sex and epilepsy evolution time. Longitudinal, prospective and randomized studies in people with and without epilepsy are necessary for a better definition of the relationship between of psychiatric comorbidities and possible mechanisms in people with epilepsy.

### Conflict of Interest

The authors declare that they have no conflicts of interest.

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