

Series on Childhood-onset Schizophrenia - 1**Childhood Onset Schizophrenia: Clinical Features, Course and Outcome****Mamta Sood, MD, Shivanand Kattimani, MD****Address for Correspondence:** Dr. Mamta Sood, Assistant Professor, Department of psychiatry, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029. Email: soodmamta@gmail.com.**ABSTRACT**

Schizophrenia in children is diagnosed by using adult criteria. Based on the age of onset, patients with childhood onset schizophrenia (COS) are subdivided into those with very early onset (before age 12-14 years) and those with early onset (between 14-17 years). The prevalence of COS is reported to be 1 in 10,000 before the age of 12 years; however, there is a significant increase around puberty and early adolescence and by 18 years of age, 20% of the patients with schizophrenia will have the illness. Simple delusions and hallucinations revolving around childhood themes, language and communication deficits and flat affect have been reported in COS. Follow-up studies suggest that the outcome is generally poor to fair. Predictors of poor outcome are age of onset (<12 years), insidious onset and marked premorbid abnormalities.

Key words: *Childhood onset schizophrenia, clinical features, phenomenology, course, outcome*

INTRODUCTION

Descriptions of conditions resembling schizophrenia in children have existed in the literature for more than a century. The various conditions included under the construct of childhood schizophrenia shared certain features: onset during childhood, profound impairment at presentation and chronic course. Most conceptualization of childhood schizophrenia were broad and would have included the current constructs of schizophrenia, schizotypal personality disorder, and pervasive developmental disorders.¹

Onset before puberty was highlighted as a classificatory principle, for the first time in the second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II), which grouped all psychotic disorders in childhood and autism under the rubric of childhood schizophrenia. However, Rutter reported that children with autism did not show symptoms of schizophrenia when they were followed up into adulthood;² and Kolvin established conclusively that like adults, children with schizophrenia had hallucinations, delusions and formal thought disorder while autistic children had none of these.³ Schizophrenia arising in childhood was differentiated from pervasive developmental disorders and diagnosed using the same criteria as for adults in the DSM-III and the ninth revision of the International Classification of Diseases (ICD-9). Green et al replicated Kolvin's findings while using DSM-III criteria to diagnose children with schizophrenia and infantile autism.⁴ Subsequent revisions of both classificatory systems continue with the practice of diagnosing schizophrenia in children using adult criteria. However, a literature review to aid in the development of DSM-IV found that the approach was not popular with researchers till then.⁵

In the last two decades, there is resurgence of interest in COS because of the belief that it may be a more homogenous and severe form of the disorder; hence research in this area may contribute to a delineation of biological etiology and the development of early intervention for at risk adolescents.⁶ However, the debate on the differences in the nature of COS and adult onset

schizophrenia (whether they are different illnesses, exist on a continuum, or COS is an atypical form of schizophrenia that is potentiated by biological stressors) is still unsettled.⁷

DEFINITION

The youngest reported cases of schizophrenia had onset at the age of 3 years and 5.7 years.^{4,8} While there would be little difficulty in labeling these cases as having early onset, the terms ‘childhood-onset,’ ‘adolescent-onset,’ and ‘early-onset’ schizophrenia have been used interchangeably and without uniform or precise definitions. Based on the age of onset, COS has often been divided into very early onset (VEOS: before age 12-14 years) and early onset (EOS: onset at age 14-17 years). However, other authors have used different age criteria.⁹ The American Academy of Child and Adolescent Psychiatry uses the convention of defining EOS as onset before age 18 years and VEOS as onset before 13 years.¹⁰ The term prepubertal is not used to avoid ambiguity.

The relationship between age of onset and puberty has been linked to the maturation of critical dopaminergic pathways that normally start functioning fully at puberty. It is assumed that adolescence is a challenging period that is likely to evoke much activity in these pathways and hence produce an overload in individuals with inherently vulnerable systems.¹¹ However, there is no evidence yet to suggest that COS is associated with alterations in indices of sexual/pubertal development, e.g. menarche.¹²

EPIDEMIOLOGY

The following points should be kept in mind while considering the epidemiology of COS. There are no general population based studies on COS owing perhaps to its rarity. Also, many clinical epidemiology studies on COS are suspect because of the inclusion of large proportion of patients suffering from other psychosis in samples.¹³⁻¹⁵

Kraepelin estimated the prevalence of dementia praecox in children before the age of 10 years to be 3.5% and in children aged 10-15 years to be 2.7%.¹⁶ In his review on COS, Remschmidt noted that earlier authors like Bleuler and Lutz had reported that 4% of children with schizophrenia had an onset of illness before 15 years of age and 0.5%-1% before age 10.¹⁷ Similarly, a Danish study reported that in their sample of 312 inpatients with schizophrenia, only 4 had an onset under the age of 13 years and 28 under the age of 15 years.¹⁸

Based on three large clinic based studies (N=61-121) from Germany, Remschmidt reported the overall prevalence of COS before the age of 12 years was 1 in 10,000.¹⁷ The VEOS (<14 years) subgroup comprised approximately 11% of all COS patients. Overall, there appears to be a significant increase in prevalence of schizophrenia around puberty and early adolescence and by 18 years of age, 20% of patients with schizophrenia will have the illness.¹⁹

CLINICAL FEATURES

Type of onset

A majority of children with COS have an insidious onset.^{19,20} Insidious onset is more common in children with VEOS and in males;^{3,4,21} while young adolescents may have both acute and insidious onset.^{3,4,21-25} Insidious onset has been associated with poor outcome, particularly in children with onset of the illness before age 12 years, poor premorbid adjustment, and with predominantly negative symptoms.²⁶

Premorbid functioning

Many studies have reported a wide range of premorbid difficulties in children with COS, including social withdrawal and isolation, disruptive behavior disorders, academic difficulties,

motor, speech and language problems, and developmental delays.^{14,26,27} The majority (up to 90% in some studies) of patients with COS, especially those with VEOS have premorbid abnormalities.^{3,4,12,23,28-30} Onset before age 14 years is associated with higher rates of language problems.³⁰

Social withdrawal and aberrant peer relationships differentiate the premorbid histories of youth with COS from those with bipolar disorder.²² Also, children with chronic schizophrenia had poor rating on modified Premorbid Adjustment Scale compared to children with major depressive disorder.²¹

Psychopathology

Symptoms in children with EOS are almost identical and occur with similar frequency as seen in adult onset schizophrenia.^{5,31} Hallucinations, thought disorder, and flat affect have been consistently reported in children with COS, while systematic delusions and catatonic symptoms are less frequent. Elementary auditory hallucinations are frequent, while visual and tactile hallucinations are rare. Delusions seem to be less complex and revolve around age appropriate themes.

In their classic study, Kolvin et al, examined 33 children with COS (onset between 5-15 years) diagnosed according to adult onset criteria.³² About 82% of the patients had auditory hallucinations, while 30%, 58% and 60% had visual hallucinations, delusions and thought disorders, respectively. In a study on 173 adolescents with schizophrenia in Japan, delusional activities (mostly persecutory - vague and fragmentary) were observed in about half, and hallucinations (mostly auditory) in more than one-fourth of the patients.³³

An Indian study on COS (N=43, age 10-16 years) diagnosed using International Classification of Diseases - Diagnostic Criteria for Research (ICD-10 DCR);³⁴ reported delusions in 72%, auditory hallucinations in 58%, negative symptoms in 47% and inappropriate affect in 70% of the sample.³⁵ However, another Indian study (N=30, age 4-16 years) with schizophrenia diagnosed as per International Classification of Diseases (ICD-10), reported delusions in 20%, hallucinations in 17% , formal thought disorder in 33%, bizarre/motor behavior problems in 47% and emotional disturbance in 50% of cases.³⁶ The reasons for these discrepant findings are not clear, but may relate to the use of more stringent research criteria in the former study.

In retrospective studies carried out in Los Angeles (N=35) and New York (N=38) on children (<12 years) with VEOS, 80%-84% of children had auditory hallucinations, 74%-84% flat or inappropriate affect, 55%-63% delusions, 40%-100% formal thought disorder, and 37%-47 % visual hallucinations.³⁷ Suicide attempts were observed in 38% of the Los Angeles sample, with an additional 38% reporting suicidal ideation but no attempts.⁸ A German study on VEOS (N=13) showed that 77% of children had positive symptoms and more than 50% manifested hallucinations. However, in the patients with insidious onset, negative symptoms prevailed.³⁸

In a German study on EOS (N=61), evaluation with the Present State Examination revealed that delusions, anxiety symptoms, depressive symptoms, and suicidal ideation were reported by 77%, 83%, 73% and 45% of the patients, respectively.³⁹ A comparative study of inpatients with EOS showed that subjects from New Zealand (N=33) had fewer well formed delusions and auditory hallucinations as compared to subjects from the United States (N=24).⁵

Comparison of phenomenology in cases of schizophrenia (diagnosed based on ICD-10 DCR) with VEOS (N=15), EOS (N=20) and adult onset (>18yr, N=20) revealed that there was no difference in positive symptoms between the three groups but negative symptoms were more common in the former two.³¹ A Chinese study compared 19 cases each of EOS (onset <15 years) and adult onset (15-35 years) schizophrenia; and reported that EOS cases had significantly

greater negative symptoms and lower performance intelligence quotient (IQ). No group difference in positive symptoms and full IQ was noted.⁴⁰

Analysis of speech samples obtained from children with schizophrenia and affective disorders showed that the former group often presented thoughts without adequate reasoning, had impairment in processing and organizing thoughts, used fewer connecting words for shifting topic, but did not have the expected poverty of speech of content.⁴¹ The formal thought disorder in COS is hypothesized to be due to three characteristic communication deficits: loose associations, illogical thinking, and impaired discourse skills.⁴²

Association between positive symptoms and age, IQ and acute onset has been reported; whereas negative symptoms are associated with subtle brain damage, lower IQ, and insidious onset.^{43,44} Patients with COS also suffer from significant sleep disturbances, which are associated with the severity of symptoms.⁴⁵

Some studies have examined the occurrence of prodromal symptoms before the confirmation of COS diagnosis. In the study conducted in Los Angeles, the mean age at onset of general psychiatric symptoms (non specific behavioral or psychological problems) was 4.6 years, the mean age at onset of psychotic symptoms was 6.9 years and the mean age at the time of diagnosis of COS was 9.5 years.⁴⁶ Another study reported that the violent aggression and school problems were the initial presenting symptoms of COS and childhood onset schizoaffective disorder. Age of first recognized psychotic symptoms ranged from 2-11 years, followed 2 years later by a diagnosis of schizophrenia.⁴⁷ Occasionally, COS patients may present with obsessive-compulsive symptoms (with little distress and insight) of many years duration before the confirmation of schizophrenia.⁴⁸ Such children usually have a high incidence of insidious onset and negative symptoms.

Symptom dimensions and subtypes

Schizophrenia is generally characterized as having two broad sets of symptom clusters, positive and negative. Disorganized behavior has been suggested as an independent third dimension.⁴⁹ Bunk et al examined the symptom dimensions of COS (N=44) at 2 time points (during the first episode and at follow-up investigation 42 years later). At the follow up assessment, all subjects were re-diagnosed according to DSM-IV. The symptomatology was evaluated at both time points with the Positive and Negative Symptom Scale (PANSS). At the onset of psychosis, factor analysis revealed five symptom dimensions: cognition, social withdrawal, antisocial behavior, excitement, and reality distortion. At follow-up, a factor structure comprising of positive, negative, excitement, cognitive, and anxiety/depression dimensions; that was similar to adult-onset schizophrenia emerged. Positive and global symptoms decreased significantly during the course of illness.⁵⁰

Reports vary regarding the proportion of patients belonging to various subtypes of COS (paranoid: 49%-63%, undifferentiated: 10%-30%, disorganized: 27%, catatonic: 14%, hebephrenic: 5%, unspecified: 2%, residual: 2%). Early in the course, the disorganized type was the most common subtype seen; in the middle, the most common subtype seen was paranoid type; and in later (long term) stages, catatonic and disorganized types were predominant. Overall, paranoid type was the commonest subtype during the entire course of the illness.^{17,48} In another study, hebephrenic and simple subtypes were frequently observed but the catatonic form was relatively rare.³³

Diagnosis

Schizophrenia in children can be diagnosed reliably using unmodified adult diagnostic criteria.^{46,51,52} However, developmental differences in language and cognition may affect the range and quality of symptom presentation.^{15,33,53} Also, the failure to meet expected social or

academic milestones may be a better descriptor for COS rather than a deterioration in functioning as is used in adult who are supposed to have achieved full functioning in social and interpersonal domains.⁵⁴

A high rate of diagnostic agreement between DSM-III-R, DSM-IV and ICD-10 was noted in hospitalized adolescents with schizophrenia.^{55,56} Also, a high degree of diagnostic stability of COS has been shown using DSM-III-R and DSM-IV with 80%-90% of subjects maintaining the diagnosis over a period ranging from 2-14.8 years.^{27,57,58} A comparison of retrospectively assigned life-time ICD-10 diagnosis of COS with the diagnosis made 42 years later also revealed good diagnostic stability and high concordance with DSM-III-R diagnosis.⁵⁹

COURSE AND OUTCOME

Compared with the literature on schizophrenia in adults, there are few follow-up studies with adequate sample sizes in patients with COS, owing perhaps to its low incidence and prevalence. Hence, relatively little is known regarding the course and outcome in patients with COS.

Studies examining the longitudinal course and outcome of COS have used the same criteria as in adult onset schizophrenia for diagnosis (Table 1). Duration of follow-up across studies has varied from 1-42 years and most have used measures to assess outcome. However, definition of outcome is not uniform and outcome has been reported as clinical, symptomatic, psychosocial and functional outcome based on clinical observation and instruments used. Considerable heterogeneity in outcome has been noticed. Good outcome in the form of complete remission, minimal dysfunction or 'improved' is reported to be in the range of 8-30.5% in majority of studies.^{22,57-63} However, contrasting results have been reported by Asarnow et al;^{7,64} who reported that up to 55% of their sample had a good outcome. Weinberger also noted that 56% of his sample had a good/moderately good outcome at 2-7 years follow up and commented that the overall outcome was similar to the adults with schizophrenia. However, the children in this study received extensive treatment, which may have prevented worse outcomes.⁷ Also, since the eligibility criteria for the follow up evaluation was not-hospitalization at the time of the evaluation; it is likely that the cases with particularly poor outcome (2 out of 21) had been excluded from the sample. Children with schizophrenia have severe impairments in social relationships and encounter considerable difficulty in independent living compared with children having other psychotic disorders and bipolar disorder at a similar age.^{22,54,57} One possible explanation for this association could be low premorbid IQ or deterioration of IQ from baseline which may have an unfavorable impact on social outcome and service utilization once schizophrenia develops.⁶⁴

The risk of suicide or accidental death directly due to behaviors caused by psychotic thinking is at least 5%.^{7,25,39,59} Renschmidt et al studied the long-term (42 years) course of 76 consecutive inpatients with a suspected diagnosis of COS. About half of the sample were deemed to meet the ICD-10 diagnosis of schizophrenia. In the 16 COS patients who could be personally investigated at follow-up, 10 displayed severe or moderate depressive symptoms. The death rate (including suicide) was significantly higher in the schizophrenia group.⁵⁹

Table 1: Follow up studies on outcome in childhood onset schizophrenia^{7,22,33,38,39,58-61,63,64}

Authors	Sample size (n)	Diagnosis	Duration of follow up	Outcome measure	Outcome
Kimura et al, 1978	23	Clinical	> 3 years	Course of illness	30.5% good outcome 56.5% partial outcome 13% worse outcome
Krausz, 1990	59	Present State Examination	5-10 years	DSM-III-R course	8% improved 29% episodic 49% chronic
Werry et al, 1991	30	DSM-III-R	4.3 years	DSM-III-R course	23% improved 13% subchronic 64% chronic
Gillberg et al, 1993	23	DSM-III and ICD-9	11-17 years	Psychosocial outcome	13% good 9% intermediate 78% poor
Krausz & Müller-Thomsen, 1993	61	Present State Examination	11-16 years	Course of illness	21% improved 16% episodic 53% chronic
Asarnow et al, 1994	18	DSM-III	2-7 years	Global Assessment Scale	56% good 44% poor-deteriorating
Eggers and Bunk, 1997	44	DSM-IV	42 years	Course of illness	25%-complete remission 25%-partial remission 50%-poor remission
Asarnow et al, 1999	18	DSM-III-R	1-7 years	Global Assessment Scale	55% good 45% worse
Lay et al, 2000	96	ICD-10	10 years	Social disability	20% minimal dysfunction 44% obvious dysfunction 36%-very serious dysfunction
Fleischhaker et al, 2005	101	DSM-III-R; ICD-10	9.5 years	Global Assessment of Functioning	20% ≥good 40% fair-poor 40% ≤very poor
Remschmidt et al, 2007	76	ICD-10	42 years	Global Assessment Scale	Schizophrenia group has poor outcome 16% good 24% moderate 60% poor outcome

Many long-term outcome studies provide useful information about predictors for poor outcome. Some of the replicated predictors are age of onset before 12 years and insidious onset;^{26,30} predominant catatonic symptomatology;⁶⁵ higher initial levels of psychopathology in the form of higher scores on negative scale; lower cognitive abilities; more developmental motor abnormalities; and poor premorbid functioning.^{5,22,57,64,66-68} Fleischhaker et al reported poor prognosis in patients with premorbid developmental delays and those who were introverted and withdrawn before their psychotic state.⁵⁸ Those with obsessive-compulsive symptoms prior to diagnosis of COS were found to have more negative symptoms, longer prodrome, more imaging abnormalities and poor outcome even in absence of familial load of disorder. Error: Reference source not found Munro et al reported that a long duration of inpatient stay was predictive of poor functional outcome.⁶³

These long-term follow up studies also yielded other important insights. Krausz and Müller-Thomsen found that at 5 years follow up about half of their sample of EOS (N=61) patients had spent almost half of the follow up period in the hospital, with an average of four to five stays.³⁹ Vyas et al reported that in their EOS patients (diagnosed based on DSM-IV, N=23)

the mean duration of untreated psychosis was 2.95 months and that the subjects had an average of 2.09 hospitalizations.⁶⁸

Eggers and coworkers reported that 25% of the patients with diagnosis of schizophrenia were re-diagnosed as bipolar disorder over the follow up period (up to 50% of cases with childhood onset bipolar disorder in their sample were initially diagnosed as schizophrenia).⁵⁶ Weinberger also reported that only 14 of the 18 children initially diagnosed with schizophrenia continued to meet the criteria for the disorder 1 year after discharge from the hospital. About 13% had received a diagnosis of schizoaffective disorder. However, Eggers and Bunk reported that diagnostic stability was high for COS based on DSM-III-R criteria.⁵⁷

Few studies have compared childhood onset schizophrenia to adult onset schizophrenia. Onset before 15 years of age was associated with higher ratings of negative symptoms in adulthood.⁴⁰ Greater social impairment has been noted in patients with onset before the age of 21 years.⁹ Biswas et al assessed childhood onset and adolescence onset schizophrenia patients with the WHO life chart schedule and noted that one third of these subjects had a static or downhill course; however, no difference in outcome was seen between adolescent and adult onset schizophrenia.³¹ These studies support the clinical observations that as compared to adult onset schizophrenia, COS may have a more insidious onset, chronic course, and less favorable outcome.

The research in this area is fraught with a number of methodological problems. Most of the reported studies are retrospective and rely on the case notes for assessing the age of onset, initial psychopathology, treatment received, therapeutic response and subsequent course. As is evident from the above studies, the definition of the ages that constitute childhood and adolescence varies widely. Different diagnostic criteria have been used and duration of follow up period has been variable. In addition, the results could have been influenced by diagnostic errors, since bipolar disorder has been frequently misdiagnosed as schizophrenia in children.²² Pharmacotherapy remains a mainstay of various interventional strategies²⁰ and influence of treatment on the course of COS has not been adequately studied. Also, retrospective studies of the young are hampered by the fact that definitive diagnoses are often not documented for fear of potential stigmatization.

SUMMING UP

Awareness of COS is rapidly increasing. COS show clinical features predominantly characterized by elementary auditory hallucinations, less complex delusions with childhood themes and flat affect. For about three decades, researchers as well as clinicians have diagnosed COS using the same criteria as in adults. The longitudinal course and outcome for patients with COS is generally considered poor, and perhaps worse than that of the adult onset schizophrenia. Future research in this area needs to address the cause for the earlier age at onset in some subjects, and the biological and psychological underpinnings of schizophrenia occurring at an early age. Definitions of outcome need to be specified consensually to allow for more rigorous course and outcome studies and identification of robust predictors of outcomes.

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