Psychosis in children: diagnosis and treatment

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The diagnosis of childhood psychosis raises a host of unresolved problems, despite the Diagnostic and Statistical Manual Of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) *giving identical symptoms and definitions for children, adolescents, and adults. The fantasy lives of children, and issues of developing language and cognition (including retardation), all impair diagnostic accuracy, particularly when differentiating between childhood-onset schizophrenia (COS) (≤12 years), bipolar affective disorder, major depressive disorder, and even obsessive-compulsive disorder and attention-deficit/hyperactivity disorder: the catch-all classification, psychosis not otherwise specified (PNOS), is always available for conundra that prove unsolvable. Typical if nonpathognomonic features include neurocognitive difficulties. Multiple screening instruments and specialized versions of semistructured diagnostic interviews are available. Although smooth-pursuit eye-tracking movements may prove a genetic marker for COS, etiologies are likely to be oligogenetic rather than related to a single gene. No specific biological markers or neuroimages have been identified. As such, psychoses may be indicative of a more general pattern of brain dysfunction. Drug treatments are largely based on the adult literature because of a dearth of controlled data below age 18. There are still no rigorous studies of psychosocial treatments and psychotherapy specific to childhood psychosis.*

Psychosis presenting in childhood and adolescence has been a controversial topic throughout the history of the field of child psychiatry because of the conundrum of diagnostic clarity. As the necessity of diagnostic accuracy informs treatment as well as prognosis, an important question is whether the various psychoses of childhood are contiguous with the adult forms, or whether the symptoms labeled as psychotic in youth, particularly in prepubertal children, are exactly the same as those seen in adults. Historically, the definition of psychosis in children and adolescents has been particularly vague because of confusion regarding the developmentally appropriate role of imagination and fantasy in children and adolescents with and without psychiatric disorders. Formulations of "childhood psychosis" and psychosis were originally conceptualized as part of the spectrum of the pervasive developmental disorders, but currently, symptoms of psychosis and definitions of psychotic disorders do not differ for children, adolescents, or adults in the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR)*.[1]

The word "psychosis" applies to a state of being (ie, a psychotic state) as well as distinct diagnostic entities. The psychotic symptoms described in *DSM-IV-TR* include disorganization or gross disturbance of thought form or speech, thought content, or behavior, or extreme negativism. A psychotic symptom, or symptom cluster, is associated with a specific disorder as defined by a certain number of symptoms occurring over a circumscribed duration of time with demonstrated impairment. Hallucinations and delusions are usually thought to establish the diagnosis of psychosis. However, neither of these symptoms are pathonomonic of psychosis, as they can occur in other organic medical or neurological conditions, such as dementias or complications of seizure disorders. Normal children with active fantasy lives can often misperceive their thoughts as actual

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Selected abbreviations and acronyms

ADHD	*attention-deficit/hyperactivity disorder*
AE	*adverse effect*
BPAD	*bipolar affective disorder*
BPRS	*Brief Psychiatric Rating Scale*
CDRS	*Child Depression Rating Scale*
CGAF	*Clinical Global Assessment of Function*
CGI-I	*Clinical Global Impressions–Improvement*
CGI-S	*Clinical Global Impressions–Severity*
COS	*childhood-onset schizophrenia*
DICA	*Diagnostic Interview for Children and Adolescents*
DISC	*Diagnostic Interview Schedule for Children*
EPS	*extrapyramidal symptom*
K-PANSS	*Kiddie Version of the Positive and Negative Symptoms of Schizophrenia*
K-SADS	*Schedule for Affective Disorders and Schizophrenia for School-Aged Children*
MDD	*major depressive disorder*
MRI	*magnetic resonance imaging*
^{1}H-MRS	*magnetic resonance spectroscopy*
OCD	*obsessive-compulsive disorder*
PNOS	*psychosis not otherwise specified*
Y-MRS	*Young Mania Rating Scale*

events and can insist in a firm way that a thought or a dream actually occurred, which would seem to meet the definition of hallucination and delusion.

Schizophrenia is perhaps the best studied of the adult psychiatric disorders. Its symptoms and phenomenology are well established, and there is a comparative wealth of neuroimaging, genetic, and neurocognitive research that informs the understanding of this illness. When the criteria are applied to older adolescents, an age group when first episodes often occur, the diagnosis is often reliable. However, in the younger age group, the issues of developing language and cognition interfere with the dependability of diagnostic accuracy. The adult form of schizophrenia is not a monadic entity, but rather appears to be a collection of etiologically distinct disorders with similar clinical presentations. No consistent or gross neuropathology that identifies the illness.

These issues also apply to bipolar affective disorder (BPAD). The template of symptoms and presentation can apply easily to older adolescents as well as adults, but the situation is less clear in younger children.

Because of variability of symptom presentation, psychotic symptoms that can occur within the spectrum comprising childhood-onset schizophrenia (COS, age of onset ≤12 years), eg, schizophreniform disorder, schizotypal disorder, and schizoaffective disorder, are difficult to distinguish from psychotic and nonpsychotic symptoms related to BPAD and major depressive disorder (MDD). Psychotic symptoms in children and adolescents need to be differentiated from other, intense, repetitive, but nonpsychotic phenomena, such as obsessions related to obsessive-compulsive disorder (OCD), anticipatory anxiety related to non-OCD anxiety disorders, rumination related to depression, perseverative thoughts related to developmental disorders, simple disorganization related to attention-deficit/hyperactivity disorder (ADHD), and overvalued ideas. In addition, language deficits and cognitive deficits related to mental retardation may suggest psychosis in nonpsychotic children. Furthermore, nonspecific symptoms, such as anxiety, distractibility, and irritability, may precede a psychotic break and confuse diagnosis based on course of illness. Psychosis not otherwise specified (PNOS) is intended to classify psychotic symptoms not associated with COS, BPAD, or MDD. Accurate and reliable diagnosis of psychosis during childhood remains elusive, and is indicative of the necessity for more thoughtful study.

Prevalence

Sparse epidemiological data suggest that psychosis is rare in children. Schizophrenia with onset during middle to late adolescence is fairly common, with 1% prevalence, compared with the extremely rare COS with a prevalence of 0.2 to 0.4/10 000.[2] The largest study of COS to date, involving 1400 national referrals to the National Institute of Mental Health (NIMH) over 10 years, identified 260 children with psychosis.[3] Only 71 patients met criteria for COS at study entry,[3] whereas only 54 children retained the diagnosis of COS (Rapoport JL, personal communication, 2000). In contrast, MDD may occur in 1% of children and 5% of adolescents,[4,5] whereas BPAD occurs in 1% to 2% of adolescents.[6,7] Mood disorders with psychosis are considerably rarer in children and adolescents. The prevalence of psychosis NOS and BPAD in children is hard to ascertain because of controversy about validity.

Phenomenology

Childhood-onset schizophrenia

As with schizophrenia diagnosed at any age, COS presents with two types of symptom clusters, positive psy-

chotic symptoms and negative psychotic symptoms. Positive symptoms (phenomena that are present and should not be) in children include gross disturbance of thought process or thought content, whereas delusions likely appear with increasing developmental age. Negative symptoms (phenomena that are not present and should be) include flat affect, anergy, and paucity of speech and thought.[2] Prepubertal children with psychosis seem to have less systematic delusions and lower incidence of catatonic symptoms, but are capable of exhibiting hallucinations, disordered thought process, and flattened affect.[8] Insidious course of COS and onset prior to age 12 years are predictors of a more serious outcome.[9] Other features of COS that contribute to poor outcome include severity of positive and negative symptoms in acute episodes,[10,11] lower cognitive functioning,[12] and premorbid dysfunction in language, motor development, and social relatedness.[13-15]

Bipolar disorder

The clinical picture of pediatric BPAD ranges from symptoms resembling severe ADHD to symptoms resembling paranoid schizophrenia. Children with BPAD often initially present with either rapid cycling or mixed state symptoms rather than an insidious onset as described with COS.[6] Children and adolescents with mania present with pressured speech, racing thoughts, elation, and increased risk-taking activities, which may include developmentally inappropriate or situationally inappropriate sexuality. When BPAD has first onset during adolescence, psychosis is typically the presenting symptom and an adult-like cycling pattern follows.[16] Grandiosity, a hallmark symptom of BPAD at any age, may be disguised by developmental age, as prepubertal children with BPAD appear severely oppositional instead of obviously grandiose. Unfortunately, the clinical distinction between the grandiosity of BPAD and the paranoia of schizophrenia is often too hard to distinguish. Mood symptoms, such as euphoria or irritability, may also be disguised by developmental age. One researcher described poorly formed euphoria in manic adolescents that resembles a carefree, "spacey," or "delirious-like" quality that may present as disordered thought process (Popper C, personal communication, 2001). Interpersonal difficulties may exist secondary to symptoms associated with BPAD; however, children with BPAD do not seem to have the social withdrawal or the impoverished social relatedness seen in COS. While these children may present with language disorders or learning disabilities, they do not appear to have the extent of deficits seen in children with schizophrenia. Children and adolescents with BPAD involving severe mood instability have a more chronic and treatment-refractory course then adults.[17,18] Over half of all bipolar adolescent patients with prolonged episodes show significant functional impairment in the long term compared with their premorbid state. When children with premorbid social withdrawal and poor interpersonal relationships were compared in terms of diagnosis, children with BPAD had lower rates of positive and negative symptoms at 1-year follow-up than children diagnosed with schizophrenia or schizoaffective disorder.[19]

Major depression

Flat affect related to psychosis is often difficult to distinguish from severely depressed or restricted affect at any age; similarly, anergy of psychosis may be hard to distinguish from psychomotor retardation of depression. Children who present with a psychotic depression may also appear to have impoverished thoughts and social withdrawal; however, the mood symptoms are expected to improve with resolution of the episode. In contrast, the negative symptoms of schizophrenia may not improve with resolution of the episode. In children presenting with psychosis in the context of depression, 50% to 60% will develop BPAD, and their risk for suicide is markedly increased.[20,21]

Schizoaffective disorder

As the name implies, schizoaffective disorder shares many symptoms with the affective disorders, which can complicate the diagnosis. In the initial phases of psychotic illness in children and adolescents, affective symptoms related to adjustment and demoralization may overshadow the presence of psychotic symptoms. According to *DSM-IV-TR*, delusions or hallucinations of 2 weeks' duration must occur in the absence of mood symptoms to distinguish schizoaffective disorder from a mood disorder with psychotic features. Traditionally, the diagnosis of schizophrenia has relied on the presence of bizarre hallucinations or delusions instead of mood-congruent hallucinations or delusions related to BPAD or MDD. However, the determination of "mood congruent" at times appears too subjective. For instance,

youngsters who initially present with mood-incongruent hallucinations, marked thought disorder, and paranoia have later been diagnosed with BPAD as prominent mood cycling appeared.[18] In contrast, some children initially diagnosed with schizoaffective disorder on the basis of prominent mood symptoms later develop significant symptoms of thought disorder, while the mood symptoms only accompany the psychotic episodes. Schizoaffective disorder is associated with the poorest outcome and chronic impairment in children.[17]

Psychosis not otherwise specified

The diagnostic category of PNOS may be used by default when full criteria are lacking for psychotic disorders in the schizophrenic or mood disorders spectrum. There are divergent opinions about the validity of PNOS. The diagnosis is sometimes given to children who present with self-reports of hallucinations and/or delusions in the absence of a formal thought disorder, severe mood disturbance, or other clinical context suggesting a state of psychosis. The validity of self-reported hallucinations and delusions was questioned in a study of children diagnosed with PNOS with brief psychotic episodes and hallucinations, but without formal thought disorder or psychotic behaviors.[22] One group of researchers found high incidence of physical/sexual abuse in children diagnosed with PNOS,[23] and suggested a scenario of dissociative symptoms accounting for the self-report symptoms. The NIMH study group decided that children who did not meet criteria for COS were better served with a diagnosis of PNOS, and described a subgroup called multidimensionally impaired disorder (MDI),[24] which has also been called multiplex developmental disorder,[25] for a group of children presenting with brief transient psychotic symptoms, emotional lability, normal social interest with poor interpersonal skills, and multiple deficits in information processing.[26] Preliminary follow-up suggests that this cohort does not progress to a more severe psychotic disorder; however, there is a high rate of schizophrenia spectrum disorders in their first-degree relatives. There are also similarities in brain morphologic abnormalities between the MDI group and children with schizophrenia.[27]

Schizotypal disorder

The inclusion of a personality disorder in a discussion of childhood psychosis reflects the controversy of psychosis in children. Researchers and clinicians are generally uncomfortable diagnosing personality disorders in the pediatric population, and the distinction of state versus trait symptoms remains controversial at all ages. Poor social relations, odd thinking, and perceptual problems, such as illusions and ideas of reference without actual psychosis, are the characteristics of schizotypal disorder as defined in adults. In one study of adolescents with schizophrenia, the social skills of the adolescents mirrored those reported in adults with schizotypal personality disorder.[28] These adolescents had more difficulty in labeling positive emotions than other emotions and performed worse than a control group on social role-playing tasks. Neuropsychological deficits correlated with the presence of negative signs in adolescents with schizotypal personality disorder.[29] Subjects who exhibited more negative signs had a high association with dysmorphia and lower cognitive ability, suggesting early developmental instability.[30]

Features associated with psychosis in children

Neurodevelopmental delays

Children with COS have been described as having developmental differences as early as infancy. These children show abnormal or delayed development including gross and fine motor delays, hypotonia, poor coordination, sensory integration difficulties, and language delays.[9,31,32] These children also exhibit stereotypies, such as hand flapping, perseverative smelling, and touching, ie, symptoms typically seen in children with pervasive developmental disorders. These children also have attentional problems, distractibility, and other disinhibitions of executive functioning, which meet criteria for ADHD, possibly an indicator of poor prognosis.[33] Children who have other schizophrenia spectrum disorders also have a history of developmental delays and cognitive deficits.

Children with COS have a high incidence of language disorders, not only expressive and receptive, but also with specific impairments and deficits that directly contribute to thought disorder and disorganization. Children with delayed expressive and receptive language development were able to catch up with their peers, although they continued to have deficits in their linguistic capacities.[34] Children with schizophrenia use fewer linguistic or cohesive

devices to connect ideas expressed within and across sentences compared with a sample of children without schizophrenia.[35] They also exhibit decreased use of conjunctions, referential cohesions such as pronouns, lexical cohesions illustrated by the use of antonyms and synonyms, and increased use of ellipses (eg, deletion of words or phrases whose referent is located in the previous utterance). Such difficulties in conveying language lead to three components of thought disorder: exophora, which is the diversion of speech from the context of a conversation to the immediate environment; loose associations or topic maintenance; and cohesion.[36,37] In a larger study of schizophrenic children who were compared with a control group, children with COS are distinctly impaired in their ability to organize their thinking, present adequate reasoning, and prepare the listener for a change in the topic of conversation above and beyond differences in mental age.[38] Children with COS make more references in their conversation to the immediate situation rather than to the context of the conversation. They are also unable to use clarifying references on a consistent basis so that the listener can understand the context. These deficits may be related to the freedom from distractibility factor of the Wechsler Intelligence Scale for Children–Revised (WISC-R) rather than global intellectual deficits.[39] Subjects with COS and premorbid speech and language impairments had a higher familial loading for schizophrenia spectrum disorders as well as more obstetrical complications, and the relatives of these children had worse smooth-pursuit eye-tracking movements.[40] These data suggest that the pathophysiology of schizophrenia involves abnormal development of language-related functions.

There is little in the literature about developmental difficulties in children with psychotic mood disorders. Children with early onset BPAD show evidence of delayed language, social, and motor development.[41]

Neurocognition

Children with COS as a group appear to have lower IQ scores than the normal population.[12] It has been speculated on the basis of neurocognitive studies that these lower IQ scores reflect prodromal neurocognitive deficits, rather than exposure to environmental factors.[42] Cognitive functioning, such as attention, memory, and motor functioning, has been found to be abnormal in many schizophrenic subjects. Since the above cognitive findings are similar to findings in children with ADHD, researchers compared these two groups with each other and with normal controls. Adolescents with schizophrenia showed more deficits in visual memory than ADHD or normal controls. In addition, they had lower scores in abstraction-flexibility, spatial organization, and motor function. Subjects with ADHD had significantly worse auditory processing and distractibility, which may indicate selective impairments in visual memory specifically related to schizophrenia.[43] In addition, the subjects with COS had more difficulty on tests requiring shifting of sets, which is seen as a function of working memory. Furthermore, it has been reported that subjects can show impairments on the span of apprehension task when they are acutely psychotic, as well as interepisode.[44] This neurocognitive test is a measure of thought disorder. Deficits in both verbal and spatial working memory lead to limited information-processing capacity in children with COS.[45,46]

The IQ of adolescent subjects with COS was studied to determine whether the postpsychotic decline in full-scale IQ is secondary to a dementing process or whether it reflects a failure to acquire new information and skills.[47] Those areas in which scores declined significantly postpsychosis were picture arrangements, information, and block design. This research group also used magnetic resonance imaging (MRI) to detect changes in the brain anatomy and found a significant correlation between decrease in hippocampal volume with a smaller increase in the raw score on the information subtest. The authors concluded that the IQ decline during adolescence of subjects with COS is secondary to an inability to acquire new information and skills.

Studies of the families of children with COS indicate first-degree relatives and other relatives have similar neurocognitive difficulties. Nearly 30% of nonpsychotic parents of COS probands showed neurocognitive impairments.[46] Children of schizophrenic parents, affectively ill parents, and psychiatrically normal parents have been studied to search for predictors of future illness.[48] Measures of attention deviance, verbal memory, and gross motor skills were utilized based on studies of relatives of adult psychiatric probands. This report suggests that these may be phenotypic indicators, as the deficits were present before clinical symptoms, independent of the illness date, more prevalent in relatives of schizophrenic patients than in comparison subjects, and comparatively specific to the risk for schizophrenia versus the risk for affective disorders. Verbal memory and

attention were tested over several evaluations and found to have longitudinal stability and persistence of impairment. These neurobehavioral deficits may represent a prodromal indicator of risk if they are sustained.
Children with COS and children with PNOS shared a similar pattern of generalized cognitive deficits including deficits in attention, learning, and abstraction, which are also observed in adult patients with schizophrenia.[49]
Learning disabilities and language disorders occurred in children with BPAD during the illness and between episodes.[50] There was a significant discrepancy between the verbal IQs of children of bipolar parents and normal controls.[51]
These studies viewed as a whole would suggest that the syndromes of the psychoses, and in particular that of COS, are indicative of a more general pattern of brain dysfunction. If these findings can be replicated, then they would contribute to a theory of neurodevelopmental pathogenesis that investigators in adult psychiatry are debating.

Diagnostic assessments

In general, the psychiatric assessment of psychosis in children follows the model for comprehensive psychiatric assessment of children and adolescents, which includes a medical and psychiatric history, mental status examination, physical examination, and standardized psychiatric assessment instruments. The psychiatric history focusing on psychotic symptoms must carefully delineate family history, course of illness, and comprehensive review of symptoms. Particularly, the extent, nuance, and context of the psychotic phenomena must be clarified to identify mood congruence, mood incongruence, bizarre content, and stability of symptoms. Most importantly, psychosis must be ruled out when the phenomenology does not hold under close diagnostic scrutiny. While no medical assessment procedure is diagnostic of COS or any other psychiatric condition associated with psychosis, use of imaging studies, electroencephalography, and laboratory tests may help detect medical conditions associated with psychosis in children and adolescents.

Screening instruments

Before a formal diagnosis is established, and in addition to using a reliable and valid structured or semistructured interview, screening instruments may help identify psychiatric disorders associated with psychotic symptoms. Screening instruments for depression in children and adolescents include the Children's Depression Inventory,[52] which has normative data for children and adolescents. The Young Mania Rating Scale (Y-MRS)[53] has normative data for adolescents with BPAD. There is no screen with normative data for children with schizophrenia or other psychotic disorders.

Semistructured diagnostic interviews

The stringent use of adult criteria to delineate psychotic symptoms in children and adolescents, and the development of reliable and valid rating instruments to clarify the presence and severity of these symptoms suggest that some children with psychotic illness are exhibiting an early manifestation of the adult form of the illness. Homogeneous diagnostic criteria have demonstrated that COS can be diagnosed using adult standards,[54,55] and studies using *DSM-III* and *DSM-III-R* criteria confirmed these findings.[9,56] Rigorous application of *DSM-III* criteria can accurately diagnose childhood BPAD.[57] Standardized interviews, such as the Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present and Lifetime Version (K-SADS-PL),[58] the Diagnostic Interview for Children and Adolescents (DICA),[59] and the Diagnostic Interview Schedule for Children (DISC)[60] are reliable and valid measures for diagnosing MDD, BPAD, COS, and other psychiatric disorders in childhood that present with psychosis. The K-SADS is the probably the gold standard. Currently, specialized versions of the K-SADS, such as the Washington University at Saint Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-K-SADS), offer the advantage of focused diagnosis in prepubertal and early adolescent manifestations of mania with and without rapid cycling.[61]
The real importance of the standardized diagnostic instruments is establishing diagnostic stability, symptom dimensions, clinical characteristics, and predictive validity. Long-term studies utilizing the same diagnostic tests over time[62,63] indicate that there is stability of symptoms with the differentiation of features of the various illnesses and establishment of the clinical characteristics of the individual illnesses. A more recent example of symptom predictability involved a prospective study of a birth cohort (n=761), who were given structured diagnostic

interviews at age 11 years and then again at 26 years.[64] The group was divided into those who had weak symptoms and strong symptoms based on the reports of hallucinations or delusions, their severity, and the presence of other symptoms meeting criteria for a psychotic disorder. No children were diagnosed with COS. Those children who reported strong symptoms were 16 times more likely to have a schizophreniform diagnosis by age 26 years. Furthermore, 90% of the strong symptom children had occupational and social dysfunction as adults. Even those children who reported weak symptoms were significantly more likely to meet diagnostic criteria for adult schizophreniform disorder. Forty-two percent of diagnosed schizophreniform cases at age 26 interviews were associated with the presence of either weak or strong symptoms at age 11 years. The authors suggest that children experiencing hallucinations or delusions in the absence of a thought disorder may be experiencing prodromal changes, which could lead to the onset of frank psychotic symptoms.

Rating scales

Once a diagnosis has been established, rating scales are useful for monitoring symptoms of psychotic disorders during treatment and over time. Useful pediatric rating scales include the Child Depression Rating Scale (CDRS)[65] and the Kiddie Version of the Positive and Negative Symptoms of Schizophrenia (K-PANSS) for COS.[66] Rating scales such as the Clinical Global Impressions–Severity and Improvement (CGI-S and CGI-I)[67] and the Clinical Global Assessment of Function (CGAF)[68] are also useful to measure severity of impairment both at diagnosis and over time for any psychiatric disorder.

Research that may inform diagnostic testing in the future

Genetics

Evidence from twin, family, and adoption studies indicate genetic factors play an etiological role in schizophrenia.[69] A possible susceptibility gene for schizophrenia is localized in the region 8p22-8p21.[70] Studies of children with velocardiofacial syndrome (VCFS) suggest that chromosomal region 22q11.2 may have a role in development of schizophrenia because the autosomal dominant syndrome sometimes leads to chronic paranoid schizophrenia.[71] An ongoing study at the NIMH in 47 subjects with COS demonstrated that 5 patients (10.6%) had cytogenetic abnormalities[72]: 3 patients had VCFS, 1 had Turner's syndrome (involving a deletion of part of the long arm of one X chromosome 46,X,i[Xq24]), and 1 had a balanced translocation of chromosomes 1 and 7.

Smooth-pursuit eye-tracking movements have been proposed as a possible genetic marker for schizophrenia due to the association of eye-tracking pursuit abnormalities in adult-onset schizophrenia before and after treatment, in family members of schizophrenic probands, and in children of schizophrenic parents.[73-75] Unique eye-tracking findings in schizophrenia include specific difficulties in the high rates of catch-up saccades and the failure to suppress saccadic anticipation of target motion.[76,77] In a study of children with COS compared with patients with adult-onset schizophrenia and their family members, smooth-pursuit eye-tracking movements and P50 event-related potential predicted bilineal genetic loading.[78] On the basis of results of family studies and early genetic studies, oligogenetics rather than genes of major effect may better explain complex psychiatric disorders such as MDD, BPAD, and schizophrenia.

Biological markers

Adolescents with schizotypal disorder had an increase in minor physical anomalies including abnormal hair whorls, larger or small head circumference, epicanthal folds, hypertelorism, asymmetrical or low-seated ears, curved fifth finger, webbed toes, and other dysmorphic features, dermatoglyphic asymmetries, and higher mean cortisol values.[79] Children and adolescents with COS had higher rates of skin conductance responses and heart rate compared with controls; however, their skin conductance level was marginally lower and declined more slowly over time than the controls.[80] Impaired skin conductance rates, more erratic habituation, and smaller anticipatory heart rate responses to stimuli were also described. Cerebrospinal fluid monoamine metabolite concentrations in COS subjects 6 weeks after clinically effective haloperidol or clozapine treatment did not differ from drug-free levels.[81] An increase in homovanillic acid during week 2 of treatment and a decline around week 6 were also apparent. The haloperidol treatment group also exhibited a substantial increase in serum pro-

lactin levels. All of the above findings are consistent with findings with schizophrenia of later onset.

Neuroimaging

Magnetic resonance imaging

The NIMH study group on COS has reported sequential MRI results suggesting brain anatomy changes consistent with adult studies. On the initial scan, children with COS have larger lateral ventricular volumes as well as smaller cerebral volumes,[82] whereas the temporal lobe volumes appear relatively spared.[83] A strong association between smaller cerebral volumes and negative symptoms was reported.[84]

Adolescents with COS also had larger globus pallidus, caudate, and putamen volumes at the initial scan.[85] When the subjects were scanned 1 to 4 years later, subjects with COS exhibited decreases in total cerebral volume, and globus pallidus, caudate, and midsagittal thalamic volumes associated with significant increases in ventricular volume as compared with the control group, which had similar findings, but no changes in ventricular volumes or thalamic anatomy. Subjects with COS who were treated with atypical neuroleptics had even greater decreases in the globus pallidus and caudate volumes on rescan. The progressive changes in ventricular volumes and thalamic area correlated significantly with each other, and the increases in ventricular volume were significantly related to prepsychotic adjustment problems rated on the premorbid adjustments scale and Brief Psychiatric Rating Scale (BPRS).[86] A 2-year follow-up study of subjects with COS showed significant decreases in the volumes of the right temporal lobe, bilateral superior temporal gyrus, posterior superior temporal gyrus, right anterior superior temporal gyrus, and left hippocampus compared with controls.[87] The decline in the right posterior superior temporal gyrus volume was associated with high scores for positive symptoms.

Of subjects with COS, 12.5% had enlarged cavum septi pellucidi consistent with a rate found in adult-onset schizophrenia.[88] The researchers posited that dysgenesis of the hippocampus or the corpus callosum could lead to larger than normal cavum septi pellucidi. In a 2-year follow-up study of adolescents with COS, healthy controls showed decrease in cortical gray matter in the frontal and parietal regions, but patients with very early-onset schizophrenia had a fourfold greater decrease in cortical gray matter volume, not only in the frontal and parietal areas, but also in the temporal lobe volume.[89] The decreases in frontal and temporal gray matter are consistent with MRI findings in adult-onset schizophrenia. Using whole-brain voxel-based morphometric analyses in both children and adolescents with COS, the volume of the posterior lateral ventricles was significantly increased rather than the anterior regions.[90] In a controlled comparison of children with COS and children diagnosed with PNOS, the two groups were shown to have similar brain volumes.[91] However, children with COS had a smaller midsagittal thalamic area compared with controls and PNOS. Neither group showed a decrease in the volume of the temporal lobe.

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (^{1}H-MRS) performed on subjects with COS showed significantly lower *N*-acetylaspartate to creatine ratios bilaterally in the hippocampal area and the dorsolateral prefrontal cortex compared with normal controls, suggesting malfunction or neuronal damage.[92] Findings of reduced *N*-acetylaspartate in the frontal areas were replicated.[93] Elevated glutamate/glutamine levels in both frontal lobes and basal ganglia were detected in 10 children with BPAD.[94] These children also had elevated lipid levels in the frontal lobes, but not in the temporal areas. The significance of the elevated lipids is yet to be determined, but an increase in excitatory amino acids could be associated with manic behaviors.

Ultrasound

In examining the ventricular size of fetuses of mothers with schizophrenia, mild ventriculomegaly was apparent and associated with older mothers and a shorter gestation.[95,96]

Psychopharmacological treatment

This section presents pharmacological approaches to treating psychosis in children, which can be divided into three categories: (i) COS; (ii) psychosis related to depression; and (iii) psychosis related to bipolar disorder. Neuroleptics may be needed for acute management of substance-induced psychosis or psychosis related to a general medical condition or delirium, but the details

are beyond the scope of this manuscript. PNOS that cannot be better conceptualized in children and adolescents as part of the schizophrenia spectrum or a mood disorder may be better managed with observation and psychosocial interventions, unless severe aggression or agitation warrants acute use of a neuroleptic.

Treatment of childhood-onset schizophrenia

The majority of data on neuroleptic treatment of schizophrenia is from adult studies of typical and atypical neuroleptics. Several neuroleptics are Food and Drug Administration (FDA)–indicated for psychotic disorders in children and adolescents, but none of the indications is based on adequate controlled treatment data in individuals below age 18 years[97]: chlorpromazine (Thorazine®) for ages ≥6 months; thioridazine (Mellaril®) for ages ≥2 years; and haloperidol (Haldol®) for ages ≥3 years. Only two published controlled studies of typical neuroleptics demonstrated efficacy (both included haloperidol; one also included loxitane) in the treatment of COS. Only one published controlled study of an atypical neuroleptic (clozapine) demonstrated efficacy in the treatment of COS. Despite the presence of efficacy data, haloperidol, loxitane, and clozaril are not considered to be first-line treatments of COS or any psychosis in children and adolescents because of their adverse effect (AE) profiles. Atypical agents, such as risperidone and olanzapine, are more likely first choices because of easier tolerability, although weight gain has emerged as a problematic AE.

Typical neuroleptics

Both haloperidol (2-16 mg/day) and loxitane (10-200 mg/day) proved superior to placebo in a 4-week treatment study of 75 adolescents (aged 13-18 years) with acute schizophrenia.[98] All treatment groups showed noticeable improvement based on ratings on the BPRS; subjects rated as severe or very severe tended to show more improvement on active medication. Sedation occurred in more than half the subjects on active drug: about 50% on haloperidol and about 80% on loxitane experienced sedation. Extrapyramidal symptoms (EPSs) occurred in about 70% of treated subjects. Haloperidol later proved superior to placebo based on Clinical Global Judgment and BPRS ratings in a 10-week, double-blind, crossover study of 16 children (aged 5-11 years) with schizophrenia.[99] The dosage of haloperidol ranged from 0.02 to 0.12 mg/kg/day, or 0.5 to 3.5 mg/day. As expected, EPSs and sedation were the most problematic AEs.

Atypical neuroleptics

Clozapine proved superior to haloperidol for treating positive and negative psychotic symptoms in a double-blind, 6-week study of 21 adolescents with schizophrenia.[100] As with prior adult studies of clozapine, AEs of concern included seizures and neutropenia. Several open studies of clozapine in COS also demonstrated neutropenia, as well as other AEs, such as sedation and drooling.[101]

A review of 15 studies of clozapine in COS, including controlled and open data,[102] suggested that clozapine had a greater antipsychotic effect than typical antipsychotics during acute episodes, more improvement in chronic forms of the illness with prominent negative symptoms, and "good tolerability" with fewer reports of EPS. In another review of atypical neuroleptics (including clozapine, risperidone, olanzapine, sulpiride, tiapride, amisulpride, remoxipride, and clothiapine) for COS,[103] clozapine seemed to have the most robust effect on the symptoms of COS, and risperidone and olanzapine also had utility in the treatment of COS. Overall, clozapine remains a tertiary treatment option for COS due to its association with potentially dangerous AEs, including agranulocytosis, seizures, tachycardia, and arrhythmia.

Risperidone has proven useful in the treatment of a number of pediatric disorders, but no controlled treatment study of risperidone has been performed for COS. Open studies of risperidone (up to 10 mg/day) have been promising for adolescents and children and adolescents with COS based on the CGI-I, BPRS, and K-PANSS.[104,105] In both studies, the AEs included sedation and EPS. In a controlled study of risperidone for adults with first-onset schizophrenia, doses of 2 to 4 mg/day were superior to 5 to 8 mg/day. By extrapolation, the open studies of pediatric patients described above likely utilized too high a dose of risperidone. The only published controlled data on risperidone use in pediatric subjects is a treatment study of adolescents with conduct disorder.[106] Weight gain has been the most problematic AE in two open-label studies of risperidone treatment of children and adolescents with aggression and other psychiatric problems.[107,108]

There have been no published controlled studies of olanzapine in COS. Open-label studies of olanzapine for COS indicate a positive impact on psychotic symptoms,[109-111] and report primary AEs including weight gain, sedation, and akathisia, ie, a profile similar to that reported in adults. A pharmocokinetic study suggested similar olanzapine exposure (defined as area under the concentration–time curve) in children and adolescents with COS compared with adults.[112] The authors suggested that 10 mg/day olanzapine is the target dose for treating psychosis in pediatric patients, consistent with dosing in adults.

There have been no published controlled studies of quetiapine in COS. A pharmacokinetic study of quetiapine in adolescents with psychotic disorders demonstrated slightly higher quetiapine exposure in adolescents than in adults.[113] Quetiapine had a beneficial effect on positive and negative symptoms and was well tolerated; the most common AEs were insomnia and postural tachycardia.

Ziprasidone was released on the US market in March 2001. No controlled data on ziprasidone treatment for COS have been published. However, a placebo-controlled study of ziprasidone (5-40 mg/day) was carried out in 28 children and adolescents (aged 7-17 years) with Tourette's syndrome.[114] Somnolence and EPSs were rare and resolved with dose decrease: 1 subject had brief but severe somnolence on 40 mg/day, and 1 subject experienced akathisia on 40 mg/day. No significant weight gain was noted in subjects.

Adverse effects

The relative impact of neuroleptics at various receptor types determines the AEs. Depending on which dopamine receptor D_2 tracts are blocked, AEs of neuroleptics include EPS (nigrostriatal pathway), increased negative symptoms (mesocortical pathway), and hyperprolactinemia (tuberoinfundibular pathway). Prolactin levels were studied in 35 children and adolescents with COS treated with haloperidol, olanzapine, and/or clozapine.[115] After 6 weeks of treatment, all subjects on haloperidol and 70% of subjects on olanzapine showed increased prolactin above the upper limits of normal, whereas no subjects on clozapine showed increased prolactin level. In addition to an impact on D_2, typical neuroleptics have an anticholinergic effect (muscarinic acetylcholine receptor, M_1) including sedation, dry mouth, blurry vision, and constipation; an antihistaminergic effect (histamine receptor, H_1) including sedation and weight gain; and antiadrenergic effects (adrenergic receptor, α_1) including dizziness and hypotension.

Atypical neuroleptics also have capacity to impact M_1, H_1, and α_1 receptors, and may additionally block D_1, D_2, and D_4, as well as the serotonin (5-hydroxytryptamine) receptors 5-HT_3, 5-HT_{2C}, and 5-HT_3. In vitro data suggest that the atypical agents have unique receptor blockade selectivity. For instance, clozapine blocks all of the above receptors, whereas risperidone blocks only 5-HT_{2A}, 5-HT_{2C}, α_1, and D_2 receptors. Serotonergic blockade by atypical neuroleptics appears to modify antipsychotic effect and AEs related to dopamine blockade, and it may have a mood-stabilizing effect. Significant prolongation of QT_c duration (Q-T interval adjusted for rate) is associated with butyrophenones, phenothiazines, and pimozide, and does not appear to be clearly associated with any of the atypical neuroleptics.[116] However, electrocardiographic monitoring of QT_c intervals is recommended with ziprasidone. lthough atypicals contribute to less EPS, cardiac toxicity, and hyperprolactinemia than typical neuroleptics, atypical neuroleptics are more likely contribute to prominent weight gain and have higher risk for agranulocytosis than typical neuroleptics. Neuroleptic malignant syndrome (NMS) is possible with both typical and atypical neuroleptics.

Treatment of psychosis related to pediatric bipolar disorder

No controlled study of pharmacological treatment for pediatric BPAD with psychosis has been published. The only controlled medication treatment study to date for pediatric BPAD included 25 subjects with concomitant substance-abuse problems.[117] In this study of lithium monotherapy, bipolar symptoms and substance use decreased significantly in subjects treated with lithium. Divalproex, lithium, and carbamazepine each showed a large effect size (Cohen's d>1.00) in an open study 42 children and adolescents (aged 8-18 years) with BPAD based on outcome measures of CGI and Y-MRS.[118]

A retrospective chart review of risperidone in juvenile BPAD indicated improvement in manic and psychotic symptoms.[119] Open studies of olanzapine in acutely manic children are promising.[120,121] Because of the robust antimanic effect demonstrated with atypical neuroleptics in adults with BPAD,[122] future controlled pediatric studies of neuroleptics for BPAD are likely.

Treatment of pediatric major depression with psychotic features

No controlled studies of pharmacological treatment of psychosis associated with pediatric MDD exist. To date, only two controlled studies of antidepressants have shown efficacy in treatment of pediatric MDD. Fluoxetine (5-20 mg) proved superior to placebo in a study of 96 children and adolescents with MDD based on CGI and Hamilton Depression Rating Scale (HAM-D).[123] Paroxetine proved superior to placebo in a study of 275 adolescents with MDD, according to HAM-D and CGI rating.[124] An open study of chlorpromazine plus nortriptyline for psychotically depressed adolescents showed some benefit from the combination,[125] however, neither nortriptyline nor chlorpromazine now appear desirable as treatment in pediatric mood disorders or pediatric psychosis because of their side effect profiles.

Psychosocial treatment

To date, there have been no published rigorous studies of psychosocial or psychotherapy treatments specific to the psychoses of childhood. Clinical practice standards include detailed education of the patient and parents about the illness, the provision of supportive psychotherapy during the recovery phase of the acute illness, and practical guidance regarding behavior. Continued supportive work interepisode appears to help patients with social and developmental crises. Clinicians also act as advocates with the parents for their patients with schools and other social agencies to ensure that these children and adolescents can continue with their education and that their specials needs are recognized. Families should be given information about the various patient advocacy groups, such as the National Alliance for the Mentally Ill. These groups not only aid on a national and state level to address the mental health needs of family members, but also act as a resource for support as these families struggle with these serious illnesses.

Discussion

COS is the best studied of the psychotic disorders of childhood. The neurobiological studies include neuroimaging, family studies (which point to phenotypic markers), and neurocognitive findings, and strongly support continuity with the adult form of schizophrenia. Further work is needed in describing the neurocognition of children with affective disorders. The affective psychotic disorders including BPAD, while indicating continuity with adult forms, would clearly benefit from a comprehensive study, as has been seen in COS. Hopefully, the controversy over the identification of psychosis and the diagnosis of these valid disorders will narrow the focus. Long-term follow-up studies including genetic and other vulnerabilities, neuroimaging, and neurometabolic studies will inform researchers and clinicians as to the care and treatment of these very ill children. There are clearly too few studies of atypical neuroleptics in the pediatric population. The long-term effects of chronic treatment in the developing child are unknown. Careful, well-designed studies of available medications in the various psychotic disorders in order to guide appropriate treatment should be a priority. Novel medications with potential antipsychotic applications, such as dopamine partial agonists, also require pediatric study. The current trend in treatment research of COS involves large controlled treatment studies of atypical neuroleptics for COS. There is also need for studies in the psychotherapies and psychosocial treatments to help the patients and their families to manage their illness. ❑

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Psicosis en niños: diagnóstico y tratamiento

El diagnóstico de la psicosis infantil da origen a un sinnúmero de problemas no resueltos, a pesar del Texto Revisado del Manual Estadístico de Trastornos Mentales en su cuarta versión (DSM–IV–TR) que entrega síntomas y definiciones idénticas para niños, adolescentes y adultos. Tanto la vida imaginaria de los niños como los temas del desarrollo del lenguaje y la cognición (incluido el retardo) dificultan la precisión diagnóstica, particularmente para diferenciar entre la esquizofrenia de inicio infantil (EII) (≤12 años), el trastorno afectivo bipolar, el trastorno depresivo mayor, e incluso el trastorno obsesivo compulsivo y el trastorno por déficit de atención con hiperactividad. La amplia clasificación que incluye las psicosis no especificadas en otro lugar está siempre disponible para resolver dificultades que parecen insolubles. Especialmente en las EII, las características típicas, aunque no patognomónicas incluyen las dificultades neurocognitivas, las que están presentes a menudo en los probandos desde una edad precoz y también en el 30% de los padres no psicóticos. Se dispone de diversos instrumentos de evaluación y de versiones especializadas de entrevistas semiestructuradas principalmente para adultos. Aunque los movimientos de seguimiento ocular pueden representar un marcador genético de la EII, las etiologías parecen ser más bien oligogenéticas que debidas a un gen único. Se han identificado marcadores biológicos y neuroimágenes no específicos. Estas psicosis pueden traducir, por lo tanto, un patrón más general de disfunción cerebral. Los tratamientos con fármacos se utilizan ampliamente, al igual que en los adultos, a pesar de una escasez de estudios controlados en menores de 18 años. Tampoco se cuenta con investigaciones rigurosas de tratamientos psicosociales o psicoterapias específicas para las psicosis infantiles.

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Psychoses de l'enfant : diagnostic et traitement

Le diagnostic des psychoses de l'enfant soulève une multitude de problèmes non résolus bien que le Diagnostic and Statistical Manual Of Disorders, 4e édition, Textes Révisés (DSM-IV-TR) en donne des symptômes et des définitions identiques pour les enfants, les adolescents et les adultes. La vie imaginative des enfants d'une part et les problèmes de développement du langage et de la cognition (y compris le retard) d'autre part perturbent l'exactitude du diagnostic, en particulier lorsqu'il s'agit de différencier la schizophrénie survenant dans l'enfance (Childhood-onset schizophrenia, COS) (≤12 ans), les troubles affectifs bipolaires, les dépressions sévères, voire les troubles obsessionnels compulsifs et les troubles à type de déficit de l'attention/hyperactivité ; la classification fourre-tout, représentée par la psychose non autrement spécifiée (PNAS), est toujours disponible pour les cas énigmatiques qui se révèlent insolubles. Les tableaux typiques ou non pathognomoniques, en particulier dans les COS, incluent les difficultés neurocognitives souvent présentes chez ces patients à partir du plus jeune âge mais également chez 30 % des parents non psychotiques. De nombreux examens de dépistage et des versions spécialisées d'interviews diagnostiques semi-structurées pour adultes sont disponibles. Bien que les mouvements oculaires sans à-coups au cours du test de poursuite oculaire puissent constituer un marqueur génétique de COS, les étiologies semblent être plutôt polygénétiques que provenant d'un seul gène. Aucun marqueur biologique ou de neuro-imagerie spécifique de COS n'a été identifié. De telles psychoses pourraient être un indicateur d'un tableau plus global de dysfonctionnement cérébral. Les traitements médicamenteux sont globalement les mêmes que chez l'adulte malgré un manque de données contrôlées en dessous de 18 ans, et nous ne disposons toujours pas d'études rigoureuses sur les traitements psychosociaux et la psychothérapie spécifique dans les psychoses de l'enfant.

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