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Prevalence of Familiality, Obstetric Complications, and Structural Brain Damage in Schizophrenic Patients

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Schizophrenic in-patients with and without a family history were identified prospectively. The two groups did not differ with respect to clinical variables, ventricular enlargement, prevalence of cortical sulcal widening, or a history of obstetric complications, even when a variety of definitions of familiality were used.

The genetic basis for schizophrenia has been firmly established by adoption and twin studies (Kety, 1980; Gottesman & Shields, 1982), but the nature of the interaction between gene and environment has yet to be clarified. Murray *et al* (1985) have suggested that research into the role of environmental factors in schizophrenia would be facilitated by dividing patients into 'familial' and 'non-familial' groups. It was proposed that the 'non-familial' cases result from a variety of causes, including environmentally induced brain damage, while genetic factors play a more important role in the 'familial' cases. The evidence for the value of such a research strategy was strengthened by investigation of ventricular dilatation in schizophrenia. A proportion of schizophrenic individuals have enlarged lateral ventricles on brain CT scans (Weinberger *et al*, 1979*a*; Owens *et al*, 1985). Reveley *et al* (1984) showed that in twin pairs discordant for schizophrenia, the mean ventricular volume in schizophrenic probands was higher than in healthy co-twins. In addition, enlargement was more frequent among patients without a family history of psychiatric illness. These results received support from some studies (Cazzullo *et al*, 1985; Turner *et al*, 1986; Lewis & Murray, 1987) that suggested the presence of environmentally induced brain damage, but not from others (Campbell *et al*, 1979; Pearlson *et al*, 1985; Farmer *et al*, 1987). One study reported greater likelihood of a positive family history among patients with a ventricular enlargement (Nasrallah *et al*, 1983). Differences in definitions for familiality, selection criteria, and age of the probands make it difficult to compare these studies.

Cortical atrophy can also be rated from CT scans by estimating sulcal widening. Weinberger *et al* (1979*b*) and Nasrallah *et al* (1982) found cortical atrophy more frequently in schizophrenic patients than in normal control subjects. Oxenstierna *et al* (1984) reported a higher prevalence of cortical atrophy in 'non-familial' than in 'familial' types of schizophrenia.

Considerable interest has focused on the role of obstetric complications (OCs) as a possible cause for the putative brain damage. The classical studies of Pasamanick *et al* (1956) suggested a link between perinatal trauma, brain damage, and behavioural dysfunction in children. More recent studies have borne out the relationship between obstetric complications (OCs) and periventricular haemorrhage leading to cerebral damage; the latter being manifested as ventricular dilatation and neurodevelopmental delays in children (Leichty *et al*, 1983; McCarton-Daum *et al*, 1983; Fletcher *et al*, 1984). In adults, Reveley *et al* (1984) reported an association between OCs and ventricular enlargement in normal twins. A link between OCs and CT-scan abnormalities among singletons with psychiatric illness has also been reported (Roberts, 1980; Schulsinger *et al*, 1984; Owen *et al*, 1988). McNeil & Kaij (1978) found an increased prevalence of OCs in schizophrenic individuals, and suggested a causal relationship between obstetric and perinatal complications, and subsequent schizophrenia. Further support for this hypothesis has come from Lane & Albee (1966), Woerner *et al* (1973), Jacobsen & Kinney (1980), and Parnas *et al* (1982). Moreover, schizophrenic patients with OCs are more likely to manifest ventricular dilatation (Pearlson *et al*, 1985; Turner *et al*, 1986; DeLisi *et al*, 1986). If OCs and a genetic predisposition are discrete aetiological factors, patients with a positive family history should have a lower prevalence of OCs than patients without such a history (Dalen, 1972). Although McNeil (1986) did not find such a relationship, Lewis & Murray (1987) reported a large retrospective survey showing that schizophrenic patients with a history of psychiatric admissions among first-degree relatives had OCs less frequently than 'non-familial' probands. These workers also found that abnormality on CT scans occurred more often in patients with OCs.

Much of the research reviewed above supports the strategy suggested by Murray *et al* (1985), although

some of the studies quoted suffer from methodological defects. The retrospective survey of case-notes can lead to bias because of inadequate collection of data, and difficulties in applying operational diagnostic criteria. Moreover, studies involving CT scans have been confounded by both the choice of controls (Smith & Iacono, 1986), and lack of attention to racial origin as a factor influencing VBR and cortical atrophy. In summary, there exists considerable indirect evidence linking obstetric complications, ventricular enlargement, and schizophrenia, although definite proof is lacking. The present study was designed to assess prospectively the relationship between family history, obstetric complications, and CT-scan findings in a series of schizophrenic patients.

Method

Patients

Consecutive admissions to the Maudsley Hospital between October 1985 and June 1986 were screened. Clinical information was obtained by administering the Schedule for Affective Disorders and Schizophrenia (SADS; Spitzer & Endicott, 1978), and also by reviewing case-notes. All patients meeting the Research Diagnostic Criteria (RDC) for schizophrenia (Spitzer *et al*, 1977) were included in the study. Obstetric histories were obtained from case-records and by interviewing a close relative. OCs were rated as follows: 0 = no OC; 1 = uncertain; 2 = definite (*see* Lewis & Murray, 1987). Information about psychiatric morbidity among relatives was obtained from the same sources, using a structured questionnaire (A. Reveley, unpubl.). Case-records of relatives who had attended hospitals were also obtained. Each set of data was rated separately by one of the authors (RMM), who was blind to the clinical details. Psychiatric morbidity among relatives was rated using the Family History RDC (Endicott *et al*, 1975). The lifetime neuroleptic dose for each patient was calculated using standard conversion tables (Davis, 1976).

Of 61 patients eligible for the study, four were discharged before a full assessment could be made, and one declined consent. Information about relatives, and obstetric records, were obtained from the following sources: mothers (35 cases); other first-degree relatives (13 cases); or second-degree relatives (6 cases). Family history of psychiatric illness could not be obtained for two patients, and obstetric data were unavailable for four. Interviews with informants yielded details regarding 242 first-degree relatives and 535 second-degree relatives.

CT scans

Brain CT scans were performed on a model 1010 scanner (EMI) in 47 cases and on a model 9800 scanner in five. Only scans from the former were used to assess lateral ventricular–brain ratio (VBR). Four patients declined to have a scan. The size of the lateral ventricles and of the intracranial space was measured by manual planimetry, at the slice showing the largest area of lateral ventricle (Weinberger *et al*, 1979*a*), by VN, who was blind to clinical details. Each index was measured repeatedly until two identical values were obtained. These were used to calculate VBR by the method of Synek & Reuben (1976). The interrater reliability for measuring VBR in comparison with an independent observer was 0.78 (Pearson's coefficient of correlation, $P<0.05$).

The mean VBR of Caucasian patients among the cohort was compared with age, sex and race-matched control subjects from either hospital staff or members of the Salvation Army. None of the control subjects had a history of alcoholism or psychiatric disorder. All control scans were obtained on the model 1010 scanner and were kindly lent by colleagues at the Institute of Psychiatry and King's College Hospital, London.

Sulcal widening

Sulcal widening was rated using three variables: 1. cortical sulcal widening (CS); 2. widening of Sylvian fissure (SF); and 3. widening of the interhemispheric fissure (IH), according to the methods of Weinberger *et al* (1979*b*), Lishman (1981), and Ron (1983). The first two parameters were rated on a four-point scale (0–3), while IH was rated on a three-point scale (0–2). Photographs of standard scans were used for reference. The lower limits in each category correspond to the standards proposed by Nasrallah *et al* (1983) and Weinberger *et al* (1979*b*). The scans were rated by VN, who remained blind to the clinical details, family history, OCs, and VBR. In each case, the sum of the ratings on the three indices (the 'total score', TS) was calculated. The test–retest reliability and the interrater reliability for measurement of TS were satisfactory (intraclass coefficients = 0.90 and 0.92 respectively; Bartko & Carpenter, 1976). The values for TS were also dichotomised into zero and non-zero scores (interrater reliability, $\kappa = 0.69$, $P<0.002$, test–retest reliability, $\kappa = 0.60$, $P<0.01$).

Results

Family history of psychiatric illness

The distribution of patients according to diagnosis of psychiatric illness among relatives is shown in Table I. Approximately a third of the cohort had a first-degree relative diagnosed as having a psychotic illness. Of these, equal numbers of probands had relatives with schizophrenia or affective psychoses. Nearly half the probands had a first-degree relative with a psychiatric illness. The number of probands who had first or second-degree relatives with similar illnesses was proportionately greater.

The demographic and clinical characteristics of patients with a history of psychotic illness among first-degree relatives were compared with those of patients without a history of psychosis among first or second-degree relatives (Table II). The two groups did not differ with respect to age, sex, race, marital status, duration of illness, number

TABLE I
Distribution of probands according to psychiatric illness among relatives

Relatives' diagnosis	*Number of probands (n = 54) with*	
	First-degree relatives	*First or second-degree relatives*
Schizophrenia	6	8
Schizoaffective psychosis	3	4
Bipolar affective psychosis	6	6
Other psychoses	3	6
Non-psychotic mental illness	7	11
Total	25	35

The diagnosis "other psychoses" includes psychotic illnesses, for which a precise diagnosis could not be made because of their short duration, atypical nature, or because of inadequate information

TABLE II
Demographic and clinical characteristics of 'familial' and 'non-familial' patients

Characteristic	*'Familial' patients (n = 18)*	*'Non-familial' patients (n = 30)*
Age	32.2 ± 3.0	32.3 ± 1.9
Sex (male/female)	11/7	21/9
Race (Caucasian/Afro-Caribbean/other origin)	8/7/3	19/11/0
Marital status (single/cohabiting/separated)	12/3/3	24/3/3
Duration of illness (months)	94.3 ± 17.9	82.3 ± 13.5
Number of hospital admissions	3.0 ± 0.7	2.8 ± 0.5
Age at onset of illness	25.0 ± 2.1	23.2 ± 1.1
Duration of present episode (weeks)	35.5 ± 12.9	80.4 ± 27.0
Number of relatives ascertained/case:		
First-degree	6.5 ± 0.9	4.0 ± 0.2*
First and second-degree	17.8 ± 1.4	14.4 ± 0.9

'Familial' patients are those with a first-degree relative known to suffer from a psychotic illness, while 'non-familial' patients are those without a history of psychotic illness among either first or second-degree relatives. Duration of illness denotes the time elapsed since a close relative first noticed behavioural abnormality in the proband to the date of the present admission. Values are mean ± s.e.m. Comparisons were made using the Mann–Whitney U test or the chi-squared test, as appropriate.
*$P < 0.05$.

TABLE III
Distribution of definite obstetric complications (OC) among 'familial' and 'non-familial' patients

Definition of familiality	*Familial group*		*Non-familial group*	
	No OC	*Definite OC*	*No OC*	*Definite OC*
First-degree relative with				
schizophrenia	2	1	14	6
Affective psychosis	5	1	14	6
Any psychosis	9	3	14	6
Any psychiatric illness	13	4	8	5
First or second-degree relative with				
Schizophrenia	3	2	14	6
Affective psychosis	5	1	14	6
Any psychosis	11	5	14	6
Any psychiatric illness	17	6	8	5

Familiality among probands was defined on the basis of different categories of psychiatric illness in first or second-degree relatives. For comparison, the 'non-familial' group consisted either of patients without a family history (first or second-degree relatives) of psychosis, or of any psychiatric illness for comparison with probands with a psychotic relative, or for comparison with probands who had relatives with any psychiatric illness respectively. The table shows the distribution of patients with or without definite history of obstetric complications (OC) in the different categories. Data about patients with equivocal obstetric histories was excluded. Comparisons between familial and non-familial groups were made using the Yates chi-squared test. No statistically significant differences were found.

TABLE IV
Ventricular–brain ratio (VBR) in familial and non-familial cases

Definition of familiality	*Familial*	*(n)*	*Non-familial*	*(n)*
First-degree relative with				
Schizophrenia	10.1 ± 0.3	(3)	10.0 ± 0.4	(27)
Bipolar affective psychosis	9.3 ± 1.0	(3)	10.0 ± 0.4	(27)
Any psychosis	10.3 ± 0.6	(14)	10.0 ± 0.4	(27)
Any mental illness	10.4 ± 0.4	(20)	9.9 ± 0.6	(18)
First or second-degree relative with				
Schizophrenia	10.5 ± 0.7	(6)	10.0 ± 0.4	(27)
Bipolar affective psychosis	9.4 ± 1.0	(5)	10.0 ± 0.4	(27)
Any psychosis	10.2 ± 0.5	(19)	10.0 ± 0.4	(27)
Any mental illness	10.2 ± 0.4	(28)	9.9 ± 0.6	(18)

The definition of familiality depended on the presence of psychosis or other psychiatric illness in first or second-degree relatives of probands. The 'non-familial' group consisted of patients who did not have any first or second-degree relatives with a diagnosis of psychosis or psychiatric illness, as appropriate. Comparisons between familial and non-familial groups used analysis of variance. Log-transformed values for VBR were used as independent variables. Age, duration of illness and lifetime neuroleptic dose (G chlorpromazine equivalent units) were used as covariates. A significant effect of familiality was not found in any of the groups. Values are shown as mean ± s.e.m.

TABLE V
Distribution of sulcal widening among patients and control subjects

	Total score for sulcal widening (TS)	*Proportion with any sulcal widening (TS>0)*
Normal controls	1.0±0.2	15/24
Patients of Caucasian origin	1.8±0.3*	20/27
Patients of Afro-Caribbean origin	1.0±0.2	12/21
'Familial' patients	2.0±0.4	12/15
'Non-familial' patients	1.2±0.3	17/29
Patients with no OCs	1.2±0.2	17/24
Patients with definite OCs	2.1±0.6	7/11

Obstetric complications (OCs) were rated as described. 'Familial' patients are those with a history of psychosis in a first-degree relative. 'Non-familial' patients are those without a history of psychosis in a first or second-degree relative. Analysis of total scores followed log-transformation. Normal control subjects and Caucasian patients were compared by the paired *t*-test. Analysis of variance using age, duration of illness, and lifetime neuroleptic dose (G chlorpromazine equivalent units) was used to investigate differences between the other groups. Yates' chi-squared test was used to analyse differences in proportions of patients with any sulcal widening (TS>0) between groups. Values as mean±s.e.m.
*$P<0.05$ (two-tailed)

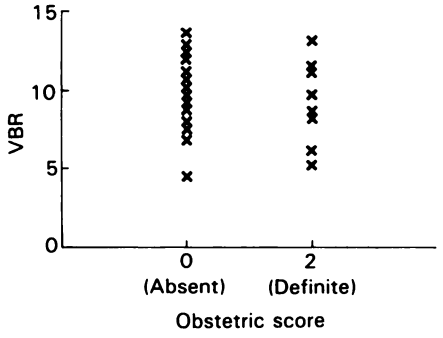

FIG. 1 Relationship between ventricular-brain ratio (VBR) and obstetric score. Scores were rated as described. Data for two cases were missing in each group. No significant difference between the two groups was found using analysis of variance, with log-transformed values for VBR as independent variables and age, duration of illness, and lifetime neuroleptic dose (G chlorpromazine equivalent units) as covariates.

of hospital admissions, age of onset, or duration of present psychotic episodes. The total number of first and second-degree relatives ascertained in the two groups were similar, but fewer first-degree relatives were ascertained in the 'non-familial' group.

Obstetric complications

A history of definite obstetric complications was obtained in 11 cases, and of possible complications in 16 cases. Twenty-five individuals had entirely normal obstetric histories. The frequency of definite OCs among the patients, using different criteria for 'familiality' is given in Table III. There was no significant difference in the prevalence of definite OCs between familial and non-familial cases for any of the comparisons examined, but a proportionately smaller number of probands with a first-degree relative diagnosed as having affective psychosis had definite OCs, in comparison with appropriate 'non-familial' patients. A similar trend was noted if 'familiality' was defined on the basis of affective psychosis in second-degree relatives.

VBR

All comparisons between groups were made following log-transformation of VBR, as the distribution of VBR among the patients was skewed. The schizophrenic patients had a higher mean VBR than the normal control subjects (control subjects: 9.1±2.8, schizophrenic patients: 10.4±1.7, $n=23$ each group, $P<0.02$, paired Student's *t*-test. Values are mean±s.e.m.). The Afro-Caribbean patients had smaller VBRs than Caucasian patients, but this difference was not statistically significant (Caucasian, 10.3±0.4, $n=24$, Afro-Caribbean 9.6±0.6, $n=20$). No differences were found between different categories of 'familial' compared with 'non-familial' patients (Table IV). Similarly, there was marked overlap in VBR between groups with or without obstetric complications (Fig. 1).

Sulcal widening

The total scores for sulcal widening (TS) among Caucasian patients were compared with those of age, sex and race-matched normal control subjects, performed on the same machine. The mean value for TS was significantly greater in the schizophrenic group of Caucasian origin, but there was no significant difference in the proportion of subjects showing any sulcal widening (TS>0) (Table V). No significant differences were noted between patients of Caucasian descent and those of Afro-Caribbean origin, although the mean TS for Afro-Caribbean patients was lower, and was similar to the mean value for normal control subjects. Differences between patients with or without a family history of psychosis in a first-degree relative were analysed with respect to these two parameters. There were no significant differences in TS between familial and non-familial patients, and those with and without definite OCs (Table V).

Discussion

This study was designed to assess the relationship between structural brain damage and potential aetiological factors in an unselected group of schizophrenic patients. Data about family history gathered by interviewing a close relative and obtaining

medical records of affected relatives is superior to examination of case-notes alone, but yields less information than a direct diagnostic interview of each relative (Thompson *et al*, 1982). Detailed family histories were obtained in all but two cases, enabling the prevalence of psychotic and non-psychotic illnesses in both first and second-degree relatives to be ascertained. A significant number of relatives could not be definitely categorised as having either schizophrenia or bipolar affective disorder, and were designated as 'other psychoses'. No significant clinical differences between the 'familial' and 'non-familial' groups were detected, in agreement with Baron *et al* (1982).

If genetic predisposition and obstetric complications are discrete aetiological factors for schizophrenia (Owen *et al*, 1988), a higher proportion of OCs should be found in the 'non-familial' cases. The present finding does not support this hypothesis. However, firstly, the familial/non-familial strategy is likely to be most effective with large samples, and the cohort reported here is small compared with previous studies. For example, a replication of Lewis & Murray's (1987) findings of a difference in prevalence of OCs between familial and non-familial groups would require at least 300 patients in each group (Pocock, 1983). Furthermore, the strategy itself has been criticised as prone to 'false positives' or 'false negatives' (Eaves *et al*, 1986; Goldin *et al*, 1987; Gottesman *et al*, 1987), resulting in the possibility of the non-familial group including patients with a genetic predisposition. In the present study, the likelihood of the latter was reduced by including in the 'non-familial' group only those patients without psychiatric illness in either first or second-degree relatives. Secondly, bias may result from differences in family size. In the present study, lists of all first and second-degree relatives were obtained for each proband. The informant was then questioned about the medical and psychiatric details of each individual. Although similar numbers of first and second-degree relatives were ascertained in the 'familial' and the 'non-familial' groups, a proportionately smaller number of first-degree relatives were noted in the non-familial group. It is possible that some of the non-familial patients would have been classed as 'familial' if they had more first-degree relatives i.e. an increased possibility of a genetic predisposition being expressed. Thirdly, the interaction between OCs and a familial predisposition could occur on a more subtle level, analogous with the interaction of HLA types and coxsackie B virus in the aetiology of diabetes mellitus. Finally, it may be argued from the present findings that OCs are epiphenomena of the illness, rather than aetiological factors. In this context, it is of interest that patients who had a family history of affective psychosis were less likely to have OCs.

Overall, the findings that schizophrenic patients had both higher VBRs and ratings of sulcal widening than matched controls are in keeping with earlier studies (reviewed by Weinberger, 1984). Ethnic differences are a potential source of bias in the VBR measurements. In order to overcome this, controls were matched to the schizophrenic group not only by age and sex, but also by race. We did not find significant differences in the VBR between 'familial' and 'non-familial' patients. Moreover, a trend for more sulcal widening in the familial group was noted (Table V). This is inconsistent with the predictions of Murray *et al* (1985), or the findings of Owen *et al* (1988). What are the reasons for such differences? The argument concerning sample size is less convincing here, because familial–non-familial differences in VBR have been reported using groups of comparable size (e.g. Turner *et al*, 1986).

Two factors may also help to explain the discrepancy between this study and others from the Maudsley. Firstly, previous studies (Reveley *et al*, 1984; Owen *et al*, 1988) have all examined samples in which the likelihood of organic abnormality was maximised (e.g. twins or schizophrenic patients referred for CT scans). In contrast, this study examined unselected schizophrenic subjects, and in addition included a significant proportion of subjects of Afro-Caribbean origin, who are reported to have higher rates of schizophrenia in Britain, and in whom different aetiological factors may be operating. Non-significant trends for smaller ventricles and less sulcal widening were found in this group.

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