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Research report

Parental and comorbid epilepsy in persons with bipolar disorder

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ABSTRACT

Background: Population-based studies have demonstrated an overrepresentation of bipolar disorder (BPD) in individuals with epilepsy. However, few studies have examined the reverse association, i.e. comorbid epilepsy in individuals selected based on BPD diagnosis. No previous population-based study having examined the co-occurrence of BPD and epilepsy has adjusted for parental psychopathology. Such an adjustment is motivated by population-based studies reporting an overrepresentation of various types of parental psychiatric disorders in both BPD and epilepsy. Furthermore, an association between epilepsy in first-degree relatives and BPD has previously only been examined and demonstrated in a small clinical sample. The objective of this study is to examine the associations between parental and comorbid epilepsy and BPD, adjusting for parental psychopathology.

Methods: This nested case-control study identified 1861 cases with BPD, age up to 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: BPD was associated with comorbid epilepsy (adjusted OR 2.53, 95% CI: 1.73–3.70) but not with parental epilepsy. Epilepsy was found in 3.33% of cases versus 1.29% of controls, 2.69% of cases' parents versus 2.53% of controls' parents.

Limitations: The diagnoses were register-based, not based on standardized procedures with direct ascertainment.

Conclusions: An association between BPD and comorbid epilepsy persists even after adjusting for parental psychopathology. Lack of familial clustering of BPD and epilepsy would suggest that the elevated co-occurrence of these disorders is influenced by non-genetic factors.

1. Introduction

Genetic as well as environmental factors contribute to the etiology of both bipolar disorder (BPD) and epilepsy. Higher concordance rates in monozygotic as compared to dizygotic twins have been reported in epilepsy (Corey et al., 2011; Kjeldsen et al., 2001) and BPD in particular (Kendler et al., 1993; Kieseppä et al., 2004; McGuffin et al., 2003), thereby establishing the role of genetic factors in these disorders. They also seem to share a number of similarities in terms of biochemical underpinnings (i.e. changes in neurotransmitters, voltage-opened ion channels and second messenger systems), clinical course and response to pharmacotherapy (Mula et al., 2010). For instance, epileptic activity as well as acute mania has been associated with increased intracellular calcium concentrations (Dubovsky et al., 1994; Speckmann et al., 1993). Both BPD and epilepsy have an episodic course, and without treatment, a progression with increased rate of episodes and shortening of symptom-free intervals is commonly seen in both BPD (Angst and Sellaro, 2000) and epilepsy (Kwan and Sander, 2004). Moreover, antiepileptic drugs (AEDs) are also used in the treatment of BPD due to their mood stabilizing properties (Mazza et al., 2007), particularly one of the older AEDs, valproate and a newer AED, lamotrigine (Italiano et al., 2015). Intriguing questions are raised by these similarities including whether BPD and epilepsy have an overlapping etiology and to what degree the association is genetically versus environmentally mediated.

At present, the epidemiological evidence of a link between BPD

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and epilepsy is mostly restricted to studies on comorbidity. Population-based studies have demonstrated an association between BPD and epilepsy (Adelöw et al., 2012; Bakken et al., 2014; Chang et al., 2013; Clarke et al., 2012; Ettinger et al., 2005; Jerrell et al., 2010; Martin et al., 2014; Ottman et al., 2011; Wotton and Goldacre, 2014), and most of them selected the cases based on epilepsy diagnosis. Two of the previous studies (Jerrell et al., 2010; Wotton and Goldacre, 2014) examined the association by selecting the cases based on BPD diagnosis (Wotton and Goldacre, 2014, examined the association in both ways). In addition, Wotton and Goldacre (2014) included separate analyses for both sexes and found the occurrence of comorbid epilepsy to be similar in female versus male cases with BPD.

The epidemiological evidence of a familial clustering of BPD and epilepsy is still scarce. A recent clinical study, based on a small hospital sample, found that the rate of epilepsy among first-degree relatives of individuals with BPD compared to controls was 15.2% versus 2.0% (Jidda et al., 2014). A population-based study by Clarke et al. (2012) examined familial vulnerability to epilepsy and psychotic illness utilizing, similarly to our study, the Finnish Hospital Discharge Register (FHDR). The results of the study indicated that epilepsy and psychosis cluster within families. Individuals with a parental history of epilepsy had a two-fold increase in the risk of developing a psychotic disorder. Reciprocally, individuals with a parental history of a psychotic disorder had a 1.6-fold increase in the risk of having some type of epilepsy. However, the study included only BPD with psychotic symptoms when defining a psychotic disorder and this definition included other types of psychoses as well.

Epidemiological research has shown that many psychiatric disorders, especially schizophrenia-spectrum and affective disorders are more frequent in parents of offspring with BPD compared to parents of offspring without BPD (Castagnini et al., 2013; Dean et al., 2010; Laursen et al., 2005; Mortensen et al., 2003; Sucksdorff et al., 2014). Furthermore, maternal unipolar depression (Morgan et al., 2012) and parental psychoses (Clarke et al., 2012) have been associated with epilepsy in offspring. Therefore, parental psychopathology, especially psychoses and affective disorders, may be a potential confounder while examining the co-occurrence of BPD and epilepsy. However, to our knowledge none of the previous studies on the association between BPD and epilepsy has adjusted for parental psychopathology.

This is a population-based nested case-control study utilizing linkages between two national registers. The objective of this study was to examine the associations between parental and comorbid epilepsy and BPD. Analyses for all individuals and for males and females separately were conducted. Furthermore, the association between BPD and comorbid epilepsy was examined adjusting for parental psychopathology.

2. Methods

2.1. Study design

This study is part of a nationwide population-based epidemiological study called the Finnish Prenatal Study of Bipolar Disorders (FIPS-B). 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 FIPS-B capitalizes on linkages between various national registers. The personal identification code (PIC), which is assigned to all Finnish residents and is unique for each person, allows for the linkages between the registers. This study has been authorized by the Ministry of Social Affairs and Health in Finland. The ethics committee of the hospital district of Southwest Finland, the National Institute for Health and Welfare and the Institutional Review Board of the New York State Psychiatric Institute have given approval for the study. The full description of the FIPS-B study design is available (Chudal et al., 2014).

2.2. National registers

This study utilizes two national registers, the Finnish Hospital Discharge Register (FHDR) and the Finnish Central Population Register. In Finland, medical diagnoses are routinely registered in the FHDR. Starting from 1969 the FHDR 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. All diagnoses are based on the International Statistical Classification of Diseases (ICD): ICD-8 from 1969 to 1986, ICD-9 from 1987 to 1995 and ICD-10 from 1996 onwards. The FHDR is maintained by The National Institute of Health and Welfare (THL).

The Finnish Central Population Register is maintained by the Finnish Population Register Centre and local register offices and includes basic information such as name, PIC, birth municipality and family relations about Finnish citizens and people residing permanently in Finland.

2.3. Identification of cases and controls

The cases were identified from the FHDR. The cases were then linked to the Finnish Central Population Register to find potential candidates for controls. Next, a linkage back to the FHDR was performed in order to identify/exclude control candidates having diagnoses according to exclusion criteria (see below).

The cases consist of individuals ($N=1861$) born between 1983 and 1998 and according to the FHDR diagnosed with BPD by December 31, 2008 (age range up to 25 years). They were identified based on ICD-9 codes 2962A G, 2963A G, 2964A G and 2967A and ICD-10 codes F31x.

The controls were defined as individuals without BPD, schizophrenia or diagnoses related to these disorders. Therefore the controls were excluded for any of the following ICD-codes: ICD-10 diagnoses F30 single manic episode, F31 BPD, 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 BPD, 295 schizophrenic psychoses, 297 paranoid states, 298 psychoses aliae, 3010A paranoid personality, 3012A schizoid personality and 3012C schizotypal personality.

Every singleton case was first matched to two controls ($N=3722$) on sex and date of birth (± 30 days). However, 79 controls belonging to a twin birth were excluded resulting in a total of 3643 controls. The matched control was required to be alive and living in Finland on the day the case was diagnosed. Date of birth was included as a matching factor to control for secular changes in prevalence of exposures and to control for potential confounding by season of birth, which is a particularly important factor in other studies in the FIPS-B.

2.4. Identification of parents

The parents of cases and controls were identified from the Finnish Central Population Register by linking this register to the FHDR. The husband of the mother at the time of the child´s birth