Subtle Signs of Prenatal Maldevelopment of the Hand Ectoderm in Schizophrenia: A Preliminary Monozygotic Twin Study

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Genes that predispose to psychosis may act by making individuals more vulnerable to the disruptive effects of various prenatal insults. Fetal organogenesis is mostly completed in the first prenatal trimester. The second trimester is a critical period of massive neuronal migration from the periventicular germinal matrix to the cortex. A peripheral appendage developing simultaneously with this neural migration to the cortex is the distal upper limb. The ectodermal cells of the fetal upper limb migrate to form the hand skin during the fourth and fifth months of gestation (first two-thirds of the second prenatal trimester). Discrepancies in hand morphology between two identical (monozygotic [MZ]) co-twins may be temporal markers, that is, the "fossilized" evidence of various ischemic and other nongenetic insults that may have affected one fetus more than his MZ co-twin during that early part of the second trimester. In twins, prenatal insults (e.g., ischemia) frequently do not affect both co-twins to the same extent, so we examined seven putative markers of prenatal injury to the hand in 24 MZ twin pairs discordant for schizophrenia or delusional disorder. Compared with well co-twins, the affected co-twins had significantly higher total scores of fourth- and fifth-month dysmorphological hand anomalies.

Introduction

Recent epidemiologic studies suggest that some patients with schizophrenia may have been exposed to a physical insult during the second prenatal trimester (Mednick et al 1988). The second trimester is a critical period of massive neural migration from the periventricular germinal matrix to the cortex (Jakob and Beckmann 1986; Rakic 1988; Friede 1989). Organogenesis is mostly completed in the first trimester, before the massive neural migration begins (Hamilton et al 1972; Gluck 1977). One of the few organs whose prenatal development is simultaneous with the neuronal migration to the cortex is the distal upper limb. The ectodermal cells of the fetal upper limb migrate to form the hand

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skin between weeks 14 and 22 of gestation (i.e., during the first two-thirds of the second prenatal trimester) (Hamilton et al 1972; Schaumann and Alter 1976; Cummins and Midlo 1943). While under obvious genetic programming (Holt 1968), dermal cell migration is also sensitive to nongenetic (e.g., ischemic, toxic) insults in the relevant trimester of pregnancy (Newell-Morris et al 1989; Hamilton et al 1972; Wakita et al 1988; Schaumann and Alter 1976; Alter and Schulenberg 1966).

Conditions associated with such subtle dysmorphology in the distal upper limb include in utero viral infections (e.g., rubella and cytomegalovirus) (Achs et al 1966; Schaumann and Alter 1976; Purvis-Smith and Menser 1973; Wright 1973), fetal alcohol syndrome (Jones et al 1973), developmental reading disorder (Jamison 1988), and some cases of mental retardation (Wakita et al 1988; Catzel 1976). A detailed record of distal-upper-limb morphology can be easily obtained even in extremely symptomatic psychotic patients.

It has been documented that prenatal insults do not always affect both co-twins to the same extent (Hamilton et al 1972; Spellacy 1988). Intrapair discrepancies in dysmorphological signs between two monozygotic (MZ) co-twins may serve as temporal markers of intrauterine insults that affected on co-twin more than the other (Schaumann and Alter 1976).

We controlled for the substantial genetic contribution to hand ectodermal features by comparing the intrapair differences in MZ twin pairs discordant for schizophrenia or delusional disorder. We hypothesized that dysmorphology scores would be larger in the affected MZ twin.

Method

Subjects

The subjects were 24 pairs of MZ twins (48 individuals) from the United States and Canada recruited between 1983 and 1990 by the Twin Study Unit at NIMH as part of a multidimensional study of MZ twins discordant for schizophrenia—one twin diagnosed with schizophrenia and one MZ co-twin, normal. All twin pairs were monozygotic, as determined by 19 red blood cell antigens. Each individual was interviewed with the Structured Clinical Interview for DSM-III-R (SCID I and II) (Spitzer and Williams 1986) and all psychiatric diagnoses were made according to DSM-III-R criteria (American Psychiatric Association 1987). After complete testing, 23 pairs were determined as discordant for schizophrenia, and one was determined as discordant for delusional disorder. The minimal length of discordance was 4 years based on low rates of conversion beyond the 4-year period (Belmaker et al 1974). Nine of the 24 pairs were female and 15 were male. Quantitative Magnetic Resonance Brain Imaging data on the majority of these pairs has been recently published (Suddath et al 1990).

Procedure

Using standard inking techniques, we obtained handprints on both hands for all 48 co-twins (Faurot Crime Detection Equipment, Elmsford, NY). The handprints of each MZ pair were visually inspected for the presence of seven putative fourth- and fifth-month injury signs (dysmorphological signs) in the distal upper limb (one in the thumb, one in the distal phalanges, and five in the palmar ectoderm). The seven items were selected a priori and were based on our previous clinical dysmorphological observations in patients

Table 1. Clinical Evaluation of Prenatal Maldevelopment of Distal Upper Limbs of Monozygotic Twins Discordant for Schizophrenia

Smaller thumbs: smaller or shorter thumbs compared with the monozygotic co-twin
Microphalagia: distal phalanges smaller in size than the monozygotic co-twin
Broken proximal palmar line: proximal palmar line not continuous compared to monozygotic co-twin
Broken distal palmar line: distal palmar line not continuous compared with monozygotic co-twin
Thenar hypotrophy: thenar of palm much smaller in size compared to monozygotic co-twin
Fewer thenar ridges: much fewer lines in the thenar area compared to monozygotic co-twin
Malformed pattern: greater merging of the "triradius b" line and the "triradius c" line or more disrupted patterns compared to monozygotic co-twin

with mental retardation, developmental disorders, or chronic psychosis. Table 1 gives a description of each of the putative clinical signs. Throughout all handprint evaluations, the evaluator had no knowledge of which set of handprints belonged to a twin diagnosed with schizophrenia.

Statistical Analysis

For each of the seven signs, a score of zero was given for absence of a sign, and a score of one was given for presence of a sign for each of the 48 co-twins. This was done for each hand, resulting in seven indicators per hand (14 indicators per individual). The sum of all the indicators was derived for each subject, yielding a single ordinal "Hand Maldevelopment Score" (HMS) (range 0–14) for each of the 48 co-twins. We kept separate the right and left hand scores to address the issue of asymmetry. Each individual had a total "Right Hand Maldevelopment Score" (R-HMS) and a total "Left Hand Maldevelopment Score" (L-HMS) (each ranging from 0 to 7).

Monozygotic twin data represent a unique case in which each twin can serve as his or her twin's control. In order to test the null hypothesis that within each twin pair HMSs will not be different, a Wilcoxon signed-rank test (a nonparametric ordinal-paired test) was computed (Siegel 1956).

Next we analyzed asymmetry to test whether or not the intraindividual asymmetry would be greter in the affected twin group as compared to the well twin group. We tested for intraindividual asymmetry, within both the affected twin group and the well twin group, by comparing each individual's R-HMS with L-HMS. This too was tested using the Wilcoxon signed-rank test.

The one-tailed p value was used for all tests because the direction of the differences was predicted a priori. We hypothesized that the HMS would be larger in the affected group, and that if intraindividual asymmetry differences were found, they would be within the affected group, and the R-HMS would be the larger of the two. Alpha was set at $p < 0.05$ for all analyses.

Results

The Wilcoxon sign-rank (paired test) computed on HMS was significant (sum of ranks with less frequent sign = 56.0, $p = 0.018$). Table 2 depicts the median, mean, and standard deviation for HMS, L-HMS and R-HMS in the affected and well twin groups, and Table 3 shows the list of the seven, separate dysmorphological signs in order of their

Table 2. Median, Mean, and Standard Deviation for Hand Maldevelopment Scores (HMS), Left-Hand Maldevelopment Scores (L-HMS), and Right-Hand Maldevelopment Scores (R-HMS) in the Affected and Unaffected Twin Groups

	HMS	L-HMS	R-HMS
Affected twin group (n = 24)	Median 2[a] Mean 2.9 ± 2.0	Median 1 Mean 1.3 ± 1.0[b]	Median 1 Mean 1.7 ± 1.4[b]
Unaffected twin group (n = 24)	Median 0.5[a] Mean 1.3 ± 2.0	Median 0 Mean 0.7 ± 1.1	Median 0 Mean 0.6 ± 1.1

[a] $p < 0.05$..
[b] $p < 0.10$.

percent-prediction accuracy. Both analyses performed to test for intraindividual asymmetry differences within the two groups (L-HMS vs R-HMS) did not reach statistical significance (affected group $p = 0.08$, unaffected group $p = 0.31$).

Discussion

Hand Maldevelopment Scores in the affected [symptomatic] co-twins were in the hypothesized direction (i.e., higher). The median Hand Maldevelopment Score in the affected co-twin group was four times the magnitude of the median in the unaffected (well) co-twin group.

We also hypothesized that, if intraindividual asymmetry differences were found, they would be within the affected group and the right-hand maldevelopment score would be the larger of the two. We found a trend in the hypothesized direction (maldevelopment of the left hemisphere-drive structure more pronounced). This trend is consistent with a prenatal brain process that may have affected the development of the patients' left hemispheres to a greater degree, but is essentially bilateral.

Intrapair discrepancies in hand morphology in MZ co-twins are temporal markers; that is, the "fossilized" results of random minor, mostly unrecognized insults that take place during the second trimester (Cummins and Midlo 1943; Schaumann and Alter 1976). Dysmorphological hand maldevelopment signs are unaffected by medication, alcohol, or drug abuse and are easily differentiated from scars and effects of malnutrition or smoking. These signs are not permanently affected by postnatal insults, such as burns, to the subject (Hamilton et al 1972; Holt 1968; Federal Bureau of Investigation 1984).

Table 3. List of the Seven Dysmorphological Signs in Order of Percent Prediction Accuracy[a]

	Indicator	Percent accuracy
1	Broken proximal palmer line	88.0
2	Microphalagia	78.0
3	Broken distal palmer line	71.4
4	Thenar hypothrophy	71.0
5	Smaller thumbs	70.0
6	Malformed patterns	61.0
7	Fewer thenar ridges	57.1

[a]Percent Prediction Accuracy = the number of correct predictions divided by the total number of predictions for that specific sign (ties omitted).

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Dermatoglyphic measures as clinical or genetic tools have been surpassed by newer methods. However, dermatoglyphic and related dysmorphological measures are used in current prenatal-injury research (Newell-Morris et al 1989; Wakita et al 1988) and serve as useful markers of a deleterious intrauterine experience (Hamilton et al 1972; Alter and Schulenberg 1966; Catzel 1976). Dermatoglyphic and related dysmorphological measures are most powerful when the genetic variance is fully controlled as in this study.

Studies of discordant MZ twins have played a central role in sorting out the genetic and environmental variance in psychotic illness such as schizophrenia. Recent studies of a portion of this twin group have shown that the affected co-twin has larger ventricles and smaller temporal-lobe tissue compared with the nonaffected co-twin (Suddath et al 1990). Such important findings localize the insult (in schizophrenia) in space but not in time, that is, the brain cell loss could have occurred anytime prior to the scan. The study reported here utilized, for the first time, the twin strategy to localize the insult in time. Such localization in time may be necessary to obtain a lever on primary prevention of schizophrenia. Insults in the second trimester of pregnancy that could result in dysmorphological hand anomalies include ischemia, anoxia, anemia, toxic exposure, twin transfusion syndrome, and various infectious insults. All the above-listed epigenetic insults during the second trimester can possibly increase the expressivity of a genetic vulnerability to various human disorders, including psychotic disorders.

Genetic research in schizophrenia is confounded by the obvious presence of a strong nongenetic contribution to causality (Gottesman et al 1982; Kennedy et al 1988; Suddath et al 1990). Genes that predispose to psychosis may act by making individuals more vulnerable to the disruptive effects of various prenatal insults. The etiology of schizophrenia in twins is unlikely to be different from that of singletons (Gottesman et al 1982). Furthermore, our findings are consistent with other studies of physical anomalies in singletons with schizophrenia (Green et al 1989). Unaffected twins in MZ twin pairs discordant for schizophrenia are considered to be examples of "unexpressed genotypes of schizophrenia," presumably because they had not encountered a putative environmental "stressor" or "releaser" (Gottesman 1989). The nature of the "stressors" or "releasers" has long been debated (Gottesman et al 1982). This qualitative clinical dysmorphological study suggests that high scores of fourth- and fifth-month [second trimester] injury signs are associated with the adult onset of psychotic disorders in genetically predisposed individuals when compared with unaffected genetically identical controls.

Recent epidemiologic data suggest that at least some patients within the schizophrenic syndrome have been exposed to brief second-trimester insult, which may be a few days long (Mednick et al 1988) or even shorter (Lohr and Bracha 1989). The fact that not all schizophrenic co-twins in this study show dysmorphological evidence of fourth- and fifth-month insult is not surprising; distal-upper-limb-cell migration and cortical-cell migration are only partly overlapping. The migration of neurons from the periventricular germinal matrix to the cortex continues after the upper-limb-dermal migration is completed, and ***late*** second-trimester prenatal insults do not produce visible hand maldevelopment, although they do interfere with cortical cell-migration. Also, the length of discordance in this study was as low as 4 years. Although rates of conversion to concordance beyond the 4-year period are low (Belmaker et al 1974), at least one of the twin pairs in the present study may eventually turn out to be concordant for schizophrenia (based on risk rates). Follow up of this sample will be essential. This preliminary clinical study is limited by its qualitative nature. Quantitative studies of these and other similar prenatal injury signs in MZ twins discordant for mental illness are warranted.

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