PSYCHIATRIC COMORBIDITIES AMONG PATIENTS WITH EPILEPSY IN MONTENEGRO

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SUMMARY – The aim of this study was to evaluate the prevalence of psychiatric comorbidities, depression and anxiety, among patients with epilepsy in the outpatient Clinic for Epilepsy, Clinical Centre of Montenegro. Patients aged 18 and above with a diagnosis of epilepsy for at least one year were consecutively enrolled during a six-month period. Patients anonymously filled out a questionnaire which included data on the gender, age, education, marital status and degree of seizure control. The Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A) were used to evaluate the presence or absence of anxiety and depression. Total number of study patients was 70, including 52 patients with partial seizures and 18 patients with generalized tonic-clonic seizures. The mean patient age was 37±7.92 years. The prevalence of depression in our sample was 32.8%, whereas the prevalence of anxiety was 21.4%. Patients with partial seizures were more depressed, while those with idiopathic generalized seizures were more anxious ($p<0.01$). Depression was associated with a lower educational level, unemployment and poor seizure control ($p<0.05$). The number of antiepileptic drugs showed a trend towards negative association with depression ($p=0.005$). Anxiety was associated with the level of education and uncontrolled seizures ($p<0.01$). Neither depression nor anxiety was associated with age, gender, marital status, age at onset and duration of epilepsy. Psychiatric disorders among patients with epilepsy are quite common but yet under-recognized. Therefore, appropriate recognition and efficient treatment of these disorders in patients with epilepsy might improve their quality of life and could consequently lead to better treatment success.

Key words: *Epilepsy; Depression; Anxiety disorders - classification; Psychiatric status rating scales; Comorbidity; HAM-D; HAM-A*

Introduction

Epilepsy is a spectrum disorder characterized by recurring seizures, affecting around 50 million people worldwide. But, what makes this disorder so hard to manage, is the fact that for the affected individual, epilepsy is much more than just having seizures. In addition to physical and cognitive impairments they encounter, psychiatric disorders constitute a considerable burden for patients and their families[1]. Depression and anxiety are the most common types of psychiatric disorders found in patients with epilepsy[2]. For many years, it was believed that psychiatric disorders in epilepsy were a consequence of maladaptation to a chronic and highly stigmatized disease[3], but today we know that there is a bidirectional relationship between epilepsy and psychiatric disorders, depression

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in particular. In other words, not only that psychiatric disorder may result from epilepsy but a psychiatric disorder, especially depression, may promote the development of epilepsy *via* shared pathogenic mechanisms. These pathogenic mechanisms include neurochemical, structural and functional abnormalities, iatrogenic processes, reactive process and genetic predisposition. Clinical features of epilepsy, such as age at onset, type, frequency and severity of seizures, epilepsy syndrome and laterality of focus have also been investigated in order to establish potential association between these factors and rates of psychiatric comorbidities[4-6]. The results from these studies are contradictory.

Several community based studies suggest that the prevalence of depression is 20%-30% in patients with recurrent seizures and 6%-9% in those in remission. Also, both hospital and community based studies of epilepsy found the prevalence of an anxiety disorder to be between 10% and 25%[7]. Regardless of this rather high prevalence, both disorders remain under-recognized and when diagnosed, the treatment is based on empirical data.

The aim of the present study was to determine the prevalence of depression and anxiety among patients with epilepsy in outpatient Clinic for Epilepsy, Clinical Centre of Montenegro. The possible relationship between these disorders, clinical determinants of epilepsy and demographic variables of study patients were also investigated.

Patients and Methods

In this cross-sectional questionnaire study, patients that met inclusion criteria were consecutively recruited in the outpatient Clinic for Epilepsy, Clinical Centre of Montenegro over a six-month period. The total number of enrolled patients was 70. Inclusion criteria were age 18 and above, a diagnosis of epilepsy for at least one year, and the use of antiepileptic drugs (AEDs), while exclusion criteria were active psychotic symptoms (delusions and hallucinations), symptomatic epilepsy secondary to brain neoplasms, cerebrovascular disease or vascular malformations, no history of psychotropic medication use including benzodiazepines, and refusal to give an informed consent. The focus of the present study was exclusively on interictal mood disorders. There were 26 male and 44 female patients. We classified patients in primary generalized and partial epilepsy based on the clinical features of seizures according to the International League Against Epilepsy Classification of Epileptic Seizures (Commission on Classification and Terminology of the International League Against Epilepsy 1981) and supported by electroencephalogram (EEG) findings. Patients with simple partial, complex-partial and partial-onset secondary generalized seizures and/or focal epileptiform activity were classified as having partial epilepsy. Patients that were classified as primary generalized epilepsy had generalized seizures and generalized epileptiform activity. Fifty-two patients had partial seizures and the rest had idiopathic generalized seizures. All eligible patients were administered a questionnaire that included details about gender, age, educational level (secondary school or less, university or higher), employment (employed, unemployed), marital status (unmarried, married) and seizure control (controlled, uncontrolled). The Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A) were administered to evaluate the level of depression and anxiety in epilepsy patients. HAM-D consisted of 21 questions but only the first 17 were scored. Eight items are scored on a scale of 0 (not present) to 4 (severe) and nine are scored as 0-2. Patients with score 8 or more were classified as being depressed. HAM-A consisted of 14 questions and all of them are scored on a scale of 0 (not present) to 4 (severe). Patients were classified as having an anxiety syndrome when their score was 18 or more.

Statistical analysis

Demographic variables (i.e. gender, age, educational level, employment and marital status) as well as clinical determinants (age at seizure onset, duration of epilepsy in years, seizure control, presence of depression and anxiety, number of AEDs used) were summarized in order to characterize the study population. Statistical analysis included descriptive statistics, χ^2-test and regression analysis. Continuous data are presented as mean ± standard deviation (SD), while non-continuous variables are given as percentages. In order to assess which factors are associated with HAM-D and HAM-A logistic regression was performed, with demographic factors and clinical determinants such

Table 1. Demographic characteristics of study patients (N=70)

		Male	Female
Gender		37.15%	62.85%
Age (yrs)	37±7.92	36±8.01	37.34±7.93
Educational level			
Secondary school or less	65.71%	57.69%	70.45%
University	34.29%	42.31%	29.55%
Employment			
Employed	65.71%	57.69%	70.45%
Marital status			
Married	18.58%	15.38%	20.45%

Non-continuous variables are presented as percentages; continuous variables are presented as mean ± SD.

as age at seizure onset, duration of epilepsy in years, seizure control and number of AEDs as independent variables. The value of p less than 0.05 was considered statistically significant. All statistical analyses were performed using the E-views software.

Results

Table 1 summarizes demographic characteristics of study patients. The study was performed on 70 patients, with the majority of patients being female (n=44). The patient age range was 21 to 52, mean 37±7.92 years. A vast majority of patients finished secondary school and were unemployed. Over 80% of study patients were not married. The HAM-D score had a mean value of 9±4.46. Over 30% of patients were classified as being depressed. The HAM-A score had a mean value of 15±2.45, with 21.42% of patients classified as having an anxiety syndrome. Clinical determinants of epilepsy are summarized in Table 2. Patients with partial seizures (74.28%) were more depressed, while those with idiopathic generalized seizures (25.71%) were more anxious ($p<0.01$). Almost 60% of patients had controlled seizures and more than half were on monotherapy.

Association of depression and anxiety with demographic and clinical characteristics was evaluated using logistic regression analyses. Demographic variables

Table 2. Clinical determinants of epilepsy

		Depression	
		Yes	No
Type of seizure			
Partial (simple, complex, with secondary generalization)	74.28%	38.46%	61.54%
Generalized tonic-clonic seizures	25.71%	16.67%	83.33%
Age at seizure onset (yrs)			
	21±8.66	32.85%	67.15%
Duration of epilepsy in years			
	16±7.97	32.85%	67.15%
Seizure control			
Controlled	58.57%	9.75%	90.25%
Uncontrolled	41.43%	65.51%	34.49%
Number of AEDs used			
1	55.71%	15.38%	84.62%
2	28.57%	45%	55%
3 or more	15.72%	72.72%	27.28%
Depression			
Present	32.85%		
Anxiety			
Present	21.42%		

Non-continuous variables are presented as percentages; continuous variables are presented as mean ± SD; AEDs = antiepileptic drugs

Table 3. Results of regression analysis (depression and anxiety as dependent variables)

Variable	Depression	Anxiety
	regression p value	regression p value
Gender	0.352	0.198
Age	0.269	0.365
Educational level	**0.0005**	**0.002**
Employment	**0.003**	0.468
Marital status	0.447	0.878
Age at onset	0.278	0.372
Duration of epilepsy	0.268	0.374
Seizure control	**0.048**	**0.019**
Number of AEDs used	0.05	0.593

AEDs = antiepileptic drugs

such as gender, age and marital status were nonsignificantly associated with either depression or anxiety. On the contrary, educational level was found to have a negative statistically significant association with depression. In other words, patients with higher education were less depressed compared to those that had just finished secondary school or less (-0.39, p<0.01). The same association was found among patients with anxiety (-0.36, p=0.02). Employment was also positively associated with depression (0.38, p<0.01), but this association was not found among patients with anxiety. Clinical characteristics of epilepsy such as age at onset and duration of epilepsy were not statistically significantly associated with either of the psychiatric disorders under study. Uncontrolled seizures, on the other hand, were positively associated with both depression and anxiety (0.21, p<0.05 and 0.26, p=0.01, respectively). The number of AEDs used had no statistically significant association with anxiety (-0.03, p=0.59), but did show a trend towards negative significant association with depression (-0.11, p=0.05). Summarized results are shown in Table 3.

Discussion

The altered brain activity due to seizures can lead to depression, and the stress of living with still highly stigmatized disorder, on the other hand, can worsen the feelings of anxiety and depression. Comorbidity of epilepsy may be due to the shared pathophysiological mechanisms, genetic, iatrogenic or psychosocial factors.

The present cross-sectional questionnaire study investigated the association of certain demographic and clinical variables with depression and anxiety in patients with epilepsy. Our results confirmed the results of previous studies stating that depression and anxiety are common psychiatric disorders in patients with epilepsy[2]. In our study population of epilepsy patients, the prevalence of depression was 32.85% and of anxiety 21.42%. A similar prevalence of depression among epilepsy patients was found in a Croatian study conducted by Hećimović *et al.*[8]. The effect of gender on the psychiatric disorders in epilepsy varied among the studies, from those that found female gender to be more susceptible to depression to those that found no statistically significant connection[9-13]. Regarding anxiety in epilepsy, gender is generally considered to have a subtle effect[11]. Our study failed to find this connection in either of the two disorders. In addition, we demonstrated the level of education to be inversely correlated with psychiatric comorbidities. Patients with higher education were less depressed compared to those that had just finished secondary school or lower. Patients with higher levels of education most likely have greater cognitive ability, which helps them adapt better to life with epilepsy. They probably use more efficient psychological approaches in order to actively cope with their illness, as well as with social stigma. Patients with epilepsy often have low self-esteem and feel socially rejected. Therefore, it is not surprising that, in our study, unemployment was positively associated with depression. This association was not found among patients with anxiety.

Our study found no association between the age at onset and duration of epilepsy with depression and anxiety. Many other studies also report no association between the age at onset and duration of epilepsy and depression[10,14]. Depression is reported to be more common in patients with complex partial seizures than in patients with generalized epilepsy[15,16]. Mendez *et al.* also showed in their study that patients with coexisting epilepsy and depression had fewer generalized tonic-clonic seizures compared to people with epilepsy without depression[17]. In our sample, patients with partial seizures were more depressed, whereas patients with general tonic-clonic seizures were more

anxious. In a study by Nenadović *et al*.[18], patients with generalized epilepsy had significantly lower levels of anxiety compared even to the control group. Contrary to ours, these findings are in accordance with literature data. Namely, in the literature, the risk of anxiety disorders appears to be higher in focal than in generalized epilepsies[19,20]. Seizure control plays an important role in the patient psychosocial adjustment and well-being. In our study, patients with uncontrolled seizures were more depressed and more anxious. This is probably a result of unpredictability of seizures and restrictions in everyday activities. Hamed *et al*. report that patients with the lack of control on AEDs were also more depressed[21]. Seizure frequency was linked with the severity of anxiety in some[22], but not in all studies[23]. Depression in epilepsy patients has been associated with AED polytherapy[17]. In terms of anxiety, most of the studies demonstrated that AED polytherapy was associated with an increased risk of anxiety disorders[24,25]. However, it is unclear whether there is a direct causal relationship between AED polytherapy and anxiety. In our study, the number of AEDs used was not found to have statistically significant association with anxiety, but showed a trend towards negative association with depression.

Epilepsy is a common neurological condition with a high prevalence of psychiatric comorbidities. These disorders should not be under-recognized, as they could intensify epilepsy symptoms and adversely affect the patient quality of life.

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Sažetak

PSIHIJATRIJSKI KOMORBIDITETI U BOLESNIKA S EPILEPSIJOM U CRNOJ GORI

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Cilj ovoga istraživanja bio je ispitati učestalost psihijatrijskih bolesti, depresije i anksioznosti, u bolesnika s epilepsijom u Dispanzeru za epilepsije Kliničkog centra Crne Gore. Bolesnici u dobi od 18 godina i više s dijagnozom epilepsije od najmanje jedne godine uključivani su u studiju kroz šest mjeseci. Bolesnici su ispunjavali upitnik koji je uključivao podatke o spolu, dobi, obrazovanju, bračnom stanju i stupnju kontrole napadaja. Ljestvice *Hamilton Depression Rating Scale* (HAM-D) i *Hamilton Anxiety Rating Scale* (HAM-A) su korištene za procjenu prisutnosti ili odsutnosti depresije i tjeskobe. Ukupno je bilo uključeno 70 bolesnika: 52 bolesnika s parcijalnim napadajima i 18 bolesnika s generaliziranim toničko-kloničkim napadajima. Prosječna dob bolesnika je bila 37±7,92 godine. Učestalost depresije u našem uzorku je bila 32,8%, dok je učestalost anksioznosti bila 21,4%. Bolesnici s parcijalnim napadajima su bili više depresivni u odnosu na bolesnike s idiopatskim generaliziranim napadajima, koji su bili anksiozniji ($p<0,01$). Depresija u bolesnika s epilepsijom je bila povezana s niskim stupnjem obrazovanja, nezaposlenošću i lošom kontrolom napadaja ($p<0,05$). Uporaba antiepileptika je pokazala trend ka negativoj povezanosti s depresijom ($p=0,005$). Anksioznost je bila povezana s razinom obrazovanja i nekontroliranim napadajima ($p<0,01$). Nijedan od ovih psihijatrijskih poremećaja u bolesnika s epilepsijom nije bio povezan s dobi, spolom, bračnim stanjem, dobi nastupa i trajanjem epilepsije. Psihijatrijski poremećaji u bolesnika s epilepsijom su veoma česti, ali se još uvijek slabo prepoznaju. Odgovarajuće prepoznavanje i učinkovito liječenje ovih bolesti u bolesnika s epilepsijom moglo bi značajno poboljšati kvalitetu njihova života i posljedično bi moglo dovesti do bolje uspješnosti liječenja.

Ključne riječi: *Epilepsija; Depresija; Anksiozni poremećaji - klasifikacija; Komorbiditet; HAM-D; HAM-A*