The Egyptian Journal of Hospital Medicine (January 2024) Vol. 94, Page 280-284

A Study of Plasma Neurotrophin 4/5 Level as a Biomarker in Bipolar Disorder Patients during Manic Episode

Hussien E. El Sheikh, Mohamed M. El-Hamady, Hisham M. Al Sayed, Nehal M. Barhoma * and Marwa M. Dahroug

Department of Psychiatry, Faculty of Medicine, Benha University, Benha, Egypt.

***Corresponding Author:** Nehal Mohamed Abdel Hamid Barhouma**, Email:** nehalbarhoma@gmail.com **Phone:** 01026505539

ABSTRACT

Background: Bipolar disorder (BD) is characterized by mood swings involving both manic and depressive symptoms. The absence of confirmed biomarkers for BD results in its diagnosis and management being primarily empirical. Neurotrophin 4/5 (NT-4/5) has garnered attention in mood disorder research due to its involvement in neuronal processes and association with antidepressant effects.

Objective: To compare NT 4/5 levels between bipolar disorder cases during manic episodes and a control group, while also exploring correlations between NT4/5 levels and various clinical parameters.

Subjects and Methods: The study examined thirty (30) bipolar patients and thirty (30) healthy controls matched for age and sex. Structured Clinical Interview for DSM (SCIDI) confirmed the diagnosis of bipolar disorder, supplemented by assessments using the Young Mania Scale. Plasma NT4/5 levels were measured in both groups.

Results: Bipolar patients experiencing manic episodes, whether mild, moderate, or severe, exhibited significantly lower plasma NT-4/5 levels compared to healthy controls ($p<0.001$). Moreover, moderate and severe cases showed notably lower NT 4/5 levels compared to remitted cases ($p=0.014$, $p=0.001$ respectively). No significant differences were observed between remitted bipolar cases and controls.

Conclusions: Lower NT 4/5 levels were suggested as an independent risk predictor for bipolar disorder development, while higher NT 4/5 levels were suggested as an independent predictor for bipolar disorder remission.

Keywords: Plasma Neurotrophin 4/5, Biomarker, Bipolar Manic Episode.

INTRODUCTION

Bipolar disorder is estimated to affect approximately 3% of the general population [1]. The disorder is characterized by successive periods of elation (mania) and depression interspersed with periods of euthymia, an asymptomatic phase in which patients are in clinical remission [1].

Shorter periods of euthymia between relapses are associated with poorer functioning, increased odds of suicidality, disability, unemployment and hospitalization [2]. A major research goal is thus to identify predictors of upcoming relapse in order to facilitate timely treatment [3]. Yet, predicting relapse using existing clinical diagnostic tools or demographic information has proven largely ineffective in bipolar disorder [4].

The etiopathogenesis of BD is multi-faceted with genetic, environmental and psychosocial factors playing a role; also the diagnosis and management of BD are purely on empirical grounds as we lack confirmed biomarkers for this condition [5]. NT-3 and NT-4/5 have also become a focus of investigation in mood disorders because of their role in neuronal processes and association with antidepressant actions [6].

Thus, the aim of the current study was to evaluate the levels of neurotrophin 4/5 in bipolar disorder during manic episodes and to assess the relation between its level and severity of bipolar disorder measured by Young Mania Rating Scale. Moreover, to try to find if neurotrophin 4/5 has a predictive or prognostic value.

PATIENTS AND METHODS

This is a comparative cross-sectional study conducted on thirty (30) bipolar patients during manic episodes and thirty (30) healthy controls, matched for age, sex, residency, marital status, and occupational status. Patients were recruited from Benha Mental Hospital. Recruitment and data collection took place from November 2016 to November 2018 until the required sample size was achieved. SCIDI was utilized for confirming the diagnosis of bipolar disorder, excluding comorbidities, and ruling out any psychiatric disorders in both cases and control groups. Further assessment involved the use of the Young Mania Scale.

Additionally, blood samples were collected from all participants to assess the plasma level of NT 4/5. Participants were informed about the potential academic use of the obtained data. The study included both genders aged between 18 and 50 years. Patients on psychotropic medications were included if the dosage had not been adjusted in the past week. Exclusion criteria involved individuals under 18 or over 50 years old, currently pregnant or lactating females, patients with severe cognitive impairments hindering brief psychiatric interviews, those with comorbid psychiatric disorders or experiencing a current depressive episode, individuals with comorbid medical disorders (such as seizures, major head trauma), major illnesses (like cancer, IHD, renal or liver failure), endocrine diseases (hypopituitarism, hyperprolactinemia, thyroid disorders), and neurological conditions that could impact mood.

Received: 02/07/2023
Accepted: 03/09/2023

Methods:

All participants (cases and control) were subjected psychometric test measuring psychiatric disorders (Structured Clinical Interview for DSM Disorders) (SCIDI) for diagnosing the major Axis I DSM-IV disorders) [7]. The Arabic version of the SCID-I was used in this study [8]. Assessment included Young Mania Rating Scale (YMRS) [9] for bipolar patients. The Arabic version of the YMRS was used in this study [10]. Biological investigations: plasma NT 4/5 level measurement.

Ethical consideration: All procedures followed were approved from the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients for being included in the study.

Statistical Analysis:

The collected data were reviewed, coded, tabulated, and processed using Statistical Package for the Social Sciences (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and MedCalc Statistical Software version 18.11.6 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019). Quantitative data were presented as mean and standard deviation (SD) or as median and range, and were compared by Student's t-test, Mann-Whitney U test, and Kruskal-Wallis test. Qualitative data were presented as frequency and percentage and were compared by Chi-Square test and Fisher's exact test. All reported p-values were two-tailed, and statistical significance was set at $p < 0.05$.

RESULTS

Sociodemographic data among studied bipolar cases and control group are shown in **Table 1**.

Table (1): Comparison of sociodemographic data among studied bipolar cases and control group

			BP n=30		Control n=30		P
Age	**Age (years)**	**Mean ±SD**	38.9	11.1	36.2	9.8	0.499
	<35	**N, %**	12	40.0%	14	48.3%	0.522
	>35	**N, %**	18	60.0%	15	51.7%	
Gender	**Males**	**N, %**	18	60.0%	18	60.0%	1
	Females	**N, %**	12	40.0%	12	40.0%	
Marital status	**Single**	**N, %**	12	40.0%	10	33.3%	**0.025**
	Married	**N, %**	9	30.0%	16	53.3%	
	Separated	**N, %**	8	26.7%	1	3.3%	
	Widow	**N, %**	1	3.3%	3	10.0%	
Education	**Illiterate**	**N, %**	7	23.3%	2	6.7%	0.244
	Secondary	**N, %**	9	30.0%	7	23.3%	
	Technical	**N, %**	5	16.7%	6	20.0%	
	Bachelor	**N, %**	9	30.0%	14	46.7%	
	post grad	**N, %**	0	0.0%	1	3.3%	
Occupation	**Unemployed**	**N, %**	14	46.7%	7	23.3%	0.109
	housewife	**N, %**	6	20.0%	7	23.3%	
	Student	**N, %**	0	0.0%	2	6.7%	
	Worker	**N, %**	6	20.0%	4	13.3%	
	Clerk	**N, %**	4	13.3%	9	30.0%	
	high performance	**N, %**	0	0.0%	1	3.3%	
Residence	**Rural**	**N, %**	19	63.3%	15	50.0%	0.297
	Urban	**N, %**	11	36.7%	15	50.0%	
Smoking	**No**	**N, %**	4	13.3%	24	82.8%	**<0.001**
	Yes	**N, %**	26	86.7%	5	17.2%	

Mann-Whitney test was used.

We can notice that separated subjects were significantly associated with moderate and severe BD grades. Otherwise, no significant association was found between studied groups regarding marital status **(Table 2).**

Table (2): Comparison of marital status among studied bipolar cases and controls:

	Bipolar (N=30)								Control N=30		P.mi.c	P.mo.c	p.s.c	p.r.c	p.mimo	p.mis	p.mir	p.mos	p.mor	p.sr
	Mild N=2		**Moderate N=10**		**Severe N=14**		**Remission N=4**													
Single	0	0%	5	50.0 %	4	28.6 %	3	75.0 %	10	33.3 %	0.325	0.457	0.752	0.274	0.470	0.383	0.400	0.403	0.580	0.245
Married	2	100 %	2	20.0 %	4	28.6 %	1	25.0 %	16	53.3 %	0.492	0.082	0.124	0.601	0.091	0.125	0.400	0.633	0.837	0.888
Separated	0	0%	3	30.0 %	5	35.7 %	0	0.0 %	1	3.3 %	0.793	**0.042**	**0.009**	0.711	0.371	0.308	-	0.770	0.505	0.287
Widowed	0	0%	0	0.0 %	1	7.1 %	0	0.0 %	3	10.0 %	0.639	0.560	0.759	0.508	-	0.696	-	0.388	-	0.582

P.mi.c: Percentage of Mild cases among Bipolar, P.mo.c: Percentage of Moderate cases among Bipolar, P.s.c: Percentage of Severe cases among Bipolar, P.r.c: Percentage of cases in Remission among Bipolar, P.mimo: Percentage of Mild cases among Controls, P.mis: Percentage of Moderate cases among Controls, P.mir: Percentage of Severe cases among Controls, P.mos: Percentage of cases in Remission among Controls, P.mor: Percentage of cases that are Single among Controls, P.sr: Percentage of cases that are Married among Controls.

Urban residency was significantly associated with severe BD when compared to moderate and remission cases. While urban residency was significantly associated with moderate cases when compared to control group. Otherwise, no significant association was found between residence and studied groups. Mild, moderate and severe BD cases showed significantly higher frequency of smoking when compared to control group **(Table 3)**.

Table (3): Comparison of residence and smoking among studied bipolar cases and controls:

	Bipolar (N=30)								Control N=30		P.mi.c	P.mo.c	p.s.c	p.rc	p.mimo	p.mis	p.mir	p.mos	p.mor	p.sr
	Mild N=2		**Moderate N=10**		**Severe N=14**		**Remission N=4**													
Rural	2	100.0%	9	90.0%	4	28.6%	4	100.0%	15	50.0%	0.486	**0.032**	0.181	0.113	0.640	0.125	-	**0.005**	0.512	**0.023**
Urban	0	0.0%	1	10.0%	10	71.4%	0	0.0%	15	50.0%										
Smoking	2	100.0%	8	80.0%	13	92.9%	3	75.0%	5	17.2%	**0.045**	**0.001**	**<0.001**	**0.036**	0.488	0.696	0.439	0.550	0.837	0.405

P.mi.c: Percentage of Mild cases among Bipolar, P.mo.c: Percentage of Moderate cases among Bipolar, P.s.c: Percentage of Severe cases among Bipolar, P.r.c: Percentage of cases in Remission among Bipolar, P.mimo: Percentage of Mild cases among Controls, P.mis: Percentage of Moderate cases among Controls, P.mir: Percentage of Severe cases among Controls, P.mos: Percentage of cases in Remission among Controls, P.mor: Percentage of cases that are Single among Controls, P.sr: Percentage of cases that are Married among Controls.

Severe cases showed significantly longer duration of illness as well as higher number of attacks when compared to those achieved remission. In addition, moderate and severe cases showed very significantly higher frequency of hospitalization in comparison to remitted cases. Severe cases showed significantly higher frequency of hospitalization in comparison to moderate and mild cases. Otherwise, no significant association was found regarding FH, and previous ECT (**Table 4)**.

Table (4): Comparison of clinical data of bipolar studied groups:

		Bipolar (N=30)								p.mimo	p.mis	p.mir	p.mos	p.mor	p.sr
		Mild N=2		**Moderate N=10**		**Severe N=14**		**Remission N=4**							
Negative FH	**N, %**	2	100.0%	5	50.0%	8	57.1%	2	50.0%	0.470	0.500	0.467	0.729	1	0.800
Positive FH	**N, %**	0	0.0%	5	50.0%	6	42.9%	2	50.0%						
Duration of illness	**Median, range**	9.5	(1-18)	9.5	(2-30)	20.0	(2-30)	3.5	(2-7)	0.589	0.176	0.634	0.240	0.175	**0.019**
Number of attacks	**Median, range**	4.0	(1-7)	5.5	(1-11)	8.0	(2-11)	2.0	(2-6)	0.450	0.106	0.695	0.555	0.218	**0.015**
No hospitalization	**N, %**	2	100.0%	4	40.0%	0	0.0%	4	100.0%	0.455	**0.008**	1	**0.020**	0.040	**<0.001**
Hospitalization	**N, %**	0	0.0%	6	60.0%	14	100.0%	0	0.0%						
Previous ECT	**N, %**	0	0.0%	4	40.0%	10	71.4%	1	25.0%	0.515	0.125	0.439	0.211	0.597	0.245

FH = Family History, ECT = Electroconvulsive Therapy.

Total number of bipolar patients including mild, moderate, severe cases showed significantly lower level of NT 4/5 in comparison to control group. In the same line, moderate and severe bipolar cases showed significantly lower level of NT 4/5 when compared to remittent cases. On the other hand, no significant differences were found between remittent cases in comparison to control and mild cases **(Table 5)**.

Table (5): Comparison of NT 4/5 level among bipolar studied cases and controls:

NT 4/5 (pg/mL)	Bipolar N=30					Control N=30	P.t.c	P.mi.c	P.mo.c	p.s.c	p.rc	p.mimo	p.mis	p.mir	p.mos	p.mor	p.sr
	Total N=30	**Mild N=2**	**Moderate N=10**	**Severe N=14**	**Remission N=4**												
Median	2.8	4.61	2.84	1.73	6.06	7.92	**0.030**	**<0.001**	**<0.001**	**<0.001**	0.166	0.268	0.078	0.471	0.240	**0.014**	**0.001**
Minimum	0.96	3.87	1.44	0.96	4.22	1.46											
Maximum	7.10	5.34	3.87	2.83	7.10	12.90											

P.mi.c: Percentage of Mild cases among Bipolar, P.mo.c: Percentage of Moderate cases among Bipolar, P.s.c: Percentage of Severe cases among Bipolar, P.r.c: Percentage of cases in Remission among Bipolar, P.mimo: Percentage of Mild cases among Controls, P.mis: Percentage of Moderate cases among Controls, P.mir: Percentage of Severe cases among Controls, P.mos: Percentage of cases in Remission among Controls, P.mor: Percentage of cases that are Single among Controls, P.sr: Percentage of cases that are Married among Controls.

DISCUSSION

Bipolar affective disorder is a chronic and complex disorder of mood that is characterized by a combination of manic, hypomanic and depressive episodes, with substantial subsyndromal social cognitive impairment that commonly presents between major mood episodes [11]. Bipolar disorder (BD) is known for impairments in neurotrophic and neuroprotective processes, which translate into emotional and cognitive deficits affecting various brain regions [12]. BDNF is the most abundant neurotrophin in the CNS, particularly in the amygdala, hippocampus, and prefrontal cortex, brain areas directly involved in emotional regulation and several aspects of cognition (including attention, memory, and executive functioning) [13].

However, little attention has been paid to the study of NT-4/5, neurotrophin that modulates basal synaptic transmission and long-term potentiation in the hippocampus. NT4/5 promotes survival and differentiation of hippocampal noradrenergic and dopaminergic neurons. Striatal dopaminergic neurons are believed to be one of the key neurons in the pathophysiology of bipolar disorder, thus the association between mood disorders and NT-4 level is probable, but the results are controversial [14].

So, this study aimed to investigate whether there is a reliable relation, which could serve as biomarker between levels of NT 4/5 in bipolar patients during manic episodes and healthy controls. In addition to find out the correlation between NT 4/5 levels and severity of manic episode, different sociodemographic factors and clinical data of bipolar patients.

As regard smoking, bipolar cases had significantly higher prevalence of smokers when compared to control group. This was similar to a study, which found that smoking initiation and lifetime smoking are likely to be a causal risk factor for developing bipolar disorder [15]. Another study also found important clinical correlates of tobacco smoking in BD subjects [16]. This may be explained because of impulsivity, which is a core feature of bipolarity even in females or as a trial to reduce side effects of treatment.

Also, it was noticed that divorced subjects were significantly associated with bipolar patients in moderate and severe manic episodes. This could be explained either by stressful nature of the illness that have many negative consequences on the marital life or the stressful nature of the divorce that could affect patients' mental health.

On the other hand, urban residency was significantly associated with severe BP when compared to moderate and remissive bipolar patients and urban residency was significantly associated with moderate cases when compared to control group. Evidence suggests individuals residing in urban areas experience increased risk of mood disorder. Mechanistic pathways include increased exposure to noise, light and air pollution, poor quality housing, reduced diet quality, physical inactivity, economic strain and diminished social networks [17].

Also, a cohort study found that there was a strong association between urban residence and the incidence of psychotic bipolar, but no association for bipolar without psychosis [18].

In the studied group, family history of mood disorder was absent in mild bipolar cases but present in moderate and severe cases. This association was linked to earlier onset, more phases, rapid cycling, suicide attempts, increased manic symptoms (such as racing thoughts and distractibility), lower quality of life, higher neuroticism, and greater personality disorder scores in patients with a family history [19] indicating a connection between family history and symptom severity.

Additionally, the study revealed that longer illness duration was associated with more severe manic symptoms and increased frequency of mood episodes. This is likely due to the accumulation of inter-episode residual symptoms and various adverse consequences, including frequent hospitalizations, higher disability rates, elevated suicide risk, impaired cognitive functioning, medical conditions, interpersonal difficulties, and reduced overall quality of life [2].

Severe cases exhibited significantly higher hospitalization rates compared to moderate and mild cases. This can be attributed to the heightened risk of suicide, complex medication regimens, treatment non-compliance, and the need for comprehensive assessment and treatment in severe cases. In contrast, mild cases typically exhibit fewer symptoms, which are often culturally accepted and may seek alternative treatments, such as traditional healing, rather than psychiatric intervention.

Total number of bipolar patients either in mild, moderate or severe manic episodes had significantly lower NT 4/5 levels compared to the control group. In the same line, moderate and severe bipolar cases showed significantly lower level of NT 4/5 when compared to remittent cases (p =0.014, p =0.001 respectively).

No significant differences were observed between patients in remission and the control group, as well as between mild bipolar patients and the control group.

These findings could be explained by the fact that both NT-4/5 and BDNF act on the same receptors (TrkB and p75), with NT-4/5 appearing to be more potent than BDNF in influencing neurite outgrowth [20].

Previous studies have reported decreased levels of BDNF in acute mood episodes and decreased levels of NGF in mania, and this study observed decreased NT-4/5 levels in mania as well, suggesting a general decrease in neurotrophins during acute mood episodes in bipolar disorder. Neurotrophic factors play a crucial role in preserving neuronal plasticity and protecting against various insults.

These results align with a study [21], which found that lower NT-4/5 plasma levels in patients with bipolar disorder, both in mania and remission, compared to a control group [22]. Another study did not find significant differences in NT-4 mRNA expression levels among patients with major depressive and bipolar disorders in both current and remissive states [22]. While in contrast to another study, which found that levels of NT 4/5 levels were significantly higher in bipolar disorder patients compared to controls [23].

CONCLUSION

This study revealed that NT4/5 level showed significant lower levels when comparing bipolar manic patients either in mild, moderate or severe episodes with control group ($p<0.001$, $p<0.001$, $p<0.001$) respectively as well as moderate and severe cases showed significant lower level of NT 4/5 when compared to remittent cases p =0.014, p =0.001 respectively, while no significant difference was found between remittent cases when compared to mild cases and control group.

Financial support and sponsorship: Nil
Conflict of Interest: Nil.

REFERENCES

1. **Grande I, Berk M, Birmaher B *et al.* (2016)**: Bipolar disorder. Lancet, 387:1561-72.
2. **Peters A, West A, Eisner L *et al.* (2016)**: The Burden of repeated mood episodes in bipolar I disorder: Resultsfrom the National Epidemiological Survey on Alcohol and Related Conditions. J Nerv Ment Dis., 204:87-94.
3. **Harrison P, Cipriani A, Harmer C *et al.* (2016)**: Innovative approaches to bipolar disorder and its treatment. Ann N Y Acad Sci., 1366:76-89.
4. **Vieta E, Berk M, Schulze T, *et al.* (2018)**: Bipolar disorders. Nat Rev Dis Primers, 4:18008.
5. **Muneer A (2020)**: The discovery of clinically applicable biomarkers for bipolar disorder: A review of candidate and proteomic approaches. Chonnam Med J., 56:166-79.
6. **Duman R (2004)**: Depression: a case of neuronal life and death? Biol Psychiatry, 56:140-5.
7. **First M (2005)**: Structured clinical interview for DSM-IV-TR axis I disorders. APA Psyc., 13:3-11.
8. **Massey S, Backes K, Schuette S (2016)**: Plasma oxytocin concentration and depressive symptoms: a review of current evidence and directions for future research. Depression and anxiety, 33:316-22.
9. **Young R, Biggs J, Ziegler V *et al.* (1978)**: A rating scale for mania: reliability, validity and sensitivity. The British Journal of Psychiatry,133:429-35.
10. **El Sheikh H, El Sayed H, El Bakry S *et al.* (2019)**: Sleep patterns among bipolar disorder patients. Egyptian Journal of Psychiatry, 40:5.
11. **Haggarty S, Karmacharya R, Perlis R (2021)**: Advances toward precision medicine for bipolar disorder: mechanisms & molecules. Mol Psychiatry, 26:168-85.
12. **Gandhi A, Kaleem I, Alexander J *et al.* (2020)**: Neuroplasticity improves bipolar disorder: A review. Cureus, 12:e11241.
13. **Teixeira A, Barbosa I, Diniz B *et al.* (2010)**: Circulating levels of brain-derived neurotrophic factor: correlation with mood, cognition and motor function. Biomark Med., 4:871-87.
14. **László A, Lénárt L, Illésy L *et al.* (2019)**: The role of neurotrophins in psychopathology and cardiovascular diseases: psychosomatic connections. J Neural Transm (Vienna), 126:265-78.
15. **Vermeulen JM, Wootton RE, Treur J, *et al.* (2021)**: Smoking and the risk for bipolar disorder: evidence from a bidirectional Mendelian randomisation study. Br J Psychiatry, 218:88-94.
16. **Medeiros G, Lafer B, Kapczinski F *et al.* (2018)**: Bipolar disorder and tobacco smoking: Categorical and dimensional clinical correlates in subjects from the Brazilian bipolar research network. Compr Psychiatry, 82:14-21.
17. **Hoare E, Jacka F, Berk M (2019)**: The impact of urbanization on mood disorders: an update of recent evidence. Curr Opin Psychiatry, 32:198-203.
18. **Rowland T, Marwaha S (2018)**: Epidemiology and risk factors for bipolar disorder. Ther Adv Psychopharmacol., 8:251-69.
19. **Antypa N, Serretti A (2014)**: Family history of a mood disorder indicates a more severe bipolar disorder. J Affect Disord., 156:178-86.
20. **Runge E, Hoshino N, Biehl M *et al.* (2012)**: Neurotrophin-4 is more potent than brain-derived neurotrophic factor in promoting, attracting and suppressing geniculate ganglion neurite outgrowth. Dev Neurosci., 34:389-401.
21. **Barbosa I, Morato I, Huguet R *et al.* (2014)**: Decreased plasma neurotrophin-4/5 levels in bipolar disorder patients in mania. Brazilian Journal of Psychiatry, 36:340-3.
22. **Otsuki K, Uchida S, Watanuki T *et al.* (2008)**: Altered expression of neurotrophic factors in patients with major depression. J Psychiatr Res., 42:1145-53.
23. **Walz J, Magalhães P, Giglio L *et al.* (2009)**: Increased serum neurotrophin-4/5 levels in bipolar disorder. Journal of Psychiatric Research, 43:721-3.