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# Childhood Onset Schizophrenia and Early Onset Schizophrenia spectrum disorders

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## Synopsis

The clinical severity, impact on development, and poor prognosis of Childhood Onset Schizophrenia (COS) may represent a more homogeneous group. Positive symptoms in children are necessary for the diagnosis and hallucinations are more often multi modal. Both in healthy children, as well as in children with a variety of other psychiatric illnesses, hallucinations are not uncommon [1] and diagnosis should not be based on these alone. COS is an extraordinarily rare illness which is poorly understood but appears continuous with the adult onset disorder. Additionally, as seen in other areas of medicine, early onset populations have more prominent progressive brain changes, and genetic risk factors [2].

Diagnosing a child with schizophrenia has profound effects on the treatment course, including the potential for neglecting another disorder, as psychosis often becomes the primary focus. Since onset is almost always insidious, the “episodes” so common in later onset disorder are rarely seen. The gold standard for diagnosis remains the use of unmodified DSM criteria, based on extensive collateral information. Once a diagnosis is affirmed, aggressive medication treatment, in majority of cases with Clozapine, combined with family education and individual counseling may defer further deterioration.

### Keywords

Schizophrenia; Childhood Onset Schizophrenia; Childhood Psychosis

## Introduction

The clinical severity, impact on development, and poor prognosis of Childhood Onset Schizophrenia (COS) may represent more homogeneous forms of the disorder. Additionally, the deleterious effects of incorrectly diagnosing COS are equally important to recognize. Despite the relatively high (up to 5%) prevalence of psychotic symptoms in otherwise healthy children [3, 4], COS is very rare and so epidemiologic incidence data with diagnoses based on standardized clinical assessments are lacking. It is generally accepted that the incidence of COS is less than 0.04% based on the observations from the National Institutes of Mental Health (NIMH) cohort. Approximately 30 to 50% of patients with affective or other atypical psychotic symptoms are misdiagnosed as COS [5-9], and over 90% of the

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initial referrals to the NIMH study of COS to date received alternate diagnoses. Because our attempt is to study schizophrenia in its most homogeneous form, we exclude children with a diagnosis of schizoaffective disorder. In general, we have had very few schizoaffective children over the years, precluding any meaningful data analyses.

Although neurobiologically and phenomenologically continuous with its adult counterpart, COS represents a more severe form of the disorder [10, 11], with more prominent pre-psychotic developmental disorders, brain abnormalities and genetic risk factors [2, 9]. The use of various screening and diagnostic tools has not proven to be as valuable as the longitudinal assessment by a judicious clinician. A unique benefit of the NIMH COS study is the washout period, where patients are observed inpatient, medication free for up to 3 weeks. If a provisional diagnosis of COS is appropriate based on the screening process (clinical interview, records review, structured interview), the patient is admitted to the unit and begins the rigorous process of tapering all medications (up to 4 weeks). During this period, and the subsequent medication free phase (up to 3 weeks), patients are observed by staff, receive weekly ratings and have the support of up to 2 individually assigned staff members (i.e. 2:1 staffing). This process has ruled out COS in almost 40% of the children provisionally diagnosed as COS.

Realizing the framework and limitations of the environment in which psychiatric providers operate, our model is not feasible outside of the NIMH. However, it has taught us that the keys to attaining accurate diagnoses and optimizing treatment planning lie in evaluating children suspected of having COS for speech/language/educational deficits, obtaining extensive collateral information, and observing patients and their families over several visits. Furthermore, COS carries with it a commitment to use a class of medications with a significant side effect profile and significant long term health risks [12]. Given the implications of the diagnosis, it is important for clinicians to exercise a considerable amount of caution and care when evaluating children with COS, being careful not to focus solely on addressing the psychotic symptoms and subsequently overlooking common comorbidities such as receptive and expressive language disorders.

Research on the effects of a delayed diagnosis in COS is sparse, and our study design excludes children whose diagnosis may have been delayed, occurring after the age of 13. Additionally, even the adult literature is limited by the lack of a standardized measurement [13, 14]. However, in adults, it has been shown that a delay in diagnosis results in a longer duration of untreated psychosis; having a robust but moderate effect on clinical outcome [14, 15]. Although we advocate a measured, thoughtful approach to diagnosis; making a timely diagnosis is also important.

## Premorbid Phenotype

67% of children with COS show premorbid disturbances in social, motor, and language domains as well as demonstrate learning disabilities and have what seem to be comorbid mood or anxiety disorders. Additionally, although not reported in studies of the premorbid history of adult-onset schizophrenia[16, 17], 27% have met criteria for Autism/Autism Spectrum Disorders prior to the onset of their psychotic symptoms [18]. Outcome and prognosis have been positively correlated with the presence and severity of these developmental abnormalities [19-21] with some studies suggesting the severity of these deficits may actually represent a premorbid phenotype for COS [22-27].

The data on the premorbid functioning and symptomatology of the NIMH patients confirms and extends these findings. A review of our cohort (n=47) in 2000 showed that 55% had language abnormalities, 57% had motor abnormalities, and 55% had social abnormalities several years before the onset of psychotic symptoms. There was also a high rate of failed

grades and special education placement [24, 28]. Gender, familial psychopathology, and familial eye-tracking dysfunction have shown significant relationships with at least some aspect of the probands' premorbid development; Table 1 [24].

These results have been strengthened by a 2012 review of our cohort (n=118). Of the 118 children in the cohort, 65 (55.08%) had premorbid academic impairments, 85 (72.03%) had premorbid social/behavioral impairments, 60 (50.85%) had premorbid language impairments, 52 (44.07%) had premorbid motor impairments, and 24 (20.34%) screened positive for pervasive developmental disorder. (Table 2) The average number of abnormalities (15 domains) in each child was 3.89 and 103 (87.29%) of the children had premorbid impairment in at least one domain. Additionally, 47% of children who did not have a pervasive developmental disorder (e.g., Autism, Asperger, PDD-NOS), received pre-psychotic mental health treatment and/or a psychiatric or psychological evaluation.

## **Definition/Symptom Criteria

Since Kolvin's classic studies, it is generally agreed upon that Childhood-onset schizophrenia can be diagnosed with the unmodified DSM IV-TR Criteria for Schizophrenia (Table 3) [29]. In addition, the NIMH study has defined COS where the onset of psychotic symptoms is before the 13$^{th}$ birthday, combined with a premorbid IQ of 70 or above and absence of any significant neurological problem. The DSM V proposes a reorganization to reflect a gradient of psychopathology, from least to most severe, and updated severity dimensions. [30].

## Clinical Findings

### Physical examination

The diagnosis of Childhood-onset schizophrenia requires exclusion of an underlying medical or psychiatric illness. It is only after all other identifiable causes of 'organic psychosis' have been excluded a diagnosis of COS can appropriately be considered. Details regarding the components of the physical examination of individuals suspected of having a primary psychiatric illness are discussed in this volume by *Kumra and Goerke: Substance abuse and psychosis: etiological contribution and clinical considerations*. A physical and thorough neurologic exam is essential to the diagnostic process and clinicians should be vigilant to any abnormal physical and/or neurologic findings as COS is a diagnoses of exclusion. It is also important to have in mind the rare medical etiologies and frequently missed diagnoses during the evaluation. Although discussed elsewhere in this volume, a select summary list is provided in Table 4.

### **Rating scales and Diagnostic modalities

Frequently used rating scales will be discussed in subsequent chapters. For the NIMH COS study we use the Social Communication Questionnaire (SCQ), previously known as the Autism Screening Questionnaire (ASQ), and Kiddie-Sads-Present and Lifetime Version (K-SADS-PL), using the supplemental ratings as indicated by the results of the K-SADS-PL, for all probands. The Schedule for Affective Disorders and Schizophrenia (SADS) and the Structured Interview for DSM-III Personality (SIDP) are used to evaluate all family members for Axis I and Axis II disorder respectively. During follow-up visits the probands are evaluated using the Scale for the Assessment of Positive Symptoms (SAPS), Scale for the Assessment of Negative Symptoms (SANS), Brief Psychiatric Rating Scale for Children (BPRS – C), Clinical Global Impressions Scale (CGIS), Children's' Global Impressions Scale (CGAS), Bunny-Hamburg Global Ratings, Simpson-Angus Scale (SAS), and Abnormal Involuntary Movement Scale (AIMS) [34].

As previously mentioned, it is simply not feasible to apply what is done at NIMH in the community. In clinical practice, we routinely recommend to outpatient providers they use the SAPS and SANS to monitor clinical progress and the AIMS to monitor for potential side effects of the medication regimen. (Table 5)

### **Imaging

Structural brain abnormalities are an established feature of schizophrenia, characterized by decreased total gray matter (GM) volume reduction in cortex, hippocampus, and amygdala [35-43]. The number of imaging studies of Childhood and Early Onset Schizophrenia is growing with most them coming from the NIMH cohort. Advances in computational image analysis permit regional GM density, or cortical thickness measurements, which, when automated, can be applied to large samples, increasing statistical power [44-47]. This provides unprecedented anatomic detail of cortical GM change across both the entire cortex and time (Figure 1) [43, 47]. Prospective longitudinal brain MRI rescan measures for the NIMH COS sample show, progressive changes in COS, particularly during adolescence, highlighting this period as critical, and particularly vulnerable to treatment influences. These changes occur only during a limited period as the rate and degree of cortical loss if continued would resemble the extreme loss seen in some dementias [43, 47]. As it is, the GM volume of COS is 8-10% less than that of age matched controls.

Longitudinal analysis of quantitative brain imaging data suggests the rate of gray matter loss slows as these COS patients reach age 20 as shown in [50-52]. These studies also support the previous findings that, although representing a more severe form, COS is continuous with its adult onset counterpart. The total, frontal, temporal, and parietal GM loss, not seen in healthy children and adolescents nor in those with atypical psychosis, appears to be diagnostically specific for COS. [50]

## Pathology

Identifying the neurobiological basis and pathophysiology of schizophrenia is an essential future goal for establishing its diagnostic validity, delineating meaningful subtypes or alternate diagnoses, and finding causative mechanisms and novel targets for drug development [53, 54]. To date, the etiology of schizophrenia is unknown. There is general agreement that this is a brain disease, with alterations of white and gray matter, disconnectivity, and *in vivo* brain function. Research measures such as neural synchrony, sleep architecture, smooth pursuit eye movements (SPEM), and pre-pulse inhibition (PPI), all reflect widespread disorder. The few narrower models are discussed in this publication by *Frazier, Dvir, and Cochran in Autism and Schizophrenia* and by *Dvir, Frazier, and Deneitolis in Trauma and Psychosis*.

The general model of schizophrenia as a neurodevelopmental disorder is widely held. One version focused on schizophrenia as a static lesion, occurring during fetal brain development [55], while others argued that schizophrenia occurs as a result of a second “hit” in the form of abnormal brain development during adolescence such as excessive synaptic and/or dendritic elimination resulting in aberrant neuronal connectivity [9, 56, 57]. These theories have merged and it is now generally understood that COS is a multifactorial illness, characterized by multiple genetic elements, each contributing a modest degree of risk [58] an interacting with the environment. There are also various other hypotheses focused on the cortical amino acid neurotransmitter systems (i.e., dopamine, glutamate, GABA, serotonin) [59, 60].

Alterations in genetics, neurodevelopment, and neurotransmitter systems [61] remain among the most promising directions for further research. Schizophrenia risk genes are associated

with transcripts that are enriched in, or unique to, the human brain. Some also show preferential expression in the fetal brain [62]. Studies have revealed aberrant neuronal development, specifically localized to prefrontal and temporal cortices [56]. Alterations in timing of developmental disruption of GABAergic interneurons as the basis for several different neurodevelopmental disorders are gaining increasing support [63]. It is almost certain that both dopamine and glutamate transmission are abnormal in this disorder [64-66] and striatal dopamine over-activity may be critical to conversion to psychosis or psychotic symptoms generally [56, 67, 68].

Not only does the etiology of COS/EOS elude us, several roadblocks to progress toward finding one remain. First, the phenotypic, biological and etiological heterogeneity of schizophrenia may account for the fact that the effect size of these individual risks do not support any single neurobiological finding as a core deficit in the illness [54, 69, 70]. Second, we remain handicapped by the difficulty in studying the human brain and the lack of good animal models. Recent post-mortem studies, indicate time specific developmental genetic effects It remains clear however that schizophrenia, including COS/EOS, has no clearly definable neuropathologic markers (e.g. demyelinated neurons in Multiple Sclerosis) [54]. While the study if COS suggests it may have more salient genetic effects [71], there is no finding of even a rare form of genetic dominant transmission for COS.

## Diagnostic Dilemmas

The diagnosis of childhood onset schizophrenia (COS) is a difficult, time consuming process. Although early developmental abnormalities in social, motor, and language domains in COS are more striking compared to the later onset cases[22-24, 28, 72], they are not diagnostic and do not cumulatively represent a reliable premorbid phenotype. Additionally, not only do healthy children experience hallucinations, but children with various other psychiatric and behavioral disturbances present with positive symptoms [73, 74]. Pressure from families, the severity of the clinical picture, and time limitations placed on providers coalesce to make the diagnosis of COS a tedious process fraught with pitfalls. The most common disorder misdiagnosed as COS are affective disorders, organic psychosis, pervasive developmental disorders, and a group referred to as “Atypical Psychosis” or “Multi Dimensionally Impaired (MDI).” Details regarding these disorders, the latter of which is an important differential and is described in detail below, and achieving diagnostic clarity will be described elsewhere in this volume.

The NIMH cohort has been going on since 1990, using nationwide recruitment. Over the past 22 years, over 3000 charts have been reviewed. Of these, 90% are rejected from further consideration as they fail to meet the criteria for childhood onset schizophrenia. Over 300 children have been screened in person, of whom approximately 60% receive other psychiatric diagnoses such as affective disorders, anxiety, or behavioral disorders. Over 200 children who appeared likely to meet criteria for COS were admitted to the research unit and underwent an initial observation period followed by complete medication washout. After being observed off medications for up to three weeks, an additional 20% of children did not meet criteria for childhood onset schizophrenia and received alternative diagnosis. A 4- to 6-year follow up study of the ‘ruled out’ cases indicated good stability of the alternative diagnoses and non schizophrenic status[75]. The most frequent alternative diagnosis have been affective disorders, and anxiety disorders. A subgroup of children has also shown a form of atypical psychosis; provisionally labeled as “Multi Dimensionally Impaired (MDI) [76-78] based on a unique set of features which warrants further description.

### The "Multi Dimensionally Impaired (MDI)" group

To-date 33 children have been given the provisional diagnosis of "MDI" after the medication washout period and have been followed prospectively along with the COS children. This heterogeneous group of children, in general, has severe functional impairment associated with transient psychotic symptoms, multiple developmental abnormalities, abnormal neuropsychological test profiles, eye movement abnormalities, and familial risk factors that are not adequately characterized by existing DSM-IV categories [76, 79, 80]. Despite the presence of overlapping symptoms with childhood and early onset schizophrenia, there are distinct features which have been used as the 'operational diagnostic criteria' by the NIMH group to distinguish these individuals. [76, 79]:

1. Brief, transient episodes of psychosis and perceptual disturbance, typically in response to stress.
2. Nearly daily periods of emotional lability disproportionate to precipitants.
3. Impaired interpersonal skills despite the desire to initiate peer friendships (distinction from childhood onset schizophrenia).
4. Cognitive deficits as indicated by multiple deficits in information processing.
5. No clear thought disorder (clinically can be difficult to define, especially in presence of communication disorder).

**ADHD is highly comorbid in the MDI group.

At first glance, the symptom cluster these patients present suggests these children will likely progress to develop schizophrenia spectrum disorders; in the current DSM these patients could be considered as psychosis NOS. These children are similar in some way to some of the other syndromes described such as the Multiple complex developmental disorder (MCDD), Borderline Syndrome of Childhood or other Borderline Disorders of Childhood [80-83]. However, contrary to MDI, these other syndromes have more predominant symptoms of pervasive developmental disorder; greater evidence of formal thought disorder, and onset before age five [80, 84, 85]. The MDI group appears to have a distinct course, with none progressing to schizophrenia at long term follow-up [86], but strikingly, 38% developing Bipolar Disorder, Type I [87]. This long term data emphasizes to us that when diagnosing a child with schizophrenia, there are significant short and long term implications, including the potential for neglecting other disorders, as psychosis often becomes the primary focus.

## Process of elimination

It has long been known that hallucinations, delusions, and 'disordered thoughts' can occur in healthy non psychotic children [88] but usually diminish after age 6 [89]. Transient anxiety and stress related visual hallucinations are also occasionally reported in preschool children [90], and the prognosis of these phenomena is benign. However, when psychotic phenomena occur in school age children, they generally tend to be more persistent and associated with drug toxicity or more significant mental illness [1, 91-93].

## Comorbidities

Childhood-onset schizophrenia is highly correlated with other illness and disorders (Table 6) [24]. During the evaluation of a child with suspected COS, it is imperative they are screened, with a high index of suspicion, for other comorbid illnesses and disorders, both psychiatric [18] and medical [94] (Table 5) [95], the latter of which account for almost 60% of premature deaths not related to suicide in adult schizophrenia patients [94, 96].

## Conclusions / Summary: *Implications for Clinical Practice*

Schizophrenia is a devastating illness, particularly when presenting in childhood or adolescence. Despite the presence of premorbid characteristics, a reliable pre-morbid phenotype has not been defined and research into the pathophysiology of the syndrome remains ongoing without a substantial target demonstrated in a systematic way. The frequency and duration of psychotic episodes has deleterious neuropsychological, neurophysiological, and neurostructural effects [97-101], making prompt, aggressive treatment an important component of care. Once the diagnosis is established and other comorbid conditions are adequately assessed, clinicians should treat this illness aggressively. Treatment planning should encompass psychopharmacological, psychotherapeutic and early psychosocial intervention such as support and education of the family about the disorder, particularly during the first years of the evolution of the disease, as these can actually improve the course of illness [102]. Additionally, clinicians should not shy away from the use of Clozapine, as evidenced by the epidemiological studies demonstrating that its use occurs even much later than that recommended by the clinical guidelines [102].

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## Abbreviations

| | |
|---|---|
| **AIMS** | Abnormal Involuntary Movement Scale |
| **ASQ*** | Autism Screening Questionnaire* *See SCQ for new name* |
| **BPRS-C** | Brief Psychiatric Rating Scale for Children |
| **CGAS** | Childrens' Global Impressions Scale |
| **CGIS** | Clinical Global Impressions Scale |
| **COS** | Childhood Onset Schizophrenia |
| **K-SADS-PL** | Kiddie-Sads-Present and Lifetime Version |

| | |
|---|---|
| **MDI** | Multi Dimensionally Impaired |
| **NIMH** | National Institutes of Mental Health |
| **PPI** | Pre-pulse inhibition |
| **SADS** | Schedule for Affective Disorders and Schizophrenia |
| **SANS** | Scale for the Assessment of Negative Symptoms |
| **SAPS** | Scale for the Assessment of Positive Symptoms |
| **SAS** | Simpson-Angus Scale |
| **SCQ*** | Social Communication Questionnaire* *Formerly ASQ* |
| **SPEM** | Smooth pursuit eye movements |

### Key Points

- Childhood-Onset Schizophrenia (COS) is an extraordinarily rare illness with an incidence less than 0.04%. In both healthy children and children with a variety of other psychiatric illnesses, hallucinations are not uncommon; diagnosis should not be based on these alone.
- The evaluation of a child with suspected COS, includes collecting extensive collateral information, observing patients/families over several visits, excluding underlying medical illnesses and evaluating, with a high index of suspicion, for speech/language/educational deficits and comorbid mood or anxiety disorders.
- Once the diagnosis is established and other comorbidities are addressed, treatment planning should encompass aggressive psychopharmacological, psychotherapeutic and psychosocial interventions.
- Clozapine is an excellent third line medication for use in COS. Epidemiological studies demonstrate that its use often occurs much later than recommended by the clinical guidelines.

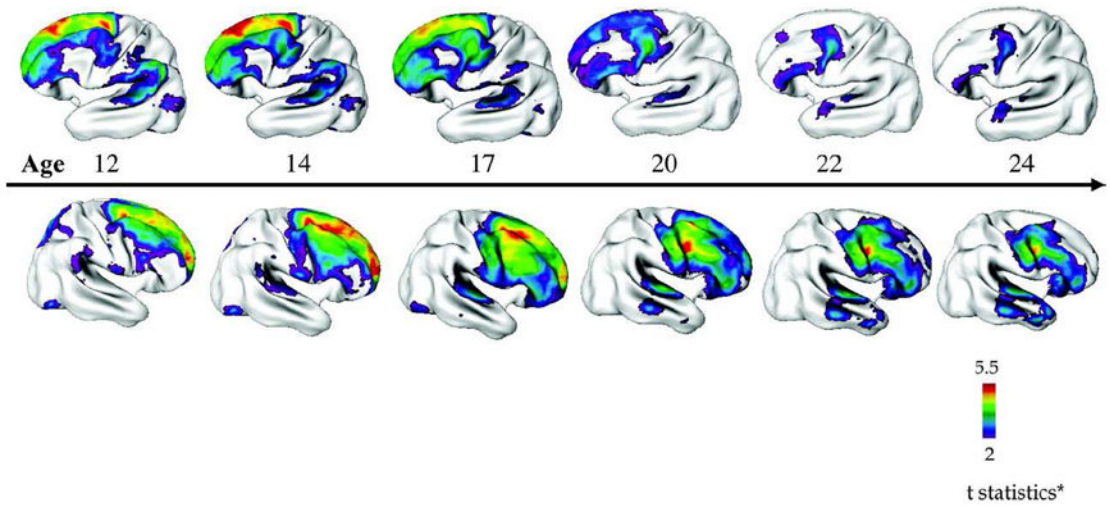


**Figure 1.**

Progression of Cortical Gray Matter (GM) Loss in Childhood-Onset Schizophrenia (COS) (n = 70, 162 scans) Relative to Age-, Sex-, and Scan Interval–Matched Healthy Controls (n = 72, 168 Scans) From Adolescence to Young Adulthood (age 12–24 years).

[48, 49] Progression of Cortical Gray Matter (GM) Loss in Childhood-Onset Schizophrenia (COS) (n = 70, 162 scans) Relative to Age-, Sex-, and Scan Interval–Matched Healthy Controls (n = 72, 168 Scans) From Adolescence to Young Adulthood (age 12–24 years). Analyses were done using mixed model regression statistics and covaried from mean cortical thickness. Side bar shows t statistic with threshold to control for multiple comparisons using the false discovery rate procedure with q = 0.05. Differences are from mixed model regression with age centered at approximate 3-year intervals for middle 80% of the age range, and colors represent areas of statistically significant thinning in COS.81 [43].

## Table 1

Relation of Premorbid Impairments to Schizophrenia Risk Factors for 49 Patients with COS.

| Premorbid Impairment and Risk Factor | Present (N) | Absent (N) | p Value |
|---|---|---|---|
| Speech and Language Impairment | | | |
| Sex | 27 | 22 | 0.57 |
| Score for family loading for schizophrenia spectrum disorders | 27 | 21 | 0.04 |
| Mean family score for eye tracking | 22 | 17 | 0.04 |
| Motor Impairment | | | |
| Sex | 28 | 21 | 0.009 |
| Score for family loading for schizophrenia spectrum disorders | 28 | 20 | 0.50 |
| Mean family score for eye tracking | 22 | 17 | 0.25 |
| Social Impairment | | | |
| Sex | 27 | 22 | 0.56 |
| Score for family loading for schizophrenia spectrum disorders | 27 | 21 | 0.15 |
| Mean family score for eye tracking | 19 | 20 | 0.37 |

**Table 2**

Realms of premorbid developmental problems based on 2012 chart review

| | N (%) |
|---|---|
| Social/Behavioral | 85 (72.03%) |
| Academic | 65 (55.08) |
| Language | 60 (50.85%) |
| Motor | 52 (44.07%) |
| Pervasive Developmental Disorder | 24 (20.34%) |

## Table 3

DSM IV-TR Criteria for Schizophrenia

| | |
|---|---|
| A. Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated): | **1** delusions<br>**2** hallucinations<br>**3** disorganized speech (e.g., frequent derailment or incoherence)<br>**4** grossly disorganized or catatonic behavior<br>**5** negative symptoms, i.e., affective flattening, alogia, or avolition |
| B. Social/occupational dysfunction: | 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 (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement). |
| C. Duration: | Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., 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 present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences). |
| D. Schizoaffective and Mood Disorder exclusion: | 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. Substance/general medical condition exclusion: | The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition. |
| F. Relationship to a Pervasive Developmental Disorder: | If there is 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). |

Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.

**Table 4**

Differential Diagnoses of Childhood-onset schizophrenia

| | |
|---|---|
| Medical Etiologies | • Seizure Disorder<br>• Anti-NMDA (N-methyl D-aspartate) receptor encephalitis<br>• Herpes simplex encephalitis (HSE)<br>• Lysosomal storage diseases<br>• Neurodegenerative disorders<br>• Central nervous system (CNS) tumors<br>• Progressive organic CNS disorder (e.g., sclerosing panencephalitis)<br>• Metabolic Disorders<br>• Chromosomal disorders: 22q11 deletion syndrome ^ |
| Misdiagnosed Psychiatric Illnesses | • Psychotic Depression<br>• Bipolar Disorder<br>• Autism-Spectrum Disorders Pervasive Developmental Disorders<br>• Obsessive–compulsive Disorder (OCD)<br>• Generalized Anxiety Disorder<br>• Post-Traumatic Stress Disorder<br>• “Multidimensionally impaired” (not a formal DSM diagnosis, but discussed further below) – individuals with multiple language or learning disorders, mood lability, and transient psychotic symptoms |

^ rates significantly higher than expected [31-33]

## Table 5

Tools used by the NIMH Child Branch in the Evaluation of COS

| Tool | Description |
|---|---|
| **Initial Evaluation:** | |
| • Social Communication Questionnaire (SCQ) previously known as the Autism Screening Questionnaire (ASQ) | Brief instrument helps evaluate communication skills and social functioning in children who may have autism or autism spectrum disorders. Completed by a parent or other primary caregiver in less than 10 minutes |
| • Kiddie-Sads-Present and Lifetime Version (K-SADS-PL) | A semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to DSM-III-R and DSM-IV criteria. |
| • Psychotic Disorders Supplement **<br>• Affective Disorders Supplement **<br>• Anxiety Disorders Supplement **<br>• Behavioral Disorders Supplement **<br>• Substance Abuse and Other Disorders Supplement ** | Supplements to the K-SADS-PL used for diagnostic exploration and clarification; administered in the order in which symptoms appeared. |
| **Follow-up:** | |
| • Scale for the Assessment of Positive Symptoms (SAPS) * | Assessment of positive symptoms of psychosis devised primarily to focus on schizophrenia |
| • Scale for the Assessment of Negative Symptoms (SANS) * | Assessment of negative symptoms of psychosis devised primarily to focus on schizophrenia |
| • Brief Psychiatric Rating Scale for Children (BPRS - C) | A 21-item, clinician-based rating scale designed for use in evaluating psychiatric problems of children and adolescents. |
| • Clinical Global Impressions Scale (CGIS) * | A primary outcome frequently used in medical care and clinical research to measure in studies evaluating the efficacy of treatments. |
| • Children's Global Impressions Scale (CGAS) * | An adaptation of the CGIS for children. |
| • Bunny-Hamburg Global Ratings<br>* Psychosis subscale<br>* Depression subscale | Two subscales that, when used together, best exclude COS as a viable diagnosis (62% accuracy at screening, 85% accuracy at the medication-free period) ^ |
| • Simpson-Angus Scale (SAS) | An established instrument for neuroleptic-induced parkinsonism |
| • Abnormal Involuntary Movement Scale (AIMS) | 12 item clinician administered and scored anchored scale used to detect and follow the occurrence of tardive dyskinesia (TD) in patients receiving neuroleptic medications |

* available in the Handbook of Psychiatric Measures (Book with CD-ROM for Windows) by the American Psychiatric Association

** Used as indicated by the results of the K-SADS-PL

^ [34]

**Table 6**

Select Comorbidities for Childhood-onset schizophrenia

| |
|---|
| Psychiatric Comorbidities |
| • Obsessive–compulsive Disorder (OCD) |
| • Attention Deficit Hyperactivity Disorder (ADHD) |
| • Expressive Language Disorders |
| • Receptive Language Disorders |
| • Auditory Processing Deficits |
| • Executive Functioning Deficits |
| • Mood disorder primarily MDD |
| Medical Comorbidities associated with treatment |
| • Diabetes * |
| • Hyperlipidaemia * |
| • Cardiovascular disease * |
| • Obesity * |
| • Hyperprolactinaemia * |
| • Dyskinesia |

* highly correlated with the treatment of Schizophrenia [95].