Simple Peripheral Markers For Inflammation In Drug-Naive, Comorbidity-Free Adolescents With Obsessive-Compulsive Disorder

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ABSTRACT

Obsessive Compulsive Disorder (OCD) is a psychiatric disorder and has different etiopathogenic mechanisms. One of these mechanisms is immunologic factors. Studies on immunologic factors, various cytokines, and cellular elements were investigated. In order to evaluate the immunological factors in psychiatric disorders, hemogram parameters which is a simple and inexpensive method, have been examined. In our study, we aimed to assess hemogram parameters in drug-naive, comorbidity-free adolescents with OCD comparing with controls.

Drug-naive, comorbidity free 31 OCD patients and 47 healthy adolescents without organic or psychiatric disease were included in our study.

Lymphocytes, RDW, platelets, and PCT values of the adolescents with OCD were significantly lower than those of the control group. Hemogram parameters such as WBC, hemoglobin, RBC, HCT, MCV, MCH, MCHC, MPV, Neutrophils, neutrophil–lymphocyte ratio, and the platelet-lymphocyte ratio of the study group and control group were similar.

Our results indicate that lymphocytes and RDW prone to be lower in adolescents with OCD. The results of our study are consistent with the previous studies, showing decreased hemogram parameters associated with inflammation in adolescents with OCD. Our study suggests that we need further follow-up study to enlighten the role of inflammation in the etiology and treatment of OCD comprehensively.

Key words: Obsessive–compulsive disorder, adolescent, inflammation, hemogram parameters, lymphocytes

Introduction

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder with recurrent obsessions and/or compulsions that cause distress, time-consuming and/or significant disruption (1). The prevalence of OCD is %1-3 (2). OCD is divided into 2 groups according to the age of onset; early onset (12-14 years) and late onset (20-22 years) (3,4). Childhood-onset OCD is suggested to be distinguished with late-onset OCD by different etiopathogenic mechanisms (4,5).

The pathophysiology of OCD is still unknown, recent studies have focused primarily on neuro-transmitters, such as serotonin, dopamine, and glutamate (6,7). The previous studies have focused on environmental factors such as psychosocial stressors, trauma, and other infectious and their effects on inflammatory process. The inflammatory processes alter gene expression in a way that influences the serotoninergic and dopaminergic systems, catecholamine modulation, and glutamate pathways (8,9). Although the etiopathology is still unclear, these changes in the paths that process corticostriatal information are thought to be because of epigenetic mechanisms and have a causative role in OCD symptoms (10).

Studies regarding the pathophysiology of OCD have emphasized the importance of immunological mechanisms (10-12). The relation between Group A β-hemolytic streptococcus infections and OCD onset or exacerbation in some children also show that immunological factors play a role in the etiology of OCD (13). Besides to streptococcus infection, other infectious diseases such as Borrelia burgdorferi, mycoplasma, Toxoplasma gondii, or Borna disease virus have been related with OCD (11,14).

Table 1. Socio-demographic Characteristics of the Participants

	Patient group n (%)	Control group n (%)	p
Gender			
Male	15 (48.4)	32 (68.1)	.082*
Female	16 (51.6)	15 (31.9)	
Age	14.90 ± 2.38	14.65 ± 1.37	.609**
BMI	19.50 ± 2.62	19.97 ± 3.25	.597**

BMI: body mass *Chi-square test ** Student's t-test

PANDAS (Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection) is a well-known disease which develops as an autoimmune response following to streptococcal infection. Role of immunologic mechanisms in the etiology of OCD is increasing interest even though the PANDAS criteria are not fully met (14). Some studies have mentioned a dysregulation of the immune function in OCD based on alterations in innate and adaptive immune-related parameters such as proinflammatory cytokine levels (15-17), antineuronal antibodies (12,18,19), or hypothalamus-pituitary-adrenal axis dysregulation (20,21). As it has been shown in other psychiatric disorders, HPA axis dysregulation is exhibited in OCD patients and specifically increased levels of cortisol (22-26), and plasma ACTH (22) have been shown.

In the literature, it is seen that inflammatory processes in OCD are investigated in various aspects. The processes used in researches are difficult and expensive techniques to use in daily practice. On the other hand, several hemogram parameters have been investigated to evaluate the inflammatory states in both organic (27,28) and psychiatric disorders in recent publications. There are several studies investigating the hemogram parameters of adult patients with a major depressive disorder (29,30), bipolar disorder (31) and schizophrenia (32). Basic points in the investigation of these parameters are based on the ease of use and economical in daily practice. In the studies conducted on this subject, it is seen that there is only one study evaluating hemogram parameters in adult OCD patients (33). There is no study evaluating hemogram parameters in adolescents with OCD in terms of inflammation in the literature. Since one of the most common onsets of OCD is the adolescence period, the investigation of the relationship between inflammation and OCD through hemogram parameters in this period may provide important contributions to the literature.

We aimed to evaluate the hemogram parameters of treatment-naive and comorbidity-free adolescent OCD patients by comparing controls to determine the role of inflammation in OCD.

Materials and Methods

Study Population: Our sample consisted of 31 adolescent patients with OCD and 47 controls. The study group composed of the patients who admitted to the Child and Adolescent Mental Health Outpatient Clinic of Van Training and Research Hospital between February 1 and November 31, 2017, and diagnosed with OCD. The clinical diagnosed was made by researchers with the help of semi-structured interviews. The control group consisted of the voluntary adolescents who were referred to a pediatrics outpatient clinic without physical or psychiatric diseases. The controls and the study subjects were similar regarding age, sex, and body mass index (BMI). Before starting the study, Ethics Committee approval was obtained from the Van Training and Research Hospital Ethics Committee (January 26, 2017, no.: 2017/1). All participants in the study and their relatives were informed about the study, and their informed consent was obtained. Blood samples of the adolescent with OCD were taken from the same nurse from antecubital vein before starting the treatment. The exclusion criteria were determined as having the comorbid mental disorder, chronic or inflammatory diseases, local or systemic infection in the last month, using alcohol or substance, smoking and using any medical drug. Obesity was also one of the exclusion criteria because chronic systemic inflammation has a role in the etiopathogenesis of metabolic syndrome in obesity (34). Children's height and weight measurements were taken by the same child nurse and BMI were calculated by the researchers initially. Participants filled out a ınformation collection form regarding their sociodemographic characteristics. Diagnostic interviews of adolescents were conducted with KSADS (Affective Disorders and Schizophrenia Schedule for School Age Children Present and Lifetime) by researchers.

Table 2. Hemogram parameters for paricipants

Variables	Patient group		Control group		t	p
	Mean	SD	Mean	SD		
WBCs ($10^3/\mu L$)	7.01	1.66	7.35	1.56	-0.766	.444**
Hemoglobin (g/dL)	14.98	1.25	14.59	1.14	1.414	.161*
RBCs ($10^6/\mu L$)	5.35	0.45	5.31	0.31	0.398	.692*
HCT (%)	43.90	3.10	43.09	2.73	1.216	.228*
MCV (fL)	82.32	5.67	81.34	4.09	0.888	.377*
MCH (pg)	28.10	2.32	27.53	1.71	1.240	.219*
MCHC (g/dL)	34.12	1.11	33.83	1.09	1.137	.259*
MPV (fL)	10.05	0.90	9.88	1.09	0.683	.496*
RDW (%)	12.81	0.95	13.48	1.10	-2.768	.007*
Neutrophils ($10^3/\mu L$)	3.84	1.30	3.81	1.21	-0.266	.791**
Lymphocytes ($10^3/\mu L$)	2.48	0.66	2.80	0.58	-2.216	.027**
Platelets ($10^3/\mu L$)	263.90	54.74	309.63	67.14	-3.160	.002*
PCT (%)	0.26	0.05	0.39	0.47	-3.446	.001**
NLR	1.63	0.63	1.57	1.19	-1.486	.137**
PLR	112.76	34.60	114.29	29.99	-0.207	.837*

Notes: The data are expressed as the mean ± standard deviation(SD). * Student's t-test. ** Mann–Whitney U-test

Data Collection Materials

Sociodemographic Form: The sociodemographic data were collected by the help of a self-report survey created by researchers regarding participants socio-demographic characteristics, such as age, sex, and previous or current physical diseases, smoking, alcohol and/or drug use.

Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL): K-SADS-PL is developed by Kaufman et al. (35) and has been translated into Turkish by Gökler et al. (36). It is a semi-structured diagnostic interview, which helps clinicians to make a diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders.

Sampling and Analyses of Hemogram Blood Test: Blood samples were taken early in the morning at least after 12 hours of fasting. Blood samples of the subject were received from their antecubital veins and performed in the Biochemical Laboratory using a Sysmex XN1000.

Statistical Analysis: Statistical analysis was performed with SPSS 22. The mean and the standard deviation values with minimal and maximal levels were used for the statistical expression of the groups. Student's t-test was used for comparing of the continuous and normally distributed variables between the groups, as the Mann–Whitney U test was performed the comparison of abnormally distributed and non-parametric variables. The value of Cohen's d and the effect-size correlation were calculated using the means and standard deviations of the two groups.

Chi-square test was used for comparing of categorical variables of the groups. A p value of < 0.05 was evaluated as statistically significant.

Results

Socio-demographic features of groups such as age, gender and BMI of study group were similar. The mean ages of study group (14.90±2.38) and the controls (14.65±1.37) were similar; 48.4% (n=15) of the patient group and 68.1% (n=32) of the control group were boys. And also there was no difference between the groups in term of gender. The BMI of patient group (19.50±2.62) and the control group (19.97±3.25) were similar in terms of average. The characteristics of the participants are shown in (Table 1).

Hemogram parameters for participants are shown in (table 2). Lymphocytes (Cohen's d=-0.51, effect size r=-0.24), RDW (Cohen's d=-0.65, effect size r=-0.30), platelets (Cohen's d=-0.74, effect size r=-0.34), and PCT (Cohen's d=-0.38, effect size r=-0.19) values of the adolescents with OCD were significantly lower than those of the control group. WBC, hemoglobin, RBC, HCT, MCV, MCH, MCHC, MPV, Neutrophils, NLR, and PLR parameters were similar between two groups.

Discussion

In our study, we aimed to evaluate hemogram parameters to understand the inflammation state of

adolescents with OCD by comparing controls. The results of our study showed that the lymphocyte and RDW values in adolescents with OCD were lower than those of controls and there was no difference between the groups on NLR, PLR, and MPV which are other essential hemogram parameters explored in psychiatric disorders.

Inflammation plays a critical role in OCD etiology (10-12). HPA axis disorders, various cytokines, and cellular elements were investigated in various studies in this field (33,37). In the study investigating the HPA axis, Gustafsson et al. showed a similar hypercortisolism in child and adolescent populations as previously demonstrated in adult OCD patients (23). When we look at cytokine studies in OCD, a study conducted by Fluidman et al. has been reported an increase in cortisol levels and a significant decrease in TNF-α and IL-6 levels in OCD patients after exposure therapy (24). In another study, Denys et al. found a marked decrease in TNF-α and NK activity levels in OCD patients compared to controls (37). The other study reported higher levels of IL-1 and lower levels IL-2, IL-6 and TNF-α in OCD patients (38). A meta-analysis of 12 studies related to proinflammatory cytokines in OCD patients demonstrated a significant reduction in IL-1β levels in OCD patients relative to controls, while there were no differences in TNF-α and IL-6 plasma levels (15). In the literature, it is mentioned that hypercortisolism suppresses the immune system and reduces some cytokines (39,40). The results of this study are compatible with the previous studies indicating decreased hemogram parametres associated with inflammation in adolescents with OCD. So, we deduced that adolescent OCD is related to inflammation, although the exact nature of the relation and the mechanisms involved are not yet understood exactly.

In the study evaluating hemogram parameters in adults with OCD, Atmaca et al. reported that there were no significant differences between groups regarding hemogram parameters except neutrophil count. In this study, there was no difference between lymphocyte counts while neutrophil counts were low (33). In the study of Denny et al., there was no significant difference in hemogram parameters of OCD patients when compared to controls. In our study, lymphocyte counts were found to be significantly lower than the control group, and there was no significant difference in other blood cell counts related to inflammation from the control group. Regarded as a result similar to previous studies this low rate may be related to the elevated levels of cortisol which is an immune suppressor hormone in OCD.

On the other hand, publications evaluating the reciprocal relations between lymphocytes and pro-inflammatory cytokines such as IL-1 and TNF-αare present in the literature. There are publications investigating the relationship between TNF-α and central neurotransmitters, especially serotonin. Therefore, it can be evaluated that a significant decrease in lymphocyte in our study is a result parallel to publications that indicate low levels of TNF- levels in OCD. This low level may indirectly affect central neurotransmitters. Investigations of lymphocyte-cortisol hormone and lymphocyte-proinflammatory cytokine associations in larger studies may provide significant contributions to literature.

Another remarkable result of our study was that the RDW levels were significantly lower in OCD group than the control group RDW, one of the hemogram parameters is calculated by an automatic hematology analyzer and predicts erythrocytic variability. Increased RDW level reflects inefficient erythropoiesis, which may be a result of systemic inflammation (41). In a study exploring inflammation in autistic children, there was no significant difference in mean RDW of the patient group compared to controls (42). In a study evaluating adolescent patients with depression, there was no significant difference in terms of RDW levels when compared to the control group (43). RDW has been investigated children with acute appendicitis (27), acute rheumatic carditis (44) and sepsis (45). RDW which is an indicator of inflammation in organic diseases in children is not evident in psychiatric disorders. The results of our study showed that RDW was significantly lower in the patient group, consistent with previous studies indicating that the immunity might be suppressed

NLR, PLR, and MPV are the prominent hemogram parameters to assess inflammation in psychiatric disorders. In the study evaluating hemogram parameters in adults with OCD, Atmaca et al. reported that there were no significant differences between groups regarding hemogram parameters except neutrophil count (33). In a study conducted in patients with adolescent depression, while only NLR in the patient group was significantly higher than the control group, there were no significant differences between the two groups regarding PLR and MPV (43). The results of our study can be interpreted as similar to the studies in which no significant difference in these variables was found with other psychiatric disord

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contribute more information to literature.

The most important limitation of our study was the lack of a scale that assessed the severity of OCD. The second limitation of our study is that our findings

cannot be generalized to all OCD patients because our sample is relatively small. Another limitation of our study is that we only examined complete blood count; HPA axis and other parameters associated with inflammation were not evaluated. Not being sensitive or specific of the hemogram parameters which were assessed in our study for OCD diagnosis may be regarded as a limitation. The relationship between RDW and iron deficiency may also be considered as another limitation of our study. However, in our study, the use of a semi-structured scale for diagnosis, inclusions of patients who have not started any medication and did not have comorbidities are considered strength aspects of our study.

In this study, we reported that lymphocytes and RDW tend to be lower in adolescents with OCD. A simple, cheap method hemogram may also help clinicians assessing the OCD. We propose the clinicians that this simple blood test can give an idea about the presence of the inflammatory process in OCD. However, studies on these parameters in larger samples with OCD patients will contribute more information to literature. Further follow-up studies are required to enlighten the role of inflammation in the etiology and treatment of OCD.

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