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Age at onset mixture analysis and systematic comparison in schizophrenia spectrum disorders: Is the onset heterogeneity dependent on heterogeneous diagnosis?

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ABSTRACT

A major obstacle to the identification of the neurobiological correlates of schizophrenia is the substantial diagnostic heterogeneity of this disorder. Dividing schizophrenia into "early" and "late" subtypes may reduce heterogeneity and facilitate identification of biomarkers related to this disease. Our objective was to assess the presence of different sub-groups in schizophrenia by age at onset analysis. The participants in this study were 612 unrelated patients with schizophrenia. Admixture analysis was applied in order to identify a model of separate normal distributions of age at onset characterized by different means, variances and population proportions to evaluate the effect of winter birth and ethnicity on early onset schizophrenia. The best-fitting model suggested three subgroups with means and standard deviations of 17.11 ± 2.09, 21.96 ± 3.43 and 30.02 ± 7.1 years, comprising 34.6%, 42.6% and 22.8% of the sample respectively. We considered as predictors of early onset schizophrenia: male gender, winter birth, white ethnicity and positive family history for psychiatric disorders. Earlier onset was significantly associated with male gender. We also compared our age at onset distribution with those published in other studies and we found significant differences with several studies suggesting heterogeneity in age at onset that is likely influenced by diagnostic heterogeneity in applying the DSM-IV criteria. Overall, our study showed that a typical early onset schizophrenia patient is more likely to be a white male with cannabis abuse and positive family history of psychiatric disorders. The heterogeneity in reporting age at onset across different studies suggests the application of more stringent criteria in diagnosing schizophrenia.

1. Introduction

Among the numerous clinical features of schizophrenia spectrum disorders, age at onset (AAO) is widely recognized as a significant clinical and prognostic factor (Leung and Chue, 2000; Öngür et al., 2009).

Males with schizophrenia have consistently earlier onset, (Leung and Psych, 2000) and other factors such as winter birth (Davies et al., 2003; Torrey et al., 1997), alcohol/drug use (Hambrecht and Häfner, 1996; Dixon, 1999; Chambers et al., 2001), positive family history (Byrne et al., 2002; Mortensen et al., 1999) and ethnicity (Cantor-Graae and Selten, 2005) have also been associated with developing early onset schizophrenia.

Moreover, AAO has been proposed to be the single most important clue to understanding disease etiology (DeLisi, 1992; Tsuang, 2000). There is a growing body of literature demonstrating the clinical interest in early-onset schizophrenia (DeLisi, 1992; Leung and Chue, 2000; Aleman et al., 2003). However, the majority of age cut-off values for early and late onset are arbitrarily chosen and varied across studies (Schürhoff et al., 2004; Köhler et al., 2009; Panariello et al., 2010; De Luca et al., 2012; Vinokur et al., 2014). Therefore, it is expected that there will be significant differences when comparing the AAO distributions across different studies.

In this study, our aim was to obtain empirically derived subgroups of AAO using the admixture analysis. We investigated the effect of ethnicity and winter birth on the AAO in schizophrenia. Based on specific selection criteria, we also provide a review of the studies that have identified sub groups of AAO in schizophrenia. Furthermore, the cut-offs

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from the reviewed studies were applied to our sample in order to compare the distributions.

2. Methods

2.1. Study sample

A cross-sectional study of 612 unrelated patients was conducted. Patients were recruited for participation through the Centre for Addiction and Mental Health in Toronto as part of a study examining the genetics of schizophrenia. The study subjects were referred through the Schizophrenia Clinics at CAMH that assess patients with psychosis of age between 16 and 75. The patients were recruited by two Clinician-Scientists (JLK and VDL) from 1995 to 2012. To meet the criteria for inclusion patients needed to be diagnosed with Schizophrenia or Schizoaffective Disorder ascertained using the Structured Clinical Interview for DSM-IV (SCID-I/P) (First et al., 2002). Patients were not eligible for the study if they were not able to read/ understand English or had a history of major neurological disorders or head injury with significant loss of consciousness or developmental delay.

Written informed consents were obtained from all patients included in the study. The AAO was defined as the age when the subject first experienced psychotic symptoms. Participants were categorized into two ethnic groups: White Caucasian and non-White Caucasians. This study was approved by the Centre for Addiction and Mental Health ethical review committee. The age range of participants was from 17 to 71 years of age.

2.2. Demographic and clinical variables

The following variables were extracted from interviews and medical records: age, sex, date of birth, winter birth, AAO of schizophrenia/ schizoaffective disorder, place of birth, ethnicity, presence of suicide attempt lifetime, lifetime cannabis, alcohol and other substance abuse. Abuse or dependence for different street drugs (sedatives–hypnotics–anxiolytics, stimulants, opioids, hallucinogens, cocaine) was considered as a single factor.

Winter birth was deemed to be from December 20th to March 21st. The number of previous hospitalization was recorded and the median value of four was used to separate the subjects with high number of hospitalizations (≥ 4) and low number of hospitalizations (<4).

2.3. Mclust analysis

We used the admixture analysis to determine if our AAO data were derived from one or more normal distributions using the MCLUST software package in the R language (1999, 2003, Fraley and Raferty, 2006).

Admixture analysis uses the maximum likelihood to estimate the probability that the observed AAO would be found when assuming one or more normal distributions.

To determine the most likely number of normal distributions, we estimated the Schwarz's Bayesian information criterion (BIC) and the Akaike information criterion (AIC) for one to nine populations separately. We chose to select the best fitting using both BIC and AIC, on the other hand bootstrapped likelihood ratio procedures have also been used in admixture modeling (Chen and Chen, 2001; Di and Liang, 2011).

Once the number of normally distributed groups had been obtained, the means and standard deviations of the AAO distributions that are most likely to generate the data are provided and the probability that an individual originated from each group was obtained according to the formula:

$$p(G_i|x) = \frac{f(x|G_i)p(G_i)}{\sum_j f\left(x|G_j\right)p\left(G_j\right)}$$

where x represents the AAO of an individual, G is the AAO group and $f(x|G_j)$ is the normal probability density function with the parameters for group G_j (Hamshere et al., 2009). We allocated each individual into one of the groups such that the probability of membership was maximized. Then, the theoretical AAO function defined the AAO probability density across different ages and the level of uncertainty of group allocation for an individual was obtained by subtracting the maximal group membership probability from one. Each patient's probability of belonging to each AAO subgroup was calculated using the theoretical AAO function. Patients were then assigned to the distribution they had the highest probability of belonging to. The theoretical AAO function was used to calculate these probabilities and to locate cut-off points.

2.4. Finite mixture model analysis

We applied the finite mixture model analysis to our AAO distributions generated by MCLUST using the FMM package running under STATA 11.0 (StataCorp, 2009), to test the following predictors: ethnicity, winter birth, gender and positive family history of mental illness and cannabis use. We considered as predictors, the factors that can have a causal effect on the AAO since they are determined before the onset of schizophrenia.

The FMM package was also used to compare the groups generated by the MCLUST analysis with respect of the confounding effect of the length of illness, substance use, alcohol use (Deb, 2007).

The finite mixture model offers an intuitively feasible representation of heterogeneity in a finite, usually small, number of finite mixtures latent classes (Deb et al., 2011). The advantage of using the FMM package is the possibility to obtain a linear (parametric) coefficient for each normal distribution to overcome the problem of non-normality of the AAO data.

2.5. Review of previous studies investigating AAO in schizophrenia

When our best fitting model was chosen, our study sample AAO distribution was compared to that of other studies. In order to identify studies of potential relevance in the past ten years (2002–2012), we searched the PubMed database for keywords “schizophrenia” AND “age of onset” and limited the results to primary research and English only. In order to be considered relevant, the study must: 1) have definitive age/ages which separates study sample into subgroups; 2) have an overall sample size > 100; 3) reports the number of participants in each subgroup.

2.6. Comparison with other studies using the two sample Kolmogorov–Smirnov and χ^2 test

The largest absolute difference value (D) between the empirical cumulative distribution function of the present study with those obtained in previously published studies using the admixture analysis was used to determine whether the fitted function obtained in this study was consistent with those obtained in previously published studies. A significant P-value of the two sample Kolmogorov–Smirnov Test (KS) rejects the hypothesis that the two AAO distributions are equal. The KS test assumes that the two samples have continuous random variables (i.e., no individuals will have identical AAO). As the AAO data in our sample are

Table 1
Clinical and demographics (n = 612).

	Percentage in the total sample
Male gender	69.8%
White Caucasian ethnicity	69.2%
Winter birth	23.0%
Suicide attempt history	33.6%
Alcohol use lifetime[a]	31.2%
Drugs use lifetime[a]	39.4%
Marijuana use lifetime[a]	36.5%

[a] Abuse and dependence were considered as a unique risk factor.