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# Award Paper

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# A Comparative Study of Clinical Correlates in Schizophrenia with Onset in Childhood, Adolescence and Adulthood

*Parthasarathy Biswas, MD, Savita Malhotra, MD, PhD, FAMS, Anil Malhotra, MA, PhD, Nitin Gupta, MD*

**Address for Correspondence:** Professor Savita Malhotra, Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh – 160012. Tel: (O) +91-0172-2747585-94, Ext 6801 & 2744503, Fax: 91-0172- 2744401, 2745078, Email: savita.pgi@gmail.com

**ABSTRACT:**

**Background:** Childhood onset schizophrenia (COS) is a rare disorder. Comparative data on the effect of differential age of onset on clinical profile in schizophrenia are very few. **Method:** Subjects with COS (n=15), adolescence onset schizophrenia (AdOS, n=20) and adulthood onset schizophrenia (AOS, n=20) were compared on socio-demographic, clinical and genetic history parameters using Instrument for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS), Positive and Negative Symptoms Scale (PANSS), Family Instrument for Genetic Studies (FIGS), Wechsler's Adult Intelligence Scale-Revised (WAIS-R), Malin's Intelligence Scale for Indian Children (MISIC) and WHO Life Chart Schedule (WHO LCS). **Results:** Significantly higher rate of socioeconomic dependence, poorer academic performance, and non-paranoid subtype was seen in the COS group as compared to the AdOS and AOS. The total score on PANSS was maximum in the COS group with AdOS taking an intermediate position. COS patients had more somatic and obsessive symptoms whereas, AdOS patients had more self-injurious behaviour and suicidal attempts. The response to typical antipsychotic medication was poorer in the COS group as compared to the other two groups. In spite of treatment with atypical antipsychotics (including clozapine), 1/3$^{rd}$ of the COS patients continued to show limited response. The COS group scored least on the Mean IQ. The outcome was significantly poorer in patients of COS (33%), and it correlated significantly with low IQ. **Conclusions:** COS seems to be a more severe form of the schizophrenic illness with high degree of socioeconomic dependence, poorer response to treatment, greater and more florid psychopathology, poorer course and outcome, greater neurocognitive deficits and qualitative differences in the type of schizophrenia and non-specific symptom profile as compared to the later onset schizophrenias.

**Key words: Childhood onset schizophrenia, Adolescence onset schizophrenia, Adult onset Schizophrenia**

## INTRODUCTION

Schizophrenia occurring in childhood is regarded as a rare disorder. Kraepelin had mentioned that "Dementia praecox" could begin in childhood and estimated that at least 3.5% of

his cases had onset before 10 years with another 5-7% having onset between age group 10-15 years. Similarly, Bleuler estimated that 0.5-1% of the schizophrenic cases had onset before age 10 years and 4% before 15 years. A recent study showed that the prevalence of COS (onset before age of 12) was 1 in 10,000 children.[1]

Early onset schizophrenia has generally been divided into childhood and adolescent-onset schizophrenia.[2] The latter has onset between 13 and 17 years of age.[3] Onset before 12 years,[4, 5] 14 years[6, 7] of age has been suggested as the cutoff for childhood onset schizophrenia. Using the latter cutoff, childhood onset schizophrenia can be subdivided into very early onset (VEOS) defined by onset before 12 years of age and early onset schizophrenia (EOS) defined by onset between 12 to 14 years of age.[8, 9] In a study from India, onset prior to 16 years of age was used as cutoff for cases of Early Onset Schizophrenia.[10]

**Clinical Features**

Kolvin and coworkers[11] reported a mean age of onset of 11.1 years in their study of 33 COS patients. Various studies, using DSM–III criteria, reported mean age of onset to vary from 7.86 to 9.96.[12, 13] A recent study,[6] using ICD 10[14]/ DSM-IV[15] criteria, found the mean age of first psychiatric symptoms was 11.8 years and age of first psychotic symptoms was 13.0 years.

Most studies on COS have reported an insidious onset.[6, 16] In another study patients of COS (onset before age of 12 years) had an insidious onset while patients with AdOS had an acute onset.[6] Krauz and Muller Thomsen reported that though majority of adolescent patients had an insidious onset, a substantial number of patients had an acute or subacute onset.[17]

Studying phenomenology of COS has been difficult because of lack of operational criteria, relative rarity of the disorder; developmental limitations of the children in describing complex internal symptoms; and overlap between psychopathology and normal experiences in childhood (e.g. vivid fantasy versus delusion).[18] Secondly, researchers prior to DSM-III lumped together children with autism, schizophrenia and other psychotic illnesses in a single group.

***Positive symptoms***

Most studies found formal thought disorder (FTD) to be the commonest presentation[2, 13] where as two studies[12, 19] reported auditory hallucination as the commonest. A recent study of Juvenile–onset schizophrenia[3] found that though symptoms were similar to AOS, formal thought disorder was less common, hallucinations were of elementary nature and delusions were less complex.[2, 6] In the only Indian study[10], 42 patients of early onset schizophrenia (age group 10-16 years) were studied using ICD-10 Diagnostic Criteria for Research (DCR) criteria[14]. Persecutory delusions were the most common symptoms (72%), followed by inappropriate affect (69.7%) and non-affective auditory hallucinations (58.3%). Negative symptoms were seen in 46.5% of the subjects.

***Subtypes***

Remschmidt et al using both DSM–III-R and ICD 10 diagnostic criteria, found that 63% of COS were of the paranoid, 27.3% were of the disorganized and 9.7% were of the undifferentiated subtype.[16] Reddy et al, using ICD 10 DCR criteria, found paranoid subtype to be the commonest (48.83%) followed by undifferentiated (30.23%), catatonic (13.95%), hebephrenic (4.65%) and unspecified (2.3%) subtypes in their group of juvenile schizophrenic patients.[10] As in COS, paranoid and undifferentiated types are most common subtypes in AdOS.[6, 20] The general consensus is that there is no excess of undifferentiated and disorganized subtypes, and the paranoid subtypes was diagnosed at a similar frequency as seen in adults disorders.[21]

***Family Studies***

It has been suggested that an earlier onset of schizophrenia might result from an increased genetic load, and is expected to result in increased familiality.[22] Initial studies[11, 23]

revealed higher rates of schizophrenia ranging from 8.8% - 12.2% in parents of children with early onset psychosis, but small sample size and lack of standardized diagnosis resulted in difficulties in interpretation of these results. In recent studies, although rates of schizophrenia and schizoaffective disorders in relatives of COS patients were similar to those seen in relatives of AOS patients, there appeared to be an excess of schizotypal and paranoid personality disorder in relatives of COS probands.[21, 24] In a direct comparison of parental schizophrenia spectrum disorders in childhood-onset and adult-onset schizophrenia, it was found that parents of COS patients had significantly higher morbid risk of schizophrenia spectrum disorders (24.74%) as compared to parents of patients with AOS.[25]

***Course and Outcome***

Outcome studies with up to 14 years follow–up indicate stability of diagnosis with roughly 50% of cases continuing to show severe impairment and a substantial minority showing a deteriorating course.[6, 26, 27] The premorbid functioning appeared to be the best predictor of course and outcome in all the above studies on COS.

As compared to COS, AdOS is associated with a more chronic course.[18, 28] In a follow–up study of AdOS who were assessed at 5 and 11 years after onset of illness, many were judged to have a continuous illness and required substantial care. Suicidality was high in this group and females were associated with a better outcome.[17] AdOS patients have been shown to have poorer social judgment, severe functional impairment, and high socioeconomic dependence, suggesting that they had a more severe illness than the adult-onset schizophrenics.[29]

It was hypothesized that earlier onset schizophrenia would cause more socio-economic dependence, severe psychopathology, neurocognitive deficits and poorer outcome than later onset ones. The aim of the study was to compare schizophrenia (as per ICD-10) with onset in childhood, adolescence and adulthood on socio-demographic, clinical, course, outcome and genetic history parameters. A subsidiary aim of the study was to generate a comprehensive clinical profile of COS from India.

## METHODS

The sample was selected form the patients attending the Outpatient clinic of the Department of Psychiatry at Postgraduate Institute of Medical Education and Research, Chandigarh – a tertiary care referral center located in Northern India. Patients of COS were recruited by purposive sampling by screening the COS case registry and identifying those who were in active follow up and were likely to be available and accessible. The sample consisted of three groups, 15 patients of schizophrenia with onset of illness at less than 14 years of age (COS), 20 patients of schizophrenia with onset of illness at greater than 14 years and less than 18 years of age (AdOS), and 20 patients of schizophrenia with onset of illness at greater than 18 years (AOS) of age.

International classification of disease (ICD10 DCR)[14] criteria was used for diagnosis of schizophrenia. All patients had duration of illness of less than 10 years and were clinically stable and co-operative for clinical assessment. Clinical stability was defined as absence of agitation, violence or acting on psychotic symptoms; and being on a stable dose of a particular antipsychotic for more than 2 years which was indirect evidence that there was absence of change in psychopathology over time. All the three groups were matched for gender and duration of illness. Subjects with concomitant mental retardation, organic brain disease, other major psychiatric illness, substance abuse (with exception of tobacco), major physical illness and movement disorders were excluded. Informed consent from both patient and their primary caretakers was taken. The ethics committee of the institute approved this study.

All three groups were administered the IRAOS (Instrumental for the Retrospective Assessment for Onset of Schizophrenia)[30] to ascertain the age of onset of schizophrenia. IRAOS allows a systematic, objective, reliable and valid assessment of age of onset, clinical symptoms, psychological impairments, demographic and social characteristics and helps in detailing the

reference points (in time) of the early (and later) course of psychosis. This instrument is administered as a semi-structured interview to both the patient and a key informant. The obtained information is supplemented by systematic examination of clinician's case notes. IRAOS has adequate inter – rater reliability (Kappa values of 0.62-1.00) of various operationalizations of the onset of schizophrenia.

After determining the age of onset, the average age of presentation was obtained for each group. All groups were administered the sociodemographic profile sheet to record gender, marital status, occupation, education (including number of years), income and locality (i.e. urban or rural). The type of onset of schizophrenia was assessed using the IRAOS. The subtyping of schizophrenia was done by clinical assessment and case notes. The IRAOS was also used to systematically assess the previous and current antipsychotic treatment. The dose of various typical and atypical antipsychotic medications was converted into chlorpromazine (CPZ) equivalents. The process of calculation of CPZ equivalent dose has been derived from Table 1 of APA Clinical Practice Guidelines for treatment of Schizophrenia[31] and from findings of a study by Gerlach & Peacock.[32]

Assessment of psychopathology was done using the Positive and Negative Symptoms Scale (PANSS).[33] PANSS has been used extensively to assess psychopathology in children.[27, 34] The assessment of genetic loading was done using the Family Instrument for Genetic Studies (FIGS).[35] FIGS is a guide for gathering diagnostic information about relatives in a pedigree finder study. FIGS has 3 parts viz. the general screening questions, face sheet, and symptoms checklist. The information about each person on the pedigree is pooled from the interview of all relatives. IQ assessment was done using Hindi version of WAIS-R (Wechsler's Adult Intelligence Scale – Revised) [36] for subject with age greater than 16 years. Malin's intelligence scale for Indian Children (MISIC) [37] was used for children with age less than 16 years. The course and outcome was assessed using the WHO Life Chart Schedule.[38] It is a valid and reliable test to know that exact course and outcome of patients of schizophrenia.

**Statistical Analysis**

Mean and standard deviation was used to represent continuous variables. Analysis of variance (ANOVA) was used to evaluate and compare continuous variables. Chi-square test was used for discrete variables. Suitable Post-Hoc (i.e. Duncan's test and post-hoc chi-square test for parametric and non-parametric variables, respectively) analysis was applied to find difference between the three groups. Correlation between two continuous variables was done using Pearson's correlation and correlation between two ordinal/discreet variables or one ordinal/discrete and one continuous variable was done using the Spearman's 'rho'. Two-way univariate analyses of covariance (ANCOVAs) were carried out with group as fixed factor, WAIS-R (Hindi version) scores as dependent variable and PANSS scores as covariates to assess the effect of positive and negative symptoms on the assessment of IQ in the three groups of patients.

**RESULTS**

Table 1 shows the socio-demographic characteristics of the sample. The mean age at intake (for present study) of the patients with COS was 18.52±3.98 years which was comparable to AdOS (21.81±2.31) years but significantly lower than AOS group (31.45±8.35 years). These patients were already under treatment and follow-up at this centre and the onset of schizophrenia was during the specified cutoff for each group. Significantly higher proportion (i.e. 35%) of AOS patients were married and employed as compared to those in the COS and AdOS groups. Breaks in occupation were most frequent in AOS (the issue was less relevant in the other two groups).

**Table 1: Comparison of childhood onset schizophrenia (COS), adolescent onset schizophrenia (AdOS) and adult onset schizophrenia (AOS) on socio-demographic variables**

| Variables | COS[1] (n=15) n (%) | AdOS[2] (n=20) n (%) | AOS[3] ( n=20) n (%) | Chi-square /ANOVA (df=2) |
|---|---|---|---|---|
| Average age at intake for study (in years) ϕ | 18.52±3.98 | 21.81±2.31 | 31.45±8.35 | 25.92 *** (3>1,2)# |
| Sex | | | | |
| Male | 7(46.7) | 10(50.0) | 10(50.0) | NS |
| Female | 8(53.3) | 10(50.0) | 10(50.0) | |
| Marital status | | | | |
| Single/divorced | 15(100.0) | 19(95.0) | 13(65.0) | 10.75** |
| Married | - | 1(5.0) | 7(35.0) | (3>2=1) |
| Occupation | | | | |
| Unemployed/student | 15(100.0) | 17(85.0) | 13(65.0) | 7.27* |
| Prof/ semiprof/skilled/semi/unskilled worker | - | 3(15.0) | 7(35.0) | (3>2=1) |
| Break in occupation | | | | |
| No/not relevant as never employed | 15(100.0) | 15(75.0) | 6(30.0) | 19.84*** |
| Yes | - | 5(25.0) | 14(70.0) | (3>2>1) |
| Education | | | | |
| Matric and below | 9(60.0) | 7(35.0) | 3(15.0) | 7.67* |
| Above matric | 6(40.0) | 13(65.0) | 17(85.0) | (3=2>1) |
| Average educational years ϕ | 9.86±3.70 | 11.45±2.74 | 14.75±4.52 | 8.00 ** (3>1=2) |
| Break in education | | | | |
| No | 2(13.3) | 1(5.0) | 9(45.0) | 10.25** |
| Yes | 13(86.7) | 19(95.0) | 11(55.0) | (1=2>3) |
| Income | | | | |
| Rs 3000 and below | 15(100.0) | 17(85.0) | 13(65.0) | 7.27* |
| Above Rs 3000 | - | 3(15.0) | 7(35.0) | (3>2=1) |

***p<0.05, **p<0.01, ***p<0.001, NS= Not Significant; ϕ mean±standard deviation, #Duncan's post hoc test**

Understandably, significantly higher number of patients with COS did not complete their matriculation education (some of them were not past the age for this achievement); whereas the average number of educational years and continuity of education was more in AOS than other two groups (Table 1). Significantly more AOS patients were earning less than Rs. 3000/- per month. Majority of patients in COS (53.3%), AdOS (70%) and AOS (80%) groups were Hindus. More than 2/3$^{rd}$ of the patients were from nuclear families and belonged to urban background. Approximately half of the patients in the three groups were residents of Punjab and Chandigarh

The age of onset in the COS, AdOS and AOS groups were 12.25±1.61 years, 16.07±1.09 years, and 26.05±7.08 years, respectively ($\chi^2$ value=39.34, df=2, p<0.001). The duration of illness in the three groups (group matched) was 6.28±3.03 years, 5.75±2.27 years, and 5.45±2.51 years, respectively. In between 15% to 30% of patients in each group had an acute/subscute onset, with the difference between the groups being non significant. Dichotomization of diagnostic subtypes (paranoid versus non paranoid) suggested that while only 20% of the COS group had a paranoid subtype, 70% and 95% of the AdOS and AOS groups had this subtype, with the difference between the three groups being significant ($\chi^2$ value=21.61, df=2, p<0.001).

Table 2 shows that the global psychopathology as well as positive and negative symptom scores on PANSS was maximum in COS and least in AOS group.

**TABLE 2: Comparison of psychopathology scores on PANSS between Childhood Onset Schizophrenia (COS), Adolescent Onset Schizophrenia (AdOS), and Adult Onset Schizophrenia (AOS).**

| Variables | COS[1] (n=15) Mean±SD | AdOS[2] (n=20) Mean±SD | AOS[3] (n=20) Mean±SD | f-ratio (Duncan's post-hoc test) {df=2} |
|---|---|---|---|---|
| PANSS –Positive symptoms score | 12.13 ± 4.91 | 9.40 ± 2.58 | 8.15± 1.63 | 6.99** (1>2,3) |
| PANSS –Negative symptoms score | 18.86±7.28 | 12.95±4.04 | 10.15±3.11 | 13.89*** (1>2,3) |
| PANSS –General psychopathology score | 29.13±7.32 | 23.50±4.13 | 19.35±2.87 | 17.26*** (1>2>3) |

**p<0.01 ***p<0.001

Assessment of phenomenology on IRAOS revealed no significant difference on positive symptoms across the three groups. Common psychotic symptoms seen in COS were delusion of reference (73.3%), delusion of persecution (60.0%) and second person auditory hallucination (53.3%). The frequency of negative symptoms was comparable across all three groups, except that lack of energy (anergia) was reported significantly more often in the COS group (93.3%) as compared to AdOS (70.0%) and AOS (55.0%) ($\chi^2$ value=6.11, df=2, and p <0.05). In the non-psychotic domain of IRAOS, AdOS group reported significantly higher number of attempted suicide (i.e. 45%) as compared to the other two groups ($\chi^2$ value=8.27, df=2, and p <0.05). Self mutilatory/injurious behavior was significantly higher ($\chi^2$ value=8.27, df=2 and p<0.05) in AdOS (45.0%) as compared to AOS group (15.0%) and COS group (6.7%). Increased distractibility and weakness of intentional thinking was significantly higher ($\chi^2$ value=14.03, df=2, and p<0.01) in COS and AdOS groups than AOS group. Magical thinking and obsessions were significantly higher ($\chi^2$ value=10.21, df=2 and p<0.05) in the COS group (i.e. 53.3%) than in the other two groups.

Family history of schizophrenia and schizophrenia spectrum disorders as assessed by FIGS was comparable across the three groups. AOS group had positive family history in 7.1% of relatives (n=99) as compared to 3.3% in COS group (n=60) and 3.7% in AdOS groups (n=80).

Eighty-seven percent, 75% and 60% of patients, respectively in the COS, AdOS and AOS groups had received previous antipsychotic treatment. Among those who had such a medication, between 67% and 85% in each group had received atypical antipsychotics. The average dose of the first medication in chlorpromazine equivalents in the COS, AdOS and AOS groups was 355.76±161.10 mg, 455.00±188.31 mg, and 422.91±154.64 mg, respectively. The duration of treatment with the first antipsychotic medication in the three groups was 1.82±2.18 years, 1.10±1.37 years, and 0.93±1.16 years respectively. More than 60% of subjects in each group had shown partial to good response to the first antipsychotic medication. Between 7% and 25% of patients in each group did not have any side-effect during treatment with their first antipsychotic medication, and between 58% and 85% of subjects in each group had extrapyramidal symptoms or acute akathesia. While no COS subject developed tardive dyskinesia/akathisia, 20% of subjects in the AdOS group and 17% of subjects in AOS group developed such adverse effects. Between 30% (n=6) to 57% (n=8) of subjects in each group were shifted to a second antipsychotic medication (approximately half in each group to atypical antipsychotic). All patients showed a partial or good response to the second antipsychotic medication. At the time of intake, between 60% and 94% of subjects in each group were on atypical antipsychotics. The average dose of the current antipsychotic medication in chlorpromazine equivalents in the COS, AdOS and AOS groups was 403.33±185.61 mg, 489.47 ±284.10 mg, and 328490.00±206.85 mg, respectively. The duration of treatment with the second antipsychotic medication in the three groups was 2.03±2.43 years, 2.21±1.90 years, and 2.63±

2.63 years. More than two-thirds of patients in each group had shown a good response to the current antipsychotic medication, and the remaining patients had shown at least a partial response. No side effects were reported by 37% to 60% of subjects in the three groups. Extra-

pyramidal symptoms/signs were seen in 7%-35%, tardive dyskinesia/akathisia in 0-10%, and weight gain in 7%-22% of patients in the three groups. In subjects who developed Tardive dyskinesias, majority were receiving typical antipsychotics including depot neuroleptics. It is worth noting that since most of COS patients were on atypical antipsychotics, they did not develop Tardive dyskinesia or tardive akathisia.

The mean IQ was significantly less in COS patients (88.33±11.13) as compared to AdOS (99.15±13.78), which in turn had lesser mean IQ than AOS group (109.60±9.96) [$p<0.001$; Duncan's post hoc test AOS >AdOS>COS]. Inter test scatter was non-significant across all three groups.

As shown in Table 3, the majority of the COS group patients had a continuous course. However, the difference was not significant statistically when compared to the other two groups because of group matching. Majority of AdOS and AOS patients continued to get better during the course of illness whereas one-third of COS patients had a static/deteriorating course.

**Table 3: Comparison of childhood onset schizophrenia (COS) with adolescent onset schizophrenia (AdOS) and adult onset schizophrenia (AOS) on WHO-LCS course and outcome scores.**

| Variables | COS[1] (n=15) n (%) | AdOS[2] (n=20) n (%) | AOS[3] ( n=20) n (%) | Chi-Square (df) |
|---|---|---|---|---|
| Overall course | | | | |
| Episodic course | - | 1(5.0) | 4(20.0) | NS |
| Continuous course | 13(86.7) | 15(75.0) | 13(65.0) | (df=4) |
| Neither episodic nor continuous | 2(13.3) | 4(20.0) | 3(15.0) | |
| Overall time trend | | | | |
| Getting much better | 4(26.7) | 13(65.0) | 15(75.0) | 14.27* |
| Getting somewhat better | 6(40.0) | 6(30.0) | 5(25.0) | (df=6) |
| Staying the same | 4(26.7) | 1(5.0) | - | (2=3>1) |
| Getting somewhat worse | 1(6.6) | - | - | |

***p<0.05, Not Significant**

Earlier onset categories were positively correlated with unmarried marital status (Spearman's $\sigma=0.473$, $p<0.001$), lesser educational achievements (Spearman's $\sigma=0.352$, $p<0.01$), less educational years (Pearson's $r=0.355$, $p<0.01$), unemployment (Spearman's $\sigma=0.359$, $p<0.01$), lower income (Spearman's $\sigma=0.379$, $p<0.01$) and lesser mean IQ (Pearson's $r=0.386$, $p<0.01$). Also, earlier onset categories were negatively correlated with breaks in education (i.e. lesser the age of onset greater are the breaks in education) (Spearman's $\sigma=-0.379$, $p<0.01$), breaks in occupation (Spearman's $\sigma=-0.591$, $p<0.001$), paranoid subtype of schizophrenia (i.e. earlier onset has more of non-paranoid subtype) (Spearman's $\sigma=-0.595$, $p<0.001$), PANSS scores (i.e. earlier the onset more severe the psychopathology): positive scale (Pearson's $r=-0.286$, $p<0.05$), negative scale (Pearson's $r=-0.402$, $p<0.01$), general psychopathology scale (Pearson's $r=-0.436$, $p<0.01$), and good outcome [time trend] (Spearman's $\sigma=-0.400$, $p<0.01$).

The effect of PANSS subscale scores on the mean IQ was assessed. It was found that even after taking various subscale scores of PANSS as covariates, the mean IQ differences across the three groups did not alter significantly using ANCOVA. The ANCOVA results showed that mean IQ in COS was less than AdOS but this was not statistically significant (p value=0.508). The differences across AdOS and AOS (p value=0.042) and COS and AOS (p value=0.033) were maintained even after controlling PANSS scores.

## DISCUSSION

The present study was designed to examine the clinical profile of patients with childhood onset schizophrenia and to evaluate it in a developmental perspective by comparing schizophrenia with onset in childhood (COS) to those with onset in adolescence (AdOS) and

adulthood (AOS). COS as a group as compared to AOS had least number of educational years; lowest proportion of subjects with education above matriculation; and least (none) number of subjects who were employed or earning above Rs 3000/- per month, and had greater breaks in occupation. The onset of illness at an earlier age was correlated with disruption of academic achievement and greater socio-economic dependence. These findings are broadly in keeping with those reported in literature.[13, 16, 28]

***Clinical features***

The mean age of onset for the COS group was 12.25 years. This was higher than that reported in earlier studies, where mean age of onset ranged from 9.58 years to 11.1 years.[12, 13] In most of the previous studies mean age of onset was arrived at by clinical evaluation. However, our finding on mean age of onset was comparable to that reported by Eggers et al, who used the IRAOS.[6]

Type of onset in COS has been reported to be insidious in most studies and our findings are in keeping with it. [12, 13] However, onset in AdOS has been reported to be mostly acute.[6, 39] In our study all three groups had a predominately insidious onset. Matching the three groups on duration of illness may have influenced the selection of cases with insidious onset in n unspecified way.

In the COS group, non-paranoid subtype (mainly undifferentiated and unspecified) was the commonest (80.0%). Some previous studies.[2, 40] have also reported the undifferentiated subtype to be more common in COS, while others[6, 10, 21] have reported the paranoid subtype to be more common. In our study, AdOS and AOS patients exhibited more paranoid subtype which is in keeping with previous literature.[41] Low frequency of paranoid and high frequency of non-paranoid subtype in COS could be related to limited cognitive development at onset of the illness in the COS group (cognition may be important for the development of delusions and hallucinations).

Auditory hallucinations (2nd person and Schneiderian type) occurred in approximately half of the COS sample. However, this was less than that reported in western literature. [2, 11, 12] Delusion of reference was the most common delusion and was seen in almost 3/4th of COS patients. Very few COS patients presented with thought disorders, a finding similar to that in an earlier study from India.[10] Western data[12, 13] on the other hand show contrary findings where FTD is the commonest symptom.

Negative symptoms like generalized slowness of activity, affective flattening, lack of energy, social withdrawal etc. were seen in a sizeable number of COS patients. Remschmidt et al.[42] had reported the same, though the previous study from India[10] found this in less than half of their sample. Apart from anergia, which was seen in significantly more number of COS patients (93.3%) all three groups were comparable on other negative symptoms.

Non psychotic symptoms like worrying, weakness of intentional thinking, increased distractibility, disturbances in memory, decreased attention and concentration, magical thinking and obsessions were reported in majority of COS patients. Similar findings have been seen in a previous study on phenomenology of childhood psychosis.[43, 44] COS, AdOS and AOS seemed to be on a continuum with regard to positive and negative symptoms. However, a significantly greater presence of non-specific symptoms in COS needs to be studied further for its relevance to diagnostic or psychological evaluation.

A comparison of AdOS and COS groups showed that suicidal and self-mutilatory attempts were significantly higher in the AdOS group, a finding similar to western literature on adolescent schizophrenics.[8, 45]

In spite of long and comparable duration of illness (where stabilization of psychopathology would have occurred) in the three groups, COS patients continued to show significantly higher scores on positive, negative and general psychopathology sub-scales of PANSS. However, the scores on negative sub-scales was higher than that on the positive sub-scale reflecting that negative symptoms were more prominent than the positive symptoms in these patients. This finding could be a function of the chronicity of illness (duration approximately 6 years) and of treatment with antipsychotics. Presence of significant

psychopathology is similar to that reported in earlier studies where higher scores were obtained in these patients (in spite of adequate treatment) as compared to later-onset schizophrenia and other early onset psychosis (e.g. schizoaffective and bipolar disorder).[26, 40]

AdOS patients had significantly lesser scores on negative symptoms and general psychopathology than the COS group despite comparable duration of illness, nature and dose of antipsychotics. This is in contrast to the ESSEN study where no difference on psychopathology was found between the two groups. PANSS scores were lower in AOS group when compared to COS and AdOS group. The question arises whether the overall severity of illness was less or whether the illness responded better to treatment in AOS as compared to the other two groups.[6]

***Treatment***

Majority of the COS patients were initially treated with adequate doses of typical antipsychotics for adequate duration of time. However the response was poor and patients often developed extrapyramidal side effects. At intake, majority of the COS group was on atypical neuroleptics (93.3%) like olanzapine (33.3%), risperidone (33.3%) and clozapine (26.7%). In spite of the trial of one or more antipsychotics (including atypical) in adequate doses and for adequate duration, one-third of the patients continued to show poor response. Previous studies[26, 46] have reported poor response with typical antipsychotics; however, favourable response was seen with atypical antipsychotics like clozapine and olanzapine in open-label trials.[34, 47-49] Very little data is available on differential response to treatment in schizophrenia with different age of onset. In this study, the three groups were mostly comparable on treatment parameters.

***Genetic loading***

In the present study only 3.3% of subjects in the COS group showed positive family history of schizophrenia and spectrum disorders using FIGS. Previous studies had reported higher rates (8-13%), however, they used different family history diagnostic tools.[23, 26] In India, since infant and childhood mortality rates are higher than that in the western countries it is possible that children at risk for schizophrenia may not have survived to the risk period.

All the three groups were comparable on genetic loading. However, previous literatures report that genetic loading is lower in AOS as compared to COS and these researchers have hypothesized that there is greater role of genetic factors in development of COS.[22, 24] In a recent study, it was found that parents of COS had a greater morbid risk of schizophrenia spectrum disorders (24.74%) as compared to parents of AOS (11.35%).[25] It is possible that inheritance in both COS and AOS is multifactorial. One Non-genetic (perinatal complications etc.) and environmental factors may play a role in the development of COS.[22]

***Course and outcome***

Overall the COS group had a continuous course and static or poor outcome of illness as compared to AdOS and AOS. About 1/3$^{rd}$ of COS group were either getting worse or were static whereas in western studies more than half of the patients had a deteriorating course.[16, 20] AOS patients in India and other developing countries have shown a better course and outcome in form of more remission rates than the western patients.[50] This may apply to COS as well. Despite use of multiple medications (including atypical antipsychotics including clozapine) the outcome was not good in almost 1/3$^{rd}$ of COS patients. It may mean that COS is a more severe form of illness. No difference in the overall course was seen between AdOS and AOS group, which is contrary to the findings of a follow-up study.[29]

The mean IQ for the COS group was in the borderline range (IQ=88) whereas mean IQ for AdOS and AOS was 99 and 109 respectively. The mean IQ of COS group obtained in present study is similar to that reported earlier.[19, 46] AdOS group manifested with a neuropsychological profile similar to COS as found in the previous studies,[51, 52] though the deficits were significantly less than the COS group. Controlling for PANSS scores did not influence the IQ. It is important to note that the neuropsychological dysfunction in the same cohort, published elsewhere, supports the above findings.[52]

In conclusion, though COS seems be qualitatively similar to AdOS and AOS, the results suggest that schizophrenia with onset at different ages seems to fall on a continuum with COS as the most severe form of illness, AOS the least severe form and AdOS falling in between these two extremes. COS has a high degree of socioeconomic dependence, poorer response to treatment, greater and more florid psychopathology, poorer course and outcome and greater neurocognitive deficits as compared to the later onset schizophrenias. Qualitatively there were subtle differences in the subtype of schizophrenia and non-specific symptom profile in the COS as compared to the later onset types.

The present study had a few limitations. Firstly, the sample size of childhood onset schizophrenia (COS) was small. This has been the limitation of most studies and is attributed to the rarity of the disorder. Moreover, we could not recruit all patients of COS coming to our clinic because some had dropped out of follow-up or their addresses had changed and some were institutionalized. Case notes could not be used in these cases because accurate estimation of age of onset as per IRAOS requires use of information from 2 additional sources, i.e. patient and a key informant. Finally, comparison of a retrospective (present) study with prospective studies has inherent difficulties. Further studies that include assessment of brain dysfunction, e.g. brain imaging (like functional MRI or PET scan), neurophysiological (like evoked potential) studies, etc would help in developing an understanding of neurobiology of schizophrenia, including COS.

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Dr. Parthasarathy Biswas, MD, Senior Resident; Professor Savita Malhotra, MD, PhD, F.A.M.S.; Professor of Psychiatry, Professor Anil Malhotra, MA, PhD; Dr. Nitin Gupta, MD, Ex-Assistant Professor, Postgraduate Institute of Medical Education and Research, Chandigarh – 160 012, India