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A Study of Mode of Inheritance in One Hundred Subjects with Manic Depressive Psychosis

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Abstract

The family history data obtained from patients with manic depressive psychosis was evaluated to find out the mode of inheritance. The results suggested an autosomal dominant mode of inheritance with incomplete penetrance. The scope of molecular genetics in understanding the nature of inheritance of manic depressive psychosis is indicated.

Key words -
Manic depressive psychosis,
Autosomal dominance,
Incomplete penetrance,
Molecular genetics

Since the time of nosological classification of psychiatric disorders, there has been continuous interest in eliciting the genetic etiology and it is well known that in both schizophrenia and affective disorders genetic factors play an important role in the causation [1]. Understanding the exact mode of inheritance would be very helpful for purposes of diagnosis, management and prognosis. Some of the earlier studies have no doubt been classical but yet for comparison with more recent data fall short of strict criteria. This is the reason why at least from the past two decades several collaborative programmes are being carried out among different centres in a country [2] as well as between centres in different countries. . There have also been well standardised diagnostic criteria evolved so as to make the results of studies in different centres easily comparable [3], [4].

The present paper reports observations made during a study of mode of inheritance investigated in patients with manic depressive psychosis (MDP).

Material and Methods

The clinical material for this study was obtained from patients coming for consultation in the psychiatry department at this centre. Patients who had a history of mania and depression, and who fulfilled the criteria of bipolar type of affective disorder [4] were selected for this study. All the patients were in the acute manic phase and were placed on lithium therapy and thus were available for follow-up over a period of time. In all these patients details relating to family history was obtained from parents, sibs or close relatives who accompanied the patients. For purposes of uniform collection of data a special proforma was used. The data obtained was subjected to special statistical methods, specially the maximum likelihood method of Johnson [5].

Observations

One hundred patients with MDP were available for this study. These included 58 males and 42 females. Table 1 shows the distribution of the cases in different age groups.

Table 1 - Distribution of patients in different age groups

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The ages ranged from 18-55 years with a mean around 32.56 years.

Table 2 shows the age at onset of the illness.

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The mean age at onset was 26.86 years.

The family history revealed a similar illness among close relatives and the details are given in Table 3.

Table 3 - The history of similar illness among close relatives

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Twenty one cases of MDP showed father to son transmission and out of this only two showed the history of illness on the maternal side. This finding of father to son transmission obviously rules out X-linked mode of inheritance. This is also supported by the fact that the illness was present in brothers and sisters of index cases with no preference to any one sex.

Some representative pedigree charts are indicated in Figures 1 to 6.

Fig. 1. The index case is a 43 years old male, both his parents had a history of similar illness and the mother is reported to have made an attempt at suicide. Two of the brothers are affected and one committed suicide. There is also history of paternal uncle and two of his sons having the history of

similar illness

Fig. 2. The patient is a female aged 65 years. Her husband and his paternal uncle had a similar history. Out of the nine children of the patient seven had a history of similar illness and two committed suicide

Fig. 3. The patient is a 34 years old male and his son is also affected. This shows father to son transmission

Fig. 4. The patient is a 44 years old male. There is father to son transmission in the family. Besides this the patient's son, paternal aunt and paternal grand father are also affected

Fig. 5. The patient is a 29 years old male, his mother and two of his sisters are affected. A number of relatives are affected on the maternal side

Fig. 6. The index case is a male aged 30 years; the father is also an MDP. The patient's elder brother and paternal aunt had history of similar illness and both committed suicide. A history of MDP is seen on the paternal side as well as in the family of the great grand paternal uncle

Out of the one hundred index cases, only in nine, the parents were consanguineously related. The low consanguinity rate would not support the possibility of a recessive mode of inheritance.

As could be noted from the data in Table 3, there is an apparent evidence to indicate autosomal dominant type of inheritance. One of the methods of testing this is by using the maximum likelihood estimate (MLE) under a single ascertainment [5]. If any one parent is affected, the MLE is estimated as 0.222. This differs from the expected value of 0.5 for a single autosomal dominant. When we selected the penetrance probability as 50% we note that the probability was 0.25 which is not significantly different from 0.222 (the calculated segregation probability). Thus from the statistical calculations of our data obtained from hundred patients there is evidence for the operation of a single autosomal dominant gene with a reduced penetrance (approximately 50%).

Discussion

From the data relating to history of similar illness in the relatives of patients included in this study and the calculation made using the special statistical methods, it looks as if an autosomal dominant type of inheritance with incomplete penetrance is present. There is no evidence however either for X-linked or autosomal recessive type of inheritance.

For genetic investigations in psychiatric disorders, three different methods have been used viz. Family History method. Twin Studies and Adoption Studies [1]. Recently Thomson et al [6] reviewed the Family History and Family Study method both of which have been utilized in the study of genetic analysis applied to psychiatric illnesses. They suggested that it is better to use the Family Study method when possible, but that Family History can be used if one bears in mind that it underestimates the presence illness if false negative rates are not corrected by a proper variable. Much of this can be overcome if long-term acquaintance with these families is possible, which compensates for the disadvantage of Family History over Family Study method in testing the hypothesis [7]. This is possible when one selects the bipolar patients who come with manic episodes and who are placed on lithium and brought periodically for follow up, an advantage which we had in our study. Despite the convincing evidence for single major locus (SML) model the findings of Winokur and Tanna [8] on the association of certain markers located on X-chromosome which indicate a likelihood of X-linked inheritance cannot be easily ruled out unless one looks for the parameters like the Xg blood group which Winokur and Tanna [8] have extensively investigated.

For some unknown reasons genetic contribution to affective illness has not provoked controversy as in schizophrenia and hence twin and adoption studies are less abundant. However, a few studies that are available have substantiated a genetic etiology [9].

While the exact mode of inheritance is a matter of controversy it is likely that different subpopulations could have different mode of inheritance. From the evidence obtained from work published so far as well as from the preliminary findings of the present study there is no doubt that genetic factors play an important role in the etiology. Using the modern techniques of molecular genetics attempts have been made to study the locus of MDP gene [10].

The analysis of the segregation restriction fragment length polymorphism (RFLP) in an old order Amish pedigree has made it possible to localise a dominant gene conferring a strong predisposition to manic depressive disease to the tip of the short arm of the 11th chromosome [11]. The use of DNA based diagnostic procedures have a tremendous potential, specially in identifying individuals who inherit the gene but do not manifest the illness. It is also known that the structural gene encoding tyrosine hydroxylase is present on the same segment of chromosome 11 and this enzyme catalyzes an important step in dopamine synthesis pathway. It is now well known that dopamine plays an important role in developing the major mental illnesses. While the findings of molecular genetics are extremely revolutionary some workers have stated that the dominant gene causes affective disorders only in 60-70% of those who inherit it [12].

Thus future studies on molecular genetics have to concentrate on the reasons why some escape the illness despite their having the genotype. If this is understood this knowledge might help in evolving suitable strategies of management for the rest of the subjects who have the genotype and also manifest the illness. Thus the scope for molecular genetics in psychiatric disorders has unlimited potentialities. Only very few centres in the world are now engaged in this work [10], [11], [12], [13].

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