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Research Paper

Is an Early Age at Illness Onset in Schizophrenia Associated With Increased Genetic Susceptibility? Analysis of Data From the Nationwide Danish Twin Register

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ABSTRACT

Background: Early age at illness onset has been viewed as an important liability marker for schizophrenia, which may be associated with an increased genetic vulnerability. A twin approach can be valuable, because it allows for the investigation of specific illness markers in individuals with a shared genetic background.
Methods: We linked nationwide registers to identify a cohort of twin pairs born in Denmark from 1951 to 2000 ($N = 31{,}524$ pairs), where one or both twins had a diagnosis in the schizophrenia spectrum. We defined two groups consisting of; $N = 788$ twin pairs (affected with schizophrenia spectrum) and a subsample of $N = 448$ (affected with schizophrenia). Survival analysis was applied to investigate the effect of age at illness onset.
Findings: We found that early age at illness onset compared to later onset in the first diagnosed twin can be considered a major risk factor for developing schizophrenia in the second twin. Additionally, we found that the stronger genetic component in MZ twins compared to DZ twins is manifested in the proximity of assigned diagnosis within pairs.
Discussion: Early onset schizophrenia could be linked to a more severe genetic predisposition, indicating that age might be perceived as a clinical marker for genetic vulnerability for the illness.

1. Introduction

Age at onset has been proposed as the most important characteristic of schizophrenia that provides knowledge about the origin of the disorder (DeLisi, 1992). Studies have reported early age at illness onset to be characterized by a worse course of illness, with more positive family history of psychosis and an increased risk of illness in siblings (Rabinowitz et al., 2006; Byrne, 2002; Hosmer et al., 2008; Husted et al., 2006). Therefore it can be viewed as a distinct phenotypic liability marker for schizophrenia because it may represent a specific subtype of the disorder (Goldberg et al., 2011). The risk of developing schizophrenia has consistently been reported higher in males (Aleman et al., 2003), while the peak in age at onset is equal between sexes at around age 22, with a difference in the mean age at onset being later for females (Pedersen et al., 2014; van der Werf et al., 2014; Thorup et al., 2007). This underlines the importance of addressing possible sex differences when studying illness vulnerability. In this regard, a meta-analysis found that the presence of a family history of psychosis influenced an earlier age at onset in both sexes compared to families without a history of psychosis in which only the male sex was associated with early illness onset (Esterberg et al., 2010). A recent study focused on illness course and did not find an association between gender and age at onset on the course of illness when adjusting for symptom severity at illness presentation, indicating that these features offer little prognostic value (Drake et al., 2016). This suggests that early age at illness onset might be a relevant clinical marker for increased genetic vulnerability in which sex may be a modifying factor, rather than a marker for symptom severity and illness course.

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Exposure to specific environmental factors increases the risk to develop schizophrenia in vulnerable individuals (van Os et al., 2010), thus environmental and genetic factors may both influence age at illness onset in schizophrenia. Accumulated exposures such as obstetric complications, trauma, urbanicity and cannabis use seem to have a major impact on lowering age at onset in male patients (Stepniak et al., 2014). A Swedish register-based study combined the study of environmental and genetic risk, by measuring sibling risk of schizophrenia both in affected and unaffected families and described an increased risk in siblings in affected families compared to unaffected families. The risk was modified by factors like higher age at onset in probands, advanced paternal age and immigrant status of parents (Svensson et al., 2012). These findings support a role for environmental risk factors in age at schizophrenia onset. Specific genetic polymorphisms are also associated with early age of schizophrenia onset, although only present in male patients (Hänninen et al., 2007; Yuan et al., 2013). A GWAS study could not draw significant conclusions regarding genetic association with age at onset, severity of disorder or disease associations by family history of schizophrenia and sex (Bergen et al., 2014); however, a more recent study identified a correlation between specific genetic variations and a lower age at schizophrenia onset (Chow et al., 2016). In conclusion, there is a lack of evidence for a simple genetic association between the timing of illness onset and sex or family history, or to what extent genetic risk affects age of illness onset in both sexes.

In general, twin studies allow for the study of phenotypic, endophenotypic and biological discordance in individuals with a shared genetic background, which makes it a valuable tool in studying complex human traits and disorders such as schizophrenia. The classic twin study compares phenotypic resemblances of monozygotic (MZ) and dizygotic (DZ) twins to identify genetic variation in disease susceptibility (Boomsma et al., 2002). A twin design can examine "age at illness onset" as a specific liability marker of schizophrenia, in relation to the genetic impact on disease liability, and furthermore investigate possible sex differences.

This study aims to examine age at illness onset and risk of schizophrenia and schizophrenia spectrum disorders in a national twin cohort identified in the Danish Twin Register using information from the Danish Psychiatric Central Research Register. In the study we will focus on two diagnostic categories; a narrow definition of schizophrenia as outlined in ICD-8 and ICD-10, and a broader phenotypic outcome representing the schizophrenia spectrum in ICD-8 and ICD-10. Specifically, we will investigate if an early onset of schizophrenia and schizophrenia spectrum in the first diagnosed twin (<22 years of age) increases the risk of illness in the second twin. In addition, we examine the importance of genetic effects in the timing of illness onset in twin pairs by testing whether the higher genetic similarity in MZ twins compared to DZ twins is associated with closer proximity of assignment of diagnoses in the twin pairs.

2. Methods

The study is approved by the Danish Data Protection Agency and the Danish National Board of Health.

2.1. National Registers

The present sample is based on linkage of two nationwide registers, the Danish Twin Register and the Danish Psychiatric Research Register, thereby identifying a sample of twin pairs born 1951–2000. At birth all individuals are registered with a unique identification number in the Danish Central Civil Registration System, and using this register it is possible to identify all individuals across registers (Pedersen et al., 2006). The Danish Twin Register includes twin pairs born in Denmark from 1870 onwards, it was initiated in 1954 and the ascertainment of liveborn twin pairs is complete from 1968 (Skytthe et al., 2011). Zygosity information is not available from all twins in the register (Skytthe et al., 2011). Twins with unknown zygosity (UZ) are removed from the sample, since our aim is to investigate the genetic predisposition in relation to early illness onset, and in UZ twins the degree of shared genetic material is unknown. The Danish Psychiatric Central Case Register contains information on all admissions to a psychiatric facility in Denmark; it was initiated in 1938, computerized in 1969 and from 1995 outpatient contacts were included in the register (Mors et al., 2011).

2.2. Disease Classifications

From 1969 to 1993 the ICD-8 classification system was used while the ICD-10 was used from 1994 onwards (World Health Organization, 1967, 1992). For this study schizophrenia was defined as a main or secondary lifetime diagnosis in the following ICD versions (ICD-10: F20.xx and ICD-8: 295 (excluding 295.79, schizoaffective disorder)) and schizophrenia spectrum was defined as a main or secondary lifetime diagnosis in (ICD-10: F2x.xx and ICD-8: 295, 297, 29829, 29839, 29889, 29899, 29905, 29909, 30109, 30129). We defined a lifetime diagnosis as a diagnosis received at any time during the planned observation period, in this study, from birth until June 1st, 2011. Specifically this is defined as the first date of diagnosis of schizophrenia, thus ignoring a possible diagnosis in the schizophrenia spectrum before this date. For schizophrenia spectrum it is the first date of diagnosis.

2.3. Statistical Analysis

Survival analysis (i.e. Cox proportional hazard modeling) was applied to investigate the effect of age at onset (below/above age 22) of the first diagnosed twin on illness outcome in the second twin (Hosmer et al., 2008). The cut-off point at age 22 is based on the peak in incidence rates at this age (Thorup et al., 2007; van der Werf et al., 2014) and a study that validated two distinct illness subtypes with an onset before and after age 22 when observing the distribution of age at onset in a large clinical sample of patients with schizophrenia (Panariello et al., 2010). To examine a possible association of increased risk of illness with decreasing age intervals we further divided the age at onset in the first diagnosed twin into 4 categories; <18, [18–22), [22 − 30) and [30, onwards). Survival analysis was also applied investigating the age intervals. Each co-twin was followed from birth until date of schizophrenia, censoring or death. By estimating zygosity-specific Kaplan-Meier curves for the affected twin pairs we aim to investigate if the proximity between age at onset in twin pairs mirrors the higher genetic similarity among MZ pairs compared to DZ pairs. Data analyses were carried out using Stata version 13. The models were all adjusted for zygosity and sex to minimize bias.

2.4. Role of the Funding Source

The study sponsor had no role in study design, data analysis, data interpretation or writing of the paper.

3. Results

All individuals were followed from the computerization of the Danish Psychiatric Central Research Register in 1969 until June 1st, 2011. The present dataset contains MZ and DZ twin pairs born in Denmark from 1951 to 2000, $N = 31{,}524$ pairs. Of these $N = 788$ pairs (842 individuals) were affected with schizophrenia spectrum disorder and a subsample of $N = 448$ pairs (472 individuals) were affected with schizophrenia. The sample characteristics are described in Table 1. As mentioned in method section all UZ twin pairs have been removed in the final sample of $N = 31{,}524$ twin pairs. This includes $N = 138$ UZ pairs (157 individuals) affected with schizophrenia spectrum and a subsample of $N = 76$ UZ pairs (88 individuals) affected with schizophrenia.

Fig. 1 displays the distribution of age at onset among all twins affected with schizophrenia and schizophrenia spectrum. We observed that

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