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Age of onset of bipolar disorder: Combined effect of childhood adversity and familial loading of psychiatric disorders

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ABSTRACT

Background: Family history and adversity in childhood are two replicated risk factors for early onset bipolar disorder. However, their combined impact has not been adequately studied.
Methods: Based on questionnaire data from 968 outpatients with bipolar disorder who gave informed consent, the relationship and interaction of: 1) parental and grandparental total burden of psychiatric illness; and 2) the degree of adversity the patient experienced in childhood on their age of onset of bipolar disorder was examined with multiple regression and illustrated with a heat map.
Results: The familial loading and child adversity vulnerability factors were significantly related to age of onset of bipolar and their combined effect was even larger. A heat map showed that at the extremes (none of each factor vs high amounts of both) the average age of onset differed by almost 20 years (mean = 25.8 vs 5.9 years of age).
Limitations: The data were not based on interviews of family members and came from unverified answers on a patient questionnaire.
Conclusions: Family loading for psychiatric illness and adversity in childhood combine to have a very large influence on age of onset of bipolar disorder. These variables should be considered in assessment of risk for illness onset in different populations, the need for early intervention, and in the design of studies of primary and secondary prevention.

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1. Introduction

Previous studies have reported an earlier age of onset of bipolar disorder in those with a positive family history of bipolar disorder (Leverich et al., 2002, Pavuluri et al., 2005, Post et al., 2014a) and in those with a history of adversity in childhood (Brown et al., 2005, Garno et al., 2005, Larsson et al., 2013, Leverich et al., 2002). More recently it has also been revealed that the burden of other psychiatric illnesses, beyond that of just bipolar disorder, in the direct progenitors (parents and grandparents) of patients also contributed to the vulnerability early onset bipolar disorder (Post et al., 2015c,d). However, the combined effects of these two vulnerability factors – genetic/familial loading of psychiatric

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illnesses and psychosocial adversity in childhood – as they affect age of onset of bipolar disorder has not been examined in detail.

Here we present statistical and graphical evidence in the form of a heat map of how these two risk factors independently and in combination affect the age of onset of bipolar disorder. The heat map allows one to directly visualize how each factor alone and their combined presence (when both factors converge and are present in the same individuals), influence the mean age of onset of bipolar disorder. We hypothesized that the two vulnerability factors for early onset bipolar disorder –genetic/familial burden of psychiatric illness and psychosocial adversity in childhood – would combine in a clinically robust fashion, further helping to explain some of the very large variations in the age of onset of bipolar disorder. We further discuss some of the mechanistic and clinical implications of these inter-relationships.

2. Methods

2.1. Patients

968 outpatients (average age 41) with bipolar disorder (about 75% BP I) diagnosed by SCID interview were recruited from advertisements and local clinics in four cities in the United States (Los Angeles, Dallas, Cincinnati, Bethesda) and three in Europe (Utrecht, the Netherlands and Freiburg and Munich, Germany) from 1995 to 2002. Patients gave informed consent for participation in the network and completed a detailed self-rated questionnaires on family history, psychosocial adversity in childhood, and their retrospective course of illness (Leverich et al., 2003, Leverich et al., 2002, Post et al., 2014a, Post et al., 2013a, Post et al., 2010a, Post et al., 2014b, Post et al., 2010b).

2.2. Family history

The family history diagnoses rated included: 1) unipolar depression, 2) bipolar disorder, 3) history of a suicide attempt or completed suicide, 4) alcohol abuse, 5) drug abuse, and 6) “other illness” with the specific examples given as: “(i.e., anxiety, panic attacks, eating disorders, attention-deficit disorder, behavioral problems, obsessive compulsive disorder, autism, etc.)”. Each parental and grandparental diagnosis was rated by the patient as definite, likely, unlikely, or not present, and a definite or likely rating was taken as a positive diagnosis for that relative (Post et al., 2014a,b). The same history ratings were also inquired about for the patients' siblings, spouse, and offspring as described elsewhere. Since a history of a suicide attempt is not a formal diagnosis, we also refer to these 6 categories as illnesses or difficulties. The total score of the presence or absence of these difficulties in either parent or any of the four grandparents was then used as the measure of total illness burden in two generations of the direct progenitors of the patients. We had previously seen that the grandparental loading of multiple illnesses also conveyed vulnerability to the development of an adverse course of bipolar disorder in the patient (Post et al, 2015c,d). The maximum score for family loading of illness could be 36, but the range was typically 0 to 16 with one patient having a score of 28.

2.3. Age of onset of bipolar disorder

The questionnaire also elicited answers pertaining to demographics, stressors in childhood, and course of illness characteristics, including the age of onset of bipolar disorder. This was described as the age of onset of the first major depression associated with dysfunction or the first manic or hypomanic episode. Age of onset was inquired about for the first onset of depression, mania or both in the same year. The age of onset used here was the age at which ever phase came first.

2.4. Childhood adversity

Stressors in childhood included a total score for the report of verbal, physical, and sex abuse, each rated as never = 0, rarely = 1, occasionally = 2, and frequently = 3 (Leverich et al., 2002; Post et al., 2015b). A maximum score of 9 would thus reflect the most frequent experience of all three types of abuse. We examined all three together, based on previous analyses that verbal abuse in addition to what is usually considered more severe forms of abuse – physical and sexual – contributed independently to the impact on age of onset and other poor prognosis factors (Post et al., 2015b). The same questions were repeated for abuse experienced in adolescence and again in adulthood, but only those experienced in childhood were utilized here, since this provided the greatest likelihood that these stressors would have occurred prior to the onset of the bipolar disorder.

The relationship between the burden of family illness (sum of parental and grandparental illnesses) and childhood adversity score to age of onset independently and as they combined was examined by multiple regressions controlling for country and sex.

2.5. Heat map

A heat map illustrating these relationships to age of onset of bipolar disorder was constructed using the full range of total family history positivity for psychiatric illness (0–28) and total amount of adversity the patient reported experiencing in childhood (0–9). A heat map is a graphical representation of the data where values are color coded in a matrix. The heat map supplements the statistical analysis by providing a way of visualizing the impact of each vulnerability factor and their combined effect on age of onset of bipolar disorder in a single graphic which also allows for specific examination of the actual mean ages of onset involved.

For ease of visualization, mean ages of onset were color coded to reflect the usual separation of ages of onset in the literature for childhood, adolescent, early adulthood and late adulthood (Perlis et al., 2004, Post et al., 2010a). Mean ages of onset in childhood (prior to age 13) were coded in red; in adolescence (prior to age 19) were coded in pink; in young adulthood (prior to age 30) were coded in blue; and in older adulthood (age 30 or greater) were coded in grey. As the numbers of patients involved in the mean ages of onset of bipolar disorder varied considerably, a separate illustration of the Ns for each category is presented and color-coded similarly to the first figure for ease of visualization.

2.6. Statistics

The statistical significance of the hypothesized relationships of family burden of illness and childhood adversity to age of onset of bipolar disorder was tested with a multiple regression with the effects of sex (gender) and country (US versus European) accounted for. The US versus European “country” variable was entered as previous data had shown a very substantially earlier age of onset of bipolar in the US than in Germany and the Netherlands (Post et al., 2014a). Sex was examined as sexual abuse is more likely to occur in women than in men. We studied the interaction of these two variables, family burden of illness and childhood adversity, on age onset in a separate regression. This was necessary because we were unable to include both the individual terms and the interaction in the same model, as including both resulted in a failure to meet the underlying assumptions required to run a regression; these diagnostics could include linearity, normality, and homoscedasticity.

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