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Autism Spectrum and Psychosis Risk in the 22q11.2 Deletion Syndrome. Findings from a Prospective Longitudinal Study

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Conflict of interest

All authors declare that there are no conflicts of interest in relation to the subject of this study.

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Abstract

Background—Individuals with 22q11.2 deletion syndrome (22q11DS) have a 25% risk for schizophrenia and related psychotic disorders. Some have hypothesized that Autism Spectrum Disorders (ASD) diagnosed in children with 22q11DS may actually represent the social-communicative defects often observed during the early developmental stages of schizophrenia.

Methods—We prospectively studied 89 children with 22q11DS to test this hypothesis. At baseline, the Autism Diagnostic Interview was used to assess ASD, evaluating both current and early childhood behaviors. At follow-up, the Schedule for Affective Disorders and Schizophrenia for School-age Children (K-SADS) was used to determine development of a psychotic disorder or psychotic symptoms.

Results—The average age (±SD) at first and last assessments was 14.3±1.9 and 19.0±3.0 years, respectively. Nineteen (21.3%) children developed a psychotic disorder. Contrary to our hypothesis, there was no significant difference in the proportion that developed a psychotic disorder, comparing those with (n=9, 17.3%) and those without ASD at baseline (n=10, 27%; OR = 0.500, 95% CI = 0.160 – 1.569, p = 0.235). Similar results were obtained using autistic symptom severity as quantitative predicting variable, psychotic symptoms as the outcome, and when correcting for age, gender and full scale IQ.

Conclusion—Results indicate that in children with 22q11DS, early childhood autistic features are not associated with an increased risk for subsequent development of psychotic disorders or symptoms, replicating previous retrospective findings in adults with 22q11DS. These results indicate that ASD and psychotic disorders can emerge independently, as pleiotropic phenotypes in the context of 22q11DS.

Keywords

Schizophrenia; comorbidity; 22q11DS; velocardiofacial syndrome; high risk; genetic

1. INTRODUCTION

Over the past two decades, the 22q11.2 deletion syndrome (22q11DS) has consistently emerged as the strongest single genetic risk factor for schizophrenia and related psychotic disorders (Karayiorgou et al., 2010). Individuals with this microdeletion have a 25-fold increased risk for developing a psychotic disorder (Bassett et al., 2005; Murphy et al., 1999; Schneider et al., 2014b; Shprintzen et al., 1992; Vorstman et al., 2006), and account for 0.5–1% patients with schizophrenia in the general population (Karayiorgou et al., 2010; McDonald-McGinn et al., 2015). 22q11DS offers an appealing model to examine the developmental trajectory of schizophrenia (Drew et al., 2011; Insel, 2010).

In children and adolescents with 22q11DS, a range of neurodevelopmental and psychiatric disorders are reported, including attention deficit hyperactivity disorder (ADHD), anxiety disorders and autism spectrum disorders (ASD) (Schneider et al., 2014a). Regarding the latter, several authors have proposed that the repetitive behaviors and social-communicative deficits observed in children with 22q11DS may be early prodromal symptoms of schizophrenia (Crespi and Badcock, 2008; Eliez, 2007; Karayiorgou et al., 2010; Vorstman

et al., 2006). However, in a retrospective study in adults with 22q11DS, no significant association between childhood ASD and later onset of schizophrenia was found (Vorstman et al., 2013). In the current study, we used a prospective longitudinal study design to investigate the hypothesis that among children with 22q11DS, those with a diagnosis and/or symptoms of ASD are more likely to subsequently develop a psychotic disorder than those without ASD.

2. METHODS

2.1. Participants and procedures

The participants were children with 22q11DS, confirmed by either fluorescence in situ hybridization (FISH) or multiplex ligase-dependent probe amplification (MLPA(Jalali et al., 2008)) using standard probes, who were referred to our specialized psychiatric 22q11DS clinic as part of standard clinical care(Bassett et al., 2011). The study protocol is part of a larger ongoing longitudinal behavioral and genetic study on 22q11DS patients that has been approved by the local research ethics board (Dutch Central Committee on Research Involving Human Subjects; C.C.M.O). Written informed consent was obtained from participants and their parents or guardians.

Our clinical follow-up program implies that approximately 3 to 4 years after the baseline measurement (T0) the child is invited for a follow-up visit, regardless of the presence or absence of any behavioral concerns. In the interim, parents can contact our center at any time in case of emerging concerns.

2.2. Psychiatric and cognitive assessments

All psychiatric and cognitive assessments were performed by the same multidisciplinary team. The baseline measurement included a semi-structured assessment of DSM-IV items, the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL (Kaufman et al., 1997)) mood disorder and psychosis sections, and the Autism Diagnostic Interview – Revised (ADI-R (Lord et al., 1994)) scored by certified interviewers. Demographic variables and psychotropic medication use were recorded. All instruments except the ADI-R were re-administered at follow-up.

ASD, including Autistic Disorder (n = 5, 5.6%) and Pervasive Developmental Disorder Not Otherwise Specified (n = 47, 52.8%) and psychotic disorders, including Schizophrenia (n = 4, 4.5%), Brief Psychotic Disorder (n = 2, 2.2%) and Psychotic Disorder Not Otherwise Specified (n = 13, 14.6%) were defined according to DSM-IV criteria and ascertained based on direct patient observation, interview of patient and caregivers, and collateral information from school or residence. ASD symptom severity was quantified by the raw ADI-R score, using the sum of the scores obtained on the 37 algorithm items(Bruining et al., 2010). The ADI-R, an instrument with established reliability in a population with mild to moderate intellectual disability (de Bildt et al., 2004), yields information on early childhood behaviors (age 4 – 5 years) as well as on current behaviors. Psychotic symptoms were recorded as present if the child obtained a score of 2 or higher on one or more items of the positive psychotic symptoms subscale of the K-SADS.

To assess intellectual level (IQ), we used the Dutch versions of the entire Wechsler scales(Wechsler, 1991): WISC-III (n=73), WISC-R (n=3), or WAIS-III (n=5).

2.3. Statistical analyses

All statistical analyses were conducted with SPSS version 22 statistical analysis software (APSS, Chicago, IL). Power analysis(Faul et al., 2009) indicated that our sample size (n = 89) provides a power of 80% to detect a moderate effect size (OR > 2 (2.1 or higher)) with respect to the association between ASD and the development of a psychotic disorder in 22q11DS (α= 0.05, two-sided, expected rate of psychotic disorder 25%). The ASD group and the non-ASD group were compared on the possible confounding variables age, gender, interval (time between first and last measurement), full scale IQ (FSIQ) and medication use (any psychopharmacological medication, or any antipsychotic), by means of chi-square and one-way ANOVA analyses.

To test the primary hypothesis that ASD at baseline is associated with a psychotic disorder at follow-up, we initially conducted a chi-square analysis. To allow for the consideration of possible confounders we used a binary logistic regression model (model 1), with predictor variables a diagnosis of ASD, age, gender and FSIQ and with outcome variables either psychotic disorder at follow-up (model 1) or persistent psychotic symptoms at follow-up, regardless of whether formal diagnostic criteria for a psychotic disorder were met (model 2).

To investigate the association between ASD symptom severity (dimensional) at baseline and the presence of a psychotic disorder at follow-up, another binary logistic regression model was used, using the raw ADI-R scores as a predictor variable, and adding possible confounders to the model (model 3). The same analysis was conducted to investigate the association between ASD symptom severity at baseline and the presence of psychotic symptoms at follow-up (model 4).

Post-hoc, we compared the use of any psychopharmacological medication or antipsychotic medication (during the interval time between first and last measurement) between the ASD and non-ASD groups, and added this to the regression models, to test if medication use affected the predictive effect of ASD symptoms/diagnosis on psychotic symptoms/diagnosis.

3. RESULTS

At baseline, there were 52 (58.4%) participants in the ASD and 37 (41.6%) in the non-ASD group. There were no significant differences between the ASD and non-ASD groups on any of the variables examined (Supplement Table 1). The average interval (±SD) between first and last measurement was 56.6±29.6 months.

The results revealed no significant predictive effect of a diagnosis of ASD on the subsequent development of a psychotic disorder (p = 0.270), see Table 1. The findings remained similar when age, gender and FSIQ were added to the regression model (OR = 0.500, 95% CI = 0.160 –1.569, p = 0.235). In fact, in the ASD group the proportion of individuals who developed a psychotic disorder (17.3%, n=9) was lower than in the non-ASD group (27%, n=10), albeit not statistically significantly. Accordingly, there was no significant difference

in the proportions of patients who developed psychotic symptoms, regardless of a diagnosis of a psychotic disorder, between the ASD-group and the non-ASD group (model 2; OR = 0.977, 95% CI = 0.362 – 2.634, p = 0.963).

Next, we investigated the association between the severity of autistic symptoms - regardless of whether or not a formal ASD diagnosis was present- and the subsequent development of psychotic disorders. There was no significant difference in the total raw score on the ADI-R between the group that did not develop a psychotic disorder at follow-up (mean = 24.2; SD = 12.9) and the group that did develop a psychotic disorder (mean=21.0; SD=16.0; model 3; OR = 0.968, 95% CI = 0.922 – 1.016, p = 0.188; see Supplement Figure 1). Thus, consistent with results from the categorical analyses (models 1 & 2), there was no support for a predictive effect of symptom severity in the domains of social interaction, communication or repetitive behaviors on the development of subsequent psychotic disorders. Comparing ASD symptom severity at baseline between those with psychotic symptoms at follow-up (mean=22.8, SD=15.6) and those without (mean=23.9, SD=12.7) provided similar results (model 4; OR = 0.996, 95% CI = 0.995 – 1.038, p = 0.835).

A between-group comparison of the use of psychopharmacological medication, and just antipsychotics, during the interval time between first and last measurement between both groups revealed no significant differences (ASD vs. non-ASD; 30.8% and 16.2%, p = 0.117; 19.2% and 13.5%, p = 0.478 respectively) and post-hoc addition did not alter the results for any of the four regression models.

Thirteen subjects were already diagnosed with a psychotic disorder at T0 (see Supplement Figure 2). Therefore, we reran the analyses post-hoc, defining psychotic disorder (or symptoms) at *any* time point, i.e. including T0, as the main outcome. The results of these analyses (both categorical and dimensional) were similar to those of the main analyses.

4. DISCUSSION

Our results reveal no association between ASD in early childhood and the subsequent development of psychosis in individuals with 22q11DS. Both phenotypes were analyzed at the level of symptoms and at the level of diagnosis, generating similar results. The findings of this prospective study replicate those of a previous retrospective study investigating this issue in an independent cohort (Vorstman et al., 2013). They indicate that ASD and psychotic disorders should be considered as relatively independent neuropsychiatric consequences of 22q11DS and that symptoms characteristic of ASD are unlikely to represent a prodromal stage of schizophrenia.

These results reflect both the incomplete penetrance and pleiotropy of the neuropsychiatric phenotype in 22q11DS patients; not all patients develop a psychotic disorder (indicative of incomplete penetrance), and other neuropsychiatric phenotypes (i.c. ASD) can occur independently, in patients with the 22q11.2 deletion (indicative of pleiotropy). This is consistent with the high degree of phenotypic heterogeneity observed in other pathogenic copy number variations (Bassett et al., 2010; Vorstman and Ophoff, 2013), indicating that 22q11DS may be a useful genetic model through which the associations between different

neuropsychiatric phenotypes in the context of the same CNV can be better understood (Malhotra and Sebat, 2012). Possibly, (non-) genetic risk factors in addition to the high-impact CNV modulate which neurobiological pathways are affected and therefore which psychiatric phenotype is manifested(Bassett et al., 2010; Craddock and Owen, 2010; Merico et al., 2015). In such a model, a high-impact CNV (such as a 22q11.2 deletion) could act as a first hit that renders certain neurobiological pathways vulnerable to the effect of additional risk factors (Girirajan and Eichler, 2010) (Vorstman et al., 2009) (Merico et al., 2015; Vorstman and Ophoff, 2013).

4.1 Advantages and limitations

The available sample size (n = 89) provided 80% power to detect a moderate effect size (OR >2) regarding the association between ASD and subsequent psychotic disorder in 22q11DS. The fact that the results replicate those of a comparable, retrospective study using an independent cohort (Vorstman et al., 2013), provides further confidence in the conclusion that there is no clinically relevant association between ASD and subsequent psychotic disorders in 22q11DS.

The main analysis was conducted in a prospective way; i.e. to assess to what extent ASD, determined at T0, is associated with the subsequent development of psychosis. Given that we were primarily interested in the predictive effect of early autistic symptomatology on psychotic disorders at any point in life, we performed post-hoc analyses with psychotic disorder at *any* time point as the outcome variable, and these showed similar results.

The relatively young average age of our sample at the time of the last measurement (19.0 years) can be considered a limitation of this study as individuals in the non-psychotic group may still develop schizophrenia or related psychotic disorders. However, given the average age of onset of the first psychotic episode in 22q11DS (estimated around 18 years for samples ascertained as children (Gothelf et al., 2013; Vorstman et al., 2015)), this effect is expected to be modest. In addition, broadening our outcome measure to psychotic symptoms instead of a formal psychotic disorder generated similar results.

The relatively large proportion of children diagnosed with ASD in our cohort, the majority of whom were diagnosed with PDD-NOS, might imply a potential clinical bias to these diagnoses in our sample. We therefore added a dimensional measure of autism-like symptom severity, regardless of a formal ASD diagnosis, to the study design (i.e. the raw ADI-R score). Findings from this dimensional analysis did not differ from the results using the categorical approach (i.e. ASD diagnoses). This indicates that early impairments in social and communicative functioning and repetitive or stereotyped behaviors, regardless of whether formal ASD diagnostic criteria were met, are not associated with later psychotic disorders in 22q11DS.

In conclusion, the results of this prospective study, together with similar findings in an independent cohort (Vorstman et al., 2013), indicate that in 22q11DS, autistic symptoms and/or a diagnosis of ASD are not predictive of developing a psychotic disorder or persistent psychotic symptoms later in life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

22q11DS	22q11.2 deletion syndrome
ASD	autism spectrum disorder
ADI	autism diagnostic interview
FSIQ	full scale intelligence quotient

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TABLE 1

DISTRIBUTION OF PATIENTS WITH AND WITHOUT ASD AT BASELINE WHO DEVELOPED A PSYCHOTIC DISORDER AT FOLLOW-UP (MODEL 1)

Total N = 89 (100%)|	**Psychotic disorder n = 19 (21.3%)**	**No psychotic disorder n = 70 (78.7%)**	**Analysis**			
	n (%)	**n (%)**	**OR**	**95% CI**	***p*[a]**	***p*[b]**
ASD n = 52 (58.4%)	9 (17.3%)	43 (82.7%)	.500	.160 – 1.569	.270	.235
Non-ASD n = 37 (41.6%)	10 (27%)	27 (73%)				

Abbreviations: ASD: Autism Spectrum Disorder; FU: Follow-up, OR: Odds Ratio, CI: Confidence Interval.

[a]Chi-square.

[b]Binary logistic regression. Corrected for age, gender, FSIQ.