Childhood Onset Diagnoses in a Case Series of Teens at Clinical High Risk for Psychosis

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Abstract

Reasons: Schizophrenia is typically an adult neurodevelopmental disorder that has its antecedents in childhood and adolescence. Little is known about disorders “usually first diagnosed in infancy, childhood and adolescence” (e.g., childhood-onset disorders) in “prodromal” teens at heightened clinical risk for psychotic disorder.

Main Findings: Childhood-onset disorders were prevalent in putatively prodromal teens, including anxiety and disruptive disorders, attention-deficit/hyperactivity disorder (ADHD), and, surprisingly, elimination disorders. These may reflect developmental antecedents in psychotic disorders such as schizophrenia.

Key Data and Statistics: A case series of 9 teens (ages 13–17) identified as prodromal to psychosis were evaluated with the Kiddie Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Version (K-SADS-PL). Childhood-onset diagnoses commonly endorsed (threshold or subthreshold) included ADHD (5/9), oppositional defiant disorder (5/9), enuresis or encopresis (4/9), conduct disorder (2/9), separation anxiety (3/9), and transient tic disorder (2/9). Enuresis was identified in 3 of the 4 older teens (ages 15–17).

Major Conclusions: An understanding of the childhood-onset disorders that occur in teens at risk for psychotic illnesses, such as schizophrenia, can shed light on the pathophysiology of schizophrenia and potentially inform early identification and intervention.

Introduction

SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS have their antecedents in childhood and adolescence (Rutter et al. 2006). Although much is known about concurrent co-morbidity in schizophrenia (Bermanzon et al. 2000; Green et al. 2003), such as substance misuse (Westermeyer 2006), depression (Häfner et al. 2008), and obsessive compulsive disorder (Bottas et al. 2005), little is known about disorders “usually first diagnosed in infancy, childhood and adolescence” (e.g., childhood-onset disorders) in individuals with schizophrenia. Population cohort studies reveal a number of abnormalities throughout development that are more common in children who later develop schizophrenia, including delays in developmental milestones in infancy and toddlerhood, more isolated play and speech difficulties from ages 4 to 6, and “clumsiness” at ages 7 and 11 (Meares 1959; Done et al. 1994; Jones et al. 1994; Tarrant and Jones, 1999). Attentional and social difficulties are also identifiable precursors of schizophrenia (Olin et al. 1998). In offspring of individuals with schizophrenia, deficits in attention and motor skills precede psychosis onset (Erlenmeyer-Kimling 2001). Early signs in the development of schizophrenia

have been characterized as “pandepvelopmental dysmaturation” (Fish et al. 1992).

Little is known, however, about diagnoses that characterize children and teens that go on to develop schizophrenia. We know of only one study of diagnoses in offspring of individuals with schizophrenia—the Jerusalem Infant Development Study—which found prevalent affective and anxiety disorders (~25% each), and “disruptive behavior disorders” (37%) in this group at high genetic risk (Hans et al. 2000). Remarkably, there appear to be no retrospective studies of childhood-onset diagnoses in schizophrenia, which may belie an underappreciation of the developmental features of schizophrenia (Rutter et al. 2006) and/or concerns about recall bias years later. Retrospective studies with adults with first-episode psychosis suggest that a prodromal period in teen years is common (Häfner et al. 1998), and is characterized by social withdrawal, affective symptoms (especially depression), and the emergence of subthreshold psychotic symptoms, e.g., illusions, overvalued ideas, and suspiciousness (Moller and Husby 2000; Corcoran et al. 2007). The existence in a teen or young adult of subthreshold positive symptoms in the context of functional decline has been characterized as a “clinical high risk” or putatively

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“prodromal” state, with a positive predictive value of 35–50% (Miller et al. 2003; Yung et al. 2004; Cannon et al. 2008). There exist four previous studies of “co-morbid” diagnoses in clinical high risk or “prodromal” patients (Preda et al. 2002; Meyer et al. 2005; Haroun et al. 2006; Rosen et al. 2006).

Among these four studies that assessed diagnoses in “prodromal” patients, two were done at the same site. The earlier study employed chart review and found in a cohort ages 12–35 (mean 17, standard deviation [SD] 5) primarily mood disorders (23%), attention-deficit/hyperactivity disorder (ADHD) (17%), and rare instances of autism spectrum disorders (4%) and oppositional defiant disorder (ODD)/conduct disorder (CD) (2%) (Preda et al. 2002). The later study had improved methodology in that a structured interview was used to determine diagnosis (i.e., the Structured Clinical Interview for DSM-III-R–Patient Version [SCID-P]), but albeit one designed for adults (Rosen et al. 2006). Not surprisingly, these investigators identified prevalent mood (59%) and anxiety (28%) disorders and substance abuse/dependence (31%), but there was a paucity of childhood-onset diagnoses (Rosen et al. 2006). A third study, done at the University of California, San Diego (UCSD), also found prevalent mood (50%), anxiety (33%), and substance (38%) disorders in a prodromal cohort, using both the SCID and Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (although childhood-onset diagnoses were largely not described). A fourth study, done at the University of California Los Angeles (UCLA), used the K-SADS, which can capture childhood-onset diagnoses, but limited its use to participants younger than 15, using the SCID-P for older teens (Meyer et al. 2005). In this cohort of 24 teens ages 12–19, mood disorders were common (e.g., major depressive disorder [MDD] 50%), anxiety disorders less so (17% for generalized anxiety disorder [GAD], 4% each for panic, posttraumatic stress disorder [PTSD], specific, and social phobia), but there were only rare reports of ADHD and other childhood-onset disorders. *Post hoc* chart review demonstrated prevalent ADHD among the older teens who had not been administered the K-SADS. Herein, we build on the results of this study by Meyer et al. by employing the K-SADS in assessing diagnoses in prodromal teens as old as 17. We hypothesized that mood and anxiety disorders would be common, as well as ADHD. We also expected to uncover childhood-onset diagnoses in older teens which may not have been described previously.

Methods

The Center of Prevention and Evaluation (COPE) is a longitudinal clinical cohort study of adolescents and young adults identified as at heightened clinical risk for or “prodromal” to psychosis. Located in northern Manhattan, COPE recruits ethnically diverse individuals from the New York metropolitan area through the use of: (1) Mailed brochures to schools, religious institutions, clinics, and community programs; (2) oral presentations, both in academic and community settings; and (3) web pages and links at Columbia, New York State, and schizophrenia-related websites. Patients are primarily referred by clinicians, although referrals also occur from schools, clergy, and by young people themselves or by their family. No general screening of the general population occurs.

Cases were identified as “prodromal” to psychosis by virtue of subthreshold psychotic symptoms using the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al. 2003). Reliability for the SIPS/Scale of Prodromal Symptoms (SOPS) was established with the Recognition and Prevention prodromal research group at Hillside Hospital (intraclass correlation coefficient

[ICC] > 0.70 for individual scale items and 100% for syndrome ratings.) Prodromal cases are between the ages of 12 and 30 and must fulfill criteria for at least one of three prodromal syndromes: Attenuated positive symptoms, brief intermittent psychotic symptoms, and/or functional decline in the context of genetic risk (Miller et al. 2003). Potential participants are excluded for lack of fluency in English, any history of psychosis, serious risk of harm to self or others, major medical or neurological disorder, or mental retardation (intelligence quotient [IQ] < 70, with functional impairment). Substance use is not an exclusion criterion as long as positive symptoms have not occurred solely in the context of substance use or withdrawal. This study was approved by the Institutional Review Board at the New York State Psychiatric Institute (NYSPI). Parents provided written informed consent, and their children provided written assent.

“Co-morbid” diagnoses in patients younger than 18 were assessed with the Kiddie-Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version (K-SADS-PL) (Kaufmann et al. 1997). Parents and children were interviewed separately. Although every effort was made to interview both parents for the K-SADS if a second parent was available, only two of the nine K-SADS relied on information gathered from both parents. Summary ratings were obtained from all sources of information. The psychosis section was not administered to participants, because they were known to have attenuated positive symptoms. All interviews were conducted by psychiatrists and psychologists with advanced training in diagnosis. Final diagnoses were reached by consensus meetings with experts in the administration and use of the K-SADS-PL (Kaufmann et al. 1997). Diagnoses were considered “subthreshold” if symptoms were present but full criteria were not clearly met. For example, diagnoses of “subthreshold” enuresis or encopresis were made when parents were unable to recall the exact frequency or duration of the incontinence.

Results

This is an ethnically diverse and predominantly male case series of 9 prodromal patients with a wide range of exposures to diverse psychotropic medications and prevalent family history of psychosis. All cases met criteria for at least one subthreshold or threshold diagnosis (Table 1). There were only 2 females in this cohort; 1 had a diagnosis of enuresis and the other no diagnosis. By contrast, males had a mean of four threshold diagnoses each. There were no ethnic differences in diagnosis, although Hispanic patients appeared less likely to have received medications than Caucasian patients. Among cases with a history of psychosis in a first-degree family member, there was a paucity of diagnoses among the younger group but an average of six threshold diagnoses in the older group.

Anxiety disorders were prevalent: Only 1 of 9 cases did not have at least a subthreshold anxiety diagnosis. Of the 9 cases, 4 met criteria for obsessive compulsive disorder (OCD), and both specific and social phobia were present in three cases. One third had major depression. As for childhood-onset diagnoses, ADHD and ODD were both diagnosed in 5 of 9 individuals, enuresis ($\pm$ encopresis) in 4 teens, separation anxiety in 3, conduct disorder in 2, and transient tic disorder in 2. No cases of substance abuse or dependence were diagnosed in these teens, despite prevalent cannabis misuse in prodromal cases 18 and older (Corcoran et al., 2008). The 1 case (17 years old) who met subthreshold criteria for nicotine dependence, alcohol abuse, and cannabis abuse was the 1 patient who converted to psychosis (mania). This case was also the only one prescribed a mood stabilizer.

TABLE 1. CHILDHOOD DISORDERS IN TEENS AT CLINICAL HIGH RISK FOR PSYCHOSIS

<i>Sex</i>	<i>Age</i>	<i>Race</i>	<i>Medication history</i>	<i>Psychosis family history</i>	<i>GAF</i>	<i>Threshold diagnoses</i>	<i>Subthreshold diagnoses</i>
F	13	Caucasian	No	No	53	Enuresis ^a	ODD ^a
M	13	Caucasian	Antipsychotic Antidepressant Stimulant	N/A (adopted)	40	ADHD ^a ODD ^a OCD	MDD
F	14	Hispanic	No	Yes	51	No	ADHD ^a CD (lies) ^a ODD ^a GAD
M	14	Caucasian	Antipsychotic Antidepressant	No	48	OCD Social phobia Specific phobia	No
M	14	African American	Antipsychotic Stimulant	Yes	51	Tic ^a	SAD ^a ADHD ^a ODD ^a
M	15	Hispanic	No	Yes	48	Enuresis ^a SAD ^a Specific phobia GAD OCD PTSD	No
M	16	Hispanic	Antidepressant Sedative/hypnotic	Yes	41	SAD ^a Specific phobia GAD MDD PTSD Social phobia	No
M	17	Caucasian	Antipsychotic Antidepressant	No	41	GAD MDD OCD Social phobia	ADHD ^a Encopresis ^a Enuresis ^a TIC ^a
M	17	Caucasian	Antipsychotic Antidepressant Mood stabilizer Sedative/hypnotic	No	44	CD ^a Enuresis ^a ODD ^a PTSD	ADHD ^a Alcohol abuse Cannabis abuse Nicotine dependence

^aDisorders usually first diagnosed in infancy, childhood, or adolescence.

Abbreviations: GAF=Global Assessment of Functioning; F=female; M= male; N/A=not applicable; ODD=oppositional defiant disorder; ADHD=attention-deficit/hyperactivity disorder; MDD= major depressive disorder; OCD=obsessive-compulsive disorder; CD=conduct disorder; GAD=generalized anxiety disorder; TIC=transient tic disorder; SAD=separation anxiety disorder; PTSD=posttraumatic stress disorder.

Six cases had been prescribed medications, primarily antipsychotics ($n=5$) and antidepressants ($n=5$; prescribed primarily to patients with mood and/or anxiety disorders). Two cases were given stimulants and appropriately had diagnoses of threshold or subthreshold ADHD. One of these cases also had a tic disorder, which led to prescription of an antipsychotic. Of note, the 1 patient who met criteria for six diagnoses was prescribed no medications at all.

Of these 9 cases, 4 were 15 and older, a prodromal subgroup that is rarely assessed using the K-SADS. There were a number of childhood-onset disorders in this older group of 4 cases: Separation anxiety ($n=2$), subthreshold ADHD ($n=2$), ODD ($n=1$), CD ($n=1$), transient tic disorder ($n=1$), enuresis ($n=3$), and encopresis ($n=1$). As for disorders that also occur in adults, 3 of the 4 older cases had generalized anxiety disorder and 3 had posttraumatic stress disorder (PTSD). This older group also had more threshold diagnoses (mean=5) than the younger group (mean=1.6).

The temporal sequence of diagnoses for 2 of the older prodromal patients, who each had a mother with psychosis, was quite similar, with a series of anxiety disorders, beginning with separation anxiety and simple phobia, then GAD, and culminating in PTSD in the

context of physical trauma. For both young men, subthreshold psychotic symptoms included unusual perceptual experiences (auditory, tactile, and visual), primarily at night, suspiciousness and a sense of being watched, and a preoccupation with the paranormal, including premonitions, extraterrestrials, ghosts, ouija boards, etc. One of these young men developed a phobia of barbershops at age 13 and then became preoccupied with his "widow's peak," worried he would be teased, and missing several days of school as a consequence. The other young man had symptoms of depression and stopped going to school altogether.

The 2 other older prodromal patients had no family history, and both had symptoms of enuresis from a young age until the ages of 9–11. One of these young men also had an unfolding of diagnoses, beginning with social phobia (ages 4–5), then the onset of encopresis (age 7), a diagnosis of ADHD at age 8, and observed frequent handwashing by age 9. He had enuresis from very young until the age of 11. His transient tic disorder resolved when stimulants were stopped. Then, in his teen years, he became odd and socially withdrawn, with declining academic performance and subsequent school refusal, depressed mood, and trouble concentrating. His subthreshold psychotic symptoms included a sense of

premonition, guilt about his wish to be important, and a sense of spiritual journey and a special relationship with God. He worried about people looking at him in a negative manner and sometimes felt singled out and watched. He could at times hear his own thoughts.

The other older patient without a family history had been essentially normal until the age of 10 (except for enuresis), when he quit sports, refused to see friends, and his grades declined. He became aggressive to family members and started fires, such that his family placed him in a "therapeutic" boarding school at age 13. He returned 2 years later emotionally detached, socially withdrawn, and "placid." He developed attentional difficulties and PTSD symptoms, and briefly used drugs. Increasingly, he described a sense that something was wrong with his brain ("a chemical change as if it is separated in half") and feelings of confusion and a fake reality ("all I feel is white light"), which culminated in a psychotic episode.

Discussion

In these 9 prodromal youths administered the K-SADS-PL, all had at least one threshold or subthreshold diagnosis. Anxiety disorders were particularly prevalent (89%), characterizing all but 1 individual. The prevalence of specific anxiety disorders and major depression was 33–44%. Childhood-onset disorders were also prevalent: 56% for ADHD and ODD, respectively, 44% for enuresis ($\pm$ encopresis), 33% for separation anxiety, and 22% for conduct and transient tic disorders, respectively. The diagnosis of childhood-onset disorders was even more common among the 4 older teens, suggesting that it is important to assess these disorders among older prodromal patients as well.

Of interest, anxiety disorders were more common in our cohort (89%), compared with rates of 28% (Rosen et al. 2006) and 17% (Meyer et al. 2005) in other cohorts. By contrast, we found substantially less depression (33%) than in these other cohorts: 59% (Rosen et al. 2006) and 50% (Meyer et al. 2005). This may be related to differences in ascertainment and patient characteristics. The patients studied by Rosen et al. (2006) were in a randomized clinical trial, and may therefore have been more ill than our patients, who are in an observational cohort study. Likewise, the cohort studied by Meyer et al. (2005) had higher rates of previous hospitalization than ours (38% vs. 0%). The prevalence of substance use was 11% in our study, compared with 31% in the Rosen et al. (2006) study, and 0% in the Meyer et al. (2005) study, which had substance abuse/dependence as an exclusion criterion.

The use of the K-SADS in teens up through age 17 led to much higher prevalences of childhood-onset disorders in our sample as compared to other studies (Preda et al. 2002; Meyer et al. 2005; Rosen et al. 2006). More than one half of our sample had ADHD, compared with 17% or lower in the other studies (Preda et al. 2002). More than half of our sample had ODD, as compared with $\approx$ 2% in other studies (Preda et al. 2002). Enuresis was prevalent in our cohort (44%), although not reported in the other studies (Preda et al. 2002; Meyer et al. 2005; Rosen et al. 2006). A total of 22% of our sample had tic disorders, compared to only 5% in Meyer et al. (2005), which was documented only in chart review. Among the older teens in our cohort, childhood-onset diagnoses were quite prevalent, including separation anxiety and ADHD, and surprisingly enuresis/encopresis.

The prevalence of these childhood-onset diagnoses in a putatively prodromal sample is consistent with the literature that describes developmental abnormalities during childhood that precede

the onset of psychosis in schizophrenia, including attentional and behavioral deficits, social difficulties, and motor abnormalities. ADHD is an expected childhood diagnosis for prodromal patients, found both in our cohort and that of Meyer et al. (2005), because attentional deficits are well-documented in schizophrenia (Cornblatt and Malhotra 2001), including in its putative prodromal stages (Cornblatt et al. 2003; Niendam et al. 2006). Social difficulties may be reflected in the prevalence of separation and social anxiety disorder, as well as in behavioral disorders, such as ADHD, ODD, and CD (Marsh et al. 2008).

The findings of elimination disorders (44%) in our cohort are of particular interest given the motor abnormalities that are well-documented in schizophrenia (Bombin et al. 2005) and its prodrome (Mittal and Walker 2007; Mittal et al. 2008) and are found as early subtle signs in development leading to schizophrenia. Walker and colleagues theorize a common mechanism for motor dysfunction, cortisol dysregulation, and vulnerability to psychosis (Mittal et al. 2007). Nocturnal enuresis has been associated in children with minor motor dysfunction (Von Gontard et al. 2006).

The finding of a variety of childhood-onset disorders in a cohort at risk for psychosis and schizophrenia highlights the limitations of the descriptive nosological system used in psychiatry that focuses on constellations of symptoms defining present syndromes. The very same diagnosis defines similar symptom sets, even when the context may fundamentally differ in terms of risk for other later disorders. Longitudinal research in both population and clinical cohorts can determine when such apparent diagnoses are intermediate phenotypes in the development of disorders that typically have a later onset in adulthood.

We illustrated among the older cases how different diagnoses unfold over development in young people at risk for psychosis and schizophrenia. Separation anxiety disorder is typical, and it yields to generalized anxiety and then PTSD when these vulnerable youths are exposed to trauma. Marked social withdrawal then occurs with the evolution of subthreshold psychotic symptoms in the context of anxiety and depressed mood. Of interest, the self-disturbance reported by the 1 young man, who has since converted to psychosis, may be a later event in the trajectory to psychosis, because it has been proposed that such self-disturbance is a phenotypic marker of psychosis (Nelson et al. 2008).

Limitations

The major limitations of this study include a small sample size in which psychosis outcome is largely not yet known. Therefore, these diagnoses will not be antecedents of psychosis in all cases, and the attenuated positive symptoms used to identify prodromal caseness may likewise be sequelae of other primary disorders, such as mood disorders. Another drawback is the limitation of assessment of childhood-onset diagnoses to those putatively prodromal individuals younger than 18. We will continue to assess childhood-onset diagnoses in our prodromal cohort and expand this assessment to all ages, through the upper limit of 30 in our cohort. Taking this developmental perspective of a disorder typically diagnosed in adolescence or adulthood will help us to elucidate the phenomenology of schizophrenia as it unfolds over time, with influences from genetic, developmental, neurobiological, and environmental factors (Carlson and Meyer 2006; Rutter et al. 2006).

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