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Depressive disorders in patients with pharmaco-resistant mesial temporal lobe epilepsy

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Abstract

Objectives: To assess depressive disorders in patients with mesial temporal lobe epilepsy (MTLE) refractory to medical treatment.

Methods: Adult patients with refractory MTLE completed two questionnaires (Mini International Neuropsychiatric Interview (MINI) and the Beck Depression Inventory (BDI) had a semi-structured psychiatric interview and a high resolution MRI scan. For complete neuropsychiatric diagnosis, as per International Classification of Diseases (ICD-10), the results were combined with clinical history and additional information from the patients' family.

Results: Of the 40 patients identified for this case series study which took place from 2008–2012, 31 (77.5%) had a depressive disorder: 14 had dysthymia, 11 had recurrent depressive disorder and 6 had bipolar disorder. Of the nine patients without a firm diagnosis of mood disorder, seven had isolated symptoms of depression or anxiety and two presented with mixed depression/anxiety symptoms. Only 8/31 (25.8%) patients were receiving antidepressant treatment. There was no association between BDI scores and seizure frequency. No significant difference was found between patients with and without depression and the presence or laterality of HA.

Conclusions: Depressive disorders are common, underdiagnosed and undertreated in patients with refractory MTLE.

Keywords

Depressive disorders, refractory epilepsy, temporal lobe epilepsy, mesial temporal lobe epilepsy

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Introduction

Epilepsy is a common neurological disorder and has been associated with an increased rate of comorbidities[1,2] including psychiatric disorders.[3–10] Temporal lobe epilepsy

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(TLE)[11] is one of the most common focal epilepsies in adults and is usually associated with hippocampal sclerosis or mesial temporal sclerosis.[12] The latter is a specific syndrome (mesial temporal lobe epilepsy; MTLE) characterized with seizures that usually begin in childhood and is frequently refractory to drug treatment but has good prognosis with surgical treatment (i.e., 50-70% patients became seizure-free after surgery).[13–16] Pharmaco-resistant epilepsy, or refractory epilepsy, may be defined as a failure of two trials of appropriately chosen antiepileptic drugs (AEDs) using maximum tolerated doses.[17] In 30–40% of adult patients with focal epilepsy, seizures remain refractory to pharmacological treatment. [18] Furthermore, the uncontrolled epilepsy is associated with cognitive impairment, psychosocial disorders, and increased morbidity and mortality.[18]

Some authors have reported prevalence rates of psychiatric disorders of 44–88% in patients with refractory focal epilepsy.[19,20] Depression is the most frequently occurring comorbid psychiatric disorder in epilepsy,[42,21] and it may have a direct impact on the severity of the symptoms of MTLE, seizure control and its pathogenesis.[4] Some studies[4,5,22–25] suggest that the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV[26] for depression, may be valid for the MTLE population. Indeed, depression has been associated with MTLE, especially in patients with left hippocampal atrophy (HA).[27] Cognitive impairments, such as memory and learning losses are marked in patients with left MTLE[7] and there is a suggestion that these difficulties may be associated with depression.[28]

Hippocampal volume abnormalities have also been observed in patients with depression and MTLE[29,30,] with reduced volumes either ipsilateral or bilateral to the origin of the seizures. Several studies have shown that in epilepsy, untreated depressive symptoms may potentially hinder seizure control,[24,27–29,31–35] suggesting that prompt diagnosis and treatment of depression is essential in these patients.[36] Intrinsic biological and extrinsic psychological factors have been suggested as the cause of the association between MTLE and depression.[22] In addition, reports suggest that the relationship between epilepsy and psychiatric disorders is bidirectional[4,5,22,37,39] and propose that hippocampal sclerosis, bitemporal lesions and pharmaco-resistance may be relevant risk factors. For example, the pharmacological treatment of depression and other psychiatric disorders in patients with MTLE may be challenging in patients using multiple AEDs, particularly drugs with enzyme inducing effects which may affect the incidence of side effects and/or efficacy of concomitant antidepressants.[40–42]

The objective of this present study was to assess depressive disorders in patients with MTLE refractory to medical treatment.

Methods

Patients

In this case series study, patients were recruited from the outpatient Epilepsy Clinic at University of Campinas, Sao Paulo, Brazil from 2008–2012. Patients with MTLE who had not responded to two or more trials of AEDs in mono or polytherapy[17] and continued with seizures for more than two years (i.e., seizure frequency of at least once every two months) prior to evaluation were eligible for this study. The diagnosis, clinical symptoms, electroencephalogram (EEG) reports and video-EEG were reviewed from patient medical records by two epileptologists (F.C. and C.L.Y.). The diagnosis of MTLE was made according to the International League against Epilepsy (ILAE) criteria[11,12] and further confirmed by MRI scans.[15]

All patients had ictal semiology described by a close relative or documented by a medical staff during clinic visits or

video-EEG monitoring.[43] In addition, all patients had other clinical and EEG features consistent with the diagnosis of MTLE[11,12,14] and had no other findings suggesting extratemporal focal epilepsy. The following inclusion criteria were met: (i) clinical manifestations indicative of MTLE, including stereotyped focal seizures with déjà vu or epigastric sensation, associated or not with fear and other autonomic symptoms (i.e., auras), followed by impaired awareness seizure, some with motor symptoms (i.e., previously known as complex partial seizure now defined as dyscognitive or focal seizure with impaired awareness)[44] consisting of staring and lip smacking or masticatory automatisms or both, accompanied or not by hand automatisms and contralateral arm dystonia; (ii) EEGs during wakefulness showed no clear cut epileptiform abnormalities outside the temporal lobe electrodes; (iii) epileptiform EEG abnormalities over temporal regions on interictal EEGs; (iv) no seizures, or use of antihistamine or alcohol for at least 12 hours prior to the psychiatric evaluation.

Exclusion criteria were as follows: (1) presence of dementia, low intellectual level, or language problems; (2) dual pathology; (3) metal objects in the body preventing MRI scans; (4) continuous use of alcohol or illicit drugs; (5) serious history of diabetes mellitus, hypertension, liver disease or kidney diseases; (6) other psychiatric disorders than those of class F.30-39 of International Classification of Diseases (ICD)-10.

All subjects provided signed informed consent and this study was approved by the Ethics committee at the University of Campinas – UNICAMP, Campinas, Sao Paulo, Brazil.

Assessments

The Mini International Neuropsychiatric Interview (MINI)[45–47] and the Beck Depression Inventory (BDI)[47–50] were used as screening tools for depression. The MINI is a short standardized diagnostic interview that evaluates key DSM-IV[26] and ICD-10, psychiatric disorders.[47] Modules A and B were used which distinguish symptomatology between current major depressive episode (with or without melancholia) from major depressive episode in the past and dysthymia. The BDI is an instrument that detects and evaluates the severity of recent depressive symptoms over the past two weeks. According to the Brazilian Portuguese validated version,[50] from a total score of 0-63, a cutoff point of 12 is used to indicate mild depression, above 20 moderate depression and above 36 severe depression.

In addition to the questionnaires psychiatric evaluations were performed by a board-certified psychiatrist (E.B.G.) using a semi-structured interview[51] for appropriate clinical and depressive disorder diagnosis and to exclude other psychiatric disorders according to ICD-10.[47] For a complete neuropsychiatric diagnosis, results from the semi-structured psychiatric interview and the two questionnaires were combined with clinical history and additional information from the patients' families.

All patients had a 3T MRI scan to assess the presence of HA and other signs of hippocampal sclerosis as part of the clinical routine investigation. The definition of HA was made by visual analysis by a researcher and her advisor (E.B.G. and F.C.) MRI signs of hippocampal sclerosis were defined as the presence of HA, with or without signal change (i.e., white matter hyperintensities in T2 and fluid attenuated inversion recovery [FLAIR]) and changes in hippocampal shape and internal structure.[12,17]

Statistical analyses

Statistical analyses were performed using SPSS software (version 22.0 for Windows®; (IBM SPSS, Armonk, NY: IBM Corp,

Table 1. Comparison of clinical data between patients with and without depressive disorder as per International Classification of Diseases (ICD-10) in pharmaco-resistant mesial temporal lobe epilepsy (MTLE).

	With depression ($n = 31$)[#]		Without depression ($n = 9$)[##]		
	Mean ± SD	Range	Mean ± SD	Range	Statistical significance
Age, years	44.1 ± 7.4	29.0–59.0	42.3 ± 11.6	24.0–60.0	*ns*
Duration of epilepsy, years	34.6 ± 9.2	13.0–56.0	29.4 ± 12.9	16.0–52.0	*ns*
Seizures per week*	1.83 ± 1.16	0.00–4.70	1.30 ± 1.12	0.05–3.50	*ns*
BDI score	22.5 ± 8.6	12.0–46.0	7.0 ± 2.7	3.0–12.0	$P < 0.01$

SD = standard deviation; BDI = Beck depression inventory.
[#](22 women/9 men)
[##](4 women/5 men)
*The average was determined based on the seizure frequency in the year before the psychiatric interview

USA). The χ^2 and Fisher's exact tests were used to compare categorical variables between groups and Mann-Whitney test was used to compare numerical variables. For comparison of three or more groups Kruskal-Wallis test was used due to the absence of a normal distribution of the variables.[52–54] All statistical analyses were 2-sided and a P-value < 0.05 was considered to indicate statistical significance. Spearman's rank correlation was used to examine associations between BDI scores and epilepsy duration and seizure frequency.

Results

Forty patients with pharmaco-resistant MTLE were included in the study. Their ages ranged from 24 to 60 years and 26 (65%) were women (Table 1). MRI analysis showed evidence of HA in 38 (95%) cases; two patients had a normal MRI scan. Based on EEG and MRI data, HA occurred most commonly on the left side (22 [55%] patients); 12 (30%) patients had a right HA and four (10%) patients had bilateral HA.

Thirty-one of the patients with MTLE were diagnosed as having a mood disorder. There were no statistically significant differences in age or duration of epilepsy between patients with and without depression (Table 1). Additionally, there was no difference in seizure frequency between the depressed patients and those without depression. Unsurprisingly, the difference in BDI scores was statistically significant with the highest scores observed in the group with depression.

All but one patient used two or more AEDs. Carbamazepine combination treatments were the most commonly used therapies (31/40 [77.5%] patients) and clobazam in combination with carbamazepine was used by 12/40 (30%) patients. Only 8/40 (20%) patients were receiving antidepressant medications.

Of the 31 patients with mood disorders, 14 had dysthymia (ICD-10, F34.1), 11 had recurrent depressive disorder (i.e., more than two episodes with duration of at least two weeks each and separated apart by more than one month; ICD-10, F33), six patients had bipolar disorder (ICD-10 F31), with current depressive episode (ICD-10, F31.3). Four patients in this last group had mild to moderate depressive episodes [ICD-10 F31.3] and two had severe current depressive episodes without psychotic symptoms [ICD-10 F31.4]. Additionally, among the six patients in the last group, five had suicidal ideations but none had attempted suicide.

Correlations between BDI scores and epilepsy duration ($r = 0.12$) or between BDI scores and seizure frequency ($r = 0.11$) were not statistically significant. In addition, no significant difference was found between patients with and without depression in the presence or laterality of HA.

Of the 31 patients with depression, 17 had left HA, nine right HA, three had bilateral HA, (two predominantly left, one predominantly right), and two patients had a normal MRI scan. Of the 22/31 (71.0%) cases with moderate to severe depressive disorder, 12 patients had left HA (four had major depressive disorder and eight had moderate), eight patients had right HA and two patients had normal MRI scans.

A large proportion 23/31 (74.2%) of patients characterized as having a depressive disorder had not been previously diagnosed. Although 10/31 patients had previously received antidepressants (some for migraine and/or neuropathic pain) only 8/31 (25.8%) patients had received antidepressants for depression. Results showed that there had been 4/10 suicide attempts (3 patients with depression) and isolated suicidal ideation occurred in 10/40 patients (nine patients with depression).

Among the 40 patients involved in the study, epilepsy occurred in family members in 19 (47.5%) cases, alcoholism in 16 (40.0%) and mental disorders in 15 (37.5%). In addition, there were six (15%) psychiatric hospitalizations among the family members, three of which were for suicide attempts. There was no difference between patients with and without depression in the frequency of epilepsy or psychiatric history of family members.

Discussion

Accurate estimates of psychiatric comorbidities are difficult,[55] as most are based on studies with considerable heterogeneity of the variables and factors. A strength of this current study was the use of relevant instruments, especially the semi-structured psychiatric interview, which produced a reliable diagnosis of the psychiatric comorbidity. Based on our results and in accordance with other studies[4], the clinical presentation of depressive disorders in epilepsy was similar to that of patients without epilepsy. Interictal depression in epileptics is the most common type of recognized mood disorder and usually presents as a chronic depression that more often than not tends to mimic a dysthymic disorder with endogenous features and an intermittent course.[4] We used reliable methods to categorize the patients into the ICD-10 equivalent of these disorders.

This current study showed a high frequency (77.5%) of depressive disorders in patients with pharmaco-resistant MTLE. These findings are similar to several studies[6,19,55] but higher than those found in some reports.[4,8,9,10,23,56] The difference in results may be related to the severity of the current study group; patients had severe epilepsy and were candidates for epilepsy surgery. Despite its relatively high prevalence, depression in patients with epilepsy remains poorly recognized and without adequate treatment.[4] In this study, most patients with major depressive disorder (74.2%) had no previous diagnosis of the condition and only 25.8% had been treated with antidepressants.

In a preliminary study from our centre involving 25 patients, we found that the duration of epilepsy was significantly higher in patients with a depressive disorder compared with those without depression.[57] In this current study, the sample size was increased to 40 patients but a correlation between duration of epilepsy and depression was not observed probably because most patients had a mood disorder (i.e., 77.5%) which skewed the sample population. In addition, we found that there was no association between BDI and seizure frequency.

However, the relationship between depressive disorders and severity of epilepsy is considered controversial by several authors.[7,18,31,58]

Evidence suggests a bi-directional relationship between depression and MTLE[22–25,37] and a study in patients with MTLE has shown increased gray matter atrophy in patients with depression compared with those without depression.[30] This evidence suggests that common biological factors may be related to both depression and MTLE. Dysthymia was identified as the most common depressive disorder in patients with epilepsy (14/40, 35.0%), followed by recurrent depressive disorder (11/40, 27.5%). These findings are in accordance with those of others who suggested that dysthymia is the most common comorbidity in patients with MTLE,[4] In addition, we found several patients (6/40, 15%) had a bipolar disorder. A previous study found that 11.8% of 143 adult patients with epilepsy had bipolar disorder according to DSM-IV critieira,[59] and another study using the MINI-Plus version detected 9.6% of 73 MTLE patients had bipolar disorder (80.8% had refractory epilepsy).[60] It is speculated that refractory MTLE could be involved with neuropathogenic mechanisms related to depression[25] and there could possibly be a similar association between MTLE and affective disorders.[37]

Further studies should be conducted to understand the comorbidity of depression with refractory MTLE because it is important to identify and provide adequate treatment to prevent adverse consequences such as suicide ideation and/or suicide attempts. Importantly, suicide is two to five times higher in patients with epilepsy than in the general population.[4,27–29,31–34] This rate is even higher among patients with MTLE (i.e., the risk is 25 times higher), rising in the presence of a comorbid depressive disorder to 32 times higher[21,61] A high rate of suicide attempts (10%) was observed in this study which is in accordance with previous findings.[4,21,61] Clearly, untreated depression has an important impact on patient's quality of life and early diagnosis and adequate treatment of depression may prevent brain dysfunction and assist in epilepsy improvement.

Similar to other studies,[62,63] a high frequency of epilepsy was found in the relatives of patients (47.5%). The rates of familial alcoholism and psychiatric disorders were also high (40% and 37.5%, respectively). In a previous study that involved 82 patients with pharmacoresistant MTLE and 62 with treatment-responsive MTLE, the presence of family psychiatric history was more frequent in pharmaco-resistant patients.[64] In this present study no differences was found between patients with and without depression in the frequency of epilepsy or in psychiatric family history. However, all patients had refractory MTLE and the number of patients without depression was small. Indeed, a major limitation of this study was the small sample size. However, the overall results support the importance of psychiatric evaluation in MTLE patients with symptoms suggestive of mood disorders, particularly in individuals with pharmaco-resistance.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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