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Research paper

Parental and comorbid migraine in individuals with bipolar disorder: A nationwide register study

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ABSTRACT

Background: Genetic studies imply a shared genetic etiology between bipolar disorder (BD) and migraine. Epidemiological studies have demonstrated elevated comorbidity between these disorders, but haven't controlled for parental psychopathology. No previous nationally representative studies exist on familial clustering of BD and migraine. This study examines the association between parental and comorbid migraine and BD, controlling for potential confounders.

Methods: We identified 1861 cases aged ≤25 years, 3643 matched controls, and their parents from Finnish national registers. Conditional logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) and two-sided significance limits of $p < 0.05$.

Results: Parental migraine, controlling for parental BD, was associated with offspring BD diagnosed at age ≥18 years (OR 1.52, 95%CI: 1.08–2.14). Associations between BD and comorbid migraine persisted following adjustment for parental BD and parental migraine in all subjects (OR=2.46, 95% CI: 1.76–3.42), both age groups of BD-diagnosis (<18 years, ≥18 years) and both sexes.

Limitations: The diagnoses were register-based, not directly ascertained.

Conclusions: This study indicates that parental migraine, even in the absence of parental BD, is a risk factor for offspring BD. Thus, a genetic link between BD and migraine could potentially explain some of the elevated comorbidity between these disorders. However, BD shows a stronger association with comorbid migraine than with parental migraine, suggesting that much of the elevated comorbidity is related to non-genetic factors. Increased understanding of mechanisms underlying the comorbidity of BD and migraine is important since it is associated with poorer health-related outcomes compared with BD alone.

1. Introduction

Several epidemiological studies have demonstrated an association between bipolar disorder (BD) and migraine. However, only few studies utilizing nationally representative samples have explored the association between these disorders. The German Health Survey found a 2.8-fold association between migraine and BD (Ratcliffe et al., 2009). Another survey representing the U. S. adult population showed that 15.2% of individuals with BD had migraine, whereas among individuals without BD only 7% had migraine (Hirschfeld et al., 2003). The 2002 Canadian Community Health Survey reported a higher prevalence of migraine in individuals with BD as compared to the general population, 24.8% versus 10.3% (McIntyre et al., 2006). In addition, a cohort study conducted in the state of South Carolina, U. S., demonstrated an association between BD and migraine in a sample of 1841 children and adolescents with BD (Jerrell et al., 2010).

Individuals with both BD and migraine suffer from poorer health-related outcomes compared with individuals with only BD (Brietzke et al., 2012; McIntyre et al., 2006). The underlying mechanisms causing this clinically relevant elevated comorbidity are still poorly understood. However, BD and migraine have pathophysiological similarities in terms of altered neurotransmission of dopamine (Cousins et al., 2009; Peroutka et al., 1997) and serotonin (Hamel, 2007; Mahmood and Silverstone, 2001). Genetic

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factors contribute greatly to the development of both BD and migraine, and genome-wide linkage and association studies have found overlapping regions between these two disorders (Oedegaard et al., 2010a, 2010b). If the co-occurrence of BD and migraine is predominantly due to a genetic link between these disorders, then a familial clustering of BD and migraine would be expected. However, there is very limited epidemiological research exploring this possibility. Dilsaver et al. (2009) examined two groups of patients, 87 individuals with BD and 153 individuals with unipolar major depressive disorder. Within both groups, individuals with a family history of BD were more likely to have comorbid migraine than individuals without a family history of BD. To our knowledge, only one previous study has examined family prevalence of migraine in individuals with BD (Baptista et al., 2012). Unexpectedly, they found a lower frequency of migraine in first-degree relatives of individuals with in- and out-patient admissions for BD in comparison to the general population. However, there were methodological limitations in the study by Baptista et al. (2012) potentially influencing the results. The number of individuals with BD in the sample was fairly small, not comparable to a nationwide sample, and while the cases were drawn from several different states, the individuals representing the general population were collected from one state only.

Some previous population-based studies have shown that the frequency of migraine in individuals with BD is dependent on the age of onset of psychopathology. Saunders et al. (2014) reported an earlier age at onset of BD by 2 years in individuals with versus without comorbid migraine (16.2 years vs. 18.5 years). Several other studies as well have shown that BD with an earlier onset is more often accompanied by comorbid migraine (Brietzke et al., 2012; Gordon-Smith et al., 2015; Mahmood et al., 1999; McIntyre et al., 2006). It is thus plausible that BD with comorbid migraine could have distinct etiological features compared to BD only, and that an early onset of BD would be an indicator of such an etiology. Moreover, if the assumed etiological differences are genetically mediated, we would expect the familial clustering of BD and migraine to be stronger among offspring with an early onset of BD.

Population-based studies have shown an association between parental psychopathology, particularly parental BD, and BD in the offspring (Castagnini et al., 2013; Dean et al., 2010; Laursen et al., 2005; Mortensen et al., 2003; Sucksdorff et al., 2014). Similarly, studies have demonstrated an association between parental psychopathology and offspring headaches including migraine (Feldman et al., 2010; Marmorstein et al., 2009). However, to our knowledge, no previous study has examined the association between BD and comorbid migraine, adjusting for parental psychopathology.

This population-based study aimed to examine the following associations. First, we examined parental migraine and BD in the offspring; we controlled the results for parental BD applying a four level categorical variable in order to evaluate whether parental migraine in the absence of parental BD is a risk factor for BD in the offspring. Second, we examined the comorbidity of migraine in BD adjusting for parental BD and parental migraine. In addition, separate analyses were conducted on both parental and comorbid migraine for BD cases with age of BD-diagnosis younger than 18 years and $\geq$ 18 years. This study has a nested case-control design and is based on linkages between two national registers.

2. Methods

2.1. Study design

This study is part of the Finnish Prenatal Study of Bipolar Disorders (FIPS-B), a nationwide register linkage study. It is derived from all singleton live births in Finland between January 1, 1983 and December 31, 1998 (n = 1,009,846) and is based on a nested case-control design. The personal identification code (PIC), assigned to all Finnish residents and unique for each person, allows for the linkages between the registers. The study has received approval from the Ministry of Social Affairs and Health in Finland, the Finnish National Institute for Health and Welfare, the ethics committee of the hospital district of Southwest Finland and the Institutional Review Board of the New York State Psychiatric Institute. A detailed description of the FIPS-B study design and the sample is available (Chudal et al., 2014).

2.2. National registers

This study is based on two national registers, the Finnish Hospital Discharge Register (FHDR) and the Finnish Population Information System.

In Finland, diagnoses are routinely recorded in the FHDR. Beginning in 1969 it covers all inpatient care units in Finland; somatic and psychiatric hospitals, inpatient wards of local health centers, military wards, prison hospitals and private hospitals. Since January 1, 1998 the FHDR also includes outpatient care in public specialized hospital units. The FHDR records the primary diagnosis as well as subsidiary diagnoses at discharge from an inpatient unit and at each visit to an outpatient unit. All diagnoses are based on the International Statistical Classification of Diseases (ICD): ICD-8 from 1969 to 1986, the Finnish version of ICD-9 from 1987 to 1995, and ICD-10 from 1996 onwards. The FHDR is maintained by The National Institute of Health and Welfare. There are a substantial amount of studies on the quality of the FHDR covering a wide range of diseases, both psychiatric and somatic, and demonstrating the usefulness of the FHDR in epidemiological research (Sund et al., 2012).

The Finnish Population Information System is maintained by the Finnish Population Register Centre and local register offices. It contains basic information, such as name, PIC, birth municipality and family relations, on Finnish citizens and people residing permanently in Finland.

2.3. Identification of cases and controls

The cases were identified from the FHDR. They were linked to the Finnish Population Information System, which was used to identify the matched controls.

The cases were individuals (N = 1861) born between 1983 and 1998 and diagnosed with BD by December 31, 2008 (aged up to 25 years). They were identified based on the following FHDR-derived codes for BD: ICD-9 (Finnish version) codes 2962A-G (bipolar disorder, manic episode), 2963A-G (bipolar disorder, depressive episode), 2964A-G (bipolar disorder, mixed) and 2967A (bipolar disorder, unspecified) and ICD-10 codes F31x.

The controls were defined as individuals without BD, schizophrenia or diagnoses related to these disorders. The ICD-codes for the exclusion of controls were: ICD-10 diagnoses F30 single manic episode, F31 BD, F34.0 cyclothymia, F38.0 other mood disorders; mixed affective episode, F39 unspecified mood disorder, F20–29 (schizophrenia, schizotypal disorder, persistent delusional disorders, acute and transient psychotic disorders, induced delusional disorder, schizoaffective disorders, other nonorganic psychotic disorders, unspecified nonorganic psychosis), F60.0 paranoid personality disorder and F60.1 schizoid personality disorder; ICD-9 diagnoses 2962A-G/2963A-G/2964A-G/2967A BD, 295 schizophrenic psychoses, 297 paranoid states, 298 psychoses aliae, 3010A paranoid personality, 3012A schizoid personality and 3012C schizotypal personality.

All singleton cases were first matched to two controls