Journal of Affective Disorders 190 (2016) 26–33

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

The specificity of the familial aggregation of early-onset bipolar disorder: A controlled 10-year follow-up study of offspring of parents with mood disorders

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ARTICLE INFO

Article history:
Received 23 June 2015
Received in revised form
29 September 2015
Accepted 2 October 2015
Available online 23 October 2015

Keywords:
Mania
Age of onset
Family aggregation
High-risk study
Major depression
Substance use disorders

ABSTRACT

Background: Two major sources of heterogeneity of mood disorders that have been demonstrated in clinical, family and genetic studies are the mood disorder subtype (i.e. bipolar (BPD) and major depressive disorder (MDD)) and age of onset of mood episodes. Using a prospective high-risk study design, our aims were to test the specificity of the parent-child transmission of BPD and MDD and to establish the risk of psychopathology in offspring in function of the age of onset of the parental disorder.
Methods: Clinical information was collected on 208 probands ($n=81$ with BPD, $n=64$ with MDD, $n=63$ medical controls) as well as their 202 spouses and 372 children aged 6–17 years at study entry. Parents and children were directly interviewed every 3 years (mean duration of follow-up = 10.6 years). Parental age of onset was dichotomized at age 21.
Results: Offspring of parents with early onset BPD entailed a higher risk of BPD HR = 7.9(1.8–34.6) and substance use disorders HR = 5.0(1.1–21.9) than those with later onset and controls. Depressive disorders were not significantly increased in offspring regardless of parental mood disorder subtype or age of onset.
Limitations: Limited sample size, age of onset in probands was obtained retrospectively, age of onset in co-parents was not adequately documented, and a quarter of the children had no direct interview.
Conclusions: Our results provide support for the independence of familial aggregation of BPD from MDD and the heterogeneity of BPD based on patterns of onset. Future studies should further investigate correlates of early versus later onset BPD.

1. Introduction

The lack of successful identification of genetic markers underlying mood disorders has led to increasing scrutiny of sources of heterogeneity of the mood disorder spectrum (Kennedy et al., 2015; Major Depressive Disorder Working Group of the Psychiatric et al., 2013). Two of the major sources of heterogeneity of bipolar disorder are the subtypes of mood disorders, particularly bipolar disorder (BPD) and and major depressive disorder (MDD), and the age of onset of mood disorders (Etain et al., 2012; Geoffroy et al., 2013). Our recent evidence for the independence of familial transmission of BPD and MDD as well as their major components manic and major depressive episodes (Merikangas et al., 2014; Vandeleur et al., 2014) suggests that these mood disorder subtypes may represent distinct underlying continua rather than increasingly severe manifestations of a common underlying diathesis (Hickie, 2014). Studies of offspring of parents with BPD or MDD have confirmed elevated risks of BPD (Axelson et al., 2015; Birmaher et al., 2009; Duffy et al., 2010; Henin et al., 2005; Nurnberger et al., 2011) and of MDD (Hirshfeld-Becker et al., 2012) among offspring, but the independence of the familial aggregation of the two mood disorder subtypes could not be appropriately tested given the absence of controlled studies that simultaneously included parents with BPD and MDD.

There have also been numerous studies of subtypes within BPD (Phillips and Kupfer, 2013) and MDD (Lamers et al., 2013), but to date, the only consistent subtype that has been demonstrated in family studies of adults and high risk studies of offspring is early age of onset of mood disorders. Family studies have documented

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http://dx.doi.org/10.1016/j.jad.2015.10.005
0165-0327/

elevated rates of mood disorders among adult relatives (Bellivier et al., 2003; Grigoroiu-Serbanescu et al., 2001, 2014; Schurhoff et al., 2000; Somanath et al., 2002), siblings (Lin et al., 2006), and offspring (Oquendo et al., 2013) of probands with BPD with an early onset as compared to those with a later onset. Two studies however in adult relatives (Schulze et al., 2006) and high-risk offspring (Goldstein et al., 2010) did not find the risk of BPD to be determined by parental onset, reinforcing a lack of conclusiveness regarding the pertinence of this subtype of BPD. Regarding MDD, one study observed higher rates of MDD among the relatives of adult MDD probands with an age at onset before age 20 compared to those of probands with a later onset or controls (Weissman et al., 1984), whereas another study that followed probands from childhood to adulthood found the rates of MDD to be independent of the age of onset of the proband's MDD (Harrington et al., 1997). Recent large scale collaborative genetic studies of MDD have also shown that there is increased single nucleotide polymorphism (SNP)-based heritability of early onset MDD (Ferentinos et al., 2015).

To date, no controlled prospective study that included probands with both BPD and MDD has examined the incidence of mood disorder subtypes and other psychopathology in offspring by the age at onset of parental disorders. This design minimizes recall bias regarding the age of onset and permits evaluation of the sequence of onset of mood disorder subtypes and that of other types of psychopathology. Accordingly, using the high-risk design, the aims of the present study were to:

1. test the specificity of the parent-child transmission of BPD and MDD and establish the cumulative risk of non-mood psychopathology in offspring;
2. establish the risk of mood and non-mood psychopathology in offspring as a function of parental mood disorder age of onset. Age of onset was stratified at age 21 based on prior evidence (Etain et al., 2012; Geoffroy et al., 2013; Grigoroiu-Serbanescu et al., 2014) for age 20–21 as an early age of onset cut-off.

2. Methods

2.1. Sample

The sample stemmed from a large family study of mood disorders conducted in the French-speaking part of Switzerland (Vandeleur et al., 2014). Probands with BPD and MDD were consecutively recruited from the inpatient and outpatient facilities of the psychiatric departments of Lausanne and Geneva between 1996 and 2004. Inclusion criteria for mood disorder probands were: (1) lifetime bipolar-I ($n=53$), bipolar-II ($n=10$), schizoaffective bipolar disorder ($n=18$), or MDD ($n=64$), (2) age between 18 and 65 years, (3) ability to speak sufficient French or English to complete the diagnostic interview, and (4) availability of diagnostic data on one or more offspring (aged 6.0–17.9 years at study intake) from a minimum of two assessments with at least one direct interview. Comparison probands ($n=63$) were recruited from the orthopedic departments of Lausanne and Geneva. Inclusion criteria for the comparison probands were: (1) the absence of a lifetime mood or psychotic disorder, (2) age between 18 and 65 years, (3) ability to speak sufficient French or English to complete the diagnostic interview, and (4) the same inclusion criterion for offspring as that of the mood disorder cases. The choice of recruiting medical controls rather than subjects from the general population was motivated by our goal to create a comparison group that was selected from the same clinical settings as the probands with affective disorders. The specific choice of recruiting in orthopedic rather than other medical facilities was motivated by the fact that orthopedic problems are less likely to be induced by a psychiatric problem than other medical problems (e.g. cardiovascular or metabolic problems) and that a relatively large proportion of orthopedic patients are in the same age range as psychiatric patients (18–65 years).

An effort was made to interview all co-parents of biological offspring. Data on 202 co-parents were available of whom 60% had been directly interviewed. Parents and offspring were invited to take part in follow-up assessments at predetermined ages of the offspring (7, 10, 13, 16, 19, 22, 25, 28, 31 and 34 years). The average number of assessments of the 372 offspring was 4.2 (s.d.=1.3; range: 2–7) with a mean duration of 10.6 years follow-up (s.d.: 3.6). Three quarters of the assessments included direct interviews. The mean offspring age at the first assessment was 10.0 years (s.d.=4.3 years) and 20.6 years (s.d.=5.6 years) at the last assessment.

2.2. Procedures

Diagnostic methods for this study were also described in previous publications (Vandeleur et al., 2012). Information on parents and adult offspring was obtained using the semi-structured Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) and offspring younger than 18 years were directly interviewed using a French translation of the modified version of the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-E) (Orvaschel et al., 1982). In addition to direct interviews, information on children and parents was systematically elicited from all participants who were at least 15 years old using the Family History-Research Diagnostic Criteria (FH-RDC) (Andreasen et al., 1977). The validity and French translation of the DIGS (Berney et al., 2002; Leboyer et al., 1995; Preisig et al., 1999), the reliability of the K-SADS-E (Chambers et al., 1985; Gammon et al., 1983; Orvaschel et al., 1982; Vandeleur et al., 2012), and the validity of the FH-RDC (Rothen et al., 2009; Rougemont-Buecking et al., 2008; Vandeleur et al., 2008; Vandeleur et al., 2015) have been extensively tested. Interviewers were required to be masters-level psychologists and were trained over a two-month period. They were blind to the disease status of the other family members. Each interview was reviewed by a senior psychologist.

Diagnoses were made over lifetime using a best-estimate procedure (Leckman et al., 1982), which relied on the combination of information from direct interviews, family history report(s), and medical records. Diagnostic algorithms for “Other Specified Bipolar and Related Disorders” (OSBARD) and “Other Specified Depressive Disorders” (OSDD) were defined according to the DSM-5 to assign subthreshold diagnoses. Non-mood disorders were defined according to the DSM-IV. The SES of the families was based on income and education level of both spouses of the household (Hollingshead, 1975). The severity of probands' disorders over lifetime was assessed using the DSM-IV Global Assessment of Functioning (GAF) scale, which provides an assessment of the probands' level of psychological, social and occupational functioning.

This research project was approved by the local institutional review board. All participants gave written informed consent for their own participation prior to the assessments. In addition, parents gave written consent for the participation of their offspring younger than 18 years.

2.3. Data analysis

Between-group analyses were performed using the chi-square, *t*-tests or ANOVA and using multilevel models for non independent data in offspring. Hazard ratios were computed using serially adjusted shared gamma frailty models for survival data