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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.

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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.

Keywords

bipolar disorder; epilepsy; parental psychopathology; population-based study; register; epidemiology

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 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

twofold 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-code, 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 was assumed to be the father of the child. In case of unmarried mothers, the paternity was confirmed by acknowledgment of the father. Furthermore, DNA testing for paternity is available free of charge provided that the man agrees to such testing. Paternity was established in 97.9% of the cases and 98.9% of the controls.

2.5. Identification of parental and comorbid epilepsy

Epilepsy in cases, controls and in parents of cases and controls was identified from the FHDR. Epilepsy was defined based on ICD-8 (years 1969–1986) code 345 (epilepsy including status epilepticus), ICD-9 (years 1987–1995) code 345 (epilepsy including status epilepticus), and ICD-10 (from 1996 onwards) codes G40 (epilepsy) and G41 (status epilepticus). The most recent epilepsy diagnosis was used for identification. The parents were followed up from 1969 to the end of 2009.

2.6. Definition of parental psychopathology

Parental psychopathology, for which the association between BPD and comorbid epilepsy was adjusted for, refers to schizophrenia-spectrum and affective disorders. These parental disorders had to be diagnosed prior to the birth of the offspring. Parental psychopathology was defined based on the following ICD-codes.

ICD-8 diagnoses: 295 schizophrenia, 296 affective psychoses, 297 paranoid states, 298 other psychoses, 301.00 paranoid personality, 301.20 schizoid personality, (in ICD-8 the schizotypal personality is included in the code 295).

ICD-9 diagnoses: 295 schizophrenia, 296 episodic mood disorders, 297 paranoid states, 298 other psychoses, 3010A paranoid personality, 3012A schizoid personality and 3012C schizotypal personality.

ICD-10 diagnoses: 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), F30 single manic episode, F31 BPD, F32 major depressive disorder, single episode, F33 recurrent depressive disorder, F34 persistent mood disorders, F38 other mood disorders, F39 unspecified mood disorder, F60.0 paranoid personality disorder and F60.1 schizoid personality disorder.

Parental psychopathology was analyzed as a binary variable (yes/no). Parental psychopathology was classified as “yes”, if either mother, father or both parents had a psychiatric diagnosis.

2.7. Statistical methods

The associations were expressed as odds ratios (ORs) calculated in conditional logistic regression analyses. The following associations were evaluated: the association between BPD and parental epilepsy as well as the association between BPD and comorbid epilepsy. A multivariate analysis adjusting for parental psychopathology was included in the evaluation of comorbid epilepsy.

All associations were examined calculating ORs with 95 % confidence intervals (CIs). P-values were calculated by Wald’s χ^2–test with a two-sided statistical significance limit of $p<0.05$. Statistical analyses were performed with SAS statistical software (SAS Version 9.4; SAS Institute Inc., Cary, NC).

Note that in the parental epilepsy analysis all cases and controls were included, even if the father was unknown.

3. Results

The mean age of diagnosis of BPD in the sample was 19.8 years (standard deviation 3.1, age range 4–25 years). Table 1 presents frequencies and percentages of epilepsy for cases and their matched controls. Furthermore, it depicts the unadjusted and the adjusted ORs (with 95% CIs) for epilepsy with separate analyses conducted for all subjects, females and males. Significant associations between BPD and epilepsy were found in all analyses, with the associations being very similar between the sexes. The adjusted OR (with 95% CI) for all cases was 2.53 (95% CI: 1.73–3.70), for females 2.48 (95% CI: 1.26–4.90) and for males 2.55 (95% CI: 1.61–4.04).

Table 2 shows frequencies and percentages of parental epilepsy for cases and their matched controls and the ORs (with 95% CIs) for parental epilepsy. Statistically significant associations between BPD and parental epilepsy were not found in the analyses of all subjects, females or males.

The frequencies and percentages for parental psychopathology diagnosed prior to offspring birth, cases versus controls, were as follows: All subjects, 58 (3.12%) vs. 32 (0.88%); females, 34 (2.67%) vs. 21 (0.84%); males, 24 (4.09%) vs. 11 (0.96%). The corresponding OR for parental psychopathology was 3.64 (95% CI: 2.34–5.68, $p<0.0001$) for all cases, 4.52 (95% CI: 2.15–9.51, $p<0.0001$) for female cases, and 3.21 (95% CI: 1.84–5.59, $p<0.0001$) for male cases.

4. Discussion

This study demonstrates an association between BPD and comorbid epilepsy that persists even after adjusting for parental psychopathology (i.e. schizophrenia-spectrum and affective disorders in parents diagnosed prior to the birth of the offspring). Furthermore, in accordance with the study by Wotton and Goldacre (2014) we found no differences in the associations between sexes. The fundamental question nevertheless is what explains the elevated occurrence of epilepsy in BPD. Various potential explanations should be considered. For instance, individuals with BPD may be more prone to accidents (Hsieh et al., 2012; Khalsa et al., 2008) and traumatic brain injuries are risk factors for epilepsy (Christensen et al., 2009; Yeh et al., 2013). BPD is associated with alcohol abuse (Kessler et al., 1994; Regier et al., 1990), which is a risk factor for epilepsy (referring to ICD-10 diagnosis G40.51 Epilepsy associated with alcohol). Furthermore, there are studies suggesting that psychiatric history before the onset of epilepsy may lower the seizure threshold (Hitiris et al., 2007; Kanner et al., 2009). Speculations have been presented over possible deleterious neurobiological processes that could be linked to psychiatric disorders and interact with those producing seizures (Hitiris et al., 2007).

Yet another possible explanation for these findings is that BPD and epilepsy are at least partly genetically related to each other. However, epilepsies can be caused by both genetic and acquired/environmental factors (such as head traumas, strokes, severe perinatal injuries

and postinfectious lesions) (Mazza et al., 2007). Therefore, the possible genetic relation to BPD would most likely apply for only some part of the epilepsies. Yet, if such a genetic overlap exists, an association between epilepsy in close relatives and BPD is expected to be found, provided that the sample size is large enough. However, there were no differences in the associations between parental epilepsy and BPD in cases versus controls in our sample. This was contrary to our expectations considering the results of the previous two studies (Clarke et al., 2012; Jidda et al., 2014) addressing the issue. The study by Jidda et al. (2014) reported high rates of epilepsy in first-degree relatives of probands with BPD (15.2% in cases versus 2.0% in controls). However, the study relied on a small clinical sample and therefore the results cannot be generalized on a population level. The study by Clarke et al. (2012) on the other hand was a population-based study relying, similarly to our study, on the FHDR.

They reported an association between parental epilepsy and offspring psychotic disorder, with BPD with psychotic symptoms being included in the definition of a psychotic disorder. The sample in Clarke et al. (2012) comprised 23404 offspring; 232 had a psychotic disorder. One possibility is that the association was related to a genetic link between epilepsy and psychoses other than BPD. It is also plausible to speculate that a heritable genetic link to epilepsy may only apply for the most severe forms of BPD presenting with psychotic episodes. Yet another possible explanation for our negative finding is that the sample size in our study, while substantial, is not large enough to detect an association between BPD and parental epilepsy. Further population-based studies examining the issue with even larger samples are warranted.

The following limitations need to be considered in interpreting the findings of this study. First, among individuals receiving treatment for a certain disorder, the medical attention may lead to possible comorbidities being detected more easily compared to the average population. This could cause some degree of over-estimation of the co-occurrence of BPD and epilepsy. Second, the sample size was not large enough to allow separate analyses on different types of epilepsies. Third, the cases in our sample consist of individuals who have utilized public specialized mental health services, where BPD has been diagnosed. It is possible that some individuals suffering from less severe forms of the disorder may never utilize specialized mental health services and the BPD goes unrecognized. However, access to public health care, including specialized services, is not dependent on income since healthcare services in Finland have public financing. Fourth, psychiatric private clinics are not recorded in the register. However, all psychiatric inpatient units in Finland are public and the register has complete coverage of inpatient treatments. Therefore, even if the psychiatric outpatient treatment was carried out solely in the private sector, the cases will be missed only if they have never received any inpatient treatment for BPD. Fifth, the diagnoses of cases, controls and parents are derived from registers, rather than a standardized procedure with a direct ascertainment of the diagnoses. However, the validity of the FHDR for psychoses and BPD I was found to be good (Kieseppä et al., 2000; Perälä et al., 2007). A review-article summarized the substantial amount of studies that exist on the quality of the FHDR (Sund, 2012). These studies cover a wide range of diseases, both somatic and psychiatric, and demonstrate the usefulness of the FHDR in epidemiological research.

In conclusion, we found that BPD is associated with comorbid epilepsy but not with epilepsy in parents. These results suggest that although a genetic overlap between BPD and epilepsy may exist, factors other than susceptibility genes are also likely to play part in the elevated comorbidity of epilepsy in individuals suffering from BPD. Identifying such environmental factors should be a priority for future research.

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Highlights

- This is the first study to examine familial clustering of bipolar disorder (BPD) and epilepsy utilizing a nationally representative sample, and it was derived from all 1983–1998 singleton live births in Finland (n=1009 846).
- We also examined comorbid epilepsy in BPD, adjusting for parental psychopathology which has not been adjusted for in the previous comorbidity studies.
- BPD was associated with comorbid epilepsy but not with parental epilepsy.
- Our results indicate that non-genetic factors influence the elevated comorbidity of epilepsy in BPD.

Table 1

Frequencies, percentages and odds ratios (ORs) with 95% confidence intervals (CIs) for epilepsy, cases versus controls.

	Case n (%)	Control n (%)	Unadjusted ORs (95% CIs)	Adjusted ORs[1] (95% CIs)
EPILEPSY				
All subjects				
No	1799 (96.67)	3596 (98.71)		
Yes	62 (3.33)	47 (1.29)	2.59 (1.77–3.79)***	2.53 (1.73–3.70)***
Females				
No	1232 (96.70)	2461 (98.72)		
Yes	42 (3.30)	32 (1.28)	2.62 (1.34–5.12)**	2.48 (1.26–4.90)**
Males				
No	567 (96.59)	1135 (98.70)		
Yes	20 (3.41)	15 (1.30)	2.58 (1.63–4.09)***	2.55 (1.61–4.04)***

[1] adjusted for parental psychopathology;

** p<0.01;

*** p<0.0001

Table 2

Frequencies, percentages and odds ratios (ORs) with 95% confidence intervals (CIs) for parental epilepsy, cases versus controls.

	Case n (%)	Control n (%)	ORs (95% CIs)	p-values
PARENTAL EPILEPSY				
All subjects				
No	1811 (97.31)	3551 (97.47)		
Yes	50 (2.69)	92 (2.53)	1.07 (0.76–1.51)	0.7001
Females				
No	1237 (97.10)	2434 (97.63)		
Yes	37 (2.90)	59 (2.37)	1.24 (0.82–1.87)	0.3138
Males				
No	574 (97.79)	1117 (97.13)		
Yes	13 (2.21)	33 (2.87)	0.78 (0.41–1.47)	0.4361