Note: Treatment in Psychiatry is a new feature that begins with a hypothetical case illustrating a problem in current clinical practice. The authors review current data on prevalence, diagnosis, pathophysiology, and treatment. The article concludes with the authors' treatment recommendations for cases like the one presented. Instructions for submission to this series are in the Instructions for Authors at ajp.psychiatryonline.org.

The Schizophrenia Prodrome

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A 13-year-old girl, currently in the eighth grade and with a history of attention deficit hyperactivity disorder, was brought by her mother to a university-affiliated outpatient psychiatric clinic after a gradual decline in her academic performance was noted. She had a previous history of receiving grades of B and C in all her classes, but currently she was getting Ds and Fs. At age 8 years she had begun receiving stimulant medication, with some benefit. She had tasted alcohol in the past but denied current use. She had also used marijuana a half-dozen times. She reported having a small number of close friends. Although she said that there were no recent changes in her peer relationships, her parents claimed that she had been withdrawn and had appeared sad and that at times they needed to prompt her to take a shower. She had a maternal aunt with bipolar affective disorder and a great uncle who had been institutionalized for unknown reasons. During the clinical interview, she was dressed in Goth attire, including a black T-shirt with images of letters dripping blood; she had dyed black hair. Her affect was blunted but was slightly more animated when her parents left the room. She denied thoughts of suicide. She reported occasionally hearing whispering voices calling her name and saying that she is worthless. She also reported the belief that her friends did not like her as much as they had. Her mother, who recently met a parent of a child with schizophrenia, posed the question of whether her daughter has schizophrenia.

Challenges of the Schizophrenia Prodrome

The century-old term "latent schizophrenia" and the more recent term "schizophrenia prodrome" emerged from a retrospective piecing together of the early course of illness in individuals with schizophrenia. Linking the word "prodrome" with "schizophrenia," as in the title of this article, implies that those who are identified as having symptoms of the prodrome will later develop schizophrenia. Yet the constellation of symptoms in the schizophrenia prodrome tends to be nonspecific, especially in the early stages. Thus, prodromal symptoms are not deterministic from a prospective point of view, and considerable research is directed toward identifying which patients with prodromal symptoms will later develop schizophrenia.

The clinical vignette reflects these challenges. The early adolescent patient presents with a number of symptoms consistent with a schizophrenia prodrome, including a long-standing history of difficulties with attention, a recent history of cognitive decline, social withdrawal, and what appears to be psychotic symptoms. Yet these symptoms could also be explained in terms of major depression with psychotic features, bipolar affective disorder, substance use disorder, posttraumatic stress disorder (PTSD), or even an aberration in the maturation and solidification of personality structure. Furthermore, these diagnoses are complicated by their emergence within the developmental framework of the child, and thus developmental norms must also be taken into account. For example, a 5-year-old with imaginary friends is quite different from a 15-year-old with imaginary friends. More than 8% of healthy children have been reported to have hallucination-like events at some point during development (1).

Faced with nonspecific symptoms, clinicians are often expected to make an accurate diagnosis without the opportunity to observe the evolution of the symptoms over time. Clinicians who work with youths and their families must balance the number and severity of nonspecific symptoms with the prognosis and stigma associated with different psychiatric diagnoses.

In this article we use the issues raised in the clinical vignette as a framework for considering the diagnostic and treatment decisions faced by clinicians who encounter children or adolescents with nonspecific behavioral and cognitive changes associated with questionable psychotic symptoms. Patients with these characteristics are often seen in settings where children and adolescents with mental health problems are treated.

Developmental Pathophysiology and Psychopathology

Considerable evidence suggests that childhood- and adolescent-onset schizophrenia follows a continuum of neurobiological development similar to that in adult-onset schizophrenia (2–6). Less well understood are the neurobiological changes that take place before the onset of the illness. Even ventricular enlargement—perhaps the most consistent (2), although nonspecific (7), neurobiological finding in studies of schizophrenia—has yet to be reported in prodromal populations. Studies have demonstrated gray matter (8) and hippocampal volume (9) decreases in individuals whose illness progresses from the prodrome into schizophrenia. The findings of these and other similar studies will help differentiate the trajectory of neurodevelopmental changes associated with schizophrenia from the genetically determined endophenotypes (10).

"Caution the family that the evolution of prodromal symptoms into a disorder may not occur for several years."

Operationally, the prodrome is defined by duration of time, starting with the onset of decline in the baseline level of functioning and ending at the time when the criteria for a schizophrenia spectrum diagnosis are met (11). This time period can be considered as a continuum, with the level of risk increasing as the symptoms emerge or evolve during the prodrome. A number of approaches have been developed to assess the prodromal state, which has also been called the "at-risk mental state" (ARMS) (12–15). (See reference 16 for a review of ARMS instruments. Although there are small differences between these scales, there is considerable overlap.) The young woman in the clinical vignette has a number of at-risk symptoms, including a decline in cognitive and overall function, increased social isolation, difficulties with attention, decreased personal hygiene, and a change in her emotions with some flattening of affect. She also has what has been described by the Melbourne group as brief limited intermittent psychotic symptoms (14). However, she did not present with evidence of a thought disorder, impaired motor function, or a first-degree relative with psychosis or a schizophrenia spectrum disorder. Her dressing in Goth attire may be consistent with identity experimentation attributed to adolescent development. However, certain adolescent subcultures are more accepting of differences and thus may have a greater representation of individuals with psychiatric disorders.

Differential Diagnosis

Nonpsychiatric Disorders

The question of whether the patient may have a physical or neurological disorder that shares the symptoms associated with the schizophrenia prodrome should be in the forefront of the clinician's mind. In the case of this adolescent girl, the presence of cognitive decline raises the possibility of a degenerative neurological disorder. The differential diagnosis of nonpsychiatric conditions is broad, covering multiple systems, including the neurological, genetic and metabolic, endocrine, and autoimmune systems. Physical disorders with symptoms that overlap with those of the schizophrenia prodrome are rare, and nearly all can be ruled out with a thorough history, physical examination (including neurological examination), laboratory studies, and neuroimaging or EEG studies (17). Because treatments are available for many of these nonpsychiatric illnesses, it is imperative that these conditions be ruled out. Figure 1 shows a list of nonpsychiatric conditions that should be considered in the differential diagnosis of schizophrenia.

Laboratory studies should include liver function tests, tests of thyroid function, screening for the presence of heavy metals, and a urine test for substances of abuse. In addition, as indicated, laboratory tests may include measurement of serum ceruloplasmin, vitamin levels, HIV antibodies, cortisol levels, and lues serology (*Treponema pallidum* hemagglutination assay, VDRL test). These additional laboratory studies are indicated when abnormalities are found in the physical or neurological examination or in the initial laboratory studies. A family history of a specific medical or neurological condition may prompt additional studies directed toward ruling out that specific illness.

An EEG is indicated if there is a history of episodic loss of consciousness, repetitive movements or vocalizations, periodic staring spells, or similar ictal symptoms. Chromosomal analysis is indicated in the presence of a family history of chromosomal abnormalities or mental retardation or in the presence of dysmorphic features, such as those found in fragile X or chromosome 22q11 deletion syndrome. Magnetic resonance imaging is indicated in patients who have a marked cognitive decline, neurological abnormalities, or an atypical presentation or constellation of symptoms. Even though these additional tests rarely result in positive findings, the prodromal or early stage of the illness is the best time to consider their administration.

Affective Disorders

The patient in the case vignette was described by her parents as appearing sad at times, which raises the question of whether a primary affective illness was responsible for her symptoms. Although parents often interpret negative symptoms as evidence of an affective illness, even clinicians may find it challenging to distinguish symptoms of depression from the negative symptoms of schizophrenia. Further complicating the challenge is the fact that it is not uncommon for an affective illness to predate the onset of psychosis. Yet differentiating schizophrenia from an affective illness is often the focus of interest for both the psychiatrist and the family, because of a presumed difference in prognosis. Families often have difficulty accepting a

FIGURE 1. Nonpsychiatric Conditions That Have Been Associated With Psychosis

Metabolic disorders
- Renal failure
- Hepatic failure
- Pancreatic disease
- Hypernatremia/hyponatremia
- Hypercalcemia/hypocalcemia
- Hyperglycemia/hypoglycemia
- Porphyria
- Dehydration
- Hyperosmolarity

Endocrine disorders
- Addison disease
- Cushing disease
- Hypothyroidism/hyperthyroidism
- Hyperparathyroidism
- Panhypopituitarism

Nutritional deficiency states
- Thiamin deficiency
- Folate deficiency
- B_{12} deficiency
- Niacin deficiency

Autoimmune disorders
- Systemic lupus erythematosus
- Temporal arteritis

Motor disorders
- Parkinson disease
- Wilson disease
- Huntington disease
- Sydenham chorea
- Idiopathic basal ganglia calcification
- Spinocerebellar degeneration

Myelin diseases
- Adrenoleukodystrophy
- Metachromatic leukodystrophy
- Marchiafava-Bignami disease
- Multiple sclerosis

Substance-induced disorders
- Street drugs (including alcohol, hallucinogens, heroin, inhalants, psychostimulants, and phencyclidine)
- Prescription drugs (including steroids and stimulants)
- Withdrawal from alcohol, hallucinogens, opiates, psychostimulants, or sedative-hypnotics
- Poisoning (e.g., with anticholinergics, carbon monoxide, or heavy metals)

Infections
- Herpes simplex
- HIV
- Syphilis
- Parasites

Miscellaneous conditions
- Neoplasm
- Cerebrovascular accident
- Trauma (especially to frontal and temporal regions)
- Inborn errors of metabolism
- Seizure (especially complex partial seizures)
- Hydrocephalus
- Hypoxic encephalopathy
- Narcolepsy

change in diagnosis to schizophrenia from what was once thought to be depression or just "going through a phase"(18).

Both overlapping and differentiating symptoms must be considered in order to distinguish affective illnesses from the schizophrenia prodrome. The schizophrenia prodrome resembles an acute episode of bipolar disorder in that sleep problems, irritability, and depression may occur in both conditions. Differences exist, however, in the domains of peer relationships, with social withdrawal and avolition (negative symptoms) associated with the schizophrenia prodrome and increased energy, elated mood, and increased activity associated with the bipolar prodrome (19, 20). However, even if clinical symptoms that help differentiate these trajectories are present, the process of making a diagnosis is often fraught with uncertainty. The best resolution is to caution the family that the evolution of symptoms from the present prodrome into a disorder such as schizophrenia, an affective illness, or a personality disorder may not occur for several years. For children or adolescents in whom the prodrome progresses into schizophrenia, the diagnosis tends toward greater stability (21).

Substance Use Disorders

Substance use is common among adolescents seen in psychiatric clinics and has been documented in more than 50% of adolescent patients (22, 23). Two factors should be considered when evaluating comorbid substance abuse and other psychiatric disorders. The first is whether the substance use is responsible for the patient's clinical symptoms. This determination can best be made by observing the patient during a period of abstinence from the drugs of abuse. The second factor is whether the drugs of abuse have interacted with an individual's illness susceptibility, pushing the patient over the threshold into illness. Recent studies have implicated early adolescent cannabis use coupled with a specific genetic vulnerability as a risk factor for the development of schizophrenia (24).

Pervasive Developmental Disorders

Some children who later develop schizophrenia present earlier with a history of developmental delays, including abnormal language development, communication difficulties, impairment in social connectedness, and narrow interests. These children may receive a diagnosis of an autism spectrum disorder. The early developmental history should be considered in differentiating pervasive developmental disorders from the schizophrenia prodrome. For example, the presence of hallucinations and delusions and a distinct period of typical early development may distinguish schizophrenia syndrome from autism spectrum disorders.

Personality Disorders

A certain percentage of young patients who enter and remain in the schizophrenia prodromal phase over the long term may receive a diagnosis of schizotypal personality disorder as adults. Prodromal symptoms that are more characteristic of schizotypy, compared with schizophrenia, include greater depressive symptoms, greater sleep difficulties, less suspiciousness, less odd behavior, and less loss of role functioning (25). It is interesting to note that adolescents who later develop borderline personality disorder or antisocial personality disorder can have a personality disorder prodrome during adolescence that is nearly identical to the schizophrenia prodrome (26).

PTSD

Children who experience considerable abuse and deprivation can present with psychotic symptoms, including auditory hallucinations and dissociative episodes (20). The lack of nightmares and of a history of abuse and the

absence of symptoms of reexperiencing a traumatic episode may distinguish patients with the schizophrenia prodrome from those with PTSD.

Cognitive Problems

The patient in the clinical vignette presented with cognitive decline coupled with a long-standing history of problems with attention. Although attentional problems are common in the population, affecting 3% to 7% of the general population, they predicted the transition to schizophrenia in 58% of the offspring of patients with schizophrenia (29). Mirsky et al. (28) and Cornblatt et al. (31) concluded that poor performance on attention tests in high-risk children is predictive of development of schizophrenia in early adulthood. In addition to problems with attention, impairments in motor performance, verbal memory, and visuospatial processing have also been shown to be predictive of the transition from the prodrome into schizophrenia (30, 31).

Assessment and Treatment

The first step in the assessment of an individual with prodromal symptoms is a careful diagnostic assessment, including physical and neurological examinations, neuropsychological tests, laboratory studies, and neuroimaging studies. A number of semistructured research tools are available for assessment of individuals with prodromal symptoms, or ARMS (16). Clinicians who have familiarized themselves with these tools are better equipped to integrate the nuances of the nonspecific prodromal symptoms into their differential diagnosis.

Currently no consensus exists for pharmacological interventions at this early phase in diagnosis. In making treatment decisions, the clinician must weigh both the negative effects of the prodromal symptoms and the risks of psychopharmacological intervention. To determine the appropriateness of intervention, it is often helpful to evaluate the level of derailment of the developmental trajectory of the child or adolescent. Fortunately, studies of pharmacological treatment for youths at high risk for transitioning to psychosis have been promising (32–34). Antipsychotic treatment had better outcomes in youths with a shorter duration of untreated psychosis (35) and was associated with fewer patients transitioning from ARMS into schizophrenia (32, 33). Psychotropic interventions that target depression and anxiety, including antidepressants, mood stabilizers, and anxiolytics, have been used successfully to treat specific symptoms within the prodrome (34).

Cognitive behavior therapy (CBT) is emerging as an effective nonsomatic treatment for schizophrenia spectrum disorders. For example, data from the Early Detection and Intervention Programme of the German Research Network on Schizophrenia have shown that client and family CBT interventions that include psychoeducation and crisis management have promising effects on symptoms and social and occupational functioning in patients with an "early initial" prodromal state (36).

Conclusions

Although the schizophrenia prodrome is associated with substantial diagnostic and management challenges, it is an area of intense study with considerable progress. The presentation of the young adolescent in the clinical vignette is characteristic of these challenges. The clinician's most useful diagnostic tool—the patient's history of symptoms over time—is limited in the early stages of the prodrome. In addition, developmental factors that can modulate the symptoms must be taken into account. For the patient in the clinical vignette, a diagnosis of a schizophrenia spectrum disorder would be premature, given the available history. However, she has a number of clinical features that place her at an increased risk. The timing and intensity of treatment in this case would be determined by weighing the effects of the prodromal symptoms on the patient's developmental trajectory. After a thorough evaluation, this young patient would benefit from CBT with psychoeducation and possibly pharmacological intervention within an overall framework of a well-supported family network.

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