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Impact of comorbid migraine on the clinical course of bipolar disorder

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Abstract

Background: Recent evidence suggests an association between migraine and bipolar disorder (BD), although the impact of this association in the clinical course of BD is relatively unknown.

Objective: This study aimed to compare 2 groups of individuals with BD (with vs without comorbid migraine) and evaluate differences in severity of clinical course.

Methods: Three hundred thirty-nine adults with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*–defined bipolar I or II disorder were enrolled and divided into 2 groups: with and without comorbid migraine. Demographic and clinical data were obtained using standardized interviews.

Results: Patients with comorbid migraines had more mood episodes, especially those with depressive polarity. In addition, comorbid migraine was associated with a higher prevalence of psychiatric and general medical comorbidities. Differences between the 2 groups in number of lifetime hospitalizations for depression/mania, rates of rapid cycling, and history of suicide attempts were not observed after Bonferroni correction.

Conclusions: Comorbid migraine seems to be associated with poor outcomes in BD. Additional studies should be conducted to investigate shared vulnerabilities and pathophysiologic mechanisms as well as treatment optimization of both illnesses.

1. Introduction

Bipolar disorder (BD) is a chronic, often severe, mood disorder, which affects 2% to 4% of the general population [1]. Bipolar disorder has been associated with several general medical comorbidities, such as metabolic syndrome, type 2 diabetes mellitus, cardiovascular diseases, and migraine [2,3].

Migraine is defined by the International Headache Society as a recurrent headache disorder characterized by unilateral throbbing headaches that last 4 to 72 hours that are aggravated by routine physical activity and may be associated with nausea, photophobia, and phonophobia [4]. The global prevalence of migraine is approximately 10% for current migraine and 14% for lifetime [5-7]. Its male-to-female ratio among adults varies from 1:2 to 1:3 [8]. Migraines may lead to substantial levels of disability in patients and their families as well as to high costs to society.

Unfortunately, the scope and scale of the burden of migraine are underestimated, and headache disorders are universally underrecognized and undertreated [9]. Migraines are associated with psychiatric conditions, such as major depressive disorder, anxiety disorders, and suicidal behavior [10,11]. Recent evidence suggests an association between migraine and BD [12]. Some studies have reported that the prevalence rates of migraine among individuals with BD may be as high as 39% [2,13]. In addition, migraine seems to have an impact on the clinical course of BD and to be associated with more severe features, such as an earlier onset

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of BD, a greater prevalence of comorbid anxiety disorders, and atypical symptoms of depression [12,14].

The comorbidity of BD and migraine has been described in previous studies, but the impact of this association in the clinical course of BD is relatively unknown. This study compared 2 groups of individuals with BD (with vs without comorbid migraine) and evaluated possible differences in severity of clinical course.

2. Methods

Data for analysis were collected from baseline assessments of individuals with BD enrolled in a standardized program of naturalistic BD follow-up adopted in 3 outpatient centers specialized in the treatment of this disorders and members of the Brazilian Research Consortium for Bipolar Disorder. Participants were divided into 2 groups, "with migraine" and "without migraine," according to whether they had a previous diagnosis of this condition made by a physician. The study was approved by the ethics committees of the participant institutions, and all participants provided written informed consent.

Eligible participants for the study were 18 to 60 years old and had a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*–defined bipolar I and II disorders confirmed by the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Participants were allowed to continue their pharmacologic treatment for BD. Exclusion criteria were schizophrenia or other psychotic disorders, schizoaffective disorders, and organic mental disorders. Demographic data and psychiatric history were obtained from structured clinical interviews conducted by trained psychiatrists using the same protocol in the 3 institutions.

2.1. Statistical analysis

Statistical analysis was conducted using the SPSS 16.0 software (SPSS, Inc, Chicago, IL). Demographic and clinical characteristics of participants with and without migraine were compared using a χ^2 test for categorical variables, a *t* test for independent samples, and the Mann-Whitney *U* test for continuous variables when appropriate. Multiple comparisons were approached using Bonferroni correction. A logistic regression was used to examine the effect of migraine on severity after controlling for potential confounders. The variables "sex" and "rapid cycling" were included in each model as covariates because the results of the Mann-Whitney *U* test showed that they were significantly associated with the dependent variables. A similar analysis was conducted to evaluate the association of migraine and suicide attempts after controlling for sex and number of depressive episodes. Statistical significance was set at $P < .05$.

3. Results

3.1. Sample characteristics

A total of 339 individuals with BD were included in the study, and 33.9% of them (n = 115) had comorbid migraines. Demographic and characteristics related to BD and its treatment in the studied sample are shown in Table 1. There were no significant differences in demographic characteristics between the 2 groups, except that there were a higher percentage of women in the group with migraine than in the group without. Illness severity, defined by presence of rapid cycling, number of mood episodes of all polarities, number of depressive episodes, and number of lifetime hospitalizations for depression/mania and suicide attempts, was different between the 2 groups and greater in the migraine group, but these differences were not observed after correction for multiple comparisons.

Table 1
Clinical and demographic characteristics of the groups with and without migraine

	With migraine (n = 115)	Without migraine (n = 224)	*P*
Sex (% female)	82.6	65.2	.004[a]
Age in years (mean, SD)	41.6 (11.20)	41.5 (12.32)	.921[b]
Current tobacco use (%)	52.9	55.3	.857[b]
Current use of hormonal contraceptives (%, only women)	25/80 (31.2%)	52/146 (35.6%)	.836[a]
Type of BD (% of type I)	88.7	91.1	.736[a]
Medications in use (%)			
Lithium	43.4	39.7	.515[a]
Anticonvulsants	50.4	43.5	.273[a]
First-generation antipsychotics	1.73	3.57	.475[a]
Second-generation antipsychotics	14.7	28.2	.339[a]
Benzodiazepines	30.5	16.8	.388[a]
Antidepressants	32.8	9.5	.08[a]
Age at illness onset (y) (mean, SD)	24.8 (13.48)	26.7 (11.81)	.817[b]
Psychotic symptoms in first episode (%)	75.7	48.9	.558[a]
Depressive polarity in first episode (%)	53.0	48.2	.553[a]
Rapid cycling (%)	28.7	16.1	.210[a]
No. of hospitalizations (median, 25-75 percentile)	3.0 (1.0-5.0)	2.0 (1.0-4.0)	.104[c]
History of suicide attempt (%)	53.0	38.8	.350[a]
No. of suicide attempts (median, percentile 25-75)	1.0 (0.0-2.0)	0 (0.0-2.0)	.184[c]
No. of episodes (median, percentile 25-75)	19.0 (6.5-31.5)	7.0 (4.0-14.0)	.012[c]
No. of depressive episodes (median, percentile 25-75)	10.0 (3.0-20.0)	3 (1.5-11.0)	.009[c]
No. of manic episodes (median, percentile 25-75)	5.5 (2.0-15.0)	5 (2.0-10.0)	.204[c]

[a] χ^2 Test.
[b] *t* test.
[c] Mann-Whitney *U* test (with Bonferroni correction).

Age at the first mood episode, polarity of the first episode, and presence of psychotic symptoms did not differ between groups.

3.2. Effect of comorbid migraine on BD severity

To evaluate the association with migraine, a logistic regression was conducted with number of episodes as the independent variable and sex, rapid cycling, and number of depressive episodes (n = 126) as covariates. The total number of episodes was predicted by comorbidity with migraine (B = −0.75; P = .048). After stratification of the sample according to sex, an association between migraine and number of total mood episodes was found among women (P = .043) but not in the group of men (P = .19). We also conducted a logistic regression analysis using presence of suicide attempt as the independent variable and sex and number of depressive episodes as covariates (n = 137). No association was found between migraine and previous suicide attempts (B = 0.585; P = .11).

3.3. Association between migraine and psychiatric and clinical comorbidities

Comorbidity with migraine was associated with a higher prevalence of psychiatric comorbidities (Table 2). Drug abuse and dependence, anxiety disorders, obsessive-compulsive disorders, and eating disorders were significantly more common in the group with migraine, but only differences in rates of eating disorders and anxiety disorders remain significant after correction for multiple comparisons. The analysis of general medical comorbidities revealed that 64.3% of the individuals in the migraine group had at least one of them, but no particular comorbid condition was more frequent than the others.

Table 2
Differences in psychiatric comorbidities

	With migraine (n = 115)	Without migraine (n = 224)	Test value	P
At least 1 psychiatric comorbidity (%)	72.6	47.4	11.755	.001
Alcohol abuse or dependence (%)	25.2	24.1	1.704	NS
Drug abuse or dependence (%)	21.7	14.3	8.754	NS
At least 1 anxiety disorder (%)	66.1	38.8	24.798	.000
OCD (%)	15.7	6.7	7.987	NS
Eating disorders (%)	10.4	2.7	11.756	.008
At least 1 additional general medical comorbidity (%)	64.3	44.2	12.348	<.000
Obesity (%)	49.6	39.3	3.28	NS
Seizures/epilepsy (%)	13.0	8.9	9.196	NS
Asthma (%)	20.0	13.8	2.154	NS
Diabetes mellitus (%)	9.6	9.4	1.063	NS
Hypothyroidism (%)	13.9	12.1	3.560	NS
Systemic hypertension (%)	9.6	7.2	1.052	NS

χ^2 Test with Bonferroni correction. NS indicates nonsignificant; OCD, obsessive-compulsive disorder.

4. Discussion

Results of this study suggest that comorbidity with migraine is a correlate of BD severity. We showed that individuals with BD and comorbid migraine have a different clinical course of the disorder, with more mood episodes (especially depressive episodes) and more clinical and psychiatric comorbidities. Higher rate of antidepressant use probably reflects the tendency of individuals with migraine to have more depressive episodes. The higher rate of migraine among women is compatible with the higher prevalence of migraine in the general female population.

The findings of this study are similar to those described by Ortiz et al [14], who have suggested that migraine is associated with suicidal behavior and comorbid anxiety disorders. However, bipolar II disorders were not associated with migraine in our report. Although some authors classify migraine as a marker of "soft" bipolarity [15], our results suggest that comorbid migraine is an important marker of severity of both bipolar I and II disorders.

Some methodological limitations should be taken into consideration in the analysis of our results. The database analyzed in this study was not designed a priori to address the association of migraine and BD severity. The occurrence of migraine was determined by self-report, which might have been affected by memory bias. In addition, no standardized method was used to evaluate the prevalence of migraine [4]. The logistic regressions included only cases without missing data, and the results obtained in this analysis may not be applicable to the whole sample.

The understanding of the neurobiology of BD and migraine has improved considerably in the last 2 decades, but several aspects of their pathophysiology remain obscure, such as the reasons why their simultaneous occurrence is so frequent. Both migraine and BD seem to share hereditary vulnerabilities [12] and some specific genetic polymorphisms [16]. These 2 conditions have been associated with abnormalities in the serotonergic [17,18], dopaminergic [19], and glutaminergic systems [20]. Moreover, some drugs are successful in the prevention of both disorders, most notably valproate [21] but also lamotrigine, topiramate, quetiapine, and lithium, whose effectiveness in mood regulation has already been established [22,23].

Our findings corroborate previous studies that showed that individuals with BD and migraine generally have a more severe clinical course. This association has theoretical and practical implications. The harmful impact of comorbid migraine suggests the existence of pathophysiologic intersections between the 2 disorders, which should be explored in future studies about the neurobiology of these illnesses. In addition, the adequate treatment of migraine

may have a beneficial long-term impact for patients who have both conditions. Enhanced attention to detection and early treatment of comorbid migraine might minimize potential deleterious consequences of this condition, such as substance abuse and inadequate use of analgesic and antidepressive drugs as well as a potential decrease in the frequency of suicidal behaviors and suicide attempts.

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