Functional outcome in childhood-onset schizophrenia in Nigeria: a 3-year longitudinal study

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Received 11 February 2016
Accepted 1 May 2016

Egyptian Journal of Psychiatry
2016, 37:118–124

Background
The outcome of childhood-onset schizophrenia (COS) is generally regarded as poor. Few prospective studies have been reported from developing countries.
Aim
The aim of the present study was to assess the functional outcome in COS and the factors associated with poor outcome.
Methods
This 3-year prospective study included 19 patients with COS. Diagnosis was based on the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., criteria using the Kiddie-Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version; severity was assessed through the Positive and Negative Symptoms Scale, whereas the measure of outcome used was Children's Global Assessment Scale.
Results
The mean duration of follow-up was 39.53 (SD ±5.37) months. The mean age of onset of COS was 10.47 (SD ±0.91) years. At the end of the study, 31.6% of the participants had good outcome, 42.1% had moderate outcome, and 26.3% had poor outcome. Factors associated with poor outcome included history of perinatal complication, more negative symptoms, and longer duration of untreated psychosis.
Conclusion
More than a third of the sample showed good outcome over the few years of follow-up. On the basis of the findings of this study, we recommend an early intervention.

Keywords:
childhood-onset schizophrenia, functional outcome, prospective follow-up study

Egypt J Psychiatr 37:118–124

1110-1105

Introduction

Schizophrenia most commonly emerges during late teens and early adulthood, but it can also be diagnosed during childhood (American Psychiatric Association, 2013). Childhood-onset schizophrenia (COS) is a severe form of psychotic disorder that occurs at the age of 13 years or younger and is often chronic and persistently debilitating (Remschmidt *et al.*, 2007). It is a severe form of the late adolescent and early adult-onset disorder (Rapoport and Inoff-Germain, 2000).

COS is a rare disorder; in preadolescents, the estimated prevalence is less than one case per 10 000 (Asarnow *et al.*, 2004). The number of new cases significantly increase during late adolescence, reaching an approximate prevalence of 1% for later-onset schizophrenia. It occurs more in males unlike the adult-onset type that has equal ratio.

Individuals with COS present with more premorbid impairment than do those with late-onset, with an increased prevalence of genetic abnormalities (Addington and Rapoport, 2009). A clinical and outcome study by Hassan and Taha (2011) reported that about 24% of patients with early-onset schizophrenia had good outcome, and that premorbid adjustment, intelligence quotient, negative symptoms, and gradual onset were associated with poor outcome. In a recent systematic review, good outcome for early-onset schizophrenia was 15.4%, with male sex and longer follow-up periods as predictors of poor outcome (Clemmensen *et al.*, 2012). Most studies around the world have reported poor prognosis for COS (Jarbin and von Knorring, 2003; Gonthier and Lyon, 2004; Röpcke and Eggers, 2005; Remschmidt *et al.*, 2007), although a recent meta-analysis reported better outcome in patients with early-onset schizophrenia compared with the adult-onset group (Amminger *et al.*, 2011).

Because COS is a rare disorder, it is poorly understood and has not received adequate attention from researchers (Bartlett, 2004; Clemmensen *et al.*, 2012). It is

 DOI: 10.4103/1110-1105.195549

important that clinicians have a better understanding of the manifestation and prognosis of COS to better recognize and treat it (Taylor, 1998). Few studies on COS have been reported in sub-Saharan Africa, mainly from South Africa (Maydell *et al.*, 2009; Paruk *et al.*, 2009). Both manual and electronic searches did not yield studies on COS in Nigeria. This study, therefore, serves as a template for further work in this area, especially prospectively following patients with COS into late adolescent and early adulthood. In this preliminary work, we report the outcome in terms of functioning of children with COS after 3 years of follow-up in Aminu Kano Teaching Hospital, Nigeria.

Methods

Design and setting

This was a prospective, longitudinal study of children with schizophrenia in the Child and Adolescent Mental Health Unit of Department of Psychiatry, Aminu Kano Teaching Hospital, Kano, Nigeria.

Sample

The study population included 19 patients among the 28 patients that were followed up for schizophrenia. Among the 28 patients, four patients had a change of diagnosis later, whereas five did not complete the study; thus, the dropout rate was 16.7%. All patients had been followed over a period of 3 years, with a mean of 39.53 (SD ±5.37), in a naturalistic pattern with full-structured clinical interviews. The follow-up involved a clinician-administered interview questionnaire to assess the progress of psychopathology, side effect of medications, and return to normal functioning. As COS is a rare disorder, the sample of 19 patients studied was largely adequate, which followed other studies around the world with samples ranging from 9 to 81 (Clemmensen *et al.*, 2012). Those included in the study met the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (American Psychiatric Association, 1994) criteria for schizophrenia, and had the onset of illness before the age of 13 years. Patients with primary diagnosis of intellectual disability were excluded from the study.

Instruments

Sociodemographic Record and Clinical Profile Questionnaire: The sociodemographic record included were age, sex, educational level of parents, family history of mental illness, and age of parents at birth of the patients. The clinical profile included history of associated risk factors like obstetric complications during birth of the patient, delayed developmental milestone, history of head injury, family history of diabetes mellitus, etc.

Kiddie-Schedule for Affective Disorder and Schizophrenia – Present and Lifetime Version (K-SADS-PL)

The K-SADS-PL is a semistructured instrument used in the diagnosis of childhood and adolescent mental illnesses. Depending on the severity of key current and past symptoms reported in the screening interview, any five diagnostic supplements (affective disorders, psychotic disorders, and others) can be administered. The interrater agreement of the instrument in scoring screens and diagnoses was high, with a range of 98–100% (Kaufman *et al.*, 1996). The K-SADS-PL has been used extensively in the studies on psychiatric disorders in the child and adolescent age groups in several countries, including Nigeria (Adewuya *et al.*, 2007; Shahrivar *et al.*, 2010; Umar *et al.*, 2015).

Brief Psychiatric Rating Scale for Children (BPRS-C)

The BPRS-C (Overall and Pfefferbaum, 1982) is a 21-item clinician-based rating scale designed for use in evaluating psychiatric problems of children and adolescents. It focuses on problems as rated by the clinicians to provide a descriptive profile of symptoms applicable to a broad range of child and adolescent psychiatric disorders as a compliment for clinician ratings of functional impairment. It is used as an outcome measure in research, managed care, and public sector child/adolescent clinical settings. Ratings are based on a seven-point scale: not present, very mild, mild, moderate, moderately severe, severe, and extremely severe. The interrater reliability of item ratings of the scale ranged from 0.46 to 0.89, while Cronbach's α's ranged from 0.69 to 0.91 for the seven subscales of BPRS-C.

Positive and Negative Symptoms Scale (PANSS)

The PANSS is a standardized instrument for the assessment of two distinct symptoms of schizophrenia – positive and negative symptoms (Kay *et al.*, 1987). The scale has 30 items that are rated on a seven-point symptoms score. The ratings provide summary scores on seven-item positive scale, seven-item negative scale, 16-item general psychopathology scale, and a composite (positive minus negative) index.

Children's Global Assessment Scale (CGAS)

CGAS is a numeric scale (1–100) designed to provide a global measure of level of functioning in children and adolescents (Shafer *et al.*, 1983). This assessment scale (CGAS) was used to assess the social, educational, and psychological functioning of the adolescents, with a score of less than or equal to 70 indicating functional impairment. Individuals were rated as having good functioning when they scored greater than 70,

moderate functioning when they scored between 40 and 70, and poor functioning when they scored less than 40. The CGAS has been used in children and adolescent in Nigeria (Bakare *et al.*, 2011; Tunde-Ayinmode *et al.*, 2012).

Procedure

The study was approved by the Ethics Committee of Aminu Kano Teaching Hospital, Kano, Nigeria. Parents or guardians gave written informed consent before enrolling their children into the research. This was a prospective follow-up study of 19 patients with COS who were followed up using structured instruments for 3 years. To standardize the diagnosis of psychiatric disorder in suspected cases of schizophrenia, apart from clinical interview, structured clinical assessment with various instruments where carried out for children and adolescents consulting the Child and Adolescent Mental Health Unit of Aminu Kano Teaching Hospital, Kano, Nigeria. On each clinic visit, sets of instruments were used for further evaluation and assessment of diagnosis, functioning and improvement in clinical features during the course of the follow-ups, and side effects from medication. For patients with schizophrenia, the K-SADS-PL was used to confirm the clinical impression at 2–4 weeks from the first visit. The level of global dysfunction was assessed using the CGAS during the first visit and after every 6 months. The BPRS-C and PANSS were used to assess the severity of symptoms of schizophrenia at the start of the clinic visit.

Data analysis

Data analysis was done using the Statistical Package for Social Sciences (SPSS) Version 16 (Released 2007. SPSS for Windows, Version 16.0. Chicago, USA, SPSS Inc). The frequencies and cross tabulations of variables were done to check for data entry errors and missing values. The sociodemographic and clinical correlates were determined using descriptive statistical tools like means, SDs, and frequency tables. The relationship and significance between COS and clinical variables, and CGAS at 3 years and clinical variables were tested using the χ^2-test with the Yates correction and *t*-test wherever appropriate. The level of significance was set at 0.05 (two-tailed). Logistic regression was carried out for variables found to be significantly associated with poor outcome.

Results

Demographic and premorbid characteristics of the patients

The clinic had 24 patients with COS during this period but only 19 completed the study. There were nine (47.4%) males and 10 (52.6%) females. Nearly half (47.4%) of them were first born. More than half of the total number of parents of the patients had tertiary education (Table 1). There was family history of mental illness in 57.9% of the participants. Eight (42.1%) patients had a history of perinatal complications and delayed developmental milestone (Table 1). The history of head trauma was recorded in five (26.3%) patients (Table 1).

Clinical characteristics

The mean age of patients was 14.37 (SD ±1.07) years, whereas the mean age at onset of schizophrenia was 10.47 (SD ±0.91) years (Table 2). The onset of illness was acute (<6 months) in nine (47.4%) patients and

Table 1 Demographic and premorbid characteristics of the patients

Variable	Frequency (%)
Sex	
Male	9 (47.4)
Female	10 (52.6)
Birth order	
First	9 (47.4)
Second	3 (15.8)
Others	7 (36.8)
Mother's educational level	
None	3 (15.8)
Primary	2 (10.5)
Secondary	4 (21.1)
Tertiary	10 (52.6)
Father's educational level	
None	5 (26.3)
Secondary	2 (10.5)
Tertiary	12 (63.2)
Family history of mental illness	
Yes	11 (57.9)
No	8 (42.1)
Family history of diabetes mellitus	
Yes	8 (42.1)
No	11 (57.9)
Perinatal complications	
Yes	8 (42.1)
No	11 (57.9)
Delayed developmental milestone	
Yes	8 (42.1)
No	11 (57.9)
Childhood illness	
Yes	7 (36.8)
No	12 (63.2)
Life event before onset	
Yes	7 (36.8)
No	12 (63.2)
Comorbid conditions	
Yes	11 (57.9)
No	8 (42.1)
History of head trauma	
Yes	5 (26.3)
No	14 (73.7)

insidious (>6 months) in 10 (52.6%) patients. The mean duration of untreated psychosis (DUP) was 10.47 (SD ±10.89) months, whereas the mean duration of illness was 46 (SD ±12.28) months (Table 2).

Table 2 also shows that the mean BPRS-C from the beginning of the study was 49.11 (SD ±10.84), the mean of the negative subscale of PANSS was 29.00 (SD ±8.85), and the mean of the positive subscale was 28.16 (SD ±8.34). The CGAS at the start of the study was 32.95 (SD ±7.51).

Table 2 Clinical characteristics of patients

Variable	Mean (SD)
Age (years)	14.37 (1.07)
Age at onset (years)	10.47 (0.91)
Duration of illness (months)	46.00 (12.28)
Duration of untreated psychosis	10.47 (10.89)
BPRSC	49.11 (10.84)
PANSS total	103.21 (16.93)
PANSS positive subscale	28.16 (8.34)
PANSS negative subscale	29.00 (8.85)
CGAS	32.95 (7.51)

BPRSC, brief psychiatric rating scale for children; CGAS, children's global assessment scale; PANSS, positive and negative symptoms scale.

Outcome of childhood-onset schizophrenia

The data show that 31.6% of the participants had good outcome in terms of their functioning, 42.1% had moderate outcome, whereas 26.3% had poor outcome. Using Spearman's correlation, the presence of less negative symptoms (r=0.53; P=0.020) was significantly associated with good outcome.

Factors associated with poor outcome

Participants with poor outcome were more likely to have a record of history of perinatal complications compared with those with moderate to good functioning at 3 years of treatment (50 vs. 10%). This was statistically significant (χ^2=4.108; P=0.043). Those that had poor functioning had more negative symptoms score on PANSS at 37.40 (SD ±8.62) compared with 26.00 (SD ±6.98) for participants that eventually had moderate to good outcome (Table 4). This was also statistically significant (t-test=2.957; P=0.009). Individuals with poor outcome had 13.86 (SD ±10.83) months of DUP compared with 1.00 (SD ±0.78) months of DUP. This was statistically significant (t-test=2.607; P=0.018). Moreover, the participants with poor outcome had

Table 3 Factors associated with poor outcome in childhood-onset schizophrenia

Variable	Outcome		χ^2	P-value
	Poor	Moderate to good		
Sex				
Male (n=9)	3 (33.3)	6 (66.7)	0.435	0.509
Female (n=10)	2 (20.0)	8 (80.0)		
Family history of mental illness				
Yes (n=11)	3 (27.3)	8 (72.7)	0.012	0.911
No (n=8)	2 (25.0)	6 (75.0)		
History of trauma				
Yes (n=5)	0 (0.0)	5 (100)	3.652	0.056
No (n=14)	5 (35.7)	9 (64.3)		
Perinatal complication				
Yes (n=8)	4 (50.0)	4 (50.0)	4.108	0.043
No (n=11)	1 (10.0)	10 (90.0)		
Delayed developmental milestone				
Yes (n=8)	3 (37.7)	5 (62.5)	0.885	0.347
No (n=11)	2 (18.2)	9 (81.8)		
Childhood illness				
Yes (n=7)	2 (28.6)	5 (71.4)	0.029	0.865
No (n=12)	3 (25.0)	9 (75.0)		
Life Events				
Yes (n=7)	1 (14.3)	6 (85.7)	0.883	0.347
No (n=12)	4 (33.3)	8 (66.7)		
Comorbid conditions				
Yes (n=11)	4 (36.4)	7 (63.6)	1.452	0.228
No (n=8)	1 (12.5)	7 (87.5)		
Predominant negative symptoms				
Yes (n=8)	5 (62.5)	3 (37.5)	11.316	0.001
No (n=11)	0 (0.0)	11 (100)		

df=2.

Table 4 Factors associated with poor outcome in childhood-onset schizophrenia

Variable	Outcome		*t*-test	*P*-value
	Poor mean (sd)	Moderate to good mean (sd)		
Age of onset	10.38 (0.45)	10.80 (1.01)	0.936	0.362
Duration of untreated psychosis	13.86 (10.83)	1.00 (0.45)	2.607	0.018
Duration of illness	59.57 (12.51)	46.00 (0.78)	2.382	0.029
PANSS positive score	22.20 (7.05)	30.29 (7.91)	2.012	0.060
PANSS negative score	37.40 (8.62)	26.00 (6.98)	2.957	0.009
PANSS total score	105.40 (21.68)	102.43 (15.81)	0.328	0.747
BPRSC	50.79 (11.30)	44.40 (8.74)	1.140	0.270

BPRSC, brief psychiatric rating scale for children; PANSS, positive and negative symptoms scale. df=17.

longer duration of illness at 59.57 (SD ±12.51) months compared with 46.00 (SD ±0.78) months. This difference was statistically significant (*t*-test=2.382; *P*=0.029).

Sex of the patients was not associated with poor outcome even though more males had poor outcome at 33.3% compared with 20% for females (χ^2=0.435; *P*=0.509). Other factors like family history of mental illness, history of trauma, delayed developmental milestone, comorbid psychiatric conditions, and presence of life-events in the last 1 year were not associated with poor outcome (Table 3). The mean of the age of onset was 10.38 (SD ±0.45) years for those with poor prognosis, and was lower than 10.80 (SD ±1.01) years for those with moderate to good outcome (Table 4). This difference, however, was not statistically significant (*t*-test=0.936; *P*=0.362).

Logistic regression on factors associated with poor outcome

The factors that were associated with poor outcome in COS were put into a logistic regression analysis. These factors included perinatal complications, DUP, duration of illness, and having predominant negative symptoms. All the four factors did not show further association on logistic regression.

Discussion

A slightly larger number of females completed the present study compared with males, which is in keeping with other studies (Eggers and Bunk, 1997; Hassan and Taha, 2011), but a number of studies have reported a male predominance (Lay *et al.*, 2000; Remschmidt *et al.*, 2000). This may just be as a result of referral bias. Over the 3 years of follow-up in our study, the dropout rate was 16.7%, which is similar to that of a number of outcome studies on early-onset psychosis (Asarnow *et al.*, 1994; Ledda *et al.*, 2009). High dropout rates are common in psychiatric outcome studies (Harrison *et al.*, 2001).

In the present study, 31.6% had good outcome, 42.1% had moderate outcome, and 26.3% had poor outcome. In an Egyptian study, as in this study, patients with poor outcome comprised 25% of the sample, but the percentage for individuals with good outcome was low at 27% and that of individuals with moderale outcome was high at 48.7% (Hassan and Taha, 2011). The results of our study are similar to that of other studies that reported a fourth of their patients with poor outcome (Reichert *et al.*, 2008; Ledda *et al.*, 2009). This is in contrast to a systematic review that reported that only 15.4% of the patients with early-onset schizophrenia had good outcome, 24.5% had moderate outcome, and 60.1% had poor outcome (Clemmensen *et al.*, 2012). The relatively better remission in this study could be attributed to the shorter duration of the follow-up (Hassan and Taha, 2011), the use of different outcome measures, and possibly to the adult pattern of better outcome of schizophrenia in developing countries (Hopper *et al.*, 2007; Haro *et al.*, 2011).

Factors associated with poor outcome in this study included longer DUP, longer duration of illness, perinatal complications, and more negative symptoms. A number of studies have reported that longer DUP, like in this study, is associated with poor outcome in COS patients (Hassan and Taha, 2011; Fraguas *et al.*, 2014; Díaz-Caneja *et al.*, 2015). This brings the idea of early intervention in COS into consideration, as it may be more cost effective and also reduce further burden in adulthood (McCrone *et al.*, 2013; Patton *et al.*, 2014).

Negative symptoms were associated with poor outcome in this study. This was also the case in a systematic review of predictors of outcome in early-onset psychosis, where the presence of prominent negative symptoms was a risk factor for poor outcome (Díaz-Caneja et al., 2015). In addition, those with perinatal complications had poor negative outcome in this study. It has been proposed that premorbid difficulties may

continue into primary negative symptoms in childhood schizophrenia (Hollis, 2003). Therefore, there may be a greater risk in having poor outcome in individuals with more neurodevelopmental load (Strauss *et al.*, 2012). Thus, the presence of early developmental problems and negative symptoms may be regarded as predictors of functional and clinical outcomes, which also gives more credence to the neurodevelopmental theory of schizophrenia (Fatemi and Folsom, 2009).

Conclusion

Out of the small sample of COS patients included in the present study, more than a third had good outcome. Factors that were associated with poor outcome included longer DUP, longer duration of illness, perinatal complications, and presence of more negative symptoms at the onset of the illness. There is a need for early diagnosis of COS with optimal intervention given to reduce the burden of the condition.

Acknowledgements

The authors thank Mallam Danjumai Abdu, the record and health information officer in the Child and Adolescent Mental Health Unit of Aminu Kano Teaching Hospital.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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