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Heritability of Schizophrenia
A Controlled Family History Investigation in Nigeria

O. GUREJE, R. BAMIDELE and Y. A. ADERIBIGBE

Thirty-six consecutively admitted patients with schizophrenia and 20 with mania were studied for the morbid risk of psychosis in their first-degree relatives. Using the family history method of ascertainment, the morbid risk for schizophrenia in the relatives of schizophrenic probands was 4.12% compared with 1.42% in the relatives of manic probands. While this difference was not statistically significant, that between the morbid risk for affective psychoses in the relatives of manic patients (7.81%) was significantly higher than for the relatives of schizophrenic patients (0%).

One of the best demonstrated biological substrates of schizophrenia is the existence of a genetic predisposition to it. For example, studies of relatives show that, compared with the life-time expectancy for schizophrenia of the order of 0.3–2.8% in the general population, much higher figures have been found in relatives of schizophrenic patients (Tsuang *et al*, 1991). Thus, children whose parents have had schizophrenia have at least a 25% chance of developing the illness. Siblings of a person with schizophrenia show an expected risk of between 8 and 14% while the risk for parents is 5–10%. On the other hand, the risk to second-degree relatives varies at around 2.5%. Kendler suggests that the genetic heritability of schizophrenia may be between 0.60 and 0.70, while environmental familial factors may account for less than 20% of the variance in liability to the illness (Kendler, 1988*a*).

The data relating to the heritability of schizophrenia have been derived mainly from studies conducted among Anglo-Saxon patient groups. While the clinical phenomenology and outcome of schizophrenia and bipolar illness have received research attention (Makanjuola, 1985, 1989; Gureje & Bamgboye, 1987; Makanjuola & Adedapo, 1987; Gureje, 1989), no study, to our knowledge, has used a standardised procedure to determine the extent to which schizophrenia may be a heritable disease in a black African population. Such study is necessary in view of the culture-related differential outcome already demonstrated for operationally defined schizophrenia, with Nigerian patients being among those reported to show a better short-term outcome (Sartorius *et al*, 1986). It is generally believed that the outcome of schizophrenia is influenced by whether it is familial or sporadic. Also, the observation that unipolar mania rather than bipolar presentation is more characteristic of Nigerian patients with affective disorder (Makanjuola, 1985) raises the question of whether the familiarity of mania is different among such patients than that demonstrated elsewhere.

It has been suggested that studies demonstrating familial aggregation for schizophrenia may be fatally flawed as a result of cases misdiagnosed as being those of affective illness. As argued by Kendler (1988*b*), such an error should also lead to an increased rate of affective illness in relatives of schizophrenic probands. Any attempt to determine the heritability of schizophrenia ought to have as its control or one of its control groups a sample of patients with affective disorder diagnosed using an identical system. We have chosen this approach because it has the added advantage of providing evidence for the validity of the diagnostic groups.

Method

Over a 1-year period, consecutively admitted patients to the psychiatric wards at the University College Hospital, Ibadan with evidence of psychosis were interviewed by a trained research assistant using the Composite International Diagnostic Interview (CIDI) (Robins *et al*, 1988). The CIDI is a fully structured clinical interview that assesses a comprehensive list of psychiatric diagnoses. Its core version allows for the derivation of a diagnosis according to the criteria of a number of systems, including the Research Diagnostic Criteria (RDC) (Spitzer *et al*, 1978). In this study, patients were administered the sections of the instrument that relate to the RDC diagnoses of depression, mania, and schizophrenia. The instrument was administered in its Yoruba translated version as soon after admission

as each patient was able to attend such an interview. The aim was to evaluate whether any particular patient with evidence of psychosis on admission met the RDC criteria for schizophrenia, mania, or psychotic depression. (As part of a much larger study, the patients were also administered a range of other instruments, including the Scale for the Assessment of Negative Symptoms (SANS) and the Brief Psychiatric Rating Scale (BPRS).)

During admission, arrangements were made to interview a first-degree relative of each patient. This interview was conducted by another research worker who was blind to the CIDI diagnosis of the proband. The interview was structured according to the suggested guidelines specified in the Family History Research Diagnostic Criteria (FH-RDC) (Andreasen *et al*, 1977). (The interviewer was a senior trainee psychiatrist trained by the first author in the use of the FH-RDC.) It assessed the presence or absence of depression, mania, and psychosis and obtained information about previous hospitalisation, types of treatment received, and functional status of every first-degree relative of each proband. For each proband, a family tree was drawn and all the individuals who were aged 15 years or above were identified. Information was collected thereafter about each of the relatives, whether dead or alive, to establish the presence of psychosis at any time in the relative's life. Hospital casenotes were also examined in the cases of relatives with a history of previous admission, especially when the admission was to the University College Hospital.

Full pedigree data were obtained from 36 schizophrenic study probands and 20 manic controls.

In the analysis, we adopted the abridged Weinberg method for age correction. Thus, relatives over the age of risk for a particular illness were given a value of 1, those within the age of risk were given a value of 0.5, and those below it were given a value of 0. These age-corrected denominators then were used in the determination of the morbid risk for that illness. Limits for these ages of risk for schizophrenia were 17–45 years, while those for depression and mania were 15–59 years. Morbid risks were compared according to the method proposed by Breborwicz & Trzebiatowska-Trzeciak (1976).

Results

Out of a total of 231 relatives of schizophrenic patients, 133 were aged between 17 and 45 years while 55 were aged over 45 years. Of these 231 persons, 171 were aged between 15 and 59 years while 26 were aged over 59 years. Out of a total of 147 relatives of manic patients, 74 were aged between 17 and 45 years while 33 were aged over 45 years. Of these 147, 90 were aged between 15 and 59 years while 19 were aged over 59 years.

A total of six relatives were affected by schizophrenia. All had been admitted previously, four of them at the University College Hospital. Five of these were related to schizophrenic probands, while one was related to a manic patient. One further relative of a schizophrenic was given a diagnosis of 'probable schizophrenia'. Even though admitted previously, her casefile could not be located for detailed evaluation and therefore she has been excluded from analysis. As can be seen in Table 1, relatives of schizophrenics had almost a threefold morbid risk for the illness when compared with relatives of manic patients, although the difference was not statistically significant.

Table 1
Morbid risks of schizophrenia and affective psychoses in the relatives of schizophrenic and manic probands

Proband diagnosis	No. of relatives	No. of affected relatives	'Lifetime at risk' (*Bezugsziffer*)[1]	Morbid risk (s.e.d.) (%)
Schizophrenia in relatives				
Schizophrenia	231	5	121.5	4.1 (2.0)
Mania	147	1	70	1.4 (1.4)
Affective psychoses in relatives				
Schizophrenia	231	0	111.5	0 (0)
Mania	147	5	64	7.8 (3.7)[2]

1. Corrected denominator to allow for relatives who have not lived through the period of risk.
2. $P=0.0027$.

There were five relatives with a history of affective psychoses: three with depressive psychoses and two with mania. Three of these relatives had a history of hospital admission for their mental illness, two of them at the University College Hospital. The others had only received traditional treatment. All the five individuals with a definite diagnosis of affective psychoses were relatives of manic controls. Another relative of a manic patient had a history of previous admission for a mental illness, the nature of which could not be ascertained from the family history interview. As can be seen in Table 1, the relatives of manic probands had a morbid risk of affective psychoses that was almost eightfold that of the relatives of schizophrenics. The difference was statistically significant.

Discussion

The results of the family history data analysis suggest that both schizophrenia and mania are heritable diseases and that familiar aggregation is probably stronger for mania. Relatives of schizophrenics showed almost a threefold increase in morbid risk for the illness compared with manics, while relatives of manics showed about an eightfold increase in morbid risk for mania compared with schizophrenics. While the former observation was not statistically significant, the latter was.

The morbid risk of 4.12% for schizophrenia among relatives of schizophrenic patients found in this study is similar to those of many previous authors who have used contemporary narrow criteria for the diagnosis of schizophrenia. Guze *et al* (1983), in a study of relatives of patients diagnosed using the modified Washington University criteria for schizophrenia (Feighner *et al*, 1972), reported a morbid risk of 3.6% for definite schizophrenia. These authors also reported a morbid risk of 0.56%

for schizophrenia in relatives of non-schizophrenic psychiatric patients. These values were derived from data obtained from 111 lifetimes at risk in the former group and 1076 in the latter group. The difference was statistically significant ($P=0.0008$). Kendler *et al* (1985) reported a value of 3.7% for the morbid risk for schizophrenia among relatives of schizophrenic patients who were diagnosed according to the DSM–III criteria. Frangos *et al* (1985) obtained a value of 4.0% in their sample of relatives of schizophrenic probands who were diagnosed using the DSM–III criteria. While all these reports were based on the family study (or direct interview) method, Kendler *et al* (1985) conducted a blind family history study of 330 relatives of schizophrenic probands, diagnosed using the Washington University criteria and 119 relatives of medical controls. Using FH–RDC, they found eight cases of schizophrenia in relatives of schizophrenic probands, giving a morbid risk of 3.0%, and no cases of schizophrenia in relatives of control probands ($\chi^2=3.13$, $P=0.077$). Using a set of less restrictive criteria (ICD–9), Scharfetter & Nusperli (1980) found a morbid risk of 8.9% among the relatives of their schizophrenic probands and 3.3% among those of patients with affective illness.

A few reports have not been consistent with this general observation. Pope *et al* (1982) reviewed the charts of 39 consecutively admitted patients with definite DSM–II schizophrenia. Using family history information recorded in the chart, they found no cases of schizophrenia among the 199 first-degree relatives of the patients. No controls were studied. Abrams & Taylor (1983), using a set of criteria described by themselves, studied 30 consecutively admitted schizophrenic patients. Of the 181 living relatives of the probands, 70 were personally interviewed either by telephone or in person while information was collected on the remaining 111 by family history methods. Two cases of schizophrenia were found for a morbid risk of 1.6%. No control group was used. Apart from certain methodological problems discussed earlier by Weissman *et al* (1983), diagnostic practices may also explain these results. As noted by Tsuang *et al* (1991), Abrams & Taylor might have employed overly restrictive sets of diagnostic criteria and thus attenuated a real pattern of familiar transmission. Coryell & Zimmerman (1988) studied 91 consecutively admitted patients with schizophrenia ($n=21$), schizoaffective depression ($n=43$), or psychotic depression ($n=27$) along with 36 never-ill controls. The total lifetimes at risk among the relatives of the schizophrenic probands was 72, while it was 160 among the relatives of the never-ill controls. These authors reported a morbid risk of 1.4% in the former group and 0% in the latter, a difference that was not statistically significant. In reviewing the findings of this study, Kendler (1988*b*) has pointed out that problems relating to small sample size and ascertainment procedure might have reduced the chance of detecting a higher morbid risk among the relatives of the schizophrenic probands.

Compared with the morbid risks of 0.7% (when family history method was used) and 1.0% (when family study method was used) reported by Andreasen *et al* (1987) and that of 1.1% reported by Rice *et al* (1987), the morbid risk of 1.42% for schizophrenia among the relatives of manic probands reported here is also consistent with the findings of early studies among predominantly Anglo-Saxon populations. The failure of the difference between the morbid risk for schizophrenia among the relatives of schizophrenic probands and that among the relatives of manic probands to reach statistical significance may be due to the small sample sizes involved. It must, however, be noted that a number of authors have reported a higher rate of schizophrenia in the relatives of non-schizophrenic psychotic probands than in subjects with no such relationship, suggesting that relatives of patients with any form of psychotic disorder may have an increased risk for schizophrenia.

Our results suggest that first-degree relatives of schizophrenics have an increased liability to the illness that is about 5–10 times that of the general population, often quoted to be about 0.86% (Tsuang *et al*, 1991). Compared with this general population figure, the results also suggest that the risk for schizophrenia among relatives of manic probands may be higher than what is expected by chance. Unfortunately, no figures for the morbid risk of schizophrenia in the general population in this culture are known to us.

The relatives of manic probands have significantly higher morbid risk for affective psychoses than those of probands with schizophrenia. Out of a total number of five affected relatives of manic patients (with an overall morbid risk of 7.81%), three had an unambiguous diagnosis of psychotic depression (giving a morbid risk of 4.69% for this illness), while two had a diagnosis of mania (morbid risk: 3.13%). Because the depressed relatives had clear evidence of psychosis and because there was often the suspicion that they may also have had manic or hypomanic episodes, it is difficult to make a rigid subtype of their illnesses as bipolar I, bipolar II, or unipolar. To this extent, comparison with previous reports is difficult. However, the results support the general observation of others that there is a familiar aggregation of affective disorders (Andreasen *et al*, 1987; Rice *et al*, 1987; Gershon *et al*, 1988). On the

other hand, no evidence was found for an increased morbid risk for affective disorders in relatives of probands with schizophrenia. This observation is similar to that of a number of other authors. Compared with controls, Kendler *et al* (1986) found no increased incidence of affective disorders in relatives of schizophrenic probands. Similar findings were reported by Frangos *et al* (1985). Baron *et al* (1982) found little affective illness in relatives of schizophrenic probands compared with relatives of probands with affective disorders. To our knowledge, the only published exception to this observation is that made by Gershon *et al* (1988), who found an increased morbid risk for affective disorders in relatives of probands with schizophrenia.

The family history method of determining psychiatric diagnosis is used routinely in clinical practice. As information concerning prevalence of mental illness among the relatives of patients is frequently used to validate diagnostic categories and also to explore the extent to which the disorders follow recognisable familiar genetic or non-genetic patterns of transmission (Perris, 1968; Reich *et al*, 1975; Gershon *et al*, 1980; Weissman *et al*, 1982; Egeland & Hostetter, 1983), the family history procedure is also a common research tool. Compared with the family study approach, which involves the direct interview of relatives, the family history method is cheap and provides a relatively simple way to assess a large number of subjects (Mendlewicz *et al*, 1975; Andreasen *et al*, 1977, 1986; Thompson *et al*, 1982). It provides information concerning all family members and is relatively unaffected by factors that might lead to under-reporting, such as refusals, suicide, or inaccessibility of potential respondents. However, even though excellent reliability and sensitivity have been demonstrated for the FH–RDC (Andreasen *et al*, 1977, 1986; Zimmerman *et al*, 1988), especially when compared with other family history methods, the family history method is generally perceived as being less sensitive when compared with the family study ascertainment method. The method is particularly less likely to detect or may misclassify cases of atypical psychoses and disorders that may belong to the schizophrenia spectrum (such as schizotypal personality disorder and mood-incongruent affective psychosis). In view of the observation that the inclusion of such cases tends to increase morbid risk estimates (Tsuang *et al*, 1991) and concordance in twin studies (Farmer *et al*, 1987), our morbid risk figures in the families of schizophrenic probands may have been underestimated.

In this report, familiar aggregation of schizophrenia was observed among the relatives of schizophrenic probands, while that of affective psychoses was observed among the relatives of manic probands. In comparing the rates of illness in both groups of probands, the higher morbid risk for schizophrenia in the first-degree relatives of schizophrenics compared with that in the first-degree relatives of manics did not attain statistical significance, while the rates of affective psychoses in both families were significantly different. Given the observation that the FH–RDC may have relatively low sensitivity for schizophrenia, especially when defined narrowly (Andreasen *et al*, 1986), it is likely that there was an attenuating effect on the first comparison, resulting from low detection of cases. Morbid risk for schizophrenia in the first-degree relatives of schizophrenics also may have been spuriously low as a result of the demonstrated capacity of genotypes for schizophrenia sometimes to be unexpressed in their carriers (Gottesman & Bertelsen, 1989).

In summary, these data support the traditional separation of schizophrenia and affective disorder; there is evidence to suggest strong familiar aggregation for each of these rather broad groups of disorders. However, the data also cast doubt on an unambiguous separation of the disorders. In view of the increased morbid risk for schizophrenia in the relatives of manic probands compared with the general population figure, an interpretation along the strict Kraepelinian-like dichotomy cannot be made from the findings. Such a dichotomy requires two independent psychiatric disorder categories: schizophrenia on the one hand and bipolar disorder on the other. A demonstration of the independence of such categories would require that the disorders breed true and that there be no cross-liability. The results of this study do not provide support for that view. On the other hand, a unitary hypothesis of psychosis as proposed by Crow (1986) would suggest that there must be at least gradations of "affectivity and schizophrenicity" (Gershon *et al*, 1988). Such a model would imply a multifactorial threshold model as a continuum of liability, going from schizophrenia to affective disorder (Gershon & Rieder, 1980). Failure to demonstrate an increased liability for affective disorder among the first-degree relatives of schizophrenic probands in the present study provides no support for such gradations. The demonstration by others (Baron *et al*, 1987; Egeland *et al*, 1987; Mendlewicz *et al*, 1987) of at least one single-locus form of bipolar affective disorder also makes such a view inappropriate. On the other hand, and as articulated by Gershon *et al* (1988), a unitary model of schizophrenia and schizoaffective and bipolar illness, with single-locus (non-multifactorial) transmission, is not ruled out by linkage findings in bipolar

disorders, "as we do not know at this point that schizophrenia cannot be transmitted by alterations at the same gene locus as bipolar illness". In the case of affective disorder, linkage findings already have provided evidence that a single-locus genetic tendency can be expressed as bipolar and unipolar disorders. It is possible, therefore, that the manic probands in the present study with a higher-than-chance-expectation liability to schizophrenia in their first-degree relatives are genotypically liable to schizophrenia, but present with phenotypic manic illness as a result of alterations at the gene locus. Unfortunately, such a speculation may be simplistic, given the disconfirmation by others of recent linkage findings (Gershon *et al*, 1980; Hodgkinson *et al*, 1987; Gill *et al*, 1988).

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*Oye Gureje, MBBS, PhD, FMCPsych, FWACP, *Senior Lecturer and Consultant*; R. Bamidele, MBBS, *Registrar* and Y. A. Aderibigbe, MBChB, *Senior Registrar, Department of Psychiatry, University College Hospital, PMB 5116, Ibadan, Nigeria*

*Correspondence

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