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Research report

Association between family history of mood disorders and clinical characteristics of bipolar disorder: Results from the Brazilian bipolar research network

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ABSTRACT

Objectives: To compare clinical characteristics of bipolar disorder (BD) in patients with and without a family history of mood disorders (FHMD) in a large sample from the Brazilian Research Network of Bipolar Disorders.
Methods: Four-hundred eighty-eight DSM-IV BD patients participating in the Brazilian Research Network of Bipolar Disorders were included. Participants were divided between those with FHMD ($n=230$) and without FHMD ($n=258$). We compared these two groups on demographic and clinical variables and performed a logistic regression to identify which variables were most strongly associated with positive family history of mood disorders.
Results: BD patients with FHMD presented with significantly higher lifetime prevalence of any anxiety disorder, obsessive-compulsive disorder, social phobia, substance abuse, and were more likely to present history of suicide attempts, family history of suicide attempts and suicide, and more psychiatric hospitalizations than BD patients without FHMD. Logistic regression showed that the variables most strongly associated with a positive FHMD were any comorbid anxiety disorder, comorbid substance abuse, and family history of suicide.
Limitations: Cross-sectional study and verification of FHMD by indirect information.
Conclusion: BD patients with FHMD differ from BD patients without FHMD in rates of comorbid anxiety disorder and substance abuse, number of hospitalizations and suicide attempts. As FHMD is routinely assessed in clinical practice, these findings may help to identify patients at risk for particular manifestations of BD and may point to a common, genetically determined neurobiological substrate that increases the risk of conditions such as comorbidities and suicidality in BD patients.

1. Introduction

Bipolar disorder (BD) in general affects up to 4.5% of the population, and BD type I in particular affects 1.0% of the population causing significant suffering for patients and their families due to the severe, recurrent and disabling nature of the disease (Merikangas et al., 2007; Goodwin and Jamison, 2007; Phillips and Kupfer, 2013). BD is highly heritable (Smoller and Finn, 2003; Barnett and Smoller, 2009). The disease risk in first-degree relatives of BD patients is approximately ten times higher than for the general population (Barnett and Smoller, 2009). Relatives of BD patients are also at increased risk for mood disorders in general. The risk for major depressive disorder (MDD) among relatives of BD patients is three times higher than among relatives of healthy controls (Smoller and Finn, 2003; Barnett and Smoller, 2009). Not only does BD diagnosis aggregate in families but some clinical characteristics of the disease do as well, including early age at onset, psychotic symptoms, comorbid panic disorder, alcohol use disorders, rapid cycling, and suicidal thoughts (Rice et al., 1987; Leboyer et al., 1998; O'Mahony et al., 2002; Schulze et al., 2006; Bellivier, 2006; Saunders et al., 2008; Hua et al., 2011). In clinical settings, these increased risks translate into a common situation for a BD patient in which one or more parents or siblings also suffer from BD or from MDD. Because of the high heritability of mood disorders in general, and of BD in particular, it is assumed

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that such families have a high genetic loading for mood disorders. However, whether this high genetic loading translates into a more severe disease in patients from such families is poorly understood.

One way to investigate this question is to compare BD patients with a positive FHMD to those BD patients whose family history is negative for mood disorders. In MDD patients, having a positive FHMD is associated with a younger age at disease onset, long duration of episodes, increased suicidality, female gender, and higher neuroticism (Nierenberg et al., 2007; Husain et al., 2009; Holma et al., 2011). In BD, three studies reported that a positive FHMD was associated with early disease onset, increased number of episodes, suicidality, and more hospitalizations (Mrad et al., 2007), and increased rates of comorbid anxiety disorders (Mantere et al., 2012; Serretti et al., 2013). On the other hand, FHMD was not associated with comorbid Axis I conditions, manic or depressive symptoms severity, or number of manic or depressive episodes in a 1-year follow up period (McElroy et al., 2001; Nolen et al., 2004).

The aim of this study was to investigate associations between clinical correlates of disease and FHMD among BD patients with high genetic loading for mood disorders. We compared BD patients with and without FHMD among first- and second-degree relatives on several clinical characteristics of the disease that could indicate greater disease severity. Our hypothesis was that BD patients from families with positive FHMD would present with more severe disease than patients without a family history of mood disorder. As FHMD is easily and routinely investigated in clinical practice, findings of this study can potentially help clinicians to understand and identify characteristics associated with more severe disease courses.

2. Methods

2.1. Patients

The sample was comprised of 488 consecutive BD outpatients from three research centers participating in the Brazilian Research Network for Bipolar Disorders. Center 1: Bipolar Disorder Program (PROMAN), Department of Psychiatry, University of São Paulo Medical School; Center 2: Bipolar Disorder Program (PROTAHBI), Department of Psychiatry, Federal University of Rio Grande do Sul; and Center 3: Center for Treatment of Affective Disorders (CETHA), Department of Psychiatry, Federal University of Bahia. Inclusion criteria included age over 18 years and a DSM-IV BD diagnosis. The study protocol was approved by the local Ethics Committee of each institution and all patients gave written informed consent to participate in the study. All study procedures were carried out according to the Declaration of Helsinki.

2.2. Psychiatric assessments

Diagnostic assessments were all conducted by research-trained, board-certified psychiatrists, using the Structured Clinical Interview for DSM-IV Disorders (SCID), versions for patients (First and Pincus, 2002). The 17-item Hamilton Depression Rating Scale (HAMD-17) (Hamilton, 1960) and the Young Mania Rating Scale (YMRS) (Young et al., 1978) were administered to assess severity of depressive and manic symptoms, respectively. Demographic and clinical characteristics of the disease, including age of onset, rapid cycling, hospitalizations, suicide attempts, family history of mood disorders or substance use disorders were obtained using the same standardized protocol and information from the SCID. Patients were classified as euthymic when they did not meet criteria for any mood episode in the last 2 months and also had a HAMD-17 score and YMRS score lower than 7 in the week before the assessment. They were classified as non-euthymic if they were in a full mood episode or had subsyndromal symptoms. FHMD was evaluated using a standardized questionnaire to assess presence or absence of mood disorders (major depressive disorder or bipolar disorder) in first- and second-degree relatives. Presence was defined as the presence of a lifetime clinical diagnosis of major depressive disorder or bipolar disorder by a psychiatrist.

2.3. Statistical analysis

Participants were divided into two groups: BD patients with and without FHMD. Demographic and clinical characteristics of these two groups were compared using exact χ^2 tests for cross-tabulated categorical data and Mann–Whitney U test or T test for ordinal and interval scale data. A stepwise binary logistic regression analysis was then conducted to compare the existence of clinical features in BD patients with positive or negative FHMD. For the regression analyses, we included only variables with significant associations in the univariate analyses. The corresponding chi-square values, odds ratios, and 95% confidence intervals (CIs) are reported. Significance was set at $p=0.05$ (two-tailed). SPSS (SPSS, Inc., Chicago, IL) version 14.0 was used to perform all the analyses.

3. Results

Four hundred eighty-eight BD patients participated in the study. Of those, 140 (28.7%) were male and 348 (71.3%) were female. Mean age $\pm$ standard deviation (S.D.) was 40.6 $\pm$ 11.4 years, ranging from 18 to 74 years old. Four hundred and thirty-nine (90%) patients were classified with BD type I, 36 (7.4%) with BD type II and 13 (2.7%) with BD not otherwise specified (NOS).

Two hundred and thirty BD patients reported the presence of a clinical diagnosis of a mood disorder in at least one first- or second-degree relative (positive FHMD) and 258 BD patients did not present any history of mood disorders among first- and second-degree relatives (negative FHMD). For first-episode psychosis, three patients had missing data; for family history of substance use disorder, three patients had missing data; and for rapid cycling, four patients had missing data. Analyses were repeated without these missing data and results did not change.

BD patients with positive FHMD presented with significantly higher lifetime prevalences of any anxiety disorder ($p<0.001$), obsessive-compulsive disorder ($p=0.002$), social phobia ($p=0.02$), and substance abuse ($p=0.02$) than BD patients with negative FHMD. BD patients with positive FHMD were also more likely to make at least one lifetime suicide attempt ($p=0.01$), to have a positive family history of either completed suicide ($p=0.02$) or suicide attempts ($p=0.03$), and to have more psychiatric hospitalizations ($p=0.03$) than BD patients with negative FHMD. Results from the univariate analyses are displayed in Table 1.

Stepwise binary logistic regression showed that the variables most strongly associated with a positive FHMD among BD patients were in decreasing order of risk: any comorbid anxiety disorder, comorbid substance abuse and family history of suicide. The results of the logistic regression are shown in Table 2.

4. Discussion

This study compared demographic characteristics and clinical correlates in BD patients with and without FHMD. We found an association between positive FHMD and history of suicide attempts, family history of suicide, comorbid anxiety and substance use disorders, and more hospitalizations in BD patients.

Half of our population reported having positive FHMD among first- and second-degree relatives, consistent with some (Dilsaver et al., 2006; Mrad et al., 2007; Mantere et al., 2012) but not all