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Cerebral Ventricular Enlargement in Non-Genetic Schizophrenia: A Controlled Twin Study

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Summary: In a group of schizophrenics of twin birth, no evidence of ventricular enlargement was found where there was a family history of major psychiatric disorder. Among those schizophrenics without such a family history, cerebral ventricular size was significantly increased ($P < 0.01$), and there was also evidence of birth complications. Among normal control twins, those who reported complicated births had significantly larger ventricles.

An increased frequency of cerebral abnormalities, in particular cerebral atrophy or ventricular enlargement, has been demonstrated among schizophrenics since the 1920s (Haug, 1962). Since computerised tomographic (CT) scanning revolutionized the study of the brain, comparatively large groups have been studied, and an assessment of the evidence from many sources (*Lancet,* 1982) suggests that a significant subgroup of schizophrenics may show a mild-to-moderate degree of ventricular enlargement. However, the pathogenesis of the enlargement is obscure: attempts to delineate this group of patients more clearly by neuropsychological testing, clinical symptoms or course have met with only limited success; furthermore, Rieder *et al* (1983) have recently drawn attention to the occurrence of ventricular enlargement in *other* psychiatric disorders, such as bipolar illness or schizoaffective psychosis.

The genetic contribution to the aetiology of schizophrenia has been established over generations of research (reviewed by Gottesman and Shields in 1982). The pattern of inheritance can best be described as multifactorial: random or specific environmental factors coincide and interact with many unspecified genes, some of which may have major effects. Some possible environmental precipitants have been identified in schizophrenia, e.g. obstetric complications (McNeil and Kaij, 1978); and as long ago as 1932 Schulz noted that among schizophrenics for whom there were obvious organic precipitants genetic predisposition (indicated by a family history of psychiatric disorder) was significantly lower than among schizophrenics without antecedent illness or injury (Slater and Cowie, 1971). It is possible that those with significant genetic predisposition require little else to become psychotic; that others with less genetic liability become psychotic only after additional environmental influence; and that some people develop a psychosis secondary to environmental influences alone (Reveley and Reveley, 1983).

Our 1982 study of identical (monozygotic) twins discordant for schizophrenia (Reveley *et al,* 1982) was an attempt to assess the relative contributions of genes and environment to cerebral ventricular size in schizophrenia. Monozygotic (MZ) twins share all their genes, so the intra-pair differences must be the result of environmental influences. We found that cerebral ventricular size was under a high degree of genetic control among normal twins, with relatively small intra-pair differences; but among MZ pairs discordant for schizophrenia the mean intra-pair difference was significantly greater, and the schizophrenics had consistently larger cerebral ventricles than both their non-schizophrenic co-twins and the normal controls. This suggested that ventricular enlargement in schizophrenia reflects the presence of an environmental process, and led us to hypothesize that schizophrenics with manifest genetic predisposition (such as those with other ill family members) would not show ventricular enlargement.

Schizophrenics from identical twin-pairs are a useful group in which to test this hypothesis, since separate genetic and environmental influences are particularly apparent among MZ twins, for several reasons. Firstly, twins are especially liable to perinatal cerebral injury (Norman, 1982). In a previous study (Reveley *et al,* 1981) we found psychosis to occur significantly more often among twins when the co-twin died in the perinatal period, compared with cases where both survived past puberty: it appears that the perinatal

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factors leading to the death of one twin may have contributed to the later development of psychosis in the other. Secondly, genetic predisposition to schizophrenia in MZ twins may be assessed both from the family history of psychiatric disorder (family other than the co-twin) and also from the psychiatric status of the co-twin.

In this study we have attempted to assess the relationships of (1) genetic predisposition, (2) organic cerebral insults, and (3) chronicity and severity of the schizophrenic illness to cerebral ventricular enlargement. We did not attempt to investigate the role of neuroleptics, since all but one of the schizophrenic subjects were taking them at the time of the study. Nor did we attempt to relate current symptomatology to ventricular size: the twins had been followed over many years and some had shown considerable variation in the clinical manifestations of their illness.

Method

Cerebral ventricular volume was assessed in 21 schizophrenics from 21 MZ twin-pairs and in 18 controls from 18 healthy MZ pairs.

The schizophrenics were diagnosed according to the *Research Diagnostic Criteria* (RDC) of Spitzer *et al* (1975) from information gathered by personal interviews according to the *Schedule for Affective Disorders and Schizophrenia* (Spitzer and Endicott, 1977), interviews with relatives, and the hospital records of all previous admissions. All the schizophrenic subjects had living MZ co-twins. In 12 cases (5 female, 7 male) there was no evidence that the co-twin was suffering or had ever suffered from schizophrenia or any psychotic illness; in 9 cases (6 female, 3 male) the co-twin met the RDC criteria for schizophrenia. Only one member of each concordant pair, the first to be scanned, was included in the present study.

MZ twins, identified from the Institute of Psychiatry normal volunteer twin register and selected to be as close as possible in age to the schizophrenics, were also asked to participate in the study: 18 pairs (9 male, 9 female) agreed. The first twin to have the scan from each pair was selected as a control.

All the twin-controls, schizophrenics and co-twins and, where possible, their mothers were interviewed in the same way for medical history, birth history, family history and demographic features. Births were classified as 'complicated' if they were reported as featuring a breech or difficult forceps delivery, a blue baby, or a birthweight less than 3 lb 4 oz (1.48 kg) (Farr, 1975). There were many reports of prematurity, which by itself was not considered a birth complication. One female control reported epilepsy (untreated) as did four schizophrenics (3 male, 1 female): all the epileptics had had complicated births. There were no other neurological or cerebral abnormalities among the twins, and none had had significant cerebral injury later than the perinatal period. We had previously excluded one schizophrenic who had a history of very heavy drinking, as the known association of alcohol abuse with increased ventricular size would have complicated interpretation of the data.

TABLE I

Cerebral ventricular volume among schizophrenics and controls

	Schizophrenic group (n = 21)			
	Family history positive (n = 7)	Family history negative (n = 14)	Total (n = 21)	Controls (n = 18)
Total ventricular volume (voxels) mean ± S.E.M.	557.6 ± 151†	1502.7 ± 244*	1188 ± 195‡	712.2 ± 89
Age (years): mean ± S.E.M.	36.4 ± 3.2	41.4 ± 3.8	39.7 ± 2.7	39.8 ± 2.9
Age of onset (years) mean ± S.E.M.	21.3 ± 3.3	26.6 ± 1.6	24.9 ± 1.6	—
Length of illness (years) mean ± S.E.M.	15.0 ± 2.8	14.45 ± 2.6	14.63 ± 2.0	—
Years as an in-patient: mean ± S.E.M.	5.13 ± 2.5	3.89 ± 1.7	4.31 ± 1.4	—
Number of concordant pairs	3	6	9	—
Number reporting birth complications	0	6	6	8

*t = 2.98, P <0.01 compared with 'family history positive' schizophrenics; t = 3.39, P <0.01 compared with controls
†n.s. compared with controls (t = −1.07)
‡n.s. compared with controls (t = 1.86)

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Family history was regarded as positive if the twin reported, and case notes or relatives confirmed, that a first- or second-degree relative had suffered from a major psychiatric illness (Thompson *et al*, 1982). We did not attempt to specify a diagnosis for such an illness in the relatives, other than to exclude substance abuse. We found that one control (female) and seven schizophrenics (5 female, 2 male) had a positive family history.

CT scans of all subjects were obtained on the Maudsley CT 1010 scanner and examined using an independent viewing console. Voxels, of density 0–25 Hounsfield Units, were assigned to CSF within the ventricular area (excluding cisterns and subarachnoid space) on each slice visually selected by the operator. All slices showing ventricle were measured (1 voxel = 0.15 × 0.15 × 1.0 cm = 0.0225 cm^3). The total number of voxels of the specified density thus provided an estimate of the total volume of the third and lateral ventricles. The total ventricular volumes (TVVs), expressed as voxels, are shown in Table I.

All subjects were blindly examined, from coded floppy discs, by the same operator (M.A.R.). The test-retest reliability of measurements of volume was 0.98, and the correlation with VBR (ventricle:brain ratio = ventricular area/brain area × 100) was 0.97. As the VBR did not correct for any sex differences in ventricular size, it offered no advantage over the direct estimate of TVV and is therefore not reported.

After square-root transformation of TVV to normalize the distribution, statistical analysis was performed using Pearson correlation, Student's *'t'* statistic (two-tailed), and analysis of variance using the classical approach.

Results

Schizophrenics vs controls

Total ventricular volumes for schizophrenics and controls are shown in Table I. The schizophrenic group as a whole had a greater mean TVV than the controls, but the difference was not significant after square-root transformation of the data ($t = 1.86$, n.s.). Sex, age and birth-order of the twin were not significantly associated with TVV in either group.

Effects of complicated birth

To our surprise, the control twins who reported birth complications (4 male, 4 female) had very significantly larger TVV than those controls who did not (Table II). Analysis of variance of TVV by sex and reported birth-complications, using age as a covariate to control for the effect of age, showed that the effect of birth-complications was highly significant ($F = 16.086$, $P = 0.001$: Table III). The same analysis of TVV for the schizophrenics did not yield a significant

TABLE II

Cerebral ventricular volume among controls with and without a history of complicated birth

	Birth complicated ($n = 8$)	Birth not complicated ($n = 10$)
Total ventricular volume (voxels) mean ± S.E.M.	1015.25 ± 120	469.8 ± 58*
Age (years): mean ± S.E.M.	43.38 ± 5.03	36.9 ± 3.3
Number with positive family history	1	0

*$P < 0.001$, $t = 4.30$

TABLE III

Results of analysis of variance of birth complications and ventricular volume among controls

Source of variation	Mean square	d.f.	F	Significance of F
Age (covariate)	67.172	1	2.700	0.125
Birth complications	400.142	1	16.086	0.001
Sex	23.474	1	0.944	0.349
Explained	135.240	4	5.437	0.009
Residual	24.876	13	—	—

TABLE IV

Correlations of illness-related factors with ventricular volume among schizophrenics

	Pearson correlation	Partial correlation to exclude age
Age	0.37†	—
Age of onset	0.45*	0.29
Length of illness	0.17	−0.25
Total time spent as in patient	−0.08	−0.21

*$P < 0.05$

†Partial correlation excluding age of onset gives $r = 0.09$

TABLE V

Results of analysis of variance of family history, twin concordance, birth complications and ventricular volume among schizophrenics

Source of variation	Mean square	d.f.	F	Significance of F
Age (covariate)	445.173	1	3.681	0.076
Family history	904.756	1	7.480	0.016
Concordance	147.416	1	1.219	0.288
Birth complications	118.777	1	0.982	0.339
Explained	266.941	6	2.207	0.104
Residual	120.953	14		

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result (F = 0.83, P = 0.777); many without birth-complications showed increased ventricular size. However, all schizophrenics with birth complications had a negative family history and five out of six came from pairs discordant for schizophrenia (see Table I). Four schizophrenics with complicated births had epilepsy; they had quite small ventricles (219, 687, 1098 and 1391 voxels). One control also suffered from epilepsy (TVV 927 voxels).

Illness-related

No significant correlations were found between ventricular volume and the length of the illness prior to the scan (r = 0.17), total time as an in-patient (r = 0.08) or age (r = 0.26). Age of onset was significantly correlated (r = 0.45, P <0.05); the schizophrenics with later onset had larger ventricles. The effect was no longer significant after controlling for present age, although it was still apparent (Table IV).

Genetic predisposition

By far the most significant association for TVV among the schizophrenics was with presumed genetic predisposition: those with a positive family history (family other than the co-twin) had small TVV (160, 162, 207, 569, 680, 1052 and 1073 voxels). Analysis of variance of ventricular volume by family history, twin concordance and birth complications (controlling for present age by analysis of covariance) showed family history to be the only significant effect (F = 7.480, P = 0.016: Table V). Since older age at onset was also correlated with increased TVV to some extent, and since those schizophrenics with negative family history had later onset, we repeated the analysis of variance with age at onset as an additional covariate. This did not change the conclusion, although the significance of the family-history effect was slightly reduced (F = 6.053, P = 0.029).

Discussion

Genetic predisposition

Our hypothesis that enlarged cerebral ventricles would be found only among schizophrenics without obvious genetic predisposition was confirmed: all the schizophrenics with a positive family history had ventricular volumes below the mean of the schizophrenic group as a whole. When assessing the family history of psychiatric disorder as positive, we did not require a diagnosis of schizophrenia among the relatives, just evidence of major psychiatric illness (apart from substance abuse). Thus the proportion of patients in this category was higher (33 per cent) than if we had used a criterion of definite schizophrenia (9.5 per cent). We adopted this stratagem partly because of evidence that a spectrum of disorders may be genetically related to schizophrenia (Kety et al, 1975). Despite our widely applicable criterion for a positive family history, however, our patients showed the usual association (Gottesman and Shields, 1982) of increased severity with greater genetic predisposition: those with a positive family history of psychiatric disorder had an earlier mean age of onset and had spent a longer time as in-patients than those without such a family history. There was no association of positive family history with concordant co-twins (Table I), as we might have expected, perhaps because concordance among MZ pairs could arise as a result of shared environment just as well as from identical genes. However, there was a complete absence of reported birth complications among the schizophrenics with a positive family history (Table I).

Birth complications

The association of perinatal trauma and TVV among the controls was most striking—and unexpected, as we had assessed birth complications in this group only to provide a consistent comparison with the schizophrenics. All the controls were apparently healthy volunteers, and none of the control scans was read as abnormal by a radiologist. This finding provides direct evidence of an association between birth complications and increased ventricular size in a normal population. Schulsinger (1982) has also noted that among the offspring of schizophrenic mothers, signs of prematurity at birth are associated with increased ventricular size of adult life.

The proportion reporting birth complications among our twin controls was high (44 per cent) and we would not expect perinatal injury to make such a significant contribution to ventricular size among a comparable group of singleton birth; however, we *would* have expected a similar finding among our schizophrenics. But amongst our 14 schizophrenics with negative family history, the six reporting birth complications had a lower mean TVV (1314 ± 458 voxels) than the eight who did not report complicated birth (1644 ± 581 voxels): the latter group also had very significantly larger TVVs than the control twins (t = 4.18, P <0.001). Some unknown process or processes must have led to ventricular enlargement among these schizophrenics; close inspection of the eight did not reveal them to have any discernible features in common.

Diathesis and stress

A variety of cerebral events may lead to ventricular enlargement, and numerous organic insults or specific genetic syndromes have been associated with schizophrenia (Propping, 1983). We suspect that a schizophrenic illness may not be the invariable result of any

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given stress or particular genetic background. The present study supports this view: we have shown an association of ventricular size with perinatal difficulty in normal twins, yet those twins are not schizophrenic, and twins do not appear to suffer from schizophrenia appreciably more often than people of single birth (Gottesman and Shields, 1972). Furthermore, ventricular enlargement is associated with a variety of clinical manifestations other than schizophrenia, (Rieder *et al*, 1983). We believe that in the continuum of liability to schizophrenia those with a lighter 'genetic load' may require environmental influence to manifest the illness and even then may show less severity, while those with greater genetic predisposition may become schizophrenic on this basis alone or with a minimal environmental contribution.

Can our findings be generalized from twins to other schizophrenics? We think so, although the same trends may be harder to detect. The perinatal stressors operating on twins are non-specific, but the frequency of such events in twins may make the contrast between 'mainly genetic' and 'environmentally triggered' schizophrenia more obvious. We suggest that ventricular enlargement may be just one non-specific indicator of the past or present cerebral pathology necessary to produce a psychotic illness in those with low genetic predisposition.

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