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THE GENETICS OF AFFECTIVE DISORDER -A PEDIGREE STUDY

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SUMMARY

A study on the genetics of affective disorder was carried out using pedigree methodology. The index case presented with features of bulimia which was diagnosed to be Bipolar affective disorder. The pedigree was analyzed for 4 generations and included evaluation of 76 individuals, of whom the oldest was 103 years of age. The evaluation was done clinically to demonstrate various concepts concerning affective syndromes, the presence and extent of gene borne influences and mode of inheritance. Data was compared with other genetic research studies and suggestions for further research are made.

INTRODUCTION

The term Affective disorder, though it encompasses conditions marked by pervasive pathological changes in mood (Jeste & Lohr, 1990), has all along eluded definition, contributing to the varied estimates of its prevalence in the general population, as well as a multitude of theories to explain its causation. Even though the Bio-psycho-social model is accepted for the aetiology of all the major psychiatric conditions, it is agreed that heredity plays an overwhelming role in affective disorders. Genetic studies in general are beset with uncertainties in behavioral research and this uncertainty is particularly evident in affective disorders; it extends from epidemiological issues to genetic hypotheses involving nature of illness, expressivity, linkage, biochemical correlates etc. (Mahmood et al, 1983; Kidd, 1987).

The evidence for a genetic basis has come predominantly from the major (psychotic) affective disorders, while in the non-psychotic division, there are difficulties in interpretation of results as the categories overlap and fall on a continuum; these are understood to be the result of many genes interacting with the environment (Kidd, 1987). Among the major affective disorders, genetic and related studies have helped recognize the following categories: [a] Unipolar disorder (Arieti, 1978; Angst & Perris, 1982) characterized by a single episode or repeated episodes of depression, usually accompanied by sleep and appetite disturbances, feelings of guilt and thoughts of suicide. [b] Bipolar Disorders Type I: Depression preceded by mania, Type II: Depression preceded by Hypomania (Fieve & Dunner, 1975) and Type III: Depression in a person with a history of Bipolar illness among first degree relatives (Winokur et al, 1971). Fieve and Dunner (1975) have coined the term "Bipolar Other" for the putative sub-types who had a minimum of 2 weeks of depression and mania of 3 days or more in out-patient cases.

Unipolar depression has been divided into 3 categories by Winokur et al (1971); (i) Familial pure depressive disease (FPDD), (ii) Depressive spectrum disease (DSD) and (iii) Sporadic depressive disease (SDD) utilizing the family history and clinical picture.

In the review of available literature, there is agreement that the illness runs in families (Venkoba Rao, 1992), though there is disagreement over the exact prevalence among relatives. Jeste and Lohr (1990) represent the agreed figure in the literature. The important findings are:

UNIPOLAR DEPRESSION:

1. The life-time incidence in the general adult population is fifteen to twenty percent.
2. Forty to sixty percent of affected individuals have a first degree relative with an Affective disorder.
3. The morbidity risk for an Affective disorder in the relatives or probands with unipolar disorder is 13% for parents, 15% for siblings and 21% for children.
4. The relatives of unipolar patients are at a much higher risk for developing unipolar than bipolar illness.

BIPOLAR DISORDER:

1. The life time incidence in the general adult population is one to two percent.
2. Eighty to ninety percent of individuals with Bipolar disorder will have a first degree relative with an affective disorder.
3. Morbidity risk for an affective disorder is 22% for parents, 25% for siblings and 39% for children of probands.
4. Relatives have a high risk for developing either bipolar or unipolar illness, the risk for bipolar being some what greater.

Regarding the pattern of inheritance, many different genetic hypotheses have been proposed "ranging from single gene for major depression, different single genes for manic depressive illness to continue on a polygenic multifactorial scale with manic depressive illness being simply a different manifestation of a more extreme form of same etiology" (Kidd, 1987). However, till now there is no evidence sufficient to explain any one hypothesis. This paper presents the pedigree analysis of a case of affective disorder who had presented with features of bulimia. An attempt is made to look into the spectrum concept and various genetic issues in the families of affective disorder.

INDEX CASE

A 15 year old male patient was brought for psychiatric consultation in June, 1989 with a 2 year history of episodic excessive eating, with each attack lasting 2-10 days and occurring once every 2-3 months. He would eat up all that was edible, demanding further food every few minutes. Restlessness, anxiety, irregular sleep disturbances, fre-

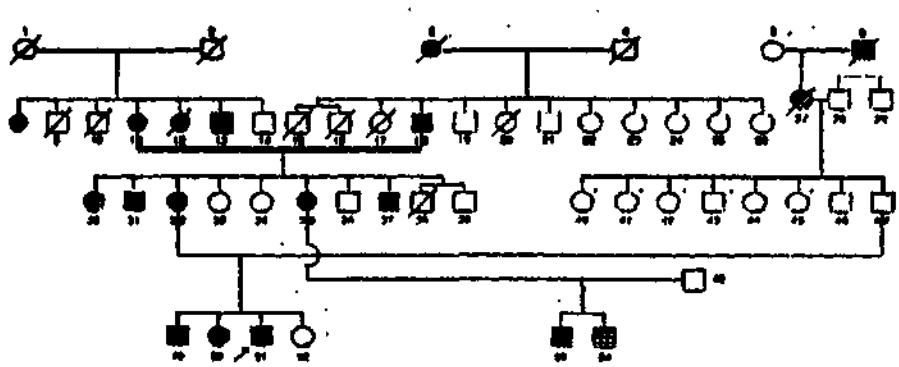

DIAGRAM DEPICTING PEDIGREE OF INDEX CASE; INDIVIDUALS HAVE BEEN SERIALLY NUMBERED.
(*) INDICATES CASES NOT AVAILABLE FOR INTERVIEW.

quent visits to the toilet and occasional vomiting were reported during the episodes. A history of nocturnal enuresis, once or twice a week, but more frequent during the above phases was reported. He had been admitted with a history of severe abdominal pain in Jan 1989 and again in July 1989. Early development and childhood details were not adequately obtained, but he was reported to be just average. He had studied up to 8th standard in an English medium school and had to discontinue studies due to parental and financial problems at home. At the time of admission, he was working as a helper at his uncle's watch shop. Physical examination revealed an obese boy with no significant systemic abnormality. Examination during the active phase revealed an anxious boy, depressed, restless and attention seeking; primary mental functions were within normal limits. E.E.G. showed bilateral temporal, generalized and irregular spike and slow-wave activities. Biochemical investigation and C.T. Scan findings were within normal limits. Detailed psychometry revealed an IQ of 71; Children's Personality Questionnaire and Malhotra's Temperamental Schedules revealed a proneness for intense emotional outbursts, withdrawing in social interactions, variations in mood, low ego-strength and integration. On Rorschach, no psychotic features were evident. He responded well to carbamazepine.

FAMILY STUDY:

(See figure) the detailed pedigree is represented in the diagram. Two of the authors evaluated the cases separately for arriving at the final diagnosis which were made according to DSM-III-R. A maternal cousin of the index case was seen a few days later in the department and though initially recognized as a hyperkinetic syndrome, was later confirmed to have juvenile mania (no. 53). Case no. 54 had a hyperkinetic syndrome; a sister of the index case received treatment for hysterical hyperventilation and neurotic depression in 1989-90. The eldest sibling, aged 20 years, was diagnosed to be MDP Circular currently euthymic. There were 3 episodes of running away from home, each time for 2-3 months and was once kept in a remand home for 2 years.

The mother of the index case (no. 32) had a past history of major depression as also cases no. 35, 18, 12 (committed suicide), 11 (67 years old, diagnosed to have mania in 1975 for which he was admitted and treated in a psychiatric hospital) and case no. 3 (aged 103 years, had major depression with melancholia for two years prior to his death in 1992).

Bipolar affective disorder was recognized in Case no. 31 (a total 4 episodes in the last 8 years), and Dysthymic disorder in cases no. 8 and 30. The father of the index case was not available for evaluation but the details of earlier treatment, his letters and available history were suggestive of paranoid schizophrenia. He currently had active delusions of persecution and infidelity and was not staying with the family. The details regarding cases no. 6, 13 & 27 were not adequate to make a final diagnosis. Only cases no. 18 & 31 had a history of occasional alcohol intake.

DISCUSSION

Genetics play a key role in modern psychiatric research and practice in general, and affective disorders in particular. Rainer (1990) emphasizes 3 different issues in behavioral genetic research:

1. To demonstrate the presence and extent of gene borne influences
2. To determine the mode of inheritance
3. To demonstrate relationship between gene products and symptoms and syndromes.

Family, twin and adoption studies, pedigrees and population family risk data, study of genetic markers, longitudinal studies of high risk persons, recent molecular technologies incorporating recombinant DNA methodology including mini satellites (Jeffreys et al, 1985), tandem repeat sequences (Nakamura et al, 1987) for study of linkages etc, have contributed to the understanding of genetic and environmental aspects in the production of behavioral syndromes.

Genetic studies of affective disorders are beset with problems of diagnoses as well as mode of inheritance. It was Kraepelin who observed that a large number of relatives of patients with Manic Depressive Psychosis had a similar illness (Venkoba Rao, 1986). In Kallmann's twin family study (1953), the expectancy of MDP varied from 16.7% for half siblings, 22.7% and 25.5% for siblings and

dizygotic twins respectively, 100% for monozygotic twins and 23.4% for parents. Though a perfect concordance of 100% for monozygotic twins is considered the "artificial maximum", Kallmann's study has shown that MDP followed a dominant type of inheritance with incomplete penetrance and variable expressively of a single autosomal gene.

Leonhard (1959) made the clinical distinction of unipolar and bipolar categories in psychotic affective disorders and the work of Angst and Perris (1972) and Mendlewicz et al (1972) have contributed to its understanding, as well as the spectrum nature of the illness. The family represented in our study had, in addition to patients with Major depression and Bipolar affective disorder, individuals with neurotic illnesses, Bulimia, Hyperkinesis, suicidal behavior, alcoholism and personality disturbances adding weight to the spectrum concept of Winokur et al (1969). Case no. 3, who was reported to be 103 years old at the time of his death, had developed depressive features at 101 years of age. This brings us to the point of pitfalls encountered in the assessment of prevalence, incidence, expectancy and morbidity risk of illness, as enough provision need to be made in obtaining corrected figures.

The expectancy rate was calculated (Rainer, 1980) using Weinberg's abridged method where the number of observed cases among relatives (the numerator) is related, not to the total number of relatives, but to all those who had survived the period in which the disease was certain to manifest, plus half the number who were still within the age limits during which the disease usually manifests (the denominator).

As Affective disorders can manifest through all age groups (as noted in our sample) no cut-off age could be utilized for calculating the denominator. The expectancy rate obtained in our sample family was 42.4% with both the maternal and paternal family members put together, while in the maternal family alone the expectancy was 47.8% with the risk for female relatives being 20.9%, and for males 11.8%. The above assessment was done only for the first three generations where adequate data was available.

The above findings compare well with studies by Winokur and Clayton (1969) which revealed a 34% risk for parents, 35% in siblings if information was obtained through family histories, and 41% in parents, 42% in siblings and 50% in children, if relatives were actually interviewed. Both unipolar and bipolar cases were found in the first degree relatives and the risk for female first degree relatives was considerably higher than males. Similarly, Mendlewicz and Rainer (1974) reported a morbidity risk for all affective illness of 33.7% for parents, 39.2% for siblings and 59.9% for children. The risk was significantly higher for female relatives (48.2%) than for male relatives (30.7%).

In the sample family, some clinical evidence is available to understand the linkage. This study shows transmission from both the parents, particularly from mothers to sons and daughters but no specific male to male transmission of illness. Hence, there is a possibility of X-linkage but these findings need to be interpreted with caution as the study involves only one family pedigree. However, other family studies have also noted that the rates of affective illness among the fathers and sons of male probands were lower than those among mothers and daughters (Rainer, 1980). Risch et al (1986) proposed that up to 30% of all cases of bipolar illness could be X-linked. Evidence has been presented in several studies of Color blindness and Glucose 6 Phosphate Dehydrogenase deficiency (G6PD) and both have been mapped to the tip of the long arm of the X Chromosome, segregating in some families with bipolar illness (Baron et al, 1987; Berritini et al, 1990). Recent studies on a Belgian pedigree (Mendlewicz, 1987) and the findings related to Chromosome 11 in a large Amish Pedigree in Pennsylvania (Egeland et al, 1987) have cast doubt on X-Linkage hypothesis. However, as has been reviewed (Blackwood, 1990), there are a minority of families showing X-Linkage, but most do not, and this non-replication of linkage could be due to genetic heterogeneity.

Another area to draw attention was suicide. Case no. 12 had committed suicide and suicidal ideas were reported by the mother of the index case and also cases no. 31, 35, 8, 11 & 50. A review of literature demonstrates the occurrence of suicidal deaths in families. For long psychosocial issues had overshadowed the role of genetics (Kety, 1985), and Venkoba Rao et al (1987), in their review on the biological basis of suicidal behavior, have reported in particular about the high incidence of suicide among individuals suffering from affective disorder. As Kety (1985) had noted, current studies, though not indicative of an exclusive genetic determinism of suicide behavior, enable one to conclude that among people who have a life experience that could lead to suicide, only those with the genetic predisposition will actually do so. Clinical experiences bears testimony to this fact.

CONCLUSION

The pedigree presented and available literature, no doubt, confirms a genetic basis for affective disorder. However, as noted by Kidd (1987) "A truly genetic hypothesis predicts that the frequency of illness in the parents of an affected individual should be the same as the frequency of illness in the offsprings of that affected individual"; we have found a four to five fold difference in this frequency. There is no purely genetic hypothesis that will explain the difference. This would be a possibility, if affective or any other psychiatric disorder could meet requirements (Kidd, 87) such as:

1. Standardized, reliable diagnostic criteria
2. Methods for systematic assessment of symptoms
3. Large extended families with many affected individuals
4. Polymorphic genetic loci distributed throughout the genome
5. Appropriate statistical methods

Many of the areas noted are clinical and even though

enough progress has been made over the past decade towards meeting the above requirements, these are still a long way from realization. Unknown etiology, uncertain inheritance and genetic heterogeneity call for continued research. The answer lies in the advances made in molecular genetics which aim to identify defective genes responsible for major mental illnesses (Blackwood, 1990). If successful, this approach may lead to a proper understanding of the interplay of genetic endowment, environmental influences and learned behaviors which determine their onset, clinical features and outcome. In this complexity lies the challenge and the hope for further research.

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