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Evaluation of serum inflammatory markers in treatment-resistant manic patients and adequate responder manic patients

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ABSTRACT

Mania is accompanied with immune activation as indicated by increased pro-inflammatory cytokines, acute phase proteins; and carcinoembryonic antigen (CEA) is known to accompany signs of immune-inflammatory responses in bipolar disorder (BD) and medical disorders. In this study, it was aimed to compare high sensitivity C-reactive protein (hsCRP), CEA levels and white blood cells (WBCs) counts in the treatment-resistant BD (Group 3), the treatment-responsive BD patients (Group 2), and the healthy control group (Group 1). The socio-demographic data form, the Young Mania Rating Scale (YMRS), the Hamilton Depression Rating Scale (HDRS), and the Clinical Global Impression Severity of Illness (CGI-S) Scale were applied to the patients. In Group 3, the WBCs counts, and CEA levels were significantly higher than the other two groups. There was a positive correlation between WBCs counts and YMRS and CGI-S scores in all manic patients. There was a positive correlation between CEA levels and YMRS, HDRS and CGI-S in manic patients. This study shows that there is an activation of the immune-inflammatory response system in treatment resistant manic patients; and, WBCs counts and CEA levels are associated with severity of disease in manic patients.

1. Introduction

Bipolar disorder(BD) is a chronic disorder which is mostly seen as depression and mania or hypomania episodes in many patients (Merikangas et al., 2007). Treatment resistance changes depending on different clinical situations in the bipolar disorder. Treatment resistance could be regarded as an inability to achieve sufficient recovery regarding both clinical and psychometric scales although two different medications are used at adequate doses and time required for the specific episode of the disease (Geddes and Miklowitz, 2013). In many studies, the inability to achieve sufficient response to two or three treatment attempt in the past is accepted as a threshold for resistance (Perlis et al., 2006). The most current definition of treatment resistance is made by the International Society for Bipolar Disorders (ISBD) (Tohen et al., 2009). Response to treatment is evaluated in two different ways, syndromic and symptomatic treatment (based on rating criteria) (Tohen et al., 2009). Treatment response in acute mania is defined as successful response to treatment for mania (50% improvement in mania symptom severity using YMRS) includes the lack of exacerbation of depressive symptoms (Tohen et al., 2009).

1.1. Treatment resistant acute mania

It is characterized by insufficient decrease in Young Mania Rating Scale (YMRS) with lack of exacerbation of depressive symptoms despite the 6-week to 8-week treatment duration (Tohen et al., 2009).

1.2. Treatment resistant maintenance period

It is characterized by the unchanging frequency of episodes, Hamilton Depression Rating Scale (HDRS) scores above 6, and YMRS scores above 7 despite the 1-year treatment duration (Tohen et al., 2009). In a study by Perlis et al., they have states that the treatment resistance is very common in patients with bipolar disorder and recurrence occur in about half of the patients in remission, even though under optimal management treatment. The recurrence is found to be associated with the presence of residual sypmtoms (Perlis et al., 2006). Early onset, advanced age, interim residual symptoms, additional psychiatric disorder diagnosis, manic episodes more than 10, mixed periods, and long depressive periods are the factors that have negative effects on the course of rapid cycling and adequate response to

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treatment (Gitlin et al., 1995). Treatment resistance can be predicted by these factors. However, there is no biochemical marker that can predict the treatment resistance.

Treatment-resistant BD patients are thought to have other underlying mechanisms. Recently, the studies focusing on the role of immunological and inflammatory processes in mood disorders has become prominent. The immune-inflammatory-response system(IRS) is activated in BD is evidenced by increased M1 macrophage cytokines, T helper (Th)-1 pro-inflammatory cytokines, interleukin (IL)-6 trans-signaling, positive acute phase proteins (APPs), and complement factors. This activation of IRS is occured especially during acute phase of ilness. Compensatory immune-regulatory reflex system (CIRS) is a novel term defined by Maes et al. which is involved in MDD and BD by regulating the primary immune-inflammatory-response. After acute phase of BD, activated IRS and CIRS pathways are persisted which indicating that immune system did not return the original hemoastasis after an acute episode (Maes and Carvalho, 2018; Maes et al., 1997).

C-reactive protein (CRP) is a classical acute phase reactant that is produced in the liver and secreted into the blood. This protein is a direct and quantitative measure of the overall acute phase response (de Ferranti and Rifai, 2007). In chronic infections and inflammatory conditions, CRP levels are observed to be increased (Lowe, 2005). Protein levels start to increase after 4–6 h from tissue damage or injury. It doubles every 8–9 h and can reach several hundred times within 24–48 h (depending on the stimulus and case). Serum CRP levels continue to increase if the acute phase response continues. It returns to its original level when normal tissue structure and function are provided. Therefore, it is regarded as a marker of systemic inflammation (Sugano et al., 2005). CRP, is a useful and sensitive marker for inflammatory activity in the clinical practice (Akil et al., 2015). Even though CRP and hs-CRP are the same analyte, more sensitive CRP immunoassays than those previously used were developed by use of ultrasensitive ELISA or particle-enhanced techniques and these assays were named as “high-sensitivity” or “highly sensitive” CRP (hsCRP) (Yucel, 2014).

CRP elevation is higher in manic episodes than in depressive episodes and it is thought that there may be a more activation of the immune-inflammatory response system (IRS) in the manic episode. It is not yet known why CRP is higher in the mania not in depressive or euthymic patients (Fernandes et al., 2016; Ortiz-Dominguez et al., 2007).

Carcinoembryonic antigen (CEA) is an oncofetal protein and has a molecular weight of 180 kDa. CEA is used as a tumor marker in adenocarcinomas and particularly in colorectal cancer types. The function of CEA is not fully known, however, in the previous studies, the findings showed that CEA stimulates the production of endothelial adhesion molecules and proinflammatory cytokines by stimulating monocytes and macrophages (Ganguly et al., 2003). In a previous study, CEA levels were found to be higher in the euthymic period in the BD than in the control group, and this high level was associated with the inflammatory processes (Kaplan et al., 2015).

WBCs count is an indication of general immunological activity. In many studies on bipolar disorder, the WBCs counts has been shown to increase particularly in the manic episode (Fernandes et al., 2016). It has been suggested in previous studies that BD may be associated with immunological activation (Knijff et al., 2006). Previous studies show that both CEA levels, hsCRP levels, and WBCs counts vary during different periods of the BD (Fernandes et al., 2016; Horsdal et al., 2017; Kaplan et al., 2015). The states of these inflammation markers are not known in treatment-resistant manic patients. We have thought that variations in CEA levels, hsCRP levels, and WBCs counts can be used as the inflammatory markers in BD, particularly in treatment-resistant mania.

The aim of this study is to investigate the states of the immunologic parameters, part of activated IRS and CIRS, such as CEA levels, hsCRP levels, and WBCs counts in the treatment resistant mania and adequately treatment-responsive mania.

Materials and methods

Local ethics committee approval was obtained to conduct the present study (Local ethics committee approval number: 331). 60 patients, who were diagnosed with BD-I manic episode in accordance with the DSM–5 criteria and who were receiving treatment for at least six months, and 30 healthy volunteers were included in this study. The patients were selected consecutively.

Participants were divided into three groups. **Group 1:** Healthy control group, **Group 2:** Treatment-responsive manic patient group, **Group 3:** Treatment-resistant manic patient group

The Young Mania Rating Scale (YMRS) (Karadag et al., 2002), the Hamilton Depression Rating Scale (HDRS) (Akdemir et al., 2001) (38) and the Clinical Global Impression-Severity scale (CGI-S) (Guy, 1976) were applied to the patients as well as written consent form and sociodemographic data form.

2.1. Treatment resistance manic episode criteria

In our study, inconsistent with Gitlin et al. (1995) and Tohen et al. (2009), treatment-resistance manic episode were accepted in patients who met all of the following criteria:

1 Patients without 50% and a higher rate of improvement in YMRS.
2 Patients whose YMRS score was 18 and above, whose CGI was 4 and above.
3 No increase in depressive symptoms on follow-up despite receiving two or more antimanic treatments during bipolar manic episode for at least six weeks, as being one of them was an approved mood stabilizer and one was antipsychotic.
4 Failure or intolerance of (i) lithium carbonate, (ii) valproic acid or carbamazepine, and (iii) two or more antipsychotics (any combination of typical and/or atypical antipsychotics excluding olanzapine) in previous manic episodes.

2.2. Study inclusion criteria

1- Being diagnosed with the BD-I manic episode for at least six months according to DSM-5 diagnostic criteria
2- Being at the age between 18–65 years
3- Providing consent to participate in this study
4- Having the competence to give consent
5- Receiving at least one mood stabilizer (lithuril, valproic acid, carbamazepine, lamotrigine) and at least one antipsychotic (first or second generation) drug

2.3. Study exclusion criteria

1- Patients younger than 18 years or older than 65 years
2- Patients with neurological comorbidities (Dementia, Parkinson, Cerebrovascular Event)
3- The history of infection in the last three months
4- Rheumatologic disease
5- Mental retardation
6- Pregnancy
7- Severe endocrinopathies
8- Severe cardiac insufficiency
9- Cranial or medulla spinalis trauma
10- Vascular diseases
11- Comorbid psychiatric illness
12- Morbid obesity
13- Patients on a special diet or exercise program

2.4. Measurement of inflamatory markers

2.4.1. Measurement of high-sensitive CRP

After serum samples was centrifuged at 5000 rpm for 10 min at 4 °C, hs-CRP levels were evaluated using a nephelometric assay (Beckman Immage800) at the Central Laboratory of the Faculty of Medicine of Dicle University. The results were reported in mg/L.

2.4.2. Measurement of carcinoembryonic antigen (CEA)

Serum samples were centrifuged at 5000 rpm for 10 min at 4 °C. Serum samples prepared, and CEA amount (in μg/L) were determined using chemiluminescence immunoassay (Roche Modular E170) at the Central Laboratory of the Faculty of Medicine of Dicle University.

2.4.3. Measurement of WBCs count

For measurement of complete blood count, blood was drawn into a vacutainer tube, containing EDTA, and analyzed in an automated hematology analyzer (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, IL, USA) was used to measure WBC counts (K/UL).

2.5. Statistical analysis

Statistical analysis was performed using SPSS version 18.0 software (SPSS Inc. Chicago, IL, USA). Descriptive statistical methods (mean, standard deviation) were used in the evaluation of the data. Student's *t*-test, one-way ANOVA and ANCOVA methods were used to compare the continuous data of three groups with normal distribution, and chi-square ($\chi 2$) test was used in the comparison of qualitative (categorical) data. Non-parametric Kruskal–Wallis test and parametric *T*-test were used for multiple comparisons. Pearson and Spearman correlation analyzes were used to evaluate the relationship between variables. Partial correlation was conducted for adjusting the effect of the confounding factors such as age, sex, smoking status and drug state. Results were evaluated within 95% confidence interval and a *p*-value of <0.05 was considered statistically significant.

3. Results

3.1. Sociodemographic findings of patient groups

Sociodemographic characteristics of the participating patients are shown in Table 1. In the comparison of mean age, sex, marital status, socioeconomic level, and duration of education, any difference was not observed between the groups ($p > 0.05$) (Table 1).

In the control group, there was not any suicide attempt history. Considering the suicide history of the patients, there was no significant difference between Group 2 (36.7%; $n = 11$) and Group 3 (26.7%; $n = 8$) ($\chi^2 = 0.693$, $df = 1$, $p = 0.290$).

Psychiatric history of patients in group 3 and 3 are given in Table 2. None of the participants were used antidepressants. Comparison of drugs used by patient groups are given in Table 2.

Comparison of the mean scale scores of the groups are given in Table 3.

3.2. Comparison of hsCRP levels, CEA levels, and WBCs counts of the study groups

The comparison of hsCRP levels, CEA levels, and WBCs counts of Group 1, Group 2 and Group 3 are given in Table 4. There were no significant differences between groups regarding to hsCRP levels ($p > 0.05$). CEA levels of Group 3 were found to be significantly higher than both Group 1 and Group 2 ($p < 0,05$). WBCs counts of Group 3 were found to be significantly higher than both Group 1 and Group 2 ($p < 0.05$). Comparison of hsCRP levels, CEA levels, and WBCs counts of the groups are given in Table 4.

3.3. The relationship between blood parameters and clinical scales

In the partial correlation analysis performed in patients (Group 2 + Group 3) adjusted for age, sex, smoking status and drug state, a positive correlation was found between the CEA and YMRS ($r = 0.337$, $p = 0.015$), HDRS ($r = 0.367$, $p = 0.008$), CGI-S ($r = 0.289$, $p = 0.040$). In addition, a positive correlation was found between the WBCs counts and YMRS ($r = 0.316$, $p = 0.024$), CGI-S ($r = 0.317$, p = 0.023) (Table 5).

4. Discussion

One of the important finding in the present study was that WBCs counts were significantly higher in treatment-resistant manic patients (Group 3) than healthy subjects (Group 1) and treatment-responsive manic patients (Group 2) (Table 4). There was a positive correlation between WBCs counts and YMRS ($r = 0.316$, $p = 0.024$), CGI-S ($r = 0.317$, $p = 0.023$) (Table 5) in manic patients (Group 2 + Group 3). The increase of WBCs counts is an indicator of a strong inflammatory response and is used as a marker of general immune system activation (Kohler et al., 2017). In a study by Köhler et al., they found out a relationship between the changes in WBCs counts and severity of the mood symptoms. They also found 2.1 points increase in Bipolar Inventory of Symptoms Scale (BISS) severity, and 1.1-point increase in Montgomery-Asberg Depression Rating Scale (MADRS) per 1.0 × 109/L increase in the WBCs counts. However, this change was only observed

Table 1
The sociodemographic characteristics of the study groups.

	Group 1 ($n = 30$) Mean ± SD	Group2 ($n = 30$) Mean ± SD	Group 3 ($n = 30$) Mean ± SD	***F***	***p***
Age	35.03 ± 8.71	33.83 ± 13.0	30.27 ± 10.0	1.598	0.208
	Group 1 *n*(%)	**Group 2 *n*(%)**	**Group 3 *n*(%)**	χ^2	***p***
Female	8 (26.6%)	12 (40%)	8 (26.6%)	1.659	0.436
Male	22 (83.3%)	18 (60%)	22 (83.3%)		
Married	22 (83.3%)	17 (63.3%)	14 (46.6%)	4.498	0.106
Single	8 (26.6%)	13 (36.7%)	16 (54.4%)		
Illiterate	1 (3.3%)	1 (3.3%)	3 (10%)		0.651
5 years	7 (23.3%)	11 (36.6%)	7 (23.3%)	5.963	
6–8 years	7 (23.3%)	3 (10%)	8 (26.6%)		
9–12 years	9 (30%)	9 (30%)	6 (20%)		
University	6 (20%)	6 (20%)	6 (20%)		
Yes	1 (3.3%)	19 (63.3%)	18 (60%)	27.966	<0.001
No	29 (96.7)	11 (36.7%)	12 (40%)		
Yes	1 (3.3%)	13 (43.3%)	22 (73.3%)	30.833	
No	29 (96.7)	17 (56.7%)	8 (26.7%)		<0.001

Group 1: healthy control, Group 2: manic patients who responded to treatment, Group 3: treatment-resistant manic patients.

Table 2
Psychiatric history and comparison of medications used by patient groups.

	Group 2 (n = 30) Mean ± SD	Group 3 (n = 30) Mean ± SD	t		p	
Age of onset	21.9 ± 6.9	21.2 ± 5.3	0.442		0.66	
Duration of the disease	11.9 ± 11.4	9.1 ± 8.0	1.125		0,265	
Number of total episodes	5.266 ± 4.322	5.633 ± 4.664	−0.316		0.753	
Number of manic episodes	3.4 ± 3.0	3.3 ± 2.4	0.191		0.849	
Number of depressive episodes	1.7 ± 1.8	2.0 ± 3.1	−0.466		0.643	
Number of mixed episodes	0.17 ± 0.46	0.37 ± 0.67	−1.349		0.183	
Medications	Group 2 (n = 30) % (n)	Group 3 (n = 30) % (n)	χ^2	df		p
Lithium	43.3% (n = 13)	30% (n = 9)	1.148	1		0.284
Mood stabilizers	96.7 (n = 29)	93.3 (n = 28)	0.351	1		0.554
Atypical Antipsychotic	100% (n = 30)	96.7% (n = 29)	1.017	1		0.313
Typical Antipsychotic	3.3% (n = 1)	13.3% (n = 4)	1.964	1		0.161

Group 1: healthy control, Group 2: treatment-responsive manic patients, Group 3: treatment-resistant manic patients.

Table 3
The mean scale scores of the study groups.

Mean Scale Scores	Group 1 (n = 30) Mean ± SD	Group 2 (n = 30) Mean ± SD	Group 3 (n = 30) Mean ± SD	F	*ANOVA* p
YMRS	0.20 ± 0.484	2.17 ± 0.913	27.97 ± 4.694	40.83	<0.001
HDRS	0.90 ± 0.960	2.96 ± 1.170	11.70 ± 3.164	20.83	<0.001
CGI-S	1.00 ± 0.000	1.23 ± 0.430	4.60 ± 0.964	5.114	<0.001

Group 1: healthy control, Group 2: treatment-responsive manic patients, Group 3: treatment-resistant manic patients YMRS: Young Mania. Rating Scale HDRS: Hamilton Depression Rating Scale CGI-S: Clinical Global Impression-Severity of Illness.

in male patients. Both the high and the low WBCs counts were associated with the symptom severity and specific symptom clusters in men. Manic, irritability and psychotic symptoms were found to be associated with higher WBCs counts (Kohler et al., 2017). In another study including 765 patients with BD, a significant relationship was found between variation in WBCs counts and severity of illness in male patients. In this study, ait was presented that the changes in WBCs counts in male and female patients was worsening the different symptom clusters in MADRS. Furthermore, it was determined that low and high WBCs counts and some manic and psychotic symptoms tended to be getting worse (Kohler-Forsberg et al., 2017). The relationship between specific semantic clusters and changes in WBCs counts could not be investigated due to the limited number of patients included in our study. Contrary to previous studies, there was no statistically significant difference between the sexes regarding WBCs counts in our study (t = 0.480 p = 0.634). In a follow-up study that compared schizophrenia, bipolar disorder, and depressive patients, WBCs counts were found to be higher in the patients who were not receiving antipsychotics and had somatic comorbidities. WBCs counts were returned to lower values at the end of the stuy. However, there was no association between number of recurrences and WBCs counts (Horsdal et al., 2017). In our study, no relationship was found between the number of previous episodes, the duration of illness, and the age of onset. Our findings suggested that activation of IRS is associated with the symptom severity. Not only that but also the higher WBCs counts in the treatment-resistant manic patients suggested that activation of IRS was more prevalent in treatment-resistant mania.

The function of CEA is not fully known. However, the findings showed that CEA stimulates the production of endothelial adhesion molecules and proinflammatory cytokines by stimulating monocytes and macrophages (Ganguly et al., 2003). The expression of CEA increases in adenocarcinomas, particularly in colorectal cancer types. CEA is also excreted from normal mucosal cells. CEA levels are observed to increase in patients with pancreatitis, inflammatory bowel diseases, cirrhosis, biliary obstructions, peptic ulcer, and hypothyroidism as well as in smokers (Aarons et al., 2007; Minami et al., 2001). In BD, there is mild chronic inflammation in both the periphery and the brain (Goldstein et al., 2009; Hamdani et al., 2012). In our study, we evaluated CEA levels of patients with BD, and CEA levels were found to be high, which is supporting the thesis of other studies demonstrating the association of BD and activation of IRS. In a study by Kaplan et al., serum CEA level was found to be significantly higher in BD patients in the euthymic phase. This was interpreted as chronic immune activation and inflammatory syndrome in BD by the researchers. They reported that CEA may have increased the proinflammatory cytokine levels (Kaplan et al., 2015). Increased CEA levels in treatment resistant manic patients may have a role in the activation of IRS rather than chronic immune activation and inflammatory syndrome.

In manic patients (Group 2 + Group 3), a positive correlation was found between the CEA levels and YMRS (r = 0.337, p = 0.015), HDRS (r = 0.367, p = 0.008), CGI-S (r = 0.289, p = 0.040) (Table 5). These results indicate that higher levels of CEA may contribute to symptom severity in manic patients.

Table 4
The comparison of hsCRP levels, CEA levels, and WBCs counts of the groups.

	Group 1 (n = 30) Mean ± SD	Group 2 (n = 30) Mean ± SD	Group 3 (n = 30) Mean ± SD	F	ANOVA p	F	ANCOVA p
hsCRP (mg/L)	0.22 ± 0.276	0.18 ± 0.355	0.23 ± 0.368	0.194	0.824	0.229	0.796
CEA (μg/L)	2.49 ± 1.365	2.51 ± 1.505	3.16 ± 1.599	1.941	0.150	4.326	0.016**
WBC (K/UL)	7.56 ± 2.063	8.33 ± 1.900	9.82 ± 2.28	8.942	<0.001*	5.641	0.005***

There were no changes in significance according to covariate of lithium, mood stabilizers, atypical antipsychotic, typical antipsychotic.

* Significant difference between Group 1 and Group 3 (p = 0.008), Significant difference between Group 2 and Group 3 (p < 0.001) All results of ANCOVAs with age, gender and smoking status as covariates.

** Significant difference between Group 1 and Group 3 (p = 0.007), Significant difference between Group 2 and Group 3 (p = 0.001).

*** Significant difference between Group 1 and Group 3 (p = 0.021), Significant difference between Group 2 and Group 3 (p = 0.011)

Table 5
The correlation matrix among hsCRP, CEA, WBC and clinical data in manic patients (Group 2 + Group 3).

	HsCRP	CEA	WBC	Age of onset	DOD	YMRS	HDRS	CGI-S	NME	NDE	NMXE
HsCRP											
CEA	0.203(0.154)										
WBC	−0.034(0.811)	0.168(0.239)									
Age of onset	0.050(0.727)	0.026(0.856)	−0.083(0.562)								
DOD	−0.050(0.727)	−0.026(0.856)	0.083(0.562)	**−1.00(0.000)***							
YMRS	0.107(0.454)	**0.337(0.015)***	**0.316(0.024)***	−0.050(0.729)	0.050(0.729)						
HDRS	0.266(0.059)	**0.367(0.008)***	0.221(0.120)	−0.013(0.925)	0.013(0.925)	0.926(0.000)					
CGI-S	0.118(0.409)	**0.289(0.040)***	**0.317(0.023)***	−0.039(0.786)	0.039(0.786)	0.975(0.000)	**0.922(0.000)***				
NME	−0.006(0.965)	0.164(0.250)	0.030(0.835)	**−0.369(0.008)***	**0.369(0.008)***	0.080(0.576)	0.073(0.612)	0.058(0.685)			
NDE	−0.105(0.465)	−0.074(0.606)	0.188(0.186)	−0.057(0.692)	0.057(0.692)	0.107(0.455)	0.028(0.846)	0.064(0.656)	0.113(0.429)		
NMXE	0.127(0.373)	0.086(0.547)	−0.011(0.937)	−0.165(0.247)	0.165(0.247)	**0.280(0.046)***	0.199(0.161)	0.274(0.052)	0.209(0.140)	0.149(0.297)	

DOD: Duration of the disease, NME: Number of manic episodes, NDE: Number of depressive episodes, NMXE: Number of mixed episodes, YMRS: Young Mania Rating Scale, HDRS: Hamilton Depression Rating Scale, CGI-S: Clinical Global Impression-Severity of Illness.
Partial correlation has been done for adjusting the confounding effects (Age, sex, smoking, drug state). Listed are correlation coefficients. *P* values are shown within parentheses.
*Statistically significant values ($p < 0.05$).

There is a major change in acute phase protein concentrations in infection and infarction. Moderate changes in acute phase proteins occur after intense exercise and child birth. However, minor changes are seen during psychological stress and severe psychiatric illnesses (Gabay and Kushner, 1999). Findings in studies on bipolar disorder are also in this direction.

It is reported that, hsCRP levels were insignificanty high in BD patient (Wadee et al., 2002). In another study, including 23 major depression patients, 13 manic patients, and 31 healthy volunteers, manic patients have higher hsCRP levels insignificantly (Huang and Lin, 2007). However, in another study threre was a relationship between manic symptoms and CRP levels in manic patients (Dickerson et al., 2007).

The most consistent finding regarding the studies on CRP in bipolar disorder is the increase of CRP levels, particularly in the manic episode as well as the decrease in the CRP levels with the recovery of manic episode. In a meta-analysis by Fernandes et al., CRP levels were reported to be significantly increased in the bipolar disorder manic episode and decreased after the recovery of the episode. No relationship was observed between the CRP levels and the severity of manic and depressive episode. No relationship was observed between the duration of illness and CRP levels. In a follow-up study that included bipolar patients, no correlation was found between high CRP levels and poor prognosis (Fernandes et al., 2016). In a 12-year follow-up study (CRP measured within 30 days after the diagnosis), CRP levels were observed to be higher in bipolar manic episode compared to schizophrenia and depression. At the beginning of the study, high CRP levels were associated with increased mortality. At the end of the study, CRP levels were lower. Additionally, high CRP levels at the beginning of the study were not associated with the recurrent hospital admissions. It was also higher in patients who did not receive antipsychotics (Horsdal et al., 2017). In another study on BD, hsCRP levels were found to be significantly higher in the manic episode compared to control group. In the same study, both YMRS and hsCRP levels were reported to be decreased six weeks after the treatment. However, no change was observed in IL-6, TNF-α and INT-γ levels (Uyanik et al., 2015). In a 1-year follow up study, psychosis patients who had an episode for the first time were administered haloperidol, risperidone, and olanzapine. In the comparison of these patients, significantly higher CRP levels were detected in patients treated with haloperidol at the end of the first three months. This difference disappeared after a year, which suggests that different antipsychotics may have different effects on CRP (Diaz et al., 2010). Studies have shown that lithium and valproic acid may have anti-inflammatory properties (Baumeister et al., 2016; Chiu et al., 2013; Wium-Andersen and Wium-Andersen, 2016).

In our study, there was no significant difference in hsCRP levels between groups 1, 2 and 3. The patient group consisted of patients who received treatment for at least six weeks after the treatment was initiated. As shown in previous studies, treatment may have reduced hsCRP levels in manic patients. In addition, treatment might decrease hsCRP levels independently from treatment response. Our study suggests that no relationship was observed between the CRP levels and the duration and severity of the disease, and number of hospitalization. Additionally, there was not any relationship between CRP levels and sociodemographic variables. One reason for not having a difference in our study may be that the factors, such as age and education, which may affect CRP levels were equalized in all groups and there were no co-morbid psychiatric illnesses and other diseases. In our study, we were not able to perform the measurement at the beginning of the episode. Therefore, we were not able to provide an answer for this.

Changes in the immune system, including proinflammatory processes, were shown to play a role in the etiology of BD (Drexhage et al., 2010). The immune system markers may have potential effects on clinical treatment decisions since these findings are associated with the different treatment responses in bipolar disorder (Li et al., 2015). Thus, the immune system may play an important role in the etiology of BD

and the development of individualized treatment options. However, clinical trials conducted to date have limited numbers of patients and limited numbers of proinflammatory markers.

4.1. Strengths and limitations

To our knowledge this is the first study investigate hsCRP levels, CEA levels and WBCs counts in treatment resistant mania. Our study provides information on inflammatory changes in treatment-resistant cases in which we do not yet have sufficient knowledge of pathophysiology and provides clearer results because it consisted of other non-comorbid groups with a good general medical condition, and groups were equalized regarding sociodemographic variables, which are the strengths of our study.

The first limitation of the study was that we could not evaluate the relationship between the specific symptom clusters due to the limited number of patients. The second limitation was that we were not able to evaluate the changes in the parameters measured through the treatment since no measurement was performed before receiving any treatment.

The third limitation of the study was effect of physical exercise was not considered although it was reported that physical exercises may effect inflammation (Nimmo et al., 2013).

4.2. Conclusion

In conclusion; given the results of our study, the most important finding was that the WBCs counts, and CEA levels were higher in the treatment-resistant group than the other two groups despite the treatment received; and, it was associated with the severity of the disease. The second important finding was that there was no difference in hsCRP levels. The results obtained in this study suggest that different parts of the inflammatory system may be associated with different clinical findings in the manic patients. Firstly, higher WBCs counts and CEA levels may be associated with the severity of the symptoms. Secondly, hsCRP may be associated with acute exacerbation. Thus, treatment should be planned according to the specific sub-groups and symptoms in the development of anti-inflammatory treatment strategy for bipolar disorder. There is a need for new prospective follow-up studies, including a larger size of patients and multiple inflammatory markers, to achieve more accurate information.

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