Prenatal Growth Markers in Schizophrenia: A Monozygotic Co-Twin Control Study

James O. Davis, Ph.D., and H. Stefan Bracha, M.D.

Objective: This co-twin study investigated monozygotic twins who were discordant for schizophrenia for evidence of prenatal growth differences between the affected and well co-twins. Method: Four dermatoglyphic markers of prenatal growth were obtained by established procedures from 26 monozygotic twin pairs discordant for schizophrenia, 13 monozygotic twin pairs concordant for schizophrenia, and several normal monozygotic twin samples. Results: The a-b ridge count differences between the affected and well co-twins were greater than those found for concordant and normal monozygotic pairs. In comparison with their well co-twins, the affected twins, in discordant pairs, had developed fewer epideral ridges in the a-b interdigital area of their right palms. In contrast, no significant differences were found between the affected twins and their well co-twins on markers associated with fetal development before 13 or after 15 weeks estimated gestational age. Conclusions: Because the a-b ridges are known to complete development between 13 and 15 weeks estimated gestational age, the results provide physical evidence suggesting that the schizophrenia-affected monozygotic twins alone experienced a time-specific and time-limited dysgenesis during this time. Commonalities in the ontogeny of epidermal and neurological structures are discussed.


Several lines of schizophrenia research have investigated possible environmental influences during patients’ prenatal development. For example, greater prevalence of schizophrenia in the offspring was associated with second trimester exposure to events including influenza epidemics (1), maternal grief due to death of the spouse (2), and maternal infections (3–6). Patients’ obstetric problems (7, 8) and brain anomalies (9, 10) were also thought to be possible evidence of developmental problems during the second trimester.

In related work, affected and well co-twins in schizophrenia-discordant monozygotic twin pairs have been compared for possible early developmental differences (8, 10–16). These co-twin control studies employed the schizophrenia-discordant monozygotic twin pairs panel recruited by the National Institute of Mental Health (NIMH) Twin Study Unit (14), and, with control of genotype (13, 17, 18), it was possible to demonstrate that the affected twins had more brain and neurological anomalies (8, 10, 14). However, the affected twins did not have significantly more minor physical anomalies, obstetric complications, or lower birthweights, which would have been additional evidence of developmental difficulties (14). Apparently, these last three traits are not exclusively associated with second trimester development (13, 14, 19–21).

To further explore the timing of developmental difficulties, a co-twin study would especially benefit from use of selected developmental markers associated with narrow and specific prenatal periods. Several dermatoglyphic measures can provide such information about the fetal time periods most associated with schizophrenia (11, 12, 14, 21–24). Figure 1 identifies the developmental timelines and the estimated gestational ages for completion of finger patterns, finger ridge counts, a-b ridge counts, and adt angles (23, 24). Figure 2 illustrates the last two markers and the methods for assessment. These four dermatoglyphic markers are affected by fetal growth complications. For example, a higher number of finger whorl patterns were associated with prenatal infections (25–29), while greater whorl frequency variability, a-b interdigital ridge count asymmetry, and adt angle variability were associated with fetal alcohol syndrome (30–32). Other examples of dysgene-
sis included lower \( a-b \) ridge counts and wider \( atd \) angles in subjects selected for prenatal exposure to rubella and evidence of rubella stigmata (25, 33). In addition, greater \( atd \) angles, \( a-b \) asymmetry, finger pattern asymmetries, and ridge count asymmetries were reported in dyslexia (34–36), which, like schizophrenia, has been associated with prenatal complications including viral infections (36). In summary, prenatal complications have been associated with both dermatoglyphic anomalies and greater risk of schizophrenia, as well as other conditions.

Previous studies suggest that dermatoglyphics may help identify the timing of a prenatal dysgenesis in schizophrenia. Three studies reported \( a-b \) ridge count asymmetry in schizophrenic patients (37–39), which would implicate the period before 15 weeks estimated gestational age. In addition, in one of the NIMH co-twin panel studies, Bracha et al. (12) found that schizophrenia-discordant monozygotic twins varied more than did seven normal monozygotic twin pairs on total finger ridge counts, which could push the time back to before 13 weeks (23, 24). However, we have found reason to question the finger ridge count effects. The normal monozygotic twins were seven pairs recruited for the NIMH twin panel, and we have become aware that these normal monozygotic twins appear to have had less than representative total finger ridge counts. Their mean total finger ridge count of 150.00 (SD = 30.40) differed significantly from that reported for 400 North Americans by Schaumann and Alter (22) (mean = 131.65, SD = 50.95) (t = 2.16, df = 414, p < 0.02, two-tailed). In contrast, the total finger ridge counts of the schizophrenia-discordant monozygotic twins were more typical (mean = 135.70, SD = 31.72) (t = 1.07, df = 461, p = 0.14, two-tailed). We have calculated a very high intraclass correlation for the schizophrenia-discordant monozygotic twins (r = 0.98) on the basis of the published data (12). It follows logically that the schizophrenia-discordant monozygotic twins’ total finger ridge count could not be considered less typical than would be expected with normal development. This realization caused us to seek larger, published twin samples for new comparisons and caused our interest to focus on the \( a-b \) interdigital ridge count because of the previous findings of \( a-b \) asymmetry mentioned earlier in this article (37–39). In the absence of finger ridge count anomalies, \( a-b \) ridge count anomalies would support a second trimester timing of developmental divergence. We hypothesized that the co-twin control study method could evaluate such dermatoglyphic differences within schizophrenia-discordant monozygotic twins.

METHOD

For the present study, we took advantage of the extensive literature about epidermal ridge development to employ the four dermatoglyphic markers in figure 1 as "chronomarkers." To investigate the development of schizophrenia-discordant monozygotic twins affected by schizophrenia, we returned to the NIMH twin panel of monozygotic twins (14). Co-twin comparisons provided control of genotype (13, 17, 40), while schizophrenia-discordant monozygotic twins, normal monozygotic twins, and nontwins allowed additional comparisons.

Subjects

The NIMH twin panel included 26 pairs of schizophrenia-discordant monozygotic twins (11 female and 15 male), who had been discordant at least 5 years (mean = 14.0) at the time of testing. The panel also included 13 schizophrenia-concordant monozygotic pairs (three female and 10 male), in whom the co-twins were diagnosed as schizophrenic, or, in three cases, as schizophrenial with histories of hallucinations or antipsychotic medication, and seven control pairs of normal monozygotic twins (four female and three male). These 46 monozygotic pairs were originally recruited for a large multidimensional study organized by the Twin Studies Unit at NIMH. After complete description of the study to the subjects, written informed consent was obtained (14).

This panel of twins has been exhaustively studied and described elsewhere (8, 10–16). After being recruited through the newsletters of the National Alliance for the Mentally Ill and the Schizophrenia Society of Canada (formerly Canadian Friends of Schizophrenics), the twins traveled to Washington, D.C., for 4 or 5 days of testing.
TABLE 1. Correlation of Dermatoglyphic Prenatal Growth Markers Between Normal Monozygotic Twins and Monozygotic Twins Discordant or Concordant for Schizophrenia*  

<table>
<thead>
<tr>
<th>Monzygotic Twin Group</th>
<th>Absolute</th>
<th>a-b</th>
<th>atd</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Finger</td>
<td>Ridge Counts</td>
<td>Count</td>
</tr>
<tr>
<td>Normal (26 twin pairs)</td>
<td>0.93b</td>
<td>0.96c</td>
<td>0.85d</td>
</tr>
<tr>
<td>Schizophrenia discordant (13 twin pairs)</td>
<td>0.93</td>
<td>0.99</td>
<td>0.52c</td>
</tr>
<tr>
<td>Schizophrenia concordant (13 twin pairs)</td>
<td>0.90</td>
<td>0.98</td>
<td>0.87</td>
</tr>
</tbody>
</table>

*All correlations are significantly greater than 0; p<0.005, one-tailed test.

The correlations were used to assess similarity of twin pairs for the four dermatoglyphic traits. These correlations were compared by the t to z transformations method (46). Group means were tested with two-tailed Student's t tests. We have set the p values for these tests at 0.01, considering the fact that we are interested in four different dermatoglyphic markers. When repeated measures analysis of variance (ANOVA) was performed, cell means were tested with Fisher's least significant difference repeated measures ANOVA.

RESULTS

Similarity of Twin Dermatoglyphic Development in Utero

The intraclass correlations for the four dermatoglyphic chronomarkers are reported for each twin group in table 1. All correlations were significantly greater than zero. Among the four markers, only the schizophrenia-discordant monozygotic intraclass correlation for a-b interdigital ridge counts differed from the more twin-like appearances of the normal and schizophrenia-concordant monozygotic twins, suggesting that developmental differences were occurring between 13 and 15 weeks estimated gestational age. When compared with the 142 normal monozygotic twin pairs (r=0.85) reported by Rose et al. (43), the schizophrenia-discordant twins' a-b ridge counts (r=0.49) were clearly less twin-like (z=2.82, p<0.003). The a-b ridge count correlation was also significantly lower (z=2.32, p<0.01) for the schizophrenia-discordant (r=0.49, N=19) than for the schizophrenia-concordant (r=0.89, N=13) twins.

The intraclass correlations were used to create dermatoglyphic profiles that illustrate the developmental trends for all twin groups (figure 3). The most apparent decline in intrapair similarity in figure 3 can be seen in the 36% reduction in the common variance for the schizophrenia-discordant monozygotic twins' a-b interdigital ridge counts (r=0.49), when compared to the normal twins (r=0.85).

As planned, each dermatoglyphic variable was also assessed for within-pair differences, including symmetry, and between-twin-group differences as reported later according to estimated gestational age.

Finger Pattern Development Before 10.5 Weeks Estimated Gestational Age

No significant differences for finger tip patterns occurred between the well and affected schizophrenia-dis-
CORD TANS that might suggest that developmental differences began before 10.5 weeks estimated gestational age. Whorls for affected (mean=2.60) and well (mean=2.72) twins were not significantly different (paired t=0.55, df=25) and were comparable to the 2.62 mean whorls reported for 400 normal North American nontwins (22).

No significant trends for asymmetry of finger patterns were found. For all twin groups, the percent of homologous fingers with matching patterns fell within the normal range of 74% to 82% reported for numerous populations (22). Pattern symmetry was 80.3% for schizophrenia-discordant twins and 79.5% for the concordant twins, and the normal NIMH twins matched patterns on 81.4% of their homologous fingers. Pattern symmetry for the affected schizophrenia-discordant twins was 84.0% (SD=16.4), while well twins matched 76.6% (SD=19.1). These differences were not in a direction to suggest a developmental delay in the affected twins.

Finger Ridge Development Before 13 Weeks Estimated Gestational Age

The epidermal ridges on the finger tips that complete development by 13 weeks estimated gestational age were highly similar for the affected schizophrenia-discordant twins and their well co-twins and correlated highly (r=0.99). The mean absolute finger ridge counts of affected (mean=163.68, SD=88.46) and well (mean=162.36, SD=87.38) schizophrenia-discordant twins were nearly identical (paired t=0.44, df=25, p=0.33). The well schizophrenia-discordant twins had a little less symmetry of absolute finger ridge count (mean absolute left-right difference=17.89 ridges, SD=18.68) than the affected co-twins (mean=13.00, SD=12.18); however, the difference was not statistically significant, and it was not one to suggest a developmental delay in the affected twins (paired t=1.24, df=25, p=0.11).

As an additional check, the total finger ridge counts for the affected and well schizophrenia-discordant twins were compared and also found to be highly similar (r=0.98). The mean difference between affected twins' total finger ridge count (mean=120.81, SD=65.79) and well schizophrenia-discordant twins' ridge count (mean=122.50, SD=64.72) was extremely small (paired t=0.161, df=25, p=0.44).

Ridge Development Completed by 15 Weeks Estimated Gestational Age

The earliest significant dermatoglyphic differences to emerge between the affected schizophrenia-discordant twins and their well co-twins were found in the a-b interdigital area of the palms, which normally achieves complete development by 13 weeks estimated gestational age. The within-pair differences were greater for the schizophrenia-discordant twins (mean=7.58, SD=4.78) than for the schizophrenia-concordant twins (mean=3.15, SD=1.86) (t=3.16, df=30, p<0.001). The variability of the schizophrenia-discordant differences was greater as well (F=6.58, df=18, 12, p=0.001). At the request of a reviewer, we compared within-pair differences for female (mean=7.38, SD=4.27, N=9) and male schizophrenia-discordant twins (mean=7.31, SD=5.31, N=11); the gender differences were small and not statistically significant (t=0.15, df=18, p=0.44).

Table 2 shows the left and right a-b ridge counts for affected and well schizophrenia-discordant monozygotic twins. Asymmetry was revealed in a two-by-two repeated measures ANOVA, with diagnosis (affected versus well) by hand (left versus right). While there were no significant main effects for diagnosis (F=3.73, df=1, 18, p=0.07) or left versus right hand (F=1.78, df=1, 18, p=0.20), there was a significant diagnosis-by-hand interaction (F=6.71, df=1, 18, p=0.02). The interaction was created by the lower ridge count on the affected twins' right hands. The affected twins had 2.11 fewer ridges on their right than their left hands (Fisher's least significant difference t=3.35, df=18, p=0.002) and 3.05 fewer right-hand a-b ridges than their well co-twins (Fisher's least significant difference t=4.62, df=18, p<0.0001). The right-hand a-b ridge counts of the affected twins were 7% smaller than those of their well co-twins.

Within-pair differences in a-b symmetry were greater

<table>
<thead>
<tr>
<th>Hand</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>40.79</td>
<td>5.20</td>
<td>43.84</td>
<td>5.61</td>
</tr>
<tr>
<td>Left</td>
<td>43.00</td>
<td>3.78</td>
<td>43.63</td>
<td>3.82</td>
</tr>
</tbody>
</table>

Table 2. The a-b Interdigital Ridge Counts for Affected and Well Co-Twins in 19 Monozygotic Pairs Discordant for Schizophrenia
for the schizophrenia-discordant twins (mean=7.63, SD=4.71, N=19) than they were for the concordant twins (mean difference=3.15, SD=1.86, N=13) (t=3.74, df=30, p=0.0009), or for the 314 normal twin pairs (mean difference=2.65, SD=2.44) from the work of Rose et al. (43) (t=4.57, df=332, p<0.0003). There was also greater variability for the schizophrenia-discordant within-pair a-b differences than for the concordant twins (F=6.38, df=18, 12, p<0.005) and the normal twins (F=3.72, df=18, 313, p<0.005).

Growth of the Hand After 15 Weeks Estimated Gestational Age

Relative palm lengths, as measured by the adt angles, indicated the affected schizophrenia-discordant twins (mean=88.25 degrees, SD=12.09) were not significantly different from their well co-twins (mean=87.08 degrees, SD=11.31) (paired t=0.66, df=11). One affected schizophrenia-discordant twin possessed adt asymmetry of 17 degrees, which exceeded the mean for adt asymmetry by more than four standard deviations. When this outlier was included in a statistical analysis, the affected twins tended to be less symmetrical (mean absolute left-right difference=4.17 degrees, SD=4.65) than their well co-twins (mean difference=1.58 degrees, SD=1.31) (paired t=1.86, df=11, p=0.05, two-tailed test). When the outlier was omitted from analysis, the adt asymmetry differences were clearly not significant (t=0.85, df=10, p=0.21).

On group comparisons, the schizophrenia-discordant twins' adt angles (mean=87.66 degrees, SD=11.47) were not significantly different from those of the concordant twins (mean=83.83 degrees, SD=11.11) (t=0.80, df=20, p=0.22). Even with the outlier, the within-pair differences in the adt angles for the discordant twins (mean=3.42, SD=4.21, N=12) were not significantly greater than those for the concordant twins (mean=2.82, SD=1.89, N=9) (t=0.44, df=19, p=0.33). No comparisons were made with the NIMH normal twins because adt data were complete for only three twin pairs.

DISCUSSION

To our knowledge, the a-b ridge count and a-b symmetry differences between affected and well schizophrenia-discordant monozygotic twins are the earliest markers of developmental differences that appear in schizophrenia-discordant monozygotic twins. These results suggest that developmental differences occurred in the period between 13 and 15 weeks estimated gestational age. Growth of schizophrenia-discordant monozygotic twins after 15 weeks appears similar for affected and well co-twins, at least as indicated by the adt angles; this is consistent with evidence that the twins did not differ markedly on birthweights, obstetric complications, minor physical anomalies, or several early childhood developmental traits (14). It is possible that the skeletal hand growth of the affected twins caught up after a limited period of delay. Such a phenomenon was reported in a case of interrupted fetal bone growth during maternal viral infection (47). In addition, it may be relevant that fetal immunocompetence begins in the third trimester, although generally the capacity to produce antibodies is poor until sometime after birth (48).

Alternative explanations have also been considered. There is a possibility that a-b ridge development is more susceptible to the embryopathic influence than are the other dermatoglyphic markers. The a-b ridges develop over a longer period of time than do the finger ridges (23, 24, 42) (figure 1). However, Martin et al. (49) reported that finger ridge symmetry is especially sensitive to environmental influence, and Penrose (50) observed that the adt angle is even more sensitive to environmental effects than is the a-b count. In addition, there is the fact that the affected twins' a-b reduction is not symmetrical in that it is seen on the right hand and not the left. Other asymmetrical development in the midgestation period is seen when the left cerebral hemisphere lags behind the right (51, 52). Could postmitotic mutation explain the schizophrenia-discordant monozygotic discordance for a-b ridges? It seems unlikely because it would require an implausibly high rate of mutation to explain the relatively high monozygotic twin concordance rate for schizophrenia (12). Finally, do schizophrenia-discordant monozygotic twins represent a special case unrelated to nontwins? Torrey et al. (14) offer much evidence that the lessons learned from the schizophrenia-discordant monozygotic twin studies will apply to nontwins.

These dermatoglyphic findings are especially interesting when considered with the neurological findings previously reported in this sample of schizophrenia-discordant monozygotic twins, which included reduced hippocampi-amygdales complexes, dilation of ventricles (10, 14), and higher neurological abnormality scores for the affected twins (13, 14). Both the neurological and the epidermal differences have been interpreted as evidence of a second trimester influence in schizophrenia (3, 6, 14, 20, 21, 29), and it is well known that they share many developmental features. Both develop from surface ectoderm (53) and experience rapid development between 12 and 16 weeks estimated gestational age (43). In addition, nerve growth factor influences the development of both the CNS (23, 54, 55) and the dermal ridges (23, 55). Moreover, nerve growth factor and epidermal growth factor are influenced by testosterone (34, 56, 57), and all three substances are present in both sexes and are functioning during dermatoglyphic development (58). Of special interest may be the putative effect of testosterone on asymmetric growth of the fetal brain, which favors the right hemisphere (59). In addition, epidermal growth factor is known to stimulate astrocyte division (60) after glia cells begin to differentiate at 12 weeks estimated gestational age (53, 61). The emerging astrocyte glia cells ultimately encircle the blood vessels serving the CNS, creating an important aspect of the blood-brain barrier (53). Finally, Roberts
JAMES O. DAVIS AND H. STEFAN BRACHA


15. Davis JO, Phelps JA: Twins with schizophrenia: genes or germ. Schizophr Bull 1995; 21:13–18


18. Phillips DIW: Twin studies in medical research: can they tell us whether diseases are genetic? Lancet 1993; 341:1008–1009


34. Glenden CS: Dermatoglyphics and the Geschwind hypothesis, I: theoretical background and palmar results of dyslexia, in Trends in Dermatoglyphic Research. Edited by Duram NM,
64. Torrey EF: Are we overestimating the genetic contribution to schizophrenia? Schizophr Bull 1992; 18:159–170