

# Clinical characteristics and premorbid variables in childhood-onset schizophrenia: a descriptive study of twelve cases from a schizophrenia founder population

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## Abstract

**Objective:** To analyze clinical and demographic data of childhood-onset (12 years and younger) schizophrenia patients collected for a genetic study in schizophrenia, undertaken nationally in South Africa, using multiple parameters. **Method:** Patients with an onset of schizophrenia at 12 years or younger, were included. From the Diagnostic Interview for Genetic Studies (DIGS), patients' information and summary report data was tabulated and analyzed. Specific subgroups were further compared. This sub-population of 12 subjects was further compared with a group of the adult sample. **Results:** Of the 12 patients recruited, prominent results were: male to female ratio of 1:1; all had insidious onset of psychosis; a third had all 3 multidimensional impairment (MDI) symptoms; all patients that received ADHD treatment had ADHD treatment failure; two thirds had milestone delay; 58% had birth complications; a third were predominantly bottle fed; 42% had family history of schizophrenia; a third had family history of other major psychiatric conditions; all patients had at least one non-psychotic deviant behaviour (NPDB); no patient used cannabis; all delusions were paranoid; 92% had school achievement difficulty and a third had treatment resistance. Gender comparison included: earlier onset of psychosis in females; all females had aggression versus a third of males; more females had school achievement difficulty than males; males had more treatment resistance. Patients with MDI, compared to the sample average had: earlier onset of non-psychotic deviant behaviour; lower school drop-out rate; less social difficulty and no treatment resistance. **Conclusion:** The results compare well to previous research on this topic. The new concepts introduced by the present study require further investigation.

**Keywords:** Schizophrenia; Childhood; South Africa; Genetics; Population

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## Introduction

The study of phenotypic extremes with an early-onset has been an important approach to the understanding of disease across all medical disciplines.<sup>1</sup> In different medical illnesses, the combination of greater severity, relative treatment resistance, greater heritability and earlier age of onset has been observed.<sup>2</sup> In Alzheimer's disease and breast cancer, important molecular genetic discoveries have been

observed in subpopulations with an earlier age of illness onset.<sup>3,4</sup>

Most cases of schizophrenia have their onset in late adolescence and early adulthood, but the disorder has been identified in children since early in the 20th century.<sup>5</sup> The nosological status of schizophrenia in children was controversial for many years, however the landmark studies by Kolvin and colleagues clearly differentiated schizophrenia with onset in childhood from autistic disorder.<sup>6</sup>

Since 1990, a study of childhood-onset schizophrenia (onset of schizophrenia at the age of 12 or younger) has been ongoing at the National Institute of Mental Health (NIMH).<sup>7</sup> This study shows clear and consistent clinical and biological continuity between childhood-and adult-onset schizophrenia.

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As expected, this treatment refractory group resembled refractory, chronically ill adult patients with schizophrenia.<sup>8</sup>

The treatment resistance of patients with schizophrenia is a frequent and important clinical problem. The definition of treatment resistance remains controversial in spite of its importance. Definitions of treatment resistance differ in several domains: dichotomy (response or non-response) versus continuum of response, the type and duration of previous treatment, the psychopathologic symptoms assessed, and whether psychosocial functioning has been evaluated. The approach of Kane et al<sup>9</sup> to operationalize treatment resistance has been followed in many trials exploring new therapeutic strategies for treatment-resistant patients. However, in clinical practice there is probably no need for 3 previous trials with anti-psychotics, usually 2 trials or even 1 can be considered sufficient to show treatment resistance. The duration of level of good functioning and duration of trial periods are not practical for use in childhood-onset schizophrenia.

While obstetric complications may play a role in the development of schizophrenia in some patients, they are not as previously hypothesized, more salient in childhood-onset cases. Other environmental factors, such as socioeconomic status and unusual psychological trauma do not appear clinically to account for the earlier age of onset in this cohort. Similarly, there is no evidence that the earlier age of onset is due to early puberty. Thus, investigation of non-genetic factors for this very early onset cohort has not revealed more salient features than in adult-onset schizophrenia. Indirectly, this suggests that genetic factors may be related to the earlier age of onset.<sup>8</sup>

Patients with childhood-onset schizophrenia have more significant premorbid abnormalities than adult-onset schizophrenics and may also have a greater history of schizophrenia spectrum disorders in their first degree relatives. While eye movement abnormalities are also seen in the families, it is not clear whether the rates are higher than those for relatives of adult-onset schizophrenics. Additionally, there may be a greater rate of cytogenetic abnormalities.<sup>8</sup>

A collaborative study on the genetics of schizophrenia in an Afrikaner founder population has been ongoing since November 1997. Participants are recruited by the Department of Psychiatry at the University of Pretoria, South Africa and the necessary genetic analyses are done by the Human Neurogenetic Laboratory at the Rockefeller University in New York and now at the Columbia University in New York. The clinical database of this study contains information obtained from the Diagnostic Interview for Genetic Studies (DIGS), a chronological summary report of each subject inducing other sources of information pertaining to the subject.<sup>10,11</sup> From this database 12 subjects, thus far recruited with childhood-onset schizophrenia were selected, and data was obtained from the above mentioned sources.

While there is general agreement that using founder populations to map genes for complex traits may be meritorious, concern exists about the generalization of findings to the population at large, given the uncertainty about the accuracy of the diagnosis in disorders diagnosed exclusively as clinical syndromes as all psychiatric disorders are at present.

In this article the authors compare what is known about

childhood-onset schizophrenia with the information obtained from these 12 childhood-onset schizophrenia patients from a founder population. Furthermore, these patient's data can be compared to the adult schizophrenia patients recruited for this study.

Certain specific findings were made in this study, whilst other findings compare accurately with what is known about childhood-onset schizophrenia. The implication of the results is debated and further recommendations for further research on this topic is made.

## Method

The participants were selected from independently collected samples in South Africa. The current sample includes more than 500 probands of Afrikaner descent who meet diagnostic criteria for schizophrenia or schizoaffective disorder, according to the American Psychiatric Association 1994.<sup>13</sup> All participants provided written informed consent before the initial interview. Approval for the protocol was obtained from both the IRB committees at the University of Pretoria, South Africa and at the Rockefeller University in New York. For full detail of the sample collection, clinical evaluation and genealogical research, please refer to Karayiorgou M et al (2004).<sup>10</sup> The 260 patients discussed in this paper will be the adult reference group for comparison with the childhood onset schizophrenia.

From this database, all the participants that had an onset of schizophrenia or schizoaffective disorder at the age of 12 or younger were selected and their DIGS summaries were obtained. Selected parameters were then tabulated for comparison. The tabulated information was scrutinized and subgroups were chosen to be compared to the sample reported on. The following variables were selected and compared: gender, DSM-IV diagnoses including schizoaffective disorder and schizophrenia, psychosis onset, delusions, hallucinations, multidimensional impairment (MDI) symptomatology (refers to poor affect regulation, attention difficulty and poor impulse control)<sup>12</sup>, mental retardation (according to Intelligence Quotient tests), attention deficit hyperactive disorder (ADHD), epilepsy, milestone delays, birth complications, bottle feeding, serious stressors (divorce, moving house, death of a parent, abuse), family history of schizophrenia and other major psychiatric disorders, non-psychotic deviant behaviour (NPDB)<sup>14</sup>, learning impairment, language impairment, coordination impairment, suicide, cannabis use, school achievement difficulty, school dropout, social difficulty and treatment resistance. "Extreme odd behaviour" includes unprovoked screaming fits, disorganized or irrational behaviour or inappropriate affect.<sup>15</sup> "Non-psychotic deviant behaviour" (NPDB) includes social functioning impairment (social isolation, aggression or extreme odd behaviour), mood and anxiety problems (extreme fears or chronic sadness) and cognition and behaviour problems (attention impairment or learning disability). "Aggressive patients" in the present study only includes unprovoked aggression.<sup>15</sup> Prolonged labour, forceps delivery, Caesarean section, neonatal jaundice and low Apgar scores were all included in assessing birth complications. Patients were referred to as having treatment resistance if it was stated so by the psychiatrist or child and adolescent psychiatrist treating the patient.

## Results

Twelve early onset schizophrenia patients were recruited. The following clinical and sociodemographic data was obtained from the 12 patients in addition to the key findings noted in Table I. Out of the eleven who had hallucinations: ten had auditory hallucinations; seven had visual hallucinations. No other forms of hallucinations were reported. All delusions were of the paranoid type. When delusions and hallucinations occurred concurrently, hallucinations always started earlier than delusions in each patient, with a median age of onset of 11,09 years versus 14,36 years respectively. Eleven patients had at least one multidimensional impairment disorder (MDI) symptom. All four patients treated for ADHD had ADHD treatment failure, two of which had their ADHD treatment stopped due to adverse effects. It must be appreciated that because of the small sample size (n=12) in this study, the comparisons made were not subjected to statistical analysis.

When looking at the total sample, patients with at least one serious stressor (divorce, moving house, death of a parent or abuse) (6 out of 12) had earlier onsets of psychosis (median age of 10.67 years versus 11.17 years of the total sample).

When further analyses of patients who had non-psychotic deviant behaviour (NPDB) was undertaken: all these patients

had social functioning impairment; seven patients had mood and anxiety problems (extreme fears or chronic sadness) and seven patients had cognition and behaviour problems (attention impairment or learning disability).

When further analyses of patients with milestone impairment were undertaken: six patients had delayed walking; two had delayed sitting; four had delayed talking and two had enuresis. A third were predominantly bottle fed. Half of the patients had serious stressors in life (divorce, moving house, death of a parent, abuse).

Regarding treatment, a third were treated with typical (older) antipsychotics (clopenthixol deconate, haloperidol or trifluoperazine) of which half (2 out of the 4) were successfully treated. Seven patients were treated with second generation antipsychotics (risperidone, clozapine or olanzepine) of which five of the seven were successfully treated. Two patients were treated with clozapine of which none were successfully treated and a third (4 out of 12) were treated with risperidone of which all four were successfully treated. Two of the four patients with mental retardation had treatment resistance while a third of the total sample had treatment resistance.

### Males versus Females

When comparing males (6 out of 12) to females (6 out of 12), the following results were obtained. There was an earlier onset of psychosis in females (median age of 10,67 years for females versus 11,67 years for males). Earlier onset of delusions was seen in females (median age of 11,83 years versus 17,40 years for males). Earlier onset of hallucinations was seen in females (median age of 10,4 years versus 11,67 years for males). Five males had milestone impairment versus three females. Five females had serious stressors versus one male. All females had aggression versus a third of males. Half the females had ADHD symptoms and received treatment for it, versus one male. All the females had school achievement difficulty versus five males and half the males had treatment resistance versus one female.

### MDI symptoms

Four patients had all 3 symptoms of MDI and can therefore be called MDI patients. They had the following signs and symptoms. They had earlier onset of delusions (median age of 11,75 years versus 14,36 years of the total sample). They had later onset of hallucinations (median age of 11,75 years versus 11,09 years of the total sample). Delusions and hallucinations started in the same year in each of these four patients. All four patients had extreme odd behaviour versus seven of the total sample. All four patients had learning impairment versus seven of the total sample. None of these patients had language impairment versus two of the total sample. They had earlier onsets of non-psychotic deviant behaviour (NPDB) (median age of 3,00 years versus 4,75 years of the total sample). A quarter dropped out of school versus half of the total sample. A quarter had social difficulty versus a third of the total sample. None had treatment resistance versus a third of the total sample. Half of the total sample dropped out of school. All the patients with treatment resistance dropped out of school.

### NPDB at 1 year of age

The patients with non-psychotic deviant behaviour (NPDB) starting at 1 year of age (3 out of 12) had the following: they had an earlier onset of psychosis (median age of 9.67 years versus

**Table I: General Findings of the 12 Cases Studied**

Males	6
Females	6
Diagnosed with Schizophrenia	11
Diagnosed with Schizoaffective Disorder	1
Insidious onset of psychosis	12
Subjects with delusions	11
Subjects with hallucinations	11
Fulfilled criteria for Multidimensional impairment disorder (MDI)	12
Mental retardation	4
- Borderline mental retardation	1
- Mild mental retardation	2
- Moderate mental retardation	1
- Severe mental retardation	0
Received ADHD Treatment	4
ADHD treatment failed	4
Had non-psychotic deviant behaviour	12
Petit mal epilepsy	3
Other epilepsies	0
Milestone impairment	8
Birth complications	7
Family history of Schizophrenia (primary, secondary or tertiary relatives)	5
Family history of other major psychiatric illness (primary, secondary or tertiary relatives)	4
Attempted suicide	2
Used cannabis	0
School achievement difficulty	11
Dropped out of school	6
Social difficulty	4
Learning impairment	7
Language impairment	2
Coordination impairment	1
Poor affect regulation	8
Poor impulse control	7
Extreme odd behaviours	7
Aggression	8
Treatment resistance	4

11.17 years of the total sample); they had earlier onset of delusions (median age of 12,50 years versus 14,36 years of the total sample) and earlier onset of hallucinations (median age of 9,67 years versus 11,09 of the total sample); all (3 out of 3) of these patients had poor affect regulation versus two thirds of the total sample; all (3 out of 3) of these patients had birth complications versus seven of the total sample; all (3 out of 3) of these patients had milestone impairment versus two thirds of the total sample; all (3 out of 3) of these patients had learning impairment versus seven of the total sample; one third (1 out of 3) had language impairment versus two of the total sample; one third (1 out of 3) had coordination impairment versus one patient of the total sample; none had social difficulty versus one third of the total sample.

#### **NPDB at 3 years of age**

The patients with NPDB starting at 3 years of age (3 out of 12) had the following. They all had attention difficulty versus two thirds of the total sample. They had poor impulse control versus seven of the total sample. All these patients had ADHD symptoms and received treatment for it versus one third of the total sample. They had earlier onset of delusions (median age of 11,00 years versus 14,36 years of the total sample). These patients had slightly earlier onset of hallucinations (median age of 11,00 years versus 11,09 of the total sample). Delusions and hallucinations started in the same year in each of these patients. Two thirds had social difficulty versus one third of the total sample. None had treatment resistance versus one third of the total sample.

#### **Discussion**

It seems that the 1:1, female to male ratio of the present study, is an isolated finding in the childhood-onset-schizophrenia patients of the Afrikaner founder population. Other studies show a predominance of males compared to females, with a ratio of 2:1, in childhood onset schizophrenia.<sup>16,17</sup> One must keep in mind that the number of childhood onset schizophrenia patients in the sample is small which might contribute to the finding. Specifically given that from the total Afrikaner schizophrenia database (this included adults), 31,54% were female (n=260).<sup>10</sup>

In the present study, females had worse symptomatology as they had earlier onset of psychosis, higher incidences of ADHD symptoms, more aggression and more school achievement difficulty than males. The fact that female puberty occurs earlier than male puberty may be an additional factor to consider for the earlier onset of psychosis in females.

A higher incidence of schizophrenia compared to schizoaffective disorder was found when compared to results of an adult sample (N=260).<sup>10</sup> The adult study had 25.58% patients with schizoaffective disorder compared to only 8% (1 out of 12) that was found in the present study. The present study showed that all psychoses onset was insidious. This is consistent with other studies.<sup>16</sup>

The incidence of mental retardation in the present study is similar to other studies that have rates of 10-20%, including borderline mental retardation.<sup>16</sup> These results come from studies of patients with an onset of schizophrenia before 18 years of age. The present study has an incidence of 33%, including borderline mental retardation. Population studies normally show lower rates of mild mental retardation than borderline mental retardation, therefore the finding of higher rates of mild mental retardation in

this study may deserve further attention.

In this group of patients, the treatment of ADHD was always unsuccessful. The rate of ADHD symptoms in the present study is similar to another study by Russel et al., 1989 (quoted in Cosenza A, Bruni G, Muratori F, 2000).<sup>17</sup> Their rate was 40% compared to a rate of 33% in the present study. There is a higher incidence of petit mal epilepsy in the present study suggesting that it may be an additional factor to consider in the ethiopathogenesis of childhood onset schizophrenia.

Previous studies have described milestone impairment with predominance of delayed walking just like in the present study.<sup>19</sup> A study involving 61 patients with schizophrenia onsets before 18 years of age, showed a rate of enuresis of 36%.<sup>20</sup> This approximates the present study's enuresis rate of 17% (2 out of the 12). In the National Institute of Mental Health (NIMH) study there was no evidence of increased obstetric complications or environmental stress.<sup>21</sup>

When comparing the family history of the present study to the reported adult Afrikaner schizophrenia database (N=260), there was a higher incidence of family history of psychotic disease (primary, secondary and tertiary relatives) in the childhood onset cohort (42%, 5 out of 12) compared to the adult cohort (33,33%). There was a lower incidence of family history of other major psychiatric disease in the childhood onset cohort (33%, 4 out of 12) compared to the adult cohort (68,99%). This suggests that the childhood onset cohort has a greater genetic predisposition for schizophrenia but not for other major psychiatric diseases than the adult cohort. Another study involving patients with an onset of schizophrenia before 18 years of age, had a 12,2% rate of patients with siblings affected with schizophrenia while the present study has 8% (1 out of 12).<sup>22</sup>

The Afrikaner schizophrenia database which reported on non-psychotic deviant behaviour before the age of 10 years, had an overall rate of 68,8% compared to the present study's 100%.<sup>15</sup> When this early non-psychotic deviant behaviour was analyzed further, the study had: 30,28% social functioning impairment (social isolation, aggression or extreme odd behaviour) compared to the present study's 100% (12 out of 12); 34,86% mood and anxiety problems (extreme fears or chronic sadness) compared to the present study's 58% (7 out of 12); 39,45% cognition and behaviour problems (attention impairment or learning disability) compared to the present study's 58% (7 out of 12). This shows that the present study has much higher rates of non-psychotic deviant behaviour as well as social functioning impairment, when compared to the adult Afrikaner schizophrenia database. This would fit in with the authors' suggestion that early non-psychotic deviant behaviour may be used as an endophenotypic marker for schizophrenia genetic studies.<sup>15</sup> NPDB starting at 1 year of age and NPDB starting at 3 years of age appear to have different clinical presentations and may be different entities that should be studied individually.

The attempted suicide rate of 17% (2 out of 12) is less than the attempted suicide rate of the adult Afrikaner schizophrenia database (N=260), which is 27,76%.<sup>10</sup> None of the patients of the present study used cannabis at any stage which greatly differs to the cannabis usage rate of 34.6% of the adult Afrikaner schizophrenia database (N=260).<sup>10</sup>

The delusion and hallucination pattern is similar to the adult Afrikaner schizophrenia database (N=260). 97,26% of adults had delusions compared to 92% of the present study. 79,17% of adults had auditory hallucinations compared to 83% of the



present study, 38,89% of adults had visual hallucinations compared to 58% of the present study, 27,32% of adults had sensory hallucinations compared to 0% of the present study.<sup>10</sup> Another study involving patients with a schizophrenia onset of before 18 years (N=110) had 84% delusions and 69% hallucinations. These results are less than the present study's 92% (11 out of 12) delusions and 92% (11 out of 12) hallucinations.<sup>20</sup> The present study confirms the findings of the NIMH study that provided strong evidence that childhood-onset schizophrenia is clinically continuous with later onset forms of the disorder.<sup>21</sup>

The low rates of school dropout, social difficulty and treatment resistance found in MDI patients of the present study is consistent with previous research that pointed out that the psychotic symptoms of MDI patients get better over time and that neuroleptic treatment may not be necessary.<sup>12</sup> Second generation antipsychotics were prescribed more often to these patients than typical antipsychotics. There is a consensus among previous studies in childhood and adolescent onset schizophrenia that second generation antipsychotics may be more successful in the treatment.<sup>16,17</sup> Risperidone was more often prescribed than clozapine. Although these patients seem to be more treatment resistant, the use of clozapine remains problematic because of the side-effect profile.

#### Limitations

The present study involves a small number of patients, however childhood-onset schizophrenia is a rare entity. Furthermore, the findings uncover certain trends that may be investigated further. Since the information gathered was mainly from patients, recall bias may be a problem. This was dealt with by interviewing family members and using information from patient files (including school reports, medical specialist reports, psychological evaluations and social background information reports) to complement the information from the patient. Trained child and adolescent psychiatrists, with many years of experience, were used to interview the patients and family members to limit the recall bias as much as possible.

#### Conclusion

The present study analyzed sociodemographic and clinical data of childhood onset (12 years and younger) schizophrenia patients from an Afrikaner schizophrenia database, in South Africa, using multiple parameters. These patients were compared to information obtained from the literature on childhood-onset schizophrenia. Certain groups from the sample were then compared with each other. The main conclusion is that the Afrikaner childhood-onset schizophrenia group is very similar to other groups described in the literature. The results also give some new information, confirmed information from previous studies and allowed for the comparison of adult schizophrenia patients, with childhood onset schizophrenia patients of the same (Afrikaner) founder population. The results are useful in seeking out trends and initiating further research, possibly comparing other psychiatric disease entities like bipolar, ADHD and autism to schizophrenia.

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