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EDITORIAL

Glimpses of Neurobiological Underpinnings of Bipolar Disorder

A major development in the study of bipolar disorder, in the recent years, has been the identification of indicators of structural and functional brain abnormalities. That the unfavorable outcome of some patients could be a result of subtle brain dysfunction has been hypothesized. It has been suggested that there is something about the process of bipolar illness that may itself be the cause of this subtle brain dysfunction. For instance, hypercortisolaemia can occur in both the depressed and manic phases of the illness effecting lasting dysfunction even after the affective episode has resolved.

In fact, there are clinical perceptions as well as research-based evidence that bipolar disorder has been changing its profile. For instance, in epidemiological terms, it has been customary to quote a prevalence estimate of 1% of bipolar disorder the world over. However, as a consequence of broadening of its definitional boundaries and increasing recognition, diagnosis and clinical and epidemiological research on soft bipolar disorders, the prevalence of this illness sharply rises to about 7.5%, if not more (Angst, 2003; communication in the proceedings of the International Conference on Bipolar Disorder, Pittsburgh, June 2003).

Similarly, there is now a better understanding of the fact that bipolar disorders are a costly disease. Not only does it cost some patients' lives, the society has to pay an enormous cost – direct and indirect – for managing bipolar patients. This fact was very succinctly brought into focus by an actuarial analysis during the Annual Conference of the British Association for Psychopharmacology, held in Harrogate, UK in July 2001.

In terms of the outcome, it has now been recognized to be a potentially chronic illness, albeit in a significant minority. At least one in five cases remain chronic and *difficult-to-treat*. As evident in the World Development Report, this illness accounts for the sixth leading cause of Disability Adjusted Life Years (DALYs) loss for the age group between 15 to 44 years, globally. Besides, the World Health Organization projects it to become one of the major killer syndromes in not so distant future.

Coming to the central theme of this editorial, there are several lines of evidence that bipolar disorder may have several neurobiological underpinnings. It is very important to recognize these, as we must now consider the reasons as to why quite a few patients suffering from this disorder may have a significantly unstable stability, poor psychosocial functioning and a relatively bleak outcome! Those who started their career in psychiatry in the '70s and the early '80s experienced the so-called *affective bias* amongst their consultants who appeared happier to get a case of bipolar disorder or depressive illness as compared to obsessive-compulsive disorder or schizophrenia.

A comprehensive and holistic understanding is therefore necessary for instituting early and effective intervention and also for ensuring stable recovery and good quality of life for the bipolar patients. In this issue, the paper by the Newcastle group on the MRI findings on enlargement of third ventricular volume in bipolar patients (Bhadoria et al, 2003) highlights this concern. This editorial aims at catching some glimpses of the available evidence that suggest that bipolar disorder may indeed be a disorder resulting from/in brain damage/dysfunction.

Almost thirty years ago, Robbins and Guze, laid down a set of criteria for validity of psychiatric disorders: clinical phenomenology, genetics, course and treatment response. Even though in each of these areas our accumulated knowledge about bipolar disorder is impressive, many of the traditionally held views regarding the illness need to be reconsidered in light of the relatively recent research findings.

That bipolar disorder follows an episodic course, is well known and that it is an illness with almost no long term consequences has been the well accepted idiom of the past many decades.

Studies have cautioned, however, that around 20% of patients with bipolar disorder show poor social outcome, particularly those with continued affective symptoms. Thus it does appear as though not all patients of bipolar disorder are fortunate enough to escape some long-term consequences of this illness.

The structural and biochemical correlates of this cerebral dysfunction remain to be elucidated. However, one could gauge the subtle deficits through 'windows' assessing the CNS functional integrity viz. neurocognitive status (NCS), neurological soft signs (NSS), neuroradiology, EEG, neuroimmunology, and neuroleptic intolerance. Abnormalities on these parameters might then very well be considered as a functional correlate of brain dysfunction. For example, the findings of a few recent studies have demonstrated the presence of neurological soft signs in patients of bipolar disorder indicating cerebral dysfunction.

NEURORADIOLOGY OF BIPOLAR DISORDER

"It is possible that each affective episode is not biologically benign, but in a substantial number of patients the episodes may contribute to subtle, perhaps permanent brain changes" Altschuler (1993).

Structural differences in the brains of bipolar patients compared with normal controls have been reported. Over the past 15 years, structural brain changes have been observed using computerized tomography (CT). Lateral ventricular enlargement or increased ventricular/ brain ratios (VBRs) were the most frequent findings. Bipolar patients also tended to show, in comparison with healthy control subjects, an actual reduction in cerebral substance. In a recent study, VBRs were measured in the brains of 24 bipolar, 27 unipolar, 108 schizophrenics and 75 control subjects. The male bipolar

patients had significantly larger ventricles than all other control groups, a finding that remained significant even when controlled for age.

In addition, computerized tomography studies have suggested that the X-ray attenuation values (the extent to which X-rays fail to be transmitted through a structure) are abnormal in the white matter of patients with bipolar disorder.

As far as structural MRI studies are concerned, decrease in the volume of the medial temporal lobe or cerebrum in bipolar patients compared with normal controls have been reported in some but not all studies.

The other abnormalities that have been reported with a high frequency in patients of bipolar disorder are the white matter signal hyperintensities. Moore et al (2001) studied the white matter abnormalities on MRI in poor versus good outcome bipolar patients and normal controls. The deep white matter lesions (DWMLs) were found in significantly higher numbers in the poor outcome group as compared with the good outcome group. The severity of these lesions in the poor outcome group significantly exceeded the good outcome patients or controls; the later too not differing significantly.

Position emission tomography (PET) has shown that significant hypoperfusion and hypometabolism of the frontal lobe and anterior cingulate gyrus in patients with bipolar disorder may resist despite improvement in clinical state.

NEUROCOGNITIVE STUDIES IN BIPOLAR DISORDER

"Attacks of manic-depressive insanity... never lead to profound dementia, not even when they continue through out the life almost without interruption. Usually, all morbid manifestations completely disappear; but where that is not the case only a rather slight peculiar psychic weakness develops..." Kraeplin (1913).

Of the few studies (please refer the table), assessing neurocognitive status in euthymic or recovery phas, persistent cognitive deficits have now been reported in up to 32% of patients. However as outlined below it is with caution that these studies may be interpreted.

NEUROLOGICAL SOFT SIGNS

A neurological sign is a particular form of deviant performance on a motor or sensory test in the neurological status examination. The designation *'soft'* is usually taken to indicate that the person with the sign shows no other features of a fixed or transient neurological lesion or disorder. Unlike hard signs such as pathological reflexes and sensory motor deficits, soft signs are non-localizing neurological findings, which indicate diffuse cerebral dysfunction of vague localisation. There is some agreement that these should be valued as indicators of CNS dysfunction with causal or predictive value for associated psychological dysfunction.

Studies assessing these soft signs in affective disorders have been strikingly infrequently conducted. Nasrallah et al (1983) assessed the neurological soft signs in manic and schizophrenic patients admitted to acute inpatients psychiatric wards. They found that the neurological soft signs were significantly more common in both schizophrenia and mania compared to a control group. More importantly, there was no overall difference between the manic and schizophrenic groups. The authors concluded that neurological soft signs, like cortical atrophy, appear to be a nonspecific correlate of both schizophrenia and mania. In our opinion, most if not all, neurocognitive dysfunction and neurological soft sign assessment are response contingent situation. Therefore, it is grossly fallacious to carry out these investigations in acutely ill psychiatric patients.

Other authors have also reported the presence of neurological soft signs in bipolar disorder. Cherian and Kuruvilla (1989) studied neurological soft signs in 50 patients, both inpatients and outpatients, who were diagnosed cases of affective disorder (Mania and Depression) in comparison with 20 normal healthy controls. Their findings were similar to those reported by and Nasrallah et al in that that patients with affective disorder had more neurological soft signs as compared with the general population. The dysfunction was more in the temporal and parietal lobes.

In probably the first study of its kind Goswami et al (1998) conducted on 62 euthymic bipolar disorder patients to assess the neurological soft signs found that the patients with poor outcome had more neurological soft signs than those in the good outcome category when rated according to the guidelines given by Nasrallah et al with some modifications in the battery as adopted by the Kolakowska et al (1985). Subsequently in a later study, we found a high preponderance of neurological soft signs in euthymic bipolars vis-à-vis normal matched healthy controls too. This seems to indicate that neurological dysfunction is probably a very strong correlate of the process of bipolarity necessitating early and aggressive treatment so as to avoid these organic changes that may ensue resulting, as these may, further into treatment resistance, poor psychosocial and clinical outcome.

RESULTS OF VARIOUS NEUROCOGNITIVE STUDIES IN BIPOLAR DISORDER

Author	Findings	Comments
Sapin et al (1987)	No significant differences in information processing in 20 euthymic medication free BP vs normal controls	Small sample size and no test for frontal lobe/ memory used.
Waddington & Yousef (1988)	40 BP some of whom showed impairment on trail making B which had an association with presence and severity of involuntary movements.	Only 33 euthymic of the 40 BP All were on medication. No tests of memory or other domains of executive function.

Results of various neurocognitive studies in bipolar disorder (Contd.)

Author	Findings	Comments
Dupont et al (1990)	20 BP who performed significantly worse only on tests and speed (DSST)	Phase of illness not controlled for.
Coffman et al (1990)	Presence of prominent, diffuse, neuropsychological deficits	Exact number of bipolar subjects not clear. All had h/o previous psychotic episodes Most had hospitalizations which might represent a bias All patients were on medication (neuroleptics)
Dupont et al (1995)	Correlations found between volume of AWM and impairments on tests of fluency, speed, and free recall.	Mean scores on HRSD were 9.2±6.5 hence not all euthymic bipolars 7 of sample were manic/ hypomanic & 6 were depressed so euthymic BPs only 23
Paradiso et al (1997)	No differences seen between BP and normal controls	BP sample too small (no=11)
Kessing (1988)	No. of depressive episodes correlated well with cognitive decline with manic or mixed episodes not contributing to same	No differentiation made between unipolar and bipolar subjects at the time of analysis
Tham et al (1997)	Neurocognitive decline correlated with number of previous hospitalizations	BP sample too small (no=16)
McKay et al (1995)	Older population (66-82) of unipolar and bipolar euthymics showed deficits in at least one of the cognitive domains	BP sample consisted of only 12 subjects with 2 of these being hypomanic
Van Gorp et al (1998)	BP with and without alcohol dependence studied. Both showed verbal memory deficits; however, only those with h/o alcohol dependence showed executive deficits.	Only 13 BP without alcohol dependence present in the sample. All patients were on medication (Li)
Denicoff et al (1999)	A longer duration of illness and an earlier age at onset correlated significantly with poorer performances on the tests of attention and intelligence. Both the number of prior episodes and number of hospitalizations significantly correlated with tests of attention and intelligence, memory, and abstraction.	Not all euthymics when tested (number not specified) Statistically a large number of regression analysis conducted using many (N=15) predictor variables and only 49 subjects thus increasing the chances of type 1 error All subjects were on medication
Ferrier et al (1997)	Executive functioning and verbal memory deficits seen when patients of bipolar I disorder compared with normal controls. Post hoc t tests showed no significant differences between good and poor outcome group.	All subjects were on medication No verbal checklist used in the Rey's tests for visual complement of memory assessment.
Krabbendam et al (2000)	Significant impairment seen in BP on memory executive measures assessment.	All subjects were on medication Only 12 patients of bipolar I (power) too little.
Goswami et al (2001)	Test subjects of bipolar I (N=37) were impaired as regards executive function (correlational trend with no. of episodes) and learning and memory (correlated with duration of depressive episodes). Positive family history did not lead to any worsening in neurocognitive status. No differences were seen with regard to cognitive competence between subjects.	No measures of pre-morbid IQ employed

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