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Blood levels of interleukin-1 beta, interleukin-6 and tumor necrosis factor-alpha and cognitive functions in patients with obsessive compulsive disorder

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A R T I C L E I N F O

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A B S T R A C T

Background: Cognitive dysfunction and immune system disorders are two actual issues for the patients with Obsessive Compulsive Disorder (OCD). The cognitive dysfunctions have been considered to substantial part of clinical phenomenon of OCD but exploration of various etiopathogenesis of cognitive dysfunction is needed. Immune dysfuncion has been implicated to be important part of pathopysiology of OCD and different lines of evidence suggests immune abnormalities in OCD. But whether these immune changes are traits of disease or secondary to clinical burden of the disease such as cognitive dysfunctions has not been determined. Data regarding relation between the cognitive dysfunctions and immune system disorders in OCD is unsatisfied. In this study we aimed to investigate the relation of blood levels of interleukin 1-beta (IL-1ß), interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α) with various neurocognitive functions in patients with OCD in comparison with its autogenous/reactive subtypes and healthy controls. Further exploration of the effects of various clinical variables on cognitive functioning in patients with OCD and additional investigation of whether the cognitive dysfunction associated with this disorder differs from or overlap with that in other anxiety disorders are needed.

Methods: Forty-two patient with OCD and 45 age, sex and educational level matched healthy control were enrolled in the study. The diagnosis of OCD was made with Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Yale- Brown Obsessive-Compulsive Scale, Beck Anxiety and Depression Inventory Scales were administered. Neuropsychological test battery including Wisconsin Card Sorting Test (WCST), Trail Making Test A and B (TMT-A, TMT-B) were used for evaluation of the patients and healthy control. The plasma of interleukin-1beta (IL-1ß), interleukin-6 (IL-6), Tumor Necrosis Factor-Alpha (TNF-α) of both groups were measured with ELISA kits.

Results: Blood levels of IL-1ß, IL-6 and TNF-α were significantly higher in patients with OCD than the healthy control. There was significant difference in IL-1ß, IL-6 but not in TNF-α between autogenous/reactive subtypes and healthy controls. TNF-α is positively correlated with TMT-A, TMT-B and Stroop Test Part 5, negatively correlated with immediate memory, verbal learning, interference effect, immediate recall, delayed recall and recognition in RAVLT. IL-1ß was positively correlated with TMT-A score. IL-6 was positively correlated with scores of TMT-A, TMT-B. IL-6 was negatively correlated with immediate memory, verbal learning, interference effect, immediate recall and delayed recall in RAVLT, positively correlated with number of perseverative error and negatively correlated with the number of categories completed in WCST.

Conclusion: This is the first study that investigates the relation of IL- 1ß, IL-6 and TNF-α levels with cognitive functions in OCD. There may be a contribution to pathogenesis of OCD and subtypes then new choices for treatment might be developed. Moreover, uncovering the effect of cytokine blood levels on cognitive function of OCD, new data concerning etiopathogenesis and further treatment choices can be gained.

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1. Introduction

Obsessive compulsive disorder (OCD) is a mental health disorder characterized by obsessions and/or compulsions seen in 1.6–2.3% of the population. The etiopathogenic mechanisms involved in OCD are as yet unclear [1]. However, immune system disorders are one suggested mechanism in the development and pathophysiology of OCD. Pathophysiological studies have shown a link between pro-inflammatory cytokines and mental diseases such as major depression (MD) and schizophrenia, but there have been few systematic reviews of plasma cytokine levels in OCD [2–4]. While various studies investigating plasma cytokine levels in OCD have reported a potential involvement of cytokines in the pathophysiology of OCD, which symptoms and signs in OCD are related to which immune processes is still unclear [5,6]. Cytokines are proteins that regulate cellular immunity and inflammatory response and that are produced in both the peripheral and central nervous systems. Studies have determined an association between blood cytokine levels and OCD [7]. However, it is unclear whether changes in cytokine levels are a response to disease, or whether they should be regarded as a biomarker of a structural characteristic. In addition, we still do not know whether changes in cytokine levels have any therapeutic or prognostic significance. One study reported clinical evidence that interleukin 1-beta (IL-1ß), interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α) blood levels are involved in neurocognitive functions at the molecular level, such as synaptic plasticity, neurogenesis, or neuromodulation [8]. However, the effect of cytokines on neurocognitive functions in OCD has not been previously investigated. A wide range of cognitive defects are seen in OCD patients. One meta-analysis of cognitive functioning in OCD demonstrated significant impairment in visuospatial memory, executive function, verbal memory, verbal fluency and processing speed in patients with OCD [9]. Additionally, cognitive function impairment in OCD is defined as a mass of symptoms persisting despite treatment and representing the basis of OCD pathology [10]. Impairment of cognitive functioning in OCD is also thought to be linked to clinical expression and neurobiological etiology. It is therefore a matter of clinical importance to determine the etiopathogenesis of impairment of cognitive functions in OCD and to identify the agents involved. We expect that this study will contribute to research into the etiopathogenesis and treatment of a disorder such as OCD which exhibits heterogeneous characteristics and is still the subject of etiological studies. It is also unclear whether these immune mechanisms reported in OCD apply to all its subgroups. This study investigated the relation between blood cytokine levels and cognitive functions in OCD patients exhibiting reactive and autogenous characteristics. We think that the addition of neurobiological processes to Lee and Kwon's clinical differentiation will help identify new objectives in the treatment of the disease.

The purpose of this study was to examine the relation between inflammatory processes and neurocognitive processes and sociodemographic characteristics in OCD by comparing blood levels of IL-1ß, IL-6 and TNF-α in OCD and its autogenous/reactive subtypes and healthy controls. Our aim was to determine whether there is a difference between inflammatory processes in terms of blood cytokine levels in OCD and its subgroups, to examine the role of immune mechanisms and immune parameters specific to OCD subgroups in the etiopathogenesis of OCD, and to contribute to clarifying the still uncertain etiopathogenesis of the disorder.

2. Material and methods

2.1. Sampling and procedure

This cross-sectional study was performed with patients admitted to the psychiatry outpatient clinic of Karadeniz Technical University, Turkey, with either a current diagnosis of OCD or diagnosis in the previous 12 months based on Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). SCID-I is a structured clinical interview for the diagnosis of DSM-IV Axis I. After diagnosis with SCID-I, patients were assessed with the Yale-Brown Obsessive Compulsive Scale (YBOCS), a semi- structured scale used to evaluate the severity and type of OCD symptoms. Patients with OCD were subsequently classified into subgroups based on their primary obsessions in accordance with the diagnostic criteria reported by Lee and Kwon [11]. Patients with one or more of the primary obsessions of aggression, religious and sexual obsessions were classified as autogenous type OCD (AT). Patients with one or more of the primary obsessions of contamination, doubt, symmetry and hoarding were classified as reactive type OCD (RT). Following this subclassification of OCD patients into AT and RT, self-report inventories including the Beck Depression Inventory (BDI), and the Beck Anxiety Inventory (BAI) were administered to both patients and healthy controls. All participants were evaluated using neurocognitive tests for neurocognitive assessment. Perseverative errors, perseverative reactions and categories completed were evaluated using the Wisconsin Card Sorting Test (WCST). Selective attention and response inhibition was assessed with the Stroop test, and attention, mental flexibility, visual search, and psychomotor speed with the Trail Making Test (TMT). The TMT consists of two parts. Part A measures psychomotor speed and attention, and part B measures executive function. The Rey Auditory Verbal Learning Test (RAVLT) is used for the evaluation of immediate memory, verbal learning, interference effect, immediate and delayed recall, and recognition. The control group consisted of healthy volunteers matched with the patient group in terms of age, sex, and education, not meeting any of the exclusion criteria, and with no psychiatric disease based on SCID-I. Exclusion criteria for the patients and healthy controls were alcohol or drug abuse and receipt of electroconvulsive therapy (ECT) in the previous six months, presence of medical disease including neurological diseases, infections, allergopathies, inflammatory disorders, immunological disorders, endocrine and metabolic diseases, obesity or recent weight loss, pregnancy, color blindness, or current use of antibiotic or anti-inflammatory drugs. Written informed consent was obtained from the patients and controls, after a full explanation of the entire procedure.

2.2. Determination of biochemical parameters

2.2.1. Blood sampling

Blood samples were collected with anticoagulant tubes and placed into biochemistry tubes with separating gel. Samples were centrifuged at 1800*g* for 10 min to obtain plasma and serum. The plasma and serum samples were then stored at −80 °C until biochemical analyses.

2.2.2. Determination of IL-1ß, IL-6 and TNF-α levels

Blood IL-1ß, IL-6 and TNF-α levels were determined using ELISA kits (DIA Source, Cat No: KAP1211, KAP1261, and KAP1751, Louvain-la-Neuve, Belgium, respectively) in line with the manufacturer's instructions. Levels of TNF-α, IL-1ß and IL-6 were calculated using a standard curve created by absorbance values obtained against standard concentrations.

2.3. Statistical analysis

During statistical analysis of data from patients with OCD and healthy controls, conformity with normal distribution was determined using the Kolmogorov-Smirnov test. Comparisons of normally distributed numerical variables between two independent groups were performed using Student's *t*-test, while non-normally distributed variables were compared using the Mann-Whitney *U* test. Differences between rates of categorical variables in independent groups were determined using chi-square analysis. p values < 0.05 were considered significant. All measured data are expressed as mean ± standard deviation, while numerical data are expressed as percentages. Correlation analyses for normally distributed variables were performed with the Pearson test, and those categories with at least one non-normally distributed

Table 1
Sociodemographic and clinical variables in OCD and control groups.

	OCD	Control	
	Mean ± SD	Mean ± SD	p
Age (year)	27.48 ± 12.03	27.64 ± 11.56	0.685
Education (year)	12.12 ± 3.53	27.63 ± 11.56	0.731
Duration of illness (year)	10.33 ± 9.20		
Age at onset of illness (year)	17.14 ± 6.93		
Last treatment duration (month)	10.00 ± 16.38		
BDI	14.69 ± 8.45	1.71 ± 2.24	0.000*
BAI	11.12 ± 8.74	0.42 ± 1.26	0.000*
YBOCS			
Total score	27.90 ± 10.26	0.00 ± 0.00	0.000*
	OCD	Control	
	n (%)	n (%)	
Sex			
Female	24 (57.1)	27 (60)	0.958
Male	18 (42.9)	18 (40)	
Story of family psychiatric illness			
Yes	26 (76.59)	8(23.5)	0.000*
No	16 (30.2)	37 (69.8)	
Obsession type			
Reactive	23 (54.8)		
Autogenous	19 (45.2)		

OCD: Obsessive compulsive disorder. BDI: Beck Depression Inventory. BAI: Beck Anxiety Inventory. YBOCS: Yale-Brown Obsessive Compulsive Scale. Mean ± SD: Mean standard deviation.
* $p < 0.05$.

variable were evaluated with the Spearman test. At statistical analysis of patients with AT OCD, patients with RT OCD, and healthy controls, the Shapiro–Wilks test was applied to variables not exhibiting normal distribution. When a difference was observed, the origin of that difference was determined with Bonferroni analysis. One-way analysis of variance (ANOVA) was used to compare group means for normally distributed data, and the Kruskal–Wallis test was used for data without normal distribution.

3. Results

3.1. Sociodemographic and clinical data

Forty-two patients with OCD and 45 healthy controls were enrolled in this study. Nineteen of the patients (45.2%) had AT OCD, and 23 (54.8%) had RT OCD. The mean age of the patient group was 27.48 ± 12.03 years. The sex distribution was 42.9% (n = 18) male and 57.1% (n = 24) female, and the mean length of education was 12.12 ± 3.53 years. The mean age of the control group was 27.64 ± 11.56 years, the sex distrıbution was 42.9% (n = 18) male and 57.1% (n = 24) female, and the mean length of education was 12.12 ± 3.53 years. No significant difference in age, sex distribution or education levels was determined between the patients and healthy controls. Mean duration of disease was 10.33 ± 9.20 years, mean age at onset of the disease was 17.14 ± 6.93 years, and mean the duration of the most recent treatment period was 14.17 ± 16.47 months in the entire patient group. In the AT OCD group, the mean duration of the disease was 10.00 ± 7.78 years, mean age at onset was 17.26 ± 9.05 years, and the mean duration of the most recent treatment period was 10.00 ± 16.38 months. In the RT OCD group, the mean duration of the disease was 10.61 ± 10.39 years, mean age at onset was 17.04 ± 4.72 years, and the mean duration of the most recent treatment period was 16.82 ± 16.33 months. There was no significant difference between AT and RT type OCD in terms of disease duration, age at onset, or duration of the most recent treatment period (p = 0.666, 0.422, and 0.065, respectively). Patients with OCD had a significantly higher level of family history of psychiatric illness (p = 0.0005) than the healthy controls. Thirty-six (85.7%) patients with OCD were receiving psychopharmacological therapy, while the remaining six (14.2%) were not currently receiving such therapy. Fourteen (73.7%) patients with AT OCD and 22 (95.7%) with RT OCD were receiving psychopharmacological therapy, and the difference was not statistically significant (p = 0.075). The type of psychopharmacological therapy (antipsychotic, antidepressant or both antipsychotic and antidepressant therapy) did not differ significantly between the AT and RT OCD groups (p = 0.54, 0.61, and 0.61, respectively). The sociodemographic and clinical features of the patients with OCD and healthy controls are shown in Table 1. Sociodemographic and clinical features of patients with AT OCD and RT OCD and the healthy controls are shown in Table 2.

3.2. Clinical scales

Total BDI scores were 14.69 ± 8.45 in the patients with OCD, and 1.71 ± 2.24 in the healthy controls, the difference being significant (p = 0.0005). BDI scores were significantly higher in AT OCD than in the RT OCD and healthy control groups. Significant differences in terms of BDI scores were determined at comparisons of the AT and control groups, the RT and control groups, and the RT and AT groups (p = 0.0005, 0.0005, and 0.46, respectively). Total BAI scores were 11.12 ± 8.74 in patients with OCD, and 0.42 ± 1.26 in the healthy controls, the difference being significant (p = 0.0005). BAI scores were higher in AT OCD than in RT OCD, although the difference was not significant (p = 0.56). Patients with AT and RT OCD both registered significantly higher BAI scores than the healthy control group (p = 0.0005, and 0.0005, respectively) (Table 3). Total obsession and compulsion scores, insight scores, and general severity and reliability scores on YBOCS were significantly higher in AT OCD than in RT OCD (p = 0.004, 0.004, 0.004, 0.009, 0.017, and 0.005, respectively). The YBOCS general severity score was positively correlated with RAVLT interference effect and immediate recall in patients with OCD. YBOCS insight scores were positively correlated with TMT-A, Stroop Part 5, RAVLT immediate memory,

Table 2
Sociodemographic and clinical variables in AT OCD and RT OCD.

	AT OCD	RT OCD	Control	p
	Mean ± SD	Mean ± SD		
Age (year)	27.26 ± 12.02	27.65 ± 12.30	27.64 ± 11.56	0.918
Education (year)	12.84 ± 3.18	11.52 ± 3.75	27.63 ± 11.56	0.445
Duration of illness (year)	10.00 ± 7.78	10.61 ± 10.39		0.660
Age at onset of illness (year)	17.26 ± 9.05	17.04 ± 4.72		0.422
Last treatment duration (month)	10.00 ± 16.38	16.82 ± 16.33		0.065*
BDI	17.26 ± 7.66	12.57 ± 8.63	1.71 ± 2.24	0.000*
BAI	13.68 ± 8.14	9.00 ± 8.81	0.42 ± 1.26	0.000*
YBOCS				
Total score	32.79 ± 9.37	23.87 ± 9.31	0.00 ± 0.00	0.004*

OCD: Obsessive compulsive disorder. AT: Autogenous type. RT: Reactive type. BDI: Beck Depression Inventory. BAI: Beck Anxiety Inventory. YBOCS: Yale-Brown Obsessive Compulsive Scale. Mean ± SD: Mean standard deviation.
* $p < 0.05$.

Table 3
Comparison of IL-1ß, IL-6, TNF-α serum levels and neurocognitive test scores of patients with OCD and control group.

	OCD Mean ± SD	Control Mean ± SD	p
IL-1ß	14.99 ± 2.14	14.39 ± 2.67	0.014*
IL-6	42.15 ± 19.36	30.46 ± 13.33	0.000*
TNF-α	5.71 ± 2.46	4.81 ± 1.39	0.044*
TMT			
TMT-A	41.17 ± 22.15	28.76 ± 16.10	0.01*
TMT-B	99.93 ± 50.10	60.04 ± 31.46	0.00*
WCST	9.46 ± 4.9	5.70 ± 2.2	
Categories completed	3.17 ± 1.12	4.0 ± 1.0	0.00*
Perseverative reactions	11.24 ± 7.04	6.11 ± 2.82	0.00*
Perseverative errors	10.07 ± 5.32	5.64 ± 2.38	0.00*
RAVLT			
Immediate memory	7.17 ± 2.38	8.82 ± 1.80	0.01*
Delayed recall	9.83 ± 3.16	12.87 ± 1.85	0.00*
Verbal learning	50.79 ± 11.22	61.38 ± 6.50	0.00*
Recognition	12.88 ± 2.76	14.07 ± 1.34	0.021*
Stroop test			
Total interference score	15.43 ± 7.76	10.44 ± 4.13	0.001*

OCD: Obsessive compulsive disorder. TMT: Trail Making Test. WCST: Wisconsin Card Sorting Test. RAVLT: Rey Auditory Verbal Learning Test. Mean ± SD: Mean standard deviation.
* $p < 0.05$.

verbal learning, interference effect, delayed recall and blood levels of IL-6 in patients with OCD. Correlations between blood levels of IL-1ß, IL-6, and TNF-α and clinical characteristics and neurocognitive test scores are shown in Table 4.

3.3. Neurocognitive scales

TMT-A scores were 41.17 ± 22.15 in the patient group and 28.76 ± 16.11 in the healthy control group, while TMT-B scores were 99.93 ± 50.10 in the patient group and 60.04 ± 31.46 in the control group. TMT A and B were both significantly higher in patients with OCD (p = 0.01, and p = 0.0005, respectively). No difference was observed between AT type OCD and RT OCD in terms of TMT-A and B. Significant differences were between AT OCD and the controls, and RT OCD and the controls in terms of TMT-A (p = 0.009, and 0.009, respectively) and TMT-B scores (p = 0.0005, and 0.001, respectively). Patients' total interference scores were significantly higher than those of the healthy controls (p = 0.001) at the Stroop Test. Total interference was significantly higher in AT OCD and RT OCD than in the healthy control group, but there was no difference between AT OCD and RT OCD (p = 0.610). Scores for immediate memory, verbal learning, interference effect, immediate recall, delayed recall and recognition on the RAVLT were significantly lower in patients with OCD than in the healthy control group (p = 0.001. 0.0005, 0.001, 0.0005, 0.0005, and 0.21, respectively). Significant differences were observed in immediate memory, immediate recall and delayed recall scores between the AT OCD and control groups and the RT OCD and control groups, but no difference was determined between AT and RT OCD (p = 0.217, 0.147, and 0.417, respectively). Interference effect scores differed significantly between the AT OCD and control groups (p = 0.004), but not between the RT OCD and control and AT and RT OCD groups (p = 0.13, and 0.610, respectively). Significant differences were observed in numbers of categories completed, numbers of perseverative reactions and perseverative errors between the patients and healthy controls (p = 0.0005, 0.0005, and 0.0005, respectively) on the WCST. Significant differences were determined between the AT and control, and the RT and control groups in terms of numbers of perseverative reactions, perseverative errors, and numbers of categories completed, but no difference was observed between AT and RT OCD (p = 0.617, 0.733, and 0.46, respectively).

Table 4
Correlation of neurocognitive test scores and IL-1ß, IL-6, TNF-α serum levels in patients with OCD.

	IL-1ß	IL-6	TNF-α
	OCD	OCD	OCD
TMT			
TMT-A	0.005*	0.001*	0.005*
TMT-B	0.028*	0.000*	0.028*
WCST			
Categories completed	0.465	−0.04	0.495
Perseverative reactions	0.201	0.000	0.159
Perseverative errors	0.159	0.000	0.201
RAVLT			
Immediate memory	−0.022*	−0.000*	−0.022*
Delayed recall	−0.002*	0.000*	−0.002*
Verbal learning	−0.003*	0.000*	−0.003*
Recognition	−0.000*	0.381	−0.000*
Stroop test			
Stroop test total interference	0.98*	0.004*	0.039*

OCD: Obsessive compulsive disorder. TMT: Trail Making Test (TMT). WCST: Wisconsin Card Sorting Test. RAVLT: Rey Auditory Verbal Learning Test.
* $p < 0.05$.

3.4. Biochemical parameters

Blood TNF-α, IL-1ß, and IL-6 levels were higher in patients with OCD than in the healthy controls (p = 0.044, 0.014, and 0.00, respectively). When the AT OCD group was compared with the RT OCD and control groups, significant differences were observed in IL-1ß and IL-6, but not in TNF-α (p = 0.036, 0.000, and 0.084, respectively). Patients with RT OCD had significantly higher IL-1ß levels than the control group (p = 0.013), but there was no significant difference between the AT OCD and RT OCD groups, or the AT OCD and control groups (p = 0.471, and 0.152 respectively). IL-6 levels were significantly higher in the AT and RT OCD groups than in the control group (p = 0.00, and p = 0.01, respectively), but no difference was observed between the AT and RT OCD groups (p = 0.174). TNF-α was positively correlated with TMT-A and TMT-B (p = 0.005, and 0.028, respectively) and Stroop Part 5, and was negatively correlated with immediate memory, verbal learning, interference effect, immediate recall, delayed recall and recognition on RAVLT. TNF-α was negatively correlated with number of total correct responses and conceptual level responses and positively correlated with numbers of total error and trials to complete the first category on the WCST. IL-1ß was positively correlated with BDI, BAI and TMT-A scores. IL-6 was positively correlated with TMT-A, TMT-B, BDI and BAI scores, insight score on YBOCS, and interference score on WCST. IL-6 was negatively correlated with immediate memory, verbal learning, interference effect, immediate recall, and delayed recall on RAVLT, positively correlated with number of perseverative errors, and negatively correlated with numbers of categories completed on WCST. IL-6 was positively correlated with TNF-α and IL-1ß. No correlation was determined between TNF-α and IL-1ß. Correlations between neurocognitive scales and biochemical parameters are shown in Table 4.

4. Discussion

There is a growing body of evidence of a complex and dynamic relation between the central nervous system and the immune system [12]. The immune system has been implicated in the pathophysiology of several psychiatric diseases, including OCD [13]. Despite the presence of findings suggesting that OCD is an immune system-related disorder, the latest data indicate that the relation between OCD and the immune system is still unclear, and further research is required on the subject [14].

Cytokines are glycoproteins produced in all organs and different cell types that initiate immunological and inflammatory responses. The most commonly studied cytokines in OCD are IL-1ß, IL-6 and TNF-α [5]. In the present study, IL-1ß, IL-6 and TNF-α blood levels in OCD patients were higher than in healthy controls exhibiting no significant differences in terms of age, sex, or education levels. In terms of OCD subtypes, IL-1ß levels were significantly higher in reactive type OCD compared to the AT and control groups. IL-6 was significantly higher in both the AT and RT subgroups compared to the controls. No difference was observed in TNF-α levels. The investigated cytokines are regarded as pro-inflammatory cytokines that accelerate the immune response in order to eliminate pathogens [15]. The results of this study may therefore indicate an increased inflammatory response in OCD patients. Some previous studies have reported similar findings, while others have elicited incompatible results. In agreement with our research, some studies have reported higher TNF- α and IL-6 levels in OCD patients than in healthy controls [16]. In contrast to our research, Erbay et al. (2018) reported lower IL-6 and TNF- α levels in OCD patients than in healthy controls [17]. This difference may be due to variations in sampling, such as the inclusion of untreated and comorbid condition groups. One meta-analysis reported significantly low IL-1ß levels in OCD, while no difference was observed in IL-6 and TNF-α levels [4]. While no difference was reported in IL-1ß and IL-6 levels in OCD patients receiving no treatment, TNF-α levels were significantly lower than those in healthy controls [18]. Blood cytokine levels have been studied in other mental diseases apart from OCD, and have been reported to be higher than those in healthy controls. Higher IL-1ß, IL-6 and TNF-α levels have been determined in Alzheimer's disease progressing with loss of cognitive functions compared to healthy controls [19]. Higher IL-6 and TNF-α values have been reported in patients with schizophrenia, bipolar disorder (BD) and major depressive disorder (MDD) than in healthy controls [20].

The inconsistent results concerning blood cytokine levels in the literature may be due to sociodemographic characteristics of the study samples, such as age and sex, or to confounding factors such as other comorbid mental diseases. There is increasing evidence that blood cytokine levels increase with age and that inflammatory processes play a key role in Alzheimer's disease, vascular dementia and age-related cognitive decline [21,22]. However, we determined no difference between our patient and control groups in terms of the sociodemographic characteristics of age and sex. Some studies have reported higher cytokine levels in individuals with mood disorders accompanying OCD than in healthy subjects [4]. However, other studies have reported higher cytokine levels in OCD patients with no comorbidity and not receiving medication than in healthy controls [4,6]. Other studies have expressed different opinions. Brambilla et al. reported no relation between previous receipt of treatment or lack of treatment and low cytokine levels [23]. In terms of confounding factors, we endeavored to eliminate the effects on cytokine levels of accompanying diseases by excluding OCD patients with accompanying DSM-5 diagnoses. The majority of patients in this study (85.7%) were receiving treatment, and although blood drug levels were not investigated, we observed no correlation between duration of the last treatment period and plasma cytokine levels.

Blood cytokine levels in OCD patients were not correlated with YBOCS obsession, compulsion, or total scores, general severity or reliability subscores, although blood IL-6 levels were correlated with YBOCS insight scores. However, some studies have emphasized that cytokine blood levels may be associated with symptom type and severity in OCD [24]. The absence in this study of a correlation between blood cytokine levels and OCD symptom severity, and correlation only being determined with insight scores associated with cognitive abilities, may indicate the effect of cytokines on cognitive skills. In fact, insight is a concept that has been proposed as potentially associated with cognitive deficiencies ever since it was first defined [25]. Lee and Kwon suggested that obsessions may be divided into two different groups, autogenous and reactive models, on the basis of a cognitive model. In this study, when obsessions were divided into autogenous and reactive groups based on the cognitive model proposed by Lee and Kwon [11], IL-1ß was significantly high in RT OCD compared to the healthy controls, while IL-6 was significantly higher compared to the healthy controls in both the RT and AT groups. TNF-α exhibited no variation between the subgroups. Higher TNF-α than in the healthy controls independently of the type of obsession in OCD, while IL-1ß and IL-6 differed between the OCD clinical subtypes, may indicate the neurobiological foundation of the Lee and Kwon classification.

Considering the relation between inflammation and cognitive functions, the increases in response to inflammation in OCD patients may be a factor leading to impairment of cognitive functions. Inflammatory processes assessed with blood cytokine levels in schizophrenia and BD are reported to play a significant role in cognitive function impairment [26]. Cytokines exhibit their effects on cognitive functions through mechanisms occurring at the molecular and cellular levels, such as synaptic plasticity and neurogenesis [8]. There is considerable evidence that inflammation mechanisms lead to cognitive breakdown mediated by cytokines [27]. IL-1ß, IL-6 and TNF-α are cytokines linked to a decline in cognitive abilities in clinical and population studies [27,28]. Cytokine-mediated inflammation processes have been implicated in neurodegenerative diseases such as Alzheimer and vascular dementia [27]. However, no previous studies have investigated the relation between cytokine levels and cognitive abilities in OCD patients. Although defects have been reported in several cognitive domains in OCD, no distinct and specific neurobiological profile has been reported, and impairment has been emphasized in several cognitive function, including memory, attention, mental flexibility, inhibition, verbal reasoning and planning, and decision making [29,30]. While this cognitive impairment may be associated with symptom severity, it may also be a characteristic specific to OCD, in other words a core symptom. Studies have reported that compromise of cognitive functions in OCD persists as a symptom cluster that persists despite treatment [10]. This may also suggest that cognitive functions in OCD are a core symptom requiring evaluation separately from basic symptoms. In this study, OCD patients exhibited poorer performance than healthy controls in several neuropsychological evaluations, and a relation was determined with various cytokine levels. The neuropsychological assessments TMT-A and B were positively correlated with IL-6 and TNF-α. A relation between IL-6 levels and cognitive failure has been shown at cognitive assessments in subjects of moderately advanced age [21]. The TMT measures attention, mental flexibility, and visual and motor speed, and these abilities were poorer in the patient group than in the healthy controls, and were associated with high cytokine levels. TNF-α and IL-6 were negatively correlated with RAVLT immediate recall, verbal learning, interference effects, delayed recall, and retention of information. These abilities worsen as cytokine levels increase. Similarly, in their study of BD patients, Doğanavşargil et al. determined negative correlation between TNF-α and RAVLT delayed recall [31]. Lv et al. determined negative correlation between TNF-α levels and cognitive functions in patients with chronic schizophrenia [32]. However, other studies have determined no relation between TNF-α and IL-6 levels and cognitive functions [33]. Hikaru et al. reported that verbal learning, working memory, motor speed, verbal reasoning, attention, processing speed and executive functions in patients with chronic schizophrenia were not associated with TNF-α or IL-6 levels [33]. The WCST, which evaluates conceptualization and perseveration is negatively correlated with TNF-α, IL-1ß and IL- 6, and it may be concluded that the ability to conceptualize and persevere worsens as cytokine levels rise. In contrast, Izabela Guimarães Barbosa et al. reported that TNF-α levels had a positive effect on the inhibition executive function in euthymic BD patients, but emphasized that this finding needed to be supported by further studies [34]. In the present study, the Stroop interference score evaluated using the Stroop test exhibited positive correlation with TNF-α and IL-6. No correlation was observed between IL-1ß and the Stroop interference score. It may be concluded that TNF-α and IL-6 levels have an adverse effect on cognitive inhibition and attention in the OCD patient group. Micoulaud-Franchi et al. determined negative correlation between Stroop interference time and levels of the inflammatory marker CRP [35].

There are both limiting and powerful aspects to this study. The principal limitation is that the patients enrolled in the study were all receiving treatment. Further studies including an untreated group will permit a greater possibility of clarifying the etiopathogenesis of OCD. Due to the cross-sectional nature of the study it was not possible to determine the long-term clinical effects of the inflammatory process in OCD. Further studies may help elicit changes occurring in the course of the disease. However, the fact that ours is the first study to investigate the relation between cognitive functions and cytokines, and also to compare blood cytokine levels in AT and RT OCD groups and in healthy controls. Using a clinical interview for the diagnosis of OCD, strict control maintained over the criteria by excluding mental diseases accompanying OCD, and the exclusion of medical disease by close scrutiny of history represent powerful aspects of the study. Another powerful aspect is that bias was prevented by neurocognitive evaluations being performed by an independent psychologist blinded to the study.

5. Conclusion

In conclusion, our study findings may indicate that inflammation processes in OCD can have adverse effects on cognitive functions, which may be regarded as a core symptom of OCD. Alternatively, it may be that inflammatory processes contribute to the psychopathology of OCD by compromising cognitive functions. If these data are supported by further studies involving larger samples they may shed light on new strategies in the management of clinical cases that frequently exhibit high levels of resistance to treatment in clinical practice.

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