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Comorbid substance use disorders in schizophrenia: A latent class approach

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ABSTRACT

Schizophrenia is a complex psychiatric disorder with a characteristic disease course and heterogeneous etiology. While substance use disorders and a family history of psychosis have individually been identified as risk factors for schizophrenia, it is less well understood if and how these factors are related. To address this deficiency, we examined the relationship between substance use disorders and family history of psychosis in a sample of 1219 unrelated patients with schizophrenia. The lifetime rate of substance use disorders in this sample was 50%, and 30% had a family history of psychosis. Latent class mixture modeling identified three distinct patient subgroups: (1) individuals with low probability of substance use disorders; (2) patients with drug and alcohol abuse, but no symptoms of dependence; and (3) patients with substance dependence. Substance use was related to being male, to a more severe disease course, and more acute symptoms at assessment, but not to an earlier age of onset of schizophrenia or a specific pattern of positive and negative symptoms. Furthermore, substance use in schizophrenia was not related to a family history of psychosis. The results suggest that substance use in schizophrenia is an independent risk factor for disease severity and onset.

1. Introduction

Schizophrenia is a severe, complex psychiatric disorder characterized by lack of feeling or emotion, lack of initiative, and alterations in thoughts, perceptions, and behavior. Delusions and hallucinations, as well as misinterpretation of reality, are present in many patients as well (American Psychiatric Association, 2013). The prevalence of schizophrenia is about 0.5% worldwide (Saha et al., 2005) and the age of onset ranges from adolescence to adulthood, but the cause of the disorder remains unknown (National Institute of Mental Health, 2014). About a third of patients have a family history of psychosis, and twin studies have supported the hypothesis that inherited genetic risk factors could lead to the manifestation of the disorder (Owen et al., 2010; Sullivan et al., 2003). However, the search for causal genetic mutations has been challenging (Claes et al., 2012). In addition, de novo genetic mutations (Xu et al., 2011), prenatal adverse events (Brown, 2011; Brown and Patterson, 2011; Rothman and Greenland, 1998), and severe use of alcohol and illegal substances have been discussed as other risk factors (Barondes, 1999; Connell, 1958; Griffiths et al., 1972; Horowitz, 1969; Malone et al., 2010; McLaren et al., 2010; Minozzi et al., 2010; Moore et al., 2007; Roncero et al., 2014; Vollenweider et al., 1998).

Substance use disorders are defined as conditions in which either abuse of or dependence on substances, such as alcohol, cocaine, opioids, phencyclidine, amphetamine, cannabis or nicotine, among others, has had negative effects on the patient's family and social life, work, or school, or has resulted in financial problems. According to DSM-IV criteria, substance use disorders have been differentiated into disorders of abuse or dependence (American Psychiatric Association, 2000). In substance abuse, the consumption of substances has led to impairment or distress, but criteria of dependence have not been met. Substance dependence is characterized by tolerance and symptoms of withdrawal. It is often implied that abuse is a less severe form of substance use disorder compared to dependence, and this is reflected in the new DSM-V classifications (American Psychiatric Publishing, 2014). Genetic risk factors appear to contribute to the manifestation of substance use disorders. In several studies, a family history of substance use was an important predictor of disease onset and disease severity in substance abusers without comorbid psychiatric diagnoses (Bierut et al., 1998; Boyd et al., 1999; Coviello et al., 2004; Kendler et al., 2008; Merikangas et al., 1998).

The relationship between substance use disorders and schizophrenia has been extensively explored in multiple population-based studies (Kendler et al., 1996; Kessler et al., 1994; Regier et al., 1990).

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So far, convincing evidence has been found for a causal, dose-dependent relationship between substance use disorders and the onset of schizophrenia, if the onset of substance use disorders preceded the onset of schizophrenia (Andreasson et al., 1987; Miller et al., 2001; Tien and Anthony, 1990; van Os et al., 2002; Zammit et al., 2002). On the other hand, significant predictors of comorbid substance use disorders in patients with schizophrenia were male gender, low educational attainment, previous violent offending, and a family history of substance use disorders (Cantor-Graae et al., 2001; Dixon et al., 1991; Westermeyer, 2006). Patients with schizophrenia and comorbid substance use disorders were less likely to adhere to treatment and more likely to have adverse disease outcomes (McLean et al., 2012; Murthy and Chand, 2012). But even during the first episode of schizophrenia, substance users had more severe psychotic symptoms and an earlier age of onset compared to non-users (Mauri et al., 2006; Picci et al., 2013; Schimmelmann et al., 2012). In patients with a dual diagnosis, high rates of substance use disorders were found in first and second-degree relatives of the patients, suggesting that genetic risk factors for substance use disorders and an adverse family environment could have contributed to the onset and severity of substance use disorders in patients with a dual diagnosis (Comtois et al., 2005; Wilson et al., 2013). Even though the risk for comorbid substance use disorders in patients with schizophrenia is well recognized, not enough effort has been made to study the relationship between family history of psychosis and substance use disorders in patients with schizophrenia. Hence, we have focused on the relationship between familiarity of schizophrenia and substance use disorders in a large sample of patients ascertained for genetic studies.

2. Methods

2.1. Sample

The sample consisted of 1219 unrelated individuals of European descent and was provided by the Foundation for the National Institutes of Health Genetics Association Information Network (phs000021.v3.p2; GAIN Collaborative Research Group et al., 2007). All individuals were 18 years or older. The methods for recruitment and ascertainment have been described in detail elsewhere (Suarez et al., 2006) and hence, only a brief summary will be given here. All individuals had been interviewed and assessed with the Diagnostic Interview for Genetics Studies (DIGS) by trained health care professionals (NIMH Center for Collaborative Genomics Research and Mental Disorders, 2014). The DIGS is an extensively validated, structured clinical instrument developed by principal investigators of the National Institute of Mental Health (NIMH) for the assessment and differential diagnosis of major mood and psychotic disorders (Nurnberger et al., 1994). The instrument consists of 27 subscales for the assessment of major depressive disorder (according to DSM-IV), mania/hypomania, dysthymia and hyperthymic personality, psychosis, alcohol abuse and dependence, drug abuse and dependence, comorbidity assessment, suicidal behavior, anxiety disorders, eating disorders, and antisocial personality disorder. In addition, the instrument also contains the Modified Structured Interview for Schizotypy (MSIS), a modified Mini-Mental status examination; the Global Assessment Scale (GAS); the Scale for the Assessment of Negative Symptoms (SANS)/Scale for the Assessment of Positive Symptoms (SAPS); SIS ratings; and the OPCRIT. In addition, information on demographics, medical history, family history, somatization, the longitudinal disease course of psychiatric disturbances, medical record information, and an assessment of the reliability of the obtained information rated by the interviewer were also collected. Information gathered throughout the interview was rated for reliability, and, finally, non-hierarchical best-estimate consensus diagnoses (Leckman et al., 1982) were reached by at least three independent raters according to DSM-IV criteria (DSM-IV; American Psychiatric Association, 2000).

2.2. Variables included in the model

We included the following DSM-IV-criteria-based categorical comorbid diagnoses as indicators in the Latent Class Analysis (LCA): (1) alcohol dependence (ALCD), (2) substance dependence other than cannabis (SUBD), (3) cannabis abuse (including dependence) (CANNABIS), (4) alcohol abuse (ALCA), and (5) substance abuse other than cannabis (SUBA). In addition, we included the diagnosis of major depressive disorder (DEP) in our model because previous studies have indicated a strong correlation between symptoms of depression and comorbid substance use disorders in schizophrenia (Meesters et al., 2014). First, we conducted the LCA without covariates in the model in order to understand the substantive interpretation of the latent classes. Then, we included additional auxiliary variables as covariates, including gender (coded as one for male and two for female), family history of psychosis (coded as zero if absent and one if present), and the chronologic order of onset of schizophrenia and substance use disorders (coded as zero and one), indicating whether or not substance use disorders had been diagnosed before the onset of schizophrenia. Age of onset of schizophrenia was also included as a continuous variable. The total number of acute symptoms prior to the interview was a categorical variable, ranging from 1 to 7. The variable “symptom pattern” rated the predominance of positive or negative symptoms over the entire course of the disease, but at least over the duration of 1 year. This variable had five categories: (1) continuously positive, (2) predominantly negative, (3) predominantly positive converting to predominantly negative, (4) negative converting to positive, and (5) continuous mixture of positive and negative symptoms. The variable “pattern of severity” evaluated the degree of impairment caused by the disorder over the disease course adjusted for the disease duration. The variable had five categories: (1) episodic shift, (2) mild deterioration, (3) moderate deterioration, (4) severe deterioration, and (5) relatively stable. The variable “classification of longitudinal disease course” measured the longitudinal disease course and required that at least 1 year had elapsed since the initial onset of active-phase symptoms. The classification categories were (1) episodic with inter-episode residual symptoms, (2) episodic with no inter-episode residual symptoms, (3) continuous, (4) single episode in partial remission, (5) single episode in full remission, and (6) other or unspecified pattern. For individuals with less than 1 year of retrospective information, these variables were coded as missing.

2.3. Latent class mixture modeling

The LCA was performed in the statistical software program Mplus, Version 5 (Muthén and Muthén, 1998–2014) as described previously (Kerner et al., 2011). The estimation maximization (EM) algorithm was used to estimate the latent class membership for each individual based on the probability of endorsing a profile of variables (Muthén and Shedden, 1999). To avoid local maxima in the loglikelihood, we used 200 random sets of starting values. We compared models with an increasing number of classes until the Bayesian Information Criterion (BIC) reached a minimum. The BIC was calculated for the different class solutions, where the model with the smallest BIC was selected as the best (Nylund et al., 2007). We also compared the entropy of the latent class solutions and other fit indices, including the Akaike Information Criterion (AIC; Akaike, 1987), the BIC and sample size adjusted BIC (Schwarz, 1978), the Lo-Mendel-Rubin (LMR) test (Lo et al., 2001), and the Bootstrapped Likelihood Ratio Test (BLRT; McLachlan, 1987).