Subthreshold Psychotic Symptoms in 22q11.2 Deletion Syndrome

Sunny X. Tang, MD, James J. Yi, MD, PhD, Tyler M. Moore, PhD, Monica E. Calkins, PhD, Christian G. Kohler, MD, Daneen A. Whinna, BA, Margaret C. Souders, PhD, CNRP, Elaine H. Zackai, MD, Donna M. McDonald-McGinn, MS, CGC, Beverly S. Emanuel, PhD, Warren B. Bilker, PhD, Ruben C. Gur, PhD, Raquel E. Gur, MD, PhD

Objective: Chromosome 22q11.2 deletion syndrome (22q11DS) confers 25% risk for psychosis and is an invaluable window for understanding the neurobiological substrate of psychosis risk. The Structured Interview for Prodromal Syndromes (SIPS) is well validated in nondeleted populations for detecting clinical risk but has only recently been applied to 22q11DS. We assessed the largest 22q11DS cohort to date and report on SIPS implementation and symptoms elicited. **Method:** The SIPS, including its 19 subscales, was administered to 157 individuals with 22q11DS aged 8 to 25 years. Youth and caregiver interviews were conducted and rated separately, then compared for agreement. Implementation of the SIPS in 22q11DS was challenging because of the prevalence of developmental delay and comorbid conditions. However, by explaining questions and eliciting examples, we were able to help youths and caregivers understand and respond appropriately. Consensus ratings were formulated and analyzed with itemwise and factor analysis. **Results:** Subthreshold symptoms were common, with 85% of individuals endorsing 1 or more. The most commonly rated items were ideational richness (47%) and trouble with focus and attention (44%). Factor analysis revealed a 3-factor solution with positive, negative, and disorganized components. Youth–caregiver comparisons suggested that youths report greater symptoms of perceptual abnormalities, suspiciousness, trouble with emotional expression, and bizarre thinking. Caregivers reported more impaired tolerance to normal stress, poor hygiene, and inattention. **Conclusion:** The SIPS was adapted for 22q11DS through comprehensive and semi-structured administration methods, yielding a high prevalence of subthreshold psychotic symptoms. The significance and predictive validity of these symptoms require future longitudinal analysis. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(9):991–1000. **Key Words:** 22q11.2 deletion syndrome, psychosis, schizophrenia, prodromal, Structured Interview for Prodromal Syndromes

Chromosome 22q11.2 deletion syndrome (22q11DS) is associated with markedly elevated risk for schizophrenia and is increasingly recognized as a unique window into understanding psychosis risk.[1-4] Genetically, 22q11DS arises from a hemizygous deletion of 1.5 to 3 megabases on chromosome 22 in approximately 1:4,000 live births.[5,6] The associated phenotype is variable and can include neuropsychiatric and physical features, with cardiac, palate, endocrine, and immunologic abnormalities.[5,7-9] Psychiatric disorders are common, affecting three-fourths of individuals with 22q11DS; there is increased risk for autism, attention-deficit/hyperactivity disorder (ADHD), anxiety disorders, and, most notably, psychosis.[10-15] Approximately one-third of individuals with 22q11DS develop psychotic disorders by adulthood, representing a 25-fold increase in psychosis risk over that in the general population, and 10-fold over that in other developmentally delayed populations.[2,3,16] Therefore, 22q11DS is a unique opportunity to investigate the pathogenesis of psychosis-spectrum disorders.

Early identification of psychosis proneness has become a focus of ongoing research.[3,17-23]

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Subthreshold symptoms of psychosis are not uncommon in the general population and are more prevalent in children (17.5%) than in adolescents (7.2%) or adults (5%).[24,25] Criteria have been developed to define an "at-risk mental state" or "prodrome" for individuals with significant symptomatic burden but who do not meet criteria for schizophrenia spectrum disorders.[18,26] The Structured Interview for Prodromal Syndromes (SIPS) is a well-validated instrument evaluating subthreshold psychotic symptoms.[27,28] Interrater reliability is excellent, and criteria for the clinical high-risk state predict that approximately one-fifth convert to psychosis at 1 year and one-third at 3 years in nondeleted populations.[18,27-30] The SIPS provides 19 subscales comprising the Scale of Prodromal Symptoms (SOPS) that are theoretically grouped into positive, negative, disorganized, and general domains, with gradation of severity optimally centered around subthreshold levels.[27]

The identification of individuals with 22q11DS at clinical risk for psychosis can contribute to elucidating the pathogenesis of psychosis because it can link a specific genetic mechanism to brain and behavior phenotypes. It is therefore essential to assess subthreshold psychotic symptoms in 22q11DS and relate them to neurocognition, neuroimaging, and genomics. Only a few studies, relatively limited in sample size, have applied the SIPS to investigate subthreshold symptoms of psychosis in 22q11DS.[19-23] The investigators report that subthreshold symptoms are common in 22q11DS but vary widely across subscales, with 2% to 85% reaching subthreshold levels, depending on the scale applied.[19-21,23] To our knowledge, no prior report has presented the methodology of adapting the SIPS to a developmentally delayed population with medical comorbidity for which this scale was not designed.

In this study, we thoroughly investigate subthreshold symptoms of psychosis in the largest sample to date of young individuals with 22q11DS. Our aims are as follows: to confront the challenges in applying the SIPS to 22q11DS; to characterize subthreshold psychotic symptoms in 22q11DS and assess the effects of age, sex, and reading proficiency; to evaluate the factor structure of the SIPS and compare it to the theorized positive, negative, disorganized, and general domains; and to compare youth and caregiver reports to detect a possible informant effect on symptom reporting.

METHOD

Sample

We evaluated a cohort of 157 youths with 22q11DS, aged 8 to 25 years (Table 1). Participants were recruited primarily through the genetics clinic "22q and You Center" at the Children's Hospital of Philadelphia, in addition to social networks. All participants had a molecularly confirmed deletion of the 22q11.2 region. Exclusion criteria included inability to provide assent or informed consent, as well as moderate to severe intellectual disability based on clinical evaluation and IQ testing when available (estimated IQ <70). Individuals with significant intellectual disability were excluded because they were likely to have little insight into psychiatric phenomena, and findings would have limited generalizability to the general population.

Study procedures were conducted while the participants were medically stable and ambulatory. No changes were made in the participants' medical and behavioral treatment. Six participants had used antipsychotic medication within 6 months of the assessment. The institutional review boards of the University of Pennsylvania and the Children's Hospital of Philadelphia approved all procedures. Informed consent/assent was obtained from each participant and accompanying parent. A recent publication describes overall psychopathology and treatment for 112 of the participants.[10]

Administration of the SIPS

The SIPS was administered by bachelor's- and master's-level interviewers who underwent formal training conducted by a doctoral-level clinical psychology faculty member (M.E.C.) with extensive experience and training in the semi-structured interview assessment and diagnosis of psychotic and sub-psychotic

TABLE 1 Sample Characteristics

N	157
Age, y, mean ± SD	15.2 ± 4.8
Sex, n (%)	
Male	91 (58)
Female	66 (42)
Reading proficiency ± SD	90.1 ± 13.5
Race/ethnicity, n (%)	
White	138 (88)
African American	10 (6)
Other/mixed	9 (6)
Education, y, ± SD	
Proband	7.8 ± 4.0
Mother	14.7 ± 2.6
Psychosis spectrum, n (%)	97 (62)

Note: Reading proficiency is estimated with the Wide Range Achievement Test 4 reading segment; scores are standardized by age to mean (100, SD = 15).