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Brief report

A three generations nation-wide population study of family load estimates in bipolar disorder with different age at onset

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ABSTRACT

Objectives: This nation-wide register-based study investigates how often bipolar disorder (BD) occurs in affected families compared to control families by estimating the family load as a random effect; this effect measures the degree of dependence among family members in relation to BD. Furthermore, the study addresses the impact of certain risk factors, namely, sex, age at onset of BD, degree of urbanization, year of birth, month of birth, and maternal and paternal age at birth.
Method: A total of $N=1204$ children and adolescent psychiatric cases born between 1950 and 1997 and registered in the Danish Central Psychiatric Register (DPCR) developed BD before the age of 58 years. $N=3553$ controls without any psychiatric diagnosis were matched for age, gender, and region of residence. Psychiatric diagnoses were also obtained on the relatives, e.g. parents, siblings, and offspring as a part of the Danish Three Generation Study (3GS). A family component was obtained by using different regression models.
Results: Familial factors accounted for 20% of the variation in disease outcome when controlling for year and month of birth, sex, and degree of urbanization. Only female sex was associated with an increased hazard ratio of BD. Also having a mother, father or a sibling with the disorder was proven to be a significant risk factor. Furthermore, case relatives did not develop BD earlier than control relatives.
Conclusion: These findings based on a very large and representative dataset provide further and very solid evidence for the high family aggregation of BD.

1. Introduction

The family aggregation of bipolar disorders (BD) is a well-known clinical fact that is also substantiated by a number of systematic studies. Based on a summary estimate of all available studies published after 1960 until 2001, the general recurrence risk of BD was 8.7% for first-degree relatives (Smoller and Finn, 2003). A more recent study based on data from the Danish Psychiatric Central Register (DCPR) found that people with a first-degree relative with BD had an almost 14-fold higher risk of BD (Mortensen et al., 2003). Another study based on the same register found that the risk of BD was 24.9% in parents who were ever admitted with BD, compared with 4.4% in offspring with only one parent ever admitted and 0.48% in offspring with neither parent ever admitted (Gottesman et al., 2010).

In particular, the increased risk of BD in the children of parents with BD has been reviewed repeatedly (DelBello and Geller, 2001; Pavuluri et al., 2005). The risk of developing a mood disorder was four times higher in children of parents with BD than in children of parents without psychiatric disorder in studies conducted before 1997 (Lapalme et al., 1997). More recent offspring studies of parents with BD reported a 14–50% incidence rate of bipolar spectrum disorders in the US (Chang et al., 2000; Duffy et al., 1998) whereas a Dutch study found only a 2.8% incidence (Wals et al., 2004). The variations in incidence rates may be due to methodological differences of the studies with different sampling procedures, a wider use of standardized diagnostic approaches, and more frequent prescriptions of psychotropic medication in the US (DelBello and Geller, 2001).

However, as Pavuluri et al. (2005) have criticised in their review of these so-called top-down (parent to offspring) studies, there are numerous other shortcomings in these studies including the following: small sample sizes, inclusion of parents with heterogeneous disorders (bipolar and unipolar), failure to control for parental co-morbid disorders, lack of normal controls, retrospective assessments, various deficits of assessment in both parents and offspring, and other factors. In the so-called bottom–up study approach, first-degree relatives of youths with BD have been studied and compared to families with youth suffering from schizophrenia, unipolar depression, and normal

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controls (Pavuluri et al., 2005). The strong inter-generational link of BD has been shown also in these studies (Kutcher and Marton, 1991; Lewinsohn et al., 2000; Neuman et al., 1997; Pauls et al., 1992; Rice et al., 1987; Strober et al., 1988).

So far, only a few risk factors for the familial transmission of BD have been identified. These factors include sex, co-morbidity, age at onset, and parental age. In a recent study, Goldstein et al. (2011) found that the risk of psychosis (both non-affective and affective) in the offspring was dependent on the sex of both the offspring and the parents. Among affected mothers, the affected offspring rate was higher in males than in females whereas the reverse was true for the affected offspring among affected fathers. The authors concluded that X-linked inheritance might account for these findings. Some studies also found a greater familial loading of BD with early onset of BD (Neuman et al., 1997; Rice et al., 1987; Strober et al., 1988). Furthermore, co-morbidity has an impact insofar as relatives of children co-morbid with BD and attention-deficit hyperactivity disorder (ADHD) have a five times greater rate of BD than relatives of children with ADHD alone (Faraone et al., 1997a;b). In addition, a nationwide nested case-control study based on Swedish registers demonstrated that advanced paternal age is a risk factor for BD in the offspring (Frans et al., 2008). The explanation for this association presented by the authors is the increased risk for de novo mutations in susceptibility genes for neuro-developmental disorders with advancing paternal age.

The present register-based study deals with the analysis of family based matched case-control data in families affected with BD. The aim of the study is to investigate how often BD occurs in affected families compared to control families by calculating a family component as a random effect that measures the degree of dependence among family members in relation to the outcome. Furthermore, the study addresses the impact of certain risk factors, i.e. sex, age at onset of BD, region of residence, year of birth, month of birth, and maternal and paternal age at birth. Finally, it will also be investigated if case family members develop BD earlier than control family members. A similar approach has been applied by the authors to investigate the family load in schizophrenia (Helenius et al., 2012).

2. Methods

2.1. Description of the dataset

The dataset of the present study contains $N=1204$ case-families; each including one case-proband who was identified in the Danish Psychiatric Central Registry (DPCR) (Munk-Jorgensen and Mortensen, 1997). The DPCR differentiates between main and auxiliary diagnoses, the latter indicating psychiatric comorbidities. Case-probands were born between 1950 and 1997. They received any ICD-10 diagnosis (World Health Organization, 1992) before age 18 and had developed BD as a main diagnosis before the age of 58.

In Denmark each individual is given an individual number at birth in the Danish Central Civil Registration Register (DCR) making it possible to identify each person in different registers. For each case-proband three control-probands were identified in the DCR (Pedersen et al., 2006). A case-proband was defined as a patient having had any psychiatric diagnosis (according to either ICD-8 or ICD-10 criteria) who also received a main diagnosis of BD within the follow-up time of the study. Since onset of BD was the outcome in this study, the case-probands were followed after age 18.

Control-probands ($N=3553$) were identified in the DCR using risk set sampling, that is they were alive and without registrations in the DCPR at the case-probands index time. Furthermore, the control-probands were matched to the case-probands by age (same year and month of birth), sex, and region of residence at the index time of the case-proband. Control-probands were excluded if they received any psychiatric diagnoses according to ICD-10 criteria; therefore, not all case-probands had three control-probands. The control-probands did not receive a diagnosis of BD and were, therefore, followed from birth to the end of the study (December 1st 2009).

Taken together, the case- and control-probands are referred to as probands. In total, the dataset contains 4757 probands (1204 cases and 3553 controls), this corresponds to the number of families. Family members, i.e., mothers, fathers, siblings, and offspring were identified in the DCR and are subjects in the Danish Three Generation Study (3GS) with several ten thousands of each case-probands, control-probands, parents, siblings, and offspring (Steinhausen et al., 2009). Numbers of family members in the present study will be shown with the results. BD was defined according to ICD-8 criteria (code 296.1, 296.2, 296.3) until 1993 or ICD-10 criteria (code F31) since 1994.

2.2. Statistical analyses

Analyses were based on χ^2-tests and different types of regression modelling, i.e. conditional logistic regression, mixed logistic regression and survival analysis (Cox regression with shared frailty). χ^2-tests were applied to the data to determine if BD occurred more often in the case population than in the control population when stratifying on the family members. Conditional logistic regression was applied to determine if the status of certain family members increases the risk of the disease in the proband more than others by including three indicator variables (paternal BD, maternal BD and sibling BD) each representing whether or not a certain family member has BD. If data from a family member were missing the value of the variable was 0. Since this method takes matching into account, the matched variables were not included in the analysis whereas maternal and paternal age at birth was included separately and together. All variables were included as categorical variables with maternal and paternal age at birth divided into intervals <35 and ≥ 35 years.

Mixed logistic regression was applied to estimate a family load component. This family load component was estimated as a random effect. The random effect measures the dependence among the family members in relation to how often each family develops BD. It was divided for different age at onset groups, namely, <25 years, and ≥ 25 years at onset of BD in the case-probands. The cut-off at age 25 followed the findings by Grigoroiu-Serbanescu et al. (2001) indicating that the patterns of familial transmission of bipolar I disorders are different before and after age 25 (Grigoroiu-Serbanescu et al., 2001). Furthermore, the regression analysis included the matched explanatory variables, i.e., sex, year of birth, region of residence, and month of birth. Region of residence was converted into a dichotomous variable comparing the capital of Copenhagen to all other regions. Sex, month of birth and region of residence were included as categorical variables whereas year at birth was included as a continuous variable.

Cox regression with shared frailty was applied to investigate if case family members developed BD earlier than control family members, i.e. the probands were excluded from the analysis. The family load component is estimated as a random effect (frailty). A frailty measures the dependence among the family members in relation to the time to disease onset; this means that a family with a high value of the frailty developed BD earlier than a family with a small value of the frailty. The frailty is assumed to follow