Comparison of serum BDNF, IL-1β, IL-6, TNF-α, CRP and leucocyte levels in unipolar mania and bipolar disorder

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Abstract

Objective: Unipolar mania is not included in the diagnostic and statistical manual of mental disorders-5 (DSM-5) as a separate diagnosis, although it is defined by widely accepted diagnostic criteria. The aim of this study was to investigate the differences between unipolar mania and bipolar disorder in terms of clinical and inflammatory parameters. *Methods:* The data of 495 hospitalised patients with bipolar disorder diagnoses were analysed retrospectively. Forty met the diagnostic criteria for unipolar mania. Two patients refused to participate in the study. Thirty-eight unipolar mania patients and 42 randomly selected patients with bipolar disorder diagnosis were included in the study. The two groups were compared in terms of socio-demographic, clinical characteristics, serum brain-derived neurotrophic factor, C-reactive protein (CRP), leucocyte and cytokine levels. *Results:* A total of 40 (8.08%) of 495 patients diagnosed with bipolar disorder met the unipolar mania diagnostic criteria. The number of manic episodes and the number of hospitalisations were statistically higher in the unipolar mania group than in the bipolar disorder group. Among all the manic symptoms, the incidence of symptoms such as euphoria, increased sexual interest, grandiosity and delusions were found to be statistically higher in the unipolar mania group. Interleukin (IL)-6 and CRP levels were significantly higher in the unipolar mania group than in the bipolar disorder group. *Conclusion:* Unipolar mania differs from bipolar disorder in terms of clinical features and serum IL-6 and CRP levels.

Significant outcomes

1. There are some differences in the sociodemographic features of unipolar mania and bipolar disorder.
2. IL-6 and CRP levels were higher in the unipolar mania group.
3. There was no difference between unipolar mania and bipolar disorder in terms of serum BDNF, IL-1β, TNF-α or leucocyte levels.

Limitations

1. The diagnosis of unipolar mania may be inaccurate due to the inability to remember past depressive episodes or predict possible future depressive episodes.
2. Age, gender, smoking, alcohol use and various antipsychotic treatments may have affected cytokine, C-reactive protein, leucocyte and BDNF levels.
3. The presence of some chronic medical diseases and the drugs may have affected the levels of cytokines and BDNF in some patients.

Introduction

Unipolar mania is a bipolar disorder with recurrent manic and hypomanic episodes and without depressive episodes. Although earlier studies of unipolar mania indicated the minimum required number of manic episodes for diagnosis as one or two, more recent studies have shown that this number has increased to three or four episodes (Yazıcı, 2014). Yazıcı *et al.* (2002) reported that the absence of depressive or mixed episodes, at least 3–4 manic episodes, and at least 4 years of disease follow-up were accepted as decisive criteria for the diagnosis of unipolar mania.

Since most studies on unipolar mania have been conducted in non-Western countries, it appears as if it is more common in these countries. However, it was emphasised that this situation cannot be accepted with certainty due to the lack of intercultural studies (Mehta, 2014).

In the first large-scale study conducted on the epidemiology and course of unipolar mania, the frequency of unipolar mania in patients with classical bipolar disorder ranged between 5 and 7.2%, and approximately 18% of unipolar mania patients had depressive episodes during the 3-year follow-up period (Baek *et al.*, 2014).

Studies have shown that unipolar mania differs from bipolar disorder in terms of sociodemographic characteristics, clinical characteristics and treatment response (Angst & Grobler, 2015). In a study including nine epidemiological studies, although men were more predominant in the unipolar mania group compared to the bipolar disorder group, no difference was found between the two groups in terms of age at the onset of the first episode. In the unipolar mania group, the number of patients who attempted suicide or who had comorbid generalised anxiety disorder, panic disorder, eating disorder and substance use disorders was found to be lower (Angst *et al.*, 2019). Mehta (2014), in a meta-analysis study, observed more psychotic symptoms, grandiosity, history of cannabis and amphetamine use and hyperthymic temperament in unipolar mania patients than in bipolar disorder patients; however suicide history and loss of social, familial and occupational functionality were experienced less in unipolar mania patients.

The differences between bipolar disorder and unipolar mania patients have been examined in the literature; the results are conflicting, and there are not enough studies on this subject. Moreover, until now, there have been no studies on neuroplasticity and inflammation in patients with unipolar mania. However, it has been suggested that impaired neuroplasticity and inflammation may play an important role in the etiopathogenesis of bipolar disorder (Post, 2007; Kalelioğlu *et al.*, 2017). Brain-derived neurotrophic factor (BDNF) is one of the most common and studied neurotrophin in the brain, and it has been found to be significantly decreased in patients with bipolar disorder (Scola & Andreazza, 2015). Cytokines that play an active role in the inflammatory response and can be measured in systemic circulation are polypeptide molecules that play a key role in inflammation (Kalelioğlu *et al.*, 2017). Previous findings suggest that cytokines and BDNF may reflect the key pathophysiological mechanisms, disease activity and progression of bipolar disorder (Jacoby *et al.*, 2016).

Aims of the study

The main purpose of this study is to compare sociodemographic and clinical features, serum BDNF, C-reactive protein (CRP), leucocyte and cytokine levels in patients with unipolar mania and bipolar disorder.

Material and methods

The data of 495 patients who were hospitalised between 01 January 2005 and 02 January 2018 in the Department of Psychiatry of Trakya University Hospital with the diagnosis of bipolar disorder were retrospectively analysed. The hospital data showed that 40 patients met the diagnostic criteria for unipolar mania. These 40 patients were asked to participate in the study, and 38 agreed to participate. The diagnosis was reconsidered by psychiatric examination. Patients between the ages of 18 and 65 years who had no depressive episodes in the past, were followed up for at least 4 years, had at least four manic episodes and were still in the euthymic period were defined as the unipolar mania group. The bipolar disorder patient group consisted of 42 patients who agreed to be included in the study and met the inclusion criteria; these patients were randomly selected from among the patients who visited the outpatient clinic during the study period. The bipolar disorder patient group consisted of patients aged 18–65 years who were diagnosed with bipolar disorder type I according to diagnostic and statistical manual of mental disorders-5 (DSM-5) diagnostic criteria and who had manic and depressive episodes in the past are currently in the euthymic period. Those who were diagnosed with bipolar disorder type 2, had mixed episodes, had pregnancy, had known medical diseases (autoimmune diseases, acute infection, malignancy, dementia, neurodegenerative, and cerebrovascular diseases), had used anti-inflammatory drugs in the last 2 weeks, had used antibiotics in the last 4 weeks and had received immunosuppressive therapy were not included in the study. Lifetime history of antidepressant use was accepted as the exclusion criterion for the unipolar mania group.

The hospitalisation files and data of the patients in both groups were reviewed retrospectively, and all clinical signs of all manic episodes were checked. All symptoms of all past manic episodes were recorded to compare the symptoms during the manic episodes.

Sociodemographic data form, Young Mania Rating Scale (YMRS), Hamilton Rating Scale for Depression (HAM-D), Temperament Evaluation of Memphis, Pisa, Paris and San Diego-Autoquestionnaire (TEMPS-A), The Standardized Mini Mental State Examination (SMMSE) was administered to the participants.

Serum levels of BDNF, interleukin-1beta (IL-1β), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), CRP and leucocytes were measured in blood samples of patients in the unipolar mania and bipolar disorder groups. Blood samples were taken in fasting condition between 08:00 and 10:30 am by nurses working in Trakya University Faculty of Medicine Department of Psychiatry. The blood samples were centrifuged at 3500 rpm for 10 min in the Biophysics Laboratory, and the resulting sera were divided into Eppendorf tubes and stored in a $-80°C$ deep freezer until ELISA was performed. After the patient enrolment process was completed, serum samples were analysed in the laboratory of the Physiology Department of Trakya University Faculty of Medicine using appropriate ELISA kits for, BDNF (Boster, Catolog: EK0307), TNF-α (Boster, Catalog: EK0525), IL-1β (Invitrogen, Catolog: KHC0011) and IL-6 (BioSource Europe SA, Catolog: KAC1261) according to the manufacturer's instructions. CRP and leucocyte values were also measured in the laboratory.

Verbal and written consent was obtained from the patients who agreed to participate in the study. The study was approved by Trakya University Faculty of Medicine Ethics Committee.

Statistical analysis

Statistical analyses were performed in Trakya University Faculty of Medicine, Department of Biostatistics and Medical Informatics, using the IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. (License No: 10240642) package program. The compatibility of the quantitative data to normal distribution was examined with a single sample Shapiro–Wilk test. Student *t* test was used for comparing the quantitative values showing normal distribution between unipolar and bipolar groups, and Mann–Whitney *U* test was used to compare variables that did not show normal distribution. One-way ANOVA test was used for the comparison of quantitative values consisting of three or more categories and showing normal distribution, and the Kruskal–Wallis

test was used to compare those that did not show normal distribution. Spearman correlation analysis was used to examine the relationships between quantitative variables. P < 0.05 value was accepted as statistical significance limit value.

Results

In this study, we found that 40 (8.08%) of 495 patients diagnosed with bipolar disorder met the diagnostic criteria for unipolar mania. In the patient group with a diagnosis of unipolar mania, 16 (42.1%) were female and 22 (57.9%) were male, while 28 (66.7%) of the bipolar disorder patients were female and 14 (33.3%) were male. The mean age was 41.94 ± 8.94 years in the unipolar mania group and 42.64 ± 0.56 years in the bipolar disorder group, with no statistically significant difference in the mean ages of the two groups (p = 0.753). The comparison of the sociodemographic and clinical characteristics of the two groups is shown in Table 1.

A comparison of the two groups in terms of comorbid psychiatric diseases revealed no significant difference (p = 0.56). Eight patients (21.1%) in the unipolar mania group and eight patients (19.0%) in the bipolar disorder group had a diagnosis of hypothyroidism. There was no statistically significant difference between the groups in terms of hypothyroidism (p = 1.000).

The most commonly used mood stabilisers were lithium (50%) in the bipolar disorder group and valproic acid (50%) in the unipolar mania group, and the results were statistically significant (p = 0.032). The mood stabilisers and antipsychotics used by the patients are shown in Table 2.

We found that among all manic symptoms during manic episodes, euphoria (p = 0.004), increased sexual interest (p = 0.004), delusions (p = 0.006) and grandiosity (p = 0.017) were more common in the patients in the unipolar mania group compared to the bipolar disorder group, and the differences were statistically significant. Manic symptoms, such as elevated mood, irritability, decreased sleep, pressured speech, increased speech, flight of ideas, agitation, hostility and increased goal-directed activity, were similar in both groups during manic episodes. Depressive mood and anxiety symptoms were significantly higher in manic episodes in the bipolar disorder group (p = 0.000). The distribution of the two groups according to their clinical characteristics is shown in Table 3.

There was no statistical difference in the mean HAM-D, YMRS and SMMSE scores between the two groups. A comparison of the temperament types evaluated with the TEMPS-A scale showed that depressive (p = 0.004), cyclothymic (p = 0.005) and hyperthymic (p = 0.001) temperaments were significantly more predominant in the unipolar mania group than in the bipolar disorder group. There was no significant difference between the two groups in terms of irritable and anxious temperaments.

IL-6 levels (median [min–max], in pg/ml) were significantly higher in the unipolar mania group (17.23 [0.29–235.78]) than in the bipolar disorder group (10.74 [0.71–67.63], p = 0.046). CRP levels (median [min–max], in mg/dl) were significantly higher in the unipolar mania group (0.47 [0.30–2.58]) than in the bipolar disorder group (0.30 [0.15–1.56], p = 0.026). The mean values of TNF-α, IL-1β, leucocyte and BDNF were not statistically significantly different between the two groups. The comparison of the BDNF, TNF-α, IL-1β, IL-6, CRP and leucocyte levels of the two groups is provided in Table 4.

We evaluated the relationship between suicide attempt history and the TNF-α, IL-1β, IL-6 and CRP levels of all patients (n = 80)

Table 1. Comparison of unipolar mania and bipolar disorder groups by sociodemographic and clinical characteristics*

	Unipolar mania (n = 38)	Bipolar disorder (n = 42)	p value
Disease onset age	24.53 ± 6.74	25.40 ± 8.64	0.616
Number of manic episodes	6.89 ± 4.29	2.31 ± 1.85	**<0.001**
Number of hypomanic episodes	0.61 ± 1.67	0.83 ± 1.10	0.067
Number of depressive episodes	–	3.02 ± 1.96	–
Total number of episodes	7.53 ± 4.35	6.17 ± 2.94	0.174
Number of hospitalisations	7.00 ± 4.39	3.83 ± 4.04	**<0.001**
Disease duration (years)	17.42 ± 8.92	17.24 ± 9.39	0.929
First episode type Manic Hypomanic Depressive	35 (92.1%) 3 (7.9%) –	12 (28.6) 4 (9.5) 26 (61.9)	**<0.001**
Lifetime smoke use	27 (71.1%)	24 (57.1)	0.289
Lifetime alcohol use	9 (23.7%)	3 (7.1)	0.079
Lifetime substance use	1 (2.6%)	1 (2.4)	0.728
Lifetime suicidal thoughts in history	8 (21.1%)	20 (47.6)	**0.024**
Lifetime suicide attempt history	7 (18.4%)	16 (38.1)	0.090
Family history of mental illness	27 (71.1%)	32 (76.2)	0.789

*Student *t* test, Mann–Whitney *U* test and χ² test were used to calculate the data in this table.

included in the study. IL-6 levels (median [min–max], in pg/ml) were significantly lower in the patients with a history of suicide attempts (10.32 [2.38–54.25]) than in the patients who did not attempt suicide (17.02 [0.29–235.78], p = 0.020).

Discussion

In the literature, the prevalence of unipolar mania in patients diagnosed with bipolar disorder ranges between 1.1% and 65.3% (Yazici *et al.*, 2002; Dakhlaoui *et al.*, 2008; Baek *et al.*, 2014; Stokes *et al.*, 2020). In our study, it was found that 8.08% of 495 patients diagnosed with bipolar disorder met the diagnostic criteria for unipolar mania.

Although some studies have (Shulman & Tohen, 1994; Yazici *et al.*, 2002, Dakhlaoui *et al.*, 2008; Baek *et al.*, 2014) reported that patients who meet the diagnostic criteria for unipolar mania have an earlier age of disease onset than those meeting the bipolar disorder diagnostic criteria, many studies (Srinivasan *et al.*, 1985, Makanjuola, 1985, Aghanwa, 2001, Pfohl *et al.*, 1982) have shown that the age of disease onset of the two groups is similar, consistent with our study.

In our study, no difference was detected between the two groups in terms of the total number of episodes, but we found that the number of manic episodes was lower in the bipolar disorder group than in the unipolar mania group. Although these results are

Table 2. Drugs used by patients in both groups

		Unipolar Mania N (%)	Bipolar Disorder N (%)
Mood stabiliser	Lithium	10 (26.3)	21 (50.0)
	Valproic acid	19 (50.0)	14 (33.3)
	Lithium + valproic acid	9 (23.7)	4 (9.5)
	Carbamazepine	–	3 (7.2)
Antipsychotic	Atypical	28 (73.6)	36 (85.6)
	Atypical+ Typical	8 (21.1)	3 (7.2)
	Not using	2 (5.3)	3 (7.2)

Table 3. Distribution of both groups according to their clinical features in manic episodes*

	Unipolar mania (n = 38)	Bipolar disorder (n = 42)	p value
Presence of elevated mood	38 (100.0%)	41 (97.6%)	0.525
Presence of depressive mood	–	23 (54.8%)	**<0.001**
Presence of anxiety symptoms	3 (7.9%)	24 (57.1%)	**<0.001**
Presence of euphoria	23 (60.5%)	12 (28.6%)	**0.008**
Presence of grandiosity	27 (71.1%)	19 (45.2%)	**0.035**
Presence of irritability	37 (97.4%)	38 (90.5%)	0.212
Presence of decreased sleep	38 (100.0%)	42 (100.0%)	NA
Presence of increased sexual desire	20 (52.6%)	9 (21.4%)	**0.008**
Presence of pressured speech	35 (92.1%)	35 (83.3%)	0.200
Presence of increased speech	37 (97.4%)	40 (95.2%)	0.538
Presence of hostility	12 (31.6%)	10 (23.8%)	0.599
Presence of flight of ideas	34 (89.5%)	33 (78.6%)	0.309
Presence of increased motor activity	34 (89.5%)	38 (90.5%)	0.586
Presence of agitation	29 (76.3%)	24 (57.1%)	0.115
Presence of increased goal-directed activity	15 (39.5%)	21 (50.0%)	0.471
Presence of catatonia symptoms	1 (2.6%)	1 (2.4%)	0.728
Presence of hallucination	8 (21.1%)	8 (19.0%)	0.823
Presence of delusion	27 (71.1%)	17 (40.5%)	**0.012**
Schneiderian symptoms	5 (13.2%)	2 (4.8%)	0.248
Insight			
Present	3 (7.9%)	9 (21.4%)	**0.030**
Partial	17 (44.7%)	24 (57.1%)	
Absent	18 (47.4%)	9 (21.4%)	

*Chi-square test was used to calculate the data in this table.

consistent with previous studies (Stokes *et al.*, 2020), Perugi *et al.* (2007) reported more manic episodes in the unipolar mania group; however, the total number of episodes in this group was found to be lower than in the bipolar disorder group.

A study that evaluated the temperament characteristics of unipolar mania patients (Yazici *et al.*, 2002) found that these patients had hyperthymic temperament. In another study, depressive temperament was never seen in the unipolar mania group, while 20.6% of the bipolar disorder group showed depressive temperament characteristics (Perugi *et al.*, 2007). Another study revealed that anxious personality was two to three times more common in predominantly manic and bipolar disorder I patients than in patients with major depressive disorder and bipolar disorder II (Angst *et al.*, 2004). Similarly, we found that the anxious temperament scores of the bipolar disorder group were not higher than those of the unipolar mania group, and the mean anxious temperament scores were similar between the two groups. We further found that depressive, cyclothymic and hyperthymic temperaments were more predominant in the unipolar mania group than in the bipolar disorder group.

Patients with unipolar mania have more grandiosity (Abrams *et al.*, 1979; Pfohl *et al.*, 1982) and delusions (Pfohl *et al.*, 1982) than patients with bipolar disorder. In this study, we found that unipolar mania patients showed more euphoria, increased sexual interest, delusions and grandiosity among manic symptoms in their manic episodes compared to patients with bipolar disorder. Further, depressive mood and anxiety symptoms were found to be significantly higher during manic episodes in the bipolar disorder group. Perugi *et al.* (2007) found that the rates of symptoms, such as increased sexual interest, grandiosity and delusions during manic episodes, were similar in both groups, but euphoria was more common in the unipolar mania group, while depressive mood, anxiety symptoms and hostility were significantly higher in the bipolar disorder group.

In our study, BDNF levels were similar in the unipolar mania and bipolar disorder groups. Since the total disease duration of both groups was equal and the BDNF levels were not different, we suppose that the episode type had no effect on BDNF levels and that the duration of the disease might have more effect on BDNF. However, Kauer-Sant'Anna *et al.* (2009) observed lower BDNF levels in bipolar disorder patients with longer disease durations than those with shorter disease durations.

Many studies have examined the relationship between IL-6 and bipolar disorder. In our study, IL-6 levels were higher in the unipolar mania group than in the bipolar disorder group. In a

meta-analysis, increased IL-6 levels were found during the manic, depressive and euthymic periods of bipolar disorder, and a significant increase in the cytokine was observed, especially in manic and hypomanic episodes (Sayana *et al.*, 2017). Lu *et al.* (2019) found that serum IL-6 levels were higher in patients with bipolar disorder than in patients with major depressive disorder, and they suggested that this cytokine could be used in the differential diagnosis of depressive episodes in bipolar disorder and major depressive disorder. Wiener *et al.* (2017) found that IL-6 and IL-10 levels did not differ among patients with major depressive disorder, bipolar disorder, and their healthy control counterparts. A recent meta-analysis showed that IL-6 appeared to be a trait marker for bipolar disorder (Solmi *et al.*, 2021).

Table 4. Comparison of leucocyte, CRP, BDNF and cytokine levels of unipolar mania and bipolar disorder groups*

	Unipolar mania Median [min–max]	Bipolar disorder Median [min–max]	p value
IL-6 (pg/ml)	17.23 [0.29–235.78]	10.74 [0.71–67.63]	**0.046**
CRP (mg/dl)	0.47 [0.30–2.58]	0.30 [0.15–1.56]	**0.026**
TNF-α (pg/ml)	9.00 [7.19–46.78]	8.88 [6.77–49.25]	0.266
IL-1β (pg/ml)	0.30 [0.07–0.74]	0.34 [0.24–1.52]	0.178
Leucocyte (10^3/μl)	7.20 [4.40–17.30]	7.55 [4.80–15.50]	0.410
BDNF (pg/ml)	525.42 [23.17–1192.94]	538.26 [170.45–1299.20]	0.999

BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; IL-1β, interleukin 1 beta; IL-6, interleukin 6; TNF-α, tumour necrosis factor alpha.
*Mann–Whitney *U* test was used to calculate the data in this table.

CRP levels have been indicated as an indicator of mood episodes in bipolar disorder and may be associated with disease severity (Dickerson *et al.*, 2007; Dargél *et al.*, 2015; Wysokiński *et al.*, 2015). In a study by Becking *et al.* (2013), high CRP levels observed in patients with a diagnosis of depression were thought to be an early warning sign for manic switch. In our study, CRP levels were found to be significantly higher in patients with unipolar mania than in the bipolar disorder group. This is primarily attributable to the higher levels of IL-6 in the unipolar mania group because CRP is released in response to proinflammatory cytokines (Chung *et al.*, 2013). Further, the fact that unipolar mania patients have more manic episodes may explain their higher CRP levels, as CRP has been associated with manic symptoms (Dickerson *et al.*, 2007; Uyanik *et al.*, 2015).

Limitations

Given that the definition of unipolar mania is unclear and the number of studies examining the underlying biological differences is insufficient, our study is important in that it is the first to examine the serum cytokine and BDNF levels of patients with unipolar mania and bipolar disorder. Nevertheless, our research has some limitations that may be opportunities for future studies. The diagnosis of unipolar mania may be inaccurate due to the inability to remember past depressive episodes or predict possible future depressive episodes. The small sample size and the use of some scales based on self-reports are other limitations of our study. Further, age, gender, smoking, alcohol use and various antipsychotic treatments might have affected cytokine and BDNF levels. The presence of some chronic medical diseases (hypertension, DM, hypothyroidism) and the drugs they use may have affected the levels of cytokines and BDNF in some patients. Although there was no statistically significant difference in the number of patients with hypothyroidism in either group, the fact that hypothyroidism was not excluded might have affected the CRP and other results. The observation of depressive temperament in patients defined as unipolar mania can be further investigated in future studies.

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