The Comorbidity of Migraine in Bipolar Disorder

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ÖZET:
İki uçlu bozuklukta migren ekhastalığı

Amaç: Bu çalışmanın amacı iki uçlu bozukluğu olan hastalarda migren ekhastalık sıklığını ve bunun hastaların çeşitli demografik ve klinik değişkenleri üzerine olan etkisini belirlemektir.
Yöntem: Psikiyatri polikliniğinde düzenli olarak takipleri sürdürülen ve DSM-IV kriterlerine göre, klinik olarak iki uçlu bozukluk tanıları almış olan, iyileşme dönemindeki hastalar (n= 96, 67 kadın, 29 erkek) çalışmamıza dahil edildi. Tüm hastalarla, IHS ölçütleri uygulanarak yapılan görüşmelerde, migren ekhastalığı araştırıldı.
Bulgular: 96 iki uçlu bozukluk tanısı olan hastanın %26.0'ında migren tanısı mevcuttu. Sonuçlarımız iki uçlu bozukluklarda migren ekhastalığı yaygınlığını ve bunun cinsiyet, yaş, medeni hal, yapılan iş, eğitim düzeyi, doğum sonrası başlangıçlı iki uçlu bozukluk dönemi ve özkıyım girişimleri ile ilişkili olabileceğini gösterdi.
Sonuç: Migren ekhastalığının yaygın olması, iki uçlu bozukluğun seyrini olumsuz etkilemekte ve hastanın sosyal uyumunu bozmaktadır. İki uçlu bozukluklu hastalarda, migrenin düzenli aralıklarla takibi, bozukluğun seyrinde ortaya çıkabilecek sorunları ve komplikasyonları önlemek açısından yardımcı olabilir.

Anahtar sözcükler: Migren, iki uçlu bozukluk, ekhastalık, yaygınlık

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ABSTRACT:
The comorbidity of migraine in bipolar disorder

Objective: The aim of this study was to determine the frequency of migraine comorbidity with lifetime bipolar disorder (BPD), and the influence of this comorbidity on various demographic and clinical variables in bipolar patients.
Method: Patients (n= 96) with a previous diagnosis of BPD in remission (67 female, 29 male) were included in this study. The diagnosis of BPD was clinically made according to DSM-IV criteria, on admission of the patient to the follow-up routine of outpatient clinics. All patients were interviewed for the presence of current migraine comorbidities using the IHS-criteria.
Results: Twenty-six of the 96 bipolar patients (26.0%) were diagnosed with migraine. Our data indicate that migraine comorbidity is prevalent and it appears to may be associated with gender, current age, marital status, occupation, duration of education, postpartum onset of BPD episode, and suicide attempts in patients with BPD.
Conclusion: Migraine is a common comorbidity in bipolar patients, and it adversely affects the course of the disease and disrupts the social adjustment of the patients. Regular monitoring of migraine will help to prevent problems and complications that could arise in the course of the BPD.

Key words: Migraine, bipolar disorder, comorbidity, prevalence

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INTRODUCTION

Data from both epidemiologic and clinical samples indicate elevated rates of migraine among patients with bipolar disorder (1-3). The clinical significance of comorbid migraine has been less well delineated, though greater severity and dysfunction are suggested. Migraine is a common primary headache disorder which includes disability and loss of performance. Also, that usually begin on one side of the head (often behind the eye) and spread to the whole head (2). The highest prevalence occurs between the ages of 25 and 55 years, potentially the most productive period of life. In most countries, migraine is under-recognized and under-treated (4,5). Epidemiological studies suggest that 12% of the adult population in the United States suffers with migraine (4). The migraine prevalence in Turkish female was higher than that of reported in previous studies from other countries (2,3). They are three times more common in females and tend to affect young people who are otherwise healthy (5).

BPD is a lifelong illness with a course that is usually

chronic or recurrent. In terms of classification, in DSM-IV a distinction is drawn between bipolar disorder type I (BPD-I), in which the patient suffers full-blown manic episodes (most commonly interspersed with episodes of major depression), and bipolar disorder type II (BPD-II), in which the patient experiences depressive episodes and less severe manic symptoms, classed as hypomanic episodes (6). Rates reported in community-based epidemiological studies have varied more widely from 0.1% to 2.5% (based on DSM-III-R, or DSM-IV criteria) (7-9).

Recently studies have found that migraine occurs together with other illnesses at a greater coincidental rate than is seen in the general population (10-12). These occurrences are called "comorbidities". The term comorbidity is used to refer to the statistical association of two distinct diseases in the same individual at a rate higher than expected by chance (13). The comorbid illnesses in patients with migraine include; stroke, vascular brain lesions, heart disease, hypertension, psychiatric diseases (depression, anxiety disorders and bipolar disorder), restless legs syndrome, epilepsy and asthma (10-15).

Prodromal and accompanying symptoms of migraine attacks often are psychiatric in nature, such as depression, elation, irritability, anxiety, overactivity, difficulty thinking, anorexia or increased appetite (16). In addition, psychosocial stress is the most common precipitating factor for a migraine attack (17). Migraine is, therefore, an important differential diagnosis in relation to episodic phenomena with a mixture of somatic and psychiatric symptoms (18). Some investigators concluded that headache patients with a long history and high frequency of headaches, or patients suffering from migraine with aura or drug overuse might benefit from psychiatric evaluation. On the other hand, the majority of multiple-episode BPD patients have a comorbidity at the time of psychiatric hospitalization (19,20). A nascent database suggests that medical comorbidity in BPD is associated with several indices of illness severity, slower rate of recovery, quality of life impairment and premature mortality (20-22). The aim of this study was to determine the frequency of migraine comorbidity with lifetime BPD, and the influence of this comorbidity on various demographic and clinical variables in patients. This will help in identifying the survey of the BPD and hence treatment.

MATERIAL AND METHODS

Participants: All patients presenting at the Psychiatry Outpatients Clinics of the Ankara Atatürk Training and Research Hospital, Turkey, between February 2009 and June 2010 were considered for inclusion in the study. Patients diagnosed with BPD in the psychiatry outpatient clinics of Ankara Atatürk Training and Research Hospital were recruited for the study. The present study and its written consent form were approved by the local Research Ethics Committee.

Among patients enrolled in this unit, those who met the following criteria were included in the study: 1) aged between 18 and 60 years; 2) DSM-IV diagnosis (6) of BPD; 3) clinically in remission for at least eight week before inclusion in the study as corroborated by routinely administered scales during follow-up visits (17-item Hamilton Rating Scale for Depression (HRDS) score of< 7 (23,24) and Young Mania Rating Scale (YMRS) score of < 5 (25,26) for at least one month in two consecutive visits were used as confirmative scores for remission); and 4) written informed consent obtained before participation in the study. The diagnosis of BPD in remission was clinically made according to DSM-IV criteria (6), on admission of the patient to the follow-up routine of outpatient clinics. Exclusion criteria were 1) history of seizure, or head injury with loss of consciousness, 2) concurrent active medical disorder; 3) unwillingness to cooperate with investigators; and 4) contact loss.

Procedures: The study was conducted between February 2009 and June 2010. Respondents were selected with regards to their inclusion criteria, the patients were perfectly explained the project, signed the informed consents, and then they were referred to one psychiatrist by a coordinator. The diagnosis was reconfirmed at the time of evaluation by administering the Structured Clinical Interview for DSM-IV Axis I disorders-Clinical Version (SCID-CV) (27, 28). SCID-CV was performed by A. Ibiloglu. The administration of this version is usually carried out in one session and takes about 45 to 90 minutes. We assessed global functioning with the GAF measure (29).

Before beginning the study, performed some interviews with psychiatric patients in attendance of trainers to correct their probable mistakes. Subsequently, we conducted open interviews with the BPD patients

using SCIP-TURK (SKİP-TURK) (30) and consulted the patients' relatives for additional information not obtained from the patients. All the participants were then administered the YMRS (25,26), HRDS (23,24) and GAF (29).

The SCID, in this study, was carried out according to Benazzi and Akiskal advice to increase the chance of detecting patients with BPD (31). According to this advice: 1- if the patient answered the screening question about past hypomanic/manic episodes as negative, the clinician always had to question about all the other DSM-IV non-mood hypomanic/manic symptoms; and 2- the clinician considered at least one manic, hypomanic or mixed episode, often along with a major depressive episode to be sufficient for the diagnosis of BPD. Also, the clinician could use the past information of the patients on the hospital notes during the interview.

Instruments:

1. Sociodemographic and clinical variables of the subjects including previous hospitalizations, number and type of previous episodes, presence of psychotic features, suicide attempts and age at onset of the disorder were obtained from inpatient and outpatient medical records of the cases, patient interviews, and from first-degree relatives when available.
2. The Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-I/CV), the Turkish form of SCID-I/CV was used to assess the patients' symptoms (28). It was translated into Turkish by Corapcioglu et al. (27).
3. Diagnosis for Migraine, all respondents were systematically questioned about the diagnosis of migraines. First, study doctors (trained for general psychiatric studies but not specialized in the field of neurology) asked whether "migraine" was ever diagnosed by a physician. The physicians reviewed the key symptoms of migraines (if necessary they had to explain that migraines are "headache attacks, occurring repeatedly and often in only one side of the head, that are often beginning in the morning and typically last for hours or days"). If doctors assigned the diagnosis, they assessed additionally age of first onset and recency (e.g., when occurred last time: past month-past year-longer than past year-don't know). The International Headache Association criteria were utilized in the assessment (32).
4. Hamilton Rating Scale for Depression (HRDS), a 17-item clinician-rated instrument (23), was used to determine the level of depression. Reliability ratings have been high with the Turkish version (24).
5. Young Mania Rating Scale (YMRS) is a clinical rating scale containing 11 items assessing manic symptoms (25). Reliability ratings have been high with the Turkish version (26).
6. Diagnostic and Monitoring Form for Mood Disorders (SCIP-TURK), was developed by Ozerdem et al. (2004) in order to assess the clinical characteristics of BD patients. It collects data concerning the age of onset and treatment, duration of illness, history of physical and sexual abuse, academic and social functioning, the presence of premenstrual syndrome, and the type and severity of the first episode (postpartum onset, seasonality, or depression subtype). It also collects data on psychotic attacks during manic/depressive episodes, suicide attempts, the number of hospitalizations, the number and duration of episodes, the dominant episodic pattern, the presence of sudden onset/end of episodes, and continuity and rapid cycling of the symptoms. Data on smoking, alcohol, and drug use were also collected (30).
7. Global Assessment of Functioning Scale (GAF), Axis-V is a global assessment of functioning in which clinicians judge patients overall levels of functioning during a particular time. Functioning is considered a composition of three major areas social, occupational, and psychological. The Global Assessment of Functioning Scale is a 100-point scale, 100 representing the highest level of functioning in all areas (6). Psychometric properties of the instrument are described as adequate with evidence fore moderate reliability (29).

Ethics: The study protocol was in accordance with the Helsinki Declaration of Human Rights and was approved by the local ethics committee of Ankara Atatürk Training and Research Hospital, in Turkey. Written informed consent was obtained from each patient.

Statistical Analysis: The Statistical Package for Social Sciences (SPSS 11.0) was used for all statistical analyses. Continuous variables were expressed as the mean ±

standard deviation in the tables and values were compared using paired t-tests and repeated measure ANOVA tests. A p value < 0.05 was considered statistically significant (33).

RESULTS

Individuals who were found to present at least one lifetime migraine were included in the group "with comorbid migraine", and those without any comorbid migraine, in the group "without comorbid migraine".

1. Socio-demographic Characteristics:

The study included 96 of the patients were diagnosed in BPD. Table 1. gives socio-demographic characteristics of the bipolar patients. There were 29 (30.2%) men and 67 (69.8%) women, with a mean (standard deviation, SD) age of 38.7±9.51 years (range 23-60 years). Mean age of the patients included in the study at the time of evaluation were 38.67±10.09 years female, and 38.93±9.18 years male (Table 1). In all, 62.5% of the patients were married and mean level of education was 11.06±4.83 years. Also, mean level of education were with and without migraine, 8.84±4.74 years and 11.84±4.65 years, respectively. In addition, majority of the migraine sufferers were housewives (56.0%). Among the others, it was common among employed (20.0%) and unemployed (20.0%).

The BPD subjects with and without migraine, in the sample shown that significant differences with regard to the main demographic features of gender, current age, marital

Table 1: Sociodemographic Characteristics of Bipolar Patients

Parameters	With migraine N=25 (%)	Without migraine N=71(%)	χ^2 , df, p
Gender			
Female	24(96.0)	43(60.6)	χ^2=11.013, df=1, p=0.001
Male	1(4.0)	28(39.4)	
Groups of age			
19-24	0(0)	6(8.5)	χ^2 =11.801, df=4, p=0.019
25-34	3(12.0)	27 (38.0)	
35-44	6(46.2)	17(23.9)	
45-54	12(48)	15(21.1)	
55-60	9(36.0)	6(8.5)	
Education			
Primary school	13(52.0)	18(25.4)	χ^2 =8.269, df=2, p=0.016
Junior-senior high school	8(32.0)	21(29.6)	
Academic	4(16.0)	32(45.1)	
Marital status			
Single	1(4.0)	26(36.6)	χ^2 =12.340, df=3, p=0.006
Married	21(84.0)	39(54.9)	
Divorced or separated	3(12.0)	6(8.4)	
Occupation			
Employed	5(20.0)	35 (49.3)	χ^2 =15.887, df=3, p=0.001
Housewife	14(56.0)	12(16.9)	
Unemployed	5(20.0)	14 (19.7)	
Old age pensioner	1(4.0)	10(14.1)	
Socio-economic level			
Lower	10(40.0)	25(35.2)	χ^2 =0.314, df=2, p=0.855
Middle-lower	13(52.0)	38(53.5)	
High	2(8.0)	8(11.3)	
Living state			
City	20(80.0)	62(87.3)	χ^2 =3.466, df=3, p=0.325
Outskirts	3(12.0)	2(2.8)	
Town	2(8.0)	6(8.5)	
Village	-	1(1.4)	
Habits			
Alchol abuse	6 (24.0)	19(26.8)	χ^2 =0.078, df=2, p=0.962
Cigarette	13 (52.0)	36(50.7)	
None	6(24.0)	16(22.5)	

Table 2: Clinical Characteristics of Bipolar Patients

Parameters	With migraine N=25 (%)	Without migraine N=71(%)	χ^2 , df, p
Onset age of BPD			
19-24	11(44.0)	32(45.1)	χ^2=1.16, df=2, p=0.56
25-34	14(56.0)	36(50.7)	
35-44	-	3(4.2)	
First episode			
Mania	2(8.0)	14(19.7)	χ^2=2.109, df=3, p=0.55
Mixt	1(4.0)	4(5.6)	
Hypomania	4(16.0)	11(15.5)	
Depression	18(72.0)	42(59.2)	
Mean severity of episodes			
Mild	-	2(2.8)	χ^2=3.078, df=3, p=0.38
Moderate	20(80.0)	50(70.4)	
Severe with psychotic symptoms	-	6(8.5)	
Severe without psychotic symptoms	5(20.0)	13(18.3)	
GAF scores			
41-50	-	1(1.4)	χ^2=2.42, df=2, p=0.29
51-60	17(68.0)	36(50.7)	
61-70	8(32.0)	34(47.9)	
Seasonality			
Yes	19(76.0)	46(64.8)	χ^2=1.063, df=1, p=0.30
No	6(24.0)	25(35.2)	
Suicidal attempt			
Yes	20(80.0)	19(26.8)	χ^2=14.451, df=4, p=0.004
No	5(20.0)	52(73.2)	
Postpartum episode			
Yes	19(79.2)	19(44.2)	χ^2=7.67, df=1, p=0.06
No	5(20.8)	24(55.8)	

status, occupation, and duration of education ($p< 0.05$) but did not shown any significant differences with regard to the living state, socioeconomic level, and habits ($p> 0.05$).

2. Clinical Characteristics:

Table 2. gives clinical characteristics of the our sample. The mean age at onset of BPD was 25.04±3.98 years, mean age at onset of migraine was 26.24±5.44 years, mean time until diagnosis of BPD was 5.6±2.8 years, mean number of total hospitalization of BPD was 1.72±0.45, and mean number of total episodes of BPD was 4.56±1.37.

First episode polarity was mainly depression in those with migraine. Bipolar subjects with and without migraine did not differ with respect to the number of depressive episodes ($\chi^2 = 3.242$, df= 5, p= 0.663). However, those with migraine also had greater number of depressive episodes.

The BPD subjects with and without migraine, in the sample did not show any significant differences with regard to the some clinical features mean values of GAF scores, first episode subtype (e.g. mania, hypomania, depression and mixt episode), severity of episode, seasonality, mean number of total episode, mean number of hospitalization, and mean time until diagnosis of BPD ($p> 0.05$).

The postpartum onset and suicide attempt at BPD were more frequently in the comorbid migraine subjects than others ($p= 0.006$ and $p= 0.004$, respectively).

DISCUSSION

Our data suggest that a history of migraine can be regarded to be a "significant" for the presence of a disorder of mood, particularly BPD.

Sociodemographic Characteristics:

Epidemiological studies have suggested that age, sex, genetic characteristics, and socio-cultural differences affect the prevalence of migraine (22,34). The sex-specific prevalence of comorbid migraine in BPD was 14.9% for

males and 34.7% for females (3). Several international studies using the IHS diagnostic criteria (32) have shown that the lifetime prevalence of migraine was found to be as 4-8% in males and 11-25% in females in general population (4,35,36). We found the lifetime diagnosis of migraine prevalence to be as 26.0% in BPD samples. Also, the higher prevalance of migraine in bipolar subjects with women (35.8%), than male (3.4%). A study showed that the prevalence of migraine disease among patients with BPD was high enough for the researchers to conclude, "BPD with migraine is associated with differences in the clinical course of BPD, and may represent a subtype of BPD". In that study, prevalence of migraine in patients with BPD-II was 64.7% - 75% of women, 40% of men (16).

In clinical populations, migraine is disproportionally represented relative to the general population, with an estimated 25% of women between the ages of 25 and 45 having migraine (7,12). As in our study, migraine comorbidity with BPD, 45.8% (n=11) of women between the ages of 35 and 44. Women are significantly more likely to be affected migraine than men.

In a study, females with BPD and comorbid migraine had reported more comorbid medical disorders, and were more likely to require help with personal or instrumental activities of daily living when compared to migraine-unaffected females with BPD (36-38). The some studies reported that males with BPD and comorbid migraine were more likely to live in a low income household, receive welfare and social assistance, report an earlier age of onset of BPD, and have a higher lifetime prevalence of migraine (13,40,41). Also, the present study also gives support to a paper by Swartz et al. (44) and Jette et al. (45) that showed substance abuse/dependence disorders are not associated with migraine comorbidity.

People with migraine are more likely to have psychiatric disorders and vice-versa. Psychiatric comorbidity is associated not only with higher vulnerability to headache, but also with developing drug resistance and chronicity of primary headache (10,46). And psychologic distress may play an even greater role in the transformation and chronicity of headache than does analgesic overuse/abuse (14,47). Conversely, our study shown that, the frequency of alchol-substance abuse for BPD did not shown a significantly differences with migraine comorbidity compared to without migraine comorbidity.

Clinical Characteristics:

The number of studies focusing on the relationship between migraine and BPD were much less than those for anxiety and depression (16,48). As in our study, BPD are frequently comorbid with migraine, and result in a significant burden in patients with migraine including depression, BPD and suicide attempt. Comorbidity is associated with a more difficult course of illness and an increase in related problems (such as suicidality and violence) (1-3,20,42). Also, in the literature, two population-based studies reported the positive association between migraine and BPD in adults (2,42).

Our findings showed that, 26.0% patients with BPD included in this study had a lifetime diagnosis of migraine. Patients with migraine comorbidity showed a more onset of postpartum episode and suicide attempt for BPD than the patients without migraine comorbidity group. These results strongly suggested that a key role for hormones in the pathogenesis of migraine. Migraine attacks appear to be triggered particularly by sudden drops or increases in estrogen levels, which may explain the often reported decrease in migraine frequency during pregnancy, followed by a return of the migraine after delivery (37).

BPD has a fairly early age of onset, with the first episode usually occurring before the age of 30. In the review of epidemiological surveys mentioned previously, the mean age at onset reported by each of the six studies ranged from 17.1–29 years, with a peak in onset rate occurring between the ages of 15 and 19 years (8). In our study, the mean age at onset of BPD was 25.04±3.98 years and mean time until diagnosis of BPD was 5.6±2.8 years. BPD with migraine is associated with differences in the clinical course of BPD. A large retrospective study of patients with BPD reported that there was an average 8 years' delay from a patient's first recollected mood episode to receiving a diagnosis of BPD (49). Notwithstanding in this study, BPD with migraine comorbidity did not shown any significant differences, an earlier age of onset of the disease compared to patients without migraine comorbidity.

Migraine onset was earlier than mood disorder onset, and as in our study, Franchini et al. found no difference in migraine distribution according to the polarity of mood disorder, consistent with the findings of a previous study (11,19). In our study, the mean age at onset of migraine was 26.24±5.44 years. Of note, our results do not address

the impact of migraine severity nor subsyndromal migraine symptoms. Comorbid migraine symptoms below the threshold to meet criteria for diagnosis may still exert a pernicious effect on the course of BPD. Further research to address these issues is currently ongoing.

Current findings should be interpreted with four specific limitations in mind. First, the main limitation of this study lays in the retrospective recall of some variables, which may certainly bias some results. While we used a probing strategy that has been shown to improve recall of age of onset (50), there were doubtlessly residual errors, perhaps especially when distinguishing migraine from disorders with overlapping symptoms. Second, although the present study is the relatively small sample size that could limit our ability to generalize the results to bipolar patients in general. Third, the presence of aura with respect to migraine was not assessed in the survey. Previous studies have shown differences between migraine with aura and migraine without aura in relation to mental disorders (17,42,51). Fourth limitation includes the inability of this study to take into consideration the entire spectrum of contributors to migraine headache, such as family history of migraine and menstrually related migraine (39,52).

Despite these limitations, our data indicate that migraine comorbidity is prevalent and it appears to be associated with gender, current age, marital status, occupation, duration of education, postpartum onset of BPD, and suicide attempts in patients with BPD, in Ankara, Turkey.

In conclusion, migraine was remarkably common among our bipolar patients and our results demonstrate that the comorbidity of migraine is an independent risk factor for course of BPD. Therefore, as comorbidity has a clear impact on the course of bipolar patients, special attention to this issue should be paid when interviewing bipolar patients. Awareness of this reality should lead to greater diagnostic vigilance and more thorough diagnostic assessment, ideally accompanied by individualized treatment planning taking into account all comorbid disorders present, their interrelationships, and their prognostic implications. Further studies are needed to evaluated to the effect between other risk factors and comorbidity of migraine in BPD.

Lastly, comorbidity with migraine is very important in the management of bipolar patients due to their high prevalence, impact on the disease's course and for representing a challenge in the planning of efficient therapeutical strategies. The prospective studies would be needed in order to better address whether migraine is a risk factor for the development of BPD or whether BPD are risk factors for the development of migraine, or both.

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