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Evaluation of Depression with Mixed Features and Bipolarity Screening in Patients with Epilepsy

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ABSTRACT

Objective: To investigate depression with mixed features (MXD) and risk of bipolarity and to explore the association between clinical variables in patients with epilepsy.

Materials and Methods: A total of 62 patients who were followed up with epilepsy diagnosis at least 2 years were enrolled. Demographic and clinical data were collected using face to face interview. All subjects also performed modified hypomania checklist (mHCL), Beck depression inventory (BDI), and the mood disorder questionnaire (MDQ).

Results: According to the BDI, 25 (40.3%) of the cases required additional psychiatric examination for depression. MDQ scores indicated that 7 (9.7%) of the cases required additional psychiatric evaluation for bipolar disorder. Due to the mHCL assessment, 20 (32.2%) cases had at least 3 manic symptoms, and 9 (14.5%) cases had at least 13 manic symptoms of mixed depression. A significant positive correlation was found between the scores of BDI and mHCL ($r=0.338$, $P=.007$) and the scores of mHCL and MDQ ($r=0.694$, $P < .001$). In addition, bipolarity risk was significantly higher in patients with generalized epilepsy, than partial epilepsy ($P=.040$).

Conclusion: Our results suggest that MXD is more common and the risk of bipolarity is higher in patients with epilepsy. Therefore, clinical assessment of MXD is substantial for determining bipolarity in epileptic individuals.

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INTRODUCTION

Patients with epilepsy have a higher prevalence of psychiatric disorders than in the general population. Etiological and clinical factors related to seizures and neurobiological changes due to antiepileptic drugs (AEDs) could affect mental status.[1,2] In addition, the occurrence of unpredictable seizures and the stigmatization process can lead to sadness, hopelessness, low self-esteem, and social withdrawal. Depression is the most common psychiatric comorbidity in epileptic individuals. The prevalence of depression was estimated at between 20% and 30% in population-based studies.[3-5]

Several specifiers identify the clinical progress in the course of depressive disorders. These specifiers for depressive disorders are anxious distress, mixed features, melancholic features, atypical features, peripartum onset, seasonal pattern, mood congruent, and incongruent psychotic features. According to the latest edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*), "depression with mixed features (MXD)" and "manic or hypomanic episodes with mixed features" are accepted as new terminology instead of "mixed episode." MXD is a mood disorder which is accompanied by at least 3 mania or hypomania symptoms. The most common manic symptoms are unusual talkativeness, irritability, disconnected and racing thoughts, psychomotor agitation, and distractibility.[6] In the literature, for the rate of cases diagnosed with major depressive disorder, 22% and 50% accompanied at least one manic symptom, while between 7% and 23% accompanied at least 3 manic symptoms.[7] Previous studies reported that functional impairment, treatment resistance, relapses, and suicide risk were significantly more common in patients with MXD. In addition, MXD has been associated with positive family history of bipolar disorders and poor prognosis.[8,9] Recent epidemiologic studies have suggested the bidirectional relationship between epilepsy and mood disorders (MDs). Despite the higher prevalence of MDs in epileptic patients than in the general population, manic symptoms are less common than depression. However, similarities between epilepsy and bipolar disorder such as episodic pattern,

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kindling phenomenon, good response to antiepileptics, and hereditary features should not be overlooked.[10,11]

In this study, we aimed to investigate the mixed features of depression and explore the relationship between the risk of bipolarity and clinical variables (etiology, age at disease onset, disease duration, seizure type, and frequency, etc.) in patients with epilepsy.

MATERIALS AND METHODS

Study sample

Sixty-two consecutive outpatients, presenting for treatment of epilepsy over a two-year period, were included in this study. The study was conducted at the epilepsy outpatient clinic of the neurology department at the Kocaeli Derince Education and Research Hospital in 2018. Subjects were selected according to the seizure semiology, electroencephalogram (EEG), and cranial magnetic resonance imaging (MRI) findings in order to evaluate patients with a diagnosis of 'definite epilepsy' and to exclude possible epilepsy mimicking phenomenias such as psychogenic non-epileptic seizures. To be enrolled, patients had to be confirmed diagnosis of epilepsy according to International League Against Epilepsy (ILAE) criteria[12]. The following exclusion criteria included: to have a known chronic psychiatric disorder; cognitive impairments and acute/chronic neurological or medical diseases that may restrain the filling of self-report measurements; and psychogenic non-epileptic seizures.

Our study was approved by the local Clinical Research Ethics Committee of Canakkale University Medicine Faculty (Decision No: 2018-09). All procedures were in accordance with the ethical standards of the Helsinki Declaration. Written and informed consent was obtained from all subjects.

Instruments

Socio-demographic and Clinical Data Form: Researchers created this form in order to collect sociodemographic and clinical data of the patients for the purposes of the study. This data form comprised questions about the subjects gender, age, marital status, education, and employment status as well as clinical data such as age of seizure onset, seizure type, and frequency, and history of febrile convulsion.

Modified Hypomania Checklist (mHCL): It is a self-administered questionnaire developed by Angst et al.,[13] that identifies lifetime hypomanic symptoms. The first item assesses the mood state with a Likert-type scale in general. Other items consists of a total of 32 yes/no questions, reflecting 2 dimensions such as changes or swings in energy and risky behaviors/impulsiveness. Vahip et al.[14] validated and developed a Turkish version of the test. Cutoff score was set to be 14. We used a modified version of the mHCL to assess the prevalence and clinical correlations of concomitant (hypo) manic symptoms in depressive patients. Hence, a cross-sectional evaluation aimed to determine the mixed depression symptoms in such patients.[15]

Beck Depression Inventory (BDI): This inventory is a 21-item Likert-type self-report inventory that explores the presence and severity of depressive symptoms. Each item is rated on a 4-point scale (from 0 to 3) with a total score that ranges from 0 to 63. Subjects with $\geq$17 points are considered to have depression. Hisli established a Turkish reliability and validity of the inventory.[16]

Mood Disorder Questionnaire (MDQ): It is a brief, self-rating scale that consists of three items to identify patients with bipolar disorder. The first item includes 13 yes/no questions evaluating lifetime history of manic/hypomanic symptoms, elevated mood, irritability, sociability, self-confidence, energy, libido, sleep, attention, thought, and other behaviors. The second item explores whether the "yes" responses marked with the first question are together. The third item assesses the effect of symptoms on functionality. According to sensitivity and specificity values, the optimum cutoff point is 7. A score of $\geq$7 in the first item, "yes" in the second item, and a moderate/severe impairment of functionality in the third item is considered to have diagnostic value for bipolarity.[17] Konuk et al.[18] performed a Turkish validity for screening bipolar disorders and the ideal cutoff point of the inventory.

Statistical Analysis

SPSS 22.0 (SPSS Inc., Chicago, IL, USA) statistical software package programme was performed for the statistical analyses. Descriptive data were expressed as mean, standard deviation, median, and minimum and maximum values for continues variables and frequencies and percentages (%) for categorical variables. The normality of continuous variables was examined by Kolmogorov-Smirnov test. In the between-group comparisons, continuous variables were analyzed with Mann-Whitney U test and in the correlation analyses, the Spearman correlation test was used according to the distribution characteristics of the continuous variables. Discrete variables (seizure type and bipolarity risk) were compared with Fisher's exact chi-square test. A two-tailed *P* value less than .05 was considered to be statistically significant.

RESULTS

In our study, we enrolled 62 patients with epilepsy including 37 males (59.7%) and 25 females (40.3%). The mean age of the patients was 35.2 ± 11.9 years. Of the study group, 19 (30.6%) were single, 42 (67.7%) were married, and 1 patient (1.6%) was divorced. Twenty-eight (45.2%) patients were primary school graduates, 21 (33.9%) patients were high

school graduates, and 13 (20.9%) of the cases were college and university graduates. The sociodemographic characteristics and clinical data of the subjects are presented in Table 1.

According to the MDQ, 7 (9.7%) of the cases required additional psychiatric evaluation for bipolar disorder. mHCL results indicated that at least 3 manic symptoms in 20 (32.2%) cases and at least 13 manic symptoms in 9 (14.5%) cases were present during the depression period. The mean scores and median values of BDI, mHCL, and the MDQ are summarized in Table 2.

To investigate the relationships of bipolarity and depression scales, Spearman correlation test was used. A weak significant correlation was found between BDI and mHCL scores ($r=0.338$, $P=.007$) and between BDI and MDQ scores ($r=0.258$, $P=.043$), whereas a moderately significant correlation was found between mHCL and MDQ scores ($r=0.694$, $P < .001$) (Table 3).

To compare score of the scales between seizure types, Mann-Whitney U test was used. There were no significant differences in scores of BDI and mHCL between patients with partial and generalized epilepsy ($P > .05$). According to the MDQ, 4 (6.5%) of the cases with generalized epilepsy and 3 (4.8%) of the cases with partial epilepsy had a risk for bipolarity. Additionally, bipolarity risk was significantly higher in patients with generalized epilepsy ($P=.040$). The Fisher's exact test was used for testing relationships between bipolarity risk and seizure type (Table 4).

Table 1. Sociodemographic Characteristics and Clinical Data of Patients with Epilepsy

		(*n* [%])	Mean ± SD Median (min - max)
Age (years)			35.2 ± 11.9
			36 (18 - 66)
Gender	Male	37 (59.7)	
	Female	25 (40.3)	
Marital status	Single	19 (30.6)	
	Married	42 (67.7)	
	Divorced	1 (1.6)	
Education (years)			9.6 ± 3.3
			11 (5 - 15)
Graduation	Primary school	28 (45.2)	
	High school	21 (33.9)	
	College / University	13 (20.9)	
Employment	Employed	33 (53.2)	
	Unemployed	27 (43.5)	
	Retired	2 (3.2)	
Age of disease onset (years)			21.6 ± 12.8
			18 (1 - 59)
Seizure type	Partial	48 (77.4)	
	Generalized	14 (22.6)	
Seizure frequency	Last 3 months		2.2 ± 2.4
			1 (0 - 10)
	Last 1 year		5.8 ± 5.9
			3.5 (0 - 25)
History of febrile convulsion	Present	16 (25.8)	
	Absent	46 (74.2)	

SD: Standard deviation.

Table 2. Mean Scores and Median Values of the Questionnaires in Epileptic Patients

	Mean ± SD	Median (min - max)
Beck Depression Inventory (BDI)	16.7 ± 13.7	12 (0 - 51)
Modified Hypomania Checklist (mHCL)	7.4 ± 6.1	6 (0 - 24)
Mood Disorder Questionnaire (MDQ)	3.5 ± 3.1	2 (0 - 13)

SD: Standard deviation.

DISCUSSION

In our study, the rate of patients who required psychiatric examination for depression risk, according to the BDI cutoff score was 40.3%. Depression is one of the most common psychiatric comorbidities that are usually overlooked in epileptic patients. Its incidence ranges from 20% to 30% in a community-based sample of people with epilepsy and between 20% and 55% in specialized epilepsy centers.[5] In a study with a large sample in the United States, the prevalence of depressive disorders in adults with epilepsy was found to be 34.7%.[19] In our study, the rate of patients with a diagnosis of epilepsy who were at risk of depression was consistent with the literature. In addition, higher scores of depression scales are prominent for evaluating the severity of depression symptoms in patients with epilepsy. Moreover, manic symptoms and the correlation between depression and hypomania checklist scales suggested that mixed features are more common in depression than previously thought. The presence of the "mixed feature" specifier in depression increases the possibility of later mania or hypomania diagnosing. It is stated that "mixed features" have been found to be a significant risk factor for the development of bipolar disorder.[6] It also has been associated with greater functional impairment, less favorable responses to treatment, and poorer clinical prognosis than those without.[9,20]

Table 3. Correlation Analysis between the Questionnaires

	mHCL	BDI	MDQ
mHCL	1		
BDI	0.338*	1	1
MDQ	0.694*	0.258*	1

Spearman correlation, *P <.05.

Table 4. Relation between Bipolarity Risk and Seizure type

		Seizure Type [n (%)]		*P*
		Partial	Generalized	
Bipolarity	No	45 (72.6)	10 (16.1)	.040
	Yes	3 (4.8)	4 (6.5)	
Total		48 (77.4)	14 (22.6)	

While previous reports provide more information about the association between epilepsy and unipolar depression, data on the relationship between bipolar depression is limited. It has been reported in the literature that symptoms and the risk of developing bipolar disorder are rarer than major depressive disorder in patients with epilepsy.[21] However, it is stated that nearly half of epileptic patients diagnosed with unipolar depression may be patients with bipolar II disorder, because the symptoms of hypomania are difficult to recognize. Additionally, similar features such as episodic pattern, treatment strategies, and kindling phenomenon indicated the presence of more frequent association and common pathophysiological changes between epilepsy and mood disorders (MDs).[9,22] In a study by Ettinger et al.,[23] adults with chronic diseases (epilepsy, migraine, asthma, and diabetes, etc.) were evaluated and compared with healthy individuals. In their study, MDQ was found to be positive in 142 (12.2%) of 1236 epileptic patients. They identified that hypomanic symptoms in patients with epilepsy are approximately 1.6 to 2.2 times more than chronic diseases such as migraine, asthma, and diabetes and 6.6 times more than hypomanic symptoms in the healthy controls. In the same study, approximately half of the epileptic patients with MDQ positive have been previously diagnosed with bipolar disorder, while one-fourth of the cases diagnosed with unipolar depression and a quarter of the cases had not been clinically diagnosed. In our study, 9.7% of the cases were positive on MDQ screening and required additional assessment for the diagnosis of bipolar disorder. Thus, our results were in accordance with the study by Ettinger et al.[23] Consistent with these results, bipolar disorder may represent a prominent psychiatric comorbidity in epilepsy.

Mula et al.[24] explored the prevalence of both bipolar disorder and bipolar symptoms and evaluated the diagnostic role of potential confounding factors such as seizures and drug therapy. They reported that 11.8% of patients with epilepsy met the diagnosis of bipolar disorder according to the DSM criteria, and 14.7% were positive for bipolar symptoms according to the MDQ. According to the possible contradictions, they found that the prevalence of pure bipolar disorder and bipolar symptoms were 1.4%, and 2%, respectively. They also suggested that dysphoric or hypo (manic) symptoms of the remaining cases may be related to interictal, preictal, and postictal periods.

One of the factors that play an important role for screening bipolarity is the usage of antiepileptic drugs (AEDs). A negative psychotropic effect of AEDs on mood and behavior may cause depression, irritability, agitation, and emotional lability.[25] Therefore, clinicians should differentiate antiepileptic drug-related negative symptoms from depression and/or bipolar disorder symptoms. However, mood the stabilizer effect of some anticonvulsants (valproic acid, carbamamzepine, lamotrigine, etc.) may mask some symptoms associated with MDs.[26] In our study, some symptoms of MDs may be overlooked due to the usage of antiepileptics with mood-stabilizing potential.

Defining the biological causes of bipolar symptoms in epilepsy is difficult while the underlying mechanisms of bipolar disorder remain poorly understood. Moreover, atypical, intermittent, and pleomorphic symptomatology of MDs in epilepsy provides an incomprehensible process for the diagnosis. In the literature, there are several studies regarding the association between comorbid psychiatric symptoms with epileptogenic focus and disease severity. In particular, possible effects of the limbic system, frontal, and temporal regions on psychiatric symptoms are emphasized.[11,27] Previously, the authors claimed that patients with generalized seizures had no psychiatric symptoms, except delirium.[28]

Nevertheless, in a population-based study, Chang et al. demonstrated the association between psychiatric disorders (bipolar disorder, mental retardation, depression, etc.) and newly diagnosed epilepsy, in close relation with generalized seizures. In their report, the relative risk of developing psychiatric disorders was 3.8 times higher in patients with partial seizures, while the risk was 4.6 times higher in patients with generalized seizures, compared to patients without epilepsy.[29] In our study, bipolarity risk in generalized epilepsies was more significant than partial seizures; however, no difference was found between the depression severity among the patient groups. Difficulties in distinguishing secondarily generalized seizures from primary generalized seizures and some confounding factors, especially interictal dysphoric disorder in patients with epilepsy, may have caused this condition.

The current study has several strengths. This is the first report exploring mixed features of depression, the risk of bipolarity, and their association between disease-related variables in patients with epilepsy. Second, our study provides a new insight to understand the characteristics of epileptic people who had a diagnosis of MXD. Third, all of the valid and reliable inventories are applied by an experienced psychiatrist.

Our study has some limitations that have to be pointed out. First, our relatively small sample size reduces the statistical power of the study. Second, we did not take time intervals between seizures into consideration that could interfere

with MDs such as depression and bipolar disorder. The other limitations include the cross-sectional design of our study and mood stabilizer potential of some antiepileptic drugs. Therefore, considering the confounding factors for diagnosis, long-term follow-up is needed in the course of psychiatric disorders in epilepsy.

In conclusion, our data suggest that mixed features of depression and the risk of bipolarity are common in epilepsy. From a clinical perspective, following up depression with mixed features and the risk of bipolarity in epileptic individuals would provide a beneficial effect on treatment strategies and prognosis. Further extensive and prospective studies with larger sample sizes are needed to determine psychiatric comorbidities in patients with epilepsy.

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Ethical Committee Approval: Ethical committee aproval was received from the local Clinical Research Ethics Committee of Canakkale University Medicine Faculty (Decision No: 2018-09).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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