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Schizotypal Personality Disorder in individuals with the Attenuated Psychosis Syndrome: frequent co-occurrence without an increased risk for conversion to threshold psychosis

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Abstract

The Attenuated Psychosis Syndrome (APS), proposed as a condition warranting further study in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), is a controversial diagnostic construct originally developed to identify individuals at clinical high-risk for psychosis. The relationship of APS and Schizotypal Personality Disorder (SPD) remains unclear with respect to their potential co-occurrence and the effect of SPD on risk for conversion to threshold psychosis. We examined the prevalence and effect on conversion of SPD in a cohort of 218 individuals whose symptoms met APS criteria. Results indicated that SPD was highly prevalent (68%), and that SPD did not influence risk for conversion. Rather, total positive symptom burden measured by the Structured Interview for Psychosis-Risk Syndromes (SIPS; OR 1.12, $p=0.02$) emerged as the strongest predictor of conversion. These data suggest that when encountering a patient whose presentation meets SPD criteria, the clinician should assess whether

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Contributors

AWZ, JAB, JG, GB, and RRG designed the study. JG, MDM, CMC, GB, and RRG obtained the data. AWZ, JAB, JG, MDM performed data analyses. AWZ and JAB wrote the first draft of the manuscript. AWZ, JAB, JG, GB, and RRG edited the manuscript. All authors reviewed, contributed to, and approved the final version of the paper.

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Conflicts of interest

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APS criteria are also met and, for 1-2 years, carefully monitor positive symptoms for possible conversion to threshold psychosis.

Keywords

Attenuated psychosis syndrome; schizotypal personality disorder; clinical high-risk for psychosis; prodromal psychosis; schizotypy

1. Introduction

Schizophrenia is a chronically disabling mental illness that is a top ten cause of disability worldwide in adults aged 15-44 years (Rossler et al., 2005). Since the development of antipsychotic medications in the 1950s, there have been few advances in the treatment of schizophrenia and related disorders. The identification of individuals at clinical high-risk (CHR) for psychosis holds promise for early intervention to prevent or alter the course of psychotic illnesses, such as schizophrenia or schizoaffective disorder. For example, it is known that a longer duration of untreated psychosis during the first episode of psychosis is associated with worse overall functioning and greater symptom burden (Marshall et al., 2005). Predicting who will develop a psychotic disorder has been challenging, not only due to the heterogeneity and complexity of these disorders, but also because psychoses commonly emerge during adolescence and peak in young adulthood, when a variety of potentially severe mental illnesses first present (Lee et al., 2014). Recent research in psychosis risk prediction has focused on attenuated positive symptoms of psychosis, which are psychosis-like symptoms of lower severity and behavioral impact, and more intact reality testing. These symptoms might represent a transient state on the path to a psychotic disorder or a persistent trait, as seen in personality disorders.

Researchers have developed diagnostic concepts to capture and distinguish these state and trait phenomena, though the relationship between these entities remains unclear. The Progression subtype of the Attenuated Positive Symptom Psychosis-Risk Syndrome (APSS), operationalized by the Structured Interview for Psychosis-Risk Syndromes (SIPS), requires at least one subthreshold psychotic symptom rated at a severity of 3 to 5, occurring once or more per week during the same month (McGlashan TH, 2010; Woods et al., 2014). However, only approximately 30% of patients whose symptoms meet APSS criteria convert to threshold psychosis after 2 years (Fusar-Poli et al., 2012). The APSS construct served as the basis for the Attenuated Psychosis Syndrome (APS), included as a condition for further study in the Diagnostic and Statistical Manual 5th edition (DSM-5), with the additional requirement that a patient's symptoms be severe enough to warrant clinical attention (American Psychiatric Association., 2013). The phenotypic overlap between APS and the Progression subtype of APSS is substantial and the literature commonly groups them together, which we will do here as well.

The relationship between APSS/APS and Schizotypal Personality Disorder (SPD), which is typically considered a relatively stable entity representing a combination of cognitive, perceptual, and interpersonal difficulties beginning in late adolescence or early adulthood, is presently unclear (American Psychiatric Association., 2013; Tsuang et al., 2013). There are

several key similarities and differences between these categories. All three can present with subthreshold hallucinations and delusions, and disorganized speech and are considered part of the “schizophrenia spectrum,” suggesting they share genetic risk factors and underlying pathophysiology. However, a diagnosis of the APSS Progression subtype or APS requires that at least one positive symptom must have begun or worsened in the past year and occur at least once per week for the past month, whereas symptoms of SPD are more chronic and longstanding. The distinction is further complicated in that all three typically emerge in late adolescence or young adulthood (American Psychiatric Association., 2013). However, diagnostic criteria for SPD include inappropriate or constricted affect, odd behavior or appearance, lack of close friends, and excessive social anxiety, none of which are part of the APSS or APS constructs. It is often unknown whether a subthreshold psychotic symptom reflects a state (e.g., APSS/APS) or trait (e.g., SPD) phenomenon, and patients can have combinations of symptoms reflecting both states and traits. Thus, it is theoretically possible for APSS/APS to occur in an individual with a longstanding diagnosis of SPD, reflecting a “flare-up” of positive symptoms which never achieves a psychotic level of intensity.

There is also controversy regarding the stability of SPD, both in terms of later conversion to threshold psychosis and whether patients continue to meet diagnostic criteria over time. Rates of conversion from SPD to threshold psychosis are variable and range from 6.25-48% depending on subject population and length of follow-up (Fenton and McGlashan, 1989; Nordentoft et al., 2006; Parnas et al., 2011) and a significant portion of patients’ symptom presentations no longer meet full SPD criteria after a ten-year period (Sanislow et al., 2009).

To date, studies specifically examining the relationship between the presence of SPD and conversion in CHR (but not specifically APSS or APS) populations have yielded mixed results: two found that SPD was associated with conversion to threshold psychosis (Klosterkotter et al., 2001; Ruhrmann et al., 2010), while a third found no relationship between SPD and conversion to threshold psychosis (Schultze-Lutter et al., 2012), though the latter study was limited by a small number of SPD subjects and the use of a self-report questionnaire for diagnosis. Importantly, these studies had differing methodologies, making it difficult to compare their results. For example, they varied in their inclusion criteria (Nordentoft et al., 2006; Ruhrmann et al., 2010; Schultze-Lutter et al., 2012) and diagnostic assessment tools (Klosterkotter et al., 2001).

The unclear relationship between SPD and DSM-5 APS in particular is one of several reasons APS has not yet been accepted as a diagnosis in the DSM (Tsuang et al., 2013). To our knowledge, there are no prior studies examining rates of SPD in an exclusively DSM-5 APS cohort. The literature describing rates of SPD among people with APSS varies substantially, ranging from 2.7% (Addington et al., 2015) to 30.8% (Cannon et al., 2008), though the former was restricted to individuals under the age of 19. The European Prediction of Psychosis Study (EPOS) cohort which was comprised of individuals meeting ultra-high-risk or basic symptom-based criterion with cognitive disturbances rather than APSS or APS, published a frequency of SPD of 13.5% (Ruhrmann et al., 2010). Two other large studies involving ultra-high-risk (Nelson et al., 2013) and CHR (Carrion et al., 2016) individuals did not report the frequency of SPD in their cohorts.

Studies that have evaluated the effect of SPD on conversion in an APSS cohort are even fewer and results have been equivocal. The first phase of the North American Prodrome Longitudinal Study (NAPLS) was the largest study to investigate the effect of SPD on risk of conversion among people with APSS and found no effect of SPD (Cannon et al., 2008). However, two prior studies have found that SPD was associated with conversion to threshold psychosis in CHR cohorts (Klosterkotter et al., 2001; Ruhrmann et al., 2010). Understanding the comorbidity of APSS/APS and SPD and the effect of SPD on psychosis conversion risk could clarify our approach to individuals with mixed state and trait symptoms and shed light on the relationship between these two syndromes. Further, misdiagnosis or premature diagnosis of either APSS, APS, or SPD is problematic, as these conditions have different courses, prognoses, and treatments. In this paper, in an effort to clarify the relationship between SPD, SIPS APSS and DSM-5 APS, we present novel findings regarding the prevalence of SPD in a cohort of persons meeting both APSS Progression and DSM-5 APS criteria, and the influence of SPD on risk for conversion to threshold psychosis in this population.

2. Methods

2.1 Study population

A cohort of help-seeking participants whose presentations met both DSM-5 APS and SIPS APSS (Progression subtype) criteria were recruited to the Center of Prevention and Evaluation (COPE) at the New York State Psychiatric Institute (NYSPI). Exclusion criteria included being outside the age range (<13 or >30); lack of proficiency in English; a current or lifetime DSM Axis-I psychotic disorder, including affective psychoses; a DSM disorder better accounting for the clinical presentation; IQ < 70; medical conditions affecting the central nervous system; marked risk of harm to self or others; unwillingness to participate in research; geographic distance; or current substance abuse or dependence. Written informed consent was provided by those 18 years or older. Minors gave written assent, with written informed consent provided by a parent/legal guardian. Separate consents and assents were signed by eligible individuals electing to participate. Use of antipsychotic medication was not exclusionary, provided clear evidence that positive symptoms of an attenuated, but never fully psychotic level were present at medication onset. The study was preapproved by NYSPI's Institutional Review Board. Further details on enrollment are provided elsewhere (Brucato et al., 2017).

2.2 Clinical Assessments

All participants were evaluated using the SIPS, which includes the SPD checklist and a quantitative assessment of positive symptoms (P), negative symptoms (N), disorganization (D), and general symptoms (G). Participants were seen for follow-up with the SIPS every 3 months for 2 years, or whenever conversion was suspected. Post-conversion diagnoses were established by COPE psychologists and/or psychiatrists. SIPS administrators were certified and established scoring consensus. SPD was not diagnosed in individuals under age 18 unless symptoms were present for at least one year. Social (conflict and quality of interpersonal relationships) and role (performance in age-appropriate roles) functioning were

assessed using the Global Functioning Scale: Social (GF: Social) and Global Functioning Scale: Role (GF: Role) (Cornblatt et al., 2007).

2.3 Statistical analyses

Data from the initial and follow-up visits were integrated into a single data set. Entries with all or mostly missing data were deleted. Only subjects who completed evaluations for SPD at their initial meeting were included in this analysis. Descriptive statistics for subjects with and without SPD were calculated.

We used a two-step procedure to identify variables associated with diagnosis of SPD at baseline and, separately, with conversion to threshold psychosis. In the first step, we conducted univariate analyses (Chi-squared test or logistic regression) to screen candidate variables. In the second step, any variable with a univariate test p-value of less than 0.2, along with variables known to be associated with the outcome (SPD diagnosis or conversion to threshold psychosis) were included in a multivariate model. Variables with p-values less than 0.1 in the multivariate model were deleted but were re-incorporated if the coefficient for any remaining variable changed by more than 20%. We controlled for age and gender in both final models.

3. Results

Of 218 participants, 177 completed evaluations for SPD at baseline, and 120 (68%) had symptoms that met criteria for the disorder. Participants ranged in age from 13 to 29 years old at baseline, were predominantly male, and came from a variety of racial and ethnic backgrounds. Fifty-four participants (31%) converted to threshold psychosis over the observation period. Baseline demographic information for the entire sample, and for participants with and without SPD, are presented in Table 1.

There were 8 incident cases of SPD and 18 participants who had SPD at baseline whose symptoms did not meet criteria for SPD at some point during the follow up period. See Table 2 for baseline clinical characteristics of SPD and non-SPD participants. All four SIPS subscales were significantly associated with SPD status at baseline (see Table 2), however, only the P and N subscales remained in the final model (SIPS Positive Subscale, OR=1.3 for each point increase in the subscale, $p<0.0001$; SIPS Negative Subscale, OR=1.13, $p=0.004$).

In an unadjusted analysis, individuals with SPD at baseline were at greater risk of conversion to threshold psychosis (37% conversion versus 21%, unadjusted $p=0.04$). However, after controlling for participants' underlying symptom burden at baseline, as measured by the SIPS subscales, SPD status was no longer significant and only positive symptoms were associated with conversion to threshold psychosis (SIPS Positive Subscale OR=1.12, $p=0.02$; SPD adjusted $p=0.58$). Neither age at baseline SPD assessment and nor gender were significant in predicting conversion to threshold psychosis.

4. Discussion

We sought to clarify the relationship between persons whose symptoms meet both SIPS APSS and DSM-5 APS criteria, as well as SPD, and assess whether the presence of SPD increases an individual's risk for conversion to threshold psychosis. Our results indicate that the majority of individuals in our sample of APSS/APS patients also had long-standing symptoms consistent with SPD. This means that some individuals with longstanding SPD symptoms have a "flare-up" of their positive symptoms in the year preceding baseline assessment, which meet both the SIPS APSS Progression subtype and current DSM-5 APS criteria. These results also suggest that many APSS/APS patients do not have only one recent or worsening attenuated psychotic symptom, but, rather, present with multiple, stable symptoms, across several domains including negative symptoms and social dysfunction, in addition to at least one new or worsening symptom. While there is significant phenotypic overlap between APSS/APS and SPD, they can be reliably distinguished based on level of an individual's distress and the time course, frequency, and type of symptoms.

We also found that SPD diagnosis at baseline was associated with increased positive and negative symptom scores on the SIPS. This correlation in part reflects the overlap between the items on the SIPS and the DSM-5 diagnostic criteria for SPD such as unusual thought content or perceptual experiences, suspiciousness, odd thinking, behavior, and appearance, and inappropriate affect, among others. SPD diagnosis at baseline was associated with an increased rate of conversion to threshold psychosis. However, the association between SPD and conversion to threshold psychosis was no longer significant when taking positive symptom burden as measured by the SIPS into account. This implies that it is the presence of APSS/APS and worsening positive symptoms, rather than longstanding symptoms of SPD, that is associated with conversion to threshold psychosis. This finding is consistent with previous work that has shown that positive symptom severity, particularly P.1. Unusual Thought Content/Delusional Ideas and P.5. Disorganized Communication, is among the strongest risk factors for conversion (Brucato et al., 2017). Our finding regarding the lack of an effect of SPD on conversion is consistent with several similar studies of large cohorts of CHR and individuals meeting SIPS APSS criteria (Cannon et al., 2008; Schultze-Lutter et al., 2012). Notably, our results contrast with two prior studies that detected an increased risk for psychosis in CHR individuals with SPD (Klosterkotter et al., 2001; Ruhrmann et al., 2010).

Our cohort has a higher prevalence of SPD compared to other studies of young people at risk for psychosis (Addington et al., 2015; Cannon et al., 2008; Ruhrmann et al., 2010) and is higher than our previous report on this sample (Brucato et al., 2017). The discrepancy between this report and our previous work is explained by our case selection; for this report, we required participants to have been evaluated for SPD at baseline, whereas previous reports allowed for evaluation at any time during follow-up. Referral bias and the help-seeking required by the DSM-5 APS also likely contribute to the elevated prevalence compared to other samples.

These findings have several implications. Our data suggest that APSS/APS and SPD are distinguishable but often co-occurring diagnostic constructs in younger patients with

attenuated psychotic symptoms. This co-occurrence contrasts with a recent review of the DSM-5 APS diagnostic construct that states, “the recent onset and transitory criteria [of APS] preclude a diagnosis of schizotypal personality” (Tsuang et al., 2013). To highlight the potential for their co-occurrence, consider the example of a 21-year-old patient who has had 4 years of magical thinking, odd affect, interpersonal deficits, eccentric appearance, and lack of close friends who now endorses intensifying “whispers” twice weekly over the past two months with intact reality testing. Assuming that these symptoms were not due to another psychiatric disorder or a representation of their culture, this patient’s symptoms would meet criteria for both SPD based on long-standing social and cognitive abnormalities, as well as the SIPS APSS Progression subtype and DSM-5 APS, based on the recent onset of hallucinatory experiences with intact reality testing. This example is provided not to comment on the validity of either diagnostic construct, but rather to highlight that it is possible for an individual to meet diagnostic criteria for both conditions. The results of our study show that the recent intensification of positive symptoms (rather than their longstanding nature) is the most concerning aspect of this person’s history. We note that the APSS/APS constructs are by no means fully predictive of an individual’s risk for conversion to threshold psychosis. The NAPLS risk calculator (Cannon et al., 2016) improves upon the predictive value of the APSS/APS constructs by incorporating variables such as age and performance on select cognitive tests.

Despite the frequent comorbidity of the APSS/APS categories and SPD, we demonstrate that a large percentage of patients with a baseline diagnosis of SPD (37%) convert to threshold psychosis, highlighting that they did not truly have schizotypal personality disorder but were rather individuals on the path to developing a psychotic illness. This finding also suggests that we should question the validity of the SPD diagnosis in adolescents and young adults. Importantly, as we have shown, in an APSS/APS cohort, SPD is not an independent predictor of developing a psychotic disorder. Rather, new or intensifying positive symptoms, as defined by the SIPS APSS Progression subtype and DSM-5 APS, remain the strongest predictor of conversion, and APSS/APS individuals also meeting SPD criteria are not at further risk of conversion to threshold psychosis. Thus, we argue that when encountering a patient that meets APSS/APS criteria within the past year, even in the context of a longstanding SPD diagnosis, the clinician should carefully monitor their symptoms for 1-2 years to await possible conversion to threshold psychosis. Follow-up assessments would then reveal whether an individual converted to threshold psychosis or simply had a “flare-up” of the positive symptoms of SPD which eventually reverts to one’s longstanding baseline.

There are several limitations to the study presented here. First, 41 (19%) participants did not have an SPD assessment at baseline and were removed from the analysis. Further, since our participants were help-seeking, our results may not be generalizable to other CHR populations and may be subject to referral or ascertainment bias.

While these results require replication before clinical recommendations can be made, they provide preliminary evidence that the APSS/APS constructs, and SPD are distinct but often co-occurring diagnostic constructs. The results also demonstrate that recent onset and intensifying positive symptoms remain the strongest predictor of conversion to threshold

psychosis and that SPD, in a sample of APSS/APS patients, is not an independent predictor of psychosis. Lastly, anyone whose presentation meets criteria for SPD should be assessed for the presence of APSS/APS symptoms and, if detected, should be monitored closely for conversion to threshold psychosis for a period of at least 1 to 2 years.

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Table 1

Baseline demographic characteristics of COPE sample

	SPD	No SPD	P-value (test performed)
	N = 120 Mean (SD)	N = 57 Mean (SD)	
Age	20.3 (3.8)	19.9 (4.1)	0.556 (t-test)
Sex	Count (%)	Count (%)	
Male	87 (73%)	39 (68%)	
Female	32 (27%)	18 (32%)	0.641 (Chi-squared)
Missing	1 (0.01%)	0 (0%)	
Race			
Caucasian	49 (41%)	31 (54%)	
African American	28 (24%)	12 (21%)	
Asian	11 (9%)	3 (5%)	0.408 (Fisher exact)
Mixed	31 (26%)	11 (19%)	
Missing	1 (1%)	0 (0%)	
Ethnicity			
Hispanic	38 (32%)	16 (28%)	
Non-Hispanic	81 (68%)	41 (72%)	0.730 (Chi-squared)
Missing	1 (1%)	0 (0%)	
Education			
<High school	22 (18%)	16 (28%)	
High school	27 (23%)	10 (18%)	
Technical school	0 (0%)	0 (0%)	
Some college	48 (40%)	21 (37%)	0.682 (Fisher exact)
BA or BS	16 (13%)	7 (12%)	
Graduate school	3 (0.3%)	1 (2%)	
Missing	4 (0.3%)	2 (4%)	

COPE = Center of Prevention and Evaluation, SPD = Schizotypal Personality Disorder

Table 2

Clinical characteristics of COPE sample

	SPD	No SPD	P-value (test performed)
	N = 120 Mean (SD)	N = 57 Mean (SD)	
P total score	16.2 (3.1)	12.1 (4.2)	< 0.001 (logistic regression)
N total score	18.8 (6.2)	14.6 (6.4)	0.002 (logistic regression)
D total score	11.3 (3.5)	7.6 (3.6)	< 0.001 (logistic regression)
G total score	12.8 (4.3)	10.6 (5.5)	0.024 (logistic regression)
GF social score	5.1 (1.7)	6.4 (1.5)	0.226 (logistic regression)
GF role score	5.4 (2.2)	6.3 (1.7)	0.203 (logistic regression)
Family history of psychosis	Count (%)	Count (%)	
Yes	29 (24%)	15 (46%)	
No	74 (62%)	24 (42%)	0.326 (Chi-squared)
Missing	17 (14%)	18 (32%)	
Medications			
None	43 (36%)	26 (46%)	
AP	9 (8%)	4 (7%)	
AD	8 (7%)	2 (4%)	0.604 (Fisher exact)
Both	4 (3%)	4 (7%)	
Missing	56 (47%)	21 (37%)	

COPE = Center of Prevention and Evaluation, SPD = Schizotypal Personality Disorder, P = SOPS positive symptoms, N = SOPS negative symptoms, D = SOPS disorganized symptoms, G = SOPS general symptoms, GF = Global Functioning, AP = antipsychotic, AD = antidepressant