Original Research Article

Comparison of neurocognitive deficit among euthymic bipolar I disorder patients, their first-degree relatives and healthy controls

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ABSTRACT

Background: Bipolar patients often suffer from debilitating cognitive impairment in different stages of the disease (manic, depressive or euthymic states). We assessed and compared the frequency of neurocognitive deficit among individual with bipolar I disorder but currently in euthymic state, their first-degree blood relatives and healthy controls. In addition, we also probed further into the type of neurocognitive deficit that can be seen among them and observed the influence of sociodemographic characteristics with the occurrence of neurocognitive deficit in individual with bipolar I disorder patient.
Methods: Patients (N=30) who fulfilled the diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV TR) criteria for bipolar I disorder but currently in remission were assessed for any neurological deficits using the standard instruments. In this study, 30 first-degree blood relatives of bipolar I disorder patients and selected 30 hospital staff as healthy controls were also assessed for neurological deficits.
Results: We did not find any significant frontal dysfunction among first-degree blood relatives of bipolar I disorder patient when compared with euthymic bipolar I disorder patients. Factor that significantly affected neurocognitive performance in the bipolar patients who were in euthymic state included age, total duration of illness and number of manic episode.
Conclusions: As neurocognitive impairment is associated with number of manic episode and total duration of illness; the objective of treatment should be to prolong remission and impart psychoeducation regarding nature of illness. On the contrary, anticipating definite cognitive impairment in first-degree blood relatives of bipolar I disorder patient when compared to healthy control warrants periodic neurocognitive testing and psychoeducation about deficit and medical intervention, if required.

Keywords: Endophenotype, Euthymic state, First-degree blood relatives of bipolar I disorder, Neurocognitive deficit

INTRODUCTION

Cognitive deficits within mood disorders have been studied extensively. The relationship between mood and cognition are dynamic as some of the components are trait-dependent and others that are state-dependent. Bipolar patients often suffer from debilitating cognitive impairment in different stages of the disease (manic, depressive or euthymic states). Persistent cognitive impairment comprising of measurable decreases in the domains of attention, memory and executive function is observed in people with bipolar disorder, who are currently in euthymic state. Earlier neurocognitive deficits were thought to be secondary to the manic and

depressive symptoms, or motivational factors; however, in recent times, these deficits were regarded as trait abnormalities.[1] Executive functions, memory and tasks involving mental flexibility and psychomotor speed are specifically affected in bipolar disorder.[2] Cognitive deficits are seen in patients with bipolar disorder as well as in their relatives. It has been hypothesized that the relatives of bipolar patients would have impaired performance on cognitive tests of frontal-executive functions. Researchers proposed neurocognitive deficits as a vulnerability marker or endophenotypes for the development of bipolar I disorder.[1,3,4] However, evidence is insufficient to conclude neurological deficits as important genetic vulnerability markers for the bipolar I disorder. Hence the objective of this study was to determine if any compromise in cognitive function could be linked to the genes and thus be viewed as endophenotypes of bipolar disorder. In this scenario, we conducted a study to assess and compare the frequency of neurocognitive deficit among individual with bipolar I disorder but currently in euthymic state, their first-degree blood relatives and healthy controls. In addition, we wanted to understand the type of neurocognitive deficit among them and observe the influence of sociodemographic characteristics with the occurrence neurocognitive deficit in individual with bipolar I disorder patient.

METHODS

The study was conducted in Department of Psychological Medicine, General Municipal Hospital. This hospital has inpatient and outpatients facilities to care for the mentally ill patients.

Patients (N=30) who fulfilled the diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV TR) criteria for bipolar I disorder but currently in remission were enrolled in the study. In this study, we also included 30 first-degree blood relative of bipolar I disorder patients and selected 30 hospital staff as healthy controls. In control group, the subjects were matched for demographic parameters of age, gender, education, and marital status.

Patients included in this study had to be within the age group of 17 and 65 years. The enrolled patients had to fulfil the criteria for bipolar I disorder but without any signs and symptoms of axis I or II clinical syndromes. Patients had to be euthymic at time of inclusion into the study. In addition, the patients had to be literate, or at least should be able to understand the language. Patients with other psychiatric co-morbidity, pre-existing neurological and medical illness, mental retardation and receiving electroconvulsive therapy were excluded from the study. Informed verbal consent was obtained from all patients and their first-degree relatives fulfilling the above inclusion criteria. The enrolled patients were interviewed and assessed using following tools:

- A semi-structured proforma was used to document socio-demographic data, history of psychological symptoms and physical examination.
- DSM-IV-TR criteria to validate diagnosis of bipolar I disorder.[5]
- Young mania rating scale (YMRS) to assess manic symptoms.[6]
- Hamilton depression rating scale (HDRS) to assess depression.[7]
- Neurocognitive assessments: mini mental status examination [(MMSE: ≥24 points were considered as normal)].[8]
- Frontal assessment battery (FAB): A brief battery of six neuropsychological tasks designed to assess frontal lobe function at bedside.[9]
- Trail making test (TMT) A and B: Time taken to complete the task was noted.[10]

RESULTS

There was no significant difference in age among three groups. The mean age among bipolar disorder patients was 38.07 years. The subjects enrolled were predominantly men in all the three groups. Twenty percent of the bipolar patients were college educated as compared to 10% in the control. 63.33% of the bipolar patients were married as compared to 83.33% and 86.67% of the control group and relatives, respectively. Higher percentage of patients with bipolar disorder were divorced (6.67% vs. 0) when compared to the other two groups. One-third of the patients with bipolar I disorder had family history of bipolar disorder. Approximately one-third of the patients (40%) were unemployed and one-third was employed in private sector. Majority of the bipolar patients (60%) were well-maintained on valproate. Mean HDRS score and YMRS score for bipolar patients was 4.20 and 2.13, respectively.

Table 1: MMSE test result for neurocognitive deficit.

MMSE test	Bipolar	Control	Relative
Neurocognitive deficit	2	0	0
Percentage	6.67%*	0.00%	0.00%

MMSE: Mini mental status examination; *p=0.1293 (NS).

With respect to MMSE, 6.67% of bipolar patients presented with neurocognitive deficits but none of them in the other two groups had neurocognitive deficits (Table 1). Neurological deficit on FAB was observed in 40% of patients with bipolar I disorder and 6.67% of first-degree relatives (Table 2). None of them in control had any neurological deficits. There was a statistically significant difference on the FAB scores between the bipolar and control, as well as between bipolar and first-degree relative groups but no statistically significant difference between controls and first-degree relative groups. One-third and one-fifth of patients with bipolar I disorder showed neurological deficit in TMT A and B.

There was a significant correlation between age and MMSE, TMT A and B. The MMSE score showed a decreasing trend with increasing age and time required for TMT A and B increased with increasing age. No significant correlation was found between age of onset (in years) and neurocognitive profile. There was a significant correlation between duration of illness and the incidence of neurological deficits with increasing duration of illness, the MMSE score decreased and time required for TMT A and B increased. There was no significant correlation between total number of episodes and neurocognitive profile. There was a significant correlation between number of manic episodes and TMT A and B. With increasing number of manic episodes, time required for TMT A and B increased. There was no significant correlation between number of depressive episodes and neurocognitive profile.

Table 2: Frontal assessment battery (FAB) test result for neurocognitive deficit.

FAB test	Bipolar	Control	Relative
Neurocognitive deficit	12	0	2
Percentage	40.00%	0.00%	6.67%

DISCUSSION

Neuropsychological deficits have been documented in patients with bipolar I disorder in manic, hypomanic, depressive as well as euthymic phases. In present study, we compared the neurocognitive deficits on MMSE, FAB, TMT A and B in bipolar I disorder patients, who were currently in euthymic state with that of healthy first-degree blood relatives of the patients and healthy controls.

With increasing age, the MMSE score decreased and time required to complete TMT A and B increased. This finding suggests that with increasing age, the neurocognitive performance on test declines. A declining pattern of performance on measure of speed and memory with increasing age has been reported and is consistent with life span developmental patterns of cognitive development. Aging adversely affects some but not all cognitive domains.[11]

With increase in duration of illness, time required to complete TMT A and B also increased. Therefore, it is evident duration of illness has a direct negative effect on the neurocognitive functioning. Martínez-Arán et al found that euthymic bipolar patients (6 months of remission with score ≤8, and YMRS score ≤6) performed poorly in the domains of executive function and verbal memory when compared to healthy comparison subjects. Thus, even during remission, neurocognitive deficits are evident and thus patients show compromises in daily functioning.[12] Bora et al found that the duration of illness correlated to slowness in psychomotor speed tasks. In addition, the researchers suggested that verbal memory deficits were perhaps related to serum lithium levels and

age of onset of disease.[13] In present study, euthymic patients with higher number of manic episodes required more time to complete TMT A and B tasks. López-Jaramillo et al also found in their study that the number of manic episodes predicted poor cognitive performance, and therefore opined that recurrence of mania could have a long-term neuropsychological impact.[14] In the study by Vrabie et al greater cognitive impairment (in verbal and working memory, executive function/reasoning and problem solving) was observed in manic subgroup compared to depressive, mixed, and euthymic subgroup. Patients experiencing a manic episode displayed higher deficits in verbal and working memory, executive function/reasoning, and problem solving. Severe course of illness significantly contributed to cognitive impairment.[15]

In this study, we did not find any significant correlation between age of onset and neurocognitive decline. A meta-analysis reported significant impairment of neurocognitive function with advancing age.[16] The severity of the neurocognitive functions (in the domain of psychomotor speed and in verbal memory) correlated with age at onset. Severe impairment is evident in those who have an early onset of illness and particularly the onset during childhood or adolescence.[17]

We also observed no significant correlation between numbers of depressive episode and neurocognitive decline. Concurrent to present findings, in the systematic treatment optimization programme for early mania (STOP-EM) study, depressive episodes did not impart any additional burden on cognitive function.[18]

On FAB, 40% of bipolar patients had neurocognitive deficit compared to 6.67% relatives and 0% controls. Twenty percent of euthymic bipolar patients were found to have neurocognitive deficit on TMT B but none in control or first-degree relatives. Similar results were evident on TMT A. A meta-analysis found that euthymic bipolar patients had relatively marked impairment in domains of executive function (category fluency, mental manipulation) and verbal memory.[19] Arts et al found small, but intermediate, cognitive impairments in domains of executive function and verbal memory among first-degree relatives and suggested that it could serve as an indicator of genetic risk.[16] Bora et al concluded that deficits in verbal working memory and executive function may serve as a useful endophenotypic marker of genetic vulnerability to bipolar disorder. In this study, verbal memory and psychomotor performances of relatives were not different from control subjects. Cognitive flexibility, a particular component of executive function, was associated with family history of mood episodes with psychotic features.[4] Another meta-analysis could not find any neurocognitive deficit among first-degree relatives of bipolar I disorder.[20]

In present study, specific neurocognitive deficits as measured by TMT A and B were not found in the

relatives of the bipolar disorder patients and in controls. Similarly, neurocognitive deficits measured by FAB are not significantly present relatives of the bipolar disorder patients and in controls. On the contrary, patients in bipolar group had significant neurocognitive deficits on both FAB and TMT A and B. Therefore, we presume that neurocognitive deficits in the bipolar patients and the relatives of bipolar patients may be of different nature, deficits in bipolar patients being more global and deficits in the relatives of bipolar patients may be more specific in nature.

Verbal learning/memory and verbal working memory are the predicators of endophenotypes for bipolar disorder. Healthy first-degree relatives are more likely to have an intact performance on immediate memory, verbal fluency, and probably on general intelligence. Cognitive deficiency among relatives may not be different from that of controls.[20] However, future studies with larger samples, and comprehensive neuropsychological assessments are warranted.

CONCLUSION

We did not find any significant frontal dysfunction among first-degree blood relatives of bipolar I disorder patient when compared with euthymic bipolar I disorder patients. Factor that significantly affected neurocognitive performance in the bipolar patients who were in euthymic state included age, total duration of illness and number of manic episode. As neurocognitive impairment was associated with number of manic episode and total duration of illness, the objective of treatment should be to prolong remission and impart psychoeducation regarding nature of illness. On the contrary, anticipating definite cognitive impairment in first-degree blood relatives of bipolar I disorder patient when compared to healthy control would warrant periodic neurocognitive testing and psychoeducation about deficit and medical intervention, if required.

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