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The relationships between low grade inflammation, demographic and clinical characteristics in patients with OCD

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ABSTRACT

Objective: *To our knowledge, no study has specifically examined the relationship between C-reactive protein CRP levels and clinical features in patients with obsessive compulsive disorder (OCD), even though inflammation plays a role in the etiology of OCD. The aim of this study was to assess the associations between CRP levels and psychopathological and demographic variables in OCD.* ***Methods:*** *Ninety-eight consecutive outpatients with a diagnosis of OCD underwent a detailed clinical assessment for OCD. The study also utilized a cross-sectional patients' records design for obtaining CRP levels. Two groups of patients were compared by CRP levels at the cut-off of 3 mg/dl (high vs. normal).* ***Results:*** *Patients with high CRP levels exhibited worse insight, had earlier age of illness onset, higher rates of previous suicide attempts and positive family history for OCD compared to subjects with normal CRP levels. The logistic regression included three predictive variables for CRP status in patients with OCD (a) YBOCS-insight scores (b) age at onset and (c) family history of OCD.* ***Conclusion:*** *Our data indicates a significant association between inflammation and some clinical features in OCD. Future studies should prospectively examine longitudinal changes in CRP and its' association with clinical and demographic features.* ***(Anatolian Journal of Psychiatry 2017; 18(5):438-445)***

Keywords: *C-reactive protein, obsessive-compulsive disorder, inflammation*

OKB hastalarında düşük dereceli inflamasyonla klinik ve sosyodemografik özelliklerin ilişkisi

ÖZ

Amaç: *Son yıllarda inflamasyonun obsesif kompulsif bozukluğun (OKB) etyolojisindeki rolüne ilişkin kanıtlar artmaktadır. Bildiğimiz kadarıyla, OKB'li olgularda C-reaktif protein (CRP) ile klinik ve demografik özellikleri arasındaki ilişkiyi araştırmış herhangi bir çalışma yoktur. Bu çalışmada OKB'li olgularda CRP düzeyleri ile psikopatolojik ve demografik değişkenler arasındaki ilişkiyi değerlendirmeyi amaçladık.* ***Yöntem:*** *OKB tanısı konmuş ardışık 98 ayaktan hasta ayrıntılı olarak değerlendirildi. Inflamasyon göstergesi olarak değerlendirme sırasında bakılan CRP sonuçları hastaların bilgisayar kayıtlarından araştırıldı. Rutin olarak bakılan tetkiklerinde CRP kesme değeri 3 mg/dl olarak kabul edilerek (≥3 olan hastalar yüksek CRP; <3 olan hastalar normal CRP grubu) iki grup karşılaştırıldı.* ***Bulgular:*** *Elli sekiz hasta (%59.2) normal CRP, 40 hasta (%40.8) yüksek CRP olarak sınıflandırıldı. Yüksek CRP düzeyi grubunun iç görü düzeyleri anlamlı olarak diğer gruba göre daha kötüydü. Yüksek CRP grubundaki hastaların normal olan gruba göre anlamlı olarak daha yüksek oranda intihar girişimi, OKB için pozitif aile öyküsü olduğu ve daha erken hastalık başlangıç yaşına sahip oldukları bulundu. Lojistik regresyon analizinde üç değişkenin hastaların yüksek CRP grubunda olma riskini anlamlı yordadığı saptandı: İç görü düzeyleri, hastalığın başlangıç yaşı, OKB aile öyküsü.* ***Sonuç:*** *Bulgularımız OKB'li olgularda düşük dereceli inflamasyonla iç görünün, hastalık başlangıç yaşının, intiharın ve OKB için pozitif aile öyküsünün ilişkisine işaret etmektedir. Gelecek çalışmalarda CRP düzeyinde uzunlamasına dönemdeki değişimlerin, OKB'de psikopatoloji ile ilişkisinin araştırılması hastalığın*

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etiyolojisi ve tedavisine yönelik önemli katkılar sağlayabilir. ***(Anadolu Psikiyatri Derg 2017; 18(5):438-445)***

Anahtar sözcükler: *C-reaktif protein, obsesif kompulsif bozukluk, inflamasyon*

INTRODUCTION

Obsessive compulsive disorder (OCD) is a psychiatric disorder with a lifetime predominance of 1.6-2.3% in the general adult population.[1] The pathophysiology of OCD remains unclear, but includes dysregulation of various neurotransmitters (e.g. serotonin, dopamine and glutamate), neuroanatomical anomalies and genetic factors. The contributions of the immune system and inflammation to the pathophysiology of OCD has received specific consideration as of late.[2,3] A few authors have reported abatements of TNF-α, IL-6, and natural killer (NK) cells,[3,4] while others have discovered increased NK cell numbers in OCD patients.[5] Furthermore, a few investigators have reported noteworthy connections between psychopathology seriousness, clinical elements and proinflammatory cytokines in patients with OCD.[6,7]

C-reactive protein (CRP) is a reliable marker of inflammation.[8-10] Inflammation, as a marker for psychopathological symptoms and disorders, is of emerging interest due to recent preclinical and clinical information proposing a significant clinical connection.[11] Information regarding the role of CRP as a low-grade inflammation marker in psychiatric disorders is still contradictory. Nonetheless, a few studies have highlighted the connection between some psychiatric disorders, for example, depression, bipolar disorder and schizophrenia and raised CRP levels.[12-15]

Despite the fact that there is developing proof that underscores the role of inflammation in the aetiology of OCD, to the best of our knowledge, there are no studies that have specifically evaluated the relationship between CRP levels and clinical and sociodemographic features in patients with OCD. OCD is a heterogeneous disorder with different clinical presentation, course, outcomes and treatment response. It has been recommended that the distinctive clinical subtypes of OCD may be identified with various aetiologies and pathogenic systems.[16] Consequently, in this study, we aimed to evaluate the relationship between CRP levels and psychopathological and demographic factors in OCD. We anticipated that patients with high CRP levels would have different demographic and clinical attributes than patients with normal CRP levels. We additionally hypothesized that some clinical and demographic components would essentially predict CRP status (high versus normal) in patients with OCD.

METHODS

Subjects and study design

This was a cross-sectional study. One hundred and sixty-two consecutive outpatients with a diagnosis of OCD according to the DSM-IV-TR, were preliminarily recruited.[17] Diagnoses were made using the Structured Clinical Interview for DSM-IV.[18-20] The inclusion criteria were a) aged between 18 and 65 years and b) no dementia or cognitive deterioration according to DSM-IV criteria and the Mini-Mental State Examination (score >24).[21] The exclusion criteria were a history of alcohol or drug dependence, traumatic head injury, any past or present major medical or neurological illness and a current comorbid Axis I or Axis II diagnosis.

From the initial sample of 162 patients, 25 were excluded because they were diagnosed with a comorbid Axis I disorder, two were excluded due to cognitive deterioration, two were excluded because of mental retardation and 12 were excluded because they had an Axis II diagnosis. The study also utilized patients' records to obtain blood counts and CRP levels. Data were retrieved from the electronic medical records of all patients between October 2015 and April 2016 in Uşak University Medical Faculty Hospital. We excluded patients suffering from any acute physical illness, patients with fever (>37.9°C) or those treated with antibiotics, steroids, antipyretics or anti-inflammatory medications. In addition, six patients were excluded because they had been hospitalized for an acute physical illness at time of testing for CRP. Finally, 17 patients were excluded due to the absence of CRP and other inflammatory markers from the records. Therefore, 98 consecutive outpatients were included in the final sample.

Procedure

In our clinic, blood tests including complete blood count, metabolic measures, erythrocyte sedimentation rate and CRP are routinely performed at six-month intervals for the evaluation of drug side-effects and medical stability at certain outpatient admissions. As a part of this routine evaluation, laboratory tests of inflammation were routinely performed on the patients at admission:

CRP, white blood cells (WBC), platelet number and neutrophil to lymphocyte proportion. On the same day, those patients giving blood samples were assessed in detail for clinical and demographic variables. Sociodemographic and clinical data were collected using a questionnaire developed by the researchers. A number of standardized instruments were used in the clinical interview. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was used to determine global symptom severity.[22,23] The Y-BOCS insight item was used to rate the level of each subject's insight into their OCD symptoms.

Serum CRP levels were determined using ELISA and presented as milligrams per litre. All CRP levels were below 11 mg/l, lowering the possibility of a severe physical illness being the reason for the inflammatory state. The additional clinical information recovered included body mass index (BMI) and smoking status (smoker or non-smoker). The study was approved by our local ethics committee. The majority of the patients were sufficiently competent to provide composed informed consent, which was acquired from all patients and their families after they received full clarification of the methodology of the study.

Family history of OCD in first-degree relatives was determined by obtaining history from the proband (index patient) and at least one immediate family member (usually parents and/or siblings who live with the patient). If the patient and family member provided a history of significant OC symptoms (causing impairment in functioning, significant distress and consuming time) in any of the first-degree relatives (parents, siblings or offspring), then the patient was considered as having familial OCD. Furthermore, a patient was thought to be in remission if they had a Y-BOCS score <16 and did not satisfy DSM-IV-TR criteria for OCD.[24]

Statistical analyses

Data were analysed using the Statistical Package for the Social Sciences-PC version 16.0. The normality of quantitative data was checked using the one sample Kolmogorov-Smirnov test. Descriptive statistics are expressed as mean±SD, or rate (%). Two groups of patients were compared by CRP levels at the cut-off of 3 mg/l (elevated vs. normal). For univariate analyses, we used 2-tailed Student's *t*-tests, Mann-Whitney U test or Chi-squared test as appropriate. Multivariate analysis was performed using binary logistic regression analyses with CRP levels (elevated or normal) as a dependent variable controlling for age, sex, BMI and smoking status as covariates. A p value <0.05 was considered to indicate statistical significance.

RESULTS

Demographic and clinical characteristics

A total of 98 patients with OCD (60 women and 38 men) completed the study. The mean age of the patient groups was 31.53±10.30 years. The duration of illness was 6.06±6.01 years. The mean age at illness onset was 25.42±7.73. Table 1 shows detailed information about the sociodemographic and clinical features. Patients were classified into two groups: normal CRP level (≤3.0 mg/l) and elevated CRP (>3.0 mg/l). A level greater than 3 mg/l was considered outside the normal range for the normative values or high for this technique in our laboratory, and is consistent with values considered elevated according to the American Heart Association and the Centers for Disease Control and Prevention (AHA/CDC) statement on markers of inflammation and cardiovascular disease.[25,26]

Table 1. Demographic and clinical characteristics of the study subjects

		n	%
Obsessive-compulsive disorder (n=98)			
Gender	Female	60	61.2
	Male	38	38.8
Smoking status	No	76	77.6
	Yes	22	22.4
Marital status	Single	36	36.7
	Married	62	63.3
Socioeconomic level	Low	10	10.2
	Medium	72	73.5
	High	16	16.3

Numeric Variables	Mean±SD
Age	31.53±10.31
Years of education	11.20±3.74
Age at illness onset	25.43±7.72
Duration of illness	6.06±6.01
YBOCS-obsession	10.80±3.92
YBOCS-compulsion	8.20±4.21
YBOCS-insight (Item 11)	1.98±1.38
HAM-D	2.47±1.68
HAM-A	15.14±9.00
BMI	25.37±3.42

Table 2. Comparison of demographic features between patients with normal (<3 mg/dL) and elevated (>3 mg/dL) serum CRP levels at admission

		OCD with normal CRP (n=58) Mean±SD		OCD with high CRP (n=40) Mean±SD		Test	df	p
Age		33.82±10.09		31.75±9.80		t=2.74	96	0.070
Years of education		11.62±3.86		10.6±3.51		t=1.33	96	0.186
BMI		25.88±3.70		24.62±2.84		t=1.81	96	0.074
		n	%	n	%			
Gender	Female	36	62.1	24	60.0	χ^2=0.04	1	0.836
	Male	22	37.9	16	40.0			
Occupation	Unemployed	22	37.9	16	40.0	χ^2=1.14	3	0.766
	Worker	12	20.7	8	20.0			
	Officer	8	13.8	8	20.0			
	Housewife	16	27.6	8	20.0			
Marital status	Single	16	27.6	12	30.0	χ^2=5.12	1	0.054
	Married	42	79.4	28	70.0			
Socioeconomic level	Low	10	17.2	8	20.0	χ^2=7.84	2	0.060
	Medium	40	69.0	24	60.0			
	High	8	13.8	8	20.0			
Place of residence	Rural	18	31.0	12	30.0	χ^2=0.38	2	0.827
	Urban	40	69.0	28	70.0			
Smoking	No	43	74.1	33	82.5	χ^2=0.95	1	0.330
	Yes	15	25.9	7	17.5			

OCD: Obsessive compulsive disorder

Fifty-eight participants (36 women and 22 men) (59.2%) were classified as normal CRP and 40 (24 women and 16 men) were classified as high CRP. To validate the assumption that patients with an elevated CRP level (≥3 mg/l) present a subpopulation with an increased inflammatory state, correlation analyses were performed between CRP levels and other laboratory indices indicative of inflammation. We found that the following parameters significantly correlated with CRP levels: platelet counts, leukocyte counts and the neutrophil to lymphocyte ratio (r=0.734, p<0.001; r=0.451, p<0.001; r=0.558, p<0.001, respectively).

Two groups were compared with regard to age, gender, BMI, smoking status, education, place of residence and socioeconomic status. In addition, clinical variables were compared between patients with normal and elevated levels of CRP. A comparison of demographic information is presented in Table 2. The results showed that patients with elevated CRP levels had significantly lower mean age at illness onset than patients with normal CRP levels (t=4.89, df=96, p<0.001). Patients with high CRP levels had significantly higher rates of OCD presence in first-degree relatives (χ^2=6.18, df=1, p=0.013). According to the remission criteria mentioned above, 40 of the patients (40.8%) were in remission. We did not find any significant association between the remission status and CRP levels (high vs. normal) in patients with OCD (χ^2=0.19, df=1, p=0.89) (Table 3).

Here, we found that the most frequent obsessions and compulsions were 'contamination' (n=36, 36.7%) and 'washing/cleaning' (n=36, 36.7%), respectively. We did not find any significant difference in the rates of obsession and compulsion subtypes between the two groups (χ^2=6.31, df=6, p=0.390; χ^2=3.59, df=7, p=0.825). However, patients with elevated CRP levels had worse insight as detected by significantly higher Y-BCOS-insight scores (t=-8.97, df=96, p<0.001). There was a significant difference in the rates of previous suicide attempts between the two groups (χ^2=6.34, df=1, p=0.012). In total, 6.9% (n=4) of the patients with normal CRP levels and 25% (n=10) of the patients with high CRP levels had made at least one suicide attempt (Table 3).

Table 3. Comparison of clinical parameters between patients with normal (<3 mg/dL) and elevated (>3 mg/dL) serum CRP levels at admission

	OCD with normal CRP (n=58) Mean±SD		OCD with high CRP (n=40) Mean±SD		Test	df	p
Age at illness onset	28.28±7.02		21.30±6.82		t=4.89	96	<0.001
Duration of illness	5.48±3.50		6.90±8.41		t=-1.15	96	0.253
YBOCS-Obsession	11.00±4.12		10.50±3.63		t=0.62	96	0.507
YBOCS-Compulsion	7.59±3.78		9.10±4.67		t=-1.77	96	0.08
YBOCS-Insight (Item 11)	1.21±0.85		3.10±1.24		t=-8.98	96	<0.001
	n	%	n	%			
The status of remission							
Unremitted	34	41.4	24	40.8	χ^2=0.02	1	0.891
Remitted	24	58.6	16	59.2	χ^2=0.02	1	0.891
Previous suicide attempt							
No	54	93.1	30	75.0	χ^2=6.33	1	0.012
Yes	4	6.9	10	25.0	χ^2=6.33	1	0.012
The presence of OCD in first degree relatives							
No	53	91.4	29	72.5	χ^2=6.18	1	0.013
Yes	5	8.6	11	27.5			

OCD: Obsessive compulsive disorder

Table 4. Logistic regression for the prediction of elevated vs. normal CRP group status in patients with OCD

Predictor variables	B	S.E.	Sig.	Exp(B)	95.0% C.I.for EXP(B) Lower	Upper
Sex	-0.584	0.941	0.535	0.557	0.088	3.526
Age	0.159	0.076	0.138	1.172	1.009	1.361
Previous suicide attempt	-1.671	1.374	0.224	0.188	0.013	2.781
Smoking	0.680	1.088	0.532	1.973	0.234	16.658
BMI	0.140	0.148	0.344	1.151	0.860	1.540
Family history of OCD	-2.267	1.075	0.035	0.104	0.013	0.852
Age at illness onset	-0.384	0.122	0.002	0.681	0.537	0.865
YBOCS-insight score	2.016	0.457	0.000	7.510	3.064	18.407

OCD: Obsessive compulsive disorder

Logistic regression model of elevated CRP in patients with OCD

A binary logistic regression was applied with normal or elevated CRP levels as a dependent variable. The model contained YBCOS-insight score, age, sex, mean age at illness onset, BMI, smoking status, family history and previous suicide attempts as independent variables. The logistic regression model was statistically significant ($\chi^2_{(8)}$=85.21, p<0.001). The logistic regression equation correctly classified 93.9% of the cases. The logistic regression included three predictive variables for CRP status in patients with OCD. These variables were as follows: (a) YBOCS-insight scores (β=2.016, p<0.001); (b) age at onset of illness (β=-0.384, p=0.002) and (c) family history of OCD (β=-2.267, p=0.035) (Table 4).

DISCUSSION

In our determination, this is the first study to explicitly analyse CRP level and its' connection with OCD. The present study predominantly showed that patients with increased CRP levels displayed poor insight as measured by the Y-BOCS-insight item, had an earlier age at illness onset, higher rates of past suicide behavior and

positive family history for OCD compared to subjects with normal CRP levels.

In the present study, we found that insight, surveyed by the YBOCS-insight item, was all together poorer in patients with high CRP level than those with normal CRP levels. Additionally, current outcomes suggest that insight levels alone predict the CRP status in patients with OCD. It has been suggested that poor insight was connected with a specific clinical subtype portrayed by early disease onset, more severe obsessive compulsive symptoms and a poor response to treatment.[27,28] To date, no study has analysed the relationship between subclinical inflammation and insight in OCD. The neurobiological components supporting insight are largely obscure in OCD. However, recent studies have reported that OCD patients with poor insight may have a higher recurrence of brain abnormalities than normal patients and suggested that OCD patients with excellent and poor insight would have different neurobiological features.[29]

The penetrability of the blood-brain barrier is enhanced by CRP, and in conditions where CRP levels are raised; cytokines may have impacts on the brain.[30] Through their consequences for neurotransmitter frameworks, cytokines affect cerebral neurocircuits including the basal ganglia and anterior cingulate cortex, which can be identified in OCD with obsessive-compulsive symptoms and insight.[31] Conversely, raised CRP levels can cause cerebral atherosclerosis, which can result in small and large angiopathies. These injuries can disturb the frontal-subcortical integrity.[32] Aigner et al.[29] proposed a more extreme frontal-subcortical dysfunction in OCD patients with poor insight. Taking everything into account, these adjustments in brain neurochemistry and integrity may explain the insight contrasts related to inflammation in OCD.

A critical finding in the present study was that early illness onset was associated with high CRP levels in OCD. We have similarly found that patients with high CRP levels had a higher incidence of first-degree relatives with OCD than those with normal CRP levels. The incidence of OCD in first-degree relatives of OCD probands ranges from 5% to 22%.[33-35] The rate of familyality in our study (19%) is comparable with previous studies. Denys et al.[3] found that patients with early-onset and positive family history of OCD had lower numbers of NK cells than patients with late-onset and non-familial OCD. The investigators presumed that their outcomes may validate the existence of the Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) subgroup.[7,36] In the present study, high CRP levels in patients with familial and early-onset might be clarified by a lower NK count in a subgroup of OCD, which is conceivably identified with resistant pathology. Therefore, our findings support the hypothesis that there are distinctive clinical subtypes in OCD. Taken together, our outcomes suggest that raised CRP levels yield a particular OCD subgroup associated with a mixture of familial, early onset and poor insight groups already described in the literature.

Another interesting finding of this research is that patients with high CRP levels had significantly higher rates of past suicide attempts than those with normal CRP. Recent reports correlate suicide-related attempts with an inflammatory state, including increased levels of blood tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), and decreased levels of IL-2.[37-39] Our findings are supported by prior studies, which were carried out with depressed subjects. Recently, Gibbs et al.[38] found that as CRP level increased, the likelihood of patients' association with the suicidal group increased. However, Vargas et al.[40] did not discover any differences in CRP levels between patients with and without a history of suicide tendencies. Despite these findings, to date, there have been no studies looking at the connection amongst CRP and suicidality in patients with OCD. Currently, it is difficult to separate between the 'cause' and the 'result' because of the cross-sectional nature of the study.

Finally, we should consider the study's restrictions. To begin with, the sample size was small. Second, since this was a cross-sectional investigation of standard parameters, the long-term relationships between the factors were not examined. The research was further restricted by the accessibility to CRP levels in the medical records. None of our patients had any other psychiatric comorbidity and the sample may not be representative of all clinical populations. Such a sample however, suggests that these differences may be particular to OCD and are not created by different comorbidities. We only utilized CRP as a measure of inflammation, and obviously a more extensive analysis of inflammatory markers would have enhanced the quality of the study.

Conclusion

Despite previously mentioned limitations, our

findings suggest a significant relationship between inflammation and some clinical components, for example, insight, suicidality, age at disease onset and familiality, in patients with OCD. Our outcomes show rich insights for both logical information and clinical practice. An improved understanding of the relationship between psychopathology and subclinical inflammation in OCD may illustrate the role of inflammation, further encouraging the determination of new treatment modalities for this illness. Further research should address the pathophysiological mechanisms and the improvement capability of mitigating agents in OCD connected with raised CRP levels. In addition, future studies should tentatively look at longitudinal changes in CRP and different markers of inflammation, and their relationships with clinical and demographic features.

Contributions of authors: *O.E.: The design of the study, data collection, statistical analysis, writing manuscript, critically reviewed the manuscript. A.E.: The design of the study, data collection, carried out the diagnosis.*

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