

## PSYCHIATRIC MORBIDITY PATTERN OF THE FIRST-DEGREE RELATIVES OF SCHIZOPHRENICS: CROSS-SECTIONAL STUDY

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**ABSTRACT: CONTEXT:** Family, Twin and Adoption studies show the inheritance patterns of schizophrenia. The findings from these studies provide support to the claim that familial clustering of schizophrenia is a combined expression of genetic and environmental factors.

**AIMS:** Following the line of previous research, this study attempts to find out any difference in the psychiatric morbidity pattern among the first-degree relatives of familial and sporadic schizophrenics.

**SETTINGS AND DESIGN:** We conducted a cross-sectional survey among a convenience sample of 100 first-degree relatives (age between 18 to 55 years) of familial (n=22) and sporadic (n=29) schizophrenics from psychiatric outpatient clinic, of a Government Hospital, India. The schizophrenics satisfied the DSM-IV criteria and all the first degree relatives interviewed never had any psychiatric consultation before or were abusing alcohol or other substances or having any organic pathology.

**METHODS AND MATERIAL:** Informed consent from the patients and relatives was obtained. Survey questionnaires were administered and no personal identifying information was collected. Middle Sex Hospital Questionnaire (MHQ), Eysenck's Personality Questionnaire (EPQ), Multi-Phasic Personality Questionnaire (MPQ) and Screening Test for Co-Morbid Personality Disorders (STCPD) were administered to the participants.

**STATISTICAL ANALYSIS:** The two groups of relatives were then compared on various scales with each other. The chi-square test was used as statistical test of significance p value of  $\leq 0.01$  was taken as highly significant and  $\leq 0.05$  considered significant observation for all the variables studied.

**RESULTS:** MHQ illustrates that the two groups differ in anxiety, obsession traits, MPQ demonstrates that the two groups highly differ in schizophrenia, anxiety traits, EPQ depicts that the two groups highly differ in psychoticism, STCPD show that the two groups significantly differ in dependent, avoidant, and borderline personality disorders and The two groups highly differ in schizoid – schizotypal personality disorder, less significantly in paranoid personality disorder using diagnostic criteria for schizophrenia related personality disorder.

**CONCLUSIONS:** Significant differences exist between the first-degree relatives of familial and sporadic schizophrenics. Familial clustering of some of the psychiatric disorder and personality factors lent support to the genetic inheritance of traits/disorder in the first-degree relatives of familial schizophrenics.

**KEYWORDS:** Familial Schizophrenia, Sporadic schizophrenia Genetic transmission, Family studies.

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**INTRODUCTION:** Scientific evidence posits that schizophrenia is genetically transmissible. The two chief architects of the concept of schizophrenia, Kraepelin and Eugene Bleuler, noted that close relatives of patients with schizophrenia had odd or eccentric personality that was clinically reminiscent of schizophrenia. Family, Twin and Adoption studies have been done from time to time to study the inheritance patterns of schizophrenia.

The life time morbid risk of developing schizophrenia among the relatives of schizophrenia probands increased with the degree of genetic relatedness to the affected individuals (Gottesmen, 1991).<sup>1,2</sup> The risk to third – degree

relative was 2%; to second-degree relatives around 4% to 6%; to siblings or children around 9% to 13% and to identical twins or the off springs of dual mating, 46% to 48%. The risk increased if more than one relative was affected; the risk if a parent were affected was 17%. The risk for a parent of a proband to be affected was lower than that of other first-degree relatives (6%).

Twelve major twin studies of schizophrenia have been effectuated so far. Kendler (1984) pooled the results of 12 studies and found the probandwise concordance rate for monozygotic (MZ) twins to be 53%, as opposed to the 15% for dizygotic (DZ) twins, giving an overall heritability estimation of 68% for the underlying liability to schizophrenia.<sup>3</sup> Similarly a later Norwegian study (Onsted, Skre, et al 1991) that used DSM III-R Criteria reported that MZ twins concordance rate of 48% compared with 4% among DZ twins.<sup>4</sup> Recent results from an epidemiologic twin study of schizophrenia in Finland by Cannon, Kaprio et al (1998) indicated that 83% of variance in liability to

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schizophrenia is caused by additive genetic factors and remaining 17% is caused by unique environmental factors.<sup>5</sup>

MZ discordance for schizophrenia may be caused by reduced penetrance of a schizophrenia genotype or the presence of sporadic or non-genetic causes. The first explanation would predict an increased risk of schizophrenia and schizophrenia related disorders among the offspring of the unaffected twin of a discordant MZ pair. This was proved beyond doubt in a Danish study by Gottesman and Bertelsen (1989), which reported that the schizophrenia and related disorder among the adult offspring of discordant MZ pair was found to be strikingly similar for the affected (16.8%) and unaffected (17.4%) twins.<sup>6</sup>

Danish adoption study by Rosenthal, Wender, Kety et al (1968, 1974) provided compelling evidence that adoptees with schizophrenia had higher rates of schizophrenia in their first-degree relatives than control adoptees.<sup>7</sup> A reanalysis of these data in 1987 confirmed the original finding that biological relatives of schizophrenia adoptees had significantly higher rate of schizophrenia (4.1%) than biological relatives of non-schizophrenia control adoptees (0.5%).<sup>8</sup>

Results from another large adoption study in Finland by Tienari and co-workers (1991, 1997) found that significantly more offspring of mother with schizophrenia (9.1%) than control offspring (1.1%).<sup>9</sup>

The combined findings from these adoption studies provide important support for the conclusion derived from family and twin studies that familial clustering of schizophrenia is an expression of genetic factors to a large extent and to lesser extent, the environmental factors.

Gottesman and Shields (1967) proposed "liability threshold model" to explain the genetic transmission of schizophrenia. In this model the liability to develop schizophrenia is normally distributed in the population and is due to multiple genes of small effect acting additively and in combination with environmental factors, but only in individual whose liability exceeds a certain critical threshold manifest the illness. The number of genes involved in such a model is unpredictable and inheritance could be oligogenic - a small number of genes of moderate effect (e.g. >100).<sup>10</sup>

The first-degree relatives of familial and sporadic schizophrenia differ in their psychiatric morbidity, personality disorder, etc. Sporadic schizophrenics are more often winter born (O'Callaghan E, Lipson T, Colohan HA et al 1990,<sup>11</sup> Dassa, Sham, Van et al 1996.<sup>12</sup> Kitamura, Takazama, 1995,<sup>13</sup> Kinney, Levy 1994)<sup>14</sup> and are more likely to have obstetric complication, increased minor physical anomalies, (Griffiths Sigmandsson, 1998),<sup>15</sup> increased CT scan abnormalities, (Roy, Flaum et al 1994,<sup>16</sup> Lewis et al 1987)<sup>17</sup> and increased paternal age (Malaspina et al 2001, 2002)<sup>18</sup> than the sporadic schizophrenia.

Following the line of previous research, this study attempts to find out any difference in the psychiatric morbidity pattern among the first-degree relatives of familial and sporadic schizophrenics.

**METHODS: Participants:** We conducted a cross-sectional survey among a convenience sample of 100 first-degree relatives (age between 18 to 55 years) of familial (n=22) and sporadic (n=29) schizophrenics from psychiatric outpatient clinic, of a Government Hospital, India. The schizophrenics satisfied the DSM-IV criteria and all the first degree relatives interviewed never had any psychiatric consultation before or were abusing alcohol or other substances or having any organic pathology. Patients and their relatives were informed of the purpose and nature of this study and voluntary consent from the patients and relatives was obtained. Survey questionnaires were administered and no personal identifying information was collected.

**MEASURES: Middle Sex Hospital Questionnaire**

**(MHQ):** The MHQ is a self-rating scale of psychoneurotic symptoms and traits developed by Crown and Crisp,<sup>19</sup> comprising 6 subscales which are designed to measure free floating anxiety (FFA), phobic anxiety (PHO), obsession traits and symptoms (OBS), somatic concomitants of anxiety (SOM), Depression (DEP) and hysterical personality traits. The authors present extensive standardization data on a normal sample for the MHQ. Age and social class have no consistent relation to the test, and can be ignored in normal clinical use. The relationship of score on the subtests, to sex needs further enquiry. The MHQ has an acceptable repeat reliability and may be useful in clinical and psychosomatic research. Since its construction, various authors, all of whom demonstrated its utility and superiority over other scales, use the MHQ. Prabu (1972)<sup>20</sup> used the MHQ in the Indian setting and found it to be of same efficacy as claimed by original authors. He also found the repeat reliability of each of the sub-tests to be good and total score of the test to correlate +0.62 with N score of the E.P.I.

**Eysenck's Personality Questionnaire (EPQ)<sup>21</sup>:** EPQ is based on the personality theory of J.G. Jung initially known as personality questionnaire. This scale contains the following dimensions: Extroversion/ Introversion, Neuroticism, Psychoticism. It also contains lie scale. This scale has been widely used in English speaking countries. In India it has undergone few revisions and standardizations.

**Multi-Phasic Personality Questionnaire (MPQ):**

MPQ is short form of Minnesota Multiphase Personality Inventory (MMPI) standardized by Dr. H.M Murthy on different stage starting from the year 1965 (Dr. H. M. Murthy 1965, development of the paranoid, Hysteria, Psychopathic deviation and K scale). It is widely used in this part of the country. It is used as a diagnostic scale and as well as to identify the personality profile.

### Screening Test For Co-Morbid Personality Disorders

**(STCPD):** STCPD is a modified version of the Revised Personality Diagnostic Questionnaire (PDQ-R). The PDQ-R has 152 questions that are answered as true or false and takes about 30 minutes to complete. It allows each of the criteria for the DMS III-R PDs to be scored as present or absent (Hyler et al, 1992;<sup>22</sup> Reich & Troughton 1988).<sup>23</sup> PDQ is a self-report questionnaire and the PDQ and revised version of PDQ are easily administered (Widiger & Frances, 1987,<sup>24</sup> Reich 1989)<sup>25</sup>. As the time required by subject and scorer for this procedure may limit its use, a shorter version was devised by J.H.Dowson (1992).<sup>26</sup>

In 1992, Dowson studied to develop and investigate the use of a shorter version called screening test for Co-morbid personality disorder and found that it can predict the number of Co-morbid DSM-III R PDs. This shorter version (STCPD - Subjects version) was used in this study to assess the personality disorders. The PDs covered in this questionnaire are Avoidant, Histrionic, Dependent, and Borderline. There are 51 questions in this scale that are answered true or false. The scoring is done by the method mentioned in the scale.

### Diagnostic criteria for schizophrenia related personality disorder:

This criterion was used to assess schizophrenia related personality disorder in this study. The criteria include schizoid-schizotypal personality disorder and paranoid personality disorder related to schizophrenia. This diagnostic criterion was adapted from the authors Kenneth S. Kendler, Catherine C. Masterson, Roseann Ungaro and Kenneth L. Davis.<sup>27</sup> They have used this diagnostic criterion while studying whether family history method can be used to detect cases of schizophrenia related personality disorder in the families of schizophrenics. The authors applied these criteria in a blind family history study.

**Analyses:** The two groups of relatives were then compared on various scales with each other. The chi-square test was used as statistical test of significance p value of  $\leq 0.01$  was taken as highly significant and  $\leq 0.05$  considered significant observation for all the variables studied.

**RESULTS: Characteristics of the Sample:** A total of 51 patients were selected for the study. There were 22 patients in the familial schizophrenic group and 29 patients in the sporadic group. The sub-type of schizophrenia in probands of familial group (n=22) were: Paranoid schizophrenia =14, Catatonic =3, and Disorganized= 5. Fifty relatives (males=25 and females=25) of the probands of familial schizophrenic group were chosen. The sub-types of schizophrenia in probands of sporadic group were: Paranoid=21, Catatonic=2, Disorganized=4 and Undifferentiated=2. Fifty relatives (males=28 and females=22) of the probands of sporadic schizophrenic group were chosen.

**Findings:** The comparison of first-degree relatives (FDS) of familial and sporadic schizophrenic using MHQ illustrates that the two groups differ in anxiety, obsession and to some extent in depression scale and there is no significant observation in phobia, somatic, hysteria scales [Table 1].

The comparison of first-degree relatives (FDR) of familial and sporadic schizophrenia MPQ demonstrates that the two groups highly differ in schizophrenia, anxiety and to some extent in Mania scale. No difference is noted in other scales [Table 2].

The Comparison of first-degree relatives (FDR) of familial and sporadic schizophrenia using EPQ depicts that the two groups highly differ in psychoticism. No difference is noted neuroticism and extroversion [Table 3].

The comparison of first-degree relatives (FDR) of Familial and Sporadic schizophrenia STCPD show that the two groups significantly differ in dependent, avoidant, and borderline personality disorders [Table 4].

The two groups highly differ in schizoid – schizotypal personality disorder, less significantly in paranoid personality disorder on comparing first-degree relatives (FDR) of familial and sporadic schizophrenics using diagnostic criteria for schizophrenia related personality disorder [table 5].

**DISCUSSION:** A high significant difference (Table 2) was observed for obsession and anxiety on MHQ in the first-degree relatives of obsessive, anxiety symptoms in the first-degree relatives of familial group. The association between schizophrenia and OCD symptoms has been described in several studies that found frequency ranging from 7.8 to 40.5 % (Fenton et al 1986,<sup>28</sup> Berman, Kalinowaski et al 1995,<sup>29</sup> Elizen, and Beer et al 1997).<sup>30</sup> OCD symptoms may represent a part of a continuum of symptoms or represent a "forme fruste" of schizophrenia existing on the same psychotic continuum as suggested by Dowling et al (1995). Hence first-degree relatives are also at risk of inheriting the symptoms. However one has to interpret this finding cautiously, since the study did not include all first-degree relatives.

Another neurotic variable 'anxiety' also presents with high significance (Table 2, Table 3) and indicate that these two groups differ significantly. Both anxiety and OCD are grouped under the same "Anxiety Disorder", so it is not surprising that there is an excess manifestation of anxiety symptoms in the first-degree relatives of familial group.

Yung, Phillips et al (2000)<sup>31</sup> identified anxiety and depressive symptoms as "at risk mental state" for an impending psychosis and this strategy was utilized successfully in personal assessment and crisis evaluation services (PACE). However, in one study no excess of anxiety disorder and alcoholism has been found in the relatives of schizophrenia patients compared with relatives of control group (Kendler et al 1993,<sup>32</sup> Parnas et al 1993, Kety et al 1994).<sup>33</sup> Since it is a cross sectional study, this finding should be interpreted cautiously whether anxiety state represent a trait marker in the familial groups of schizophrenia.

Highly significant observation is made for mania (table 3) and depression (table 1). This again distinguishes the familial and sporadic form of schizophrenia. This observation is in accordance with the Roscommon patients who appear to have an increased predisposition to develop psychotic symptoms as part of an affective illness (Kendler, McGuire et al 1993).<sup>34</sup>

Taylor, Abrams (1984) reports maniacs satisfying DMS III Schizophreniform criteria had more depressive symptoms.<sup>35</sup> Berrctini (2000) examined the first-degree relatives of patients with bipolar disorder and reported an increased incidence of schizoaffective disorder.<sup>36</sup> Erlenmeyer-Kimling, Adamo et al (1997),<sup>37</sup> Subotnik (1997) reports children of patients with affective disorder were equally as likely as children of schizophrenic patients to develop schizoaffective disorder. Hence an overlap of symptoms can occur in schizophrenic first degree relatives and relatives of affective disorder. This study also confirms excess of affective symptoms in the first degree relatives of familial schizophrenic patient, however the increased incidence of affective symptoms in the first degree relatives of familial schizophrenics should be investigated further because of the cross sectional nature of the study and its limited sample size.

Significant observation is noted for psychoticism in EPQ (table 4), which is an expected finding and was recognized and described for long time. In this respect, this study is in accordance with other previous studies. Significant observation is also made for both schizoid and schizotypal personality disorder, and paranoid personality disorder. However the former shows a high significance and indicates that they are more frequently inheritable than the paranoid personality. Moreover high incidence of schizoid, schizotypal personality in the first-degree relatives of familial group confirms the model proposed for schizophrenia by Siever, Kalies et al (1993).<sup>38</sup> They suggested that the "Psychotic-like" and social defect symptoms (Paranoid ideation, ideas of reference, magical thinking etc, versus, constricted affect, excessive social anxiety and isolation) are two aspects of schizotypy. When both sets of symptoms and deficit occur in the same individual, the result is schizophrenia. In this study, there is differential occurrence of both set of symptoms probably indicate that they may have different mode of genetic transmission.

Other significant observation was made for dependent, avoidant and borderline personality disorder. Subotnik, Nuechterlein et al (1999)<sup>39</sup> found on MMPI an excess of neurotic trait like histrionic, hyperchondriasis during psychotic and clinically population. So it is possible that the first-degree relatives may have these traits. This study confirms their observation. A number of clinicians and researchers have made similar observations too. Since schizophrenia is heterogeneous in its clinical manifestation, symptoms overlap with personality disorder. Given the complex genetic mechanism like personality traits in the first-degree relatives, there is a need to find varied manifestation of personality traits in the first-degree

relatives of familial schizophrenics. However no valid conclusions regarding the excess of avoidant, dependent, borderline, personality disorder can be made from this study considering its limited sample size and its cross sectional nature and other factors that are not taken into account. Therefore this needs further exploration and clarification.

**CONCLUSION:** Significant differences exist between the first-degree relatives of familial and sporadic schizophrenics. Familial clustering of some of the psychiatric disorder and personality factors lent support to the genetic inheritance of traits/ disorder in the first-degree relatives of familial schizophrenics. Results of this study has to be cautiously interpreted, because it did not take into account of sex distribution of trait/ disorder in the first degree relative, subtype of schizophrenia in probands and did not include all the first degree relatives of the patient. However this study confirms the validity of sub classification of schizophrenia into familial and sporadic forms as proposed by Kendler.

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Disorder	FDR to Familial Schizophrenia n=50		FDR of sporadic Schizophrenics n=50		X <sup>2</sup>	P
	Above Cut off	Below Cut off	Above Cut off	Below Cut off		
Anxiety	31	19	16	34	9.030	0.003
Phobia	12	38	17	33	1.210	0.271
Obsession	34	16	13	37	17.700	0.000**
Somatic	19	31	23	27	0.660	0.418
Depression	33	17	21	29	5.800	0.016*
Hysteria	11	39	12	38	0.060	0.812

**Table 1: Comparison of first-degree relatives (FDS) of familial and sporadic schizophrenic using MHQ**

\*Significant ≤ 0.05, \*\* Highly significant ≤ 0.01

Disorder	FRD of Familial Schizophrenics n=50		FDR of sporadic Schizophrenics n=50		X <sup>2</sup>	P
	Above Cut off	Below Cut off	Above Cut off	Below Cut off		
Depression	31	19	22	28	3.250	0.071
Mania	22	28	11	39	5.470	0.019
Schizophrenia	19	31	6	44	9.010	0.003**
Anxiety	32	18	13	37	14.590	0.000**
Paranoid	16	34	11	39	1.270	0.263
Hysteria	10	40	13	37	0.510	0.480
Psychopath	9	41	3	47	3.410	0.065
K scale	7	43	4	45	0.380	0.530

**Table 2: Comparison of first-degree relatives (FDR) of familial and sporadic schizophrenia MPQ**

\*Significant ≤ 0.05, \*\*highly significant ≤ 0.01.

Disorder	FRD of Familial Schizophrenics n=50		FDR of sporadic Schizophrenics n=50		X <sup>2</sup>	P
	Above Cut off	Below Cut off	Above Cut off	Below Cut off		
Psychoticism	31	19	5	45	29.340	0.000**
Neuroticism	23	27	18	32	1.030	0.309
Extroversion	24	20	16	34	2.670	0.103
Lie scale	8	42	4	46	1.520	0.218

**Table 3: Comparison of first-degree relative (FDR) of familial and sporadic schizophrenia using EPQ**

\*Significant ≤ 0.05, \*\*highly significant ≤ 0.01.

Disorder	FRD of Familial Schizophrenics n=50		FDR of sporadic Schizophrenics n=50		X <sup>2</sup>	P
	Above Cut off	Below Cut off	Above Cut off	Below Cut off		
Histrionic	8	42	4	46	1.520	0.218
Dependent	29	21	9	41	16.980	0.000**
Avoidant	33	17	6	44	30.640	0.000**
Borderline	24	26	7	43	13.510	0.002**

**Table 4: Comparison of First Degree relative (FDR) of Familial and Sporadic schizophrenia STCPD**

\*Significant ≤ 0.05, \*\*highly significant ≤ 0.01.

Disorder	FRD of Familial Schizophrenics n=50		FDR of sporadic Schizophrenics n=50		X <sup>2</sup>	P
	Above Cut off	Below Cut off	Above Cut off	Below Cut off		
Schizoid-Schizotypal	19	31	4	46	12.700	0.000**
Paranoid	16	34	7	43	4.570	0.032*

**Table 5: Comparison of first-degree relatives (FDR) of familial and sporadic schizophrenics using diagnostic criteria for schizophrenia related personality disorder**

\*Significant ≤ 0.05, \*\* highly significant ≤ 0.01