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Premorbid adjustment and schizophrenia in individuals with 22q11.2 deletion syndrome

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ABSTRACT

The literature on idiopathic schizophrenia has consistently reported that poor premorbid functioning precedes onset of psychosis. Individuals with 22q11.2 deletion syndrome (22q11.2DS) are at heightened risk of developing schizophrenia. The present study examined the relationship between adult-onset schizophrenia and social and academic functioning across childhood and early adolescent development in 22q11.2DS.

Method: Premorbid adjustment in social and academic domains during childhood (ages 5–11 years) and early adolescence (ages 12–15 years) of 103 adults with 22q11.2DS was assessed using the Premorbid Adjustment Scale (PAS). Linear mixed-models were used to compare PAS scores between the 43 subjects who later developed schizophrenia and the 60 subjects who did not.

Results: Social functioning and academic functioning deteriorated from childhood to early adolescence among those who later developed schizophrenia compared to stable functioning, on average, in those who did not later develop a psychotic disorder. Those who developed schizophrenia had significantly higher PAS scores (indicating poorer functioning) in social ($\beta = 0.118$, 95% CI: 0.046–0.189) and academic ($\beta = 0.072$, 95% CI: 0.015–0.129) domains between childhood and early adolescence, independent of the presence of intellectual disability. The two groups had similar PAS scores during childhood.

Conclusion: Consistent with the literature on idiopathic schizophrenia, deterioration in social and academic functioning between childhood and early adolescence preceded onset of schizophrenia in this cohort of 22q11.2DS patients, regardless of functioning at baseline. These findings suggest that monitoring for changes in functioning, in addition to emergence of typical symptoms, may help to prevent delays in diagnosis and treatment of major psychotic illness in 22q11.2DS.

1. Introduction

Patients with 22q11.2 deletion syndrome (22q11.2DS) are at the highest known molecular genetic risk for schizophrenia (Costain and Bassett, 2012), with an estimated prevalence of psychotic illness of 20–25% among adults (Fung et al., 2010). 22q11.2DS is an acknowledged molecular subtype of schizophrenia with similar symptom profile and age at onset to idiopathic schizophrenia cases (Bassett et al., 2003). The associated hemizygous 22q11.2 deletions occur in an estimated 1 in 4000 births (Oskarsdottir et al., 2004), but affect about one in every 100–200 individuals with schizophrenia (Bassett et al., 2010). The phenotypes of 22q11.2DS are highly variable; classic congenital anomalies characteristic of 22q11.2DS include conotruncal cardiac malformations such as tetralogy of Fallot, velopharyngeal insufficiency, learning disabilities and subtle craniofacial features (Kobrynski and Sullivan, 2007; Bassett et al., 2011).

Birth cohort and prospective studies focused on familial high-risk individuals in the general population have reported that subtle social deficits and poor neurocognitive performance predate onset of psychosis (Hans et al., 2000; Welham et al., 2009). Premorbid adjustment, i.e. psychosocial and developmental functioning in the premorbid period, may also be measured retrospectively until the six months before the first admission to hospital or the onset of florid psychotic symptoms (Cannon-Spoor et al., 1982).

The present study investigated the relationship between premorbid adjustment and development of schizophrenia in individuals with a confirmed diagnosis of 22q11.2DS. We postulated that, consistent with the literature for idiopathic schizophrenia, individuals with 22q11.2DS

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who developed schizophrenia would have lower and/or declining premorbid adjustment scores in both social and academic domains over the course of childhood and early adolescence compared to those who did not develop a psychotic illness.

2. Methods

2.1. Subjects

All participants were part of a longitudinal study of adults (ages ≥17.5 years) with 22q11.2DS. Ascertainment and recruitment were as previously described (Bassett et al., 2005, 2007, 2008, 2009). In brief, participants were ascertained through active screening at the Toronto Congenital Cardiac Centre for Adults, Toronto, Canada or from clinical referrals from geneticists, pediatricians or psychiatrists. All participants were clinically diagnosed with 22q11.2DS, confirmed by fluorescence in situ hybridization using a probe from the commonly deleted region (TUPLE or N25) (Driscoll et al., 1993) or genome-wide microarray (Bassett et al., 2008).

Of the 133 eligible adult participants, 9 died before premorbid assessment could be completed and another 9 did not have a reliable informant for this assessment. To avoid the possibility of measuring symptoms of early-onset psychotic illness as premorbid functioning, participants with age at onset (AAO) of psychotic illness, defined as the age at which the patient first received formal treatment and/or was hospitalized for psychosis (Bassett et al., 2003), under age 16 years (n = 12) were excluded. The present study thus comprised 103 individuals (n = 50 (48.5%) male; mean age 33.6 ± 9.9 years (range = 18.0–58.4 years); n = 89 (86.4%) European descent; n = 45 (43.7%) ascertained through the adult congenital cardiac clinic, n = 35 (34.0%) through psychiatric sources and n = 23 (22.3%) through other sources).

2.2. Data collection

As previously described (Bassett et al., 2003; Chow et al., 2006), all individuals underwent extensive psychiatric, medical and neurocognitive assessment using direct assessments and review of lifetime medical records. In brief, lifetime psychiatric diagnoses were determined according to the Diagnostic and Statistical Manual of Mental Disorder Fourth Edition (DSM-IV) criteria using a modified Structured Clinical Interview for DSM (Bassett et al., 2003); individuals with schizophrenia or schizoaffective disorder were collectively termed 'schizophrenia' in this study. The Wechsler Adult Intelligence Scale-Third Edition (Wechsler, 1997) was used to measure full-scale IQ scores and classification of intellectual disability (ID) was based on DSM-IV criteria for mental retardation (Chow et al., 2006).

Premorbid adjustment was assessed with the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982; Cannon et al., 1997), which evaluates developmental achievements in childhood (ages 5–11), early adolescence (ages 12–15), late adolescence (ages 16–18) and adulthood (ages >18). Social and academic domains each comprised two items (sociability and peer relations; scholastic performance and school adaptation, respectively), rated using a 7-point anchored scale, with 0 indicating normal or good functioning and 6 indicating severe impairment. Domain-specific scores at each age period were calculated according to the usual scoring procedure, by dividing the raw scores by the maximum obtainable scores, such that they range from 0 to 1 (Cannon-Spoor et al., 1982). Only childhood and early adolescence scores were considered for analyses in order to eliminate the potential influence of psychotic illness symptoms in late adolescence and adulthood. The PAS was administered through a semi-structured interview based on retrospective report from the individuals who were most familiar with the participant's behavior at the specified age period (n = 66 mother only, n = 22 both parents, n = 7 father only and n = 8 another relative, e.g. older sibling, aunt/uncle). Respondents were blinded to the purpose of this study and the data were corroborated using information on social and academic functioning from available medical and academic records for all participants.

2.3. Statistical methods

Socio-demographic measures for the 43 individuals with schizophrenia and 60 non-psychotic participants were compared using the Mann–Whitney *U* test or student t-test for continuous variables and chi-square test for categorical variables.

Linear mixed-models were used to assess changes in premorbid social and academic premorbid adjustment over time between the two diagnostic groups. The models included an interaction term between schizophrenia and time period in order to examine the difference in change between groups over time. The covariance matrix was specified as unstructured to account for correlation between repeated measures. All models were adjusted for age at assessment and ID (Goldberg and Green, 2002) to account for potential confounding effects.

All statistical analyses were conducted using SAS® software (version 9.3, SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Sample characteristics

Of the 43 participants with schizophrenia (mean age at assessment 37.3 ± 10.5 years (range 19.0–58.4 years); n = 24 (55.8%) male; n = 35 (81.4%) of European descent; n = 25 (58.1%) with ID), mean AAO was 21.6 ± 4.2 years (range = 16.0–32.0 years). In the non-psychotic group (mean age at assessment 31.9 ± 8.6 years (range 18.0–56.4 years); n = 26 (43.3%) male; n = 54 (90.0%) of European descent; n = 23 (38.3%) with ID), eleven (18.3%) had generalized anxiety disorder, ten (16.7%) had major depressive disorder and one (1.7%) had non-psychotic bipolar disorder; the remaining 38 (63.3%) subjects did not meet DSM-IV criteria for major mood or psychotic disorders. While sex and ethnicity were similar between the two groups, the schizophrenia group was significantly older (z = 3.22, p = 0.001) and had a higher prevalence of ID (χ^2 = 3.95, p = 0.0469) and lower mean IQ (67.9 ± 7.3 vs. 72.84 ± 11.9, t = 2.39, p = 0.0187) than the non-psychotic group.

3.2. Premorbid functioning

The mean PAS scores for the two diagnostic groups are presented in Table 1. In childhood (ages 5–11 years), there were no significant differences between the two groups in social (β = 0.040, 95% CI: −0.061–0.141) or academic functioning (β = 0.021, 95% CI: −0.060–0.102) (Table 1). However, functioning between the two groups diverged significantly in early adolescence (ages 12–15 years). Those who later developed schizophrenia exhibited worse social (β = 0.168, 95% CI: 0.071–0.264) and academic (β = 0.095, 95% CI: 0.010–0.180) premorbid functioning compared to the non-psychotic group.

Results from linear mixed-models analyses are shown in Table 2. Relative to those who did not develop schizophrenia, individuals with schizophrenia showed significant deterioration in social and academic functioning between childhood and early adolescence, after adjusting for age and intellectual disability (Table 2). As expected, across the entire sample, individuals with ID had on average significantly worse academic performance than those without ID. Also, adults studied at an older age had slightly better social premorbid functioning compared to those studied at a younger age.

Developmental trajectories for social and academic functioning within each diagnostic group reflected the linear mixed-models results. In those with schizophrenia, scores deteriorated at a similar rate for these two PAS domains over time, as indicated by the mean changes in scores (Table 1). In contrast, there were only modest variations in social and academic functioning between childhood and early adolescence