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Original article

Neurological soft signs and dermatoglyphic anomalies in twins with schizophrenia

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Abstract

Schizophrenia is associated with altered neural development. We assessed neurological soft signs (NSS) and dermatoglyphic anomalies (total a–b ridge count (TABRC) and total finger ridge count) in 15 pairs of twins concordant and discordant for schizophrenia. Within-pair differences in both NSS and TABRC scores were significantly greater in discordant compared to concordant monozygotic pairs. There was no significant difference in NSS and TABRC scores between subjects with schizophrenia and their co-twins without the illness. However, monozygotic discordant twins with schizophrenia had higher ABRCs on their right hands compared to their co-twins without the illness. These findings suggest that an unidentified environmental event acting between weeks 6 and 15 of gestation affects the development of monozygotic twins who go on to develop schizophrenia but does not have a corresponding effect on their co-twins who do not develop the illness. The effect of such an event on dermatoglyphic profiles appears lateralised to the right hand in affected twins.

Keywords: Schizophrenia; Aetiology; Neurological soft signs; Dermatoglyphics; Twins

1. Introduction

Neurological soft signs (NSS) and dermatoglyphic anomalies are two indices of neural maldevelopment that offer opportunities to study the relationship between nervous system development and schizophrenia [13,17].

NSS are subtle impairments in sensory integration, motor coordination and the sequencing of complex motor acts [17]. They are indicative of non-specific brain damage in a variety of medical and psychiatric conditions [18]. Persons with schizophrenia have more NSS than control subjects [6,9,24]—even at the first episode of illness prior to the administration of antipsychotic medication [5]. The aetiology of NSS is not completely understood, but they are thought to be subject to both genetic and environmental influences [21,24]. In monozygotic twin pairs discordant for schizophrenia, affected twins have more NSS than their unaffected co-twins [7]. The unaffected co-twins, in turn, have more NSS than control twins. This supports the importance of a genetic component in the aetiology of NSS, but also suggests that environmental factors are relevant.

The human hand starts to develop at 6 weeks gestation and epidermal ridges are fully formed by week 24 [4]. Altered dermatoglyphic profiles are found in a variety of congential disorders associated with environmental insult during this period including fetal alcohol syndrome [30] and congenital rubella [1]. Turek [28] reported reduced total finger ridge count (TFRC) and reduced total a–b ridge counts (TABRC) in schizophrenia. Subsequent studies have replicated the finding of reduced TABRC in singletons with schizophrenia [13–15] and one study reported a similar finding in twins [12].

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We have conducted a systematic, comparative examination of NSS and dermatoglyphic anomalies in monozygotic and dizygotic twins concordant and discordant for schizophrenia. We hypothesized that subjects with schizophrenia would have increased NSS scores, reduced TABRC and reduced TAFRC compared to their co-twins without the illness; and that within-pair differences in each of these measures would be greater in monozygotic discordant pairs than in monozygotic concordant pairs.

2. Methods

2.1. Subjects

Ethical (Research) Committee approval was obtained. In conjunction with the Health Research Board, we wrote to psychiatrists throughout Ireland, requesting that they contact us if they were aware of any pairs of twins in their care in which one or both twins had schizophrenia. After complete description of the study to the subjects, written informed consent was obtained.

2.2. Instrument

We established psychiatric diagnoses using the Structured Clinical Interview for DSM-IIIR [2,26]. Control status was defined as the absence of current or previous psychotic illness. Concordance was defined as the presence of schizophrenia or schizoaffective disorder in both twins [23]. Discordance was defined as the presence of schizophrenia or schizoaffective disorder in one twin and the absence of schizophrenia or schizoaffective disorder in their co-twin for a period of greater than 4 years. Zygosity was determined by the examination of 19 red blood cell antigens. We assessed NSS using the condensed neurological examination [24], which comprises 19 items, of which seven are bilateral. Items are rated as present or absent (1 or 0) on ordinal scales having maxima between 2 and 6. During the neurological examination, patients were given a maximum of three demonstrations/explanations of each test. If they were unable to comply with any individual test, the entire examination was deferred until the patient was capable of following the instructions. We assessed dermatoglyphics using bilateral fingerprints obtained using an inkless method ('Pocket Print'; Printiscan Verification Systems Ltd., UK). We examined two quantitative variables [11]: TABRC (the number of ridges crossing a line between the a and b palmar triradii) and TFRC (the sum of each individual finger ridge count). Dermatoglyphics were rated blind to diagnosis.

2.3. Data analysis

We used two-tailed *t*-tests for paired samples to test for significant differences in dermatoglyphic scores and NSS scores within pairs and two-tailed *t*-tests for independent samples to compare between pairs. We used 3-factor analysis of variance (ANOVA) to examine the effects of gender, zygosity and concordance on the absolute within-pair score differences. We also investigated for synergy between these three factors. We used Pearson correlation coefficients to examine correlations between variables. We analyzed data using the Statistical Package for the Social Sciences [27].

3. Results

3.1. Sample

The sample consisted of 15 twin pairs in which one or both subjects had schizophrenia. Mean age was 32.7 years (S.D. = 7.2). Ten pairs (67%) were male and five pairs (33%) were female. There were no mixed gender pairs. There were eight monozygotic pairs, of which three pairs were concordant for schizophrenia or schizoaffective disorder. In the five monozygotic discordant pairs, two subjects who were unaffected by schizophrenia had a diagnosis of depression and one had a diagnosis of alcohol dependence syndrome. There were seven dizygotic pairs, of which one pair was concordant for schizophrenia. In the six dizygotic discordant pairs, three subjects who were unaffected by schizophrenia had a diagnosis of alcohol dependence syndrome and one had a diagnosis of depression.

3.2. Neurological soft signs

In the total sample, NSS score did not discriminate ($t = 1.8$; $P = 0.12$) between those with schizophrenia (7.2, S.D. = 4.9) and those without the illness (4.7, S.D. = 3.6). In the six dizygotic discordant pairs, NSS score did not differ between subjects with schizophrenia (4.7, S.D. = 3.7) and those without the illness (3.5, S.D. = 1.9; $t = 0.7$; $P = 0.5$). In the eight monozygotic pairs, mean absolute within-pair differences were significantly greater ($t = 2.6$; $P = 0.04$) in the five discordant (7.8, S.D. = 4.2) compared to the three concordant (1.3, S.D. = 0.6) pairs. Subjects with schizophrenia in the monozygotic discordant group showed a higher mean NSS score that did not differ significantly from that of their co-twins without the illness (Table 1). ANOVAs over all the subjects indicated that gender, zygosity and concordance did not account for a significant proportion of variance in absolute within-pair difference in NSS scores (*P* value for the *F* ratio being >0.05).

3.3. Total a–b ridge count (TABRC)

In the total sample, TABRC did not discriminate ($t = 0.5$; $P = 0.4$) between those with schizophrenia (84.1, S.D. = 11.6) and those without the illness (80.1, S.D. = 13.6). In the six dizygotic discordant pairs, TABRC did not differ between subjects with schizophrenia (91.0, S.D. = 8.8) and those without the illness (86.2, S.D. = 8.3; $t = 0.4$; $P = 0.6$). In

Table 1
Neurological soft sign scores in monozygotic twins discordant and concordant for schizophrenia

	Twin with schizophrenia	Twin without schizophrenia	Difference
Discordant pairs			
A	14	7	+7
B	19	9 [a]	+10
C	0	12 [a]	–12
D	1	0 [b]	+1
E	12	3	+9
Absolute mean (S.D.) *	9.2 (8.3)	6.2 (4.8)	7.8 (4.2)
Concordant pairs			
F	10	9	1
G	10	8	2
H	7	6	1
Absolute mean (S.D.)	9 (1.7)	7.7 (1.5)	1.3 (0.6)

S.D.: standard deviation.
* $P = 0.50$ on two-tailed t-test for paired samples ($t = 0.7$).
[a] SCID diagnosis of depression.
[b] SCID diagnosis of alcohol dependence syndrome.

the eight monozygotic pairs, mean absolute within-pair differences were significantly greater ($t = 3.3$; $P = 0.02$) in the five discordant (8.4, S.D. = 2.7) compared to the three concordant (4.0, S.D. = 1.0) pairs. Subjects with schizophrenia in the monozygotic discordant group had significantly higher ($t = 6.9$; $P = 0.002$) ABRCs than their co-twins without the illness (Table 2). This effect was more pronounced on the right hand ($t = 9.9$; $P = 0.001$) than on the left hand ($t = 2.2$; $P = 0.09$). ANOVAs over all the subjects indicated that gender, zygosity and concordance did not account for a significant proportion of variance in absolute within-pair difference in TABRC scores (P value for the F ratio being >0.05).

3.4. Total finger ridge count (TFRC)

In the total sample, TFRC did not discriminate ($t = 0.5$; $P = 0.5$) between those with schizophrenia (138.9, S.D. = 49.2) and those without the illness (151.3, S.D. = 42.5). In the eight monozygotic pairs, there was no difference in mean absolute within-pair difference in the five discordant (12.2, S.D. = 9.5) compared to the three concordant (5.0, S.D. = 3.6; $t = 0.9$; $P = 0.2$) pairs. There was no significant difference between FRC counts for the left and right hands. ANOVAs over all the subjects indicated that gender, zygosity and concordance did not account for a significant proportion of variance in absolute within-pair difference in FRC scores (P value for the F ratio being >0.05).

There was no correlation between NSS and either TABRC (Pearson correlation coefficient –0.2; $P = 0.4$) or TFRC (Pearson correlation coefficient –0.2; $P = 0.3$). Nor was there any correlation between TABRC and TFRC (Pearson correlation coefficient 0.1; $P = 0.8$).

Table 2
Total a–b ridge counts in monozygotic twins discordant for schizophrenia

Hand	Twin with schizophrenia	Twin without schizophrenia	Difference
TABRC			
A	92	84	+8
B	89	80 [a]	+9
C	70	66 [a]	+4
D	99	88 [b]	+11
E	62	52	+10
Absolute mean (S.D.) *	82.4 (15.7)	74.0 (14.8)	8.4 (2.7)
Left hand			
A	45	42	+3
B	42	41 [a]	+1
C	34	35 [a]	–1
D	51	46 [b]	+5
E	31	26	+5
Absolute mean (S.D.) **	40.6 (8.1)	38.0 (7.8)	3.0 (2.0)
Right hand			
A	47	42	+5
B	47	39 [a]	+8
C	36	31 [a]	+5
D	48	42 [b]	+6
E	31	26	+5
Absolute mean (S.D.) ***	41.8 (7.8)	36.0 (7.2)	5.8 (1.3)

S.D.: standard deviation.
* $P = 0.002$ on two-tailed t-test for paired samples ($t = 6.9$). ** $P = 0.09$ on two-tailed t-test for paired samples ($t = 2.2$). *** $P = 0.001$ on two-tailed t-test for paired samples ($t = 9.9$).
[a] SCID diagnosis of depression.
[b] SCID diagnosis of alcohol dependence syndrome.

4. Discussion

We found that within-pair differences in both NSS and TABRC scores were significantly greater in discordant compared to concordant monozygotic pairs. There was no significant difference in NSS scores between subjects with schizophrenia and their co-twins without the illness, while monozygotic discordant twins with schizophrenia had significantly higher ABRCs on their right hands compared to their co-twins without the illness.

Limitations of this study include the relatively small sample size, the lack of a comparison group of control twins, the absence of information on medication status, and the use of multiple comparison tests. In addition, some of the twins who were unaffected by schizophrenia fulfilled diagnostic criteria for other disorders such as alcohol dependence syndrome and depression. Strengths of this study include the twin methodology, the use of Structured Clinical Interview for DSM-IIIR [2,26] for diagnosis and blind rating of dermatoglyphics.

4.1. Neurological soft signs

Several studies have demonstrated increased NSS in singletons with schizophrenia [5,6,9,24] and two studies have demonstrated similar findings in twins with schizophrenia relative to their unaffected co-twins [7,20].

Cantor-Graae et al. [7] studied NSS in 22 monozygotic twin pairs discordant for schizophrenia, and found that affected twins had more NSS than their unaffected co-twins, and that unaffected co-twins, in turn, had more NSS than control monozygotic twins. The authors suggested that NSS may be a manifestation of a genetic neuropathogenic influence common to both ill and well co-twins, and that other, non-genetic factors are necessary for the development of schizophrenia in the affected twin. Our findings support this model: we found that mean NSS scores were grossly correlated with inferred genetic risk of schizophrenia in subjects unaffected by the illness, with unaffected monozygotic co-twins having higher mean NSS scores than unaffected dizygotic co-twins. This is consistent with the results of Baare et al. [3] and Cannon et al. [8] who reported similar correlations between structural brain anomalies and genetic proximity to a patient with schizophrenia in their twin samples (unaffected monozygotic co-twin > unaffected dizygotic co-twin > control twin).

This model suggests that subjects who developed schizophrenia may have experienced an additional non-genetic aetiological event, which further affected neurological function, leading to higher NSS scores. This is supported by the findings of Niethammer et al. [20] who used the Heidelberg Scale [25] to study NSS in 13 pairs of discordant monozygotic twins and found that unaffected monozygotic co-twins had significantly higher NSS scores than control twins.

Our finding of greater within-pair differences in NSS in discordant compared to concordant monozygotic pairs provides further support for this model. Our failure to demonstrate increased NSS in subjects with schizophrenia compared to their co-twins without the illness may be related to small sample size. It is notable that in four out of the five monozygotic discordant pairs, the twin with schizophrenia had more NSS than their co-twin without the illness (Table 1). In addition, our analysis did not take account of the possible effect of medication on NSS scores in schizophrenia [16].

4.2. Dermatoglyphics

Our dermatoglyphic findings contrast with those of several singleton studies [13–15,28] and one twin study [12], which found lower TABRCs in persons with schizophrenia. The greater within-pair difference in TABRC in discordant versus concordant monozygotic pairs which we found was similar in magnitude but opposite in direction to that reported by Davis and Bracha [12], who studied 26 monozygotic twin pairs discordant for schizophrenia. In our study, however, the trend towards higher TABRC was very consistent in this group: twins with schizophrenia had higher TABRCs than their co-twins without the illness in all monozygotic discordant pairs (Table 2). Moreover, this effect was consistent throughout sample subgroups, including dizygotic discordant pairs (six pairs) and monozygotic discordant pairs (five pairs). Unlike NSS, TABRC did not correlate with inferred genetic risk of schizophrenia in subjects unaffected by the illness. This is consistent with the involvement of a significant environmental component in the observed disturbance of TABRC.

The increased overall TABRC was attributable to increased ABRC on the right hand only, consistent with the suggestion that schizophrenia is associated with disturbed lateralisation [5,10,22]. This is also consistent with a recent report of neurodevelopmental instability in schizophrenia as evidenced by dermatoglyphic fluctuating asymmetry in singletons with the illness [22].

Our TFRC findings are consistent with those of Davis and Bracha [12] who found no significant differences in TFRC in monozygotic discordant twins. Interestingly, Torrey et al. [29] found reduced TFRC in twins with schizophrenia who had early divergence for the illness (seven pairs). Their finding may be specific to an ‘early divergent’ subgroup of patients.

Overall, studies of dermatoglyphics in twins with schizophrenia support the view that a significant environmental event or insult occurs before week 15 of gestation, by which time a–b ridges are fully formed. This event does not affect both twins equally. Our results suggest that even in twins who are affected by such events, the effect is not always the same: we found raised TABRCs where others found reduced TABRCs. This may attributable to an unrecognised cohort effect related, perhaps, to different environmental exposures in populations living in different geographical areas or born in different decades.

5. Conclusion

The present confluence of NSS and TABRC findings suggests that an unidentified environmental event acting between weeks 6 and 15 of gestation significantly affects the development of monozygotic twins who go on to develop schizophrenia but does not have equal effect on their co-twins who do not develop the illness. This time-frame is consistent with that (8–22 weeks) deriving from our studies of craniofacial dysmorphology in schizophrenia [19]. Our findings suggest that the effect of this event on dermatoglyphic profiles is lateralised to the right hand in affected twins.

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