

Childhood Schizophrenia: Diagnostic and Treatment Challenges

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Abstract.

This paper describes the developmental challenges involved in confirming the diagnostic criteria of schizophrenia in children, the disorders that should be included in the differential diagnosis of this disorder, and how to differentiate their symptoms from those of schizophrenia. It then reviews the psychopharmacological treatment of early-onset schizophrenia focusing mainly on the short-term and long-term adverse effects of first- and second-generation neuroleptics. The diagnostic challenges, together with the adverse effects of neuroleptics, emphasize the importance of accurate diagnosis and medical monitoring of children with schizophrenia.

Keywords: schizophrenia, early-onset, psychosis, diagnosis, neuroleptics, adverse effects.

Introduction

Schizophrenia in childhood and adolescence with onset before age 16 has been well studied during the past decade in terms of premorbid dysfunction (1), phenomenology (2-5), cognition, (See review in (6)), language (7), treatment (See review in (8)), neuroimaging (9), and genetics (10). Although there are no epidemiological studies to date, early-onset schizophrenia is considered to be more rare and severe than the adult disorder.

Supported by the seminal findings of Kolvin et al. (3) that differentiated childhood onset schizophrenia from autism, the DSM-III, DSM-III-R, and DSM-IV used the same diagnostic criteria for early-onset and adult schizophrenia. These include hallucinations (i.e., auditory, visual, olfactory, tactile, gustatory perception in the absence of an external stimulus), delusions (erroneous beliefs held despite evidence to the contrary), disorganized speech (formal thought disorder), disorganized behavior, and negative symptoms (affective flattening, alogia, avolition).

Two or more of these symptoms need to be present for a significant portion of time during a 1-month period. For a significant portion of the time and below the level achieved prior to disease onset there should also be evidence of dysfunction or failure to achieve the expected level of functioning in academic achievement, interpersonal relations, or self-care. In addition, signs of the disturbance should be persistent for at least 6 months.

In children a developmental approach is needed to assess hallucinations, delusions, and disorganized speech because there are age-related changes in children's cognition and language skill, reality testing, judgment, and thought processes in terms of both the content and organization of thoughts. Clinicians are, therefore, faced with difficulties when having to rule in or out a diagnosis of childhood-onset schizophrenia because of inadequate or sparse training on these aspects of child development, infrequent exposure to schizophrenia in children during medical and specialty training, and possible mislabeling of children's "out of control" or "bizarre" behavior as psychotic.

To address these difficulties, this paper describes the developmental challenges in diagnosing schizophrenia in children followed by the disorders included in the differential diagnosis of schizophrenia and how to differentiate their symptoms from those of schizophrenia. It then reviews the psychopharmacological treatment of early-onset schizophrenia focusing mainly on the adverse effects of neuroleptics.

The Diagnostic Developmental Challenges

Hallucinations

Hallucinations are rare in children under age seven. Therefore, reports of hallucinations in children this young might represent mislabeling or misinterpretation of behaviors suggestive of hallucinations, particularly in learning disabled or language delayed children. Examples include concern that a child covering his ears with or without a fearful response or agitated behavior might be having an auditory hallucination or that a child looking at something with a fixed look while laughing, mumbling, or acting fearfully might be experiencing a visual hallucination.

More typically, parents are “unaware” that their children have hallucinations because children do not spontaneously talk about these experiences for several reasons. First, when children tell their parents about a hallucinatory experience, parents usually respond by negating the experience and say, “It’s nothing” and/or “It’s only your imagination.” Feeling that their parents do not believe them, children stop talking about their hallucinations to their parents or anyone else. Second, some children are scared to talk about their hallucinatory experiences because people might think they are “mad.” Third, children might not want to burden their parents who might be overwhelmed with life stresses. Fourth, in some cases children feel that talking about a hallucination might make it happen.

Since most children become distressed and scared when having a hallucination, they want help to stop the experience. It is, therefore, important for clinicians to ask children about hallucinations using carefully chosen words that do not imply that the child experiences are “strange” or “mad.” For example, even children who experience hallucinations might answer “No” if asked “Do strange or bizarre things happen to you like hearing voices (seeing things, smelling unusual bad smells, feeling something touching your skin or crawling on your skin, having a bad or weird taste in your mouth). Alternatively the question, “Some children hear voices that no one else can hear, does that happen to you?” suggests that others have a similar experience, and might encourage children to talk about it.

In addition to the lack of spontaneous reporting and how best to ask children about hallucinations, clinicians might have difficulty differentiating hallucinations from children’s normal fantasies or creative inner life, imaginary friends, and fears. Children with complex and creative fantasies fully acknowledge the imaginary basis of their fantasies, and differentiate them from their other life experiences with good reality testing. In addition, children enjoy fantasies whereas hallucinations usually cause significant subjective distress (fear, agitation).

Imaginary friends are invisible or personified objects with whom children younger than age seven have a sustained form of play, pretence, daily routine and even arguments (See review in (11)). In contrast to psychotic children, these children are sociable and have a high level of language skill and good reality testing (11).

Whether experienced at night or in the day, children’s fears might appear to be visual (child sees a ghost in the cupboard) or auditory hallucinations (child hears creaks in the floors). It is necessary to determine if these fears are age appropriate or reflect the child’s life situation and living environment. For example, a child who lives in a neighborhood with frequent drive-by shootings reports hearing gunshots every night when trying to fall asleep.

In addition, vivid nightmares might appear real and cause fear when children first wake up. If, however, the child thinks the dream experience continues during the day, the possibility of a hallucinatory experience should be ruled out. Children might experience visual illusions while falling asleep or if they wake up during the night (e.g., a pile of clothes on a chair might look like a monster). These are differentiated from hallucinations by the child’s good reality testing for the imaginary quality of the experience the next morning.

Delusions

Similar to hallucinations, delusions are rare in children under age seven, and should be differentiated from normal developmental phenomena, such as fantasies and magical thinking (thoughts and wishes are equated to actions). This can be done if the child is cognizant of the imaginary or wishful thinking quality of these thoughts. Morbid fantasies (repeated elaborate thoughts involving aggression) are common given the high level of violence in the media and children's computer games. If these fantasies are pervasive and the child will act on the basis of these thoughts (e.g., child repeatedly thinks about and plans how to kill, blow up, or maim others despite possible consequences), they might be precursors of delusions.

Disorganized Speech or Formal Thought Disorder

This diagnostic criterion of schizophrenia reflects difficulties a listener has making sense of who and what the child/youth is talking about due to poor reasoning (illogical thinking), unpredicted changes in the topic of conversation (loose associations), and unclear reference to people objects, or events the child mentions (7). The ability to talk coherently and cohesively develops from the toddler period through adolescence and involves higher-level linguistic (discourse) and cognitive skills (See review in (12)).

It is, therefore, essential to differentiate the difficult to understand or disorganized speech of children who have problems understanding language and/or expressing themselves due to a language disorder or intellectual disability. Since most clinicians do not have prior training on how to assess language and discourse skills in typically developing children of different ages, ruling in or out formal thought disorder poses a difficult diagnostic challenge. In such cases, referral to a speech and language therapist would help clarify the diagnosis.

Schizophrenia

Notwithstanding the previously described need for developmental considerations, hallucinations, delusions, and formal thought disorder are found in 79%-100%, 57%-63%, and 60%-100%, respectively, of children with schizophrenia (2-5, 7). Auditory hallucinations are commanding, conversing, persecuting, and religious (2-5). Delusions often have bizarre content, and include persecutory, reference, control, somatic, religious, guilt, and nihilistic delusions (2-5). The formal thought disorder of children with schizophrenia includes illogical thinking and loose associations (7).

Differential Diagnosis of Psychotic Symptoms and Schizophrenia

The differential diagnosis of the psychotic symptoms found in schizophrenia includes the disorders listed in Table 1. Although early-onset schizophrenia is a rare disorder, prevalence of psychotic symptoms in 2%-59% of youth aged 7-19-years in community settings with disorders other than schizophrenia, first-episode psychosis, schizophrenia prodrome, and organic psychoses (13) underscore the importance of the differential diagnosis. Due to space limitations, this section focuses on diagnostic difficulties more likely to present in the clinics of general practitioners.

Table 1: Differential Diagnosis of Psychotic Symptoms

Psychotic Disorders
Schizophrenia
Affective psychoses (depression, bipolar)
Dissociative psychosis
Organic disorders (medical, neurological, iatrogenic disorders)
Substance abuse
Transient psychosis or psychotic-like
Psychosis NOS
Schizophrenia spectrum disorder
Prodromal syndrome
Multidimensionally impaired disorder
Multiplex developmental disorder
Schizotypal personality disorder
Developmental disorders (autism spectrum disorders)
Anxiety disorders (separation anxiety, generalized anxiety, OCD)
Attention deficit hyperactivity disorder
Language disorder
Learning disorder (intellectual disability)

Youth with affective psychosis (e.g., psychotic depression, bipolar disorder and psychosis) have the types of hallucinations and delusions found in schizophrenia (14, 15). In contrast to schizophrenia, the content of these psychotic symptoms is mood congruent and not bizarre. For example, a depressed child might hear a voice telling her to kill herself because she has done bad things to others (congruent with depressed affect); a child with bipolar disorder might experience grandiose delusions and hear an angel telling him he has special powers (congruent with manic affect); whereas a child with schizophrenia who thinks her mother is trying to poison her (paranoid delusion) might hear the devil command her to save her mother's soul by killing her mother (bizarre content, not mood congruent). Formal thought disorder is infrequent in affective psychosis (15).

Suicidal thoughts, plans, and acts as well as thoughts about death and dying are more frequent in youth with affective psychosis than in those with non-psychotic affective disorders (15, 16). When present in schizophrenia, suicidal symptoms are not mood congruent and appear bizarre. For example, a boy writes a note to his history teacher informing him that he is going to kill himself because the teacher does not understand the history he is teaching (illogical content that is not mood congruent).

Negative signs are a diagnostic pitfall in the differential diagnosis of schizophrenia and psychotic depression because lack of motivation and enjoyment (anhedonia), slow speech, poverty of speech (alogia), and affective flattening with little or minimal movement of facial muscles (i.e., expressivity) and emotional reactivity occur in both disorders. Identifying mood congruent or bizarre hallucinations and delusions can help distinguish between the negative signs of these disorders.

In addition to a past psychiatric history of unsuccessfully treated multiple psychiatric diagnoses and abuse (physical, sexual, or emotional), the auditory hallucinations of youth with dissociative psychosis usually involve familiar people from the child's life with one threatening and one protecting voice (17). Visual hallucinations involve apparition-like images (17). In contrast to other psychotic disorders,

these children do not appear to be distressed by their hallucinations. Delusions, other than thought withdrawal and insertion, and formal thought disorder are not features of this disorder (17).

It is always important to rule out a possible underlying neurological or medical illness that presents with psychosis. Among the neurological disorders, pediatric epilepsy is associated with an ictal, post-ictal, or interictal psychosis, albeit infrequently (See review in (18)). Unlike schizophrenia, affective psychoses, and dissociative psychosis, hallucinations in ictal psychosis are unchanging, stereotyped, and unimodal (involve one sensory system) and delusions include forced thinking. In addition, children with ictal psychosis recall the content of their hallucinations or delusions only if they occurred during an aura that was not followed by a generalized tonic clonic seizure. Similar to schizophrenia, children with interictal psychoses have multimodal hallucinations that vary in content and form; delusions; and formal thought disorder (19). However, they do not have negative symptoms. Postictal psychosis is rare in children (18).

Psychosis can occur in early stages of neurological disorders, such as acute disseminated myelitis (20), subacute sclerosing panencephalitis (21), and degenerative disorders. At disease onset, hallucinations and delusions in these cases are stereotyped and pervasive. They disappear with loss of cognitive and linguistic functions as the illness worsens and speech becomes more incoherent (formal thought disorder) and the child appears disorientated and confused.

Regarding iatrogenic psychoses, psychosis with persecutory delusions and auditory hallucinations with or without altered conscious level and disorientation is reported in children treated with corticosteroids (See review in (22)). Several antiepileptic drugs can also trigger psychosis in youth with epilepsy including ethosuximide, levetiracetam, phenytoin, topiramate, vigabatrin, zonisamide, and felbamate (See review in (23)). Similar findings are not evident in the literature on youth without epilepsy given these medications to stabilize mood.

A meta-analysis of double-blind drug studies of adderall XR, atomoxetine, modafinil, oral and transdermal methylphenidates in children with attention deficit hyperactivity disorder (ADHD) revealed psychotic symptoms at a rate of 1.48 per 100 person-years (95% Poisson exact CI: 0.74–2.65 per 100 person-years) compared to no psychosis/mania events in the placebo treatment groups (24). Hallucinations were more frequent in children under age 10-years and involved visual and/or tactile sensations of insects, snakes, or worms.

In a study of early-onset psychotic disorders, 44% of the adolescents had used cannabis for a mean of 1.8 years prior to psychosis onset (25). In fact, the association of cannabis use with earlier onset of first episode psychosis might be a toxic effect in individuals who develop psychosis (26).

Children with transient psychosis and psychotic-like disorders have several features in common. They do not meet DSM-IV diagnostic criteria for schizophrenia in term of the duration, frequency, and severity of symptoms. For example an adolescent feels he is living in a world that is a set with actors who are there to observe him (like the Truman Show). Sometimes he thinks this is his misperception while at other times he is convinced that his life is “all a set up.” A vacillating impairment of reality testing, as in this case, is a feature of these disorders (27). Regarding continuity with schizophrenia, a recent multisite prospective study on 291 youth with the prodromal syndrome demonstrated conversion to schizophrenia in 35% over a 2.5-year follow-up period predicted with an accuracy level of 68%–80% by 2–3 of the following variables: a genetic risk for schizophrenia with recent deterioration in functioning, higher levels of unusual thought content, higher levels of suspicion/paranoia, greater social impairment, and a history of substance abuse (28).

Among the developmental disorders, Asperger syndrome or high functioning autism can pose diagnostic challenges when the circumscribed preoccupations characteristic of these children involve imagination and fantasy. In such cases clinicians should determine if the child has a mental age of at least 7-years, is aware of the imaginary nature of his preoccupations, and does not act on them. For example, a child with Asperger syndrome repeatedly thought about being in a time machine. When “in the time machine,” he talked about and enacted different scenes, events, and stories. He was well

aware that there is no such thing as a time machine and that this was his imagination. In contrast, he also repeatedly drew pictures with snakes, monsters, the devil, and people in coffins. He became scared, agitated, and non-verbal when asked about these drawings. He subsequently revealed that the devil threatened to bury him alive in the coffin with the snakes and monsters. This child met diagnostic criteria for schizophrenia and Asperger syndrome.

The anxiety disorders are included in the differential diagnosis to emphasize that not all forms of worry, repeated thoughts, or difficulties separating from parents mean a child has a generalized anxiety disorder, obsessive-compulsive disorder, or separation anxiety disorder, respectively. Hallucinations or delusions might underlie these symptoms. Finally, although concentration problems are found in ADHD, some children confirm attentional difficulties when, in fact, their inattentiveness stems from worries, obsessions, compulsions (e.g., counting), hallucinations, or delusions.

Treatment

Typical neuroleptics or first-generation antipsychotic drugs with US Federal Drug Administration (FDA) approval to treat 13-17-year-old schizophrenia youth include haloperidol, chlorpromazine, thioridazine, molindone (now no longer available), and thiothixene (See review in (8)). Although effective for positive symptoms of schizophrenia (e.g., hallucinations, delusions, disorganized behavior), lack of efficacy for negative symptoms and induction of extrapyramidal symptoms (EPS) (rigidity, tremor, akathisia), tardive dyskinesia (i.e., involuntary oral-buccal-lingual masticatory movements), and weight gain have limited their use in children.

Based on efficacy and safety findings in double-blind randomized controlled studies, the FDA approved atypical neuroleptics or second-generation antipsychotic drugs including risperidone (1-3mg/d or 4-6mg/d), (29), olanzapine (2.5-20.0 mg/d)(30), and aripiprazole (10 or 30mg/d) (31) to treat 13-17-year-old patients with schizophrenia. Clozapine (mean dose 176mg/d, SD 149 mg/d) is superior to both haloperidol (mean dose 16mg/d, SD 8 mg/d) (32) and olanzapine (15-20mg/d) (33)), particularly for negative symptoms in early-onset treatment resistant schizophrenia.

Although clinicians now infrequently prescribe atypical neuroleptics to treat youth with schizophrenia, the first double-blind multisite randomly assigned trial that compared typical (molindone 10-40mg/d) to atypical neuroleptic drugs (risperidone 0.5-6mg/d, olanzapine 2.5-20mg/d) in 116 patients demonstrated no significant differences in response rates and symptom reduction between these medications (34).

In terms of adverse effects, molindone alone was associated with akathisia. But olanzapine showed the greatest risk for weight gain, as well as significant increases in fasting cholesterol, low-density lipoprotein, insulin, and liver transaminase levels. Double-blind evaluation of the long-term safety and efficacy of these three neuroleptics 44 weeks after the initial 8-week trial confirmed no significant efficacy differences or further symptom reduction following the 8-week initial trial. In contrast to the 8-week trial, in the follow-up study all three drugs were associated with weight gain, risperidone with increased prolactin, and molindone with akathisia. Of note, only 14 subjects (12%) of the original sample completed the study.

Despite the efficacy data, current available safety data highlight the short-term and long-term adverse effects of neuroleptics. The metabolic syndrome occurs with both typical and atypical neuroleptics, and increases the risk for diabetes mellitus and premature coronary artery disease (35). Three of the five following criteria are needed to diagnose this syndrome: Obesity with BMI >85th < 95th percentile, triglycerides > 110 mg/dL, high-density cholesterol < 40mg/dL, fasting glucose > 100mg/dL, and blood pressure > 90th percentile (See review in (36)).

A recent study of 338 neuroleptic naïve children and adolescents, aged 4- 19-years, found significant weight gain (BMI > 95th percentile) in 10%-36% of the subjects with neuroleptic exposure of 7 days or less if treated with olanzapine, risperidone, quetiapine, or aripiprazole for a median of 10.8 weeks (37). Although the metabolic risk profiles varied across these drugs, there were more lipid than

glucose abnormalities, rare diabetes and metabolic syndrome, and more severe weight gain and lipid abnormalities in olanzapine treated patients. The weight gain of clozapine treated schizophrenia youth falls between that of olanzapine and risperidone (See review in (36)). In addition to type of neuroleptic, polytherapy increases the likelihood of obesity, dyslipidemia, and type 2 diabetes based in 4140 children and adolescents prescribed 1 of 5 atypical or 2 conventional antipsychotics compared to a random sample of 4500 untreated children (38).

Despite the lack of long-term data on weight gain, the metabolic syndrome, and cardiovascular variables in neuroleptic treated youth, the reviewed safety findings justify the need to monitor weight, as well as lipid and glucose abnormalities in these patients. General practitioners play an important role in the comprehensive health screening and monitoring of adults treated with neuroleptics before starting treatment with subsequent repeat testing at 6 weeks, 12 weeks, and annually (See review in (35)). Correll & Kratchovil (36) suggest similar recommendations, including lifestyle changes in terms of diet and exercise, should be followed by the physicians of youth treated with neuroleptics.

Hyperprolactinemia, caused by both typical (haloperidol, pimozide) and atypical neuroleptics (risperidone>olanzapine>ziprasidone), impairs functioning of gonadotropins, estrogen, and testosterone by blocking D2 receptors in the tuberoinfundibular dopamine system of the anterior pituitary (See review in (39)). Hyperprolactinemia occurs within 4-8 weeks of treatment onset and might persist for 1-2-years in patients treated with risperidone (39). Youth with a wide range of diagnoses who have neuroleptic induced hyperprolactinemia present mainly with gynecomastia and irregular menses. However, prolactinemia can cause gynecomastia, galactorrhea, sexual dysfunction, reduced fertility, decreased bone density, and osteoporosis. Treatment recommendations in symptomatic youth include neuroleptic dose reduction and/or cross-over to aripiprazole, and use of bromocriptine or amantidine if symptoms continue (36).

Although considered infrequent, extrapyramidal symptoms including tremor, dystonia, akathisia, rigidity, withdrawal dyskinesia, and tardive dyskinesia also occur in youth treated with second-generation antipsychotics (See review in (40)). Treatment of these adverse effects includes anticholinergics (tremor, rigidity, and dystonia), beta blockers and/or benzodiazepines (akathisia), slow cross titration (withdrawal dyskinesia), as well as dose change or switch to clozapine and/or preventive use of Vitamin E (tardive dyskinesia) (See review in (36)).

Finally, neuroleptic malignant syndrome (NMS) is a serious, albeit rare, adverse effect associated with both typical (See review in (41)) and atypical neuroleptics (See review in (42)). The DSM-IV criteria include rigidity and hyperthermia with at least two of the following symptoms: diaphoresis, dysphagia, tremor, incontinence, tachycardia, tachypnea, hypertension, altering mental states from confusion to coma, and mutism. Laboratory findings include increased serum creatinine phosphokinase (CPK) and leucocytosis.

Although one cannot generalize from the findings of case reports, a review of published clinical case reports on 77 youth treated with typical neuroleptics (41) reported death in 9% and serious sequelae in 20% of the cases. However, there were no cases of death in a subsequent review of case reports of 20 youth treated with risperidone, olanzapine, and aripiprazole who had elevated CPK (42). Only 39% of these children met full NMS diagnostic criteria, while 47.8% presented with fever and rigidity. NMS onset was related to a recent increase in neuroleptic dose, and presented later and lasted less time in children treated with atypical compared to typical neuroleptics. Treatment involves neuroleptic withdrawal, fever reduction, intravenous hydration, and administration of bromocriptine. Use of anticholinergics and ECT in pediatric NMS needs to be further explored.

Conclusion

The diagnostic challenges, together with the adverse effects of neuroleptics, emphasize the importance of accurate diagnosis and medical monitoring of children with schizophrenia.

GP comment

What have I learned from this paper?

1. Schizophrenia is rare in young children but can occur.
2. This paper provides a very good guide of how to distinguish between schizophrenia and other conditions in children.
3. History taking from children requires particular skill because of the way they may express abnormal phenomena such as hallucinations or their willingness to do so.
4. There are significant adverse effects from current medical treatment. Primary care services need to be aware of these problems and to plan appropriate monitoring to help reduce long-term difficulties.

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