UNIVERSITI SAINS MALAYSIA
PROJEK PENYELIDIKAN JANGKA PENDEK
LAPORAN AKHIR

PSYCHIATRIC MORBIDITY IN THE FIRST DEGREE RELATIVES OF MOOD DISORDER PATIENTS

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1993-1995

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Short term R & D grant No. 3044/93

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ACKNOWLWDGEMENT

We wish to acknowledge with thanks the Research & Development section of the Universiti Sains Malaysia for giving us this opportunity to carry out this research project and supporting us financially, which made this study possible. We are also thankful to the Hospital Director, General Hospital, Kota Bharu for allowing us to work in the psychiatric section of the General Hospital and do research on the patients. Lastly, we express our gratitude to all the patients who co-operated with us in carrying out the study successfully.

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INTRODUCTION

The well known advances in molecular genetics have lent new importance to the evidence that the disorders are genetically transmitted, raising the hope that vulnerable individuals, rational and definitive treatments may be identified, based on the discovery of specific deficits. At the same time, epidemiological evidence points to a secular increase in mood disorders in recent decades that interacts with familial vulnerability, but also must include major nongenetic causative factors.

Twin and adoption studies show that vulnerability to a disorder has a genetic component. Family studies indicate in a particular population the degree to which a disorder is familial, which diagnostic entities or other characteristics share familial transmission with a particular disorder. and perhaps. most importantly, allow the testing of hypothesis regarding the mode of genetic transmission.

Affective disorder is a broad and heterogeneous category of psychiatric illness. Its prevalence may range up to 20% of the population or more. depending on definition (Weissman & Myers 1978). The more severe types of affective disorder, such as bipolar illness. clearly run in families. This appears to be considerably less true with the milder forms of depression.

There is increasing interest in studies of population at high risk. These studies permit the testing of psychological hypotheses regarding the vulnerability to affective illness in populations free of the effects of the illness itself or of treatment for it. They also permit the assessment of the ability of a biological or clinical characteristic to predict the presence of illness or the course of illness over time.

Mood disorders are recognized as part of an increasing number of common syndromes characterized by familial aggregates but for which the relative etiologic roles of genetic and environmental factors are not clearly delineated. It has only been since the 1960's that research interest has focused on the role of genetic factors in the etiology of these common disorders. At that time, studies [Angst, 1966; Winokur et al,1969],using different methodology, confirmed that mood disorders cluster in families. Results from family, twin, and adoption studies suggest that genetic factors, at least in a portion of cases, have important roles in the causation of bipolar and possibly unipolar mood disorders.

Genetic research on mood disorders has many practical implications. First, identification of the genes will have significant impact on treatment and prevention. Second, as mood disorders are associated with significant morbidity, family members are concerned about the risk for their close relatives.

Family studies

Family studies in affective disorder have consistently demonstrated aggregation of illness in relatives. The actual risk figures vary with the criteria used and probably many other factors (Gershon 1984). In a recent study at NIMH, 25% of relatives of bipolar probands were found to have bipolar or unipolar illness themselves, compared with 20% of relatives of unipolar probands and 7% of relatives of controls. In the same study 40% of the relatives of schizophrenia probands demonstrated affective illness at some point in their lives (Gershon et al, 1982). These data demonstrate increased risk in relatives of patients; they also show that the various forms of affective illness appear to be related in a hierarchical way: relatives of schizophrenia probands may have schizophrenia illness themselves, but are more likely to have bipolar or unipolar illness.

If pedigrees of affective patients are considered as a group, it has generally not been possible to fit single-gene models to them (Nurnberger & Gershon 1984). An alternative explanation is heterogeneity, i.e. single major genes are important in least some families, but it is not the same gene in each family. Heterogeneity is an emerging theme in consideration of the genetic of many psychiatric disorders. It is invoked to explain disparate results in schizophrenia and Alzheimer's disease as well as bipolar disorder.

This explanation seems consistent with our knowledge of the genetic of other common diseases such as coronary artery disease, hypertension, epilepsy and diabetes. It is consistent, also, with our knowledge of the multiple possible origins of the syndromes of these disorders; that is, we know that many drugs and disease may cause clinical manifestations identical to mania (Krauthammer & Klerman 1978) or depression (Wood et al 1988).

Age of onset may be useful in dividing affective illness into more genetically homogeneous subgroups. Early onset probands have increased morbid risk of illness in relatives in some data sets (Weissman et al 1988). A birth-cohort effect has been observed in recent family studies: there is an increasing incidence of affective illness among persons born more recently (Klerman et al 1985). This appears to be true for schizoaffective and bipolar as well as unipolar illness (Gershon et al 1987). It is true among relatives at risk to a greater degree than in the general population; this may be interpreted as a greater incidence of manifestation of illness among vulnerable persons.

Table 1 *Lifetime prevalence of affective illness in first degree relatives of patients and controls (adapted from Nurnberger et al 1986)*

	Number at risk	Morbid risk % Bipolar	Unipolar
Bipolar probands			
Perris 1966	627	10.2	0.5
Winokur & Clayton 1967	167	10.2	20.4
Goetzer et al 1974	212	2.8	13.7
Heltzer & Winokur 1974	151	4.6	10.6
Mendlewicz & Rainer 1974	606	17.7	22.4
James and Chapman 1975	239	6.4	13.2
Gershon et al 1975	341	3.8	8.7
Smeraldi et al 1977	172	5.8	7.1
Johnson and Lemman 1977	126	15.5	19.8
Pattersen 1977	472	3.6	7.2
Angst et al 1979, 1980	401	2.5	7.0
Taylor et al 1980	601	4.8	4.2
Gershon et al 1981, 1982	598	8.0	14.9
Rice et al (1987)	567	10.4	23.1
Unipolar Probands			
Perris 1966	684	0.3	6.4
Gershon et al 1975	96	2.1	14.2
Smeraldi et al 1977	185	0.6	8.0
Angst et al.1979, 1980	766	0.1	5.9
Taylor et al 1980	96	4.1	8.3
Weissman et al 1984b (severe)	242	2.1	17.5
Weissman et al 1984b (mild)	414	3.4	16.7
Gershon et al 1981, 1982	138	2.9	16.6
Rice et al 1987	1176	5.4	28.6
Normal probands			
Gershon et al 1975	518	0.2	0.7
Weismman et al 1984b	442	1.8	5.6
Gershon et al 1981, 1982	217	0.5	5.8

Twin studies

Twin studies, as summarized over 50 years, show consistent evidence for heritability. On average, monozygotic twin pairs show concordance 65% of the time and dizygotic twin pairs 14% of the time. Though the actual concordance figures vary widely, there is a consistent increased concordance in monozygotic as opposed to dizygotic twins.Environmental influences may be related to age of onset, timing of onset of episodes and severity of course; the most important determinants of whether or not affective illness is manifest appear to be genetic. The probands in twin studies include bipolar as well unipolar patients. Heritability for minor depression or neurotic/reactive depression has not been consistently demonstrable in twin studies (Torgersoen 1986, Kendler et al 2987, Andrews et al 1990, Englund & Klein 1990, Torgersen 1990).

Table 2 Concordance rates for major affective disorder in monozygotic and dizygotic twins

	Monozygotic		Dizygotic twins	
	Concordant pairs total pairs	Concordance %	Concordant pairs total pairs	Concordance %
Luxemberger (1930)	¾	75.0	0/13	0.0
Rosanoff et al (1935)	16/23	69.6	11/67	16.7
Slater (1953)	4/7	57.1	4/17	23.5
Kallman (1954)	25/27	92.6	13/55	23.6
Harvald & Hauge (1975)	10/15	66.7	2/40	5.0
Allen et al (1974)	5/15	33.3	0/34	0.0
Bertelsen (1979)	32/55	58.3	9/52	17.3
Torgerson (1986)	14/37	37.8	8/65	12.3
Totals	109/183	59.6%	47/343	13.7%

Adoption studies

Several adoption studies of affective illness have been performed. The results have been generally consistent with genetic hypotheses. Mendlewics & Rainer

(1977) reported the largest set of bipolar probands (29), a group of control probands and a group of probands with

poliomyelitis. The risk of affective disorder in the biological relatives of the bipolar probands was 31% as opposed to 2% in the relatives of the control probands. The risk in biological relatives of adopted bipolar was similar to the risk in relatives of bipolars who were not adopted (26%). Adoptive relatives did not show increased risk.

Two other adoption studies including a broader class of affective probands (Cadoret 1978, Cadoret et al, 1986) showed evidence for genetic factors, but also possible environmental influences. In these studies adoptive relatives of affective probands had a tendency to excess affective illness themselves, compared with the adoptive relatives of controls. Von Knorring et al (1983) did not find concordance in psyhopathology between adoptees and biological relatives when examining the records of adoptees with depression. Taken together, these data suggest that genetic factors are more clearly prominent in families with bipolar illness than in those without.

The affective disorder adoption studies also provide evidence for genetic factors in suicide. Biological relatives of adoptees with depression had a 15-fold increase in suicide in comparison with biological relatives of control adoptees (Wender et al 1986). A study by Schulsinger et al 1979) suggest that it is not only affective illness that confers a vulnerability to suicide, but that suicide itself may be "heritable" related to personality characteristics such as impulsivity, which in turn has been related to deficient central neurotransmission clinically manifested in low cerebrospinal fluid 5-HIAA (Asberg et al 1986). Autopsy studies of central serotonin receptors in completed suicide are generally consistent with this view (Stanley et al 1986).

Most previous studies have reported the types of illness seen in the children of the affectively ill without regard to the impact of the polarity of the parental disorder (Hagop et al, 1985). Rates for depression have varied from 7% to 75% depending on method of ascertaiment, diagnostic criteria, type of parental illness, and whether one or both parents were affected. In addition to major depression, dysthymic, hyperthymic, conduct, attention deficit, and substance use disorders have all been reported in the offspring.

AFFECTIVE SPECTRUM

Major affective disorder have been found in the relatives of bipolar probands but primarily unipolar disorders in the relatives of unipolars. This suggest that some unipolar illness is genetically related to bipolar illness and that some is not; however, we are unable to distinguish the types on purely clinical grounds at this time. The clinical genetic spectrum of bipolar disorders can be compared by comparing the prevalence of illness in relatives of patients with the prevalence in relatives of controls.

Bipolar II disorders

Bipolar II disorder is defined by periods of depression plus hypomania without frank mania. Most investigators find that this disorder is genetically related to bipolar I and unipolar disorder. However there is some evidence in

recent family studies for excess of bipolar II illness in relatives of bipolar II probands (Gershon et al 1987a). It has been demonstrated that bipolar II disorder tends to be a stable life time diagnosis (Dunner et al 1976).

Rapid-cycling bipolar disorder

Rapid cycling bipolar illness has been a subject of great clinical interest. The entity was defined by Dunner & Fieve (1974) as including patients with four or more episode per year, although individual patients have been described who have regular cycles of 48 hours. There in no evidence that genetic vulnerability to rapid-cycling bipolar illness is different from the genetic vulnerability bipolarity alone. Dunner and colleagues (1977) reported family history data from rapid-cycling patients; 21 of 29 rapid-cycling patients had at least one affective ill relative compared with 123 of 217 non-rapid cycles. Since relatives were not directly interviewed we would expect an underestimate of illness frequency in both groups (Gershon & Guroff, 1984).

In the NIMH series (Nurnberger et al 1988b) 29 out of 195 bipolar episodic schizoaffective patients were judged to be rapid cycles (15%). The age-corrected morbidity risk for major affective disorder was 23.5% in 179 relatives of rapid cycles and 31.0% in 189 relatives of matched non-rapid cyclers.

Unipolar mania

This entity includes bipolar I patients with no history of major depression. They tend to be male, are responsive to lithium and on further history or follow-up are usually found to have at least subclinical depression. This group is not distinguishable from other bipolar I patients on the basis of family pattern of illness (Nurnberger et al 1979).

Seasonal affective disorder

Rosenthal et al (1985) have described patients with a pronounced seasonal pattern, usually with winter depression and euthymia or hypomania during summer. This entity has not been well studied genetically.

Cyclothymia

This condition of repetitive high and low mood swings, generally not requiring clinical attention, is probably genetically related to bipolar disorder (Gershon et al 1982, Akiskal et al 1977).

Schizoaffective disorder

Patients with episodes of mood disorder with psychotic symptoms are probably not different from those without, in terms of risk of illness in family members (Rosenthal et al, 1980). Patients with episodes of mood-incongruent psychosis during depression or intermittent psychosis during euthymia have an increase in affective and schizophrenia illnesses in relatives (Gershon et al 1982). Patients with chronic psychosis and superimposed episodes of mood disorder also confer for both chronic psychosis and mood disorder to relatives but have genetic loading. Most studies of the FDR of patients with schizoaffective disorder

have shown more affective illness, particularly bipolar illness, and to a lesser extent schizophrenia in the FDRs than schizoaffective illness. Although schizoaffective probands tend to have a high frequency of affective illness in relatives, and a low incidence of schizoaffective illness, the twin studies present a very different picture. I McCabe's 1975 review, 13 out of 44 monozygotic twins versus 1 out of 45 same-sex dizygotic twins were concordant for type of illness.

Schizophrenia in Relatives of Affectively Ill Probands

The co-occurrence of schizophrenia and affective disorder also has been observed in families of affectively ill probands. For example, Angst et al (1980), in a large family study, could not find support for the unipolar- bipolar dichotomy in their group of first degree relatives of unipolar and bipolar probands. In addition, although base rates were not reported, among FDRs of their bipolar probands, the morbid risks for schizophrenia and for schizoaffective disorder were higher than expected: 1.9% and 1.5%, respectively. The risk for schizophrenia among siblings was 2.5%, whereas among the probands' children it was 4.8%. In contrast, Loranger (1981), who reported family history data for 200 manic probands, did not find a higher than expected risk for schizophrenia. However in the Loranger study, the relatives' diagnoses were apparently made by persons who were not blind to the probands' diagnoses. In addition, in a Swiss family study, Scharfetter and Nusperli (1980) compared morbid risks for schizophrenia in the first degree relatives of schizophrenic and affectively ill probands and found them to be 8.9% and 3.3%, respectively. Although relatives of normal subjects were not included for comparison, the risk for schizophrenia in relatives of other normal subjects diagnosed by similar criteria (ICD-9) is about 0.6%, suggesting the risk in the relatives of the affectively ill probands in the Scharfetter and Nusperli study is significantly higher than expected. Smeraldi et al (1977) examined the relatives of affectively ill probands in Lombardy and observed a higher than expected risk for Feighner defined schizophrenia in the siblings of unipolar, but not bipolar, probands. Lastly, in the Iowa 500 study (1980), in which the risks for bipolar affective disorder were similar in the relatives of schizophrenic and bipolar probands, the risks for schizophrenia in these relatives were also similar and statistically greater than the risk for schizophrenia in the relatives of normal comparison subjects. The morbid risks for schizophrenia in the relatives of schizophrenic, manic, and normal probands were 5.5%, 3.2%, and 0.6%, respectively. The risk for schizophrenia in the relatives of depressed probands was 1.7%. Nevertheless, failure to find an excess of schizophrenics in the first degree relatives of manic depressive patients has been reported many times. However, in an extension of one of these studies Kendler et al (1985, 1986) did find an excess risk for schizophrenia (4.3%) in the first degree relatives of probands with "psychotic affective disorder". In fact, the risk for schizophrenia in these families was higher than the risk for schizophrenia in the families of schizophrenic probands

(3.7%). The morbid risk for affective disorder in the relatives of these probands was also much higher (20.0%) than base rates, suggesting that severity of proband illness may account for some of the discrepancy among studies assessing the morbid risk for schizophrenia in the relatives of affectievely ill probands. Indeed, in a separate analysis (1985) of the same data base, the same authors estimated the risk for schizophrenia in the relatives of bipolar patients with psychotic symptoms to be 2.5%, compared to 1.0% in the relatives of normal comparison subjects ($p<0.05$). These figures were separate from those for schizoaffective disorder (1.4% versus 0.1% for normal subjects) and atypical psychosis (2.5% versus 0.3% for normal subjects), which were also higher in the relatives of schizophrenic probands. Tsuang et at. (1985) stated, "If affective disorder with psychotic symptoms is not included as a subgroup of major affective disorder, than the results, based on familial data, support the rationale behind the nosological distinction between DSM-III schizophrenia and major affective disorders. However, it seems more reasonable to conclude that the data should be excluded but, rather that the nosology should be modified. Tsuang et al. (1985) further stated. "It may be possible that some affective disorders with psychotic symptoms could be a genetic variant of schizophrenia." But they then concluded, "Therefore, including all affective disorders with psychotic symptoms in the category of DSM-III major affective disorder may lead to over diagnosis of affective disorders."

Finally. in a series of studies, Gershon et al (1982) also assessed the risks for affective disorder and for schizophrenia in the first degree relatives of schizophrenic and affectively ill probands. Relatives of schizoaffective and normal probands were also assessed. In their study they found a familial relationship between schizoaffective and affective disorders, whereas in their 1988 study, they found a familial relationship between schizoaffective disorder and schizophrenia. These findings led to their hypothesis that there are two distinct psychoses, schizophrenia and bipolar affective disorder, and that unipolar and schizoaffective disorders are somehow related to both. Crow (1990) reviewed these studies and concluded that the data strongly suggested a continuum from affective disorder through schizoaffective disorder to schizophrenia. The morbid risks for bipolar and unipolar disorder found by Gershon et al. (1988) in the FDR of schizophrenic probands (2.2% and 14.7%, respectively). They also found that the relatives of chronic psychotic patients who had abused drugs had a morbid risk for unipolar disorder of 18.8%. Coupled with findings of associated birth complications (Lyon et al, 1989) and prenatal viral exposure (1988) among schizophrenic patients, these data are consistent with the expression liability along a continuum from affective disorder through schizoaffective disorder to schizophrenia, depending on the degree of liability and the exposure to various neurologically damaging factors.

A number of studies include data on risk for bipolar illness in relatives of schizophrenia and vice versa. With the

exception of Mendlewics et al 1980, all studies have found that the risk of bipolar illness in the relatives of schizophrenia probands was about 1% and that the risk of schizophrenia illness in relatives of bipolar probands was similarly about 1%. However, some studies have found an increase in depression in relatives of schizophrenia patients (Gershon et al, 1988). This again suggest there are different types of depression on a genetic basis.

Dsythymia

Akiskal (1983) has suggested that a heterogeneous category including some unipolar depression with residual symptom and some characterologic depressive disorders. Definitive family studies remain to be performed. These disorders do not seem to aggregate in relatives of unipolar or bipolar patients (Gershon et al 1982).

Minor depression

Minor depressive episodes are more likely to be found in relatives of affective probands than in the relatives of controls (Gershon et al 1982).

Borderline personality disorder

Available evidence from family studies (Loranger et al 1982, Baron et al 1985) suggests that affective disorder, as well as, borderline personality disorder aggregate in the families of probands with borderline characteristics themselves.

Eating disorders

Family studies of anorexia and bulimia have generally found excess of affective illness in relatives. Risks for affective disorders in relatives of anorexics were very similar to the risk in relatives of bipolar probands (Gershon et al 1984). An increase in eating disorders itself was also found in relatives. A study in normal-weight bulimics did not find excess affective illness in relatives (Stern et al 1984) but the NIMH study did (Kassett et al 1989).

Attention-deficit disorder

Children with attention-deficit disorder appear to have increased depression in their relatives (Biederman et al 1987). The opposite has not been demonstrated. Again this suggest that the type of depression that is seen in relatives of those with other disorders may be distinct.

Alcoholism

There has been disagreement in the literature whether alcoholism tends to concentrate in the families of affective disorder patients. Alcoholism is probably not genetically related to bipolar illness. This controversy may be resolved by studying affective probands who have no alcoholic difficulties themselves. Winokur et al, 1971 has assembled evidence that unipolar depressive patients with alcoholic or sociopathic relatives are distinct from those without (Nurnberger & Gershon 1984). Although bipolar illness and alcoholism are not uncommonly found in the same person, alcoholism by itself without affective disorder does not appear to belong in the

genetic spectrum of bipolar manic depressive illness.

Affective Disorders in children and adolescent siblings of Bipolar illness

The descriptive psychopathological features and causes of affective disorders in prepubertal and adolescent subjects represent areas of intense current clinical research interest (Hagop et al 1985). The available evidence indicates that depression meeting "adult" criteria exits in these age groups, and that mania is not uncommon during adolescence. It has been shown that adult dysthymic and cyclothymic probands are at high risk for developing major affective episodes. Family histories of bipolar illness were common in both groups. In addition to major depression,dysthymic,hyperthymic, conduct, attention deficit, and substance use disorders have all been reported in the offspring.

The main finding is that acute depressive episodes and dysthymic-cyclothymic disorders constitute the most common psychopathologic features in the referred offspring and younger siblings of manic-depressive patients. Only 12% have psychotic depressive onset and 16% had acute manic or mixed onset. The absence of full-blown mania and psychotic depression before puberty is consistent with previous reports.

Thus, we see from the above discussion that the affective spectrum constitutes a wide range of disorders and almost all the studies have been carried out in the West. As there are very few reports from the Asian countries, we had planned this study for our population.

Aims

The present work was conducted with the aim to study the frequency and pattern of psychiatric morbidity in the first degree relatives of affective disorder patients in comparison to those of control subjects.

MATERIAL AND METHODS

I. SAMPLE:

Bipolar Affective Disorder probands:

The sample of the present study consisted of bipolar affective disorder **(BAD)** probands drawn from the in-patient psychiatric section of the Hospital Universiti Sains Malaysia and Hospital Kota Bharu. They were selected according to the following criteria.

Inclusion Criteria:

1) Diagnosis of BAD according to the DSM-III-R criteria.
2) Willingness to participate in the study.

Exclusion Criteria:

1) Past history of psychiatric illness other than mood disorder.
2) History of alcoholism, drug abuse or medical disorders known to be associated with psychopathology (e.g. endocrine and neurological conditions).

Controls

The controls were taken from an earlier study of the authors done in the same population at the primary health centers. The psychiatric morbidity was investigated in patients attending the primary health centers for minor and transient medical problems (Varma et al, 1993).

METHOD:

The first degree relatives (FDR) of 121 patients of bipolar affective disorder were studied in detail according to the following procedure:-

1. The socio-demographic variables and details of the psychiatric history, physical and mental status examination of the relatives was recorded on a semi-structured proforma. The hospital records of probands and relatives, of previous hospitalization and treatment of probands and relatives was also traced as they provide useful information.

2. The screening schedule of Verghese et al (1973) was administered to a relative/friend who was considered by the investigator to be the *"best informant"* (Varma & Sharma, 1993).

3. Detailed evaluation of the FDR was done in accordance with the Interview Guide for Family History-Research Diagnostic Criteria which was completed on the basis of an interview with the best informant.

4. Diagnosis: The affective disorder probands were diagnosed according to the DSM-III-R. The diagnosis of sick relatives was made on the basis of the pooled sources of information (1 to 3) obtained from the psychiatric history, medical records and according to the FH-RDC (Endicott et al 1975). Since FH-RDC includes only antisocial personality disorder (APD), the FH-RDC for schizophrenia related personality disorders (Kendler et al, 1984) was utilized for diagnosing schizoid-schizotypal and paranoid personality disorders (APD).

First-degree relatives of index cases

i) ***Inter-rater reliability***. Inter-rater agreement was analyzed using Cohen's kappa statistic (Fleiss, 1981). Kappa is a measurement of agreement with a "chance-expected" value incorporated. A kappa value of 1 indicates complete agreement. If observed agreement is greater than expected by chance, kappa > 0; and if less than chance, kappa < 0. While the kappa statistic depends on base rate and sample size, categorical groupings have been suggested. For most purposes, a kappa < 0.4 indicates poor agreement, a kappa ranging from 0.4 to 0.75 indicates fair/good agreement, and a kappa > 0.75 indicates excellent agreement..

Thirty-nine first degree relatives of 30 randomly selected index cases, were reviewed independently by two clinicians (AMZ & SLV.) who were blind to the name of the index case. As part of this review, diagnoses were assigned by each of the two clinicians according to the following FH-RDC categories

The overall inter-rater reliability for the diagnosis of relatives was excellent [kappa = 0.89].

ii) ***Comparison of diagnoses based on FH-RDC with those from clinical interviews*** The diagnostic categories of bipolar disorder, major depression, and other axis I diagnosis were compared with the FH-RDC diagnoses in 10 individuals from the sample. The overall inter-rater reliability was excellent (kappa = 0.78).

Age of Onset of Mood Disorder in Index Case

Age of onset for the index cases was defined as (i) the age at which the index case had significant psychosocial impairment from the specific mood disorder and/or (ii) the age at which the index case first sought medical treatment.

It was not possible to accurately assign age at onset for the majority of relatives. Age at examination data, defined as "age at death or age at the time of the genetic interview" were available for all relatives. For this reason, morbid risks rather than empirical risks were calculated.

The family data were collected by indirect methods ("family history method"), i.e., interviewing several (at least two) family members. The study did not use the "family study method" in which each family member is directly interviewed. It was recognized that the former method could result in underreporting of familial cases (Andreason et al., 1977) compared with the family study method. However, we opted to use the family history method mainly because the migratory nature of the population is such that in over 60% of families, first-degree relatives did not live within geographic proximity. In such a population, the "family study" method would have been prohibitively costly, labour intensive and impractical.

Statistical analysis was done using the EPI-INFO 6.0 and SPSS package for statistical analysis.

RESULTS

The study was carried out on the psychiatric patients diagnosed as Bipolar affective disorder according to the DSM-III-R criteria. A total of 140 patients were selected for the study out of which 19 were dropped due to various reasons which included mainly, non-availability of the family members or non cooperation. Thus, finally 121 patients of BAD were included and their first degree relatives formed the sample of the present study. The controls were taken from the earlier study done on the patients attending the primary health centers for minor medical problems, in the same population by the same authors.

Characteristics of the probands

The mean age of the 121 probands was 33.46 years (sd-12.14, range:16-68 years). The male to female ratio was 40.5% to 59.5% (ie 49 and 72 males and females, respectively). There was equal representation from the rural and urban areas. More probands had BAD-Mania as their diagnosis as compared to BAD-depression. The average number of FDRs per family was between 6 and 9, [mode=6 and median=7].

Most of the probands had various levels of education. Only 6.6% were uneducated.

Table - 3 Socio-demographic variables of the probands

Variables	Frequency	Percentage
Sex		
Male	49	40.5
Female	72	59.5
Domicile		
Rural	61	50.4
Urban	60	49.6
Diagnosis		
BAD-mania	65	53.7
BAD-dep	56	46.3
No. of FDRs		
1-3	8	6.8
4-6	39	32.2
7-9	48	39.1
10-12	20	16.5
13-15	6	5.0

Table-4 Educational level of the probands

Education	Frequency	Percent
Nil	8	6.6
< Form 1	26	21.5
Form 2	1	0.8
Form 3	10	8.3
Form 4	2	1.7
Form 5	23	19.0
SRP	11	9.1
SPM	21	17.4
SPM & above	19	15.7

The FDRs of these 121 probands formed the sample of the study. These probands had 900 FDRs who were studied in detail. The siblings constituted about 56% of the FDRs while the rest were from the other two categories.

Table-5 Details of the FDRs of the probands

FDR category	Number Male	Female	Percentage
Parents	121	121	26.89
Siblings	218	293	56.78
Offsprings	69	78	16.33
Total	900		100.00

Table-6 Psychiatric morbidity in the probands' FDR and controls

	Proband FDR N	%	Controls N	%
Sick	106	11.78	78	6.9
Healthy	794	88.22	1059	93.1
	900		1137	
	$x^2 = 14.78$		$p < 0.0001$	

The psychiatric morbidity in the FDRs of the probands was found to be 11.78% as compared the 6.9% found in the general population and this was found to be statistically significant.

Table-7 Pattern of psychiatric morbidity in the relatives of probands and controls

Psychiatric disorder	Proband's FDR N	%	Controls %	N
Bipolar affective disorder	50	5.56	0	0
Depressive disorder	36	4.0	50	4.4
Schizophrenia	7	0.78	2	0.2
Schizoaffective disorder	4	0.44	2	0.2
Attention Deficit disorder	1	0.11	0	0
Alcoholism	2	0.22	0	0
Neurotic disorder	2	0.22	14	1.3
Others	4	0.44	12	1.1
Total	106	11.78	1137	6.9
	x2 = 69.45; df = 7; p<0.0001			

When the prevalence of psychiatric morbidity in the FDR of the mood disorder patients was analyzed it was found that the parents constituted the highest morbidity followed by siblings and offsprings. The detailed analysis is given below.

Table-8 Prevalence of psychiatric morbidity in the FDR of the mood disorder patients

FDRs	Total	Sick	% Sick/total	Percent Sick/900
Parents	242	56	23.14	6.22
Siblings	511	43	8.42	4.78
Offspring	147	7	4.76	0.78
Total	900	106		11.78

Parents vs siblings = 22.96; p<0.001

Siblings vs offsprings = 1.90; p=NS

Parents vs Offsprings = 17.18 p<0.001

Table-9 Morbidity risk of Psychiatric disorders in the FDRs of the probands

Psychiatric disorder	N	Proband's BZ	FDR MR
Bipolar affective disorder	50	424	11.79
Depressive disorder	36	424	8.49
Schizophrenia	7	570	1.23
Schizoaffective disorder	4	570	0.70
Attention Deficit disorder	1	570	0.18
Alcoholism	2	570	0.35
Neurotic disorder	2	570	0.35
Others	4	570	0.70
Total	106		23.79

Table-10 Morbidity risk of Psychiatric disorders in the Parents of the probands

Psychiatric disorder	N	Proband's BZ	FDR MR
Bipolar affective disorder	31	424	7.31
Depressive disorder	22	424	5.19
Schizophrenia	1	570	0.18
Schizoaffective disorder	1	570	0.18
Others	1	570	0.18
Total	56		13.04

Table-11 Psychiatric morbidity in the siblings of the probands

Psychiatric disorder	N	Proband's BZ	FDR MR
Bipolar affective disorder	17	424	4.01
Depressive disorder	13	424	3.07
Schizophrenia	5	570	0.88
Schizoaffective disorder	3	570	0.53
Alcoholism	2	570	0.35
Others	3	570	0.53
Total	43		9.39

Table-12 Morbidity risk of Psychiatric disorders in the Offsprings of the probands

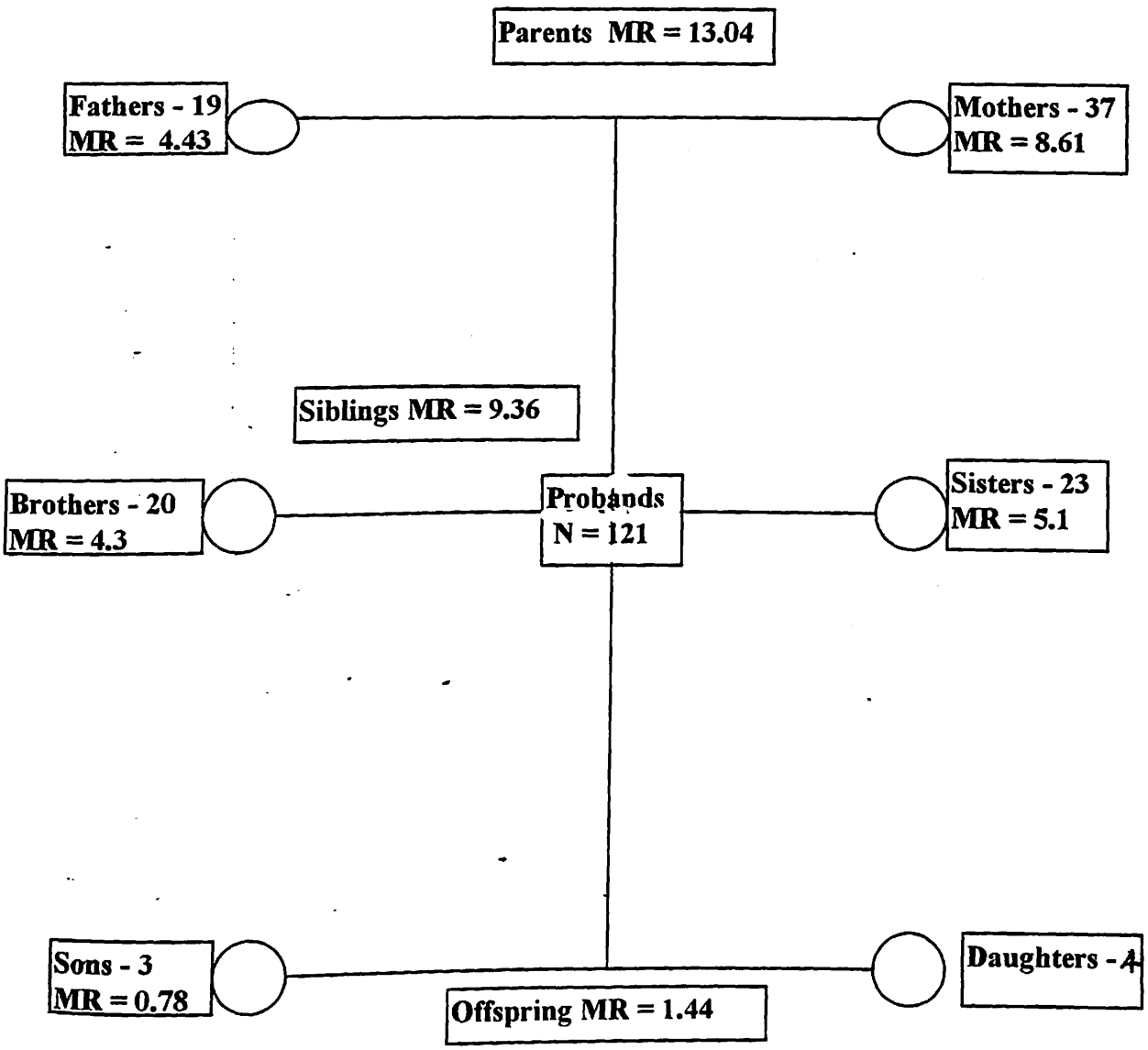
Psychiatric disorder	N MR	Proband's	FDR BZ
Bipolar affective disorder	2	424	0.47
Depressive disorder	1	424	0.24
Schizophrenia	1	570	0.18
Attention Deficit disorder	1	570	0.18
Others	2	570	0.36
Total	7		1.43

Table-13 Relationship of the diagnosis with the FDRs status (Parents, siblings and offspring)

Source of variation	Main effect	Explained	Residual	Total
Sum of squares	36.88	36.88	136.22	173.09
df	7	7	98	105
Mean squares	5.27	5.27	1.39	1.65
F	3.79	3.79		
Sig. of F	0.001	0.001		

ANOVA analysis done by SPSS package.

Figure 1 - Graphic representation of the psychiatric morbidity in the FDRs of mood disorder probands



Discussion

The present study investigated the presence of psychiatric morbidity in the first degree relatives of mood disorder patients. It employed prospective proband selection, patient and family interviews by semi-structured schedule, and diagnosis based on pooled sources of information. The mood disorder probands were diagnosed according to the DSM-III-R criteria while the first degree relatives were diagnosed according to the FH-RDC criteria. A comprehensive diagnostic data on the relatives of mood disorder probands and the controls is presented here for familial transmission of mood disorders in the Malaysian context and its implication for the mood spectrum disorders.

This study was conducted on 121 patients of bipolar affective disorder and their 900 FDRs formed the sample of the study. Psychiatric morbidity was found in 11.78% [106/900] of the FDRs which was statistically higher as compared to the controls which was 6.9%. This finding was much lower than those of 41.2% (Mendelwicz et al 1980), 33% (Baron et al, 1982), 24.7% (Gershon et al, 1981) and 35.3% (Rice et al, 1987). Very few studies have investigated the overall psychiatric morbidity in the relatives of bipolar affective disorder patients. Most of the studies have investigated the risk of BAD or unipolar disorders in the relatives. One of the reasons for lower morbidity in our study may be the poor reporting rate in this culture. The misconceptions and taboos associated with psychiatric patients is still prevalent in the society, albeit at a lower level than before.

Studies in the morbidity risks (MR) for BAD and unipolar disorders have found the MR of between 2.5 - 17.7% for the BAD and between 0.5 - 23.1% unipolar disorders in the families of BAD patients (Table 1). In our study, the MR for BAD was found to be 11.79% which was comparable with the studies of Perris, 1966 (10.2%), Winokur & Clayton, 1967 (10.2%) and Rice et al,1987 (10.4%). But their sample was small as compared to our study. They had 627, 167 and 567 relatives at risk, respectively, which was much lower as compare to 900 FDRs in the present study. Two studies (Johnson & Lemman, 1977 and Mendelwicz & Rainer, 1974) however, have reported higher MR of 15.5% and 17.7%, respectively. On the other hand some studies, Goetzer et al, 1974 and Angst et al, 1980 have even reported MR of as low as 2.8 and 2.5%, respectively for BAD in the families of BAD patients.

The MR for unipolar depression in the present was found to be 8.49% (Table 9), which is comparable to 8.7% (Gershon et al, 1975), 7.15 (Smeraldi et al, 1977), 7.2% (Patterson, 1977) and 7.0% (Angst et al,1980). Again our study had the maximum number of FDRs under study among all. Perris, 1966, however, reported a very low MR of 0.5 for the unipolar disorder while Rice et al ,1987 on the other hand, found a very high MR of 23.1 in their sample.

The morbidity risk of schizophrenia was 1.23% in our sample which is almost comparable to the general population figures and those of Rice et al ,1987

(1.1%) and Mendlewicz et al, 1980 (1.8%). On the other hand, Baron et al, 1982 and Gershon et al, 1988, reported MR of schizophrenia to be 0.7 and 0.3 respectively, which was much lower than our studies as well as some other studies.

Patients with episodes of mood disorder with psychotic symptoms are probably not different from those without, in terms of risk of illness in family members (Rosenthal et al, 1980). Patients with episodes of mood-incongruent psychosis during depression or intermittent psychosis during euthymia have an increase in affective and schizophrenia illnesses in relatives (Gershon et al 1982). Most studies of the FDR of patients with schizoaffective disorder have shown more affective illness, particularly bipolar illness, and to a lesser extent schizophrenia in the FDRs than schizoaffective illness. The morbidity risk for schizo-affective disorder in our sample was found to be 0.70 which was less as compared to the MR of 1.5 % and 1.6%, found in the study of Baron et al, 1982 and Gershon et al,1988, respectively. However, our findings was comparable to the findings of 0.70% reported by Rice et al, 1987.

The controversy whether alcoholism tends to concentrate in the families of affective disorder patients is still on. Only two (MR-0.35) patients of alcoholism were found in the FDRs (siblings) in our study which supports the notion that alcoholism is probably not genetically related to bipolar illness. Winokur et al, 1971 have assembled evidence that unipolar depressive patients with alcoholic or sociopathic relatives are distinct from those without (Nurnberger & Gershon 1984). Although bipolar illness and alcoholism are not uncommonly found in the same person, alcoholism by itself without affective disorder does not appear to belong in the genetic spectrum of bipolar manic depressive illness.

The morbidity risk of psychiatric disorders was found to be highest [13.04- (fathers - 4.43) and (mothers - 8.61)] in the parents of the probands, as compared to the siblings (9.39) and offspring (1.43). This is consistent with the anecdotal evidence that the parents, especially the mothers have the highest morbidity among all the relatives of affective disorder patients. The possible reason for low MR in the offspring might be that they have still not entered the risk period whereas the parents may have either crossed the risk period or about to cross. The diagnosis of the FDRs was found to be significantly ($p<0.001$) correlated with the relationship (parents, siblings or offspring) (Table 13). The most common diagnosis found in the mothers in our study was either bipolar or unipolar depression. Our findings of 4.48 MR for mothers is consistent with the findings of 6.4% in the study of Rice et al 1987. However, they did not find any relationship of the transmission of affective disorder to sex.

Mood disorders probably represent a group of disorders with etiologic heterogenecity (ie. different causes in different families). Autosomal dominant inheritance (with reduced penetrance) has been postulated for at least a portion of families. By definition, the risk for a mood disorder to first degree relatives of index cases in such families approaches

50%. Therefore, inclusion of "high risk" pedigrees suggestive of autosomal dominant inheritance in the calculation of morbidity risks could inflate risk data for families whose pedigrees are not suggestive of this mode of inheritance (Sadovnick et al, 1994).

From the findings of the present investigations, it is apparent that the spectrum disorders are not homogenous with respect to the genetic risk.

Implications for genetic counseling

Growing awareness in the general community concerning the heritability of psychiatric disorders is increasingly leading to requests for advice from clinicians concerning risk of illness, particularly among offspring. Although algorithms have been derived for determining the risk of schizophrenia in a wide variety of possible family combinations for that disorder, no such detailed means of prediction exists for bipolar disorder.

In general terms, there is a consensus that the risk of illness is not sufficient to justify avoiding having children. Studies from Gershon's group indicate that the offspring of a bipolar parent have a 13% risk of bipolar disorder, a 15% risk of unipolar depression and a 1% risk of schizo-affective illness. The risk becomes higher, however, for the offspring of a bipolar parent when the spouse also has an affective disorder. In that situation the rats increase to 50 to 74%.

It must be noted that such figures are statistical averages for groups of patients. Risks to individuals will be higher or lower depending on the prevalence of illness in the particular family concerned. Additionally, the risk of illness is halved for each degree of removal of the person under consideration from the closest related ill individual in the family. With regards to adoption, while in general the number of children available is declining, the proportion of those who have one or both parents with major mental illness is increasing. This has practical implications in counseling prospective adopting parents and in deciding about placement, as well as implications for future adoption studies. Adoption studies of other behaviors may be more difficult, while those of the psychoses may well be more feasible than in the past.

An overly critical analysis of this area might claim that beyond demonstrating familiarity, family studies of affective disorder reveal little else. As the genes for non-psychiatric medical disorders are found, the failure of genetics to provide similar simple and conclusive explanations for the psychiatric conditions such as bipolar disorder may be seen as reflecting a lack of success of this enterprise. However, psychiatric disorders may well be the most difficult areas for the application of genetic techniques, involving problems of diagnosis and definition, aetiological heterogenousity and incomplete and variable expression genotypes. The next few years may also find answer to the question of a major gene.

Limitations

The results of this investigations should be interpreted in the context of its methodological strenghts and weaknesses. The important methodological limitations of the study are as follows:

1.Even though the diagnosis was based in pooled sources of informations, still some underreporting is likely to have affected the results becouse a sizeable proportion of the relative could not be interviewed. However, all the patients were interviewed personally while in many western studies, all/many relatives were interviewed on telephone.

2. Whether controls from the primary health centres having mild and transient medical illness would represent true controls may be debated. A general population survey would have been a better idea, although it was beyond the scope of the present investigation.

3. Familial transmission of affective disorders would not necessarily demonstrate 'genetic' transmission since many acquired conditions, such as, tuberculosis, demonstrated strong familial transmission. However, support for the possible role of genetic factors is shed by adoption and crossfostering studies, which offer a means of separating hereditory from invironmental influences.

Conclusions

1. 121 patients of BAD were included and their first degree relatives formed the sample of the present study.

2. The mean age of the 121 probands was 33.46 years (sd-12.14, range: 16-68 years). The male to female ratio was 40.5% to 59.5% (i.e. 49 and 72 males and females, respectively).

3. The average number of FDRs per family was between 6 and 9, [mode=6 and median=7].

4. These probands had 900 FDRs who were studied in detail. The parents, siblings and offspring constituted 26.89%, 56.78% and 16.33%, of the total sample, respectively.

5. The psychiatric morbidity in the FDRs of the probands was found to be 11.78% as compared the 6.9% in the general population and this was found to be statistically significant ($p<0.0001$).

6. The morbidity risk for the FDR's was 23.79.

7. Parents constituted the highest morbidity (6.22%) followed by siblings (4.78%) and offspring (0.78%).

8. The morbidity risks among the parents, siblings and offspring was found to be 13.04, 9.39 and 1.43, respectively.

9. The psychiatric diagnosis was significantly ($p<0.001$) related to the FDR status (parents, siblings and offspring).

10. Overall more first degree relatives of the mood disorder patients are prone to develop psychiatric morbidity as compared to normals.

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Family History - Research Diagnostic Criteria*(FH - RDC)

PURPOSE

The Family History-Research Diagnostic Criteria (FH-RDC) were developed to enable research investigators to use a consistent set of criteria for diagnosing psychiatric illnesses in relatives of index subjects when it is not possible to examine the relatives directly. These criteria have been developed that, as far as possible, they are similar to those of the Research Diagnostic Criteria which are used when a subject is directly examined. The differences in the two sets of criteria are based on the need to make allowances for the usual inability of informants to supply detailed information about the psychiatric disturbances of another person. Evidence from studies comparing the family history method and the family study method indicates that there are usually more false negatives than false positives when the family history method is used.

INSTRUCTIONS

The FH-RDC may be completed on the basis of an interview (1) the Index Subject himself, or (2) an informant who can supply information regarding the relatives of the Index Subject. If the informant is one of the relatives on whom information is desired, he should be asked about himself as well. FH-RDC data sheets are available for parents, siblings, children, mates, and second degree relatives. The FH-RDC data sheet for second degree relatives is a summary sheet. Some investigators may wish to modify a data sheet for use with second degree relatives for those studies in which the investigator needs a quick and simple summary regarding the family. The data from that sheet will not be sufficiently detailed for many studies.

Before beginning to record the information on the FH-RDC data sheets the rater should explain the purpose of the interview and obtain some overview of the number of relatives to be involved for that particular study. The use of the worksheets to record numbers, names and other information should help in this task. When evaluations are being made for siblings or children, information should not be recorded on the data sheet until is some clarification of the birth order within that class of relatives since the ID numbering system requires this information.* When birth order information is obtained, all live births should be counted. Full and half siblings are counted in order of birth. Children are counted by order of birth regardless of whether they share the same co-parent.

* An ID numbering system suitable for use with the Index Subject and first and second degree relatives as well as mates has been developed. It is quite complicated but serves to link the various members of the family together by using only eight digits. A description of this system is available on request.

When completing the evaluations, the interviewer should use names whenever possible to clarify that he and the informant are discussing the same relative. The detailed questions should be asked about each relative since if one of them had a particularly dramatic problem, problems of others may not be mentioned spontaneously. Since the direction of error in the family history method is under-reporting the detailed questioning for each relative is important.

Some studies will call for the rater to obtain information on the Index Subject from an informant, others will want to rater to be blind to the condition of the Index Subject. If an FH-RDC evaluation is made of the Index Subject, a Sibling data sheet should be used, but the rater should note that it is for the Index Subject.

Whenever there is information suggestive of psychopathology, the interviewer should always ask follow-up questions seeking additional information regarding specific treatments received, course of the illness, specific symptoms, etc. Information should be obtained for each episode of illness if there was more than one. If the criteria are met for one diagnosis, ask questions about the other categories as well.

Note: With the exception of the categories Alcoholism, Drug Use Disorder, Senile Organic Brain Syndrome, and Other Psychiatric Disorder, all of the other conditions are to be diagnosed only when there is no likely known organic etiology for the symptoms, such as ingestion of a hallucinogen or arteriosclerosis.

USE OF INTERVIEW GUIDE FOR FH-RDC:

The following interview guide should be used as an AID in obtaining information about the Index Subject's relatives (including mates). The interviewer must be very flexible in deciding which questions should be asked and if it is necessary to continue with the interview regarding a particular relative. The questions should be asked for each relative in turn to assure that none is overlooked. (Obviously the appropriate name or sex should be used). Inquiry regarding the siblings and children should proceed by birth order within the family. Follow-up questions should be asked whenever there is evidence of psychopathology and the interviewer should be familiar enough with the specific criteria of the diagnoses to ask the necessary clarifying questions. Notes should be made to aid later in summarizing.

INTERVIEW GUIDE:

How old is (name)? (How old was he when he died? What was the cause of his death?) Has he ever had any emotional or psychiatric problems? What was he like? Was he ever treated for these? Did he take medication, have ECT, (other somatic therapy)? Was he ever hospitalized? (How many times?) Was he ever unable to work (take care of the house, go to school) because of these problems? What kinds of symptoms did he have? Did he ever attempt suicide? (Try to obtain a full description of the episodes of illness including course, symptoms, outcome, interval functioning). Clarify by asking the following questions for each area with appropriate modification depending upon information already available.

Depression: Did he ever have a period of more than 2 weeks he was depressed, felt sad, down in the dumps, didn't care about anything, was guilty, or some other bad mood like being anxious, irritable, or worried? Did he have any problem with his appetite, sleep too much or too little, have a loss of energy? Did he lose or gain weight, pace or wring his hands, or move and speak slower than usual?

If yes: determine nature of mood and associated symptoms; if he was treated; degree of impairment; and the course of the illness; other symptoms at the time which might suggest Schizo-affective Disorder.

Mania: Did he ever have a period when he felt euphoric, high, on top of the world or was impatient and irritable? Was he more active, sociable, or energetic than usual? Was he more talkative or jumping from one idea to another? Did he have decreased need for sleep? Did he feel he had special abilities or powers or that he could accomplish great things? Did he get involved in many activities or become more active at work, socially, or sexually? Did he show poor judgement such as spending a lot of money or going into bad business ventures?

If yes: determine nature of mood and associated symptoms; if he was treated; degree of impairment and course of the illness; and other symptoms at the time which might suggest Schizo-affective Disorder.

Schizophrenia or Schizo-affective Disorder: Did he ever have unusual ideas or beliefs (clarify to determine if they are delusions)? Did he feel controlled by outside forces? Did he hear voices or see visions? Did he behave strangely or dress strangely? Did he speak in such a way that no one could understand what he was saying?

It is important to try to clarify the nature of the delusions or hallucinations. The course of the illness should be determined especially as to the degree to which the patient was left with social withdrawal, deterioration in functioning, lack of normal affect, or failure to return to the previous level of functioning. The nature of the onset of the period of illness, insidious as compared to fairly sudden, should be clarified.

Alcoholism: Did he ever have a problem with drinking? (How long, how often?) Did he have any legal problems like being arrested or losing his driver's license? Did he have any problems with his health, like DT's, blackouts, cirrhosis, gastritis? What about problems in his marriage or with his family? Did it cause any problems with his work (ability to keep house)? Did he lose jobs or have to give up some kind of work? Was he ever treated for alcoholism, such as with antabuse, hospitalized, or attending AA or some other group for alcoholism? What about fights, losing friends?

Drug Use Disorder: Did he use drugs, such as marijuana, LSD, heroin, amphetamines, sleeping pills, or anything like that? Did he have any problems because of this? What about legal problems, having to steal to get money for drugs, or arrested for selling drugs? Did he have any problems with his health, such as infectious hepatitis, or withdrawal symptoms when he couldn't get drugs? Any problems in his marriage or with his family because of his drug use? What about problems holding a job or at work or in taking care of his home?

Antisocial: Was he ever arrested or in prison? Did he get into fights? What about stealing? When he was young did he run away from home, get expelled from school or was he often truant? Did he lie a lot? Was he out of work a lot? What about changing jobs because he was fired or quit? Was he divorced 2 or more times or did he desert his family or frequently attack his wife? If yes to 3 of the criteria: Make sure it began before age 15 and has persisted several years past age 15 and was not limited to a period of another illness (such as Mania).

Other Symptoms: If it is not already apparent, clarify if he had some psychiatric symptoms which do not fit into the criteria for a specific diagnosis. Was he a "nervous" person? Did he have special fears or certain things he had to do just right? Was he very distrustful of other people? Did he stay by himself most of the time? Did he behave peculiarly or do strange things? Did he lose his jobs frequently because of emotional problems? Was he impulsive or did he decide to do things that were unrealistic? Did he have problems with other people because of his behavior or attitude?

CRITERIA FOR ITEMS ON THE FH-RDC DATA SHEETS

In checking the items, use your best clinical judgement given the information available. Avoid question marks.

Age if living: If unknown, give best estimate.

Age at death: If alive, leave blank; if dead, give best estimate

Natural death: If alive, leave blank; check if cause of death appears to be natural.

Accidental death:* If alive, leave blank; check if cause of death appears to be accidental (describe).

Suicide attempt: Check if in your judgment there is information suggestive of a suicidal gesture or attempt.

Completed suicide:* Check if the cause of death appears to have been suicide (describe).

Period of social incapacitation for psychiatric reason: Check if at any time the person being described was apparently unable to work, go to school, take care of the house, or take care of other expected social responsibilities, as a direct or indirect (e.g., in the hospital or in jail) consequence of psychiatric problems.

Hospitalized for psychiatric reason: Check if the person being described has been in a psychiatric hospital or on a psychiatric service in a general hospital or if hospitalized because of what the family considers emotional problems.

Number of psychiatric hospitalizations: Using the above definition, note the number of different psychiatric hospitalizations. If known to be at least one, but exact number is unknown, give best estimate.

Somatic treatment for psychiatric reason: Check if the person being described has received ECT, insulin or known psychotropic drug or drugs, or other somatic treatment "for his nerves".

Psychotherapeutic treatment for psychiatric reason: Check if the person being described has ever seen a health professional (including guidance or marriage counselor or family M.D.) for "talk sessions" about their personal psychiatric problems.

Age at first psychiatric illness: Give best estimate of the earliest age at which psychiatric problems were severe enough to qualify for one of the specific diagnoses (including Other Psychiatric Disorder).

Diagnoses: If the person being described has met the criteria for more than one diagnostic category, indicate the chronological order on the Data Sheet by putting a 1 for the condition that developed first, a 2 for the next, etc.

If there is no information about a specific relative, check "No Known Mental Disorder", and under Completeness of Information "Essentially No Info."

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* The circumstances of death should be described in the comment section, especially in accidental death or when unsure how to classify death (fire, concentration camp, etc.).

A judgment of the completeness of information should be made for the particular relative being described, keeping in mind that informants rarely have detailed knowledge about their relatives.

1. **Chronic Schizophrenia** (May include paranoid states or paranoia)

A through C are required

A. No prominent symptoms of an overlapping mood disturbance (as described under A of Schizo-affective Disorder).

B. At least 1 of the following:
(1) Delusions.
(2) Hallucinations.
(3) Incoherence.
(4) Grossly bizarre behavior (e.g., carries feces around in pocket).

C. Evidence of an illness that lasted at least 1 year from which he never recovered, i.e., continued to show significant signs of the illness (e.g., impaired functioning, blunted affect, social withdrawal).

2. **Schizo-affective Disorder** (Manic and/or Depressed)

A through C are required.

A. Evidence of a prominent and persistent dysphoric or manic mood disturbance
Dysphoric mood:
Either 1) a depressive mood (e.g., sad, down in the dumps, don't care, suicidal ideation, tearful, etc.).
Or 2) some other dysphoric mood (e.g., anxious, irritable, worried) and at least 2 of the following symptoms: loss of interest, poor appetite, sleep changes, loss of energy, psychomotor agitation or retardation, guilt or self-reproach, impaired concentration.

Manic mood:
Either 1) an euphoric mood (e.g., felt great, on top of the world, laughing, singing, etc.).
Or 2) an irritable mood and at least 2 of the following symptoms: more active than usual, either socially, at work, or sexually; physically restless; more talkative

han usual; elevated self-esteem; decreased need for leep; distractible; excessive involvement in activities which indicate poor judgment.

3. 1 of the following:

1) Delusions known to be not limited to simple paranoid, lepressive, or grandiose delusions or depressive somatic lelusions (e.g., believes he has a transmitter implanted n his brain).

2) Hallucinations known to be not limited to depressive ır grandiose content.
3) Incoherence.
4) Grossly bizarre behavior not clearly due to manic nood (e.g., collects his feces).

. Some evidence that symptoms in A and B overlapped omewhat temporally.

Note if manic and/or depressed or if has had two clear-ut periods which differed, mark both on the data sheet.

Note if primarily remitting or chronic. Choose the one which best describes the course. Remitting (1): No vidence that the period of illness had an insidious onset ver a period of several years, no evidence suggestive of chronic deteriorating course and that the symptoms in lasted more than one year without subsequent full emission. Chronic (2): There is evidence of an insidious nset or a chronic deteriorating course, or the symptoms B lasted more than one year without subsequent full emission.

Depressive Disorder

Excludes grief reactions following the loss of a loved ne if all of the features are commonly seen in members f the subject's subcultural group in similar ircumstances. If the grief reaction was unusually severe r prolonged or very atypical, record it as a disorder. through E are required.

. Evidence of a dysphoric mood change to:

ither (1) a depressive mood (e.g., sad, down in the umps, don't care, worthless, suicidal ideation, tearful, c.),

r (2) some other dysphoric mood (e.g., anxious, ritable, worried), and at least 2 of the following sociated symptoms: loss of interest, appetite or weight ange, sleep change, loss of energy, psychomotor itation or retardation, guilt or self-reproach, impaired ncentration

B. At least 1 of the following is associated with symptoms in A.

(1) ECT or known antidepressant medication.
(2) Hospitalization.
(3) Suicidal behavior.
(4) Treated for either A1 or A2.
(5) Gross impairment in work, housework, or school, or social withdrawal.
(6) Had 4 associated symptoms listed in A (2).

C. No evidence suggestive of a chronic non-affective deteriorating course (but may have some residual symptoms) other than accounted for by Alcoholism.
D. No evidence that the period lasted less than 2 weeks.

E. Does not meet the criteria for Schizo-affective Disorder for the same period of illness.

Note if primarily remitting or chronic. Choose the one which best describes the course. Remitting (1) evidence that the period(s) had relatively clear onset and offset with different interval functioning; Chronic (2) evidence that the depressive disorder tended to be chronic (i.e., lasted at least one year) without clear onset and offset and without subsequent remission.

If meets the criteria for Depressive Disorder and Manic Disorder, record both.

4. Manic Disorder

A through D are required.

A. Evidence of a mood change to :

Either (1) an euphoric mood (e.g., high, felt great, on top of the world, laughing, singing, etc.),

Or (2) an irritable mood and at least 2 of the world, laughing, singing, etc.), sociable, or energetic than usual, talkative, jumped from 1 idea to another, elevated self-esteem, decreased need for sleep, excessive involvement in activities which indicate poor judgment, such as excessive spending of money.

B. 1 of the following is associated with the symptoms in A.

(1) Treated for manic-like symptoms.
(2) Impairment in work, housework, or social activities
(3) Obviously inappropriate behavior

apparently due to the manic symptoms.
(4) Euphoric mood plus 2 of the associated symptoms listed in A (2).

C. No evidence suggestive of a chronic non-effective deteriorating course (but may have some residual Symptoms).

D. Does not meet the criteria for Schizo-affective Disorder for the same period of illness.

5. **Senile Organic Brain Syndrome**

Significant impairment in memory or orientation to time, place or person, occurring after the age of 50 without complete recovery. The condition seems most likely associated with the process of aging rather than a tumor, alcoholism, or use of a drug.

6. **Unspecified Functional Psychosis***

A and B are required.

A. An episode of psychosis (as defined in B below) which does not meet the criteria for Chronic Schizophrenia, Schizo-affective Disorder, Depressive Disorder, Manic Disorder, or Senile Organic Brain Syndrome. (This category will probably include some paranoid states, remitting non-affective schizophrenia, hysterical psychosis, and other brief psychotic episodes.)

B. At least 1 of the following

(1) Delusions.
(2) Hallucinations.
(3) Incoherence.
(4) Grossly bizarre behavior.
(5) Hospitalization for several years.

If meets the criteria, note if it was a remitting disorder (i.e., no evidence that the period of disorder lasted more than one year without subsequent remission) or a chronic disorder (lasted more than one year without subsequent remission). Also note if there was any suggestion of a dysphoric mood (as in Depressive Disorder) or associated symptoms as noted under 3A. Finally, note the most likely clinical diagnosis using DSM-III categories.

7. **Alcoholism**

A and B are required.

A. Problem with drinking not limited to isolated incidents.

B. At least 1 alcohol related problem in the following areas:

(1) Legal problem (e.g.,public intoxication, disorderly conduct, traffic violations).
(2)Health problem (e.g.,cirrhosis, DT's, blackouts, etc.).
(3) Marital or family problems.
(4) Work problem or impairment as housekeeper.
(5) Treatment for alcoholism (e.g.,antabuse) or attended AA.
(6) Social problems, flights, loss of friends.

8. **Drug Use Disorder**

A and B are required.

A. Problems with drug use not limited to isolated incidents.

B. At least 1 drug-related problem in 1 or more of the following areas:

(1) Legal problem (e.g., stealing, disorderly conduct, traffic violations).
(2) Health problems (e.g., physical addiction, infectious hepatitis).
(3) Marital or family problems.
(4) Work or school problems or impairment as housekeeper.
(5) Treatment for drug abuse.

9. **Antisocial Personality**

A through C are required. (If parent of Index Subject, prison alone is sufficient unless known to be due to a minor offense).

A. Onset of problems in B probably began before age 15. The diagnosis should not be given in individuals below the age of 18.

B. At least 3 of the following:
(1) Fighting.
(2) Stealing (not limited to support of drug habit).
(3) Truancy.
(4) Ran away from home.
(5) Expelled from school for a behavioral problem.
(6) Trouble with the law leading to arrest, probation, or imprisonment.
(7) Persistent and repeated lying.
(8) Many jobs changes because of being fired or quit jobs, or never worked because of antisocial behavior.
(9) 2 or more divorces, deserted family, or

frequent physical attacks on spouse

C. Does not meet the criteria for Chronic Schizophrenia or Chronic Schizo-affective Disorders as defined in this manual.

10. **Other Psychiatric Disorder***

This category is for subjects with good evidence of significant psychopathology which is not clearly classifiable in any of the previous categories, including Unspecified Functional Psychosis. It should be used to indicate (1) episodes of psychopathology which suggest but do not meet all of the criteria for one of the preceding disorders. (2) other clinically recognizable conditions [i.e., Phobic Disorder, Briquet's Disorder (Somatization Disorder), Depressive Personality],, (3) nonspecific conditions (e.g., nervousness), or (4) symptoms which strongly suggest organicity and which cannot be categorized under Alcoholism, Drug Use Disorder, or Senile Organic Brain Syndrome. It may be the only diagnosis noted, or may be noted in addition to one of the previously specified categories.

At least 1 of the following is required:

(1) Sought help from someone or was hospitalized, apparently for psychiatric problems.

(2) Took medication for the psychiatric condition (other than occasional night-time hypnotic for insomnia).

(3) Impairment in functioning socially, with family, at home, or at work, apparently due to psychiatric problems.

(4) Had a recognized psychiatric symptom, such as prominent nervousness or irritability, extreme suspiciousness, conversion reaction, or amnesia.

(5) Had persistent odd, bizarre, or eccentric behavior.

(6) Extreme and persistent social isolation.

(7) Persistent impulsive or unrealistic behavior.

If the condition is recognizable or nearly meets the iteria of one of the specific diagnoses listed previously ite your diagnosis on the data sheet using RDC terms hen possible (e.g., "probable Manic Disorder," "Panic sorder," or "Phobic Disorder").

f meets the criteria, note if it was a remitting (lasted s than one year) or chronic disorder (lasted more than year), and if there was a dysphoric mood present (as Depressive Disorder).

11. **Bipolar**

This category is for subjects who have met the criteria for both Depressive and Manic Disorder.

12. **Recurrent Unipolar**

This category is for subjects who have had two or more episodes of Depressive Disorder and never had periods of Manic Disorder.

13. **No Known Mental Disorder**

This category is for two types of subjects: (1) those who are known to not have had sufficient signs of disturbance to warrant being given any of the previous diagnoses, including Other Psychiatric Disorder, and (2) those about whom little or no information is available. Of necessity, this category will therefore, include some false negatives because of lack of information.

Miscellaneous Information (optional)

This section contains some items of interest to many investigators. The rater may leave them blank or use his best to answer them.

Color blindness: This item might help tag "informative families".

Non-mental medical illness: The illnesses inquired for will vary by study.

DSM-III diagnoses: Sometimes the description will be sufficiently detailed to allow the rater to note a more specific diagnostic impression, e.g., Paranoid Schizophrenia. Note the diagnosis in sufficient detail to code to five digits, if possible.

Review your notes and diagnosis(es) and summarize the information on the FH-RDC Data Sheet.