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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

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Contributors

Dr. Sucksdorff wrote the first draft of the manuscript and contributed to the study design, data collection, data interpretation and literature search.

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Dr. Heinimaa contributed to the study design, data interpretation and writing.

Mrs. Suominen contributed to the study design, writing and conducted the statistical analyses.

Dr. Sourander initiated the study, contributed to the study design, data collection, data interpretation and writing.

All authors approved the final manuscript.

Conflict of interest

The authors declare no conflicts of interest.

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(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.

Keywords

Bipolar disorder; Migraine; Population-based study; Register; Epidemiology

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 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; Oedegaard et al., 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 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 (N=3722) on sex and date of birth (+/- 30 days). The controls were resident of Finland at first diagnosis of the case. However, 79 controls belonging to a twin birth were excluded resulting in a total of 3643 controls. The exclusion was done in order to avoid any biases arising from singleton versus twin births between cases and controls. 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.

2.4. Identification of parents

The parents of cases and controls were identified from the Finnish Population Information System through linkage with the FHDR. The husband of the mother at the time of the child's birth was assumed to be the father of the child. If the mother was unmarried, the paternity was confirmed by acknowledgment of the father. Furthermore, voluntary DNA testing for paternity is available free of charge. Paternity was established in 97.9% of the cases and 98.9% of the controls. The mother was known in all cases and controls. All cases and controls were included in the analyses examining parental migraine, including those with unknown father.

Parental BD referred to the following FHDR-derived codes: ICD-8 codes 296.10, 296.30, ICD-9 (Finnish version) codes 2962A-G, 2963A-G, 2964A-G and 2967A and ICD-10 codes F31x.

2.5. Identification of parental and comorbid migraine

Migraine in cases, controls and parents of cases and controls was identified from the FHDR. Migraine was defined based on ICD-8 code 346 (years 1969–1986), ICD-9 code 346 (years 1987–1995) and ICD-10 code G43 (from 1996 onwards). The parents were followed up from 1969 to the end of 2009.

All cases, controls, and parents of cases and controls with migraine, had migraine-diagnoses that were recorded either as a main diagnosis or as a subsidiary diagnosis to a somatic (not psychiatric) main diagnosis. This verification was done to make sure that the associations are not due to ascertainment bias, i.e. people with psychiatric disorders receiving migraine as a subsidiary diagnosis while hospitalized for a psychiatric disorder or at a regular visit to a psychiatrist.

2.6. Statistical methods

Conditional logistic regression was used to examine the following associations: 1) parental migraine and BD in the offspring; 2) comorbid migraine in BD. To examine whether the findings differed by age of onset, all these analyses were conducted separately for BD cases aged <18 years and ≥18 years at BD-diagnosis as well as for males and females separately. A four level categorical variable was used to examine if parental migraine with or without parental BD is associated with BD, i.e. the subjects were divided into four different categories according to their parental BD- and parental migraine-status: 1) no parental migraine, no parental BD (=reference category); 2) yes parental migraine, no parental BD; 3) no parental migraine, yes parental BD; 4) yes parental migraine, yes parental BD. The

associations between BD and comorbid migraine were evaluated adjusting for parental BD and parental migraine.

Parental BD and parental migraine were included in the statistical models as binary variables (yes/no). For example, parental BD was classified as “yes”, if one or both of the parents had a BD-diagnosis.

The associations were expressed in odds ratios (ORs) with 95 % confidence intervals (CIs). Two-sided p-values with statistical significance limit <0.05 were calculated through Wald's χ^2 -test. Statistical analyses were conducted with SAS statistical software (SAS Version 9.4; SAS Institute Inc., Cary, NC).

3. Results

The mean age at diagnosis of BD in the whole sample was 19.8 years, the standard deviation (SD) was 3.1 and the age range was 4–25 years. The mean age at diagnosis of BD was 19.8 (SD 2.8) in females and 19.7 (SD 3.7) in males.

Table 1 shows the distribution of parental migraine and parental BD among cases and their matched controls applying a four level categorical variable, with cases and controls being placed in different categories according to their parental migraine- and parental BD-status. The table presents ORs for categories “yes parental migraine, no parental BD”, “no parental migraine, yes parental BD” and “yes parental migraine, yes parental BD”, with “no parental migraine, no parental BD” as the reference category. In the category “no parental migraine, yes parental BD”, significant associations with BD were found in all examined groups: BD-diagnosis at the age of <18 years and ≥ 18 years, males and females. In the category “yes parental migraine, no parental BD” a significant association with BD was found in the group of individuals diagnosed with BD at the age of ≥ 18 years (OR=1.52, 95% CI: 1.08–2.14).

Table 2 presents the distribution of migraine in cases and controls, as well as the ORs for comorbid migraine in BD. Significant associations between migraine and BD were found in all groups (all subjects, BD cases <18 years / ≥ 18 years at diagnosis, females, males) in the unadjusted as well as in the adjusted analyses. The associations adjusting for parental migraine and parental BD were very similar among these groups with the ORs varying between OR (BD cases ≥ 18 years at diagnosis) =2.39, 95% CI: 1.61–3.56 and OR (males) =2.70, 95% CI: 1.09–6.69.

4. Discussion

This nationwide register based study demonstrates familial clustering of BD and migraine, with the odds of parental migraine, controlling for parental BD, being 1.5-fold in individuals receiving a BD-diagnosis at the age of ≥ 18 years. We also found comorbid migraine to be associated with BD; the adjustments with either parental BD or parental migraine did not have a significant impact on the associations.

A common etiologic mechanism such as shared susceptibility genes could play a part in the familial clustering and the elevated comorbidity of migraine and BD. The results of our

study indicate that parental migraine, even in the absence of parental BD, is a risk factor for BD in the offspring. Therefore, our study provides epidemiological support for genetic studies indicating a genetic overlap between BD and migraine (Oedegaard et al., 2010a; Oedegaard et al., 2010b). However, the associations with BD found in our study were stronger for comorbid migraine than for parental migraine. This could indicate that much of the elevated comorbidity between BD and migraine is related to non-genetic factors. For instance, reduced sleep, a core feature of hypomania/mania (ICD-10), is also a migraine trigger (Tran and Spierings, 2013).

In accord with previous studies, we found BD to be associated with comorbid migraine in the unadjusted analyses of all examined groups (i.e. all subjects, BD cases <18 years / 18 years at diagnosis, females, males). Adjusting for parental migraine and parental BD, the associations between BD and comorbid migraine were significant and very similar in magnitude as compared to the unadjusted analyses for both sexes. Moreover, the associations between BD and comorbid migraine, irrespective of the adjustments, were similar in magnitude in BD diagnosed before the age of 18 years versus later. However, previous studies have indicated that an earlier onset of BD is associated with a growing frequency of comorbid migraine (Brietzke et al., 2012; Gordon-Smith et al. 2015; Mahmood et al., 1999; McIntyre et al., 2006; Saunders et al., 2014). It is plausible that BD with an onset in childhood/adolescence could have a stronger genetic link to migraine than BD with a later onset. Consequently we assumed that parental migraine in our sample would be more frequent in subjects having received the BD-diagnosis before 18 years of age. However, BD in this group showed no association with parental migraine in our sample. Since the number of subjects in the group being diagnosed with BD before the age of 18 years was small, the results should be interpreted cautiously. It could indicate that while comorbid migraine based on previous studies appears to be more frequent in early onset BD, the pattern may not be genetically but rather environmentally mediated. One possible explanation could be BD causing severe psychological stress and insecurity. These stressors could be more difficult to cope with in childhood/adolescence as compared to adulthood, and eventually trigger the onset of migraine. According to a recent systematic review, stress is the most common precipitating factor for migraine (Peroutka, 2014).

Achieving a better understanding of the mechanisms behind BD and comorbid migraine has clinical relevance. It has been demonstrated that individuals with both BD and migraine suffer from poorer health-related outcomes, such as more mood episodes, higher prevalence of comorbid anxiety disorders, increased utilization of mental health care services and poorer quality-of-life, compared with individuals with only BD (Brietzke et al., 2012; Jette et al., 2007; McIntyre et al., 2006). Therefore, it is plausible to assume that improvements in the recognition of migraine precipitating factors and in the management of migraine could at the same time improve the prognosis of BD.

The results of this study should be interpreted in light of the following limitations. The cases are individuals utilizing public specialized mental health services. Some individuals with less severe forms of BD perhaps never utilize these services and may be unrecognized. However, since healthcare services in Finland have public financing, public health care including specialized services is available for all people irrespective of income. In addition,

the FHDR does not cover psychiatric private clinics. However, psychiatric inpatient units in Finland are all public, and the register has full coverage of the inpatient units. Therefore, even if the psychiatric care in terms of outpatient treatment would have been carried out exclusively in the private sector, the cases would still be included in the study if they at some point received inpatient treatment for BD. Finally, the diagnoses of cases, controls and parents are register-based, not directly ascertained by the researchers. However, the FHDR has shown good validity for psychoses and BD I (Kieseppä et al., 2000; Perälä et al., 2007).

In conclusion, this study demonstrates an association between parental migraine and BD diagnosed at the age of 18 years. The association persisted controlling for parental BD, indicating that parental migraine could be an independent risk factor for BD in the offspring. This finding warrants further research on family history of migraine as a possible risk factor for BD. However, BD showed a more robust association with comorbid migraine than with parental migraine. Therefore, it seems likely that mechanisms other than genetic overlap between BD and migraine are essential in the elevated comorbidity of these disorders. For future etiological research, improving knowledge on risk factors for BD and comorbid migraine is clinically important, since these patients often present with poorer health-related outcomes compared with BD alone.

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Highlights

- This register-based case-control study is the first nationwide study on familial clustering of bipolar disorder (BD) and migraine.
- We also examined BD and comorbid migraine, adjusting for parental BD and parental migraine.
- BD was associated with both parental and comorbid migraine, though more strongly with the latter.
- Our results indicate that parental migraine is a risk factor for BD.
- The results also suggest that non-genetic factors are essential in this clinically relevant comorbidity; health-related outcomes in BD are poorer in presence of comorbid migraine.

Table 1

Frequencies, percentages and odds ratios (ORs) with 95% confidence intervals (CIs) for parental migraine and parental bipolar disorder (BD) in BD by age of onset of the disorder and sex.

	No parental migraine, No parental BD	Yes parental migraine, No parental BD	No parental migraine, Yes parental BD	Yes parental migraine, Yes parental BD
ALL SUBJECTS				
Case n (%)	1615 (86.78)	73 (3.92)	167 (8.97)	6 (0.32)
Control n (%)	3463 (95.06)	119 (3.27)	58 (1.59)	3 (0.08)
ORs (95% CIs)	ref. ¹	1.30 (0.96–1.75)	6.05 (4.44–8.25)	3.82 (0.95–15.34)
P-values		0.091	< 0.0001	0.058
SUBJECTS, AGE < 18 YRS ²				
Case n (%)	461 (87.64)	12 (2.28)	51 (9.70)	2 (0.38)
Control (%)	981 (95.43)	33 (3.21)	13 (1.26)	1 (0.10)
ORs (95% CIs)	ref.	0.74 (0.38–1.44)	8.14 (4.34–15.29)	4.00 (0.36–44.11)
P-values		0.375	< 0.0001	0.258
SUBJECTS, AGE ≥ 18 YRS ³				
Case n (%)	1154 (86.44)	61 (4.57)	116 (8.69)	4 (0.30)
Control n (%)	2482 (94.91)	86 (3.29)	45 (1.72)	2 (0.08)
ORs (95% CIs)	ref.	1.52 (1.08–2.14)	5.46 (3.82–7.81)	3.83 (0.70–20.96)
P-values		0.016	< 0.0001	0.122
FEMALES				
Case n (%)	1114 (87.44)	49 (3.85)	107 (8.40)	4 (0.31)
Control n (%)	2372 (95.15)	80 (3.21)	39 (1.56)	2 (0.08)
ORs (95% CIs)	ref.	1.29 (0.89–1.86)	5.70 (3.90–8.32)	3.73 (0.68–20.50)
P-values		0.178	< 0.0001	0.129
MALES				
Case n (%)	501 (85.35)	24 (4.09)	60 (10.22)	2 (0.34)
Control n (%)	1091 (94.87)	39 (3.39)	19 (1.65)	1 (0.09)
ORs (95% CIs)	ref.	1.31 (0.78–2.22)	6.80 (3.96–11.67)	4.00 (0.36–44.11)
P-values		0.307	< 0.0001	0.258

¹ ref. = reference category;

² cases diagnosed with BD at age < 18 years;

³ cases diagnosed with BD at age ≥ 18 years

Table 2

Frequencies, percentages and odds ratios (ORs) with 95% confidence intervals (CIs) for comorbid migraine in bipolar disorder (BD) by age of onset of the disorder and sex.

	Case n (%)	Control n (%)	Unadjusted ORs (95% CIs)	Adjusted ORs ¹ (95% CIs)	Adjusted ORs ² (95% CIs)	Adjusted ORs ³ (95% CIs)
ALL SUBJECTS						
No	1776 (95.43)	3573 (98.08)				
Yes	85 (4.57)	70 (1.92)	2.47 (1.79–3.41) ***	2.46 (1.77–3.43) ***	2.46 (1.78–3.40) ***	2.46 (1.76–3.42) ***
SUBJECTS, AGE < 18 YEARS ⁷						
No	498 (94.68)	1007 (97.96)				
Yes	28 (5.32)	21 (2.04)	2.78 (1.54–4.99) **	2.57 (1.40–4.71) ⁶	2.78 (1.54–4.99) **	2.57 (1.40–4.70) ⁶
SUBJECTS, AGE 18 YEARS ⁸						
No	1278 (95.73)	2566 (98.13)				
Yes	57 (4.27)	49 (1.87)	2.34 (1.59–3.45) ***	2.41 (1.62–3.59) ***	2.33 (1.58–3.43) ***	2.39 (1.61–3.56) ***
FEMALES						
No	1201 (94.27)	2431 (97.51)				
Yes	73 (5.73)	62 (2.49)	2.41 (1.70–3.41) ***	2.42 (1.69–3.46) ***	2.40 (1.70–3.40) ***	2.41 (1.69–3.45) ***
MALES						
No	575 (97.96)	1142 (99.30)				
Yes	12 (2.04)	8 (0.70)	2.91 (1.19–7.13) ⁵	2.72 (1.10–6.73) ⁴	2.89 (1.18–7.09) ⁵	2.70 (1.09–6.69) ⁴

¹ adjusted for parental BD;

² adjusted for parental migraine;

³ adjusted for both parental BD and parental migraine;

⁴ p=0.03;

⁵ p=0.02;

⁶ p=0.002;

*** p<0.001;

*** p<0.0001;

⁷ cases diagnosed with BD at age < 18 years;
⁸ cases diagnosed with BD at age 18 years.

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