NEUROCOGNITIVE DEFICIT IN BIPOLAR I DISORDER PATIENTS CURRENTLY IN EUTHYMIC STATE, THEIR UNAFFECTED FIRST DEGREE RELATIVE AND HEALTHY CONTROL GROUP- A COMPARATIVE STUDY

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ABSTRACT

BACKGROUND

Neurocognitive dysfunctions particularly executive functioning, attention, processing speed, verbal learning and declarative memory are key aspects of Bipolar disorder, as they occur in all the phases of the illness, across all neuropsychological domains, even during remission of symptoms. In our study, we compared the frequency and types of neurocognitive deficits and factors influencing them in individuals with Bipolar I disorder, their first-degree unaffected relatives and healthy controls.

METHODS

It was a cross sectional, case control, comparative, study with 50 samples in each of the three groups. Diagnosis of Bipolar disorder I was made following DSM IV TR criteria and current euthymic state was established by applying YMRS and HDRS scale. Neurocognitive performance was assessed on MMSE, frontal assessment battery, trail making test A and B. Statistical tests used were chi square test, ANOVA and Pearson's correlation using SPSS 20 software.

RESULTS

Age (early onset), duration of illness, total number of episodes and number of manic episodes worsen the neurocognitive performance.

CONCLUSIONS

First degree unaffected relatives of Bipolar I disorder patients had impairment in psychomotor speed and executive functioning with alternating attention suggesting, these may be valid endophenotypic traits of bipolar disorder. Euthymic Bipolar I patients had significant frontal dysfunction and impairment in psychomotor speed, visual conceptualization and visuomotor tracking. Neurocognitive deficits in the euthymic Bipolar I patients and their first-degree unaffected relatives may be of different nature, more global in patients while more specific in relatives. Neuropsychological deficits in remission period impair socio-occupational functions which lead to poor compliance and more relapses. This highlights the need of routine assessment and early interventions even in euthymic stage. Cognitive impairment in unaffected first-degree relatives warrants periodic neurocognitive testing, psycho education and early medical intervention if required.

KEYWORDS

Bipolar Disorder, Euthymic, Cognitive Functioning

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BACKGROUND

Cognition is the ability to process information and apply knowledge. It is the highest level of information processing which includes thinking, memory, perception, motivation, skilled movements, learning and language.[1] Research suggests that Schizophrenia and Bipolar mood disorder both share common genetic risk[2] and in Bipolar disorder, cognitive domains deteriorate in remarkably similar ways as in Schizophrenia although of a lesser severity. Neurocognitive dysfunctions are the key aspects of Bipolar disorder[3] as they occur in all the phases of illness, across all neuropsychological domains,[4] even during the remission of symptoms. Cognitive dysfunctions are the trait characteristics in Bipolar disorder,[5] particularly executive functioning (e.g. inhibitory control), and attention, processing speed, verbal learning and declarative memory. Types and degree of cognitive dysfunction is similar in Bipolar disorder I and II patients.[6] Bipolar disorder has a strong genetic component, with heritability estimated to be as high as 80%.[7] Therefore, not only individuals with Bipolar disorder but also their unaffected relatives demonstrate neuropsychological deficits as compared to the normal control group in the domains of visuospatial /constructional abilities, executive functioning, visual learning memory and

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motor speed which is intermediate as compared to the normal control and Bipolar group.[8]

All patients show clinical recovery in between affective episodes but only about one third recovers functionally during same period.[9] Thus, cognitive impairment in mood disorders affects individual's ability to function occupationally and maintain a normal social life. Also, it affects patient's insight, hampers compliance to the treatment, which may lead to further relapses**.** Better neurocognitive functioning is strongly predictive of subsequent occupational recovery. Cognitive remediation improves outcome in Bipolar illness. Therefore, even after adequate symptom control there is an intense need of developing interventions targeting cognitive impairments for improving recovery rates and Quality of life in patients with Bipolar disorder. The studies on neurocognitive deficits are mostly done in patients suffering from Schizophrenia. There are very few studies about neurocognitive deficit in patients with Bipolar disorder, especially in Indian population.[10] Most of these studies lacked comprehensible neuropsychological battery, there was no distinction between unipolar and Bipolar state, did not had control of mood state at the time of study and didn't simultaneously compared euthymic Bipolar I patients and their unaffected first degree relative with healthy control.

To address these limitations, In our study we have compared neurocognitive functions in a group of euthymic patients with Bipolar I disorder, their first degree unaffected blood relatives and a control group, on a battery of tests (Mini Mental Status examination, Frontal assessment battery, Trail making test A and B).

METHODS

This observational study was conducted in department of Psychiatry of a tertiary teaching hospital after Institutional Ethics Committee approval done in the duration of 1 year. Study consisted of 50 patients, who fulfilled the DSM-IV TR criteria for Bipolar disorder I currently in remission, 50 first degree unaffected relatives of Bipolar disorder I patients and 50 healthy controls from hospital staff. Inclusion criteria being cases age 17-65 years of either age, literate, euthymic at the time of interview, fulfilling DSM IV TR criteria of bipolar I disorder and willing to participate in the study. Exclusion criteria being patients with coexisting other Psychiatric diagnoses, present or past history of neurological or medical illness, mentally retarded, or those who received ECT in last six months.

Methods of Data Collection

A semi structured proforma was used for documenting socio-demographic data, history of psychological symptoms, physical examination findings. DSM-IV-TR criteria to validate the diagnosis of bipolar I disorder. To validate the patient's euthymic state, they were assessed after rating on Young's Mania Rating Scale (Y.M.R.S.)[11], Hamilton Depression Rating Scale (H.D.R.S.)[12], Neurocognitive Battery [Mini Mental Status Examination (M.M.S.E.)[13], Frontal Assessment Battery (F.A.B.)[14], Trail Making Test[15]]

Statistical Analysis

Data was tabulated and analysed by chi square test, ANOVA and correlation was analysed using Pearson's correlation coefficient.

RESULTS

Demographic Profile

All 3 groups were comparable in relation to age, gender, marital status, education and occupation.

Mini Mental State Examination (MMSE) (Table 1)

The mean MMSE score of euthymic Bipolar disorder I patients in our study was 27.88 ± 2.455 as compared to 28.60 ± 1.212 in their first-degree unaffected relatives and 29.14 ± 0.756 in control group (Table 1). We observed that 6% (n=3) of the euthymic Bipolar disorder I patients had neurocognitive deficits on MMSE as compared to 0% (n=0) of relatives and controls and this difference was statistically significant (p=0.001).

Trail Making Test (TMT)

Trail making test measures visual conceptualization and visuomotor tracking (involves motor speed and attention function).

TMT-A (Table 2)

The mean time for completion of TMT-A for euthymic Bipolar disorder I patients was 70.68 ± 31.637 seconds as compared to 52.86 ±9.777 seconds in their first-degree unaffected relatives and 39.48 ± 7.657 seconds in control group. (Table 2) In our study 32% (n=16) euthymic Bipolar disorder I patients were found to be having neurocognitive deficit on TMT-A as compared to none of control or unaffected first-degree relative group.

TMT B (Table 3)

In our study the mean time for completion of TMT-B in euthymic Bipolar disorder I was 185.30 ± 78.239 seconds as compared to 123.96 ± 42.713 seconds and 88.84 ± 8.321 seconds in unaffected first degree relative and control group respectively. (Table 3)

Frontal Assessment Battery (FAB) (Table 4)

In our study we observed that mean score on FAB of euthymic Bipolar disorder I group was 13 ± 2.89 as compared to 14.84 ± 2.42 for their unaffected first-degree relatives and 16.20 ± 1.25 for control group (Table 4). We found that 40% of euthymic Bipolar disorder I patients in our study had neurocognitive deficit on FAB as compared to 6% relatives and 0% of control group .

MMSE	Bipolar	Relative	Control
Mean	27.88	28.60	29.14
SD	2.455	1.212	0.756
Range	22-30	27-30	28-30
Table 1. Mini Mental State Exam (MMSE)			
ANOVA: F= 7.430, df= 2,147, p= 0.001, Significant			

	Bipolar	Relative	Control
Mean	70.68	52.86	39.48
SD	31.64	9.78	7.66
Range	25-151	38-70	25-50
Table 2. TMT A			
ANOVA: F= 31.815, df= 2, p<0.001, Significant			

TMT-B	Bipolar	Relative	Control
Mean	185.30	123.96	88.84
SD	78.24	42.71	8.32
Range	90-340	60-200	80-110
Table 3. TMT B			
ANOVA: F= 44.605, df= 2, p<0.001, Significant			

FAB Test	Bipolar	Relative	Control
Mean	13.00	14.84	16.20
SD	2.89	2.42	1.25
Range	9-17	10-18	14-18
Table 4. FAB			
ANOVA: F= 27.711, df= 2, p< 0.001, Significant			

Factors		MMSE	FAB	TMT-A	TMT-B
Age of Patient	Pearson Correlation	-0.478**	-0.584**	0.492**	0.643**
	Significance	p<0.001	p<0.001	p<0.001	p<0.001
Age of Onset	Pearson Correlation	-0.373**	-0.362**	0.275	0.461**
	Significance	0.008	0.010	0.054	0.001
Duration of Illness	Pearson Correlation	-0.310*	-0.480**	0.439**	0.478**
	Significance	0.029	0.000	0.001	0.000
Number of Total Episodes	Pearson Correlation	-0.173	-0.434**	0.313*	0.352*
	Significance	0.229	0.002	0.027	0.012
Number of Manic Episodes	Pearson Correlation	-0.208	-0.445**	0.356*	0.401**
	Significance	0.147	0.001	0.011	0.004
Number of Depressive Episodes	Pearson Correlation	-0.052	-0.312*	0.143	0.158
	Significance	0.719	0.027	0.322	0.273
Family History of Bipolar Disorder	Pearson Correlation	0.088	-0.165	0.018	-0.037
	Significance	0.545	0.252	0.901	0.798
Table 5. Influence of Various Factors on Neurocognitive Profile of Euthymic Bipolar I Disorder Patients					
**= Correlation is significant at the 0.01 level (2-tailed).					
*= Correlation is significant at the 0.05 level (2-tailed).					

DISCUSSION

Cognitive deficits are found in patients of Bipolar I disorder even in euthymic state and their unaffected first-degree relatives. These deficits are considered as trait abnormalities.[16] Executive functions, memory and tasks involving mental flexibility and psychomotor speed are found to be specifically affected in patients with Bipolar disorder.[17] Thus, it has been postulated that these impairments may be associated with genetic. Our findings suggest that euthymic Bipolar disorder I patients had significant cognitive impairment on MMSE. Unaffected relatives of these Bipolar disorder patients were not found to be having neurocognitive deficit, but their mean MMSE scores were found to be less as compared to control group and this difference was statistically significant (P=.001) (Table 1). Other studies have also described that reduction in psychomotor speed continues during the euthymic period of Bipolar disorder. We observed that first degree unaffected relative of euthymic Bipolar disorder I patient took less time than Bipolar group but more time than control group and this difference was found to be statistically significant (p<.001) (Table 2) Our observation implies that impairment in visual conceptualization and visuomotor tracking (psychomotor slowing) on TMT-A was found in euthymic bipolar patients and their first-degree relatives as compared to control. Antila et al., (2007) had found significant additive heritability in verbal ability, executive functioning and psychomotor processing speed. Genetic contribution was low to verbal learning functions. High heritability, in executive functioning and psychomotor processing speed suggest that these may be valid endophenotypic traits for genetic studies of Bipolar disorder.

We observed that 24% (n=12) euthymic Bipolar disorder I patients were having neurocognitive deficits on TMT-B as compared to none of control or relative group. The relative group also took less time than Bipolar disorder I group but more time than control group and this difference was found to be statistically significant (p<.001) (Table 3). Our results are complementary to a recent study done by Frantom, 2008 and Glahn 2004, who observed that unaffected relatives demonstrated an intermediate level of performance in comparison to the normal control and Bipolar disorder I group.

Our findings are in compliance with other researchers who found impairment in executive functioning, visuomotor speed, and alternative or divided attention in euthymic Bipolar disorder I and their first-degree relatives than control. As unaffected first-degree relatives performed poorly on Trail Making Test B, this indicates poor cognitive flexibility and set shifting, which are parts of executive functioning. This reveals specific rather than generalized cognitive dysfunction which could represent trait or vulnerability marker. These findings are in consonance with some of the previous studies showing impairments of TMT-B in unaffected relatives.[18] Executive dysfunction has been seen in unaffected relatives as well as euthymic patients of Bipolar disorder I and is considered to be a potential vulnerability marker.[18] However, literature so far has been inconsistent on the types of executive function tasks that are impaired in relatives, with some studies revealing deficits in TMT-B as well as response-inhibition tasks, while others suggest a deficit in response inhibition only.[19]

FAB explores the functions related to the frontal lobes, which includes conceptualization and abstract reasoning, mental flexibility, motor programming and executive control of action, resistance to interference, self-regulation, inhibitory control and environmental autonomy. Our findings are complementary to those of recent studies implicating impairment in executive functions,[17] cognitive flexibility,[20] ability to resist, interference and planning.[21] The difference of neurocognitive deficits between euthymic Bipolar disorder I patients, their unaffected first-degree relatives and control group was statistically significant (p<0.001). (Table 4) This finding is in accordance to the findings of many researchers, who observed that the neurocognitive deficits are significantly more in the relatives as compared to controls.

Though in our study we had not used any imaging techniques to support the results, but cognitive deficits can be explained on the basis of previous studies which

correlates cognitive dysfunction with neuroanatomical deficits. The structural MRI studies by Videbech (1997) showed reduced volumes of thalamus and hypothalamus in Bipolar disorder I euthymic patients. Other studies on Bipolar disorder patients suggested that abnormalities in the fronto-subcortical neuroanatomic circuit are associated with impaired attention function,[22] abnormalities of temporolimbic structures are associated with deficits in verbal memory and attention, poor psychomotor speed with white matter hyper intensities, impaired executive functions in Bipolar disorder I and Depression attributed to frontal lobe dysfunction. Also, there can be involvement of subcortical nuclei in cognitive processing, particularly working memory and planning future behavior.

Thus, we can conclude that specific neurocognitive deficits measured by MMSE, TMT-A, TMT-B and FAB are found in both euthymic patients of Bipolar disorder I as well as in their first-degree unaffected relatives as compared to control group. Neurocognitive deficits in relatives fall in between patients and control**.** Our observations are supported by a number of studies, which have reported that with regards to verbal memory deficits, first-degree relatives perform worse than the controls but exhibit less pervasive deficits[23,24] than their Bipolar disorder probands, who have more global verbal learning and memory deficits. Deficits in visuospatial memory, working memory and some aspects of executive functions have also been identified in unaffected relatives of bipolar probands. Despite some notable exceptions, these studies provide support for considering verbal memory along with a number of other neurocognitive abilities (executive functions, some aspects of attention / working memory, visuospatial memory) as potential endophenotypic markers for Bipolar disorder.

Because some neurocognitive processes are highly heritable, neurocognitive deficits present in non-affected first-degree relatives of bipolar probands may serve as endophenotypes for the disorder, particularly if the relatives exhibit an intermediate pattern of performance in which they perform worse than normal controls but better than the bipolar probands. Influence of Various Factors on Neurocognitive Profile of Euthymic Bipolar I Disorder Patient (Table 5).

Age

In our study we observed that as age increases, the scores on MMSE and FAB decreases and time required to complete TMT-A and TMT-B increases, which suggests that with increasing age, performance on neurocognitive test gradually declines. A declining pattern of performance on measures of speed and memory with increasing age has been reported and is consistent with life span developmental patterns of cognitive development.

Duration of Illness

We observed that as duration of illness increases, score on MMSE and FAB decreases and time required to complete TMT-A and TMT-B increases, suggesting that with increase in duration of illness neurocognitive functioning starts worsening. Our findings are in harmony to the other studies, which have observed that progression in the course of illness was related to low performance on psychomotor speed, verbal memory, and overall cognitive dysfunctions.

Manic Episodes

Our study found that with increase in the number of manic episodes, performance on MMSE and FAB decreases and time required to complete TMT-A, TMT-B increases. Decline in psychomotor speed related to number of manic episodes was suggested in previous studies,[25] but contradicts observation of Goswami et al., and Kolur et al., who could not find any significant correlation between number of manic and depressive episodes and cognitive impairment. This difference might be due to heterogeneity in the nature of Bipolar disorder and presence of subclinical mood symptoms even during euthymic stage.

Total Episodes

In our study significant co-relation between total number of episodes and neurocognitive decline was found. As the number of episodes increased performance on neurocognitive tests declined. Our finding is in accordance with various previous studies[25] which have demonstrated that cognitive dysfunction symptoms are more severe in bipolar patients who experience greater number of episodes. But some studies could not find a difference between euthymic Bipolar disorder patients who have experienced one or multiple episodes of illness.[20] These differences might have risen due to difficulty in assessing the total number of episodes during history taking which is subjective as it is based on memory of patients and relatives.

Age of Onset

In our study significant co-relation was found between age of onset and neurocognitive decline i.e. earlier the age of onset, worse was the performance on neurocognitive domains. Our finding is supported by many researchers who found that there is a relationship between an early age of onset and verbal memory dysfunction, but on the contrary some researchers did not find any significant co-relation between age of onset and neurocognitive decline. These differences might be because of use of different neurocognitive tests and assessment of different cognitive parameters in these studies.

Depressive Episodes

In our study we did not find any significant co-relation between numbers of depressive episodes and neurocognitive decline. Our observation is similar to other researchers who have not found any significant co-relation between numbers of depressive episode and neurocognitive decline.[26] Multiple studies have shown that the severity of the relationship of depressive episodes with neurocognitive deficit is weaker than the relationship of manic episodes, which matches with our results.

CONCLUSIONS

Cognitive functioning of an individual is very important as it not only reflects the patient's socio-occupational functioning and ability to live independently but also about insight of their illness and compliance to treatment, leading to further relapses. Adequate cognitive remediation at an early stage of illness might improve the outcome in Bipolar illness. Therefore, development of interventions targeting cognitive impairments is imperative for improving recovery rates and quality of life in the patients suffering from Bipolar disorder. In addition, we should be vigilant for assessing neurocognitive functioning in their first-degree unaffected relatives as they are vulnerable towards development of neurocognitive deficits.

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