Schizophrenia in children and adolescents: Epidemiology, clinical features, assessment, and diagnosis

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Literature review current through: **Oct 2023.**
This topic last updated: **Aug 04, 2023.**

INTRODUCTION

Schizophrenia in children and adolescents is a syndrome consisting of positive and negative symptoms of psychosis that impact development and cognitive functioning. The etiology of this syndrome is poorly understood; early diagnosis and treatment are critical to limit the morbidity of the disorder.

Childhood-onset schizophrenia usually represents a more severe form of the disorder, with more prominent prepsychotic developmental disorders, structural brain abnormalities, and genetic risk factors [1-4].

This topic reviews the epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis of schizophrenia in children and adolescents. The treatment of schizophrenia in children and adolescents is described separately. The epidemiology, pathogenesis, clinical manifestations, course, assessment, diagnosis, and treatment of schizophrenia in adults are also reviewed separately.

- (See "Schizophrenia in children and adolescents: Treatment overview".)
- (See "Psychosocial interventions for schizophrenia in children and adolescents".)
- (See "Schizophrenia in adults: Epidemiology and pathogenesis".)
- (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)
- (See "Schizophrenia in adults: Maintenance therapy and side effect management".)

- (See "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication".)
- (See "Schizophrenia in adults: Psychosocial management".)
- (See "Evaluation and management of treatment-resistant schizophrenia".)

TERMINOLOGY

- **Childhood-onset schizophrenia** – Childhood-onset (or very early-onset) schizophrenia starts prior to the age of 13 years.
- **Early-onset schizophrenia** – Early-onset schizophrenia starts prior to age 18.
- **Adult-onset schizophrenia** – Adult-onset schizophrenia starts at or after age 18.

EPIDEMIOLOGY

Prevalence — The worldwide prevalence of early-onset schizophrenia has been estimated in epidemiologic studies at 0.5 percent of the population [5]. These studies are limited by differences in definitions (eg, early-onset) across studies, variability in the use of standardized, structured, diagnostic instruments, and by diagnostic accuracy [6]. (See 'Differential diagnosis' below.)

Childhood-onset schizophrenia appears to be much less common, having been estimated at 0.04 percent in the United States. In one of the largest samples studied, the National Institutes of Mental Health childhood-onset schizophrenia team identified 350 patients nationwide in the United States age 6 to 18 years meeting criteria with onset of symptoms before age 12. Ninety-eight of the 350 patients were assessed in person using structured interviews, and 28 were diagnosed with childhood-onset schizophrenia. Approximately 90 percent of referrals to the study were given alternative diagnoses initially [2,7-9].

Less is known about the prevalence of childhood-onset schizophrenia internationally. A study of patients treated at three large clinics in Germany found a prevalence of patients diagnosed with schizophrenia with symptom onset prior to age 12 of 0.1 to 1 percent [10,11].

Predisposing factors

- **Substance use disorder** – Studies have shown that the presence of a substance use disorder and co-occurring psychotic symptoms indicate an increased risk for developing a primary psychotic disorder in youth [12]. Cannabis, in particular, has the potential to cause

psychotic symptoms, and limited studies indicate that it may play a causal role in the development of a primary psychotic illness, although this research remains controversial [13-15]. (See "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects".)

- **Obstetric complications** – A birth cohort study of 80 patients with schizophrenia reported an association between hypoxia-associated obstetric complications and early-onset schizophrenia but not later-onset schizophrenia when comparing the cohort to siblings without schizophrenia and demographically matched nonpsychiatric comparison subjects [16].

Co-occurring disorders — Two large systematic studies demonstrated that 30 to 50 percent of patients diagnosed with childhood-onset schizophrenia had premorbid features of autism or had a comorbid diagnosis of pervasive developmental disorder, not otherwise specified, at the time of onset of psychosis [17]. Youth with early-onset schizophrenia frequently show greater premorbid deficits in attention, learning, and socialization compared with their counterparts with adult-onset schizophrenia [6].

After the onset of psychotic symptoms, those with childhood-onset schizophrenia often have other psychiatric comorbidities, including obsessive-compulsive disorder, major depressive disorder, attention deficit hyperactivity disorder, expressive and receptive language disorders, auditory processing deficits, and executive functioning deficits [18].

Studies have shown that up to 74 percent of adolescents and young adults with first-episode psychosis have co-occurring substance use, although this number is likely lower in younger populations [19].

Further research needs to be done to determine whether these comorbid diagnoses are true comorbidities or part of the constellation of symptoms that contribute to schizophrenia syndrome disorders or prodrome [17,20,21].

PATHOGENESIS

Contributing factors — Genetic vulnerability, environmental factors, obstetric complications, trauma, social adversities, and substance use can all contribute to the risk for acquiring a primary psychotic disorder [13,14,22-24].

- **Childhood adversity** – A meta-analysis reported strong evidence that childhood adversity was associated with an increased risk for psychosis in adults, although psychotic

symptoms may also be present in cases of posttraumatic stress disorder (PTSD). Thus, in cases of childhood psychosis, a comorbid or a primary diagnosis of PTSD must be considered [25,26].

- **Genetic vulnerability** – Twin studies suggest that childhood-onset of schizophrenia may have a substantial genetic component:
  - A study of twins with childhood-onset schizophrenia found an 88.2 percent concordance in 17 monozygotic twins compared with 22.9 percent concordance in 35 dizygotic twins [27].
  - The Treatment of Early-Onset Schizophrenia Spectrum Disorder study found that prematurity was present in 17 percent of 119 youth with schizophrenia spectrum disorder [28].
  - A number of psychiatric disorders have been found to be overrepresented in first degree relatives of children with schizophrenia spectrum disorder compared with the general population, including:
    - Bipolar disorder – 6 versus 2.4 percent [29]
    - Schizophrenia spectrum disorder – 10 versus 3.5 percent [30]
    - Anxiety disorders – 15 versus 7.3 percent [28,31]

  Epidemiologic and family studies looking at molecular genetics in childhood-onset schizophrenia have been limited due to low incidence of the very early-onset form of schizophrenia. These studies have shown a morbid risk for parents of patients with schizophrenia at 6 percent and siblings with 9 percent. Most of these studies utilized a candidate gene approach that was selected based on positive associations with adult-onset schizophrenia [32]. Forty-five genes have been evaluated for a positive association between schizophrenia (regardless of age of onset) and autism. Of these identified genes, 20 showed a positive association between both disorders, and 11 were associated only with schizophrenia [33].

Neuroanatomical correlates — The pathogeneses of childhood-onset schizophrenia and early-onset schizophrenia are not thought to be distinctly different from the pathogenesis of adult-onset schizophrenia, although the onset of symptoms and changes in brain structures occur at earlier ages. Cross-sectional and longitudinal studies examining structural brain alterations of patients diagnosed with childhood-onset or early-onset schizophrenia, or patients who fall in

the genetic high-risk or clinical high-risk categories, show various neuroanatomic correlations, including:

- Progressive grey matter volume reduction in the prefrontal cortex and temporal cortex [34-36]. Decreased volume of the prefrontal cortex and temporal cortex, in particular, have been linked to greater symptom severity and earlier age of illness onset [37-39].
- Smaller volumes of thalamic association nuclei (ie, pulvinar, mediodorsal nuclei) compared with healthy control groups [40].
- Decreased hippocampal volume is not a common finding in early-onset schizophrenia (in contrast to adult-onset schizophrenia) [41].

CLINICAL MANIFESTATIONS

Childhood-onset schizophrenia and early-onset schizophrenia are a heterogenous group of disorders in both the manifestation of symptom phenotypes and etiologies [42-44]. Childhood-onset schizophrenia and early-onset schizophrenia are more severe and debilitating forms of schizophrenia.

Hallucinations are much more common than delusions in youth with schizophrenia compared with adults. The most common hallucinations are auditory with comments or commands being most frequently observed [45,46]. These are often accompanied by visual and tactile hallucinations, resulting in multimodal hallucinations.

Delays in language, motor, and social development may be pronounced, particularly in childhood-onset schizophrenia; however, these delays are not diagnostic [18].

The Treatment of Early-Onset Schizophrenia Spectrum Disorder study of 168 children aged 8 to 19 found an inverse correlation between the presence of positive symptoms and intelligence quotient (IQ) in youth with early-onset schizophrenia [28]. Youth will frequently name these hallucinations, which may lead observers to initially think that the youth are referring to “imaginary companions.” Delusional content related to the hallucination may be seen and the youth may be fearful that the hallucination will hurt them or a family member [47-49].

Longitudinal studies have shown that regardless of age, transition to syndromal psychosis is associated with cognitive decline. Participants in the National Institutes of Mental Health study of childhood-onset schizophrenia showed a marked decline in IQ scores approximately two years prior to the onset of frank psychosis [50]. Cognitive deficits associated with memory and attentional functions are the most extensively documented in patients with psychosis [51-53]. A

meta-analysis looking at clinical high risk populations revealed a correlation between severity of cognitive deficits and rates of conversion to psychosis [54]. Deficits in processing speed and verbal memory also predicted faster conversion rates to psychosis [55]. Children and adolescents may be more likely to exhibit negative symptoms and less likely to report hallucinations or delusional thought content [56].

Many youth with early-onset schizophrenia have come into contact with the medical or legal system prior to diagnosis. In a study of 119 children with schizophrenia spectrum disorders (including early-onset schizophrenia and schizoaffective disorder), 45 percent had at least one prior psychiatric hospitalization, 25 percent had issues with the legal system or reported problems with aggression, and 15 percent had a history of suicide attempts [28].

COURSE OF ILLNESS

Deviance in developmental trajectories as evidenced by abnormal developmental milestones is increased in childhood-onset schizophrenia when compared with the adult form of the disorder, resulting in a worse clinical course and outcome [57-59]. Childhood-onset schizophrenia is continuous with the adult form of the disorder, although the earlier the onset, the more severe the illness.

As an example, a comparison between 119 youth with early-onset schizophrenia and a sample with adult-onset schizophrenia found that the early-onset cohort may have had more severe symptoms on the Positive and Negative Syndrome Scale [6,28].

Intellectual ability often deteriorates prior to diagnosis, and the difficulties with learning and verbal memory [60] that accompany the disorder can result in more significant impairment with earlier age of onset. In addition to a decline from baseline functioning that is associated with the syndrome, there is a failure to show age-related gains compared with healthy controls [59].

Co-occurring substance use in those with psychotic illness is associated with decreased medication adherence, poorer response to treatment, and worsened course of illness in adults [61]. Since early-onset schizophrenia is continuous with the adult form of the disorder, one might expect that, as in adults, concurrent substance use in youth would correlate with more frequent hospitalizations, suicide attempts, recurrence of psychotic symptoms, residential instability, legal problems, and health problems. This has not been studied in youth.

There is a dearth of data looking at predictors of relapse specifically in early-onset psychosis; however, a cohort study looking at relapse in first episode cases (age 15 to 60) showed

medication adherence as the only significant predictor of relapse in a three-year follow-up period [62].

ASSESSMENT

Clinical assessment includes a thorough history including past medical and psychiatric history, medication history, family, and psychosocial history. Examination includes a mental status examination, general physical examination, and neurologic examination. Although there is no gold standard laboratory work-up battery for psychosis, evaluation of complete blood count, serum electrolytes and glucose, hepatic and renal function, thyroid stimulating hormone, syphilis test, prolactin levels, hepatitis C, vitamin B12 and folate, serum ceruloplasmin if Wilson disease is a consideration, erythrocyte sedimentation rate, and antinuclear antibodies are recommended. Urinalysis, urine and serum toxicology, and human immunodeficiency virus testing should be done if there are risk factors present.

The absence of dysmorphic features, intellectual disability, or family history of mental illness should increase the suspicion of a medical or neurologic cause for symptoms. Any focal neurologic findings or history of traumatic brain injury should prompt neuroimaging by magnetic resonance imaging. Acute emergence of symptoms and evidence of delirium warrant more extensive testing and may require cerebral spinal fluid analysis, toxicology screening, and anti-N-Methyl-D-aspartate (NMDA) receptor antibodies. Positive anti-NMDA antibodies would necessitate a pelvic ultrasound and further testing and consultation to rule out ovarian teratoma in females [6,63].

Interviews of patients and families, particularly with adolescents, should be done separately due to concerns of confidentiality. Collateral information from schools can be critically important, as parents may unintentionally minimize the level of disorganization in youth or inadvertently mask some of the symptoms by compensating for their impairments through providing a level of structure in the home that would be excessive compared with age-matched peers. Asking about sleep-wake disturbances may be helpful. Children may be unaware that they are experiencing auditory hallucinations. Questioning parents about whether their child appears to be responding to voices as if they were being called, without a clear precipitant, may be helpful. Social isolation or decline in school functioning and learning is also usually present [64].

DIAGNOSIS

The diagnosis of schizophrenia in children and adolescents is made through clinical assessment, using the same American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) diagnostic criteria as those used for the adult-onset disorder [65]:

- A. Two or more of the characteristic symptoms below are present for a significant portion of time during a one-month period (or less if successfully treated):
  - 1. Delusions
  - 2. Hallucinations
  - 3. Disorganized speech (eg, frequent derailment or incoherence)
  - 4. Grossly disorganized or catatonic behavior
  - 5. Negative symptoms (ie, affective flattening, alogia, or avolition)
- B. For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset. When the onset is in childhood or adolescence: failure to achieve expected level of interpersonal, academic, or occupational achievement.
- C. Continuous signs of the disturbance persist for at least six months. The six-month period must include at least one month of symptoms (or less if successfully treated) that meet criterion A (ie, active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in criterion A that present in an attenuated form (eg, odd beliefs, unusual perceptual experiences).
- D. Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either: 1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or 2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.
- E. The disturbance is not due to the direct physiological effects of a substance (eg, a drug of abuse or medication) or a general medical condition.

- F. If the patient has a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Differential diagnosis

- **Posttraumatic stress disorder (PTSD)** – Symptoms of PTSD in adults can include delusional and paranoid thinking as well as flashbacks, which may be described by patients as auditory hallucinations. Hypervigilance and flashbacks can often be misinterpreted as paranoia and hallucinations, making distinguishing between the two disorders challenging. In cases of PTSD, these symptoms are most commonly related to trauma, and there is a lower incidence of disorganized thinking [66,67]. One meta-analysis showed strong evidence that childhood adversity is associated with an increased risk for psychosis, and therefore PTSD should be carefully considered in cases where youth have a history of childhood adversity [66].

- **Autism spectrum disorders** – Misdiagnosis of autism spectrum disorder symptoms as psychosis can also occur due to common features such as general impairment in social communication, which can be misinterpreted as negative symptoms of psychosis or stereotyped use of language, which could be confused as disorganized speech [68]. Further investigation of the developmental history and baseline thought process can be useful for distinguishing these two diagnoses.

  The presence of new-onset delusions or hallucinations lasting longer than one month, presence of disordered or delusional thinking that is distinctly different from baseline, or deterioration in social and general function are more consistent with a diagnosis of schizophrenia or for a comorbid diagnosis of autism spectrum disorder and schizophrenia [68].

- **Schizoaffective disorder** – Distinguishing between schizoaffective disorder and schizophrenia in early-onset schizophrenia may also be challenging as the psychotic syndrome continues to evolve and as the development of the youth progresses. In some cases, this may lead to a change in diagnoses over time [28]. In fact, studies examining the clinical features and functional outcomes, as well as neurocognitive testing, in these populations suggest overlapping characteristics of youth with these disorders [53,69].

- **Other mood disorders** – Major depressive disorder, with psychosis, and bipolar disorder with psychosis should also be considered. A careful history looking at mood episodes may be helpful. There is some evidence that there is more extensive gray matter loss may be seen in those with childhood-onset schizophrenia, although it is unclear if medication

effects or disease severity also contributes. Further study is needed to look at the neurobiological differences between these disorders [70].

- **Medical diseases** – Common medical conditions that may present with psychotic symptomatology include:
  - Seizure disorder
  - Encephalitis (ie, herpes simplex virus, anti-NMDA, other infectious etiologies)
  - Central nervous system tumors
  - Chromosomal abnormalities (22q11.2 deletion syndromes, particularly if there are dysmorphic features)
  - Substance or medication induced
  - Autoimmune disorders (ie, systemic lupus erythematosus)
  - Metabolic disorders (ie, Wilson disease, porphyria variegate)
- **Delirium** – Look for waxing and waning symptoms, evidence of ingestion of substances, or metabolic derangements, which would be more consistent with delirium than a psychotic illness.
- **Substance-induced psychosis** – Substance-induced psychosis (eg, secondary to steroid use) can be indistinguishable from a primary psychotic disorder at the time of presentation and toxicology screens should be considered. Newer designer recreational drugs may not be detected in current screens and elements of the history should aid in distinguishing diagnosis.
- **Nonpsychotic children** – Delusional thinking, hallucinations, and looseness of associations during childhood can occur in healthy nonpsychotic children [71] and usually diminish after age six [72]. Anxiety and related visual hallucinations are also common in preschool children [73]. Careful history including decline in cognitive functioning, attention, and presence of negative symptoms would be more indicative of psychosis.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Psychotic disorders".)

SUMMARY AND RECOMMENDATIONS

- **Terminology** – Schizophrenia in children and adolescents is a syndrome consisting of positive and negative symptoms of psychosis that impact development and cognitive functioning. (See 'Introduction' above and 'Terminology' above.)
  - **Childhood-onset schizophrenia** – Childhood-onset (or very early-onset) schizophrenia starts prior to the age of 13 years.
  - **Early-onset schizophrenia** – Early-onset schizophrenia starts prior to age 18.
- **Epidemiology** – The prevalence of early-onset schizophrenia is approximately 0.5 percent of the United States population, slightly higher than for adult schizophrenia, which has been estimated at 0.4 percent. Childhood-onset schizophrenia is much less common at 0.04 percent in the United States. (See 'Epidemiology' above.)
- **Predisposing factors** – Studies have shown that the presence of a substance use disorder and co-occurring psychotic symptoms indicate an increased risk for developing a primary psychotic disorder in youth. Cannabis has the potential to cause psychotic symptoms, and limited studies indicate that it may play a causal role in the development of a primary psychotic illness, although this research remains controversial. Obstetrical complications appear to be associated with early-onset schizophrenia. (See 'Predisposing factors' above.)
- **Co-occurring disorders** – Thirty to 50 percent of patients diagnosed with childhood-onset schizophrenia have premorbid features of autism or a comorbid diagnosis of pervasive developmental disorder, not otherwise specified, at the time of onset of psychosis. (See 'Co-occurring disorders' above.)
- **Course of illness** – Deviance in developmental trajectories as evidenced by abnormal developmental milestones is increased in childhood-onset schizophrenia when compared with the adult form of the disorder, resulting in a worse clinical course and outcome. Childhood-onset schizophrenia is continuous with the adult form of the disorder, although the earlier the onset, the more severe the illness. (See 'Course of illness' above.)
- **Assessment** – Clinical assessment includes a thorough history including past medical and psychiatric history, medication history, family, and psychosocial history. Examination includes a mental status examination, general physical examination, neurologic examination, and laboratory studies. We also obtain collateral information from schools and others when possible. (See 'Assessment' above.)

- **Differential diagnosis** – Schizophrenia in youth must be differentiated from other disorders that may present with similar symptoms, including posttraumatic stress disorder, autism spectrum disorders, mood disorders, schizoaffective disorder, substance induced psychosis, delirium, and severe anxiety. (See 'Differential diagnosis' above.)

Topic 14365 Version 12.0

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