Obstetrical Complications and Childhood-Onset Schizophrenia

Rob Nicolson, M.D., Dolores Malaspina, M.D., Jay N. Giedd, M.D., Susan Hamburger, M.A., Marge Lenane, L.C.S.W., Jeffrey Bedwell, B.S., Tom Fernandez, A.B., Ariela Berman, B.S., Ezra Susser, Ph.D., and Judith L. Rapoport, M.D.

Objective: Increased obstetrical complications have been reported in individuals with adult-onset schizophrenia, with several studies finding an association between such complications and an earlier age at onset. Consequently, obstetrical records were examined for individuals with childhood-onset schizophrenia to determine if birth complications were more prevalent. **Method:** The birth records of 36 patients with childhood-onset schizophrenia and 35 sibling comparison subjects were rated for birth complications by two psychiatrists who were unaware of group membership. **Results:** There were no significant differences between the groups in rates of obstetrical complications. Patients with such complications did not have a relatively earlier age at onset of schizophrenia. **Conclusions:** A very early age at onset of schizophrenia is probably not due to birth complications.

(Am J Psychiatry 1999; 156:1650–1652)

The study of age at onset has been an important approach to the understanding of disease across medical fields. In schizophrenia, an early age at onset has been associated with poor premorbid functioning, more neurobiological abnormalities, and a poor outcome (1).

Pregnancy and birth complications, which have been found to be more prevalent in adults with schizophrenia (2, 3), may have a role in the age at onset. Several studies, including a meta-analysis, have found an inverse relationship between age at onset and obstetrical complications (2, 4, 5). In the present study, the obstetrical records of patients with childhood-onset schizophrenia were compared with those of healthy sibling comparison subjects. Given the evidence for more obstetrical complications in adult patients with an early onset of schizophrenia, it was hypothesized that there would be an excess of such complications in this patient group.

METHOD

Through national recruitment and extensive screening, including use of the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (6), a cohort of 47 patients with DSM-III-R-defined schizophrenia with onset of psychosis by age 12 years was enrolled in a comprehensive study of childhood-onset schizophrenia.

The study was approved by the National Institute of Mental Health's Institutional Review Board. Written consent from parents and verbal assent of the patients was obtained for all study participants.

Original obstetrical records of 36 patients with childhood-onset schizophrenia were obtained; the records of the remaining patients had been destroyed or were unavailable. Because a number of these patients had no siblings with the appropriate records, the birth records of the siblings of these patients and the siblings of patients with childhood-onset psychotic disorder not otherwise specified (7) were also used as comparison subjects. The final study group consisted of 36 patients with childhood-onset schizophrenia and a comparison group of 20 full or maternal half-siblings of patients with childhood-onset schizophrenia and 15 full siblings of patients with childhood-onset atypical psychoses. None of the siblings used as comparison subjects had a schizophrenia spectrum disorder.

Birth records were scored blind to subject identity by two psychiatrists (J.N.G. and D.M.) using the scales described by Lewis and colleagues (2) and Buka and et al. (8). Reliability was good (kappa= 0.91, N=71, and kappa=0.67, N=71), and discrepancies were resolved by a consensus of the raters. Subjects were scored as positive on each scale if they had at least one definite complication.

For the paired group (probands and their siblings), the McNemar chi-square test (df=1) was used; for the independent groups (probands and siblings of patients with atypical psychoses), an independent chi-square test (df=1) was used. The chi-square values were converted to z scores by using the inverse normal approximation and then added. The resulting sum was squared, and the result, a chi-square value with two degrees of freedom, was used to compare the two groups with respect to demographic and maternal variables and

Received Dec. 22, 1998; accepted April 28, 1999. From the Child Psychiatry Branch, NIMH, Bethesda, Md.; and Columbia University, New York. Address reprint requests to Dr. Nicolson, Bldg. 10, Rm. 3N202, 10 Center Dr., MSC 1600, Bethesda, MD 20892-1600; rn54q@nih.gov (e-mail).

rates of obstetrical complications. A significance level of 0.05 (with a two-tailed test) was used for all analyses.

RESULTS

The groups did not differ with respect to demographic (sex, race, socioeconomic status) or maternal (age, number of pregnancies, number of deliveries) variables (χ^2=0.1 to 4.8, df=2, n.s.).

As shown in table 1, the two groups did not differ significantly in the rates of complications on the scales employed, the subcategories defined by Buka et al. (8) (chronic fetal hypoxia, prematurity, or other complications), or the number of subjects with a low birth weight (less than 2500 g). There were no significant differences on any of the individual complications.

Within the patient group, those with a history of birth complications did not have a lower age at onset of schizophrenia than those without birth complications by using either the Lewis et al. scale (t=1.0, df=34, n.s.) or the Buka et al. scale (t=1.5, df=34, n.s.).

Although birth complications in patients with schizophrenia may occur more commonly in men (4), there were no differences between the two groups in the proportion of men with birth complications with the use of either scale (χ^2=1.4 [Lewis et al. scale] and 3.4 [Buka et al. scale], df=2, n.s.) or in the age at onset of schizophrenia in male patients with and without birth complications, respectively (t=0.5 and 1.5, df=23, n.s.).

TABLE 1. Complications of Pregnancy and Delivery in Patients With Childhood-Onset Schizophrenia and Healthy Siblings

	Patients (N=36)		Siblings (N=35)		Analysis	
Definition of Complications	N	%	N	%	χ^2 (df=2)	p
Lewis et al. (2)	13	36.1	12	34.3	0.1	n.s.
Buka et al. (8)	10	27.8	16	45.7	2.4	n.s.
Chronic fetal hypoxia[a]	2	5.6	5	14.3	2.5	n.s.
Prematurity[a]	3	8.3	2	5.7	2.1	n.s.
Other complications[a]	6	16.7	11	31.4	1.7	n.s.
Birth weight less than 2500 g	3	8.3	1	2.9	0.5	n.s.

[a] As defined by Buka et al. (8).

DISCUSSION

Patients with childhood-onset schizophrenia did not have a higher rate of obstetrical complications than their sibling comparison subjects; the rates of complications in both groups were within the ranges reported in studies of patients with adult-onset schizophrenia and comparison subjects (5, 9). Within this cohort, patients with a history of prenatal and perinatal complications did not have an earlier age at onset than those without similar histories.

Although our group size was small, the rarity of childhood-onset schizophrenia precludes larger studies. Moreover, the size of the current study group was similar to that used in studies which found more obstetrical complications in patients with schizophrenia (2, 3, 10). Additionally, the use of original birth records, while removing any recall bias, may not have noted subtle complications. However, original obstetrical records and the scales employed here have been used in studies that did detect differences between patients with schizophrenia and comparison subjects (2, 3), suggesting that the lack of differences here were not simply a result of the measures employed. While none of the siblings used as comparison subjects had passed through the age of risk for schizophrenia and may yet develop the disorder, none had evidence of childhood-onset schizophrenia. Therefore, although inferences regarding the etiological relationship between schizophrenia and obstetrical complications cannot be made with the data from this study, the results support the conclusion that childhood-onset schizophrenia is not associated with an excess rate of complications in pregnancy and birth.

The lack of a difference in the incidence of obstetrical complications in patients and healthy siblings in the present study, and the similar rate of complications seen in these patients with an early onset of schizophrenia when compared with patients with adult-onset schizophrenia, suggests that obstetrical complications are unlikely to be important in the childhood onset of schizophrenia. Other data from this study suggest that there may be a higher genetic liability for schizophrenia in childhood-onset cases of the disorder (1).

REFERENCES

1. Nicolson R, Rapoport JL: Childhood-onset schizophrenia: what can it teach us? in Childhood Onset of "Adult" Psychopathology: Clinical and Research Advances. Edited by Rapoport JL. Washington, DC, American Psychiatric Press (in press)
2. Lewis SW, Owen MJ, Murray RM: Obstetric complications and schizophrenia: methodology and mechanisms, in Schizophrenia: Scientific Progress. Edited by Schulz SC, Tamminga CA. New York, Oxford University Press, 1989, pp 56–68
3. McNeil TF: Perinatal risk factors and schizophrenia: selective review and methodological concerns. Epidemiol Rev 1995; 17:107–112
4. O'Callaghan E, Gibson T, Colohan HA, Buckley P, Walshe DG, Larkin C, Waddington JL: Risk of schizophrenia in adults born after obstetric complications and their association with early onset of illness: a controlled study. Br Med J 1992; 305:1256–1259
5. Verdoux H, Geddes JR, Takei N, Lawrie SM, Bovet P, Eagles JM, Heun R, McCreadie RG, McNeil TF, O'Callaghan E, Stöber G, Willinger U, Wright P, Murray RM: Obstetric complications and age at onset in schizophrenia: an international collaborative meta-analysis of individual patient data. Am J Psychiatry 1997; 154:1220–1227
6. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N: Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997; 36:980–988

7. Kumra S, Jacobsen LK, Lenane M, Zahn TP, Wiggs E, Alaghband-Rad J, Castellanos FX, Frazier JA, McKenna K, Gordon CT, Smith A, Hamburger S, Rapoport JL: "Multidimensionally impaired disorder": is it a variant of very early-onset schizophrenia? J Am Acad Child Adolesc Psychiatry 1998; 37:91–99
8. Buka SL, Tsuang MT, Lipsitt LP: Pregnancy/delivery complications and psychiatric diagnosis: a prospective study. Arch Gen Psychiatry 1993; 50:151–156
9. Jones PB, Rantakallio P, Hartikainen A-L, Isohanni M, Sipila P: Schizophrenia as a long-term outcome of pregnancy, delivery, and perinatal complications: a 28-year follow-up of the 1966 North Finland general population birth cohort. Am J Psychiatry 1998; 155:355–364
10. Eagles JM, Gibson I, Bremner MH, Clunie F, Ebmeier KP, Smith NC: Obstetric complications in DSM-III schizophrenics and their siblings. Lancet 1990; 335:1139–1141