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ORIGINAL ARTICLE

Serum Brain-Derived Neurotropohic Factor among Manic And Euthymic Patients with Bipolar Disorder Type I .

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ABSTRACT

Background: Bipolar disorders (BD) have been accompanied with disturbances in neuroplasticity. Brain-derived neurotrophic factor (BDNF) plays important role in neuroplasticity. It plays a vital role in the neurobiology of such disorders. This study aimed to check BDNF serum levels in euthymic BD type I patients and correlate them with the clinical manifestations. **Methods**: Forty-eight Egyptian individuals were included in this study. They were arranged in three groups: The first one 'G-A' included twelve patients diagnosed with bipolar I disorder in manic episode; while the second 'G-B' consisted of twelve patients diagnosed with bipolar I disorder in full remission, and the third group 'G-C' consisted of 24 healthy persons as control subjects. The cases were diagnosed according to DSM-5 and psychometric analysis. The BDNF levels were assessed using the technique of quantitative sandwich enzyme immunoassay. **Results:** There was no statistical significant difference between the studied groups as regard demographic characteristics. Serum BDNF levels were lower in bipolar I patients in manic episode compared with those in euthymic state and also control subjects. **Conclusion:** patients with manic episode of bipolar I disorder have lower serum BDNF levels compared with those with euthymic state and control group.
Keywords: Brain-derived neurotrophic factor, bipolar disorder, manic episode.

INTRODUCTION

BDNF regulates the neuronal growth , controls intersynaptic activity and supports the bioactivity of neurons[1].BDNF is known to be found in in large amount in the cerebral cortex, hippocampus and many brain sites, especially those responsible for higher brain operations including memory and feelings[2].

Changes of Serum BDNF level in the periphery may be the indicator for its level alteration in the brain as it passes blood brain barrier and also many researches in animal showed that its blood level is highly associated with its level in the cerebrospinal fluid[3].

Bipolar disorder is a disease which consist of many aspects including periods of significant mood swing, dysfunction of neuropsychological ability, and alteration of immunity and biological function[4].Among causes of worldwide disability, bipolar disorder is considered one of its main cause and is linked with high incidence of death in young age as a result of suicide and associated medical problems[5].

The exact cause of bipolar disorder up till now is not explored enough, however many studies that try to know exact pathophysiology of bipolar disorder shedded light on role of genetics and epigenetics in its neurobiology. recently remodeling of the neuronosynaptic organization and change in cell growth or apopotosis have been reported to strongly correlated with the occurrence of bipolar disorder, so it can be a result of damage of neurons (e.g., after long term stress, chronic increased levels of glucocorticoids, ischemia,

decrease blood glucose level, viral infections, neurotoxins, etc.)[6].

In a way to recognize the underlying etiology of bipolar disorder, several researches examined BDNF serum level in different episodes of BD[7].

BDNF was first studied to clarify the aetiopathology of mood disorder. It was a good option as its level in blood can be a mirror image of its concentration in brain since it passes blood brain barrier freely [8].

Alteration of levels of BDNF in blood of bipolar patients have been reported by previous studies in manic episode and also depressive episode but with heterogeneity of results and lack of standard values of BDNF level[9,10]

This study was designed to test the hypothesis that serum BDNF level decrease during acute manic episode and it could be used as biomarker to distinguish these patients from bipolar patients in remission and healthy control, so the aim of study was To investigate the serum BDNF levels in patients with bipolar I disorder during manic, episode in comparison to also bipolar I patients in euthymic state and healthy control matched for age, gender and socioeconomic state.

METHODS

This is a case control research that was carried in the Zagazig university hospitals at Psychiatry department in collaboration with department of Medical Biochemistry. The research was preceded on 48 individuals classified as follow: The first one 'G-A' included twelve patients diagnosed with bipolar I disorder in manic episode (manic group); while the second 'G-B' consisted of twelve patients diagnosed with bipolar I disorder in full remission (euthymic group), and the third group 'G-C' consisted of 24 healthy persons as control subjects (control group). The sample size was estimated statistically by professor in public health department according to the power of study, which equal to 80%, confidence interval 95%, the BDNF in control equals 0.2±0.07 while in bipolar I patients equals 0.014 ± 0.04.

Recruitment occurred from 8 April 2018 to 31 December 2018 and subjects who met the following eligibility criteria at enrollment were invited to participate: 1) male and female gender were included. 2) Age ranged from 18 to 60 years-old. 3) Patients met the criteria of DSM-5 for bipolar I disorder, Current or most recent episode mania or depressed in full remission. 4) All participants in the healthy control group will be matched for age, gender and social class. We excluded subjects with: 1) Age below 18 or above 60. 2) History of any physical or general medical condition. 3) History or present symptoms of any other psychiatric disorder. 4) Mental retardation. 5) Refusal of participation. Approval from zagazig Faculty of Medicine Institutional Research Board is obtained and all participants wrote an informed consent. All subjects were interviewed by a psychiatrist subjected to:

1. **Collection of demographic data and clinical information:**all subjects have been subjected to semi-structured questionnaire specifically developed for this study which designed to collect socio-demographic data as age, sex, marital state, education, occupation, Family history and history of presenting illness: Including age of onset, the periods of current episode and total illness, count of preceding episodes, suicidality and violence.
2. **"Structured clinical interview for dsm-iv-tr axis i disorders (SCID-I)":** To exclude current psychiatric disorders of Axis I. It is structured checklist interview that helps by its end to reach DSM-IV diagnosis as it contains a majority of psychiatric disorders with its subtypes [11].
3. **"Diagnostic criteria of DSM-5 for bipolar I disorder":** to establish diagnosis of acute manic episode and bipolar I in remission according to the new diagnostic and statistical manual of mental disorders, 5th Edition (DSM-5) [12]
4. **"Young Mania Rating Scale (YMRS)":** To assess symptoms of mania and its severity. It is a highly reliable scale, consists of eleven items that screen all manic symptoms (some graded from zero to four and others from zero to eight). The rating depends mostly on the observation of the clinician and also on the words of the patients. This scale takes less than half hour to end and to consider patient in euthymia, he should have score lower than twelve[13]
5. **"Hamilton Depression Rating Scale (HDRS)":** To rate Symptoms' severity of depression. It consists of twenty one items. The scoring based on the first seventeen items that sum to give the final score while the remaining items are used to characterize manifestation of depression rather than the severity of it. This scale takes from twenty to thirty minutes to be completed and patient considered euthymic if he scored less than twelve[14]

6. **"Biochemical BDNF Assessment":** to all participants serum BDNF concentrations were measured by enzyme-linked immunoassay (ELISA) quantitatively. In which the protein which is targeted (antigen) linked by primary antibodies capture (specific for human BDNF) which coated to bottom of the well and then the researcher added secondary detection antibodies (A sample 3ml of venous blood was withdrawn under complete aseptic conditions from all subjects; and then left to clot for 30 min , centrifuged and the serum was stored in liquor at 20° C. Repeated freezing and thawing was avoided[15]

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

- Statistical analysis was done using SPSS software version twenty five. Data was presented in tables and figures.
- Quantitative data was showed as mean, median and range.
- Qualitative data was demonstrated as frequencies and relative percentages.
- Pearson's chi square (χ^2) test was used to calculate difference between qualitative variables.
- One-way ANOVA (F-test) test was used to calculate difference between quantitative variables in more than two groups in normally distributed data.
- Kruskal-Wallis (KW) test was used to calculate difference between quantitative variables in more than two groups in not normally distributed data.
- Mann Whitney test (MW) was used to analyze continuous data between two groups.
- Spearman's correlation coefficient (r) was used to test correlation between BDNF and continuous variables.
- Receiver operating characteristic (ROC) curves were plotted for the optimal cut-off values of serum BDNF. The optimal cut-off values were defined as the values that allow discrimination between case and control groups with highest sensitivity and specificity.
- For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level (P-value) and P value of <0.05 indicates significant results.

RESULTS

[Table 1] showed that there was no statistical significant difference between the studied groups as regard demographic characteristics.

In **[table 2]** there were high statistical significant differences between the studied groups as regard serum BDNF levels. Manic patients had the lowest serum BDNF level with median (155.7 pg/ml) while in euthymic group and control it was (164.5 pg/ml and 420.0 pg/ml) respectively.

[Table 3] showed that in manic group there was statistical significant positive correlation between age of onset of first manic episode and serum BDNF level (r = 0.061, P = 0.03), negative correlation between duration of bipolar illness and serum BDNF level (r = - 0. 63, P = 0.2) and also negative correlation between number of previous mood episodes and serum BDNF level (r = - 0. 59, P = 0.04). There was no statistical significant correlation between suicide (MW = 1.5, P = 0.1), violence (MW = 0.6, P = 0.6) or family history (MW = 0.2, P = 0.8) and serum BDNF level.

[Table 4] and **[figure 1]** showed that, the best Cutoff point of serum BDNF level in distinguishing patients with manic episode from Healthy controls was (166.3 pg/ ml) corresponding with (100%) diagnostic performance accuracy , sensitivity and specificity with highly significant area under the curve of (AUC) the ROC curve (p <0.001).

In **[table 5]** and **[figure 2]**, the best Cutoff point of serum BDNF level in distinguishing patients with manic episode from patients with euthymic state of bipolar I disorder was Less than (160.7 pg/ ml) corresponding with (91.7%) diagnostic performance accuracy, (100%) sensitivity and (83.3%) specificity with highly significant AUC of the ROC curve (p <0.001).

Table 1. Demographic characteristics of the studied groups.

Variables	Manic group (n=12)	Euthymic group (n=12)	Control group (n=24)	Test of sig.	P
Age (years):					
Mean ± SD Range	29.8 ± 3.2 24.0 – 35.0	27.8 ± 7.2 19.0 – 46.0	30.0 ± 7.3 21.0 – 46.0	f 1.0	0.3
Gender:					
Males Females	7 (58.3%) 5 (41.7%)	3 (25.0%) 9 (75.0%)	14 (58.3%) 10 (41.7%)	χ^2 5.1	0.1
Marital status:					
Single Married Divorced Widow	5 (41.7%) 5 (41.7%) 2 (16.7%) 0 (0.0%)	5 (41.7%) 4 (33.3%) 3 (25.05) 0 (0.0%)	10 (41.7%) 12 (50.05) 0 (0.0%) 2 (8.3%)	χ^2 9.3	0.4
Education:					
Illiterate Elementary Preparatory Secondary High education	0 (0.0%) 0 (0.0%) 1 (8.3%) 5 (41.7%) 6 (50.0%)	1 (8.3%) 1 (8.3%) 0 (0.0%) 6 (50.0%) 4 (33.3%)	0 (0.0%) 2 (8.3%) 2 (8.3%) 8 (33.3%) 12 (50.0%)	χ^2 7.2	0.8
Occupation:					
Working Not working	5 (41.7%) 7 (58.3%)	7 (58.3%) 5 (41.7%)	6 (25.0%) 18 (75.0%)	χ^2 5.5	0.1

Table 2. Serum level of brain-derived neurotrophic factor (BDNF) in the studied groups.

BDNF	Manic group	Euthymic group	Control group	KW	P
Mean ± SD	155.3 ± 4.1	166.2 ± 5.7	2332.6 ± 3110.9	52.8	**<0.001** **HS**
Median	155.7	164.5	420.0 *		
Range	149.3 – 160.3	159.0 – 176.0	172.3 – 10226.0		

* Significantly higher than other groups

Table 3. Correlation between serum BDNF level and Clinical characteristics of manic group.

Clinical characteristics	r	P
Age of onset	0.61	**0.03 (S)**
Disease duration	-0.63	**0.2 (S)**
Number of previous episodes	-0.59	**0.04 (S)**
	MW	**P**
Suicide, Median (Range): Positive, 150.7 (149.7 - 151.6) Negative, 156.9 (149.3 - 160.3)	1.5	0.1
Violence, Median (Range): Positive, 152.7 (149.3 – 159.4) Negative, 156.0 (149.7 – 160.3)	0.6	0.6
Family history, Median (Range): Positive, 155.4 (151.6 – 158.8) Negative, 157.7 (149.3 – 160.3)	0.2	0.8

Table 4. The Diagnostic performance accuracy of serum BDNF level in distinguishing patients with manic episode from Healthy controls.

Diagnostic performance	Manic group
Cutoff point	Less than 166.3 (pg/ ml)
Sensitivity	100%
Specificity	100%
Positive predictive value	100%
Negative predictive value	100%
Accuracy	100%
Likelihood ratio positive	∞
Likelihood ratio negative	0.00
Area under the curve (AUC)	1.0 (1.0 – 1.0)
P	**0.001 (HS)**

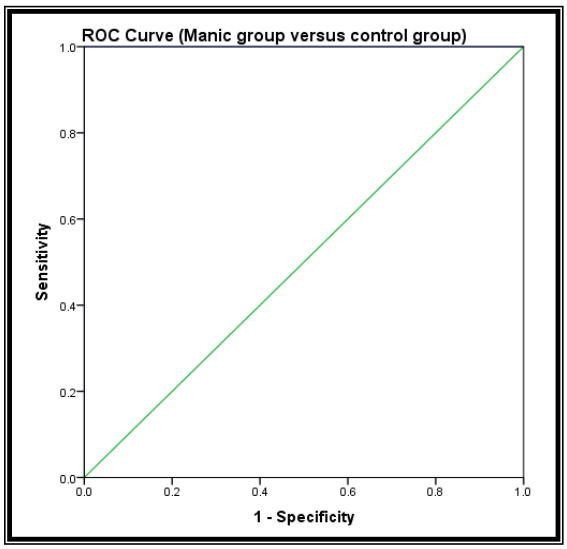

Figure 1. Receiver operating characteristic (ROC) curve using serum BDNF level to discriminate manic group patients from healthy controls.

Table 5. The Diagnostic performance accuracy of serum BDNF level in distinguishing patients with manic episode from patients in euthymic state of bipolar I disorder.

Diagnostic performance	Manic group
Cutoff point	Less than 160.7 (pg/ ml)
Sensitivity	100%
Specificity	83.3%
Positive predictive value	85.7%
Negative predictive value	100%
Accuracy	91.7%
Likelihood ratio positive	6.1
Likelihood ratio negative	0.00
Area under the curve	0.97 (0.9 – 1.0)
P	**<0.001 (HS)**

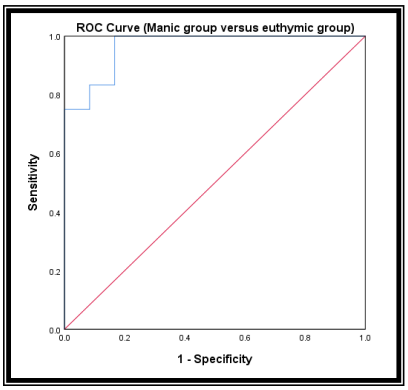

Figure 2. Receiver operating characteristic (ROC) curve using serum BDNF level to discriminate patients with manic episode from patients in euthymic state of bipolar I disorder.

DISCUSSION

Demographic characteristics of the study sample are shown in [**table 1]** and exhibits that the patients with bipolar I disorder in manic episode and euthymic state were not significantly different with the healthy controls in terms of age, gender, marital status, education and occupation.

As shown at [**table 2]** the present study showed that serum BDNF levels were decreased in bipolar I disorder patients during manic episode compared to healthy control subjects which is statistically significantly ($p<0.001$), which are consistent with previous studies like [16-18] who demonstrated that levels of serum BDNF were significantly lowered in bipolar I patients during manic episode in comparison with healthy controls . But, in contrary to these studies, [19] reported that manic patients with bipolar I disorder exhibit elevated levels of serum BDNF comparing with healthy controls.

This discrepancy may be due to the various effect of the different modality of treatment used to control manic symptoms on serum BDNF as the patients in study that showed increase BDNF in manic patients compared with control may be treated with lithium or valproate or both which assumed to increase serum BDNF as supported by [20] who reported that lithium inhibits the glycogen synthase kinase 3 (GSK-3) and valproate inhibits sodium channel function, which leads to increases cellular levels of BDNF.

In this study manic patients group were recruited in acute episode and some of them not took any medications and others were noncompliant on treatment so the decrease in serum BDNF may be owed to biological changes occurs in mania. This view is supported by study of [21] who revealed that in the manic episode of bipolar disorder , there is a marked elevation in protein kinase C (PKC) (that is a part in the pro-inflammatory response) mediated signaling, which is accompanied with BDNF dependent Ca2+ induction and subsequent decrease of serum BDNF [21]..

Also, in **Table (2)** showed statistically significant difference between manic group and euthymic group as regard serum BDNF levels ($p<0.001$).Manic group had lower serum BDNF level than euthymic group as in manic group serum BDNF level range from (149.3 pg/ml) to (160.3 pg/ml) with median (155.7 pg/ml) while in euthymic group it range from (159.0 pg/ml) to (176.0pg/ml) with median (164.5 pg/ml).

These result in agreement with [22] who showed significant decrease levels of BDNF in patients with bipolar disorder (manic episodes) in comparison euthymic patients [22].. Also, [23] reported that BDNF levels are lower during manic episode of bipolar disorder type I, but that after treatment for acute mania they are not significantly different from patient in remission.

This increase of serum BDNF level in bipolar patients in remission may owe to the effect of treatment as explained before.

Table (3) showed that in manic group there was statistical significant positive correlation between age of onset of first manic episode and serum BDNF level ($r = 0.061$, $P = 0.03$), negative correlation between duration of bipolar illness and serum BDNF level ($r = - 0. 63$, $P = 0.2$) and

also negative correlation between number of previous mood episodes and serum BDNF level (r = - 0. 59, P = 0.04). There was no statistical significant correlation between suicide (MW = 1.5, P = 0.1), violence (MW = 0.6, P = 0.6) or family history (MW = 0.2, P = 0.8) and serum BDNF level.

These findings are consistent with study of [24] which showed that levels of BDNF decrease with increase bipolar disorder duration. Also, they showed that during mania, age and duration of illness are important factors that have a role in determination of BDNF levels, and are at least partially responsible for the discrepancies of BDNF levels during mania.

This supported by other study that reported that serum BDNF has hopeful properties that capable of differentiation between patients had bipolar disorder less than three years from those with more than ten years[25].

With increase duration of bipolar illness the patient was prone more to more mood episode with more stress with more decrease in serum BDNF level. The reason might be that the protective and compensatory mechanisms were not able to sustain BDNF levels when neuronal damage were extensive in each acute episode which may reflect the neurodegeneration of late stage bipolar disorders. 8.

In contrast to this study is this obtained by [26]who found significant positive associations between serum BDNF levels and illness duration, and manic episodes only in female bipolar disorder patients. This difference can be explained by the fact that the patients in **Dias et al.** study were not in acute manic episode but in euthymic state .

In assessment of the diagnostic performance accuracy of serum BDNF in the current study, serum BDNF levels demonstrated a high accuracy of being able to discriminate bipolar I disorder in manic episode patients from healthy controls with cutoff point (166.3 pg/ ml) corresponding with highly significant area under the curve (AUC) of the ROC curve (p <0.001) as sown in **Table (4)** and **Figure (1).**

Moreover **Table (5)** and **Figure (2)** showed that, the best Cutoff point of serum BDNF level in distinguishing patients with manic episode from patients with euthymic state of bipolar I disorder was Less than (160.7 pg/ ml) corresponding with (91.7%) diagnostic performance accuracy, (100%) sensitivity and (83.3%) specificity with highly significant AUC of the ROC curve (p <0.001).

These findings are comparable to that of [24]who found highly favourable characteristics of serum BDNF with sensitivity 90% and specificity of 85% elucidate that levels of BDNF can accurately differentiate between manic patients from healthy controls.

CONCLUSIONS

By the end of this study, it is found that serum BDNF level was statistically lowered in manic episode compared with control group, also serum BDNF level was statistically higher in patients in euthymic state compared with manic episode of bipolar I disorder.The serum BDNF levels showed high diagnostic performance accuracy to distinguish bipolar I disorder patients in manic episode from healthy controls, also from euthymic state.Studies with long duration, larger number of patients in different episodes of mood and early stages of bipolar disorder are necessary to clarify exact BDNF role in bipolar disorders.

One of the essential limitations of this study is the small number of studied subjects.One more limitation was that pharmacological treatments cannot included in the statistical analysis as most patients took multiple combinations of different psychotropic medication and also most of patients weren't adherent to treatment. Moreover., due to the
high likelihood of rapid disease decompensating that is successfully controlled by chronic use of medication, stopping drugs to rule out the effect of psychotropic drugs on serum BDNF concentration is neither suggested nor ethically acceptable.

Conflict of Interest: Nothing to declare.
Financial disclosure: Nothing to declare.

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Cite This Article

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