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The neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in adolescent obsessive-compulsive disorder: Does comorbid anxiety disorder affect inflammatory response?☆

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ABSTRACT

Recent adult etiologic studies indicated evidence linking increased inflammatory parameters with psychiatric disorders. The neutrophil-lymphocyte ratio and platelet-lymphocyte ratio are easily obtainable clinical markers of inflammation and have been found to be increased in various medical and mental disorders. In this study, we aimed to investigate the neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in adolescents with obsessive-compulsive disorder (OCD). Secondarily, the effect of comorbid anxiety disorder with OCD on the inflammatory response was investigated. Sixty drug-naïve adolescents with OCD aged 12 to 18 years were enrolled in the patient group. Twenty-three of the OCD group had comorbid anxiety disorder (AD) and 37 had no comorbidities. One hundred twenty-eight adolescents in the same age range with no psychiatric disorders were recruited as the healthy control group. The severity of OCD symptoms was evaluated using the Children's Yale-Brown Obsessive Compulsive Scale. There were statistically significant differences in the neutrophil-lymphocyte ratio, white blood cell, neutrophil, and platelet counts among the three groups, even after adjusting for age and sex. The adolescents with OCD and AD had the highest neutrophil-lymphocyte ratio and white blood cell counts. A comorbid anxiety disorder diagnosis in addition to obsessive-compulsive disorder may increase the inflammatory response.

1. Introduction

Obsessive-compulsive disorder (OCD) is characterized by the presence of obsessions and/or compulsions that cause functional impairment in all ages (APA, 2013). In childhood, these symptoms may appear as clinical features of Pediatric Autoimmune Neuropsychiatric Disorders Association with Streptococcal Infections (PANDAS) or Pediatric Acute-onset Neuropsychiatric Syndrome (PANS), which are clearly immunity-based disorders (Swedo, 2010). Moreover, childhood-onset OCD is often accompanied by tic orders, which are also assumed to be related to immune abnormalities (Swedo, 2010). These data raise the question of whether pure OCD in children and adolescents is associated with immune processes (Morer et al., 2008).

Recently, it has been shown that the immune system and nervous system are in complex interaction in health and disease (Kenney and Ganta, 2014). Immune cells and mediators are involved in critical mechanisms of normal brain development and functioning (Kenney and Ganta, 2014). Abnormalities in the interaction of these two systems may result with neuropsychiatric disorders such as OCD (Wraith and Nicholson, 2012). Recent adult studies suggest the role of immune dysregulation in the underlying pathophysiology of OCD (Gray and Bloch, 2012) due to evidence of increased acute phase reactants, abnormal levels of inflammatory cytokines and activated auto antibodies (Gray and Bloch, 2012; Murphy et al., 2010; Swedo, 2010). However, discrepant results were obtained from these studies. OCD is often accompanied by anxiety disorders, major depression, and tic disorders. These high comorbidity rates of OCD are a restriction for obtaining homogeneous samples. The conflicting results may be due to the presence of comorbid psychiatric disorders, and the medication status of samples across these studies.

There is scant literature related to immune dysregulation in children and adolescents with OCD, and that exists also presents diverging results. Comorbid tic disorder is one of the main confounding factors of these limited studies. To date, only two studies have examined the

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association between ILs in pure OCD in childhood (Sivri et al., 2018; Şimşek et al., 2016). Increased TNF-α and decreased IL-12 were found in those studies (Sivri et al., 2018; Şimşek et al., 2016). Although childhood and adolescent-onset OCD have similar clinical features with adult-onset OCD, it has been suggested that early-onset OCD may have a distinct underlying pathophysiology (Cosco, 2018). This situation may be related with the high rate of comorbidities in OCD (APA, 2013). Approximately two-thirds of the adolescents with OCD were also diagnosed as having anxiety disorder; additionally a close relationship between panic disorder and OCD was shown (Rapoport and Swedo, 2003). Chronic, severe, and excessive anxiety comprise part of both OCD and AD diagnoses. Individuals with OCD and/or AD experience more debilitating anxiety than healthy people with a normative status of anxiety (APA, 2013). Recent studies have shown that chronic anxiety affects cellular and humoral immunity deleteriously (Boscarino, 2004; Sareen et al.,2005; Schneiderman et al., 2005). Although inflammatory status in AD has not been investigated sufficiently (Renna et al.,2018), a few studies with small sample sizes showed increased inflammatory activity in panic disorder (Hoge et al., 2009) and generalized anxiety disorder (Bankier et al., 2008). Inflammatory dysregulation in OCD or AD may be related with a defensive response of the body to the chronic and excessive state of anxiety (Renna et al.,2018).

The neutrophil-lymphocyte ratio is a ratio that is calculated from counts of the products of two different but complementary immune pathways (Azab et al., 2011). Thus, the neutrophil-lymphocyte ratio shows both immune pathways and may be more informative than other familiar parameters for chronic low-grade inflammation (Azab et al., 2011; Gibson et al., 2007). Neutrophil-lymphocyte ratios were found elevated in patients with Alzheimer's disease (Kuyumcu et al., 2012), major depression (Aydın-Sunbul et al., 2016), and schizophrenia (Semiz et al., 2014) compared with healthy controls. The platelet-lymphocyte ratio, a reliable inflammatory indicator (Balta and Ozturk, 2015), has also been evaluated and was found to be elevated in psychiatric diseases such as major depressive disorder, bipolar disorder, and schizophrenia (Kayhan et al., 2017).

To date, no study has evaluated the neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in adolescents with OCD. The aim of the study was to investigate immune dysregulation in adolescents with OCD who were drug naïve and had no additional psychiatric disorders (except anxiety disorder), by assessing the neutrophil-lymphocyte ratio and the platelet-lymphocyte ratio). Secondarily, the effect of comorbid anxiety disorder with OCD on the inflammatory response was investigated. We hypothesized that the neutrophil-lymphocyte ratio and the platelet-lymphocyte ratio would be higher in the OCD group compared with healthy controls.

2. Method

2.1. Sample and procedure

The study was conducted at the Child and Adolescent Psychiatry Clinic of a Training and Research Hospital. Sixty adolescents aged 12 to 18 years who were admitted to the outpatient clinic with OCD symptoms between February 2017 and February 2018 and were diagnosed as having OCD in the clinical follow-up were enrolled in the study. One hundred twenty-eight adolescents who were admitted to other pediatric policlinics at the same hospital and had no medical or psychiatric disease as assessed using the Kiddie and Young Adult Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS P/L) (Gökler et al., 2004; Kaufman et al., 1997) were recruited as the healthy control group. All participants were screened using the K-SADS P/L for comorbidities and the diagnoses of OCD were made based on the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM 5) criteria through clinical interviews. Adolescents with psychiatric comorbidities other than anxiety disorder were excluded. Additionally, the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) was applied to the patient group.

The exclusion criteria for both groups were as follows: having acute or chronic medical disorder, presence of comorbid psychiatric other than anxiety disorders, presence of neurologic or genetic disorders, current use of any kind of medications, use of any psychotropic drugs in the last 3 months before blood sampling, obesity (body mass index [BMI] $> 30\,kg/m^2$), smoking more than 15 cigarettes per day.

A sociodemographic data form was completed by the researchers using the information obtained from the participants. Written and verbal consent were obtained from the parents and adolescents. The study complied with the Declaration of Helsinki. Ethics committee approval of the study was granted from Tepecik Training and Research Hospital Clinical Trials Ethics Committee.

Seventy-eight adolescents were assessed for inclusion in the OCD group. Adolescents with subthreshold OCD symptoms (n = 2) and those who refused to participate in the study (n = 4) were excluded. When we applied the exclusion criteria to the remaining 72 adolescents, 8 adolescents were removed from the study due to accompanying psychiatric disorders other than anxiety disorders (depressive disorders n = 7; post traumatic disorder n = 1). After the data were analyzed, 4 adolescents' data were excluded due to extreme values. After all exclusions, 60 drug-naïve adolescents with OCD aged 12 to 18 years with no psychiatric comorbidities other than anxiety disorders were recruited as the patient group. Twenty-three of the patient group had comorbid anxiety disorders including social anxiety disorder (n = 10), generalized anxiety disorder (n = 2), specific phobia (n = 6), and anxiety disorder not otherwise specified (n = 5). The remaining 37 adolescents with OCD were comorbidity free.

2.2. Measurements

2.2.1. Kiddie and young adult schedule for affective disorders and schizophrenia present and lifetime version (K-SADS P/L)

This is a semi-structured interview form, which was developed by Kauffman et al. in order to examine present and lifetime psychopathologies in children and adolescents aged 6 to 18 years (Kauffman et al., 1997). The Turkish translation, reliability and validity study of K-SADS P/L was conducted by Gökler et al. (Gökler et al., 2004).

2.2.2. Children's Yale-Brown obsessive compulsive scale (CY-BOCS)

The CY-BOCS is a 10-item, semi-structured, physician-administered interview developed by Scahill et al. (1997). The interview provides a comprehensive checklist of commonly endorsed obsessions and compulsions, which are rated individually based on frequency, distress, efforts to resist, perceived control, and interference. The scores of the interview are combined to provide a composite severity score. The reliability and validity of the CY-BOCS has been established for the Turkish population (Yücelen et al., 2000).

2.2.3. Blood sample procedure

All participants underwent blood sampling after 12 hours of fasting between 08:30 and 10:30. Neutrophil-lymphocyte ratios and platelet-lymphocyte ratios were calculated using absolute cell counts.

2.3. Statistics

SPSS ver.18.0 for Windows software (SPSS, Inc. Chicago, IL, USA) was used for statistical analyses. The sociodemographic and clinical categorical variables of the patient and control groups were evaluated using number and percentage values. The Chi-square test was used for the comparison of categorical variables. The normality of the data distributions was assessed using the Shapiro–Wilk test. Variables that were normally distributed were compared using Student's *t*-test for two groups and one-way ANOVA for three groups. The Kruskal–Wallis and

the Mann–Whitney *U* test were used when normal distribution was not established. Multivariable analysis, adjusting for potential confounding factors (age and sex) was performed using analysis of variance (ANCOVA) to assess the differences in complete blood count parameters, and neutrophil-lymphocyte ratios and platelet-lymphocyte ratios between the study group. Before ANCOVA analysis, variables that had non-normal distribution were logarithmically transformed. In addition, the significant main effects for both groups were examined using Bonferroni corrections for each test to reduce type I errors. A value of $P < 0.05$ (two tailed) was considered to indicate significance. Bonferroni correction p values were determined based on the number of confounding variables. Accordingly, *P* values were 0.017 for complete blood count parameters, neutrophil-lymphocyte ratios and platelet-lymphocyte ratios. Correlation analysis was performed using Pearson's test for normally distributed variables, and Spearman's test in the presence of at least one non-normally distributed variable.

3. Results

The comparison of total OCD group (with or without AD) and healthy controls (HCs) revealed similar age and sex distributions but significantly higher numbers of white blood cells, neutrophil, platelets and the neutrophil-lymphocyte ratio and platelet-lymphocyte ratio values in the study group, as shown in Table 1.

When we analyzed the study group in terms of, only OCD, OCD + AD and HCs were similar in terms of age, sex, and education. The results are shown in Table 2.

Comparisons of blood count parameters between adolescents with OCD, OCD + AD and healthy controls are shown in Table 3. Due to binary comparisons, adolescents with OCD + AD had statistically significant higher white blood cells, neutrophils, and log neutrophil-lymphocyte ratio than adolescents with pure OCD.

ANCOVA was used to assess the confounding effect of age and sex on the results, the significant differences did not change among the three groups in terms of white blood cells, (F:13.129, $P < 0.001$); neutrophils (F:17.849, $P < 0.001$), log platelet (F:5.400, $P = 0.005$), and the log neutrophil-lymphocyte ratio (F:7.427, $P = 0.001$).

Table 1
Demographical and clinical characteristics and blood count parameters of adolescents with OCD and healthy controls.

Variables	Patient (n = 60) Mean ± SD Median(IR)	Control (n = 128) Mean ± SD Median (IR)	*t/z/x2*	*P*
Age	14.61 ± 1.81	14.37 ± 1.80	.853	0.395[a]
Female n %	43 (71.66%)	101 (78.91%)	1.194	0.274[b]
Education				
0–8 years	7 (11.63%)	13 (10.15%)	.098	0.802[b]
>8 years	53 (88.37%)	115 (89.85%)		
CYBOCS total scores	18.56 ± 4.09	2.98 ± 0.73	41.828	<0.001 [a]
Compulsion score	9.06 ± 2.21	1.51 ± 0.5	36.698	<0.001 [a]
Hb (g/dl)	13.11 ± 1.17	13.19 ± 1.39	−0.385	0.700[a]
Htc (%)	40.87 ± 8.25	40.11 ± 6.53	.678	0.799[a]
WBC (103/ul)	8.632 ± 2.258	7.220 ± 1.720	4.731	<0.001[a]
Neutrophill (103/ul)	5.139 ± 2.058	3.984 ± 1.076	5.050	<0.001[a]
Lymphocyte (103/ul)	2.677 ± .925	2.675 ± .829	−0.019	0.985[a]
Platelet (103/ul)	321.00 (86.25)	269.50 (90.00)	−3.479	0.001[c]
MPV	8.931 ± 1.141	8.867 ± .867	.428	0.669[a]
NLR	190.91 (148.00)	148.81 (0.73)	−2.996	0.003[c]
PLR	118.02 (49.96)	104.61 (44.66)	−2.872	0.004[c]

(a) Student's *t*-test; (b) Chi-square test; (c) Mann–Whitney *U* test.
OCD, obsessive compulsive disorder; CYBOCS, Children's Yale-Brown Obsessive Compulsive Scale; HC, healthy control.

4. Discussion

The present study investigated whether the neutrophil-lymphocyte ratio and platelet-lymphocyte ratio were related to OCD and OCD + AD in adolescents. The results indicated that there was a statistically significant difference in the neutrophil-lymphocyte and platelet lymphocyte ratios between adolescents with OCD and healthy controls, and adolescents with OCD + AD had higher neutrophil-lymphocyte ratios than controls and adolescents with pure OCD.

There have been a limited number of studies reporting altered levels of inflammatory biomarkers in children and adolescents with OCD. In Sivri et al.'s study, it was found that levels of serum TNF-alpha, which is an important pro-inflammatory cytokine, were significantly higher in the OCD group than in the control group (Sivri et al., 2018). However, the results of adult studies have not been consistent. Some studies found no increase in inflammatory cytokines (Carpenter et al., 2002; Denys et al., 2004), possibly due to the confounding effects of depression and medication as explained in a recent meta-analysis (Gray and Bloch, 2012). The results of the current study are compatible with studies that indicated an increase in inflammatory cytokines in drug-free patients with OCD (Konuk et al., 2007; Rao et al., 2015), and a prior study that reported the absence of a correlation between antidepressant medication dose and cytokines and chemokines (Fontenelle et al., 2012).

The neutrophil-lymphocyte ratio is inexpensive, and easily evaluated. It is calculated from the white blood cell count and is an indicator of the systemic inflammatory response. Neutrophils discharge inflammatory cytokines and these cytokines may cause immune dysregulation and cell dysfunction in various organs, including regions of the brain (Kenney and Ganta, 2014).

Chronic inflammation (e.g., allergic inflammation) was found to be related important brain areas in OCD. It has also been with associated with serotonergic and catecholaminergic systems, which have significant roles in executive functioning and OCD (Kühn et al., 2013). Recent longitudinal and experimental studies showed bidirectional immune-to-brain connections in psychiatric disorders in both humans and animals. Also, it was found that peripheral inflammatory signals could cause psychiatric symptoms and vice versa (Engler et al., 2017; Kiecolt-Glaser et al., 2015; Miller and Raison, 2015; Stewart et al., 2009). In animal studies, it was shown that chronic inflammation also activated the limbic regions of the brain, which leads to increased anxiety and avoidance behaviors (Costa-Pinto et al., 2005; Tonelli et al., 2009). In a recent study, it was found that chronic allergic inflammation was related with neuronal activity changes in the anterior cingulate cortex and the prefrontal cortex (Rosenkranz et al., 2005), which are associated with OCD. Accordingly, the results of the present study may contribute to this potential role of inflammation mechanisms in OCD.

Conflicting results have been reported current literature in inflammation of AD (Weizman et al., 1999; Brambilla et al., 1994; Hoge et al., 2009). In Hoge et al.'s (2009) study, increased cytokine levels were found in panic disorder (Hoge et al., 2009). A population-based study from Switzerland showed low-grade chronic inflammation in agoraphobia (Wagner et al., 2015) while Fluitman et al., (2010) found no cytokine difference between individuals with generalized anxiety disorder and healthy controls. In a recent review, the association between anxiety disorders and inflammatory response was investigated and it was determined that elevated and dysregulated anxiety was a fundamental diagnostic criterion for AD and OCD, and was associated with chronic low-grade systemic inflammation (Renna et al., 2018).

In the present study, adolescents with OCD and AD had the highest inflammatory response. It may be related with exacerbated stress response in these adolescents. Having these diagnoses together may cause a dysregulated and excessive inflammatory response. Basic cognitive distortions such as worry, self-criticism or intolerance to uncertainty were found similar in these two disorders (McEvoy et al.,2013;

Table 2
Demographical and clinical characteristics of adolescents OCD without comorbidity only, OCD with anxiety disorder and healthy controls.

Variables	Groups	n	Mean ± Std. Deviation	Min–Max	Median (Q_1–Q_3)	Test statistics†	*P*	Multiple comparisons
Age	O	37	14.41 ± 1.85	12–18	14 (13–16)			
	A	23	14.96 ± 1.74	12–18	16 (13–16)	2.050	0.359	–
	C	128	14.38 ± 1.81	12–17	14 (12.25–16)			
	A	23	9.35 ± 2.53	5–13	8 (8–12)	132.644		
	C	128	1.52 ± 0.5	1–2	2 (1–2)			

		Male (n = 44)		Female (n = 144)		Test statistics*	*P*	
Groups		**n**	(%)	**n**	(%)			
Gender	O	9	20.5	28	19.4	2.060	0.357	
	A	8	18.2	15	10.4			
	C	27	61.3	101	70.2			

		0–8 years (n = 20)		>8 years (n = 168)				
Education	O	6	30.0	31	18.5			
	A	1	5.0	22	13.1	2.200	0.333	
	C	13	65.0	115	68.5			

n: Sample size; O: OCD without comorbidity Only OCD; A: OCD with anxiety disorder; C: Healthy Controls.
*$P < 0.05$. **: $P < 0.01$. ***: $P < 0.001$
* Pearson Chi-square test (Column percentages are given).
† Kruskal Wallis Test.

Sowislo and Orth, 2013; Carleton, 2012). Dysregulated cognitive activation is associated with extending physiologic activation and this may the affect inflammatory and immunologic response. Dysregulated psychological and physiologic activation may also be related with hypothalamic-pituitary adrenal axis dysregulation (Michopoulos et al., 2017) and all of these dysregulated processes contribute to a state of low-grade systematic inflammation. In the current study, it was found that having only OCD might not cause the same inflammatory response as when both OCD and AD are present. This may be related with the fact that individuals with OCD and AD may have experienced more dysregulated cognitive actions than individuals with only OCD. The increased inflammatory response may be associated with this more dysregulated cognitive action.

The strongest aspect of the present study is the inclusion of adolescents who did not use psychiatric drugs and had no comorbidities (except anxiety disorder), thereby preventing confusion of the effects of medications and depression. OCD has been investigated as a multidimensional psychiatric disorder. Different symptom dimensions were not evaluated in the current study, and the relation between the neutrophil-lymphocyte ratio and the platelet-lymphocyte ratio and

Table 3
Comparisons of blood count parameters between adolescents OCD without comorbidity only, OCD with anxiety disorder and healthy controls.

Variables	Groups	n	Mean ± Std. Deviation	Min–Max	Median (Q_1–Q_3)	Test statistics	*P*	Multiple comparisons
Hb (g/dl)	O	37	13.2 ± 1.4	9.4–16.7	13.1 (12.33–14.08)		0.884	–
	A	23	13.05 ± 1.16	10–14.9	12.8 (12.3–14.2)	0.124+		
	C	128	13.16 ± 1.2	10.3–16.8	13 (12.4–13.8)			
Htc (%)	O	37	40.12 ± 6.53	28.9–98.4	39.4 (37–42.2)		0.848	–
	A	23	42.35 ± 12.68	31–98.4	39.7 (37.6–43.7)	0.329†		
	C	128	39.96 ± 3.33	32.4–50.2	39.4 (38.05–41.7)			
WBC (10^3/ul)	O	37	7.22 ± 1.72	1.33 -12.4	7.1 (6.1–8.69)		**<0.001****	**A–C: <0.001**
	A	23	9.59 ± 2.29	6.23–14.8	9.53 (7.6–10.9)	16.638+		O–C: 0.052
	C	128	8.04 ± 2.05	3.7–13.8	7.76 (6.5–9.62)			**O–A: 0.006**
Neutrophil (10^3/ul)	O	37	3.98 ± 1.08	1.9–7.1	1.49 (1.16–1.9)		**<0.001****	**A–C: <0.001**
	A	23	6.12 ± 2.31	3.14–12	2.26 (1.55–3.56)	20.256†		O–C: 0.264
	C	128	4.53 ± 1.64	1.4–9	1.83 (1.07–2.45)			**O–A: 0.031**
Lymphocyte (10^3/ul)	O	37	2.68 ± 0.83	1.2–5.66	2.5 (2.13–3.12)		0.905	–
	A	23	2.59 ± 0.78	1.38–4.59	2.5 (2.1–2.9)	0.200†		
	C	128	2.72 ± 1.01	1.52–5.8	2.42 (2–3.04)			
logPlatelet (10^3/ul)	O	37	2.44 ± 0.1	2.21–2.63	2.43 (2.37–2.51)		**0.002****	A–C: 0.098
	A	23	2.48 ± 0.09	2.34–2.7	2.47 (2.41–2.54)	6.598+		**O–C: 0.003**
	C	128	2.5 ± 0.08	2.29–2.65	2.51 (2.43–2.55)			O–A: 0.840
MPV	O	37	8.87 ± 0.87	7–11.8	9 (8.3–9.4)		0.963	–
	A	23	8.88 ± 0.95	7.7–11.2	8.8 (8.1–9.4)	0.076†		
	C	128	8.96 ± 1.26	7.2–11.6	8.8 (7.8–9.75)			
logNLR	O	37	0.18 ± 0.15	-0.2–0.61	0.17 (0.07–0.28)		**<0.001****	**A–C: 0.004**
	A	23	0.36 ± 0.24	-0.16–0.76	0.35 (0.19–0.55)	11.412+		O–C: 0.625
	C	128	0.22 ± 0.21	-0.21–0.56	0.26 (0.03–0.39)			O–A: 0.057
logPLR	O	37	2.03 ± 0.13	1.76–2.35	2.02 (1.95–2.12)		0.056	–
	A	23	2.09 ± 0.1	1.88–2.32	2.06 (2.03–2.15)	3.584+		
	C	128	2.09 ± 0.15	1.61–2.35	2.09 (1.97–2.19)			

n: Sample size; O: OCD without comorbidity Only OCD; A: OCD with anxiety disorder; C: Heathy Controls.
*: $P < .05$. **: $P < .01$. ***: $P < .001$.
+ One-way ANOVA test.
† Kruskal Wallis test.

symptoms was not investigated.

The present study is one of the first studies in the literature to evaluate the neutrophil- lymphocyte ratio and platelet-lymphocyte ratio for the potential role of inflammation in adolescents with OCD and AD. Longitudinal studies are needed to determine if there is an inflammatory role in the underlying mechanisms of OCD and AD, which may assist in diagnosis and treatment. Further studies are needed to investigate the effectiveness of new anti-inflammatory agents, which may be effective for the treatment of OCD and AD, and show the potential role of inflammation in the etiology of OCD and AD.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.131.

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental disorders: DSM 5 Washington (DC): American Psychiatric Association. APA Press.

Aydın-Sunbul, E., Sunbul, M., Yanartas, O., Cengiz, F., Bozbay, M., Sari, I., Gulec, H., 2016. Increased neutrophil/lymphocyte ratio in patients with depression is correlated with the severity of depression and cardiovascular risk factors. Psychiatry Investig. 13, 121–126.

Azab, B., Jaglall, N., Atallah, J.P., Lamet, A., Raja-Surya, V., Farah, B., Lesser, M., Widmann, W.D., 2011. Neutrophil-lymphocyte ratio as a predictor of adverse outcomes of acute pancreatitis. Pancreatology 11, 445–452.

Balta, S., Ozturk, C., 2015. The platelet-lymphocyte ratio: a simple, inexpensive and rapid prognostic marker for cardiovascular events. Platelets 26, 680–681.

Bankier, B., Barajas, J., Martinez-Rumayor, A., Januzzi, J.L., 2008. Association between C-reactive protein and generalized anxiety disorder in stable coronary heart disease patients. Eur. Heart. J. 29, 2212–2217.

Brambilla, F., Bellodi, L., Perna, G., Bertani, A., Panerai, A., Sacerdote, P., 1994. Plasma interleukin-1 beta concentrations in panic disorder. Psychiatry Res. 54 (2), 135–142.

Boscarino, J.A., 2004. Posttraumatic stress disorder and physical illness: results from clinical and epidemiologic studies. Ann. NY Acad. Sci. 1032, 141–153.

Carpenter, L.L., Heninger, G.R., McDougle, C.J., Tyrka, A.R., Epperson, C.N., Price, L.H., 2002. Cerebrospinal fluid interleukin-6 in obsessive–compulsive disorder and trichotillomania. Psychiatry Res. 112, 257–262.

Carleton, R.N., 2012. The intolerance of uncertainty construct in the context of anxiety disorders: theoretical and practical perspectives. Expert Rev. Neurother. 12, 937.

Costa-Pinto, F.A., Basso, A.S., Britto, L.R., Malucelli, B.E., Russo, M., 2005. Avoidance behavior and neural correlates of allergen exposure in a murine model of asthma. Brain Behav. Immun. 19, 52–60.

Cosco, T.D., Pillinger, T., Emam, H., Solmi, M., Budhdeo, S., Matthew Prina, A., Maes, M., Stein, D.J., Stubbs, B., Carvalho, A.F., 2018. Immune aberrations in obsessive-compulsive disorder: a systematic review and meta-analysis. Mol. Neurobiol. https://doi.org/10.1007/s12035-018-1409-x.

Denys, D., Fluitman, S., Kavelaars, A., Heijnen, C., Westenberg, H., 2004. Decreased TNF-alpha and NK activity in obsessive–compulsive disorder. Psychoneuroendocrinol. 29, 945–952.

Engler, H., Brendt, P., Wischermann, J., Wegner, A., Rohling, R., Schoemberg, T., Meyer, U., Gold, R., Peters, J., Benson, S., Schedlowski, M., 2017. Selective increase of cerebrospinal fluid IL-6 during experimental systemic inflammation in humans: association with depressive symptoms. Mol. Psychiatry 22, 1448–1454.

Fluitman, S., Denys, D., Vulink, N., Schutters, S., Heijnen, C., Westenberg, H., 2010. Lipopolysaccharide-induced cytokine production in obsessive-compulsive disorder and generalized social anxiety disorder. Psychiatry Res. 178, 313–316.

Fontenelle, L.F., Barbosa, I.G., Luna, J.V., de Sousa, L.P., Abreu, M.N., Teixeira, A.L., 2012. A cytokine study of adult patients with obsessive–compulsive disorder. Compr. Psychiatry 53, 797–804.

Gibson, P.H., Croal, B.L., Cuthbertson, B.H., Small, G.R., Ifezulike, A.I., Gibson, G., Jeffrey, R.R., Buchan, K.G., El-Shafei, H., Hillis, G.S., 2007. Preoperative neutrophil lymphocyte ratio and outcome from coronary artery bypass grafting. Am. Heart J. 154, 995–1002.

Gökler, B., Ünal, F., Pehlivantürk, B., Kültür, E.Ç., Akdemir, D., Taner, Y., 2004. Okul çağı çocukları için duygulanım bozuklukları ve şizofreni görüşme çizelgesi-şimdi ve yaşam boyu şekli-Türkçe uyarlamasının geçerlik ve güvenirliği. Çocuk. Gençlik. Ruh. Sağlığı. Dergisi. 11, 109–116.

Gray, S.M., Bloch, M.H., 2012. Systematic review of proinflammatory cytokines in obsessive–compulsive disorder. Curr. Psychiatry Rep. 14, 220–222.

Hoge, E.A., Brandstetter, K., Moshier, S., Pollack, M.H., Wong, K.K., Simon, N.M., 2009. Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. Depress. Anxiety 26, 447–455.

Kayhan, F., Gündüz, Ş., Ersoy, S.A., Kandeğer, A., Annagür, BB., 2017. Relationships of neutrophil-lymphocyte and platelet-lymphocyte ratios with the severity of major depression. Psychiatry Res. 247, 332–335.

Kenney, M.J., Ganta, C.K., 2014. Autonomic nervous system and immune system interactions. Compr. Physiol. 4, 1177–1200.

Kiecolt-Glaser, J.K., Derry, H.M., Fagundes, C.P, 2015. Inflammation: depression fans the flames and feasts on the heat. Am. J. Psychiatry 172, 1075–1091.

Konuk, N., Tekin, I.O., Ozturk, U., Atik, L., Atasoy, N., Bektas, S., Erdogan, A., 2007. Plasma levels of tumor necrosis factor-alpha and interleukin-6 in obsessive compulsive disorder. Mediat. Inflamm. 2007, 65704.

Kuyumcu, M.E., Yeşil, Y., Öztürk, Z.A., Kizilarslanoğlu, C., Etgül, S., Halil, M., Ulger, Z., Cankurtaran, M., Arıoğul, S., 2012. The evaluation of neutrophil / lymphocyte ratio in Alzheimer's disease. Dement. Geriatr. Cogn. Disord. 34, 69–74.

Kühn, S., Kaufmann, C., Simon, D., Endrass, T., Gallinat, J., Kathmann, N., 2013. Reduced thickness of anterior cingulate cortex in obsessive-compulsive disorder. Cortex 49, 2178–2185.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., Ryan, N., 1997. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J. Am. Acad. Child. Adolesc. Psychiatry 36, 980–988.

Miller, A.H., Raison, C.L., 2015. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16, 22–34.

McEvoy, P.M., Watson, H., Watkins, E.R., Nathan, P., 2013. The relationship between worry, rumination, and comorbidity: evidence for repetitive negative thinking as a transdiagnostic construct. J. Affect. Disord. 151, 313–320.

Michopoulos, V., Powers, A., Gillespie, C.F., Ressler, K.J., Jovanovic, T., 2017. Inflammation in fear-and anxiety-based disorders: PTSD, GAD, and beyond. Neuropsychopharmacology 42, 254–270.

Morer, A., Lazaro, L., Sabater, L., Massana, J., Castro, J., Graus, F., 2008. Antineuronal antibodies in a group of children with obsessive-compulsive disorder and Tourette syndrome. J. Psychiatr. Res. 42, 64–68.

Murphy, T.K., Kurlan, R., Leckman, J., 2010. The immune-biology of Tourette's disorder, pediatric autoimmune neuropsychiatric disorders associated with streptococcus, and related disorders: a way forward. J. Child Adolesc. Psychopharmacol. 20, 317–331.

Rao, N.P., Venkatasubramanian, G., Ravi, V., Kalmady, S., Cherian, A., Yc, J.R., 2015. Plasma cytokine abnormalities in drug-naïve, comorbidity-free obsessive-compulsive disorder. Psychiatry Res. 229, 949–952.

Rapoport, J.L., Swedo, S.E., 2003. Obsessive Compulsive Disorder. Child and Adolescent Psychiatry. In: Rutter, M., Taylor, E. (Eds.), Blackwell Publishing, Massachuetts, pp. 577–592.

Renna, M.E., O'Toole, M.S., Spaeth, P.E., Lekander, M., Mennin, D.S., 2018. The association between anxiety, traumatic stress, and obsessive-compulsive disorders and chronic inflammation: a systematic review and meta-analysis. Depress. Anxiety 35, 1081–1094.

Rosenkranz, M.A., Busse, W.W., Johnstone, T., et al., 2005. Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. Proc. Natl. Acad. Sci. U. S. A. 102, 13319–13324.

Sareen, J., Cox, B.J., Clara, I., Asmundson, G.J., 2005. The relationship between anxiety disorders and physical disorders in the U.S. National Comorbidity Survey. Depress. Anxiety 21, 193–202.

Schneiderman, N., Ironson, G., Siegel, S.D., 2005. Stress and health: psychological, behavioral, and biological determinants. Annu. Rev. Clin. Psychol. 1, 607–628.

Scahill, L., Riddle, M.A., McSwiggin-Hardin, M., Ort, S.I., King, R.A., Goodman, W.K., Cicchetti, D., Leckman, J.F., 1997. Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. J. Am. Acad. Child. Adolesc. Psychiatry 36, 844–852.

Semiz, M., Yıldırım, O., Canan, F., Demir, S., Hasbek, E., Tuman, T.C., Kayka, N., Tosun, M., 2014. Elevated neutrophil/lymphocyte ratio in patients with schizopheria. Psychiatr. Danub. 26, 220–225.

Sivri Çolak, R., Bilgiç, A., Kılınç, İ., 2018. Cytokine, chemokine and BDNF levels in medication-free pediatric patients with obsessive-compulsive disorder. Eur. Child Adolesc. Psychiatry 27, 977–984.

Sowislo, J.F., Orth, U., 2013. Does low self-esteem predict depression and anxiety? A meta-analysis of longitudinal studies. Psychol. Bull. 139, 213–240.

Stewart, J.C., Rand, K.L., Muldoon, M.F., Kamarck, T.W., 2009. A prospective evaluation of the directionality of the depression-inflammation relationship. Brain Behav. Immun. 23, 936–944.

Swedo, S.E., 2010. Streptoccocal infection, Tourette syndrome, and OCD: is there a connection? Pandas: horse or zebra? Neurology 74, 1397–1398.

Şimşek, Ş., Yüksel, T., Çim, A., Kaya, S., 2016. Serum cytokine profiles of children with obsessive-compulsive disorder shows the evidence of autoimmunity. Int. J. Neuropsychopharmacol. 12, 19.

Tonelli, L.H., Katz, M., Kovacsics, C.E., Gould, T.D., Joppy, B., Hoshino, A., Hoffman, G., Komarow, H., Postolache, T.T., 2009. Allergic rhinitis induces anxiety-like behavior and altered social interaction in rodents. Brain Behav. Immun. 2, 784–793.

Wagner, E.Y.N., Wagner, J.T., Glaus, J., Vandeleur, C.L., Castelao, E., Strippoli, M.P., Vollenweider, P., Preisig, M., von Känel, R., 2015. Evidence for chronic low-grade systemic inflammation in individuals with agoraphobia from a population based prospective study. PloS One 10, e0123757.

Weizman, R., Laor, N., Wiener, Z., Wolmer, L., Bessler, H., 1999. Cytokine production in panic disorder patients. Clin. Neuropharmacol. 22, 107–109.

Yücelen, A., Arman, V., Topçuoğlu, G., 2000. Çocuklar için Yale-Brown obsesifkompülsif geçerlik ve güvenilirlik değerlendirmesi. In: Sarıgerme (Turkey):10th National Child and Adolescent Mental Health Congress, Poster Presentation.

Wraith, D.C., Nicholson, L.B., 2012. The adaptive immune system in diseases of the central nervous system. J. Clin. Invest. 122, 1172–1179.