UTILITY OF SOME GENETIC MARKER IN PREDICTING RESPONSE TO LITHIUM

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SUMMARY

One hundred manic patients who were treated with lithium were studied to find out the possibility of genetic variations in response to lithium. Along with pedigree study, test of colour blindness and ABO blood grouping were used as genetic markers. The study supports the transmission by autosomal dominance with incomplete penetrance. There is no difference between the responders and non-responders in the mode of transmission and in the family history of mental illness, ABO blood grouping.

In spite of the numerous genetic studies on affective disorders the mode of transmission of affective disorders is not properly understood. The results of these various studies are equivocal and controversial. Unipolar and bipolar illnesses are genetically separate entities and each of them is also heterogeneous from genetic standpoint. In bipolar illness all the three modes of inheritance (X linked dominant trait, autosomal dominance with incomplete penetrance, polygenic) has been described (Vulnet, 1981). Shopsin et al. (1976), Gershon et al. (1976) and Vulnet (1981) support multifactorial inheritance. Although genetic factors are of basic importance (50—60%) continuously acting environmental factors (20%) have a significant influence on the manifestation of illness (Vulnet, 1981).

This genetic heterogeneity of the illness has further added to the confusion existing in the treatment of manic depressive illness. Cade (1949) demonstrated antimanic properties of lithium. Now lithium has become the drug of choice in treatment of mania and in the prophylaxis of M. D. P. Only 20% of manics respond to lithium (Schou, 1959). Hence finding the variables which determine the response to lithium has become a point of great concern. Studies are being done on demographic, clinical, biochemical variables. Genetic studies (Mendlewicz et al., 1973, Stallone et al., 1973, Venkoba Rao et al., 1982), show consistent results that a good response to lithium is related to the presence of mania in the family. Taylor (1975, 1981) disagrees with the above findings.

As mania is heterogeneous and not enough work has been done in the genetic aspects, as a predictor of response to lithium, we took up a study to determine correlation between any particular mode of transmission and response to lithium.

MATERIAL AND METHODS

The material for the study is taken from the in-patients of National Institute of Mental Health and Neurosciences, Bangalore, who were treated during the period 1981-1982. One hundred patients of both the sexes (70 males, 30 females) aged between 15-55, in whom MDP circular was diagnosed as per Feighner's criteria by 2 psychiatrists, formed the sample. They were all treated with lithium carbonate so that the serum level was maintained around 1m Eq/L (0.9-1.5 mEq). Haloperidol was given only during first week when necessary. Black Burn manic symptom rating scale was used to assess the response to therapy.

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Good responders were those who were euthymic and scored 0-3 in manic symptom rating scale by the end of 21 days with lithium only.

A detailed family history was taken from each of these hundred patients. As many 1st degree relatives as possible were interviewed. We made it a point to interview both the parents (or relatives of both sides) together as well as separately. The idea behind this was, if only parent is interviewed, cases might be over represented on that side, as that parent will not be fully aware of the family history in the other. As the mental illness carries stigma, one might not give full family history in front of the other. Hence, both the parents were interviewed separately also.

For all the patients blood grouping (A, B, O) was done. The results are compared with the blood groups of 100 inpatients of neurosurgical block of NIMHANS.

Ischihara colour blindness chart was administered to all the 100 manic patients, whenever there was a positive case, a house visit was made to administer the test to almost all the first degree relatives.

The proforma was filled to cover the following items.

(a) Age of onset:
   Early age of onset—less than 30 years,
   Late age of onset—more than 30 years.

(b) Consanguinity between parents whether:
   II degree (uncle-niece)
   III degree (I cousins)
   IV degree
   V degree (II cousins)

(c) Family history of mental illness
   Mania
   Schizophrenia were diagnosed
   Alcoholism as per Feighner's criteria.

Sociopathy by Robin's criteria. Suicide and other illnesses were also taken into account.

(d) Blood group of the patient.
(e) Colour blindness in the patient.
(f) Colour blindness in the family.

100 persons (70 males and 30 females) were selected as controls. These were neither patients by themselves nor were relatives of the patients who attended the hospital. History of consanguinity among the parents and family history of mental illness was elicited and test of colour blindness was administered to each of them. In positive cases the test was administered to almost all the first degree relatives as well.

RESULTS

In a total of 100 patients 85 were categorized as responders to 15 as non-responders.

1. Age of onset

|                  | Responders (R) | Non-responders (N.R.) |
|------------------|----------------|----------------------|
| Early onset (<30 yrs) | 60 (71%)       | 14 (93%)             |
| Late onset (>30 yrs) | 25 (29%)       | 1 (7%)               |

\[X^2=2.34, \text{ d.f}=1, \text{ N.S.}\]

2. Consanguinity between the parents

|                      | Controls (C) | R      | N.R. |
|----------------------|--------------|--------|------|
| Consanguinity+       | 15 (15%)     | 8 (9%) | —    |
| II degree relatives  | 6 (6%)       | 2 (2%) | —    |
| III degree relatives | 5 (5%)       | 2 (2%) | —    |
| IV degree relatives  | 4 (4%)       | 1 (1%) | —    |
| Non consanguinity    | 85%          | 91%    | 100% |

The difference between the three groups are not significant.
### 3. Incidence of mental illness among 1st degree relatives

| Mental Illness | G (3%) | R (1%) | N.R. |
|----------------|--------|--------|------|
| Schizophrenia  | 1(1%)  | —      | —    |
| M.D.P.         | 2(2%)  | 24(29%)| 6(40%)|
| Sociopathy     | 2(2%)  | 5(6%)  | 2(13%)|
| Alcoholism     | 3(9%)  | —      | —    |
| Suicide        | 2(2%)  | 1(1%)  | —    |
| Other          | —      | —      | —    |
| Nil            | 8(8%)  | 55(64%)| 7(47%)|
| Present        | 12(12%)| 31(36%)| 8(53%)|

\[X^2=21.16, \text{d.f.}=2, p<0.001\]

### Mental Illness among relatives of the patients

|     | I st degree relatives | II degree relatives | III degree relatives |
|-----|-----------------------|---------------------|----------------------|
| R   | 1(1%)                 | —                   | —                    |
| Schizophrenia | — | — | — |
| N.R. | — | — | — |
| R   | 24(29%)               | 19(16%)             | 6(7%)                |
| M.D.P. | — | — | — |
| N.R. | 6(40%)                | 2(13%)              | 2(13%)               |
| R   | 5(6%)                 | 4(5%)               | 2(2%)                |
| Psychopathy | — | — | — |
| N.R. | 2(13%)                | —                   | —                    |
| R   | —                     | —                   | —                    |
| Alcoholism | — | — | — |
| N.R. | —                     | —                   | —                    |
| R   | 1(7%)                 | —                   | —                    |
| Suicide | — | — | — |
| N.R. | —                     | —                   | —                    |
| R   | —                     | —                   | —                    |
| Others | — | — | — |
| N.R. | —                     | —                   | —                    |
number of patients had early age of onset (less than 30) among non-responders (93%) when compared to responders (71%).

There was no difference between the control group, responders and non-responders in the incidence of consanguinity, thus supporting autosomal dominance than polygenic theory. Even though the presence of family history of MDP is more in the patient population, there is no significant difference between the responders and non-responders, thus supporting Taylor's study (1975, 1981). This does not support the results of Mendlewicz et al. (1973) Stallone et al., (1973) and Venkoba Rao et al. (1982). In all the above said studies, good response to lithium was significantly associated with the presence of mania in the families. Regarding the incidence of colour blindness, the difference between the three groups (responders-non-responders and controls) is not significant. There is no significant difference between the number of father-son, mother-daughter pairs. The above two findings do not support X-linked dominant trait transmission thus favouring Stensted (1952), Perris, (1973), Von-Grief et al. (1973), Dunner et al. (1973), Green (1973) but not supporting Winokur and Tanna (1969), Mendelcuicz et al., (1972), Fieve et al (1973). Number of unilateral pairs (that is ill relatives belonging only to father or mother's side) is significantly more (39%) than bilateral pairs (7%) which favours the theory of autosomal dominance with incomplete penetrance. This supports Kallman, (1950), Stenstedt, (1952) and Angst, (1966) Shopsin et al. (1976) and was against Slater et al. (1971), Gershon et al. (1975b) Goetzl et al. (1974), Baker et al. (1972), who favoured polygenic theory as there were greater number of bilateral than unilateral pairs.

There was no significant difference between the three groups (control, responders and non-responders) as far as the presence of alcoholism and sociopathy was considered, thus supporting Gershon et al. (1975a). There was no difference between the three groups in ABO blood grouping, thus inheritance of MDP and response to therapy being not related to major blood groups.

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