

Children and Adolescents With Psychotic Disorder Not Otherwise Specified: A 2- to 8-Year Follow-Up Study

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Although psychotic phenomena in children with disruptive behavior disorders are more common than expected, their prognostic significance is unknown. To examine the outcome of pediatric patients with atypical psychoses, a group of 26 patients with transient psychotic symptoms were evaluated with clinical and structured interviews at the time of initial contact (mean age, 11.6 ± 2.7 years) and at follow-up 2 to 8 years later. Measures of functioning and psychopathology were also completed at their initial assessment. Risk factors associated with adult psychotic disorders (familial psychopathology, eyetracking dysfunction in patients and their relatives, obstetrical complications, and premorbid developmental course in the proband) had been obtained at study entry. On follow-up examination (mean age, 15.7 ± 3.4 years), 13 patients (50%) met diagnostic criteria for a major axis I disorder: three for schizoaffective disorder, four for bipolar disorder, and six for major depressive disorder. The remaining 13 patients again received a diagnosis of psychotic disorder not other-

wise specified (NOS), with most being in remission from their psychotic symptoms. Among this group who had not developed a mood or psychotic disorder, disruptive behavior disorders were exceedingly common at follow-up and were the focus of their treatment. Higher initial levels of psychopathology, lower cognitive abilities, and more developmental motor abnormalities were found in patients with a poor outcome. Obstetrical, educational, and family histories did not differ significantly between the groups. Through systematic diagnostic evaluation, children and adolescents with atypical psychotic disorders can be distinguished from those with schizophrenia, a difference with important treatment and prognostic implications. Further research is needed to delineate the course and outcome of childhood-onset atypical psychoses, but preliminary data indicate improvement in psychotic symptoms in the majority of patients and the development of chronic mood disorders in a substantial subgroup.

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RESearch ON PSYCHOSES in children and adolescents has been hampered by diagnostic uncertainty. For many years, all severe disorders of childhood, including autism, were grouped under the category "childhood schizophrenia," rendering much early research of limited value.¹ Even with the recognition that autism and psychotic disorders are clinically distinguishable,² studies have reported high rates of initial misdiagnosis, perhaps in part due to symptom overlap (particularly with mood disorders), the relative rarity of childhood-onset schizophrenia, and the appearance of hallucinations and delusions in pediatric patients with psychotic disorders.^{3,4}

Further evidence of this is provided by the findings from an ongoing national study of childhood-onset schizophrenia. Systematic screening and assessment found that about 80% of the patients referred for this study did not meet criteria for schizophrenia, although all had been referred with this diagnosis.⁵ A significant number of the patients assessed in person (30 of 230 [13%]), who had transient psychotic symptoms but were impaired primarily by their disruptive behavior, were diagnosed with psychotic disorder not otherwise specified (NOS).⁶ While these children and adolescents did not fulfill the criteria for a diagnosis of schizo-

phrenia, their morbidity (including recurrent lengthy psychiatric hospitalizations), risk factor profiles (including familial psychopathology), and neurobiological abnormalities (eyetracking dysfunction and brain morphometry) were similar to those of patients with childhood-onset schizophrenia.⁶⁻⁸ Although most of these patients had comorbid disruptive behavior disorders, including attention-deficit/hyperactivity disorder (ADHD), they were distinguishable from patients with a primary diagnosis of ADHD on the basis of their clinical presentations.⁶ These patients were tentatively labeled by our group as being multidimensionally impaired (MDI).⁶

Hallucinations and delusions have been recognized in children and adolescents with various behavioral disturbances for many years.^{3,4,9-15} Recent large studies of clinical¹⁶ and community¹⁷ populations have also noted hallucinations and delu-

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0010-440X/01/4204-0002\$35.00/0

doi:10.1053/comp.2001.24573

sions in a wide spectrum of pediatric patients, including those with disruptive behavior disorders.

Follow-up studies of these patients are scarce and have been marked by small samples and varied outcomes. In one early study, three pediatric patients with disruptive behavior and hallucinations had significant morbidity at least 7 years follow-up: one had developed schizophrenia, one had been diagnosed with schizoaffective disorder, and the third had antisocial personality disorder.¹⁰ More recent studies have found similarly high rates of morbidity at follow-up (ranging from 2 to 17 years), although few developed schizophrenia spectrum disorders. Garralda,¹⁸ Del Beccaro et al.¹⁴ and McLellan et al.³ all reported that some patients with psychotic symptoms and disruptive behavior continued to have hallucinations or delusions at follow-up, and many were chronically impaired,³ required residential placement,¹⁴ or had significant work and social difficulties as adults.¹⁸ Only one of the 31 patients in these three studies received a follow-up diagnosis of schizophrenia.¹⁸

As the MDI patients described above were participating in a systematic, prospective study of very early onset psychotic disorders with regular follow-up at 2-year intervals, a unique opportunity existed to examine their outcome and the relationship between follow-up status and clinical, neurobiological, and risk factor profiles. Based on their clinical differences from patients with schizophrenia,⁶ we did not expect our MDI patients to develop schizophrenia. However, recent data on the relationship between severe, treatment-refractory ADHD and bipolar disorder in children¹⁹⁻²¹ led us to hypothesize that some would develop more clearly defined mood disorders. We also anticipated that greater initial levels of personal and familial psychopathology would predict poorer outcome.

METHOD

Subjects

Since 1991, through review of more than 1,000 charts and in-person screening of over 230 subjects, 54 patients have been diagnosed with schizophrenia according to DSM-III-R or DSM-IV criteria^{22,23} with onset of psychosis by age 12.^{1,24,25}

A separate group of 30 patients, all referred with a diagnosis of schizophrenia, did not meet strict criteria for the disorder. Although these patients reported hallucinations and delusions, their symptoms were brief (i.e., lasting for a few minutes at a time) and infrequent (occurring a few times a month, usually in response to stress). They lacked the disorganized speech and

negative symptoms commonly seen in patients with schizophrenia. While they had few if any friends, this was largely due to poor social skills rather than a lack of desire for friends. Consequently, these children and adolescents were diagnosed with psychotic disorder NOS.⁶ Although their psychotic symptoms were distressing, their significant impairment was largely attributable to their dramatic affective instability and the associated aggressive behavior. As described above, we have provisionally described these children and adolescents with the term "multidimensionally impaired."⁶ This diagnosis has been made with good reliability ($\kappa = 0.81$)⁵ by two child psychiatrists using clinical and structured interviews, including the Schedule for Affective Disorders and Schizophrenia for School-Age Children.²⁶ Patients with a history of significant medical problems, substance abuse, or an IQ below 70 prior to the onset of psychotic symptoms were excluded. Family structure (i.e., intact or not) and socioeconomic status²⁷ were noted at each patient's admission to the study.

Patients who met criteria for a disorder associated with psychotic symptoms, including mood disorders and post-traumatic stress disorder, were excluded.⁶ However, the majority of these patients did receive comorbid diagnoses of disruptive behavior disorders, including ADHD ($n = 20$), oppositional defiant disorder ($n = 8$), and conduct disorder ($n = 2$).

This study was approved by the Institutional Review Board of the National Institute of Mental Health (NIMH). Parents or legal guardians of all participants provided written consent and all patients gave written assent for their participation.

Clinical Assessment

At the time of first entry into the NIMH study (mean age, 11.6 ± 2.7 years), subjects underwent extensive clinical assessment with the Clinical Global Impressions (CGI),²⁸ Children's Global Assessment Scale (C-GAS),²⁹ Brief Psychiatric Rating Scale (BPRS),³⁰ Scale for the Assessment of Positive Symptoms (SAPS),³¹ and Scale for the Assessment of Negative Symptoms (SANS).³² A psychological test battery, including the Wechsler Intelligence Scale for Children (WISC-III)³³ and the Wisconsin Card Sorting Task,³⁴ was also administered at initial admission.

Risk Factor Assessment

A number of variables potentially related to diagnosis and outcome, including familial psychiatric diagnoses and eyetracking dysfunction, proband obstetrical complications, and pre-morbid impairments were examined during the patients' initial hospitalization at the NIMH.

Original birth records of 18 probands who were seen at follow-up (the remainder had been destroyed by the hospital of birth) were assessed blind to patient identity by one of the authors (J.N.G.) to determine the presence of obstetrical complications as defined by Buka et al.³⁵

Using the method of Hollis,³⁶ original case notes, including pediatric, psychiatric, psychological, and educational reports, with supplementation by parental recall where necessary, were examined at the time of study entry (and therefore blind to outcome) to determine the presence of premorbid impairments of speech and language, motor functioning, and social interactions. Additionally, a history of repeated grades, delayed school

entry, or special education placement prior to the onset of psychosis was noted.

As abnormalities of smooth pursuit eye movements are increased in patients with schizophrenia and their relatives,³⁷ patients completed a smooth-pursuit eye movement task. The degree of eyetracking dysfunction was assessed qualitatively by one of the authors (R.N.) blind to patient identity using a scale of 1 (best) to 5 (worst) using exemplars from Shagass et al.³⁸ Eye blinks and periods when the subjects were not tracking were excluded from the assessment. Two of the authors (R.N. and G.K.T.) rated a subset of this sample ($n = 10$) with high reliability (intraclass correlation coefficient [ICC] = 0.98).

To assess the presence of axis I and II disorders, first-degree relatives over age 5 were interviewed using the Schedule for Affective Disorders and Schizophrenia³⁹ and the Structured Interview for DSM-IV Personality Disorders⁴⁰ (for relatives ≥ 18 years of age) or the Diagnostic Interview for Children and Adolescents⁴¹ (for relatives under age 18). These interviews were completed at the time of entry into the study and were therefore completed without knowledge of the proband's outcome.

Relatives over the age of 13 also completed a smooth-pursuit eye movement task, which was scored as described above. The mean score of each proband's relatives was computed and used as the familial eyetracking score.

Follow-Up

Patients were asked to return for a clinical interview and magnetic resonance imaging scan every 2 years. Of the 28 subjects eligible for follow-up prior to February 2000, one had committed suicide and one could not be located. Thus, 26 (93%) of the original 28 subjects completed a follow-up. Of these, the mean age at follow-up was 15.7 ± 3.4 years and the mean follow-up interval was 4.1 ± 2.0 years (range, 2 to 8 years). This group consisted of 21 males and 5 females, and these patients had a mean age of onset of their psychotic symptoms of 7.7 ± 2.0 years. The interview again involved clinical and structured interviews using the Schedule for Affective Disorders and Schizophrenia for School-Age Children²⁶ or the Schedule for Affective Disorders³⁹ for those patients who had reached their eighteenth birthday. Interim history was obtained from the patient, relatives, and members of their treatment team. All of the structured follow-up interviews were then scored blind to patient identity by one of the authors (F.B.). Reference to previous material (interviews, case notes) was used when required for clarification. The blinded diagnoses showed a high reliability with the interviewers' diagnoses (κ = 0.84). The only disagreement between the blinded rater and the clinicians administering the interviews involved two patients with clear episodes of mania and depression who continued to have transient, intermittent hallucinations in the absence of full mood episodes. While these two patients did not have full mood episodes at the time of follow-up, they did have prominent mood symptoms (irritability, distractibility, hyperactivity), making the distinction between schizoaffective disorder, bipolar type, and bipolar disorder unclear. This disagreement may reflect a lack of certainty in the criteria for the diagnosis of schizoaffective disorder.⁴² As at their initial assessment, patients were again rated using the CGAS, the CGI, the BPRS, the SAPS, and the SANS.

Statistical Analysis

To examine prognostic factors, patients with a poor outcome (defined as a CGI severity score of at least 5, indicative of at least marked illness) were compared with those with a CGI score of less than 5 on clinical and demographic variables assessed at initial presentation as well as potential risk factors using chi-square and *t* tests. Variables that significantly differed between the groups were entered into a stepwise logistic regression to determine predictors of outcome. A significance level of .05 (two-tailed) was set for all analyses. Results are shown as the mean \pm SD.

RESULTS

Outcome

The outcome at follow-up of this group of children with atypical psychotic disorders was varied. Their mean severity score on the CGI was 4.2 ± 1.2 , suggestive of moderate illness, with a range of 2 (borderline ill) to 6 (severely ill). Their mean level of functioning, as measured by the CGAS, was 42.4 ± 12.6 , indicating moderate impairment, with a range of 20 to 65. There was also evidence of significant morbidity: more than a third had spent over 1 year in out-of-home placements in the follow-up period, and six patients (23%) had forensic histories.

Diagnostic Stability

Thirteen patients (50%) were diagnosed with a mood or psychotic disorder at follow-up: three with schizoaffective disorder, four with bipolar disorder, and six with major depressive disorder. One of the patients diagnosed with depression had also developed mania shortly after the initiation of fluoxetine treatment, suggesting a possible bipolar diathesis.⁴³ Of these 13 patients, only the three with schizoaffective disorder continued to have psychotic symptoms. This group, particularly those with a history of manic episodes, continued to have significant morbidity even between mood episodes. Poor medication response and multiple hospitalizations or placement in a residential treatment facility were noted in most of these patients. Their significant impairment could also reflect their high level of comorbidity even in the absence of strictly defined mood episodes, with six patients continuing to meet criteria for ADHD, three for oppositional defiant disorder, and one for conduct disorder. One patient was also diagnosed with a substance use disorder at follow-up.

For the remaining 13 patients, there was no evidence of an explicitly defined mood or psy-

chotic disorder at follow-up, and they thus again received a diagnosis of psychotic disorder NOS. As most of these patients (12 of 13 [85%]) no longer had even transient psychotic symptoms, they were classified as being in remission. Seven of these patients remained free of hallucinations and delusions in the absence of treatment with antipsychotics, suggesting that their psychotic symptoms had indeed remitted. Although they no longer had psychotic symptoms, the majority of these patients continued to have disruptive behaviors: 11 were diagnosed with ADHD, seven with oppositional defiant disorder, and one with conduct disorder. Additionally, one patient met criteria for a substance use disorder at the time of follow-up.

Risk Factor Assessment

Seven of the 18 (39%) patients for whom birth records were available had a history of a definite birth complication.

Among the 26 patients who returned for follow-up, 16 (62%) had premorbid language abnormalities, 15 (58%) had motor impairments, and 23 (89%) had deviant social development. Five (19%) of the patients had either repeated a grade in school or had their entry into school delayed, while 19 (73%) had received special education placements prior to the onset of their psychotic symptoms.

All of the patients were able to complete the smooth-pursuit eye movement task, but the data for one patient was lost due to machine error. Their mean qualitative score was 3.1 ± 0.9 , reflecting the fact that 17 had abnormal eyetracking (defined a priori as a mean score of at least 2.5).

Psychopathology was assessed in 55 of 60 (92%) first-degree relatives through diagnostic interviews. The remainder, all fathers, could not be located. Four patients had been adopted. Of these 55 relatives, 13 had a schizophrenia spectrum disorder (one with schizophrenia, seven with schizotypal personality disorder, and five with paranoid personality disorder). Additionally, 28 relatives met criteria for a mood disorder (one with bipolar disorder, six with bipolar II disorder, 16 with major depressive disorder, and five with dysthymia). Twelve relatives had a substance use disorder. Among those meeting criteria for an axis II disorder, 13 had cluster B personality disorders (eight with antisocial personality disorder, four with borderline personality disorder, three with histrionic personality disorder, and two with narcissistic per-

sonality disorder [numbers do not add to 13 due to comorbidity]). Thus, among the 22 patients who had not been adopted, 11 (50%) had a relative with a schizophrenia spectrum disorder, 18 (82%) had a family history of a mood disorder, 11 (50%) had at least one relative with a substance use disorder, and 11 (50%) had a family history of a cluster B personality disorder. Furthermore, four (18%) of these 22 patients had a parent who had spent at least 1 year in prison.

Thirty-five relatives completed the smooth-pursuit eye movement task. Their mean score was 2.2 ± 0.9 , with eight (22.2%) having abnormal eyetracking.

Comparison of Good and Poor Outcome Patients

Eleven of the 26 patients seen in follow-up were determined to have a poor outcome (a CGI score ≥ 5 at follow-up). Patients with good and poor outcomes did not differ significantly on their demographic data (gender, race, socioeconomic status, parental separation, age of onset). However, those patients with a poor outcome had higher levels of psychopathology at study entry as measured by the CGI (5.0 ± 1.2 v 4.2 ± 0.6 , $t = 2.3$, $df = 21$, $P = .03$), the BPRS (39.5 ± 7.2 v 32.1 ± 5.7 , $t = 2.9$, $df = 24$, $P = .008$), the SAPS (33.5 ± 16.6 v 17.8 ± 8.2 , $t = 3.2$, $df = 24$, $P = .004$), and the SANS (29.1 ± 14.6 v 15.1 ± 10.8 , $t = 2.8$, $df = 24$, $P = .01$); predictably, they also had a strong trend towards more impaired baseline functioning as measured by the CGAS (39.3 ± 10.6 v 45.3 ± 5.8 , $t = 1.9$, $df = 24$, $P = .07$). While the results of the Wisconsin Card Sorting Task did not distinguish the groups, poor outcome patients had lower verbal (79.5 ± 17.3 v 91.5 ± 12.0 , $t = 2.1$, $df = 24$, $P = .05$) and full-scale (73.1 ± 13.4 v 85.7 ± 13.6 , $t = 2.1$, $df = 24$, $P = .05$) IQs. Patients with poor outcomes had significantly higher rates of premorbid motor impairments (9 [82%] v 6 [40%], $\chi^2 = 4.6$, $df = 1$, $P = .03$) and had a trend towards having more premorbid speech and language abnormalities (9 [82%] v 7 [47%], $\chi^2 = 3.3$, $df = 1$, $P = .07$). Good and poor outcome patients did not differ significantly in their follow-up diagnoses or their obstetrical, educational, and family histories. There were no significant differences between the groups in the eyetracking scores in the probands or their relatives. In a stepwise logistic regression using those variables that differed significantly between the groups, only baseline CGI and SAPS

entered the model. Using these two variables, 87% of patients were correctly classified as having a good or poor outcome ($\chi^2 = 11.3$, $df = 2$, $P = .004$).

Patients diagnosed with a mood disorder at follow-up did not differ significantly from the others in terms of outcome or risk factors, including familial psychopathology.

DISCUSSION

In this sample of 26 patients originally diagnosed with psychotic disorder NOS (the largest described to date), half had developed more specifically defined psychiatric disorders at follow-up, all involving mood episodes. Patients who had poor outcomes had greater levels of psychopathology and lower intelligence levels at baseline in addition to poor premorbid development.

Although half of the patients in this study continued to have poorly defined diagnoses related to their psychotic symptoms (with many no longer describing delusions or hallucinations), they did have severe and impairing disruptive behavior disorders. While the lack of progression to explicitly defined mood or psychotic disorders among this group is in keeping with the results of other studies,^{3,14,18} many of these patients are still in their early adolescence, and therefore the possibility of the development of such a disorder in the future cannot be discounted. Additionally, they may be at risk for adult personality disorders, which can be associated with behavioral disturbances and transient psychotic or psychotic-like symptoms.²³ Although it is possible that treatment with psychotropic agents could have masked the development of further psychotic or mood symptoms in these patients, we do not believe this to have been the case. At the time of follow-up, three of these 13 patients were not receiving any medications and three others were not taking antipsychotics.

Half of the patients in this study developed more clearly defined disorders, all involving prominent mood episodes. They continued to have significant levels of impairment demonstrated by recurrent hospitalizations, out-of-home placements, and special education requirements, which likely reflects the severity of early-onset mood disorders.^{44,45} As others have described,^{46,47} the presence of chronic affective instability in patients such as those described here may herald the later development of a mood disorder. While this rate of mood and psy-

chotic disorders at follow-up is higher than found in previous studies,^{3,14,18} the reasons for this are not clear. Future comparison with other ongoing studies of psychotic disorders in children and adolescents³ may help to elucidate this.

As noted in other studies of children with hallucinations and delusions, such symptoms are fairly common in patients who do not have schizophrenia. Indeed, the majority of patients screened in person for this study were not diagnosed with schizophrenia following an in-depth evaluation.²⁴ Other studies have also found that hallucinations in children are usually not associated with schizophrenia, although they do have an association with other psychiatric disorders and high levels of morbidity.^{3,14,18} As such, it is important to recognize that each of the patients involved in this study had been referred with a diagnosis of schizophrenia. The fact that an extensive evaluation led to a different diagnosis and that none of these patients has since developed schizophrenia highlights the importance of an appropriate diagnostic procedure.

Patients with poor outcomes had higher levels of baseline psychopathology, greater cognitive deficits, and a higher rate of developmental motor impairments than those with a good outcome. There have been no direct studies of good and poor outcome in patients with childhood-onset atypical psychoses, but previous studies of outcome in early onset psychotic disorders have suggested differing predictors. McClellan et al., in studies of early-onset schizophrenia, bipolar disorder, and psychosis NOS, reported that premorbid adjustment combined with negative symptoms³ or IQ⁴⁸ were the best predictors of outcome across various early onset psychotic disorders, while diagnosis did not have prognostic significance. The common finding in those studies and the present one is the importance of developmental abnormalities, which are associated with significant impairment in adulthood⁴⁹ and are also seen in adult patients with severe psychiatric disorders.^{50,51} These premorbid abnormalities may well reflect more aberrant neurodevelopment, which itself may be associated with a poor prognosis.

These findings must be considered tentative due to several limitations of this study. The small sample size limits the generalizability of the data on follow-up and outcome. In addition, while the interviews were scored blindly, they were completed

with knowledge of the patients original diagnoses and the blind rater was aware of the study purpose and hypotheses. Finally, it should be noted this sample represents a relatively homogeneous subgroup of patients diagnosed with psychotic disorder NOS. As such, our findings might not be seen in other patients with atypical psychotic disorders,^{3,14,18} including those who may more closely resemble patients with pervasive developmental disorders.⁵²

In conclusion, among this group of 26 patients

originally diagnosed with psychotic disorder NOS, half developed mood or psychotic disorders, although none developed schizophrenia, the diagnosis which all were referred with. The 26 patients in this study had significant morbidity at follow-up, and thus patients with atypical psychoses who present with severe psychopathology, including disruptive behavior disorders, should be targeted for aggressive intervention as they are at risk for a poor outcome.

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