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Brief report

Attenuated positive symptoms of psychosis in adolescents with chromosome 22q11.2 deletion syndrome

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ABSTRACT

Thirty percent of individuals with chromosome 22q11.2 deletion syndrome (22q11.2DS) develop a psychotic disorder, particularly schizophrenia. We assessed attenuated positive, negative and disorganized symptoms of psychosis and clinical-high-risk syndromes in 20 adolescents with 22q11.2DS (median age 15.1 years) using the Structured Interview for Prodromal Symptoms (SIPS). Two participants met criteria for the Attenuated Positive Symptom Syndrome, while nine participants (45%) experienced positive symptoms rated in the "moderate" to "severe and psychotic" range on the SIPS. Almost all presented with moderate to severe symptoms in the negative, disorganized, and general symptom domains.

1. Introduction

Mental disorders are common in chromosome 22q11.2 deletion syndrome (22q11.2DS), which is caused by a microdeletion at chromosomal region 22q11.2 (OMIM accession nos. **188400**, **192430**, and **145410**). Psychotic disorders, especially schizophrenia, have a lifetime prevalence of about 30% (Murphy and Owen, 2001), which is disproportionately high with respect to other neurodevelopmental disorders (Gothelf et al., 2008).

Given this genetic risk, researchers have assessed symptoms of psychosis in adolescents with 22q11.2DS. Using general psychopathology interviews, four studies have reported positive symptoms of psychosis in 14–48% of youth with 22q11.2DS (Baker and Skuse, 2005; Debbane, et al., 2006; Feinstein, et al., 2002; Vorstman, et al., 2006). However, examining subclinical psychotic-like symptoms may yield additional information about the presentation of psychosis in this at-risk population. Consequently, Baker and Skuse (2005) studied schizotypal personality disorder symptoms in adolescents with 22q11.2DS. While 48% ($n = 12/25$) reported transient psychotic-like symptoms, 84% ($n = 21/25$) endorsed at least one schizotypal symptom. They hypothesized that subclinical, schizophrenia-related symptoms may be much more common in adolescents with 22q11.2DS than the lifetime prevalence of schizophrenia in 22q11.2DS.

The Structured Interview of Prodromal Symptoms (SIPS) was developed (McGlashan, 2001) and validated (Miller, et al., 2002; Miller, et al., 1999) to assess the presence of subclinical schizophrenia-related symptoms, including attenuated psychotic symptoms (APS), in help-seeking populations. SIPS-defined clinical-high-risk (CHR) syndromes are associated with increased risk for schizophrenia (Miller, et al., 2002). In a large multicenter longitudinal study, CHR syndromes predicted the

Abbreviations: 22q11.2DS, Chromosome 22q11.2 deletion syndrome; APS, Attenuated positive symptoms of psychosis.

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development of psychosis in 35% of 291 participants over a 2 year follow-up period (Cannon, et al., 2008).

We hypothesized that adolescents with 22q11.2DS would demonstrate high rates of attenuated positive symptoms (APS) and other schizophrenia-related symptoms on the SIPS. Unlike general psychopathology interviews used in previous studies (Baker and Skuse, 2005; Debbane, et al., 2006; Feinstein, et al., 2002; Vorstman, et al., 2006), the SIPS directly assesses attenuated symptoms that are reliably associated with increased clinical risk for schizophrenia.

2. Methods

2.1. Participants

Our study was approved by the UCDHS Institutional Review Board. We recruited from a pool of participants in cognitive studies at the UCDHS M.I.N.D. Institute's Cognitive and Brain Imaging Laboratory (CABIL) and advertised as "Psychopathology in Chromosome 22q11.2 Deletion Syndrome" on the CABIL website.

We recruited 22 participants, ages 12–22 years, with 22q11.2DS. Each participant provided a record of fluorescence *in situ* hybridization verified chromosome 22q11.2 deletion. Participants and their guardians provided study assent and consent respectively. Participants were excluded if they had a history of traumatic brain injury, past or current psychotic disorder ($n=1$) or mood disorder with psychotic features, illicit substance use in the month prior to assessment, or IQ below 50 ($n=1$). Twenty were eligible for the analysis. No participant tested positive for current substance use based on urine dipsticks (Phamatech, San Diego, CA).

2.2. Procedures

The SIPS (McGlashan, 2001) contains the Scale of Prodromal Symptoms (SOPS) that rates 19 schizophrenia-related symptoms on a 6-point scale within into four domains: positive, negative, disorganized, and general. The SIPS Criteria of Prodromal Syndromes (COPS) determines the presence of a CHR syndrome. SOPS positive symptoms rated at a 3–5 severity level are within the attenuated range. We report Global Assessment of Functioning (GAF) scores based on the SIPS revision (Hall, 1995; Miller, et al., 1999). The *Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime* (KSADS-PL) (Kaufman, et al., 1997) was used in conjunction with the SIPS to specify comorbid mental disorders. As the KSADS-PL does not directly assess autistic symptoms, a diagnosis of a pervasive developmental disorder was according to the *Diagnostic and Statistical Manual, 4th Edition, Text Revised* (DSM-IV-TR) (American Psychiatric Association, 2000).

Participants and their caregivers both completed live clinical interviews. Following a general clinical interview tailored to 22q11.2DS (available on request), JS, a board-eligible psychiatrist, conducted the KSADS-PL and SIPS according to their instructions. Interviews were videotaped for review. JS and RH reviewed the clinical interview, KSADS-PL interview, and intelligence tests to determine DSM-IV diagnoses. Interviewer reliability for SIPS administration and scoring (for JS and TN) was established through standardized training (Miller, et al., 2003), both showing agreement with a Cohen's kappa greater than 0.80. Interviews were reviewed by JS and TN and consensus scores were created across all SIPS scales and syndromes.

Intelligence was assessed by M.I.N.D. Institute Assessment Core staff using the current, age-appropriate Wechsler intelligence instrument (Wechsler, 1997, 2004). Because of its association with schizophrenia (Muntaner, et al., 2004), socioeconomic status (SES) was measured using Hollingshead's four factor index (Hollingshead, 1975).

2.3. Statistical analysis

SOPS scores within each symptom domain were summed to create a total score for analysis. Domain total scores were log-transformed to improve normality. Linear regression was used to examine the effects of SES, intelligence, age, and GAF score on participants' four domain scores. Analyses were 2-tailed with alpha set at $p \leq 0.05$ to allow for recognition of smaller effects due to small sample size.

3. Results

Participant demographic and clinical characteristics are listed in Table 1. Participants presented with high rates of mental disorders (Table 2). While comorbid diagnoses were common, 5 (20%) had experienced just one mental disorder during their lifetime, and 2 (10%) had no current or past mental disorder.

SOPS data are summarized in Table 3. Nine individuals (45%) presented with APS. Participant's total positive symptoms ranged from 0 to 14. Moderate to severe symptoms in each of the negative, disorganized, and general symptom domains were also common. Two participants met criteria for SIPS "attenuated positive symptom syndrome." In both cases, the qualifying symptom was recent-onset auditory hallucinations beginning within the year prior to assessment and occurring at least once per week. Notably, no other positive symptom score was above the "questionably present" level for these two individuals, their total positive symptom scores were 4 and 5. In contrast, six of the remaining seven 22q11.2DS individuals reported long-standing APS symptoms and therefore did not meet criteria for a CHR syndrome. These six included those with the highest positive symptom total scores, 13, 13, and 14.

SOPS total scores across the four domains were not associated with age or intelligence. SES was inversely

Table 1
Participant characteristics.

	22q11.2DS $n=20$
Age (years) Median (IQR), range	15.1 (4.3), 12–22
Female	70%
SES Mean (SD)	48.9 (14.0)
FSIQ Mean (SD)	76.2 (10.9)
GAF Mean (SD)	58.8 (10.8)

Table 2
KSADS-PL determined mental disorders.[a]

	22q11.2DS $n=20$	
Diagnosis	Current *n* (%)	Lifetime *n* (%)
Any disorder	15 (75)	18 (90)
PDD NOS	5 (25)	5 (25)
ADHD	6 (30)	7 (35)
ODD	1 (5)	1 (5)
Tourette's disorder	1 (5)	1 (5)
Enuresis	2 (10)	6 (30)
Alcohol dependence	1 (5)	1 (5)
Any anxiety	11 (55)	12 (60)
SAD	1 (5)	4 (20)
GAD	4 (20)	4 (20)
OCD	1 (5)	4 (5)
Panic disorder	0 (0)	1 (5)
PTSD	1 (5)	1 (5)
ASD	1 (5)	2 (5)
Social phobia	2 (10)	5 (25)
Specific phobia	6 (30)	7 (35)
Anxiety disorder NOS	2 (10)	2 (10)
Any mood	3 (15)	5 (25)
MDD	2 (10)	4 (20)
Depressive disorder NOS	1 (5)	1 (5)
Adj. disorder with depressed mood	0 (0)	1 (5)

[a] Data are presented as the number of adolescents who met criteria for a diagnosis. Current refers to disorder present or partially remitted within 2 months prior to assessment. Lifetime refers to any history of the disorder. Abbreviations refer to the following disorders: NOS = not otherwise specified; PDD = pervasive developmental disorder; ADHD = any attention deficit/hyperactivity disorder, any subtype; ODD = oppositional defiant disorder; SAD = separation anxiety disorder; GAD = generalized anxiety disorder; OCD = obsessive compulsive disorder; PTSD = posttraumatic stress disorder; ASD = acute stress disorder; MDD = major depressive disorder; Adj. = adjustment.

Table 3
Presentation of SIPS symptoms.

	22q11.2DS ($n=20$)	
	n (%) having a score ≥ moderate[a]	Median (IQR) *range*
Positive symptoms[b]	9 (45)	4.0 (3.0) *0–14*
Unusual thought content	5 (25)	0.0 (2.5) *0–4*
Persecutory delusions/paranoia	2 (10)	0.0 (0.0) *0–3*
Grandiosity	2 (10)	0.0 (0.0) *0–6*
Perceptual abnormalities	5 (25)	1.0 (2.75) *0–4*
Disorganized communication	2 (10)	1.5 (2.0) *0–4*
Negative symptoms[b]	17 (85)	8.0 (11.5) *0–25*
Social anhedonia	7 (35)	1.5 (4.0) *0–6*
Avolition	10 (50)	2.0 (3.0) *0–5*
Expressions of emotion	7 (35)	0.5 (3.75) *0–5*
Experience of emotions and self	1 (5)	0.0 (0.75) *0–3*
Ideational richness	15 (75)	3.0 (1.75) *0–5*
Occupational functioning	4 (20)	1.0 (1.75) *0–4*
Disorganized symptoms[b]	11 (55)	3.0 (5.0) *0–15*
Odd behavior or appearance	3 (15)	0.0 (1.75) *0–3*
Bizarre thinking	1 (5)	0.0 (0.0) *0–4*
Problems with attention/focus	10 (50)	2.5 (1.75) *0–5*
Impairment in hygiene	5 (25)	0.0 (2.75) *0–4*
General symptoms[b]	12 (60)	6.0 (11.5) *0–18*
Sleep disturbance	5 (25)	0.0 (2.75) *0–4*
Dysphoric mood	9 (45)	2.0 (3.75) *0–5*
Motor disturbances	7 (35)	0.0 (3.0) *0–5*
Impaired tolerance to normal stress	8 (40)	2.0 (3.0) *0–6*

[a] Number of participants with a SOPS item scored in the "moderate" to "severe" range (3–6).
[b] For each symptom domain, the number of participants with at least one symptom at a moderate to severe level as well as the median (IQR) and range of the sum of the SIPS items in that domain are reported.

associated with the positive domain ($r=-0.51$, $p=0.020$); this strengthened after controlling for intelligence ($r=-0.65$, $p=0.005$). This finding argues for inclusion of SES measures in future studies of the schizophrenia development in 22q11DS. GAF was inversely associated with negative, disorganized, and general domains only (respectively: $r=-0.60$, $p=0.005$; $r=-0.46$, $p=0.044$; $r=-0.53$, $p=0.017$), which is expected given the overlap between these measures.

4. Discussion

This is among the first reports of APS in youth with 22q11.2DS assessed with the SIPS, a validated measure of APS. We found a high prevalence (45%) of APS in our sample, consistent with previous studies of psychotic-like symptoms (Baker and Skuse, 2005; Debbane, et al., 2006; Feinstein, et al., 2002; Vorstman, et al., 2006). Our findings complement those of Rockers et al. (2009) who assessed an older group of non-psychotic transitional adults with 22q11.2DS using the SIPS. In addition, moderate to severe symptoms across the other three schizophrenia-related symptom domains were common. Consistent with our hypothesis and the findings of Baker and Skuse (2005), our participants presented with a wide array of subclinical, schizophrenia-related symptoms varying in degree of severity. Such symptoms were much more common than might be expected given the lifetime prevalence of psychotic disorders in 22q11.2DS.

We attempted to mitigate typical sources of bias. Though we exclude any participant with a prior diagnosis of psychotic disorder or mood disorder with psychosis, ascertainment bias is a limitation. We addressed observer bias by establishing consensus for each score between two reliable mental health professionals. Still, this study would have benefited from a comparison group, such as one comprised of other individuals at high risk of schizophrenia. Too few participants were taking antipsychotic medications ($n=2$) or had first degree relatives with psychotic disorders ($n=1$) to statistically assess their impact. Participants' intelligence and mental disorders are consistent with prior studies reporting on the cognitive and behavioral phenotype of 22q11.2DS (Gothelf, et al., 2008). The high rate of schizophrenia-related symptoms found in this study may be generalized to other clinical populations of adolescents with 22q11.2DS.

The significance of schizophrenia-related symptomatology with respect to the development of psychosis in 22q11.2DS must be addressed with longitudinal studies. Because of their prevalence, the presence of schizophrenia-related symptoms in those with 22q11.2DS is not likely sufficient to determine a schizophrenia prodrome. These symptoms may also be related to other psychopathological, psychosocial, and cognitive aspects of this at-risk population. Cohort studies can determine the specificity and predictive validity of each symptom and syndrome for psychopathology in 22q11.2DS. Prior to beginning these resource-intensive studies, this study provides insight into the range of symptomatology and promise of measures like the SIPS.

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Contributors

Authors JS, RH, CC, and TS designed the study and wrote the protocol. Author JS managed the literature searches and analyses. Authors JS, TN, and RH collected and analyzed the raw data. Authors JS, TN, and TS undertook the statistical analysis, and author JS wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Author JS, TN, and TS have no conflicts of interest to declare. CC has been a "one time consultant" for Merck, Roche, Lilly, Servier and Pfizer. RH has received research grants from Forest Pharmaceuticals (escitalopram, memantine), Inc., AstraZeneca (quetiapine for schizophrenia and bipolar in children) Bristol Meyer Squibb and Otsuka America Pharmaceutical, Inc. (aripiprazole for autism), Neuropharm LTD. (fluoxetine for autism), Janssen (risperidone for autism), Autism Speaks and NIMH. He has not taken personal salary from any pharmaceutical company. No pharmaceutical company has been directly involved in this project.

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