Indian J. Psychiat., 1998, 40 (3), 201-211

NEUROBIOLOGICAL CHARACTERIZATION OF BIPOLAR AFFECTIVE DISORDERS : A FOCUS ON TARDIVE DYSKINESIA AND SOFT NEUROLOGICAL SIGNS IN RELATION TO SERUM DOPAMINE BETA HYDROXYLASE ACTIVITY

UTPAL GOSWAMI, S. BASU, U. KHASTGIR, UNNATI KUMAR, R. CHANDRASEKARAN, B.N. GANGADHAR, RAJESH SAGAR, J.S. BAPNA, S.M. CHANNABASAVANNA, P. BRIAN MOORE & I. NICOL FERRIER

ABSTRACT

In this study, the prognostic determinants were investigated involving bipolar patients classified into two groups-one with favourable course and outcome, and the other with clearly unfavourable prognosis, based on certain recommended criteria, with intermediate prognosis were excluded. As compared to the poor prognosis group, the good prognosis group had lower social dysfunctions, lower ratings on psychopathology, fewer indicators of neurodysfunction in form of neurological soft signs (NSS) and tardive dyskinesia (TD). The poor prognosis group was characterized by : (i) older age at onset; (ii) more manic than depressive episodes (5:1) and (iii) lower levels of serum dopamine-ß-hydroxylase activity (DBH). The association between poor prognosis bipolar disorder having neuroleptic intolerance (TD and NSS) with low serum DBH, suggests that it is genetically governed. Further research in this direction seems in order, particularly the follow up of first episode manic disorders.

Key Words : Bipolar disorder, dopamine -ß-hydroxylase, prognosis, neurological "soft" signs, tardive dyskinesia, neurodysfunction

In his original doctrine of dichotomy between 'manic depressive insanity' and 'dementia praecox', the father of modern psychiatric nosology, Kraepelin (1919) introduced the pivotal concept of global personality deterioration as an invariable outcome in the latter. In sharp contrast to this concept, 'manic depressive insanity' was conceived as an episodic, remitting & relapsing disorder with inbuilt favourable prognosis in that, if the patients did not die of exhaustion, starvation or suicide, they would eventually remit spontaneously. This major distinction between schizophrenia and affective disorders continued to persist, until relatively recently. The group of major affective disorders remained an essentially 'good prognosis condition', devoid of residual symptomatic or psychosocial dysfunction during remission when the individual patient returns to the pre-morbid level of functioning.

However, this traditional view that the major affective disorders were a good prognosis condition has been called into question during the last three decades with several reports suggesting that a sub-population (5% - 34%) of these disorders had poor social outcome and/or poor response to treatment (Winokur et al., 1969; Carlson et al., 1974; Johnstone et al., 1985; Harrow et al., 1990). It is gradually emerging, from carefully controlled follow-up studies that from 15% to as high as 53% of bipolar disorders tend to develop a

chronic course and poor outcome resulting from treatment resistance (Keller, 1987; Corryel & Winokur, 1992).

Evidence from the family studies, twin studies and other studies suggest that bipolar affective disorders are, to a great extent, genetically determined (Numberger & Gershon, 1992). A major development in the study of affective disorders is the identification in the recent years, of more objective indicators of abnormalities of structural and functional brain abnormalities (Altshuler, 1993). Until recently, this was restricted to the domain of research in schizophrenia, with a large body of evidence from the NIMH studies by Dr Daniel Weinberger, using neuroimaging technology; studies have however, come independently from other investigators, confirming the same (Johnstone et al., 1989).

Similarly, at one time it was believed that neuroleptic drugs were responsible for development of tardive dyskinesia (TD) only in schizophrenia syndrome. However, it has now been well documented that the diagnosis of bipolar disorder carried a very high risk of development of TD (Mukherjee et al., 1986). In this paper, the investigators documented 35% prevalence rate of persistent TD. More recently, Meltzer (1992) have postulated that development of TD is due to the individual's neuroleptic intolerance. Furthermore, recent literature on bipolar disorders, including neuroimaging studies, have provided compelling, and irrefutable data in support of structural and functional brain abnormalities in major affective disorder (Dolan et al., 1985; Coffman et al., 1990; Altschuler et al., 1991).

The data from European centres specializing in treatment of therapy resistant affective disorder also support the fact that a significant minority of affectively ill patients do run a chronic unremitting course (Ferrier, I.N., personal communication).

Dopamine-beta-hydroxylase (DBH) is a genetic marker which is a tetrameric glycoprotein that catalyses the terminal step in the bio-synthesis of norepinephrine from dopamine, and therefore it is of interest to the researchers in biological psychiatry, with particular reference to those neurochemical investigations which require assessment of the norepinephrine (NE) functions in major psychiatric disorders. Interest in DBH in psychiatric research had its roots in the classical catecholamine hypothesis of affective disorder that postulated a decrease in the NE level in depressive syndrome, and elevation of NE level in Mania (Schildkraut, 1965; Maas, 1975).

In fact, serum (or CSF) DBH activity has been extensively studied, in isolation, in affective disorders (Shopsin et al., 1972; Meltzer et al., 1976; Matuzas et al., 1982), and in schizophrenia. Likewise, a number of investigations have explored the role of DBH activity in TD also, either in isolation or in relation to TD in schizophrenia. However, as evident from last 15 years published literature, searched with the help of Medlars database, there is no published study, to characterize the group of bipolar disorders with risk of developing TD, using DBH as a genetic marker. Furthermore, not many studies address the issues pertaining to 'external validation' of the poor prognosis bipolar disorders combining other variables including inadequate treatment response, prolonged unremitting course, evidence of neuroleptic intolerance (Meltzer, 1992) in form of complications such as TD and soft neurological signs, rapid cycling, absence of full remission, neuroimaging deficits and instability during the course. Serum DBH activity could be a useful genetic marker in such a study. Therefore, the present study was undertaken with the following aims and objectives :

1. To study how serum DBH levels of Bipolar Disorders compare with age and sex matched normal controls.
2. To study if it is possible to delineate subsyndromes of TD, in terms of a genetic enzymological marker.
3. To study if it is possible to delineate subsyndromes of bipolar disorder with regard to its prognosis and characterize these prognostic variables.

4. To investigate if a pattern of serum DBH activity differentiates a sub-syndrome of poor prognosis bipolar disorder that bears positive association with neurological soft signs and tardive dyskinesia.

MATERIAL AND METHOD

The following *exclusion criteria* were employed prior to selection of the index cases as these states could interfere in serum DBH activity-(i) history of any psychotropic drug treatment during the three weeks preceding collection of the blood sample (excluding benzodiazepines); (ii) any past or current history indicative of endocrine, metabolic or nutritional disorders; (iii) any history or finding (s) suggestive of Huntington's chorea, epilepsy, multiple sclerosis, parkinsonism or other neurological disorders of ineffective, degenerative or neoplastic etiology; (iv) history suggestive of drug or alcohol dependence or non-dependent abuse during and/or immediately preceding the onset of present episode & (v) mixed affective states, bipolar II disorders, and the patients with uncertain ambiguous or intermediate prognosis were excluded.

Patient population included 132 bipolar disorder cases at the level of first screening. The diagnosis was made consensually by two qualified psychiatrist at the point of referral. Subsequently, it was determined whether the particular patients belonged to 'good', 'poor', or 'intermediate' outcome, clinically, in terms of outcome measures, particularly symptomatic recovery, social dysfunction and time spent in episodes vis a vis time spent in lucid intervals based on the operational guidelines given by Frank et al. (1991).

Out of the 132 patients, 29 cases belonged to the intermediate prognosis group and they were not further considered for recruitment in the study. From the remaining 103 patients, 11 decided not to sign the written informed consent form and officially withdraw from the study, further 16 patients dropped out for the fear that they would run the risk of contracting AIDS, and another group of 15 patients were unable to bring adequate and reliable informants for the required information. Therefore, finally we were left with 62 bipolar affective disorder patients fulfilling DSM-III (APA, 1980) criteria, equally distributed to 'good' and 'poor' outcome groups. The Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) definitions of major depressive disorder and manic disorder were then applied. Only definite cases were included.

Normal control population : The control group consisted of 65 normal volunteers, mainly from the staff and students of the institute who did not have any past history of psychiatric disturbances and had no first or second-degree relative with current and/or past history of manic-depressive psychosis and other functional psychotic disorders.

Tools

1. DSM III criteria (APA, 1980) and Research Diagnostic Criteria (Spitzer et al., 1978) for diagnosis of psychiatric syndromes under study.
2. Depression was rated by Hamilton Rating Scale for depression (Hamilton, 1960).
3. Mania was rated by Bech Rafaelsen's Mania Rating Scale (Bech et al., 1978).
4. Tardive Dyskinesia was diagnosed using Jeste et al's criteria (Jeste et al., 1979). Simultaneously patients were evaluated on the research diagnostic criteria for Tardive Dyskinesia (RDC-TD) by Schooler & Kane (1982).
5. Neurological soft signs were rated according to the guidelines given by Nasrallah et al. (1983) with some modification in the battery as adopted by Kolakowska et al. (1985); altogether there were 13 items and each sign was rated on a 1-3 scale (absent, present, marked), the sign-'adventitious movements'-was excluded from the analysis as this was related to parkinsonian tremor and TD.

An operational definition of 'Neuro dysfunction' was predetermined as a total score

of 15 or more.

6. Tardive Dyskinesia was rated using Simpson et al's scale (Simpson et al., 1979).

7. A semistructured proforma was prepared to obtain the bio-socio-demographic, as well as the relevant clinical details such as age, sex, age at onset of the disorder, total number of episodes (with the break-up of manic and depressive episodes), level of recovery in social functioning and the outcome of treatment in terms of degree of resolution of symptoms (for a conceptual discussion regarding episode, recovery, response, remission etc., please refer Frank et al., 1991).

8. Serum Dopamine-beta-hydroxylase activity was analysed in batches employing a modified spectrophotometric assay by Nagatsu and Udenfriend (1972).

Procedural details

During the study period, all the subjects in the study were hospitalized in the inpatient facility of the Department of Psychiatry, Jawaharalal Institute of Postgraduate Medical Education & Research, Pondicherry, and later, others were admitted to the inpatient facility of the G.B. Pant Hospital, New Delhi, for a period of at least 24 to 72 hours. During this period, they were allowed to adapt to the conditions of the inpatient facility. They did not, during this period of adaptation, receive any neuroleptics, antidepressants or ECTs. All subjects under the study received the standard hospital diet.

To control the circadian influences and resultant variations due to exercise, blood samples (6ml) were collected from the subjects who were fasting overnight, between 8 and 9 A.M. while lying down supine. After clotting, samples were transported on ice, within 20 minutes to the laboratory of the Department of Pharmacology, where the serum was separated, frozen and stored in - 20^0 C, immediately. All the samples were labelled with random number codes at the time of collection and storage, thereby the laboratory personnel were blind to the subjects' clinical details. Similar procedural precautions were taken for control group also.

Statistical analysis was done on data which was square root transformed to permit Gaussian statistics.

RESULTS

The normal population (N=65) consisted of 36 males and 29 females in the age range between 25 to 49 years. The individual serum DBH enzymatic activity levels ranged from 2 to 39 international units in this normal control group.

Serum DBH activity levels in the normal controls (n=65) did not differ significantly from the serum DBH activity of the bipolar disorder as a group (good and poor prognosis combined, n=62).

It is important to note (Table 1) that within the cohort of the bipolar patients, there is no difference with regard to age and sex distribution of the good and poor prognosis bipolar disorder group.

This is important as all the subsequent extrapolations do assume that these two subgroups have been comparable with regard to these variables.

One of the important findings of the present study is that Poor Prognosis Bipolar Disorder (PPBD) patients had lower levels of serum DBH activity as compared to the Good Prognosis Bipolar Disorder (GPBD) (Table 2).

The "PPBD" group had significantly

TABLE 1
AGE AND SEX DISTRIBUTION IN GOOD AND POOR PROGNOSIS BIPOLAR DISORDER PATIENTS

	Good prognosis bipolar disorder (N=31)	Poor prognosis bipolar disorder (N=31)
Age (in years)		
Mean ±S.D.	41.38±9.36	41.58±11.17
	t = 0.07, d.f.=60, N.S.	
Sex		
Male	17	17
Female	14	14

TABLE 2
SERUM DBH ACTIVITY IN GOOD AND POOR PROGNOSIS BIPOLAR DISORDER GROUPS

	Serum DBH activity Mean	S.D.
Good prognosis Bipolar disorder (N=31)	14.68	7.78
Poor prognosis Bipolar disorder (N=31)	8.77	6.46

t=3.25, d.f. = 60, p<.001

TABLE 3
TARDIVE DYSKINESIA AND NEUROLOGICAL SOFT SIGNS IN GOOD AND POOR PROGNOSIS BIPOLAR DISORDER

	Good prognosis bipolar disorder (N=31)	Poor prognosis bipolar disorder (N=31)
Tardive dyskinesia		
Present	6	19
Absent	25	12
	X^2=9.6, d.f.=1, p<.01 odds ratio = 6.6, 95% C.I. : 1.85-24.79	
Neurological soft signs		
Present	6	17
Absent	23	14
	X^2=4.3, d.f.=1, p<.05, 14 odds ratio 3.5, 95% C.I. : 1.1-11.8	

greater frequency of Tardive Dyskinesia (n=19/31) as compared to the "GPBD" group (n=6/31) (Table 3; X^2= 9.6; d.f.=1; p<.01).

The PPBD patients had higher frequency of neurological soft signs (n=17/31) as compared to the GPBD group (n=8/31) which is statistically significant. (X^2=4.3, d.f.=1, p<.05) (Table 3).

The 'age at onset' for the bipolar disorder group with poor prognosis (33.6±6.4 years) was statistically higher than the group having good prognosis (25.6±5.5 years). This means that, younger age of onset of bipolar disorder may predict a favourable outcome (Table 4).

TABLE4
CLINICAL CHARACTERISTICS OF GOOD AND POOR PROGNOSIS BIPOLAR DISORDER PATIENTS

	Good prognosis bipolar diorder (N=31) Mean±S.D.	Poor prognosis bipolar disorder (N=31) Mean ±S.D.
Manic disorder	2.6±1.5	10.3±5.3
	t=7.79, d.f. = 60, p <.001	
Depressive episodes	2.1±1.3	5.3±3.1
	t=5.33, d.f.=60. p<.001	
Total	4.7±2.0	15.6±5.9
	t= 9.68, d.f.=60, p<.001	
Age at onset	25.6±5.5	33.6±6.4
	t=5.2, d.f.=60, p<.001	

As expected, the number of manic episodes in the poor prognosis group (N=10.3±5.3) was significantly (5 folds) greater than that of the good prognosis group (N=2.61±1.5). Similarly, when compared statistically, the mean number of depressive episodes in the poor prognosis cohort (5.3±3.1) was also significantly greater than that found in the good prognosis group (2.1±1.3) as evident from table 4.

As may be expected from the characteristics of the PPBD and those of GPBD patient groups, the former had very frequent episodes of mania and depression totalling to a mean of <16, as compared to the latter, who had very few episodes, totalling to a mean of <5 (Table 4). Further, the good prognosis group had better mean social functioning and global clinical outcome score than the poor prognosis group (Table 5). Also the good prognosis patients spent longer time between the first and the last episodes (15.8±7.2 years) as compared to the poor prognosis patients, who had spent relatively shorter period between their first and the last episodes (8.93±7.9 years).

On tabulating the treatment variables (i) mainly treated with antipsychotics as opposed to those (ii) mainly treated with prophylactic drugs i.e. lithium and/or carbamazepine as in

TABLE 5
SOCIAL FUNCTIONING SCORES & GLOBAL CLINICAL OUTCOME OF POOR AND GOOD PROGNOSIS BIPOLAR DISORDER

	Good prognosis bipolar disorder (N=31) Mean ±S.D.	Poor prognosis bipolar disorder (N=31) Mean±S.D.
Social functioning score	9.42±0.81	4.78±1.98
	t=12.1, d.f.=60, p<.001	
Global clinical outcome	4.6±0.5	1.3±0.8
	t=9.05, d.f.=60, p<.001	

TABLE 6
FREQUENCY OF TARDIVE DYSKINESIA IN BIPOLAR GROUPS

Groups	Mainly treated with prophylactics	Mainly trated with neuroleptics or antidepressants	Total
Tardive dyskinesia present	6	13	19
Tardive dyskinesia absent	30	13	43
Total	36	26	62

X^2 6.40, d.f.=1, p<0.001, Odds Ratio =5, 95% confidence limits :1.7 - 19.1

table 12, the frequency of TD in these groups were calculated and subjected to chi-square analysis, which shows that TD developed with significantly lesser frequency in those bipolar cases who received predominantly prophylactic medication.

DISCUSSION

Serum DBH activity in normal population in this study deserves a closer look. In this present study it ranged from 2-39 i.u. The moot point is that this range (2-39 IU) is quite 'compressed' as compared to the range of values given by the original investigators from the USA (3 to 100 IU) as assayed among 54 normal human sera (Nagatsu and Udenfriend, 1972).

Therefore, one has to account for the lower values found in the present study. Indeed, Stone et al. (1974) had reported serum DBH activity values quite similar to those reported by Nagatsu and Udenfried (1972). However, there are reports in the 70s which published a much higher range using the same assay.

On the other hand, several investigations have reported on serum DBH activity in the controls which were significantly lower than the original range cited above (Schanberg et al., 1974; Ogihara et al., 1975; Meltzer et al., 1976). Matuzas et al., (1982) have reported a much more restricted range of DBH activity (0 to 31 IU), using the same assay procedure as that of Nagatsu and Udenfriend (1972). The present study has shown a slightly higher range (2 to 39 IU). Likewise, the normative data on DBH activity in Warsaw centre compares well with the present data Puzynaski et al., 1983). So, it is unlikely that any methodological factors have played an important role to account for this discrepancy. Rather, this wide trans-ethnic variation merits further investigations with regard to its implications.

Therefore, this alternative explanation that trans-ethnic genetic factors are operative and that DBH activity is actually lower in Asians, who may have differentially more homozygous population for the allele DBH-L, appears intriguing. Indeed, the studies in general tend to report lower serum DBH activity in blacks than in white subjects (McGuffin et al., 1976).

Most interesting and noteworthy is, of course, that the normal range of the values reported by the Japanese investigators, including Nagatsu himself (Okada et al., 1976) have been almost identical (4 to 53 IU) to those reported in the present study (2 to 39 units). However, one has to exercise caution while drawing the conclusion that the Asians are low DBH (or low norepinephrine) people. One needs to undertake population studies in order to be entitled to draw such conclusions.

Out of 148 bipolar disorder patients detail study has been done of 132 cases as 16 with intermediate prognosis were not included. None of the intermediate group had tardive dyskinesia. Therefore, in a consecutive series of 148 bipolar disorder patients, 25 cases had

developed TD, thereby corresponding to a prevalence rate of 15.5% which is higher than reported by the Vellore group (Dutta et al., 1994). This may be accounted for, among other factors, by the fact that the level of sensitization was higher in Vellore centre, leading to substantial reduction of false negatives. A differentially higher prevalence rate of TD in the affective disorder population as compared with schizophrenia has been the conclusion drawn by several studies conducted in the West, (Sandyk, 1990).

The 15.5% prevalence of TD in bipolar disorder is lower than the available western figures; Hunt and Silverstone (1991) in their catchment area study reported close to 20% prevalence in a consecutive series of patients of bipolar disorder. Likewise, Mukherjee et al. (1986) estimated that 35% of their bipolar cohort suffered from persistent tardive dyskinesia. This difference may have been due to a) varying methods of drug treatment, and b) trans-ethnic/cross-racial differences, as the methodology of the studies are comparable. However, other factors may have been operative; the neuroleptic dose is generally lower in India than in the West which is now regarded as one of the most important vulnerability factors in associations with development of TD (Cole et al., 1992; Yassa et al., 1992). In addition, ECT is relatively more frequently used mode of treatment here, which is reported to decrease the risk of TD (Cole et al., 1992). However, reports on DBH activity in affective disorders have attempted to correlate the enzyme levels in relation to subgroups of the disorder, as mentioned above, with positive and rewarding findings. The most important landmark study illustrating this point was by Meltzer et al. (1976), which showed during initial analysis, that the serum DBH activity levels between the normal controls and that of psychotic and non-psychotic depressives that taken together, did not differ significantly. However, within group analysis between psychotic and non-psychotic depressives revealed that the former had significantly lower serum DBH values than the latter. In fact, this revived the interest in the study of the enzyme in the years that followed.

The results of comparison between 'good' and 'poor' prognosis bipolar disorder group very strongly indicates that the poor prognosis sub-syndrome is characterized by significantly lower serum DBH activity levels, Actually, lower CSF DBH levels had been reported to positively correlate with increased ventricular size in bipolar disorder by Meltzer et al. (1994). However, there is no study of bipolar disorder with/without TD in terms of DBH activity to date, so it would not be possible to comparatively assess our findings.

There is a trend of findings that DBH activity is increased as an indicator of increased NE activity in TD patients with schizophrenia and not with bipolar disorder. For example, Jeste et al. (1982) found a subgroup of elderly female TD patients with schizophrenia who had 'high' plasma DBH activity. Nevertheless, they had also another group of elderly schizophrenics who had TD associated with low plasma DBH activity.

On the other hand, in contrast to the previous reports, Glazer et al. (1987) failed to detect any significant association between development of TD and serum DBH activity in 85 schizophrenic outpatients treated with neuroleptics. However, Markianos et al. (1983) found, as observed in present work, that the DBH activity was significantly lower in 42 of their dyskinetic schizophrenic cohort, using 'median split' statistical technique, while there were no differences in relation to low or high neuroleptic dose.

Significantly greater frequency of moderate to severe TD is found in poor prognosis patients, who also had very significantly higher frequency of neurological soft signs as compared to the good prognosis sub-syndrome of bipolar disorder. These signs of neuroleptic intolerance (Meltzer, 1992) could be due to diffuse cerebral dysfunction. Indeed, if lower levels of serum DBH activity is reflecting lower hydroxylation of dopamine to NE, this would

alter the homeostasis of catabolic enzymes. Consequently, this pooled up synaptic dopamine, waiting to be converted to NE, as it were, would be metabolized by monoamine oxidase (MAO); this could result in an excess of oxy-free radicals, eventually leading to brain damage (Pai et al., 1994). In fact, Cohen and Spina (1989) have convincingly demonstrated, using rate models, that catabolism of dopamine by MAO was accompanied by release of hydrogen peroxide -a cellular oxidant.

That free radicals were important factors in the toxicity of 6 hydroxy dopamine and 6 amino dopamine (Cohen & Spina, 1989) were also supported by observations by Graham, D.G. (1978) who demonstrated that cytotoxicity of various catecholamines was directly related to their rate of auto-oxidation (6OH DA> DA> NE> Epinephrine).

These considerations become extremely important in the light of the fact that, in their earlier study, Meltzer et al. (1976) had postulated that significantly lower DBH activity may itself serve as the rate-limiting enzyme in the pathway of NE formation, instead of tyrosine hydroxylase, which would result in pooling of dopamine as DBH activity is lower than the threshold value, and it (Dopamine) is not converted into NE.

The brain damage would manifest in several ways, including over-representation of tardive dyskinesia, soft neurological signs and 'neurodysfunction', and treatment-resistance with poor outcome, as evident in the data presented in this investigation.

A significantly greater number of patients without TD had received specific antimanic/prophylactic agents, such as lithium and/or carbamazepine, whereas the TD patients group had been treated significantly more frequently with antipsychotic drugs; very few of them had received lithium and or carbamazepine, and this was statistically highly significant. This is in good agreement with the observation by the Dublin group who found that specific antimanic drugs such as lithium, if not given adequately, would increase the risk of TD; they also found, as in the present study, that their bipolar patients had fewer depressive episodes (Waddington & Youssef, 1988).

In our study also, poor prognosis group has more number of manic episodes as compared to depressive episodes. On the other hand, the good prognosis bipolar patients had significantly lesser number of episodes in total, manic and depressive combined. It is interesting to note that the good prognosis bipolar patients had almost equal number of manic and depressive episodes.

These findings refute the claim by Yassa and Schwartz (1983) that depressive states could be acceptable as predictor in the development of TD. In fact, the available evidence points to a very strong possibility that frequent manic episodes may be regarded as a vulnerability marker of tardive dyskinesia.

Repeated episodes of Bipolar disorder have been associated with Neuroanatomic and Cognitive changes (Altshuler, 1993). Whereas it is possible that in some bipolar patients these anomalies may be developmental in nature (Nasrallah 1991; Beckmann and Jakob 1991), an alternative explanation for structural and cognitive change is that there is something about the process of bipolar illness that may be destructive to brain tissue. The possibility of an ongoing destructive process that accompanies the occurrence of each episode is raised. Perhaps having episodes of manias and depressions causes damage to brain tissue.

A functional correlate of such damage might be persistent cognitive deficits in the euthymic periods. Indeed, animal data suggest that hypercortisolemia-a well-known finding present in bipolar patients during affective episodes-may result in toxicity to the hippocampus, decreased glucocorticoid receptor numbers and ultimately cell death and tissue loss in the vulnerable regions (Sapolskly 1985). Alternatively, each manic episode is probably increasing the possibility of "kinding" (Post et al., 1984) which explains why the anti convulsants have significantly lesser number

of TD in our population under study.

It is worthy of note that the 'age at onset' for the poor prognosis bipolar disorder is higher than the good prognosis group. This is a finding which is in disagreement with some studies in the West. However, there are a number of clinical differences between the western and Indian observations.

There are important Socio-demographic differences, too and the age of onset of the good and poor prognosis bipolar disorder is one such patient related variable.

In conclusion, the present investigation, suggests that a subgroup of poor prognosis bipolar disorder with tardive dyskinesia has been identified with the help of the genetic marker, serum dopamine-B-hydroxylase activity, having the clinical characteristics of frequent manic episodes, evidence of diffuse brain dysfunction and not having been treated with the primary 'anti-manic' drugs. By implication, the authors wish to emphasize the need for adequate replication of findings, and further stress on the need to treat even the first episode of affective disorders with prophylactic agents.

REFERENCES

Altshuler, L.L., Conrad, A., Hauser, P., Li, X., Guze, B. & Post, R.M. (1991) Temporal lobe volume in bipolar disorder; A preliminary report. *Archives of General Psychiatry*, 48, 422-483.

Altshuler, L.L. (1993) Bipolar disorder : Are repeated episodes associated with neuroanatomic and cognitive changes? *Biological Psychiatry*, 33, 563-565.

American Psychiatric Association (1980) Diagnostic and statistical manual of mental disorder, Edn. 3, Washington D.C. : William and Wilkins.

Bech, P., Refaelsen, O.J., Kramp, P. & Bolwig, T.G. (1978) The mania rating scale self-construction and inter-observation agreement. *Neuropharmacology*, 17, 430-431.

Beckmann, H. & Jakob, J. (1991) Prenatal disturbances of nerve cell migration in the entorhinal region : A common vulnerability factor in functional psychoses ? *Journal of Neural Transmission*, 84, 155-164.

Carlson, G.A., Kotin, J., Davenport, Y. & Adland, M. (1974) Follow up of 53 bipolar manic patients. *British Journal of Psychiatry*, 124, 134-139.

Coffman, J.A., Bornstein, R.A., Olson, S.C., Schwarzkopf, S.B. & Nasrallah, H.A. (1990) Cognitive impairment and cerebral structure by MRI in bipolar disorder. *Biological Psychiatry*, 27, 1188-1196.

Cohen, G. & Spina, B. (1989) Depranyl supresses the oxidant stress associated with increased dopamine turnover. *Annals of Neurology*, 26, 689-690.

Corryell, W. & Winokur, G. (1992) Course and outcome of affective disorders. In : *Handbook of Affective Disorder*, Edn. 6, (Ed.) Paykel, E.S., pp 89-107. Edinburgh : Livingstone.

Dolan R.J., Calloway, P. & Mann, A.H. (1985) Cerebral ventricular size in depressed subjects. *Psychological Medicine*, 15. 873.

Frank, E., Prien, R., Jarett, R.B., Keller, M.B., Kupfer, D.F., Lavori, P., Rush, A.J. & Weissman, M.M. (1991) Conceptualization and rationale for consensus definitions of terms in major depressive disorder : remission recovery, relapse and recurrence. *Archive of General Psychiatry*, 48, 851-855.

Glazer, W.M., Morgenstern, H. & Jeste, D.V. (1987) Serum dopamine ß hydroxylase activity in tardive dyskinesia. *Psychoneuroendocrinology*, 12, 289-294.

Graham, D.G. (1978) Oxidative pathways for catecholamines in the genesis of neuromelanin and cytotoxic quinones. *Molecular Pharmacology*, 14, 633-643.

Hamilton, M. (1960) A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, 23, 56-62.

Harrow, M., Goldberg, J.F. & Grossman, L.S. (1990) Outcome in manic disorders : a

naturalistic follow-up study. *Archives of General Psychiatry*, 47, 665-671.

Jeste, D.V., Potkin, S.G., Sinha, S., Potter, W.Z. & Wyatt, R.J. (1979) Tardive dyskinesia-reversible and persistent. *Archives of General Psychiatry*, 36, 585-590.

Johnstone, E.C., Owens, D.G.C., Frith, C.D. & Calvert, L.M. (1985) Institutionalization and the outcome of functional psychoses. *British Journal of Psychiatry*, 146, 36-44.

Johnstone, E.C., Owens, D.G.C. & Crow, T.J. (1989) Temporal lobel structure as determined by nuclear magnetic resonance in schizophrenia and affective disorder. *Neurology, Neurosurgery and Psychiatry*, 52, 736-841.

Keller, M.B. (1987) Differential diagnosis, natural course, and epidemiology of bipolar disorder. In : Psychiatry Update. *APA Annual Review*, Vol 6, (Eds.) Hales, R.E. & Francsi, A.J., pp 10-24. Washington, D.C. : APA Press Inc.

Kolakowska, T., Williams, A.O., Jambor, K. & Ardern, M. (1985) Schizophrenia with good and poor outcome III : Neurological 'soft signs, cognitive impairment, and their clinical significance. *British Journal of Psychiatry*, 146, 348-357.

Kraepelin, E. (1919) Dementia praecox and paraphrenia (trans. by R.M. Barclay), (Ed.) Robertson, G.M. Edinburgh : Livingstone.

Liddle, P.F., Barnes, T.R.E., Speller, J. & Kibel, D. (1993) Negative symptoms as a risk factor for tardive dyskinesia in schizophrenia. *British Journal of Psychiatry*, 163, 776-780.

Maas, J. (1975) A bicohemical classification of depression. *Archives of General Psychiatry*, 32, 1357-1361.

Markianos, M., Tripodianakis, J. & Garelis, E. (1983) Neurochemical studies of tardive dyskinesia II. Urinary methoxyhydroxyphenylglycol and plasma dopamine beta hydroxylase. *Biological psychiatry*, 18, 347-354.

Matuzas, W., Meltzer, H.Y. & Uhlenhuth, E.H. (1982) Plasma dopamine -B-hydroxylase in depressed patients. *Biological Psychiatry*, 17, 1415-1424.

McGuffin, W.L., Heiss, G. & Tyroler, H.A. (1976) Longitudinal study of dopamine-ß-hydroxylase and hypertension in a biracial population sample. *Clinical Research*, 24, 248A.

Meltzer, H.Y. (1992) Treatment of the neuroleptic-non responsive schizophrenic patients. *Schizophrenia Bulletin*, 18, 515-542.

Meltzer, H.Y., Cho, H.W., Carrol, B.J. & Russo, P. (1976) Serum dopamine-ß-hydroxylase activity in affective psychosis and schizophrenia. *Archives of General Psychiatry*, 33, 585-591.

Mukherjee, S., Rosen, A.M., Caracci, G., Shukla, S. (1986) Persistent tardive dyskinesia in bipolar disorder. *Archives of General Psychiatry*, 43, 342-346.

Nagatsu, T. & Undenfriend, S. (1972) Photometric assay of dopamine-ß-hydroxylse activity in human blood. *Clinical Chemistry*, 18, 980-983.

Nasarllah, H.A., Tippin, J. & McCalley-Whitter, M. (1983) Neurological soft signs in manic patients : a comparison with schizophrenic and control group. *Journal of Affective Disorders*, 5, 45-50.

Nurnberger, J.I. & Gershon, E.S. (1992) Genetics. In : *Handbook of Affective Disorders*. (Ed.) Paykel, E.S., Edinburgh : Livingstone.

Ogihara, T., Nugent, C.A., Shen, S.W. & Goldstein, S. (1975) Serum dopamine-ß-hydroxylase activity in parents and children. *Journal of Laboratory & Clinical Medicine*, 84, 566-573.

Okada, T., Ohta, T. & Shinoda, T. (1976) Dopamine-ß-Hydroxylase activity in serum and cerebrospinal fluid in neuropsychiatric disease. *Neuropsychobiology*, 2, 139-144.

Puzynski, S., Rode, A. & Zaluska, M. (1980) Plasma DBH activity in endogenous depression. Psychiatry Poland, 14, 581-586 (as quoted by Puzynski et al., 1993).

Sapolsky, R.M. (1985) A mechanism for glucocorticoid toxicity in the hippocampus. Increased neuronal vulnerability to metabolic insults.

Journal of Neurosciences, 15, 1228-1232.

Schanberg, S.M., Stone, R.A. & Kirshner, N. (1974) Plasma dopamine-ß-hydroxylase. A possible aid in the study and evaluation of hypertension. *Sciences*, 183, 523-525.

Schildkraut, J.J. (1965) The catecholamine hypothesis of affective disorders : a review of supporting evidence. *American Journal of Psychiatry*, 122, 509-522.

Schooler, N.R. & Kane, J.M. (1982) Research diagnosis for tardive dyskinesia. *Archives of General Psychaitry*, 39, 486-487.

Shopsin, B., Freedman, L.S., Goldstein, M. & Gershon, S. (1972) Serum dopamine beta-hydroxylase activity and affecitve states. *Psychopharmacologia*, 17, 11-16.

Simpson, G.M., Lee, J.M., Zoubok, B. & Gardos, G. (1979) A rating scale for tardive dyskinesia. *Psychopharmacology*, 64, 171-179.

Spitzer, R.L., Endicott, J.E. & Robins E. (1978) Research Diagnostic Criteria. Rationales and reliability. *Arch. Gen. Psychiatry*, 35, 773-782.

Stone, R.A., Krishner, N. & Gunnels, J.C. (1974) Change of plasma dopamine-ß-hydroxylase activity and other plasma constitutents during the cold pressor test. *Life Science*, 14, 1797-1805.

Winokur, G., Clayton, P.J. & Reich, T.J. (1969) Manic depressive illness. St. Louis : Mosby.

World Health Organization (1978) International classification of disease-ninth Revision, Geneva : WHO.

Yassa, R. & Schwartz, G. (1984) Depression as a predictor in the development of tardive dyskinesia. *Biological Psychiatry*, 19, 441-444.

UTPAL GOSWAMI, M.D., Professor of Psychiatry & Drug deaddiction Centre. S. BASU, M.D., Senior Resident, UNNATI KUMAR, M.B.B.S., Junior Resident, U. KHASTGIR, M.D., Senior Specialist Psychiatrist, Lady Hardinge Medical College & Associated Hospital, New Delhi 110 001. R. CHANDRASEKARAN, M.D., Professor & Head of Psychiatry, JIPMER, Pondicherry 605 006, B.N. GANGADHAR, M.D., Additional Professor of Psychiatry, NIMHANS Bangalore 560 029, R. SAGAR, M.D., Assistant Professor of Psychiatry, All India Institute of Medical Sciences, New Delhi. J.S. BAPNA, M.D., Ph.D., Director, Institute of Human Behaviour & Allied Sciences, Shahdara, Delhi, S.M. CHANNABASAVANNA, M.D., formerly Director and Presently Professor-Emeritus, NIMHANS, Bangalore 560 029, P. BRIAN MOORE, MRCPsych, Senior Lecturer, & I.N. FERRIER, FRCPsych, Professor and Head, Division of Psychiatry, Royal Victoria Infirmary, Leazes Wing, Newcastle upon Tyne NE1 4LP.*

Correspondence