Prenatal Origin of Schizophrenia in a Subgroup of Discordant Monozygotic Twins

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Abstract

Neuropathological, obstetrical, and epidemiological evidence increasingly suggest that some cases of adult-onset schizophrenia have prenatal or neonatal etiological roots. We evaluated the developmental histories of 23 monozygotic twin pairs discordant for schizophrenia to determine when they markedly and permanently began diverging from each other in motor skills or unusual behavior. Seven of the twins (30%) who later developed schizophrenia had become permanently different from their cotwins by age 5 years. The early divergence group differed from the others by multivariate tests ($p = 0.002$) for within-twin pair effects and by univariate tests for physical anomaly scores ($p = 0.01$), total finger ridge counts ($p = 0.001$), family history of psychosis ($p = 0.004$), and serious perinatal complications or low birth weight ($p = 0.05$). It is concluded that some cases of adult-onset schizophrenia are associated with prenatal events, which may include neurodevelopmental abnormalities or specific insults such as anoxia or infectious agents.

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Some cases of adult-onset schizophrenia may have prenatal or neonatal etiological roots. This possibility is supported by studies of minor physical anomalies (Gualtieri et al. 1982; Guy et al. 1983; Sharma and Lal 1986; Green et al. 1989; O'Callaghan et al. 1991*a*), neuropathological studies suggesting prenatal changes in cerebral morphology (Jakob and Beckmann 1986; Hyde et al. 1991), a modest winter-spring birth excess in persons who later develop schizophrenia (Bradbury and Miller 1985; Boyd et al. 1986), and an increase in obstetrical complications in such persons (McNeil 1988). These findings are consistent with earlier retrospective, anecdotal and clinical observations and with studies of premorbid asociality and other behavioral problems in a subgroup of individuals who had schizophrenia (Gittelman-Klein and Klein 1969). They are also consistent with prospective studies of high-risk infants, some of whom have impaired neuromotor functioning (Fish et al. 1992). In reviewing such studies Offord and Cross (1969) concluded that "patients should be divided into two major groups, those who have difficulty in childhood before the onset of the overt schizophrenic illness and those who do not" (p. 281).

In view of these reports, we studied monozygotic twins discordant for schizophrenia to assess behavioral and neurological differences in early childhood and to ascertain whether such differences were associated with markers of prenatal and neonatal events (Suddath et al. 1990). Studies of monozygotic twins permit assessment of familial factors that affect both twins and might, in nontwins, appear to explain the behavioral or neurological change. A previous schizophrenia twin study which directly addressed this issue found that the twin who later developed

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schizophrenia had more birth complications and frequently weighed less at birth, was developmentally slower, and behaviorally more problematic (Stabenau and Pollin 1967; Pollin and Stabenau 1968).

Methods

Patients. Two members of a set of monozygotic triplets and 22 monozygotic twins from pairs discordant for schizophrenia (10 undifferentiated schizophrenia, 7 paranoid, 2 disorganized, 1 residual) or schizoaffective disorder (3) were recruited through the National Alliance for the Mentally Ill and the Canadian Friends of Schizophrenics. The protocol was approved by an institutional review board, and informed consent was obtained from the study subjects or their parents. The discordance in the 23 pairs, defined as the time since the index twin was first referred to a mental health professional, averaged 12 years (range 5 to 27 years). Based on previous twin studies, we project that a maximum of one pair may become concordant (Belmaker et al. 1974). Zygosity was initially established before testing by an experienced geneticist's evaluation of parental questionnaires and childhood photographs and was later confirmed by testing 19 red blood cell antigens.

The 23 pairs included 14 male and 9 female pairs (22 were white and 1 was black). The mean age at the time of testing was 30 years (range 17 to 44 years). All except two affected twins were receiving antipsychotic medication and three had received electroshock therapy in the past. The diagnosis of schizophrenia was established using a Structured Clinical Interview for *DSM–III–R* (SCID–P I and II; Spitzer et al. 1990*a*, 1990*b*), the Minnesota Multiphasic Personality Inventory (MMPI; Golden and Meehl 1979), and videotape review. Additional diagnoses included developmental disorder in both members of one twin pair and adolescent antisocial personality disorder in both members of another pair. One unaffected twin met criteria for simple phobia and a single past episode of reactive depression. In six pairs both twins met *DSM–III–R* criteria (American Psychiatric Association 1987) for past alcohol/drug abuse or dependence (index twin heavier user in three pairs, well twin in two, equal use in one). In one pair only the index twin met these criteria (alcohol), and in one pair only the well twin met these criteria (amphetamine). In only one index twin did substance abuse occur around the time of onset of schizophrenia; in that case psychotic symptoms predated the substance abuse. At the time of testing both members of one pair were continuing to use marijuana intermittently and one well twin was suspected of abusing alcohol.

Age of Divergence. An extensive developmental history was obtained for each twin pair from one or both parents. This included a 600-item developmental questionnaire divided by age periods; a behavioral questionnaire in which the parents were asked to compare the twins during preschool, primary school, and secondary school periods (e.g., "Which twin worried more?"); the Personality Inventory for Children (Wirt et al. 1984); and an extended semistructured interview adapted from the Vineland Adaptive Behavior Scales (Sparrow et al. 1984). Information was sought not only about the time of onset of schizophrenia but also when the twins began to diverge markedly and permanently in motor skills or unusual behavior. This age of divergence occurred during the teenage years in the majority of twins, usually blending imperceptibly into the early symptoms of illness; these twins constituted the later divergence group. Corroboration of such histories was sought from school records and other relatives, although previous studies have shown maternal recall of motor development to be reasonably accurate (Goddard et al. 1961). Determination of age of divergence was made before the blind scoring of physical anomalies, fingerprints, or obstetrical and neonatal complications.

A description of the seven twins with an early age of divergence follows:

1. At age 5 the affected twin became much more aggressive and argumentative, and she continued to be so until the onset of illness at age 14.
2. From early childhood the affected twin was noted to be very clumsy and said by his father to "trip over his own shadow." At age 8 he began having problems concentrating in school and became increasingly quiet and withdrawn. He was seen by a pediatrician who prescribed methylphenidate, which produced some improvement. He was diagnosed with schizophrenia at age 19.
3. At age 5 both twins were noted to have difficulty reading and concentrating, and at age 8 both were labeled as "borderline dyslexic." However, the affected twin was more shy, quiet, and dependent but also was more

easily upset and more argumentative. He had additional problems with enuresis until age 7, more than 3 years longer than his twin. He was diagnosed with schizophrenia at age 22.

4. The affected twin's developmental milestones (walking, talking, toilet trained) were considerably later than those of his brother. He was also much less coordinated, (e.g., problems throwing a ball or riding a bike). Behaviorally, he was shy and withdrawn and occasionally exhibited odd behavior, for example, a phobia of stairs. At age 8 the quality of his drawings was said to deteriorate. He was diagnosed with schizophrenia at age 14.

5. At age 5 the affected twin was noted by his kindergarten teacher to have "a strange gait" and to lose a previous ability to tie his shoes. He also was said to be socially immature and was asked to repeat the school year. In primary school he required speech therapy for one year, had reading problems, and was less coordinated than his brother (e.g., could not do a somersault). He also was remembered as having been intolerant of noise, sometimes holding his hands over his ears. At age 9 he began having occasional outbursts of screaming in the classroom and became more withdrawn. At age 11 he missed much of the school year because of these problems. However, he was not diagnosed with schizophrenia until age 26.

6. At age 3 the affected twin developed a hand-washing compulsion and strong fear of germs, which persisted throughout childhood. Both twins were shy and socially withdrawn although academically successful. The affected twin was diagnosed with schizophrenia at age 29.

7. The affected twin started walking 1 month after his brother. At age 5 he was referred for speech therapy because of "baby talk." In school he had difficulty concentrating, could not sit still, and was diagnosed as "borderline hyperactive." Later in primary school he had temper tantrums and inappropriate aggressive outbursts. He was diagnosed with schizophrenia at age 22.

Two other affected twins were briefly considered as candidates for early divergence but were rejected. In one pair, both twins were extremely shy and withdrawn at age 5 and labeled as dyslexic; however, since there were no significant differences between them, there was no true divergence. In the other pair, the affected twin had exhibited unusual behavior at age 4 but then reverted to a normal behavior pattern during primary school; since the unusual behavior was only temporary, this pair did not meet one of the criteria, permanency, established for divergence.

Minor Physical Anomalies. Minor physical anomalies are abnormalities in ectodermal development that may be either inherited or acquired in utero; they are known to occur more frequently in individuals with developmental disorders (Marden et al. 1964). Assessment of these anomalies is somewhat subjective and their relationship to prenatal events and postnatal development is not well understood. Each twin was examined by the same experienced developmental pediatrician using a modified Waldrop scoring system (Waldrop et al. 1968). A long list of anomalies has been described (Leppig et al. 1987): In this study, those examined using a 3-point scale (normal, minor deviation, clearly abnormal) were head circumference; hair (electric, whorls); eyes (epicanthus, hypertelorism); ears (malformed, asymmetrical, low seated, pliability, lobe adherence); mouth (palate, tongue); hands (fifth finger curvature, index finger length, transverse crease); and feet (partial syndactaly, gap between first two toes, third toe length). The examiner was not aware of any data on the person being examined, including diagnosis, although in some cases this was obvious due to residual symptoms.

Total Finger Ridge Count. All subjects were fingerprinted with standard inking techniques. Total ridge counts were determined for each finger by counting all ridges along a line connecting the triradial point to the closest point of the core and then adding the counts together (Okajima 1975; Schaumann and Alter 1975). The counts were done independently by a technician and medical anthropologist, neither of whom were aware of other data including diagnosis; the interrelater reliability was 0.98. Pattern configuration (e.g., number of arches) was also assessed.

Obstetrical and Neonatal Complications. As part of the developmental questionnaire and semistructured interview, data on pregnancy, delivery, and the neonatal period were collected by the research social worker. This information was summarized by a physician and then jointly evaluated by a psychiatric investigator experienced in obstetrical data and an obstetrician/psychiatrist (none

of whom were aware of the diagnosis and other data). All reported complications were assessed regarding the likelihood of their causing fetal damage. The complications that were operationally selected as being problematic are listed and defined in table 1, and a total score (referred to as the obstetrical score) for each twin and within-pair differences was calculated. Birth weight was analyzed independently. Hospital delivery records (available for nine twin pairs) revealed no important discrepancy from maternal recall, which supports previous studies on the validity of maternal recall (O'Callaghan et al. 1990).

Statistical Analysis. Physical anomalies, ridge counts, obstetrical scores, and birth weight data were examined using two-factor multivariate and univariate repeated measures analysis of variance. An early and later divergence group variable was used as a grouping factor, and the index and well-twin classification was used as the repeated measures factor. Physical anomalies, finger ridge counts, obstetrical scores, and birth weight measures for each twin were the dependent variables. The effects of interest were the divergence grouping factor between twin pairs, the repeated measures factor within twin pairs, and the divergence grouping by repeated measures interaction factor between the two types of effects.

The analyses of multiple dependent variables provided additional statistical power and took into account two possible sources of correlations: A repeated measures model was used to account for intrapair correlations occurring between the paired measurements, and a multivariate model was used to account for correlations occurring among the measurements of the four dependent variables in each individual. Tests were also performed using single dependent variables corrected by the Bonferroni procedure when the results of multivariate tests were significant.

An interaction factor (between the divergence grouping factor and the repeated measures factor) was included in the analysis; when significant, simple effects tests were carried out by examining each row and column of the two-way layout of between- and within-twin cells. Controlling for gender in this analysis was precluded because there was only one female twin pair in the early divergence group. All analyses were performed using BMDP4V software (BMDP Statistical Software Manual 1990).

Clinical and descriptive results comparing the early divergence and later divergence groups were

Table 1. Obstetrical/neonatal complications most associated with offspring damage

Pregnancy
Hypothyroidism
Diabetes
History of alcohol use > 2 drinks/wk
History of smoking > 1 pack/d
Use of possible teratogenic medications
Hydramniosis
Preeclampsia or eclampsia
Bleeding
Placenta previa
Viral infection associated with miscarriages
Labor and delivery
Precipitous labor (< 1 h)
Extended labor (> 9 h for first delivery; > 6.5 h for subsequent deliveries)
Intentionally extended labor with hospital transfer
Use of cyclopropane anesthesia
Breech delivery
Forceps delivery
Umbilical cord around neck
Delayed delivery of 2nd twin (> 20 min)
Ablatio placentae
Use of oxytocin to contract uterus before delivery of 2nd twin (unexpected) and subsequent extraction
Neonatal
Preterm (< 8 mo gestation)
Low birth weight (< 2,000 g)
Respiratory difficulties or suggestion of asphyxia
Persistent ductus omphalo-entericus with marked weight loss
"Hyperactivity syndrome" beginning immediately after birth
Postnatal viral infection involving long hospital stay
Postnatal viral infection, life-threatening

also analyzed using *t* tests, paired *t* tests, and Fisher's exact tests.

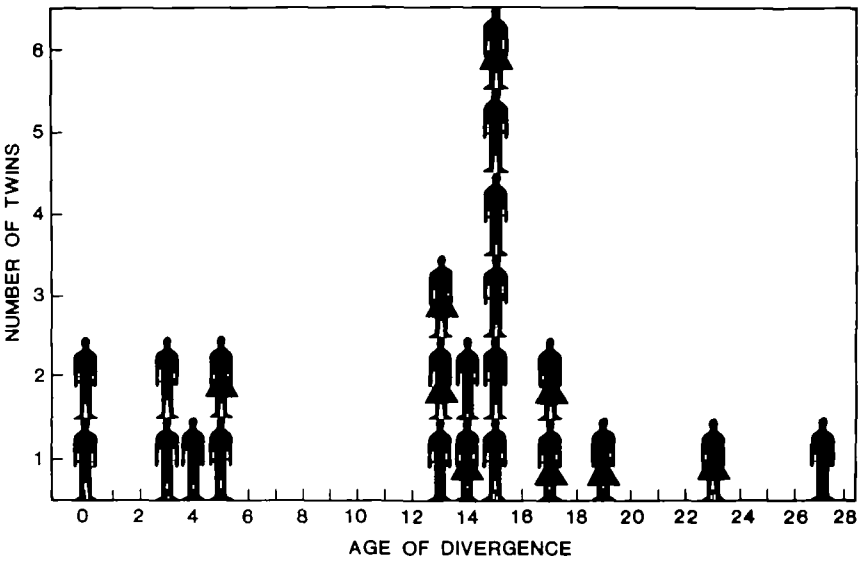
Results

In 7 of the 23 pairs (30%) the twin who later developed schizophrenia differed neurologically or behaviorally from the cotwin by age 5 years. No twins diverged between 6 and 12 years, and the other 16 pairs diverged between the ages of 13 and 27 years (figure 1). Among the seven pairs with an early age of divergence, corroborative data (e.g., school records, other relatives' recall) obtained in five cases substantiated the parents' recall.

Comparing the 7 index twins who diverged at an early age with the 16 who diverged later, we found no significant differences in birth order, age at the time of testing, years discordant, age of first hospitalization, clinical symptoms including the Scale for Assessment of Negative Symptoms (SANS; Andreasen 1984), I.Q., mental status examination, neurological examination, or current level of functioning as assessed by Axis V of the *DSM–III–R*. There was a trend for pairs with an early age of divergence to be male (6 of 7 vs. 8 of 16; $p = 0.18$), to have been born in January–April (5 of 7 vs. 5 of 16; $p = 0.17$), to have less total hospital time (mean 6 months vs. 18 months; $p = 0.08$), and to have had a good response to neuroleptic medication as assessed on a scale of 1 to 5 ($p = 0.08$; Fisher's exact test, two-tail).

A significant difference between twin pairs with early and later divergence was found for family history of psychosis. Four twin pairs had such a history (two first-degree and two second-degree relatives), and all four were among the early divergence group (Fisher's exact test, two-tail, $p = 0.004$).

Figure 1. Age of divergence in development of 23 twin pairs discordant for schizophrenia



When physical anomalies, finger ridge counts, obstetrical scores, and birth weight were used as the four dependent variables in a multivariate repeated measures test, there was a significant overall interaction effect between the within-twin pair factor and the divergence grouping factor ($p < 0.001$). The individual components of the interactions were examined using the simple effects followup tests from the repeated measures analysis. Significant within-twin pair effects were found in the early divergence group only by the multivariate test ($p = 0.002$) and by the univariate tests for physical anomalies ($p = 0.01$) and finger ridge counts ($p < 0.001$) but not for obstetrical scores or birth weight. There was also no significant difference in the configuration of dermatoglyphic patterns. The mean scores for each of the four dependent variables for both groups are shown in table 2. The physical anomaly scores and finger ridge counts were significantly different in the early divergence group but not the later divergence group. In both groups the index twins had slightly but not significantly higher physical anomaly and obstetrical means scores. Use of repeated measures simple effects multivariate and Bonferroni corrected univariate tests for all 23 twin pairs showed no significant group differences for the index or well twins on these variables.

In a further analysis of obstetrical scores, the twin pairs in the early divergence group had a significantly higher mean occurrence of the obstetrical and neonatal complications most likely to be associated with offspring impairment

Table 2. Minor physical anomalies, total finger ridge count, obstetrical/neonatal complications, and birth weight

Variable	Index twin Mean (SE)	Well twin Mean (SE)	*t* test *p* value
Early divergence (n = 7 pairs)			
Physical anomalies	7.0 (1.0)	5.3 (0.8)	0.01
Finger ridge counts	123.0 (23.0)	140.9 (21.3)	0.00
Obstetrical scores	8.0 (2.0)	6.9 (2.5)	0.64
Birth weight (g)	2393.0 (173.0)	2682.0 (182.0)	0.10
Later divergence (n = 16 pairs)			
Physical anomalies	5.1 (0.6)	5.1 (0.6)	0.87
Finger ridge counts	143.9 (13.0)	137.0 (12.0)	0.03
Obstetrical scores	3.5 (0.9)	3.3 (1.1)	0.94
Birth weight (g)	2521.0 (129.0)	2484.0 (135.0)	0.75

Note.—SE = standard error.

(table 1) than did the twin pairs in the later divergence group (p = 0.05, t test). In all three twin pairs with an intrapair birth weight difference of more than 20 percent (Tan et al. 1979), the twin who became sick was lighter and had an early age of divergence (3 of 7 vs. 0 of 16; p = 0.02; Fisher's exact test, two-tail). The two index twins with the most serious obstetrical and neonatal complications (life-threatening neonatal viral infection and a 41% birth weight discrepancy) were both in the early divergence group. When markedly different birth weights (> 20% lighter at birth) were combined with the most seriously complicated pregnancies and deliveries, the index twins in the early divergence group differed significantly in the frequency of these potentially damaging events from the index twins in the later divergence group (4 of 7 vs. 0 of 16; p = 0.004; Fisher's exact test, two-tail). Table 3 lists anomalies found in the index twin only and the obstetrical and neonatal complications for the twins in the early divergence group.

Discussion

In view of recent evidence which suggests that some cases of schizophrenia in nontwins have prenatal or neonatal roots, the identification of cases of schizophrenia in discordant monozygotic twins with an early age of neurological or behavioral divergence is not surprising. It indicates that in at least one-third of cases the disease process begins early in life. It is possible that other cases of schizophrenia also have prenatal roots but do not manifest themselves behaviorally or neurologically early in life; however, this question cannot be answered with present data. It is also possible that other discordant twins might diverge between ages 6 and 12 but simply were not represented in the present study.

The nature of this disease process is less clear. Monozygotic twins may be discordant for schizophrenia and minor physical anomalies (as in this study), but they are also commonly discordant for major anomalies of the central nervous system, including hydrocephalus and anencephaly (Myrianthopoulos 1975). The association of minor anomalies with early divergence in schizophrenia is also reminiscent of a study in which minor anomalies were associated with the early onset of hyperactivity in children (Quinn and Rapoport 1974). It is believed that most minor physical anomalies and the finger ridge count are fixed by the end of the second trimester, although their timing is not precisely established.

An association between lower finger ridge counts and birth weight is to be expected since finger ridge counts are largely determined by the fetal size in the second trimester (Bracha et al. 1991; Okajima 1975; Schaumann and Alter 1975). Monozygotic twins markedly discordant for birth weight are thought to have un-

Table 3. Minor physical anomalies and obstetrical/neonatal complications in the seven index twins with early age of divergence

Minor physical anomalies	Obstetrical/neonatal complications
Malformed ears Asymmetrical ears Ear lobes completely attached Furrowed tongue	Eclampsia (2nd and 3rd trimesters)
Head circumference 1.5 cm smaller than well twin Asymmetrical ears Palate moderately high	Extended labor (13 h) Forceps delivery Postnatal viral infection (life-threatening)
Malformed ears Asymmetrical ears Palate moderately high Partial syndactaly of two middle toes	Bleeding for first 2–3 mo Occiput posterior with forceps delivery Low birth weight (1,758 g) 35% lighter at birth
Head circumference 1.25 cm smaller than well twin Malformed ears Asymmetrical ears Ear lobes completely attached	Intentionally extended labor with transfer to hospital 1 h away Delayed delivery of 2nd twin (1 h, 12 min) Umbilical cord around neck Low birth weight (1,729 g) 41% lighter at birth
Head circumference 1 cm smaller than well twin Low-seated ears (bottom of ears in line with area between mouth and nose)	Precipitous labor (30 min)
None	Extended labor (24 h) Occiput posterior with forceps delivery
Large head circumference (60.5 cm) Malformed ears	23% lighter at birth Respiratory difficulties at birth

equal circulations, referred to as the twin transfusion syndrome, found in 10 percent of monozygotic twin births (Tan et al. 1979). Whether such decreased circulations are primary or secondary to other events is unknown. In 3 of the 23 pairs, the index twin weighed 20 percent less; all 3 were in the early divergence group. The relationship of prenatal events to obstetrical and neonatal complications is also unclear; recent research on cerebral palsy suggests that prenatal events may be risk factors for such complications (Nelson and Ellenberg 1986).

The association of family history of psychosis with early divergence suggests that genetic factors sometimes interact with prenatal or neonatal events to cause schizophrenia (Gottesman 1991). Several models exist that might account for such an interaction. There is a neurodevelopmental model in which genetic factors predispose to defective proliferation or neuronal migration in the brain's development (Weinberger 1987); such defects might also cause physical anomalies, changes in finger ridge counts, or obstetrical complications. Another possibility is that there are genetic factors that render specific brain areas more vulnerable to anoxia prenatally or at birth or that impair circulation; for example, anoxia increases the rate of fetal malformations in animals who have a specific genetic effect (Mednick et al. 1971).

Another model might be a genetic predisposition to an infectious agent that may cause both schizophrenia and physical anomalies, changes in finger ridge counts, obstetrical complications, and low birth weight. It is known that infectious agents as varied as *Treponema pallidum* and the human immunodeficiency virus may prenatally affect only one twin in a monozygotic pair (Penrose 1937; Goedert et al. 1991). An interest in prenatal viral infections as possible etiological agents in schizophrenia was recently stimulated by reports that exposure of mid-trimester pregnant women to an influenza epidemic resulted in an excess number of their offspring developing schizophrenia years later (Barr et al. 1990; O'Callaghan et al. 1991*b*), although other studies failed to find this association (Torrey et al. 1991).

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