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Prevalences of autoimmune diseases in schizophrenia, bipolar I and II disorder, and controls

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ABSTRACT

Previous studies on the relationship between autoimmune diseases, schizophrenia, and bipolar disorder are mainly based on hospital discharge registers with insufficient coverage of outpatient data. Furthermore, data is scant on the prevalence of autoimmune diseases in bipolar subgroups. Here we estimate the self-reported prevalences of autoimmune diseases in schizophrenia, bipolar disorder type I and II, and controls. Lifetime prevalence of autoimmune diseases was assessed through a structured interview in a sample of 9076 patients (schizophrenia $N = 5278$, bipolar disorder type I $N = 1952$, type II $N = 1846$) and 6485 controls. Comparative analyses were performed using logistic regressions. The prevalence of diabetes type 1 did not differ between groups. Hyperthyroidism, hypothyroidism regardless of lithium effects, rheumatoid arthritis, and polymyalgia rheumatica were most common in bipolar disorder. Systemic lupus erythematosus was less common in bipolar disorder than in the other groups. The rate of autoimmune diseases did not differ significantly between bipolar subgroups. We conclude that prevalences of autoimmune diseases show clear differences between schizophrenia and bipolar disorder, but not between the bipolar subgroups.

1. Introduction

An increasing body of evidence has linked immune dysregulation to the pathogenesis of neuropsychiatric disorders (Kayser and Dalmau, 2011). Bergink and coworkers suggested that autoimmune diseases and psychoses (schizophrenia and bipolar disorders) share features such as familial occurrence, progression from subclinical to clinical forms with cyclic exacerbations/remissions, and increased incidence in the postpartum period (Bergink et al., 2014). Studies of inflammatory biomarkers in schizophrenia and bipolar disorder have found increased levels of autoantibodies, cytokines and acute-phase proteins (Isgren et al., 2015; Miller et al., 2011; Modabbernia et al., 2013), markers of endothelial cell and glial activation (Jakobsson et al., 2015), glutamate dysregulation (Pålsson et al., 2015; Sasayama et al., 2013), higher oxidative stress and blood-brain barrier dysfunction (Najjar et al., 2013; Zetterberg et al., 2014), which imply an activation of either the adaptive or the innate immune system. In bipolar disorder, a pro-inflammatory state has been observed in both symptomatic and euthymic phases, suggesting a mood independent activation of immune signaling (Brietzke et al., 2009). Interestingly, recent genome-wide association studies of schizophrenia indicate an association with immune genes within the major histocompatibility complex (MHC) (Corvin and Morris, 2014; Sperner-Unterweger and Fuchs, 2015). Moreover, schizophrenia polygenic risk scores predict case status of several autoimmune diseases even if the MHC region is excluded (Stringer et al., 2014). Although there is less support for MHC involvement in bipolar disorder, schizophrenia/bipolar disorder cross-disorder risk variants also appear to aggregate in immune signaling pathways (Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011).

Epidemiological studies also lend support to the link between psychiatric disorders on the one hand, and autoimmunity, inflammation, and infections that might trigger autoimmune diseases on the other (Arias et al., 2012; Benros et al., 2013). Danish population-based studies reported a 29–45% higher risk of schizophrenia, and a 20–70% raised risk of bipolar disorder, in individuals with own or family history of autoimmune diseases (Eaton et al., 2010, 2006). Likewise, the risk of

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subsequent autoimmune diseases was increased by 53% in persons with schizophrenia and by 71% in persons with bipolar disorder, with the exception of rheumatoid arthritis (RA) for which the risk was decreased (Benros et al., 2014a, 2014b; Eaton et al., 2010). The positive association between schizophrenia and autoimmune diseases found in Denmark was replicated in a national sample from Taiwan (Chen et al., 2012), and the negative association between schizophrenia and RA was replicated in a recent Swedish population-based study (Sellgren et al., 2014). With respect to multiple sclerosis (MS), we recently found a strong positive association with bipolar disorder and depression, but a negative association with schizophrenia (Johansson et al., 2014).

However, an important limitation with previous national register studies is that they are mainly based on hospital discharge records. This risk introducing ascertainment bias, where patients with severe psychiatric disorders are more often hospitalized and thus more likely to be diagnosed with any other disorder including somatic diseases. Moreover, most national registries use the International Classifications of Diseases (ICD), which in contrast to the DSM-system do not clearly distinguish between two major subtypes of bipolar disorders: type I and type II. It is therefore undecided whether autoimmune diseases are more common in bipolar disorder type I than in type II. Therefore, studies using alternative strategies to collect data are needed to complement the findings of register studies.

The aim of the present study was to compare the prevalence of autoimmune diseases in schizophrenia, bipolar disorder type I and II, and controls. In order to capture autoimmune diseases that only warranted outpatient care and thus would escape a hospital register survey, we conducted a structured interview of 9076 patients (schizophrenia $N = 5278$, bipolar disorder type I $N = 1952$, bipolar disorder type II $N = 1846$) and 6485 controls.

2. Methods

2.1. Subjects

Data on persons with schizophrenia and controls was derived from the *BROAD-study*, a large Swedish, population-based, case-control study aimed to investigate the genetic architecture of schizophrenia. Subject ascertainment has been described elsewhere (Ripke et al., 2013). Briefly, the Swedish Hospital Discharge Register, which captures all public and private inpatient hospitalizations, was used to identify cases with schizophrenia (Dalman et al., 2002; Kristjansson et al., 1987). Case inclusion criteria were: ≥ 2 hospitalizations with a discharge diagnosis of schizophrenia, both parents born in Scandinavia, and age ≥ 18 years. Exclusion criterion was a hospital Discharge Register diagnosis of any medical or psychiatric disorder mitigating a confident diagnosis of schizophrenia. Controls were randomly selected from Swedish population registers with the following inclusion criteria: never hospitalized for schizophrenia or bipolar disorder, both parents born in Scandinavia, and age ≥18 years. The participation rates for cases were 53.3% and for controls 58.3%, which are similar to reported participation rates in epidemiology (Hartge, 2006; Morton et al., 2006).

Bipolar disorder study persons were ascertained through the *Swedish Bipolar Collection (SWEBIC)-study*, a genetic study on bipolar disorder. Cases were identified through the Swedish Quality Register for bipolar disorder (BipoläR) (Karanti et al., 2015), which contains individualized data on diagnoses according to the DSM-IV-TR (American Psychiatric Association, 2000), medical intervention, and outcomes. It also captures basic epidemiological features as well as longitudinal data on the natural history and clinical course of the disease.

2.2. Data on autoimmune diseases

In the *BROAD-study*, trained research nurses conducted a structured interview face-to-face with schizophrenia cases, and over telephone with control persons. In the *SWEBIC-study,* trained research nurses conducted a structured interview over telephone for cases with bipolar disorder. Along with socio-demographic and clinical variables, autoimmune comorbidities were assessed by asking all participants about the lifetime occurrence of autoimmune diseases, diagnosed either by a specialist or a general practitioner. The following autoimmune diseases were covered in the entire sample: diabetes type 1, hyperthyroidism, hypothyroidism, RA, polymyalgia rheumatica (PMR), and systemic lupus erythematosus (SLE). In the bipolar disorder sample, additional data on multiple sclerosis (MS), and myasthenia gravis (MG) were collected and thus included in the comparison between bipolar I and II patients.

Lithium is the mainstay of treatment for bipolar disorder. Its potential to induce hypothyroidism is well-established (Kraszewska et al., 2015), but its effect on thyroid autoimmunity *per se* remains controversial (Bocchetta and Loviselli, 2006). Lithium may increase the propensity to thyroid autoimmunity in susceptible subjects (Kibirige et al., 2013), although some studies failed to replicate such an association (Baethge et al., 2005; Kupka et al., 2002; Rapaport et al., 1994). To account for potential lithium effects in this study, we asked participants if their hypothyroidism debuted before or after lithium treatment. An additional comparison was performed after excluding cases of hypothyroidism developed after starting lithium treatment.

All procedures were approved by the Regional Ethical Review Board in Stockholm, Sweden, and all participants provided written informed consent.

2.3. Statistical analyses

Comparisons between diagnostic groups (schizophrenia, bipolar disorder, and controls): Socio-demographic variables were compared between the three diagnostic groups using one-way ANOVA for continuous variables and multinomial logistic regressions for categorical variables. To assess differences in the prevalence of autoimmune diseases, group comparisons were performed using multinomial logistic regressions with diagnostic group as the outcome variable and presence of each autoimmune disease as cofactor. We used the Bonferroni method to correct for multiple testing. Significance was set at a Bonferroni's corrected level of $p < 0.05$.

Comparison between bipolar diagnostic subgroups type I and II: Comparative analyses of socio-demographic variables between persons with bipolar disorder type I and II were conducted by with Student's *t*-tests for continuous variables, and with binary logistic regressions for categorical variables. Binary logistic regressions were performed to evaluate potential differences between the two subsamples in terms of each autoimmune disease, again considering diagnostic subgroup as the outcome variable and autoimmune diseases as cofactor. We applied the Bonferroni correction for multiple testing and set the significance threshold at $p < 0.05$.

All analyses were performed using the Statistical Procedures for the Social Sciences (SPSS) version 22.0 for Windows. Data for each logistic regression are presented as odds ratios (OR), 95% confidence intervals (95% CI), and *p*-values prior to Bonferroni correction. Data were adjusted for age, sex, and education.

3. Results

3.1. Socio-demographic features

Table 1 displays socio-demographic data. The whole sample comprised 15,561 subjects, whereof 5278 had schizophrenia (33.9%), 3798 had bipolar disorder (24.4%), and 6485 were controls (41.7%). Of the bipolar sample, 1952 had bipolar disorder type I (51.4%) and 1846 had bipolar disorder type II (48.6%). Age, sex, and level of education differed between the diagnostic groups and were included as cofactors into the logistic models.