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Clinical Profiles and Conversion Rates Among Young Individuals With Autism Spectrum Disorder Who Present to Clinical High Risk for Psychosis Services

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Abstract

Objective: The overlap versus independence of autism spectrum disorder (ASD) and schizophrenia is a topic that has garnered the attention of generations of clinicians and scientists. Although high rates of psychotic symptoms have been identified in individuals with ASD, the nature, prevalence, and prognostic significance of subclinical psychotic experiences in ASD remain poorly understood.

Method: This study sought to compare baseline characteristics, clinical profiles, and conversion outcomes between young individuals at clinical high risk for psychosis (CHR) who presented with or without a prior ASD diagnosis during the second phase of the North American Prodrome Longitudinal Study (NAPLS, N = 764).

Results: Patients with CHR and ASD (CHR/ASD+, n = 26) tended to exhibit greater social and social cognitive difficulties, but expressed relatively levels of core psychosis symptoms similar to those of to patients with CHR but no ASD (CHR/ASD−). Risk for conversion to co-occurring psychosis (18.2% CHR/ASD+ versus 16.8% CHR/ASD−) was equivalent between CHR/ASD+ and CHR/ASD− groups, and the NAPLS2 Psychosis Risk Calculator predicted conversion to psychosis equally well across groups.

Conclusion: These results suggest that baseline psychosis symptoms, predictors of risk for conversion, and ultimate conversion rates are similar in patients with CHR with and without ASD.

They further suggest that ASD must not be considered a mutually exclusive diagnosis when such youth present in CHR settings. Future research is needed to better track trajectories in larger cohorts of individuals with CHR and comorbid ASD and to understand whether treatment recommendations effective in the broader CHR population are useful for this particular population as well.

Keywords

schizophrenia; prodrome; symptoms; comorbidity; development

Autism spectrum disorder (ASD) and psychosis share a long and storied history,[1,2] and the overlap versus independence of the two disorders has been a topic that has garnered the attention of generations of clinicians and scientists.[3,4] ASD was initially described as a subset of schizophrenia (with childhood onset), and the disorders share symptoms of social withdrawal, theory of mind deficits, and sensory abnormalities.[5–8] Importantly, increased psychosis rates have been identified in individuals with ASD,[9–11] and recent molecular genetic,[12–14] neuroimaging,[15–19] and epidemiological[20,21] studies indicate genetic, biological, and familial overlap between ASD and schizophrenia.

Since the 1980 edition of the *DSM*, autism and schizophrenia have been conceptualized as distinct disorders. Between 1980 and 1994, the *DSM* prescribed specifically that the two diagnoses could not be applied together,[22] and there remains significant literature discounting the notion of diagnosing schizophrenia in those already carrying an ASD diagnosis.[23–25] Because of this mindset, psychotic experiences in individuals with ASD may be underqueried for or underemphasized. Clinically and in research, ASD and schizophrenia experts remain largely siloed. ASD and (prodromal) psychosis clinics operate relatively independent of one another, often referring out when the question of the other disorder arises.

It is not inconceivable that features often associated with ASD, including intellectual disability, pre-existing antipsychotic use, and difficulty with verbal self-report, result in many individuals with ASD being excluded from early psychosis and at-risk clinics and research studies.[26,27] Collectively, these factors may lead evaluators to presume that individuals with ASD will be unlikely to be successful study participants. In clinical high-risk settings, clinicians often are faced with a challenge: are psychosis-like symptoms in referred patients who enter with ASD diagnoses transient and/or a “normal” part of their ASD (ie, without representing psychosis risk as with non-ASD referrals), or do individuals with ASD who present for CHR services have a similar chance of developing full-blown psychosis, in which case psychotic symptoms must be considered in their own right?

In this report, we leverage the North American Prodrome Longitudinal Study (NAPLS) dataset to begin to unpack this question. This longitudinal study has the unique advantage of having included a subset of young individuals with a comorbid ASD diagnosis. We compare individuals at clinical high risk for psychosis (CHR) with and without premorbid ASD diagnoses in terms of baseline socio-demographics, symptomatology, social cognition, and global functioning. We also compare the accuracy of their predicted risk of conversion using the NAPLS Psychosis Risk Calculator, as well as their eventual conversion outcomes. We

hypothesize that individuals with ASD who have been referred to CHR services with a suspicion of psychosis development are at equal risk for converting to psychosis (ie, in line with the ASD–schizophrenia overlap), but predict that their baseline symptom profiles may differ, presenting a unique challenge for conversion prediction. Specifically, given core symptoms of ASD and their overlap with deficits in psychosis, we hypothesize that individuals with a comorbid ASD diagnosis would present with lower social (cognitive) functioning levels, more unusual thought content and disorganized communication, and more negative symptoms at baseline. We expect these data to contribute to better understanding of psychosis risk in individuals with ASD who have subclinical psychotic symptoms, as well as to inform clinical practice when individuals with ASD present to CHR clinics in the community setting.

METHOD

Sample Description

Data were obtained in NAPLS-2,[28] a consortium of 8 research centers studying CHR between 2009 and 2013, comprising 764 help-seeking individuals 12 to 35 years of age, alongside 279 controls, observed for up to 2.5 years. We included baseline data from enrolled individuals diagnosed with CHR, yielding a sample of 26 individuals *with* ASD (CHR/ASD+; 3 female, 23 male) and 738 individuals *without* comorbid ASD diagnosis (CHR/ASD−; 325 female, 413 male). All patients in the CHR/ASD+ group met *DSM-IV*[29] criteria for autistic disorder, Asperger's disorder, or Pervasive Developmental Disorder–Not Otherwise Specified (PDD-NOS) using a combination of *DSM-IV* checklist during baseline clinical interview, medical records, and caregiver report of historical diagnosis.

To be considered at CHR, an individual had to be help seeking and had to meet at least one of the following three Criteria of Prodromal Syndromes (COPS): attenuated positive symptom syndrome (APSS), genetic risk and deterioration (GRD), and/or brief intermittent psychotic syndrome (BIPS). APSS requires the presence of at least one attenuated positive psychotic symptom (unusual thought content, suspiciousness, grandiose ideas, perceptual abnormalities, or disorganized communication) of insufficient severity to meet diagnostic criteria for a psychotic disorder. The attenuated psychotic symptom(s) had to have begun or worsened in the past year. GRD required having a combination of both functional decline (minimum of 30% drop in Global Assessment of Function score over the last month as compared with 12 months ago) and genetic risk; genetic risk, as operationalized by the Structured Interview for Prodromal Syndromes (SIPS)[30] and applied in the NAPLS2 consortium, refers to having either schizotypal personality disorder or a first-degree relative with a schizophrenia spectrum disorder. The BIPS state required the presence of any one or more positive psychotic symptoms (unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and disorganized communication) that meet the severity threshold but are too brief to meet diagnostic criteria for psychosis.[31]

All patients in the CHR/ASD+ group and 92% of those in the CHR/ASD− group met the Criteria of Psychosis-Risk Syndromes (COPS).[32] One patient int the CHR/ASD+ group (4%) also met criteria for genetic risk and functional deterioration (GRD). Two patients in the CHR/ASD− group (0.3%) met COPS, GRD, and Brief Intermittent Psychosis Syndrome

(BIPS) criteria; 47 (6.4%) met GRD and COPS criteria, 6 (0.8%) were included based on BIPS criteria alone, and 34 (4.6%) based on GRD criteria alone.

Participants were excluded if they met criteria for any current or lifetime Axis I psychotic disorder, had an IQ below 70, and/or had past or current history of a clinically significant neurological disorder (eg, brain tumor, epilepsy; see also Addington *et al.*[31]). The Institutional Review Boards of the eight participating sites approved all study protocols. All adult subjects gave informed consent. Minor participants provided assent whereas their parents/guardians provided informed consent.

Measures

CHR Status and Clinical Symptoms.—The Structured Interview for Psychosis-Risk Syndromes (SIPS) and the Scale for Assessment of Psychosis-Risk Symptoms (SOPS)[30,32] were used to define CHR and development of full-blown psychosis. Individual items were rated, and summary scores were determined for each domain (positive, negative, disorganized, and general symptoms).

Full details regarding SIPS criteria, reliability and consensus procedures are described elsewhere.[33] The SCID[34] was used to establish *DSM-IV* Axis I diagnoses at baseline and follow-up.

Social and Role Functioning.—Functioning was assessed using the Global Functioning (GF) GF:Social and GF:Role scales,[35] specifically designed to assess functioning in at-risk adolescents and young adults. The GF:Social scale assesses peer relationships, peer conflict, age-appropriate intimate relationships, and involvement with family members. The GF:Role Scale rates performance and amount of support needed in one's specific role (ie, school or work).[36] Scales range from 1 to 10 (higher scores indicate better functioning). We used the "current" functioning scores (ie, functioning levels in the month preceding assessment) at baseline. Ratings for each scale were based on best estimates derived from all available information, an approach that yields high inter-rater reliability.[37,38]

Social Cognition.—Social perception and theory of mind were assessed using the Social Inference (Enriched) subscale of The Awareness of Social Inference Test (TASIT),[39] which includes 16 short video scenes, enriched with contextual cues, in which actors engage in everyday conversations and use lies or sarcasm. After each scene, participants answer yes/no questions about what characters are Thinking, Doing, Feeling, and Saying. For each scene, the maximum score is 4, and separate subscores can be obtained for Think, Do, Feel, and Say domains, as well as for Lies and Sarcasm. Previous research has shown social perception deficits in individuals with CHR[40] and ASD[41] using this task.

Conversion to Co-occurring Psychosis and Accuracy of Psychosis Risk Calculation.—Participants were seen at 6-month intervals and followed for up to 2 years. Consistent with prior publications,[37] conversion to co-occurring psychosis was determined by meeting the SIPS Presence of Psychotic Symptoms criteria.[32] For the vast majority of converters (86.2%), there was also a confirmatory SCID diagnosis.[28] Of these, 92%

qualified for a SCID diagnosis of a psychotic disorder. Conversion decisions were discussed and approved on a weekly consensus call.

The psychosis risk calculator created by the NAPLS consortium[42] was used to determine whether the risk algorithm predicting conversion to co-occurring psychosis was equally effective for those who enroll in a CHR study with and without a comorbid ASD diagnosis. This individualized calculator computes psychosis risk based on a small number of demographic (age, family history of psychosis), clinical (unusual thought content and suspiciousness), neurocognitive (verbal learning and memory, speed of processing), and psychosocial (traumas, stressful life events, decline in social functioning) predictor variables that were most predictive in CHR samples.[42] It is designed to be applied at an individual patient's initial clinical contact to scale their risk for developing full-blown psychosis. Details on the risk calculator algorithm and weighting of individual predictors can be found in the original calculator publication.[42]

Statistical Analyses

Analyses were performed using STATA 15.0 (StataCorp, College Station, TX). Both χ^2 and independent-sample *t* tests were used to examine differences in socio-demographics between CHR/ASD+ and CHR/ASD− groups. Using log-rank survival analyses, we explored whether a comorbid ASD diagnosis was associated with a different rate of conversion to co-occurring psychosis.

Linear regression analyses were used to examine the magnitude of differences in baseline clinical symptoms and functioning scores between the ASD group and the rest of the CHR sample. Bonferroni corrections for multiple comparisons were conducted within each instrument. Logistic regression analyses were performed to examine whether conversion could be equally accurately predicted for the group with and without ASD diagnosis using the NAPLS Psychosis Risk Calculator. Because Cox regression survival analyses could not be performed due to the limited number of converters in the ASD sample, χ^2 analyses examining accuracy of prediction calculations were restricted to 509 participants (497 CHR/ASD−; 22 CHR/ASD+) with a minimum follow-up duration of 1 year. Because of the limited number of individuals developing co-occuring psychosis in the ASD sample, these prediction analyses were exploratory in nature. Sex and age were controlled for across analyses because of significant group differences in these variables.

RESULTS

Socio-demographic Characteristics

Participants in the CHR/ASD+ group were significantly more likely to be male than those in the CHR/ASD− group [$\chi^2(1) = 10.83$, $p = .001$], consistent with the typical sex ratios in ASD.[43] The CHR/ASD+ group was also significantly younger thant the CHR/ASD− group, on average ($t = -2.22$, $p = 0.026$). Groups did not significantly differ on race or estimated IQ (Table 1).

Baseline Clinical Symptomatology

CHR Symptoms.—As can be seen in Table 1, individuals with CHR with and without a comorbid ASD diagnosis did not differ in any of the summary scores of the SOPS domains. However, examining SOPS items separately revealed that the CHR/ASD+ sample presented with higher levels of social anhedonia (mean score = 3.57, SD = 1.65) compared to the CHR/ASD− sample (mean score = 2.31, SD = 1.73; N1, $\beta = 0.15$, t = 3.95, $p < .001$, Cohen's d [corrected for uneven groups] = 0.74)

Functional Outcome.—At baseline, the CHR/ASD+ group had significantly lower social functioning scores (GF:social) compared to the CHR/ASD− group ($\beta = -0.16$, $t = -4.44$, $p < .001$, Cohen's $d = 0.89$). The CHR/ASD+ and CHR/ASD− groups did not differ on role functioning.

Social Cognition.—On the TASIT at baseline, the CHR/ASD+ group had significantly lower total Do (CHR/ASD+: mean = 13.17, SD = 1.93; CHR/ASD−: mean = 11.50, SD = 2.50; $\beta = -0.13$, $t = -3.31$, $p = .001$, Cohen's $d = 0.82$), Feel (CHR/ASD+: mean = 13.28, SD = 1.91; CHR/ASD−: mean = 11.75, SD = 1.96; $\beta = -0.13$, $t = -3.36$, $p = .001$, Cohen's $d = 0.80$), and Lies (CHR/ASD+: mean = 26.77, SD = 3.72; CHR/ASD−: mean = 23.67, SD = 4.82; $\beta = -0.13$, $t = -3.38$, $p = .001$, Cohen's $d = 0.82$) scores compared to the CHR/ASD− group. No group differences were detected in Think, Say, or Sarcasm.

Conversion to Co-occurring Psychosis and Accuracy of Psychosis Risk Calculation.—There were no between-group differences in conversion rates [2-year conversion rate: CHR/ASD+: n = 4, 18.2% versus CHR/ASD−: n = 83, 14.0%; log-rank $\chi^2(1) = 0.21$, $p = 0.65$] or in the 1- or 2-year NAPLS Psychosis Risk Calculator scores (1-year: $\beta = -0.07$, $t = -1.60$, $p = .11$, Cohen's $d = 0.19$; 2-year: $\beta = -0.05$, $t = -1.07$, $p = .29$, Cohen's $d = 0.14$). Moreover, the 1-year and 2-year conversion risk scores derived from the NAPLS Psychosis Risk Calculator suggest that transition can be predicted equally well for the CHR/ASD+ and CHR/ASD− groups. Across groups, there was a main effect of risk (1-year: $\beta = 0.32$, $t = 6.96$, $p < .001$; 2-year: $\beta = 0.32$, $t = 6.89$, $p < .001$, but no main effect of ASD status (1-year: $\beta = 0.03$, $t = 0.74$, $p = 0.46$; 2-year: $\beta = 0.03$, $t = 0.56$, $p = .58$) or risk by ASD status interaction (1-year: $\beta = -0.02$, $t = -0.48$, $p = .63$; 2-year: $\beta = -0.10$, $t = -1.31$, $p = .19$).

DISCUSSION

Our results suggest several key points regarding individuals with ASD presenting with clinical high risk for psychosis. First, as expected given the hallmark diagnostic features of ASD and previous literature comparing ASD and CHR,[44] their social functioning and social anhedonia are worse than those of the broader CHR population. However, positive symptoms and all other negative symptoms appear quite similar in individuals with CHR with and without comorbid ASD. Second, individuals with ASD appear to be at risk equal to that of other individuals with CHR for converting to psychosis (conversion rate of ~ 18%). Finally, our findings suggest that the NAPLS Psychosis Risk Calculator for predicting whether full-blown psychosis will develop works similarly well in individuals with both

CHR and ASD, despite individuals with ASD, on average, presenting to CHR clinics at a younger age.

Although our results need to be interpreted with caution given the relatively small CHR/ASD+ sample size and the restriction of the ASD sample to cognitively and verbally able individuals, our findings nonetheless may have important implications for the interpretation and treatment of psychotic experiences in individuals with ASD who present to CHR services. As individuals with ASD plus CHR profiles appear at to be at regular risk for converting to co-occuring full-blown psychosis, in the CHR setting, clinicians ought to treat ASD as with other comorbidities and continue to be alert to decline and to signs of conversion to co-occurring psychosis. In other settings, clinicians treating patients with ASD where concerns about psychosis are raised must be cautious about diagnostic overshadowing, or prematurely misattributing psychotic experiences to the core ASD phenotype. In sum, across clinical settings, psychotic symptoms in individuals with ASD must be taken seriously and followed over time, as would be clinical best practice for any individual meeting CHR criteria.

Our data raise concerns that CHR symptoms may be underdiagnosed in individuals with ASD, as well as that individuals with ASD may be followed less often in CHR settings than warranted. Previous studies indicate increased rates of ASD in psychosis,[45] as well as increased rates of psychosis in ASD[9–11,46,47]; however, in the NAPLS2 sample, the rate of ASD in CHR patients was only 3.4%. Thus, it may be the case that individuals with ASD are not being referred to CHR settings as often as they experience symptoms, that their symptoms are not being considered seriously by their primary clinicians, that those with lower functioning ASD are being turned away from CHR services, and/or that CHR clinicians have difficulty assessing psychotic symptoms in patients with ASD or fail to identify ASD comorbidity in the CHR population. It is important to note here that among the many youth with ASD who have psychotic experiences,[46,47] a large percentage will never go on to develop a full-blown psychotic episode. As in the general population and among other adolescents using mental health services,[48] it is likely that within the ASD population psychotic experiences may result in referral to CHR settings only when accompanied by distress or a notable worsening in symptoms. Whether the NAPLS2 risk calculator and the variables that it includes are equally effective for predicting conversion to co-morbid psychosis in non–help-seeking ASD populations is unknown. Our findings must therefore be interpreted in the context of the help-seeking CHR population; future prospective, longitudinal studies examining transition to co-morbid psychotic disorders in youth with ASD are warranted to explore conversion rates across ASD broadly.

Epidemiological research is needed to further assess whether CHR appears at higher rates in ASD samples than in the general population. Special consideration may need to be given to how to assess for psychotic experiences in individuals with ASD who have intellectual disabilities or poor capacity to self-report. Autism-focused clinicians may need additional training and resources regarding when and how to refer their patients with ASD for longitudinal follow-up in a CHR setting. In particular, given that worsening functioning is not part of the natural history of ASD during adolescence,[49,50] autism-focused clinicians with limited experience assessing for or treating psychosis may consider referring their

patients for further evaluation or seeking consultation when there is emergence of new symptoms, worsening of existing symptoms, or decline in cognitive function during adolescence or young adulthood. Finally, clinicians in CHR settings may need additional training regarding identification of ASD comorbidity in their patients and assessing psychotic symptoms in individuals with ASD who have cognitive impairment and/or more limited language abilities.

This study is unique in leveraging a large-scale longitudinal dataset examining adolescents and young adults at clinical high risk for psychosis to probe the expression and prognostic importance of psychotic experiences in individuals with ASD and concerns about possible psychosis. Limitations include the following: a small ASD sample (potentially concealing associations with smaller effect sizes), given that this subpopulation was not explicitly recruited in the NAPLS2 sample; lack of ASD characterization with gold-standard diagnostic assessments (which could result in both less rigorous ASD diagnosis in the CHR/ASD+ group and low detection of possible unidentified ASD in the CHR/ASD− group); and an emphasis on verbally fluent individuals with ASD without significant intellectual disability, given NAPLS2 IQ exclusion criteria. Nonetheless, our findings suggest that individuals with ASD who present to CHR services do experience relatively classic CHR symptoms and develop full-blown illness at rates similar to those in youth with CHR without a history of ASD. Future longitudinal studies that directly recruit individuals with ASD, include thorough assessments of both ASD and psychosis symptoms, monitor psychosis symptoms and conversion rates over time, and explore individual predictors of transition to comorbid psychosis in ASD are clearly warranted to validate and extend our findings. Moreover, additional research is needed to clarify whether individuals with ASD showing CHR profiles will respond equivalently to psychopharmacological, cognitive, and psychosocial supports often recommended for young people at clinical high risk for psychosis. Such work will inform much-needed best practice recommendations for conceptualizing, diagnosing, and treating psychotic symptoms in individuals with ASD who present to mental health providers with concerns about possible psychosis.

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TABLE 1

Baseline Characteristics of Inividuals at Clinical High Risk for Psychosis (CHR) With (CHR/ASD+) and Without (CHR/ASD−) an Autism Spectrum Disorder (ASD) Diagnosis

	CHR/ASD−	CHR/ASD+	Statistics
Baseline Characteristics			
Age, y (mean, SD)	18.6 (4.2)	16.7 (3.9)	$t = -2.22$, $p = .026$
Sex, male (n, %)	413 (56.0)	23 (88.5)	$\chi^2(1) = 10.83$, $p = .001$
IQ estimate (mean, SD)	103.8 (15.2)	100.3 (16.7)	$t = -1.09$, $p = .28$
Education, y (mean, SD)	11.3 (2.8)	9.8 (2.8)	$t = -2.73$, $p = .006$
White ethnicity (n, %)	419 (56.9)	18 (69.2)	$\chi^2(1) = 1.57$, $p = .21$
Baseline Symptomatology (mean, SD)[a]			
Positive symptoms	11.93 (3.82)	11.73 (3.56)	$t = 0.09$, $p = .93$
Negative symptoms	11.85 (6.11)	13.00 (4.82)	$t = 0.72$, $p = .47$
Disorganization symptoms	5.13 (3.16)	5.88 (3.14)	$t = 1.21$, $p = .23$
General symptoms	9.19 (4.27)	8.27 (4.36)	$t = -0.49$, $p = .63$
GF:social score	6.23 (1.55)	4.85 (1.43)	$t = -4.44$, $p < .001$
GF:role score	5.96 (2.22)	5.65 (1.83)	$t = -0.20$, $p = .86$
TASIT Total Score	52.51 (6.02)	47.67 (6.84)	$t = -3.17$, $p = .002$

Note: GF = global functioning; TASIT = The Awareness of Social Inference Test.

[a]Analyses are controlled for sex and age.

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