RESEARCH ARTICLE

Relation of ASC and IL-1beta with neurocognitive parameters in patients with Obsessive-Compulsive Disorder

Relation of ASC and IL-1beta with neurocognitive parameters in patients with Obsessive-Compulsive Disorder

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SUMMARY

Objective: It is now well accepted that inflammatory processes play a role in the etiopathogenesis of psychiatric disorders. NLRP3 inflammasome, which is formed by the combination of NLRP3, ASC and Caspase-1 proteins, and its activator NEK7, takes part in these processes. In this study, we aimed to investigate the relationship between inflammatory markers (i.e. IL-1β, IL-18, NLRP3 inflammasome protein levels) and cognitive functions in patients with obsessive compulsive disorder (OCD). **Method:** Forty-two patients between the ages of 18-45 who were diagnosed with OCD were included in the study. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Yale-Brown Obsessive Compulsive Scale (Y-BOCS), and Hamilton Depression Scale (HAMD) were used for clinical evaluations. In order to evaluate cognitive functions, Trail Making Test (TMT), Berg Card Sorting Test and Category Fluency Test were applied. IL-1β and IL-18 cytokine levels were determined by the ELISA method; measurement of the protein amounts of NLRP3, Caspase-1, ASC and NEK7 were performed by Western blotting. **Results:** Serum IL-1beta was negatively correlated with TMT (B-A) (rs=-.36, p= 0.019). Similarly, ASC was negatively correlated with TMT-B and TMT (B-A) (rs=-.38, p= 0.03; rs=-0.36, p = 0.04, respectively). However, no statistically significant relationship was found between other inflammatory parameters (NLRP3, Caspase-1, and IL-18) and neurocognitive tests. **Discussion:** Our results indicate that some aspects of neurocognitive impairment in patients with OCD might be related to neuroinflammatory processes, with implications for our understanding of the pathogenesis of OCD.

Key Words: OCD, Neuroinflammation, NLRP3, IL-1β, Neurocognition

ÖZET

Amaç: İnflamatuar süreçlerin psikiyatrik bozuklukların etyopatogenezinde rol oynadığı yaygın kabul görmektedir. Bu süreçlerde NLRP3, ASC ve Caspase-1 proteinlerinin bir araya gelmesiyle ve NEK7'nin aktivasyonuyla oluşan NLRP3 inflamatuarı yer almaktadır. Bu çalışmada obsesif kompulsif bozukluk (OKB) hastalarında inflamatuar belirteçler (ör: IL-1β, IL-18, NLRP3 inflamatuar protein düzeyleri) ile bilişsel işlevler arasındaki ilişkinin araştırılması amaçlanmıştır. **Yöntem:** OKB tanısı almış 18-45 yaş arası kırk-iki hasta çalışmaya dahil edilmiştir. Klinik değerlendirmeler için DSM-IV Eksen I. Bozuklukları için Yapılandırılmış Psikiyatrik Görüşme Formu (SCID-I), Yale Brown Obsesyon Kompulsiyon Ölçeği (Y-BOCS) ve Hamilton Depresyon Ölçeği (HAM-D) kullanılmıştır. Bilişsel işlevleri değerlendirmek için İz Sürme Testi (TMT), Berg Kart Eşleme Testi ve Kategori Akıcılık Testi uygulanmıştır. IL-1β ve IL-18 sitokin seviyeleri ELISA yöntemi ile belirlenirken NLRP3, Kaspaz-1, ASC ve NEK7'nin protein miktarlarının ölçümü Western blot yöntemi ile gerçekleştirilmiştir. **Bulgular:** Serum IL-1beta seviyeleri, TMT (B-A) ile negatif korelasyon göstermiştir (rs=-.36, p= 0.019). Benzer şekilde ASC, TMT-B ve TMT (B-A) ile negatif korelasyon göstermiştir (sırasıyla rs=-.38, p=0.03; rs=-0.36, p=0.04). Ancak diğer inflamatuar parametreler (NLRP3, Caspase-1 ve IL-18) ile nörobilişsel testler arasında istatistiksel olarak anlamlı bir ilişki bulunamamıştır. **Sonuç:** Elde ettiğimiz sonuçlar, OKB'li hastalarda nörobilişsel bozulmanın bazı yönlerinin nöroinflamatuar süreçlerle ilişkili olabileceğine işaret etmektedir ve bu bulgu OKB patogenezinin anlaşılmasına katkı sağlayabilir.

Anahtar Sözcükler: OKB, Nöroinflamasyon, NLRP3, IL-1β, Nörobiliş

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a common neuropsychiatric disorder with lifetime prevalence of approximately 2.3% (1). OCD is a heterogeneous disorder and its etiology is still not clear (2). Although neuroinflammatory processes are suggested to play a role in the etiopathogenesis of OCD, there is a lack of consensus mainly due to conflicting results obtained from studies where blood cytokine levels of patients with OCD were analyzed (3).

It is now well established that neuroinflammation is observed in some neuropsychiatric (i.e. major depressive disorder (MDD), bipolar disorder (BD), schizophrenia) and neurological (i.e. Parkinson's disease) disorders, indicating an altered activity of intracellular multi-protein complexes collectively named as 'inflammasomes' (4-9). The inflammasome components react to a variety of extracellular and intracellular stimuli by assembling the core inflammasome complex, which processes pro-IL-1β and pro-IL-18, to their active forms IL-1β and IL-18, respectively. This cascade eventually results in an inflammatory type of cell death, named 'pyroptosis'. It is thought that the delicate balance between activation and inhibition of inflammasomes can result in disease states.

Different types of inflammasomes share the common organizational structure: the upstream sensors, the adapters, and downstream effectors (10). One of the most well-known families of sensors is the 'nucleotide-binding oligomerization domain, leucine-rich repeat' (NLR) family. NLR family proteins are grouped based on the presence of effector domains at their N-terminal, namely NLRA (ATD domain), NLRB (BIR domain), NLRC (CARD domain), and NLRP (Pyrin domain). The largest subfamily of NLRs in humans is the NLRP family, with 14 members; two of the four most well-characterized types of inflammasomes belong to this subfamily and NLRP1, NLRP3, NLRC4, and AIM2 are named after their sensor proteins. NLRP3 is known to respond to a variety of stimuli, such as gram-positive and gram-negative bacteria, pore-forming toxins, several viral proteins, silica, aluminum, beta-glucan, ATP, K+ efflux, ROS, mitochondrial dysfunction, etc. (11). Owing to its involvement in an extended array of inflammatory responses, NLRP3 inflammasome has been studied broadly.

The other components of NLRP3 inflammasome are the adaptor protein ASC (Apoptosis associated speck-like protein containing a caspase recruitment domain), Caspase-1 (cysteine- aspartic acid protease 1), and the more recently identified upstream activator kinase NEK7 (NIMA related kinase 7) (12).

Activation of the NLRP3 inflammasome is thought to occur in two phases: priming, when stimuli activate the NF-KB pathways leading to expression of NLRP3 and pro IL-1β (13). The second signal leads to activation of the NLRP3 and formation of the inflammasome complex. NEK7 plays a role in transmission of certain stimuli to NLRP3, thereby acting as an upstream regulator. Formation of the inflammasome complex leads to maturation of procaspase 1 into active caspase-1, which cleaves pro-1L-1β and pro-IL-18 into their active forms.

On the other hand, it is also well known that neurocognitive deficits are one of the main symptoms in OCD, which leads to functional impairments, and are suggested to be associated with resistance to treatment (14-16). Particularly, defective cognition is proposed as one of the significant symptoms in neuropsychiatric disorders by the NIMH Research Criteria Project (17). OCD patients display a wide range of neurocognitive impairments: A meta-analysis of neurocognitive deficits in OCD reported that there are some impairments in inhibition, planning/problem solving, visual memory, set-shifting and reward-based decision making abilities (14). Another meta-analysis revealed that processing speed and verbal fluency are also impaired in patients with OCD (15). Changes in immune activation, as evaluated by neuroinflammatory markers, have been reported to be associated with reduced cognitive performance in patients with neurological and psychiatric disorders and healthy controls (18- 24). Therefore, it is important to investigate possible relationships between inflammasomes and neurocognitive deficits in OCD in order to better understand the pathogene-

sis of the cognitive impairment in OCD.

Our previous findings indicated that blood NLRP3 inflammasome levels are related with OCD (25). While there is plenty of evidence in the literature that indicates patients with OCD show significant neurocognitive deficits and have differences in the neuroinflammatory process, there is scarcity of studies that investigate the relationship between these two aspects (3, 14). To our knowledge, only one study examined such a relationship and found that neurocognitive abilities in patients with OCD were affected adversely by the neuroinflammation processes (26).

The aim of this study is to evaluate the possible association between NLRP3 inflammasome pathway and cognitive processes in OCD. Based on our previous observations of altered NLRP3 pathway in OCD patients and the known roles of the immune system in cognitive impairment, we hypothesized that altered NLRP3 inflammasome pathway in OCD could be associated with cognitive impairment. In this scope, we tested possible relationships between inflammatory parameters (IL-1beta and IL18 cytokine levels; NLRP3, ASC, Caspase1, and NEK7 protein levels) and neurocognitive test variables (BERG Card Sorting Test, Trail Making Test, Category Fluency Test) in OCD patients.

The findings of this study may contribute to the mechanistic understanding of inflammatory and cognitive processes in OCD and eventually it may lead to development of new treatment strategies directed to inflammatory mechanisms.

METHOD

Participants and Procedures

This cross-sectional study was carried out between February-November 2018 with 42 patients diagnosed with OCD at the psychiatry outpatient clinic of Dokuz Eylül University Hospital. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was used for OCD diagnosis. Then, sociodemographic data was collected and the patients were evaluated with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and the Hamilton Depression Rating Scale (HAM-D). For molecular studies, fasting peripheral venous blood samples were collected between 9:00 and 11:00 a.m in the morning. Berg Card Sorting Test (BCST), Trail Making Test (TMT) A and B forms and Categorical Fluency Test were used for the neuropsychological evaluation.

Individuals who were between the ages of 18-45, literate, diagnosed with OCD were included in the study by applying a random sampling method. Being diagnosed with alcohol and substance abuse, schizophrenia, bipolar disorder, neurological disorders, clinical inflammatory or metabolic disease were exclusion factors from the study. Patients who received electroconvulsive therapy, corticosteroids, statins, antihypertensive or non-steroidal anti-inflammatory treatments in the last 6 months were excluded from the study. If a participant had used an anti-inflammatory drug in the past five days, blood draws and psychiatric evaluations were postponed to a later date. Additionally, people with any signs of infection in the week before blood draw were not included in the study. For the neuropsychological evaluation, individuals who had a mental retardation diagnosis or a visual impairment at a level that could prevent the application of neuropsychological tests, or who had a neurological disorder or who had participated in any of the neuropsychological tests in the last 6 months were excluded from this study. Patients with OCD who participated in the study were diagnosed in Dokuz Eylul University psychiatry clinics prior to the study. 9 patients were not using any psychiatric medication, 21 of them were taking antidepressants and 12 of them were using drug combinations (anxiolytic, antidepressant, antipsychotics). Two of the patients were excluded from the study because they had psychotic features.

All protocols and methods were approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (2021 / 05-06, Protocol no.2021/14-27). Verbal and written informed consents were obtained from all participants.

2.2.Clinical Assessment

Sociodemographic Form: This form, which was created by the authors based on the literature, was used to gather information about the sociodemographic characteristics of the participants.

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I): It is a structured clinical interview form which was developed by First et al for DSM-IV Axis I disorders (27). It was developed to standardize SCID-I diagnostic evaluation by ensuring the application, investigating the symptoms and increasing its reliability and validity. The validity and reliability of it was conducted by Özkürkçügil et al (28).

Yale-Brown Obsession and Compulsion Scale (Y-BOCS): This scale measures the severity of obsessive and compulsive symptoms which was developed by Goodman et al. (29, 30). Turkish validity and reliability study was conducted by Karamustafalıoğlu et al. (31).

Hamilton Depression Rating Scale (HAM-D): Hamilton Depression Rating Scale is a 17 item test which measures the severity of depression and was developed by Max Hamilton (1960) (32) and structured by Williams in 1978 (33). The scale questions the symptoms of depression in the last week. Turkish validity and reliability studies of the scale were performed (34).

Neuropsychological Assessment

BERG Card Sorting Test: Berg Card Sorting Test (BCST) evaluates executive functions and cognitive flexibility by measuring perseverative responses, errors and completed categories (35). It was found appropriate to use BCST instead of Wisconsin Card Sorting Test (WCST) since it is equivalent to WCST and can be freely accessed on 'Psychology Experiment Building Language (PEBL)' (36).

Trail Making Test: The trail making test (TMT) consists of two parts that are A form and B form. While TMT-A is used for measuring psychomotor speed and focused attention; TMT-B form is used to measure executive functions, cognitive flexibility, and visual-spatial processing (37, 38). Turkish vali-dity and reliability study was conducted by Türkeş et al. (39).

Categorical Fluency Test: Categorical fluency test was used in order to evaluate executive functions. The participant is asked to count as many animal names as they can within one minute. The total number, the cluster average, and the number of transitions between clusters are evaluated (36).

Determination of Biochemical Parameters

Peripheral blood mononuclear cells (PBMCs) were isolated from fresh venous blood samples and used later for protein extraction. Expression of the NLRP3 inflammatory components were analyzed by Western Blotting using PBMCs. Antibodies used for each protein were anti-Caspase-1 (Abcam Cat # ab1872), anti-ASC (AG, Cat # 25B-0006-C), anti-NEK7 (Abcam, Cat # ab13351), anti-NLRP3 (AG, Cat # 20B-OO14-C), anti-β-actin (Abcam, Cat # ab6227). Membranes were incubated with Luminata Forte Western HRP Substrate (Luminata, WBLUF0500) and quantified using a chemiluminescence imaging system (Vilber Lourmat, ECX-F20L). Image analysis was performed using on-site software and protein levels were calculated with reference to β-actin.

Serum IL-1β and IL-18 cytokine levels were measured by Enzyme Linked Immunosorbent Test (ELISA). ELISA analysis was performed on serum samples isolated from blood collected in yellow capped gel bottom tubes. ELISA was performed according to the manufacturer's instructions for IL-1β (Thermo Scientific, Invitrogen, Cat # BMS224-2) and IL-18 (Thermo Scientific, Invitrogen, Cat # BMS267NST). Standard curves were used to determine the concentration of IL-1 and IL-18 in each sample.

Statistical Analysis

Statistical analysis was performed with Statistical

Package for the Social Sciences (SPSS) v24 (IBM). Mean±standard deviations were shown for all measured data while numerical data were indicated as percentages. Normal distribution was determined using the Kolmogorov-Smirnov test. For the non-normally distributed data, the Spearman Rank order test was used to evaluate relationships between neurocognitive and biological variables. P value <.05 was taken as statistically significant.

RESULTS

Forty-two OCD patients participated in this study. 40.5% of them were male. The mean age of the patients was 29.36, and the mean total year of education was 12.57. Participants' mean score of YBOCS was 25.33±6.67; the mean score of Hamilton Depression Score was 14.17±8.16. The mean duration of disease was 6.80±5.93 years. Other demographic variables, psychiatric comorbidities, and type of psychiatric medication used are summarized in Table 1.

Table 1. Sociodemographic and clinical characteristics of participants

Variables	*M*+*SD*	Min	Max
Age (year)	29.36+ 8.67	19	45
Education (total year)	12.57+3.53	5	18
Duration of disease (year)	6.80+5.93	0.50	21.00
YBOCS	25.33+6.67	9.00	37.00
HDRS	14.17+8.16	0.00	31.00
Gender	n(%)		
Female	25 (59.5)		
Male	17 (40.5)		
Marital Status			
Married	15 (35.7)		
Single	27 (64.3)		
Job Status			
Working	13 (31)		
Not working	29 (69)		
Comorbidities	n(%)		
Major depressive disorder (recent)	8 (19)		
Major depressive disorder remission)	5 (11.9)		
Dysthymia	8 (19)		
Generalized anxiety disorder	7 (16.7)		
Panic disorder	3 (7.1)		
Agoraphobia	1 (2.4)		
Specific phobia	5 (11.9)		
Post-traumatic stress disorder (remission)	1 (2.4)		
Psychiatric Medication	n(%)		
No medication	9 (21.4)		
Antidepressants	21 (50)		
Drug combinations	12 (28.6)		

YBOCS: Yale-Brown Obsessive Compulsive Scale, HDRS: Hamilton Depression Rating Scale.

Spearman rank-order correlation test showed that there was a significant negative correlation between IL-1β and TMT (B-A) (rs=-.36, p=0.019). ASC protein level was negatively correlated with TMT-B and TMT (B-A) (rs=-.38, p=0.03 and rs=-0.36 p=0.04, respectively) (Table 2).

Regression analysis tests for determining whether sociodemographic variables such as gender, age, and IL-1Beta and ASC levels predicts patients' TMT B-A, TMT-B scores yielded nonsignificant results.

DISCUSSION

In this study, we showed that TMT B-A is negatively correlated with serum IL-1β, while TMT B and TMT B-A are negatively correlated with ASC levels in PBMCs. The interplay between the immune system and the central nervous system is well-known to play roles in the pathophysiology of several neurodevelopmental and neuropsychiatric disorders, including OCD (40). However, it is not known whether cognitive functioning in OCD is affected by inflammation or not. Although cognitive impairments have been consistently reported in OCD including those related to mental flexibility, attention, memory, decision making, inhibition, verbal reasoning and planning (41), its neurobiological roots have not been elucidated. Cytokines affecting cognitive functions through modulating synaptic plasticity and neurogenesis can be one of the factors underlying cognitive impairments in OCD (42, 43). However, there is scarcity of studies that investigated a possible association between cognitive abilities and cytokine levels in OCD. IL-1β, a member of the interleukin family, is one of the most studied cytokines in OCD (44) and also associated with cognition-related processes. For the first time Schneider et al. demonstrated increased expression of IL-1β during long-term potentiation (LTP) which is a synaptic strengthening process central to learning and memory (45). To our knowledge, our study is the second in literature investigating the relationship between cytokine le-

Table 2. Correlations between neuropsychological tests, and NLRP3 inflammasome and cytokine levels in patients with OCD.

Variables	TMT-A	TMT-B	TMT (B-A)	CF	BCST-NC	BCST-Correct %	BCST-PE%	BCST-CLR%
IL-1β	r=0.017 p=0.913	r=-0.227 p=0.149	r=-0.362 p=0.019	r=-0.068 p=0.669	r=0.087 p=0.585	r=0.086 p=0.588	r=-0.219 p=0.164	r=0.111 p=0.490
IL-18	r=0.237 p=0.131	r=0.230 p=0.143	r=0.186 p=0.238	r=-0.246 p=0.116	r=0.042 p=0.789	r=-0.092 p=0.560	r=-0.196 p=0.214	r=-0.013 p=0.934
NEK7-western	r=-0.259 p=0.146	r=-0.373 p=0.033	r=-0.296 p=0.094	r=0.254 p=0.153	r=0.162 p=0.368	r=0.229 p=0.200	r=0.235 p=0.188	r=0.050 p=0.783
Caspase1-western	r=-0.021 p=0.909	r=-0.142 p=0.430	r=-0.166 p=0.355	r=-0.147 p=0.413	r=0.214 p=0.231	r=0.169 p=0.348	r=0.131 p=0.468	r=0.190 p=0.291
NLRP3-western	r=0.286 p=0.107	r=0.114 p=0.526	r=-0.045 p=0.802	r=-0.056 p=0.755	r=0.229 p=0.200	r=0.235 p=0.188	r=0.050 p=0.783	r=0.207 p=0.249
ASC-western	r=-0.185 p=0.310	r=-0.381 p=0.031	r=-0.364 p=0.041	r=-0.026 p=0.886	r=0.265 p=0.143	r=0.289 p=0.109	r=-0.209 p=0.250	r=0.258 p=0.155

NPT: Neuropsychological Test Performance, TMT: Trail Making Test, CF: Category Fluency, BCST: Berg Card Sorting Test, NC: Number of Categories Completed, CR: Correct Response, PE: Perseverative Error, CLR: Conceptual Level Responses

vels and neuropsychological parameters in OCD (26). Karagüzel et al. (26) showed that the TMT-A score was positively correlated with TNF-α, while IL-6 was positively associated with TMT-A and TMT-B and TNF-α and IL-6 were negatively correlated with Stroop interference effects. It may be concluded that these cytokines may have a counter effect on attention and cognitive inhibition in OCD patients (26). In our study TMT B-A was found to be negatively correlated with IL-1β, which is thought to take part in synaptic pruning and causing impaired neuroplasticity and impaired cognition (46). TMT is one of the extensively used neuropsychological evaluation tests for investigating executive functioning, speed of cognitive processing and visuo-motor speed (47). TMT-B performance was found to be related with inhibition/interference control, working memory, set-shifting and cognitive flexibility while B-A is considered as an absolute index of executive control abilities like attention and set-shifting and cognitive flexibility by eliminating visuoperceptual and working memory demands (48). Considering neurocognitive deficits in OCD, one can speculate that alterations in cytokines may play a role.

It was also reported that cytokines act as neuromodulators affecting memory and processing speed (43). A previous study showed that IL-1β as being one of the cytokine levels which was positively correlated with a faster decline in executive functioning in older adults (49). IL-1β is thought to regulate synaptic plasticity and influence hippocampal-dependent memory, also, it was suggested that an inverted U-shape pattern of IL-1β activity meaning basal level of IL1β was needed in order to maintain healthy memory functioning. Therefore, we can speculate that IL-1β is required to be at a certain level to modulate cognitive function (43, 50). Another study indicated that modest increase in IL-1β levels might lead to improvement in memory function, however, inhibition of IL-1β signaling or excess levels of IL-1β might cause memory dysfunction (51). IL-1β might modulate normal brain functioning via suppressing glutamate transmission (52). The cascade of events in inflammatory processes may damage the hippocampus, leading to difficulties in memory and learning as it was reported in a study with OCD patients (53).

Furthermore, we found a negative relationship between ASC protein levels and TMT-B and TMT B-A. ASC has been found to be related to the spread of inflammation (54). Considering its modulatory effect on inflammatory processes, another study reported that the difference in ASC protein levels between the healthy controls and patients with Mild Cognitive Impairment was greater than the difference between the patients with Alzheimer's disease (AD) and healthy controls (55). Therefore, it may be thought that ASC might be playing a protective inflammatory role particularly at early stages in the development of AD. In line with this hypothesis, we found that ASC levels might also be affecting executive functioning in patients with OCD. Therefore, it is possible to conclude that our findings are in accordance with the findings reporting that increased inflammatory cytokines are inversely correlated with cognition (56).

One of the limitations of our study is that the healthy group was not included in the study. Therefore it is hard to evaluate these variables between OCD patients and healthy people. Another limitation is the relatively small number of patients included in the study. Also medication use of patients for their depression and OCD symptoms can be the most important confounding factor, considering the known effects of certain

antidepressants on NLRP3 levels.

Further studies are needed to compare proinflammatory cytokine levels and perform various neuropsychological assessments simultaneously in a larger number of OCD patients and healthy controls. In this study, most of the patients were taking medication. In order to avoid this major confounding factor, future studies should be performed in drug-naive patients with OCD.

CONCLUSION

Considering the lack of studies searching for alterations in neuroinflammation and its association with the other neuropsychological dimensions particularly in OCD, our study is one of the pioneer studies in this field. Further research is needed in this promising area. Applying a more detailed neuropsychological battery, using pharmacological strategies that manipulates NLRP3 pathway and recruiting drug-naive OCD patients without comorbid disorders or medical conditions will provide more specific findings.

Disclosure statement

The authors declare no conflicts of interest in this work.

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