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Levels of TNF alpha, Soluble TNF Receptors (sTNF-R1, sTNF-R2) in Bipolar Disorder

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ABSTRACT

Introduction: Current evidence suggests that pro-inflammatory cytokines, particularly tumor necrosis factor alpha (TNF-α) may play an important role in the pathophysiology of bipolar disorder (BD). Our study aims to compare BD patients and controls in terms of serum TNF-α, soluble tumor necrosis factor receptor 1 and soluble tumor necrosis factor receptor 2 (sTNF-R1, sTNF-R2) levels in different phases of BD.

Methods: Eighty-three patients with BD type 1 (27 manic, 22 depressive and 34 euthymic) and twenty-nine healthy controls were included in the study. Serum levels of TNF-α, sTNF-R1, sTNF-R2 levels were evaluated with ELISA kit.

Results: Levels of sTNF-R1 were showed a statistically significant difference between groups. Levels of sTNF-R1 were higher in depression or mania patients than euthymia patients and control subjects. A statistically significant difference in the serum level of sTNF-R1 between patients in acute episode (mania and depression) group and stabile (patients in euthymic episode and controls) group was found in logistic regression analysis. The probability of having acute episode increased threefold for each unit increase in serum level of sTNF-R1. There was no statistically significant difference between the mean serum values of TNF-α and sTNF-R2 between the groups.

Conclusions: sTNF-R1 production was different between acute episode patients and controls or stable BD patients. The result of this study confirms that TNF-R1 may be a state marker representing disease activity for BD.

Keywords: bipolar disorder; TNF-α; TNF receptors

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INTRODUCTION

Current evidence suggests that bipolar disorder (BD) is associated with activated immune system, oxidative stress. These factors possibly end up with neuroprogression, a process characterized by neuronal dysfunctions such as impaired neuroprotection, neuronal damage, decreased synaptic plasticity and neurogenesis, changes in neurotransmitter signaling and receptor expression (1, 2). Parallel to innovations in biological psychiatry, there is increasing interest in biomarker research in the use of differential diagnosis, follow-up and treatment options in the activation of the disease in BD.

Patients with BD have low-grade peripheral inflammation and proinflammatory cytokines, particularly tumor necrosis factor alpha (TNF-α) may be taking part in this process by regulating the activity of immune cells and promoting the secretion of proinflammatory cytokines. A very new study investigated the involvement of TNF-α super family components in BD patients. Unlike the control group, they found that soluble tumor necrosis factor receptor 1 (sTNF-R1) and TNF-related weak inducer of apoptosis (TWEAK) plasma levels increased in BD patients regardless of mood. This study includes manic and euthymic patients and control group. (3).

A limited number of studies have reported increased TNF-α at all stages of BD. A meta-analysis of thirteen studies investigating a sum of fifteen different cytokines showed that patients in the manic episode have a higher level of sTNF-R1, TNF-α and soluble interleukin 2 receptor (sIL-2R) than healthy controls. Also, in a meta-analysis, sTNF-R1 and TNF-α levels were increased in mania patients compared to euthymia patients. Finally evaluated levels of sTNF-R1 were reported higher in euthymic patients compared to healthy controls. This meta-analysis suggested that TNF-α may be a state marker of BD. However; they acknowledged the fact that their findings were from a limited number of studies with weaknesses like small sample size, heterogeneity and lack of replicability. (4). Other meta-analysis reported that TNFα, sTNF-R 60 kDa and other some cytokine levels [interleukin 6 (IL-6), soluble interleukin 1 receptor antagonist (sIL-1RA), and sIL-2R] showed phasic differences (5). In another study, 130 patients with BD (59.2% BD I and 40.8% BD II) and 130 control subjects were compared soluble interleukin 6 receptor (sIL-6R), sIL-2R, C-reactive protein (CRP), sTNF-R1, sP-selectin, and monocyte chemotactic protein-1 levels were investigated. The BD group 57.7% of patients were euthymic, 10.8% were manic/hypomanic and 31.5% were depressive. Compared to the control group higher levels all cytokines

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were observed in BD patients. Multivariate regression analysis showed that BD II patients and patients in a depressive state had significantly lower levels of sTNF-R1 than patients with BD I ans other states (manic/hypomanic/euthymic). The authors concluded that sTNF-R1 might be a biomarker for staging BD (6). Serum soluble tumor necrosis factor receptor 2 (sTNF-R2) levels were not evaluated in these all studies.

In our previous study, we found that both TNF receptors (sTNF-R1 and sTNF-R2) levels have risen in euthymic state. This suggests that immune system activation may continue in the stable phase of BD (7). Until now, only a few studies investigated the sTNF receptors in all phases in BD. The depressive state in BD was less studied. Our study aims to compare BD patients and controls in terms of serum TNF-α, sTNF-R1, sTNF-R2 levels in different phases of BD.

MATERIALS AND METHODS

Subjects

This is a study in case-control design. We performed the study in the psychiatry outpatient clinic of Akdeniz University Faculty of Medicine between January 2015-December 2015. Eighty-three BD type I patients (27 manic, 22 depressive, and 34 euthymic) and twenty-nine healthy controls were included in the study. Ninety patients were evaluated in the beginning. Six patients refused to participate in the study. One patient was dropped out because he was taking antibiotics.

Patients with bipolar I disorder [according to The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-V) criteria] were evaluated with Young Mania Rating Scale (YMRS) (8) and Hamilton Depression Rating Scale (HDRS) (9) scores and were considered to be euthymic below 5 points in HDRS and below 7 points in YMRS. The different episodes of the disease were defined based on DSM-V criteria (Cut off for: YMRS=12; HDRS=11). Patients who had infectious diseases, using anti-inflammatory medication, autoimmune disease or with dementia and patients who had abnormal total blood count and biochemical values regarding renal, hepatic and thyroid functions and lipid metabolism in medical records were not recruited in the study. The control subjects were similar to the patient group in terms of age and sex. They had no psychiatric [as evaluated by Structured Clinical Interview for DSM-IV Clinical Version (SCID NP)] (10) and organic diagnoses. The study was confirmed by the ethics committee of Akdeniz University Medical Faculty.

Biochemical analysis

Venous blood (16 cc) was collected from a brachial vein after 12 hours of fasting. The serum was separated from the blood. These samples were kept at -80°C until analysis time. Serum TNF-α and soluble receptors levels were evaluated by an ELISA, EASI (invitrogen KHC-3011, Biosource KAC-1771, KAC-1761, USA). Results were expressed in turn as pg/mL and ng/mL.

Clinical assessment

All BD patients (depressive, euthymic, manic) were evaluated with a questionnaire designed to collect sociodemographic and clinical data. It contains age (mean±SD), gender, educational year, family history of psychiatric disorders (FHPD), onset age, duration of illness, the total number of periods, numbers of mania and depression, drug therapy.

Statistical analysis

'SPSS 22' program was used for statistics. We used the Shapiro-Wilk test for testing normality. For categorical variables, Chi-square and Kruskal-Wallis tests were used. Groups were compared by the Kruskal-Wallis test, the post-hoc test was performed using the Mann-Whitney U test and Bonferroni correction. Because levels of serum TNF-α and receptors did not conform to a normal distribution. Also, sociodemographic and clinical variables (illness duration, total episode number) did not conform to a normal distribution too. We used one way ANOVA and a Student's t-test for the compare of parametric variables and Spearman correlation test for the analysis of relationships between nonparametric quantitative variables. An alpha significance level less than 0.05 was considered as statistically significant.

Serum TNF-α and receptors levels and family history on the probability of developing acute episodes (depression and mania) in BD were analyzed by logistic regression analysis.

RESULTS

Sociodemographic and Clinical Data

Statistically, significant difference was not found between each group of bipolar patients (mania, depression, and euthymia) and control subjects concerning sociodemographic features including age, sex, education year, nicotine use (respectively: ANOVA, F=0.115 p=0.969; X^2=4.641, p=0.200; ANOVA, F=0.239 p=0.869; X^2=0.267, p=0.966). There was a statistically significant difference between the groups in terms of family history (X^2=9.678, p=0.022). The frequency of family history of psychiatric disorder was lower in the control group (proportion of patients with FHPD, respectively mania: 29.62%, depression 45.45%, euthymia 41.66% and control 10.34%).

We found statistically significant differences between each group of BD patients in terms of illness duration, number of episodes, number of depressive episodes. Differences were evaluated with Post hoc analysis. Thus, illness duration was found to be lower in the euthymic group in comparison to the other two BD groups (manic and depressive) and the mean of the illness duration was lower in the euthymic group. Total episode number was found different between euthymic and depressive groups in the Post-hoc analysis. The total episode number was more elevated in the depression group. Also, depressive episode number was found different between depressive groups and others and it was higher among depressive patients than in other BD study groups. There was no significant difference between the study groups in terms of onset age and number of manic attacks (Table 1).

All of the BD patients, except five, were on medication. In the whole BD group, nine patients were using only mood stabilizers, five patients using only antipsychotics, thirty-four patients using mood stabilizers and antipsychotics, and eleven patients using two mood stabilizers.

Biochemical Data

There was no normal distribution of serum TNF-α and receptors levels (Shapiro-Wilkins test, p>0.05). Serum levels of TNF-α, sTNF-R1, and sTNF-R2 levels were not different between the men and women in the whole study group (Z=0.954, p>0.05; Z=1.232, p>0.05; Z=-0.220, p>0.05). Similarly, there was no statistically significant difference between patients with and without a family history of psychiatric disorder (FHPD) in terms of serum levels of TNF-α and sTNF-R1, sTNF-R2, (Z=1.295, p>0.05; Z=-1.045, p>0.05; Z=-0.541, p>0.05).

To see if TNF-α, and receptors levels changed in different episodes in BD patients and controls; serum levels of TNF-α, sTNF-R1, and sTNF-R2 levels were compared between the four study groups (euthymic, manic, depressive patients and controls). A statistically significant difference was not found between groups for mean serum values of TNF-α and sTNF-R2. However, sTNFR1 was higher in depression and mania groups when compared to euthymic patients and controls in Post-hoc analysis (Table 2).

Logistic regression analysis was used to evaluate Serum TNF-α, sTNF-R1 and sTNF-R2 levels and FHPD to predict the likelihood of developing an

Table 1. Clinical features of patients

	Mania (mean ± SD)	Depression (mean ± SD)	Euthymia (mean ± SD)	Kruskal-Wallis	Bonferroni correction
Onset age	23.96±8.49	25.45±8.14	25.62±8.81	X^2=0.551 p=0.75	Eutymic-manic: p>0.999 Eutymic-depressive: p>0.999 Manic-depressive: p>0.999
Illness duration (month)	143.68±117.86	128.2±82.03	12.60±7.74	X^2=47.03 p<0.001	Eutymic-manic: p<0.001** Eutymic-depressive: p<0.001** Manic-depressive: p>0.999
Total number of mood episodes	7.4±7.0	11.6±16.81	5.12±3.65	X^2=7.38 p=0.025	Eutymic-manic: p>0.933 Eutymic-depressive: p=0.018* Manic-Depressive: p=0.348
Number of manic episodes	5.28±5.56	2.4±1.69	3.35±2.63	X^2=3.51 p=0.172	Eutymic-manic: p=0.396 Eutymic-depressive: p>0.999 Manic-Depressive: p=0.255
Number of depressive episodes	1.28±2.26	6.2±10.69	1.64±2.78	X^2=21.30 p<0.001	Eutymic-manic: p>0.999 Eutymic-depressive: p<0.001** Manic-Depressive: p<0.001**

* P<0.05; **P<0.001; SD, standard deviation.

Table 2. Serum levels of TNF-α, sTNF-R1and sTNF-R2 in different episodes

	Mania (mean ± SD)	Depression (mean ± SD)	Euthymia (mean ± SD)	Controls (mean ± SD)	Kruskal-Wallis	Bonferroni correction
TNF-α	19.64±5.97	19.91±6.26	21.30±5.77	19.37±3.86	X^2=1.63 p=0.65	Control-Eutymic: p>0.999 Control-Manic: p>0.999 Control-Depressive: p>0.999 Eutymic-Manic: p>0.999 Eutymic-Depressive: p>0.999 Manic-Depressive: p>0.999
sTNF-R1	3.84±2.05	4.44±3.35†	1.36±0.86	1.73±1.43	X^2=40.97 p<0.001	Control-Eutymic: p>0.999 Control-Manic: p<0.001* Control-Depressive: p<0.001* Eutymic-Manic: p<0.001* Eutymic-Depressive: p<0.001* Manic-Depressive: p>0.999
sTNF-R2	8.19±5.25	8.41±4.21	8.29±3.57	6.35±2.80	X^2=5.10 p=0.16	Control-Eutymic: p=0.138 Control-Manic: p>0.999 Control-Depressive: p=0.480 Eutymic-Manic: p>0.999 Eutymic-Depressive: p>0.999 Manic-Depressive: p>0.999

*P<0.001; SD, standard deviation.

acute episode (depression and mania) in BD. A statistically significant difference in the serum level of sTNF-R1 between patients in acute episodes (mania and depression) group and stabile group (patients in euthymic episode and controls) was found (p<0.01, 95% CI: 1.866–5.060). The probability of having acute episodes increased threefold for each unit increase in serum level of sTNF-R1. Serum levels of TNF-α, sTNF-R2 and FHPD did not have a deterministic effect on diagnostic predictability (Table 3).

There were statistically significant positive correlations between total illness duration, the number of depression and serum levels of sTNF-R1 in BD patients (r=0.566, p<0.01; r=0.251, p<0.05). Serum levels of TNF-α and sTNF-R2 did not show a statistically significant correlation with any of the sociodemographic and clinical variables.

DISCUSSION

Our study showed that sTNF-R1 levels were higher in patients with depression or mania than euthymic patients and controls. Logistic regression analysis showed a significant difference in sTNF-R1 levels between acute attack (mania and depression) group and stable group (euthymic and control). Furthermore, sTNF-R1 represented a positive correlation with illness duration and depressive episode number.

These findings are similar to those reported in previous studies (11–14). Indeed, Barbosa et al observed higher sTNF-R1 plasma levels in euthymic and manic BD patients than controls. Furthermore, levels of sTNF-R1 were higher in manic patients than in euthymic patients, and this was correlated with illness duration (12). Few studies have evaluated TNF in BD depressed patients. In some of these studies, a significant increase was reported in patients compared to the control group (15–17). Lou et al found that serum TNF-α and IL-6 levels were higher in BD patients in all phases of BD except euthymia than in the control group. But they did not investigate soluble TNF receptors and did not evaluate the euthymic phase (18). There are less study that reported similar levels of sTNF-R1 in depressed BD patients and healthy subjects (13). Sivek et al. compared sIL-1RA, sIL-2R, sIL-6R, sTNF-R1 and sTNF-R1 levels in bipolar disorder with healthy controls. They reported that higher sTNF-R2 levels

Table 3. Logistic regression analysis to evaluate the possibility of acute episode development in BD

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp (B)	95% C. I. for Exp (B)	
								Lower	Upper
Step 1	TNF alfa	-0.074	0.049	2.284	1	p=0.131	0.929	0.843	1.022
	sTNF-R1	1.123	0.254	1.466	1	p<0.000	3.073	1.866	5.060
	sTNF-R2	-0. 116	0.080	2.120	1	p=0.145	0.890	0.762	1.041
	Family history for psychiatric disorder	0.258	0.626	0.170	1	p=0.680	1.294	0.380	4.411
	Constant	-0.514	1.167	0.194	1	p=0.660	0.598		

BD, bipolar disorder.
S.E., standart error
df, degree of freedom
Sig., significance
Exp., Exp (B)., odds ratio

and female sex were found to be predictors of melancholia. Similarly; female gender, nicotine use, and increased sTNF R1 and sTNF R82 levels predicted the severity of depression. However, elevated levels of sTNF-R2 may be a marker of the depression, and low levels of sIL-2R and higher sTNF-R2 could be used for staging (19).

This is one of the few studies to show that circulating sTNF-R1 and sTNF-R2 levels increase in all BD episodes. The TNFR1: TNFR2 ratio has been found to be significant in the TNF response. Unregulated TNF-R1 expression coupled to changeable TNF-R2 levels in cells alters the TNFR1: TNFR2 ratio and controls the TNF, thus effectively altering the cellular and physiological responses its elicits (20). In our previous study, sTNF-R2 levels were higher than TNF-R1 levels. This rise in sTNF-R2 levels may decrease apoptosis and regulate TNF activity in the euthymia (7). But in the current study, we found that only sTNF-R1 production was different in acute episode patients when compared to controls or stable BD patients. Additionally, in logistic regression analysis, the probability of having acute episodes increased threefold for each unit increase in serum level of sTNF-R1. This suggests that sTNF-R1 may be a state marker of BD in accordance with previous literature (4, 6). Although sTNF-R2 was not different between all phases of BD. sTNF-R2 was not found as a marker reflecting disease activity. It is also compatible with studies that find sTNF-R2 high in the euthymic period (7). While sTNF-R2 provides compensation by regulating TNF activity and reducing apoptosis in the euthymic period, this compensation may be interpreted as insufficient or not yet present in acute attacks.

There was no significant difference in TNF-α levels between the groups in our study. According to previous literature, TNF is produced in peripheral tissues and collapses immediately after release. TNF-α induces the production of sTNFRs. Thus, sTNFR may reflect the activity of TNF-α instead of TNF-α (11). Finally, our results supported the findings of previous studies which suggest that the level of sTNF-R1 may be a state marker in BD and the level of sTNF-R2 is insufficient to compensate for TNF activity in acute attacks or has not yet emerged. (7, 11, 20).

Evidence suggests that BD staging may be associated with increased activation of inflammatory pathways. Serum sTNF-R1 levels and illness duration showed a positive correlation with each other (11). In bipolar and schizophrenic patients, assessments of functioning and number of hospitalizations were associated with sIL-1RA and sTNFR 60 kDa plasma levels (21). Consistent with these data, sTNF-R1 level was also correlated with illness duration and the number of depression in BD patients in our study. Higher sTNF-R1 levels reflect the sign of a more severe inflammatory process. Prolonged illness and recurrent periods may cumulatively facilitate inflammatory response (22). The high number of episodes of depression was also correlated with higher TNF-R1 levels. This result suggests that the number of depression attacks may be another indicator of the severity of the disease because depression episodes last longer than manic attacks (23).

An obvious limitation of this study was the use of drugs (psychotropics, mood stabilizers, antidepressants) in all patients except one, and drug use is known to affect inflammatory processes (24–27). Other characteristics such as genetic characteristics, living conditions, and weight were not controlled in the study. In addition, assessment of cytokine levels in the cerebrospinal fluid (CSF) may be safer in BD patients to understand actual pathophysiology

CONCLUSION

As a result, TNF-R1 may be a state marker representing disease activity for BD. The serum level of sTNF-R2 was not elevated in patients in the acute phase. The measurement of inflammatory markers, especially TNF-α and receptors in BD will be useful not only in terms of knowledge of pathophysiology but in managing clinical patient monitoring and determining treatment strategies.

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Ethics Committee Approval: Approval for this study was obtained from the ethics committee of Akdeniz University Medical School.

Informed Consent: Informed consent was obtained from patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - ÖDB; Design - ÖDB, HA; Supervision - ÖDB; Resource - ÖDB; Material: ÖDB, HA; Data Collection and/ or Processing - ÖDB, SK, SŞK; Analysis and/or Interpretation - ÖDB, BC, AE; Literature Search - ÖDB, BC, AE; Writing - ÖDB, BC, AE; Critical Reviews - BC, AE.

Conflict of Interest: The authors declare that this manuscript is an independent study, has no conflict of interest including any financial, personal or other relationship with other people or organizations within three years of beginning the submitted work.

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