



Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Negative subthreshold psychotic symptoms distinguish 22q11.2 deletion syndrome from other neurodevelopmental disorders: A two-site study

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ARTICLE INFO

Article history:

Received 27 August 2016

Received in revised form 21 December 2016

Accepted 21 December 2016

Available online xxxx

Keywords:

Velocardiofacial syndrome

Williams syndrome

Negative symptoms

Structured Interview for Prodromal Symptoms (SIPS)

Computerized Neurocognitive Battery (CNB)

ABSTRACT

About one third of individuals with 22q11.2 deletion syndrome (22q11.2DS) develop schizophrenia. Notably, a full-blown psychotic disorder is usually preceded by subthreshold symptoms. Therefore, it is important to identify early signs of psychosis in this population, a task that is complicated by the intellectual disabilities typically seen in 22q11.2DS. We aimed to identify subthreshold psychotic symptoms that distinguish 22q11.2DS from other neurodevelopmental disorders. The study included two independent cohorts from Tel Aviv and Philadelphia. 22q11.2DS ($N = 171$) and typically developing (TD; $N = 832$) individuals were enrolled at both sites and further compared to two groups with intellectual disabilities: Williams syndrome (WS; $N = 21$) in the Tel Aviv cohort and idiopathic developmental disabilities (IDD; $N = 129$) in the Philadelphia cohort. Participants and their primary caregivers were interviewed with the Structured Interview for Prodromal Symptoms (SIPS) and psychopathologies were assessed using standardized tools; general cognitive abilities were assessed with the Computerized Neurocognitive Battery. Negative/disorganized subthreshold syndrome was significantly more common in the 22q11.2DS group than in the WS (OR = 3.90, 95% CI = 1.34–11.34) or IDD (OR = 5.05, 95% CI = 3.01–10.08) groups. The 22q11.2DS group had higher scores than the two intellectual disabilities groups on several SIPS negative items, including avolition and decreased expression of emotion. Overall, there were few significant correlations between level of cognitive deficits and severity of negative symptoms in 22q11.2DS and only in the Tel Aviv cohort. Our findings suggest that 22q11.2DS individuals at the age of risk for developing psychosis should be closely monitored for negative symptoms.

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1. Introduction

The 22q11.2 deletion syndrome (22q11.2DS) is a common neurogenetic disorder with an estimated prevalence of ~1 per 3000 to 1 per 6000 live births (McDonald-McGinn et al., 2015). It is caused by a microdeletion in the long arm of the chromosome 22 and has a typical phenotype. Williams syndrome (WS) is a rare genetic disorder, occurring in ~1:20000 live births (Stromme et al., 2002) and caused by a microdeletion in the long arm of chromosome 7 (7q11.23). Both

syndromes have overlapping phenotypic manifestations, including cardiovascular anomalies, calcium dysregulation, cognitive deficits, and high rates of psychiatric comorbidities (Campbell et al., 2009). As a group, individuals with neurodevelopmental disabilities (e.g., 22q11DS, WS, fragile X, or Turner syndrome) have higher rates of neuropsychiatric, cognitive, and social-behavioral deficits including non-verbal learning disorder, visuospatial deficits, attention deficit/hyperactivity disorder (ADHD), anxiety disorders, and affective disorders, compared to typically developing (TD) individuals (Schneider et al., 2014; Siegel and Smith, 2011; Weisman et al., 2015; Zarchi et al., 2014). Additionally, individuals with 22q11.2DS have a 30-fold increased risk of developing psychosis compared to TD individuals and individuals with other neurodevelopmental disabilities (10-fold)

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(Schneider et al., 2014). Therefore, 22q11.2DS is currently considered the strongest known genetic risk factor for schizophrenia.

Intense efforts are underway worldwide for early identification and treatment of psychosis in 22q11.2DS and the syndrome serves as a promising model for deciphering the pathways leading to schizophrenia. Previous studies have shown that, as is the case in non-deleted individuals, psychotic symptoms develop gradually in 22q11.2DS and that a full-blown psychosis is typically preceded by subthreshold symptoms (Gothelf et al., 2007, 2013; Tang et al., 2014b). Finally, studies suggest that the prevalence of subthreshold psychotic syndromes vary significantly in this population, ranging between 20% and 55% of the individuals assessed (Table 1).

The Structured Interview for Prodromal Symptoms (SIPS) is a well validated and commonly used tool for the assessment of subthreshold psychotic symptoms in individuals at high risk for schizophrenia (Miller et al., 2003a). It was designed for older adolescents and young adults with intelligence within the normal range (McGlashan et al., 2010). Although it is already being used in individuals with neurodevelopmental disabilities, its validity in 22q11.2DS has not been thoroughly tested. Specifically, the SIPS scores of individuals with 22q11.2DS have not been compared to individuals with intellectual disability or other neurogenetic syndromes. Due to significant overlap between subthreshold psychotic symptoms and intellectual disabilities (e.g., problems with conceptual organization and poor ideational richness) and the difficulties of participants with developmental disabilities in understanding some questions (e.g., “Do you ever seem to live through events exactly as you have experienced them before?”, “Are you feeling emotionally flat?”), it is important to compare the rate of subthreshold psychotic symptoms between 22q11.2DS and IQ-matched control group.

Utilizing two independent cohorts in Tel Aviv (Israel) and Philadelphia (USA), we explored the following aims: establish the utility of the SIPS in 22q11.2DS by testing its ability to detect differences in the rate of subthreshold psychotic symptoms and subthreshold syndromes between 22q11.2DS, WS, and demographically matched TD controls (Tel Aviv); and between individuals with 22q11.2DS, individuals with idiopathic developmental disabilities (IDD), and demographically matched TD controls (Philadelphia). We hypothesized that individuals with 22q11.2DS would have higher rates of subthreshold psychotic symptoms and syndromes compared to WS and IDD and that the three clinical groups would have higher rates of subthreshold symptoms and syndromes compared to TD controls. We further aimed to test whether the differences in rates and severity of subthreshold psychotic symptoms between the clinical groups and within 22q11.2DS are affected by the overall cognitive deficits. Finally, we aimed to characterize the differences in psychiatric comorbidities between 22q11.2DS individuals with and without negative subthreshold psychotic syndrome. Based on previous studies in 22q11.2DS (Gothelf et

al., 2007, 2013; Yi et al., 2015), we hypothesized that those with sub-threshold psychotic syndrome would have higher rates of anxiety disorders and higher degree of social withdrawal and depressive symptoms, compared to those without subthreshold psychotic syndrome.

2. Materials and methods

2.1. Participants

The demographic characteristics of both cohorts are presented in Table 2.

2.1.1. Tel Aviv

Fifty-two participants with 22q11.2DS and 21 with WS were recruited from the Behavioral Neurogenetics Center at the Sheba Medical Center in Tel Aviv. The participants were referred from genetic clinics and through parents' associations. The diagnosis of 22q11.2DS or WS was confirmed in all participants by fluorescent in situ hybridization (FISH) and by multiplex ligation probe amplification (MLPA) (Michaelovsky et al., 2012). TD controls were recruited through advertisements within the local community. They all had normal IQ and completed the SCL90 questionnaire (Derogatis, 1992) to rule out any major psychopathology. Age and sex distribution did not differ among the groups (Table 2).

The study was approved by the Sheba Medical Center Review Board. After providing a complete description of the nature of this study, informed consent was obtained from all participants and from the parents of minors.

2.1.2. Philadelphia

The Philadelphia cohort consisted of 119 participants with 22q11.2DS, 129 with IDD and 800 TD controls. Age and sex distribution did not differ among the groups (Table 2). 22q11.2DS individuals were recruited through the “22q and You Center” at the Children's Hospital of Philadelphia (CHOP) and online social networks as previously described (R.E. Gur et al., 2014; Tang et al., 2014b). FISH and/or MLPA tests were performed for all participants to confirm the deleted region. The 129 IDD individuals are a part of the Philadelphia Neurodevelopmental Cohort (PNC) and had comorbid medical conditions with no known chromosomal anomalies. Organ systems affected were similar to those with 22q11.2DS as previously described (R.E. Gur et al., 2014). The TD group included physically healthy youth, based on history provided at evaluation and review of electronic medical records as well as no psychiatric condition based on the clinical assessment detailed below. All procedures were approved by the review boards of the University of Pennsylvania and CHOP. Informed consent/assent was obtained from each participant and accompanying caregiver.

Table 1
Studies of subthreshold psychotic syndrome in 22q11.2 deletion syndrome (22q11.2DS).

	Age in years Age range	N	Definition of prodromal syndrome	Source of information	Rates of prodromal symptoms
Stoddard et al., 2010	15.1 (4.3) 12–22	20	At least one positive symptom scored ≥ 3 on SIPS	Participants and caregivers interviewed together	45%
Antshel et al., 2010	15.0 (1.9) 12.0–19.9	70	At least one positive symptom scored ≥ 3 on SIPS	Participants and caregivers interviewed collaterally	20%
Shapiro et al., 2011	17.5 (2.5) 14–22	23	At least one positive symptom scored ≥ 3 on SIPS	Participants and caregivers interviewed collaterally	56.5%
Schneider et al., 2012	15.4 (2.3) 11–20	47	At least one positive symptom scored ≥ 3 or at least one negative symptom scored ≥ 3 on SIPS	Participants only	83% negative 40.4% positive
Tang et al., 2014a, 2014b	15.2 (4.8) 8–25	157	At least one positive symptom scored 3–5 or at least two negative or disorganized symptoms scored ≥ 3 on SIPS	Participants and caregivers interviewed collaterally	44% positive 54% positive or negative

Mean (SD); SIPS—The Structured Interview for Prodromal Symptoms.

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