Original article / *Araştırma*

Comparison of paraoxonase, prolidase activities and Hs-CRP, BDNF levels in patients with autogenous and reactive subtypes of obsessive compulsive disorder

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ABSTRACT

Objective: *Obsessions have been categorized as autogenous obsessions and reactive obsessions on the original of the cognitive theory and this study aimed to evaluate whether differences are found between obsessive compulsive disorder (OCD) subgroups in terms of biochemical markers.* ***Methods:*** *Thirty patients with obsessions defined as autogenous, 30 patients with obsessions defined as reactive group and 30 healthy volunteers were consisted the sample of the study. Sociodemographic Data Form, Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) were filled to the participants. The activity of paraoxanase, prolidase and Hs-CRP and brain-derived neurotrophic factor (BDNF) levels were detected.* ***Results:*** *There was no any statistically significant difference between autogenous and reactive obsession groups in terms of total mean score of Y-BOCS, BDI and BAI. Paraoxanase activity did not statistically significant difference between all groups. Prolidase activity showed significantly higher in reactive group than autogenous obsession and control groups. Serum Hs-CRP levels were not statistically different among participants of autogenous group, reactive group and control groups. Serum BDNF levels were significantly lower in autogenous obsession group rather than reactive obsession and control groups.* ***Conclusion:*** *This finding indicates that neurobiological processes have important role in the pathophysiology of autogenous obsessions.* ***(Anatolian Journal of Psychiatry 2019; 20(4):360-367)***

Keywords: *obsessive compulsive disorder, autogenous, reactive, neurobiology, biochemical measurements*

Otojen ve reaktif alt tipleri olan OKB hastalarında paraoksonaz, prolidaz aktivitesi ve Hs-CRP, BDNF düzeylerinin karşılaştırılması

ÖZ

Amaç: *Obsesyonlar bilişsel kuramın temelinde otojen obsesyonlar ve reaktif obsesyonlar olarak kategorize edilmiştir ve bu çalışmada obsesif kompulsif bozukluk (OKB) alt grupları arasında biyokimyasal belirteçler açısından farklılık olup olmadığı araştırılmıştır.* ***Yöntem:*** *Çalışmamıza otojen olarak tanımlanan obsesyonlara sahip 30 hasta, reaktif olarak tanımlanan obsesyonlara sahip 30 hasta ve sağlıklı gönüllülerden oluşan 30 kişi alınmıştır. Katılımcılara Sosyodemografik Veri Formu, Yale Brown Obsesyon Kompulsiyon Ölçeği (YBOKÖ), Beck Depresyon Ölçeği (BDÖ), Beck Anksiyete Ölçeği (BAÖ) uygulanmıştır. Paraoksonaz (PON1), prolidaz, high sensitif C-reaktif protein (Hs-CRP), beyin kaynaklı nörotrofik faktör (BDNF) düzeyleri ölçülerek karşılaştırılmıştır.* ***Bulgular:*** *Otojen ve reaktif obsesyon grupları arasında YBOKÖ, BDÖ ve BAÖ toplam puan ortalamaları arasında istatistiksel olarak anlamlı bir fark yoktu. Paraoksanaz aktivitesi tüm gruplar arasında istatistiksel olarak anlamlı farklılık göstermedi. Prolidaz aktivitesi reaktif grupta otojen obsesyon ve kontrol gruplarından anlamlı olarak daha yüksek bulundu. Serum Hs-*

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CRP düzeyleri otojen grup, reaktif grup ve kontrol grubu arasında istatistiksel olarak farklı değildi. Serum BDNF düzeyleri, reaktif obsesyon ve kontrol gruplarından çok, otojen obsesyon grubunda anlamlı olarak daha düşüktü. ***Sonuç:*** *Bu bulgular, nörobiyolojik süreçlerin otojen obsesyonların patofizyolojisinde önemli rol oynadığını göstermektedir.* ***(Anadolu Psikiyatri Derg 2019; 20(4):360-367)***

Anahtar sözcükler: *Obsesif kompulsif bozukluk, otojen, reaktif, nörobiyoloji, biyokimyasal ölçümler*

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a common and potentially debilitating disorder, which is characterized by recurrent intrusive thoughts, urges, or images (obsessions), accompanied by mental acts or repetitive behaviors (compulsions).[1] OCD is a relatively heterogeneous disorder due to its etiology, symptom structure and responses to treatment.[2] In the general population, OCD is estimated to have a lifetime prevalence of 2-3%.[3] To understand the pathophysiological mechanisms in OCD is vital to shed light on the varied treatment responses of patients, and designate homogeneous subgroups for the disorder.[4,5] Hence, there has been a remarkable rise in the number of studies in which several related features of the disorder are grouped together and subtypes that manifest more homogeneous specifications are defined. With respect to symptom-based grouping in OCD, studies proposed that obsessions could be categorized into two different groups termed 'reactive' and 'autogenous'.[6,7]

Reactive obsessions tend to be more common in the presence of identifiable external triggers. They are also considered less absurd and cause less discomfort therefore the individual feels less of need to conceal them. Contaminations, doubt, concern, symmetry, accidents, ordering, and hoarding obsessions are in this group.[8] Autogenous obsessions are more repeated and cause more anxiety than reactive obsessions and usually occur with no clear external triggers, and they are always perceived as ego-dystonic and distressing. Autogenous obsessions include images, thoughts or impulses that are often about religious, aggression or sexual contents.[9]

Although the neurobiological mechanism underlying in OCD is not yet fully understood, **numer**ous neuropsychological studies have pointed to likely inhibitory deficits in OCD patients.[8,10,11] Definition of homogeneous biomarker-based subtypes in the patient population could provide additional insights into patient-specific etiological mechanisms and improved treatment goals for individuals.[12,13] The previous literature underscored that grouping obsessions as autogenous and reactive would offer a homogeneous subtyping approach. Such an approach would enable an analysis of these disorders by developmental systems with respect to cognitive characteristics in various settings, as well as studies of dissimilar clinical features and use of various coping strategies.[6] Examining neurobiological factors that potentially may be responsible for differences in cognitive-development systems of subgroups could assist in detecting neurobiology-derived obsessions and pathophysiological mechanisms that possibly exemplify this domain, thereby leading to the development of new treatment models. For example, prolidase is involved in the metabolism of many biological molecules, and it plays major roles in physiological and pathological processes, including embryonic development, inflammation, cell migration, carcinogenesis, and angiogenesis.[14,15] Prolidase activity was found to be higher than healthy controls in patients with bipolar disorder and schizophrenia.[16,17] This study suggests that prolidase activity also increase in OCD.

The brain-derived neurotrophic factor (BDNF) is a protein and supports neuroplasticity, including the growth of neurons, synaptic transmission, and the arrangement of axonal and dendritic branching.[18-20] BDNF is strongly expressed in the cerebral cortex and hippocampus.[21] Previous studies reported decreased plasma or serum BDNF levels in patients with depression[22] and anxiety disorder.[23] Several studies demonstrated a potential role for BDNF in OCD. Hall et al.,[24] showed a very strong association between BDNF gene sequence variants, including Val66Met, and OCD. Suliman et al.,[25] reported reduced BDNF levels in patients with OCD. They also suggested that peripheral BDNF could possibly serve as a biomarker for OCD. Oliveira-Maia highlighted the need for consolidation of research to shed light on the potential role for BDNF in the neurobiology of OCD.[26] Beside this paraoxonase is an antioxidant, although its antioxidant mechanisms remain unclear.[27] Paraoxonase activity was lower in schizophrenia and depression patients in studies. This condition is consistent with the decrease in antioxidant activity and has been interpreted as having a similar effect with other antioxidants in etiology.[28,29]

We found no studies on OCD patients with auto-

genous obsessions and reactive obsessions that differentiated with respect to their neurobiological determinants in literature. This study hypothesized that a stronger or different neurobiological mechanisms in OCD patients with autogenous obsessions which are important in etiology and affect treatment. Therefore, the present study aimed to investigate the existence of potential differences in biochemical parameters (paraoxanase and prolidase activity and Hs-CRP and BDNF levels) in autogenous and reactive obsession subgroups.

METHODS

Patients and procedures

The study was conducted between October 2014 and June 2016 and patients with previous or recent diagnosis of OCD patients according to DSM-5 diagnostic criteria were consecutively included into the study. The exclusion criteria were patients with both reactive and autogenous obsessions in tandem at the time of the interview or in the past, medical conditions, pregnancy, neurological diseases or mental retardation, a diagnosis of any other mental illness; and drug abuse. According to Yale-Brown Obsessive Compulsive Scale (Y-BOCS), 35 patients with aggression, religious, and sexual obsessions but not exhibiting any reactive obsessions at the time of the examination or in the past were included in the autogenous obsession group. Likewise, 35 patients with a minimum of at least one reactive obsession, such as contamination, suspicion, symmetry of objects, ordering, collecting, hoarding, and somatic obsessions, but no autogenous obsessions at the time of the interview or in the past were included in the reactive obsession group. Thirty healthy volunteers were included in the control group. Five patients were excluded from the autogenous obsession group and in reactive obsession group due to hemolyzed or lipemic content of the samples or an insufficient sample quantity for serum samples.

This study was conducted according to tenets of the Declaration of Helsinki and approved by the local ethics committee. All participants gave written informed consent. The following scales were applied to the participants.

Yale-Brown Obsessive Compulsive Scale (Y-BOCS), is a semi-structured researcher-**administered** scale that measures the type and severity of obsessive compulsive symptoms among patients diagnosed with OCD.[30] The scale has a total of 19 items. To measure the intensity of symptoms alone, only the first 10 items (except items 1b and 6b) are used to determine the total number of points. The validity and reliability of the scale for a Turkish population were determined previously.[31]

Beck Depression Inventory (BDI), is comprised of 21 items, which was developed by Beck et al.[32] and Turkish adaptation was conducted by Hisli.[33] Beck Anxiety Inventory (BAI), measures the frequency and severity experienced anxiety symptoms. It is a Likert-type self-evaluation scale comprised of 21 items. It was developed by Beck et al. and Turkish validity and reliability study was performed by Ulusoy et al.[34,35]

Blood samples and measurement of biochemical variables

In the Biochemistry Laboratory of Medical Faculty in Yüzüncü Yıl University paraoxanase, prolidase, Hs-CRP, and BDNF measurements were computed by biochemistry specialists. Approximately 5cc of venous blood was obtained once only from the forearm veins of all the participants in the three groups (autogenous obsession, reactive obsession, and control). Using an NF 1200 R centrifuge device, the extracted samples were centrifuged at 4,000 rpm for 10 min to decompose the sera. The collected serum samples were stored at -80ºC.

Statistical analysis

Descriptive statistics for constant variables were illustrated, such as mean value, standard deviation, and minimum and maximum value. Categorical variables are described as numbers and percentage. With respect to constant variables, in the comparisons based on categorical variables, One-Way Variance Analysis (ANOVA) was harnessed. Subsequent to the variance analysis, Duncan's test was used to differentiate individual groups. Chi-square test was conducted to determine the relation between categorical variables. All statistical analyses were performed using SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Sociodemographic and clinical characteristics

There were 60 patients (autogenous obsession group, n=30; reactive obsession group, n=30) and 30 healthy individuals in the study group.

The mean ages in the reactive obsession, auto-

genous obsession, and control groups were 30.3±10.2 years, 27.3±7.72 years, and 28.25±7.06 years, respectively. There was no statistically significant difference between the genders and marital status among the groups (p>0.05). There was no significant difference be-

Table 1. Comparison of sociodemographic and clinical characteristics of the autogenous, reactive obsession and control groups

	Reactive obsession (n=30)		Autogenous obsession (n=30)		Controls (n=30)		p
Age (years) (mean±SD)	30.30±10.20		27.30±7.72		28.25±7.06		0.379
Age at onset of disease (years)	20.70±7.387		16.87±5.25				0.24
	n	%	n	%	n	%	
Gender							0.056
Male	7	23.3	16	53.3	11	36.7	
Female	23	76.7	14	46.7	19	63.3	
Marital status							0.20
Single	17	56.7	23	76.7	16	53.3	
Married	12	40.0	7	23.3	14	46.7	
Divorced	1	3.3	0	0			
External trigger							>0.05
No	14	47.0	17	57.0			
Trauma	1	3.0	1	3.0			
Delivery	4	13.0	2	7.0			
Marriage	1	3.0	0	0			
Social Stress	10	33.0	10	33.0			
Onset of disease							>0.05
Rapid	8	27.0	10	33.0			
Insidious	22	73.0	20	67.0			
Family history							>0.05
Yes	13	43.0	17	57.0			
No	17	57.0	13	43.0			

Table 2. The type of obsession and compulsions in autogenous and reactive obsession groups

	Reactive obsession group		Autogenous obsession group	
	n	%	n	%
Obsessions				
Religious	-		24	80
Sexual	-		22	73
Aggression	-		19	63
Contamination	25	83	-	
Suspicion	22	73	-	
Symmetry/order	18	60	-	
Somatic	3	10	-	
Collecting/hoarding	2	7	-	
Compulsions				
Cleaning/washing	28	93	-	
Control	22	73	6	20
Recurrent ritualistic behaviors	11	37	16	53
Counting	11	37	18	60
Listing/ordering	15	50	2	7
Cognitive/mental	9	30	27	90
Collecting/hoarding	1	3	2	7
Other	9	30	16	53

tween the groups with respect to smoking habits (p>0.05). The characteristics of the participants are shown in Table 1. Types of obsessions and compulsions in the autogenous and reactive obsession groups were presented in Table 2.

Comparison of the scale points of the autogenous, reactive obsession and control groups

The Y-BOCS total mean score of the reactive obsession group was 25.8, whereas it was 25.7 in the autogenous obsession group, with no statistically significant difference between the scores (p>0.05). There was also no statistically significant difference in BDI mean scores of the reactive and autogenous obsession groups (p>0.05). Furthermore, there was no statistically significant difference in the BAI mean scores of the reactive and autogenous obsession groups (p>0.05) (Table 3).

Table 3. Comparison of the mean scale points of the autogenous, and reactive groups

	Reactive group	Autogenous group	p
Y-BOCS total	25.8	25.7	>0.05
BDI total	27.3	26.4	>0.05
BAI total	28.2	29.4	>0.05

Y-BOCS: Yale Brown Obsessive Compulsive Scale; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory

Comparison of the biochemical parameters in all groups

Comparison of the paraoxonase, prolidase activity, serum Hs-CRP and BDNF levels between the three groups were presented in table 4. Firstly mean plasma paraoxonase activities were statistically similar in all groups (p>0.05). Prolidase activity was significantly higher in the reactive obsession group than autogenous obsession group and control group (p<0.05). Prolidase activity was reduced in the autogenous obsession group as compared with that in the reactive obsession group. There was no statistically significant difference in serum Hs-CRP levels of the participants between the three groups (p>0.05). In contrast, serum BDNF levels were significantly lower in the autogenous obsession group than reactive obsession and control groups (p<0.05).

In terms of antidepressant usage among the OCD patients, only 36 of the 60 patients used antidepressant drugs. There was no statistically significant difference in the paraoxonase and prolidase activity and Hs-CRP and BDNF levels of the patients who were receiving pharmacological treatment versus those who were drug

Table 4. Comparison of paraoxonase, prolidase activity, Hs-CRP and BDNF levels between the groups

	Reactive obsessions (n=30) (mean±SD)	Autogenous obsessions (n=30) (mean±SD)	Controls (n=30)(mean±SD)	p
Paraoxonase (U/L)	105.19±58.44	135.77±75.59	100.67±65.25	0.096
Prolidase (U/L)	301.35±304.58 A	71.43±110.79 B	148.66±147.20 B	0.001
Hs-CRP (mg/L)	2.11±3.42	2.29±2.52	2.17±3.05	0.970
BDNF (pg/ml)	1260.64±422.27 A	968.44±470.63 B	1282.77±536.36 A	0.022

Hs-CRP: High-sensitive C - reactive protein; BDNF: Brain-derived neurotrophic factor

Table 5. Comparison of patients who were receiving pharmacological treatment and no medications groups in terms of biochemical parameters

	Patients treated with AD (n=37) (mean±SD)	Nomedications (n=23)(mean±SD)	Control group(n=30) (mean±SD)	p
Paraoxanase (U/L)	122.42±78.80	117.37±49.95	100.68±65.26	0.432
Prolidase (U/L)	156.82±225.80	233.96±295.37	148.67±147.20	0.340
Hs-CRP (mg/L)	2.36±2.35	1.96±3.83	2.12±3.27	0.881
BDNF (pg/ml)	1111.03±514.21	1120.19±390.54	1282.78±536.37	0.33

Hs-CRP: High-sensitive C-Reactive Protein; BDNF: Brain-derived neurotrophic factor; U/L: units per liter; AD: Antidepressant

naive (p>0.05) (Table 5).

DISCUSSION

In this study, the hypothesis was that there would be a relationship between the subtypes of OCD in patients with autogenous and reactive obsessions and specific biochemical parameters (i.e., paraoxanase and prolidase activity, Hs-CRP and BDNF levels). In the present study, the most striking aspect of the sociodemographic data was the preponderance of male sex in the autogenous obsession group. This finding is in accordance with the literature. Hasler et al.,[36] reported that aggression, sexual, religious, somatic obsessions and control compulsion were more common among in men whereas contamination obsession and cleaning compulsions were more ubiquitous among females. This finding was consistent with that of a study of 133 patients by Keles Altun et al.,[9] in which there were detected to be more male patients in the autogenous groups. The aforementioned finding may be linked to the traditional preoccupation of women with house chores and cleaning and the characterization of such tasks as in their responsibility domain. Another study focusing on the correlation between obsession type and gender is the research conducted by Lochner et al. This study found that aggression appeared to be more common among men than women.[37]

The fact that autogenous obsessions surface with no evident stimulus provides tentative evidence that neurobiological mechanisms are likely to play an important role in the occurrence of autogenous obsessions. An important finding of our research was that the manifestation of autogenous obsessions occurred at a younger age than the age of onset of reactive obsessions in OCD patients. This finding supports the idea that biological mechanisms play a critical role in patients with autogenous obsessions. The presence of specific neurological disorders among early-onset OCD patients could also explain why autogenous obsessions are more ubiquitous in this group.

In terms of paraoxonase activity, we observed a statistically significant difference between the three groups. As is well known, paraoxonase functions as a crucial antioxidant against oxidetive stress and plays a vital role in the pathogenesis of a number of diseases, such as cancer and cardiovascular diseases.[38] In a study by Kandemir et al. on 28 children and adolescents diagnosed with OCD and 36 healthy controls, serum paraoxonase activity was significantly lower in the patient group.[5] Considering that age is one factor that affects paraoxonase activities, the discord between the findings of the study by Kandemir et al. and the present research may stem from the difference in the age groups of the two studies.[39] To clarify this issue, paraoxonase activities should be investigated in studies employing larger samples.

Previous research reported that increased proline activity was associated with activation of the NMDA receptor, which plays a role in the neurodegeneration process.[40] In other research, by affecting the synthesis and regulation of NO, prolidase activity mediated neuromodulation of NO, stress-induced hippocampal degenerative pathologies, and cognitive disorders. Accordingly, it was concluded that low-prolidase activity may be linked to lower NO effectiveness and increased neurotoxicity of glutamate.[41] In the same manner, witnessing lower prolidase activities among OCD patients with autogenous obsessions in comparison to the reactive group could be explained with the correlation that decreased neuroprotective effectiveness due to lowered NO activity can be linked to increased neurotoxicity that is mediated by glutamate and deteriorated neuromodulation. In the present study, serum prolidase activity in OCD patients with autogenous obsessions was significantly lower than reactive obsessions groups.

Many studies have investigated the link between psychiatric diseases, such as depression, schizophrenia, bipolar disorder, and OCD, and Hs-CRP levels.[42] In terms of the correlation between Hs-CRP and OCD literature review showed that Hs-CRP was analyzed among OCD patients. We found no studies on Hs-CRP levels in OCD patients with autogenous and reactive obsessions. In a prospective longitudinal study, Lou et al. found no significant difference in Hs-CRP levels between control groups and OCD patients at the onset of disease, and the follow-up period.[43] Likewise it was detected in our study that there was not any significant difference from the control group in terms of Hs-CRP levels among patients with reactive obsessions and autogenous obsessions. It can reasonably be suggested that inflammatory processes would play no different role in the formation systems of the autogenous and reactive obsessions.

Although many studies have shed light on BDNF levels in OCD patients, they are still quite limited in quantity. No studies have investigated BDNF levels in OCD patients with autogenous and

reactive obsessions. In a study that analyzed BDNF levels in OCD patients not receiving treatment, BDNF serum levels in the OCD group were lower than those in a healthy control group. In contrast, serum BDNF levels of OCD patients receiving treatment were not decreased.[44] Another study found significantly lower serum levels of BDNF in OCD patients not receiving treatment as compared with those in a healthy control group.[45] In the present study, the levels of BDNF in OCD patients with autogenous obsessions were significantly lower than those in the OCD patients with reactive obsessions and healthy group. The low levels of BDNF in OCD patients with autogenous obsessions in the present study are consistent with those reported in previous studies that included OCD patients, although these studies did not separate OCD into subgroups.[44,45]

In conclusion, this study is important because it sheds light on biochemical differences between autogenous and reactive subtypes of OCD. In OCD, to construe the systematic mechanism that plays role in the pathophysiology of disease, differences observed in resistance to treatments or treatment responses are significant and to investigate subgroups of the disease and determining dissimilar features of subgroups are crucial to propose novel treatment strategies. This study suggests that BDNF may play an important role in the neurobiology of autogenous obsessions by triggering a decrease or deterioration in neuroplasticity, and behavioral learning. Neurobiological processes are more effective in the pathophysiology of autogenous obsessions rather than reactive obsessions.

Authors' contributions: *P.G.O.: design, literature review, wrote the whole version of the manuscript; Ek.Y.: performed clinical assessment of the patients, writing of the manuscript; Em.Y.: carried out the labaratory assesments, performed the statistical analysis.*

REFERENCES

1. *American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association, 2013.*
2. *Lochner C, Stein DJ. Heterogeneity of obsessive-compulsive disorder: a literature review. Harv Rev Psychiatry 2003;11(3):113-132.*
3. *Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive compulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry 2010; 15:53-63.*
4. *Beşiroğlu L, Uğuz F, Sağlam M, Agargün MY, Aşkın R, Çilli AS. Psychopharmacological treatment response in obsessive compulsive patients with autogenous and reactive obsessions. Bulletin of Clinical Psychopharmacology 2007; 17(1):1-8.*
5. *Batmaz S, Yildiz M, Songur E. Psychopharmacological treatment differences in autogenous and reactive obsessions: A retrospective chart review. Nord J Psychiatry 2016; 70(1):31-37.*
6. *Lee H-J, Kwon S-M. Two different types of obsession: autogenous obsessions and reactive obsessions. Behav Res Ther 2003; 41(1):11-29.*
7. *Lee H-J, Kwon S-M, Kwon JS, Telch MJ. Testing the autogenous-reactive model of obsessions. Depression and anxiety 2005; 21(3):118-129.*
8. *Fan J, Liu W, Lei H, Cai L, Zhong M, Dong J, et al. Components of inhibition in autogenous- and reactive-type obsessive-compulsive disorder: Dissociation of interference control. Biol Psychol 2016; 117:117-130.*
9. *Keleş Altun İ, Uysal E, Özkorumak Karagüzel E. Differences between autogenous and reactive obsessions in terms of metacognitions and automatic thoughts. Neuropsychiatr Dis Treat 2017; 12:2977-2985.*
10. *Lei H, Yi J, Wang H, Zhang X, Dong J, Zho C, et al. Inhibitory deficit insemantic conflict in obsessive-compulsive disorder: an event-related potential study. Neuroscience Lett 2013; 552:162-167.*
11. *Penadés R, Catalán R, Andrés S, Salamero M, Gasto C. Executive function and nonverbal memory in obsessive-compulsive disorder. Psychiatry Res 2005; 133:81-90.*
12. *Leuchter AF, Cook IA, Hamilton SP, Narr KL, Toga A, Hunter AM, et al. Biomarkers to predict antidepressant response. Current Psychiatry Reports 2010; 12:553-562.*
13. *Beijers L, Wardenaar KJ, Bosker FJ, Lamers F, van Grootheest G, de Boer MK, et al. Biomarker-based subtyping of depression and anxiety disorders using Latent Class Analysis. A NESDA study. Psychol Med 2018; 4:1-11.*
14. *Hu CA, Phang JM, Valle D. Proline metabolism in health and disease. Preface. Amino Acids 2008; 35:651-652.*
15. *Demir S, Bulut M, Atli A, Kaplan İ, Kaya MC, Bez Y, et al. Decreased prolidase activity in patients with posttraumatic stress disorder. Psychiatry Investig 2016; 13(4):420-426.*
16. *Selek S, Altindag A, Saracoglu G, Celik H, Aksoy N. Prolidase activity and its diagnostic perfor-mance in bipolar disorder. J Affect Disord 2011; 129(1):84-86.*
17. *Güneş M, Bulut M, Demir S, İbiloğlu AO, Kaya MC, Atlı A, et al. Diagnostic performance of increased prolidase activity in schizophrenia. Neurosci Lett 2016; 613:36-40.*
18. *Hwang J, Brothers RM, Castelli DM, Glowacki EM, Chen YT, Salinas MM, et al. Acute high-intensity exercise-induced cognitive enhancement and brainderived neurotrophic factor in young, healthy adults. Neurosci Lett 2016; 630:247-253.*

19. *Calabrese F, Rossetti AC, Racagni G, Gass P, Riva MA, Molteni R. Brain-derived neurotrophic factor: a bridge between inflammation and neuro-plasticity. Front Cell Neurosci 2014; 8:430.*
20. *Borror A. Brain-derived neurotrophic factor mediates cognitive improvements following acute exercise. Med Hypotheses 2017; 106:1-5.*
21. *Alshogran OY, Khalil AA, Oweis AO, Altawalbeh SM, Alqudah MAY. Association of brain-derived neurotrophic factor and interleukin-6 serum levels with depressive and anxiety symptoms in hemodialysis patients. Gen Hosp Psychiatry 2018; 53:25-31.*
22. *Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. Biol Psychiatry 2008; 64:527-532.*
23. *Molendijk ML, Bus BA, Spinhoven P, Penninx BW, Prickaerts J, Oude Voshaar RC, et al. Gender specific associations of serum levels of brain-derived neurotrophic factor in anxiety. World J Biol Psychiatry 2012; 13:535-543.*
24. *Hall D, Dhilla A, Charalambous A, Gogos JA, Karayiorgou M. Sequence variants of the brain-derived neurotrophic factor (BDNF) gene are strongly associated with obsessive-compulsive disorder. Am J Hum Genet 200; 73(2):370-376.*
25. *Suliman S, Hemmings SM, Seedat S. Brain-derived neurotrophic factor (BDNF) protein levels in anxiety disorders: systematic review and meta-regression analysis. Front Integr Neurosci 2013; 7:55.*
26. *Oliveira-Maia AJ, Castro-Rodrigues P. Brain-derived neurotrophic factor: a biomarker for obsessive-compulsive disorder? Front Neurosci 2015; 16:134.*
27. *Atli A, Bulut M, Bez Y, Kaplan İ, Özdemir PG, Uysal C, et al. Altered lipid peroxidation markers are related to post-traumatic stress disorder (PTSD) and not trauma itself in earthquake sur-vivors. Eur Arch Psychiatry Clin Neurosci 2016; 266(4):329-336.*
28. *Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger G R, et al. The yale-brown obsessive compulsive scale: II. Validity. Arch Gen Psychiatry 1989; 46(11):1012-1016.*
29. *Karamustafalıoğlu O, Üçışık A, Ulusoy M, Erkmen H. Yale-Brown obsesyon-kompulsiyon derecelendirme ölçeğinin geçerlilik ve güvenirlik çalışması. 28. Ulusal Psikiyatri Kongresi 1993, Bursa.*
30. *Matsumoto C, Ohmori O, Hori H, Shinkai T, Nakamura J. Analysis of association between the Gln192Arg polymorphism of the paraoxonase gene and schizophrenia in humans. Neurosci Lett 2002; 321(3):165-168.*
31. *Barim AO, Aydin S, Colak R, Dag E, Deniz O, Sahin İ. Ghrelin, paraoxonase and arylesterase levels in depressive patients before and after citalopram treatment. Clinical Biochemistry 2009; 42(10):1076-1081.*
32. *Beck AT, Rush AJ, Shaw BF. Cognitive Therapy of Depression. New York: Guilford, 1979.*
33. *Hisli N. A study on the validity of Beck Depression Inventory. Journal of Psychology 1988; 6:118-122.*
34. *Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. Consult Clin Psychol 1988; 56(6):893-897.*
35. *Ulusoy M, Sahin N, Erkmen H. Turkish version of the Beck Anxiety Inventory: psychometric properties. J Cogn Psychother 1998; 12(2):163-172.*
36. *Hasler G, LaSalle-Ricci VH, Ronquillo JG, Craw-ley SA, Cochran LW, Kazuba D, et al. Obsessive-compulsive disorder symptom dimensions show specific relationships to psychiatric comorbidity. Psychiatry Res 2005; 135(2):121-132.*
37. *Lochner C, Hemmings SM, Kinnear CJ, Moolman-Smook JC, Corfield VA, Knowles JA, et al. Gender in obsessive-compulsive disorder: clinical and genetic findings. European Neuropsychopharmacology 2004; 14(2):105-113.*
38. *Uysal S, Akyol S, Hasgül R, Armutcu, Yiğitoğlu MR. Paraoxonase: A multifaceted enzyme. The New Journal of Medicine 2011; 28(3):136-141.*
39. *Kandemir H, Abuhandan M, Aksoy N, Savik E, Kaya C. Oxidative imbalance in child and adolescent patients with obsessive compulsive disorder. J Psychiatr Res 2013; 47(11):1831-1834.*
40. *Martin D, Ault B, Nadler JV. NMDA receptor-mediated depolarizing action of proline on CA1 pyramidal cells. Eur J Pharmacol 1992; 219(1):59-66.*
41. *Demir S, Bulut M, Atli A, Kaplan I, Ozdemir PG, Bez Y, et al. Is prolidase a neuroprotective molecule in post-traumatic stress disorder? Bulletin of Clinical Psychopharmacology 2015; 25(1):167-168.*
42. *Hansen-Grant S, Pariante C, Kalin N, Miller A. Neuroendocrine and immune system pathology in psychiatric disease. Textbook of psychopharmacology. Second ed., Washington, DC: American Psychiatric Press, 1998, pp.171-175.*
43. *Luo F, Leckman JF, Katsovich L, Findley D, Grantz H, Tucker DM, et al. Prospective longitudinal study of children with tic disorders and/or obsessive-compulsive disorder: relationship of symptom exacerbations to newly ac-quired streptococcal infections. Pediatrics 2004; 113:e578-e85.*
44. *Wang Y, Mathews CA, Li Y, Lin Z, Xiao Z. Brain-derived neurotrophic factor (BDNF) plasma levels in drug-naïve OCD patients are lower than those in healthy people, but are not lower than those in drug-treated OCD patients. J Affect Disord 2011; 133(1):305-310.*
45. *Maina G, Rosso G, Zanardini R, Bogetto F, Gennarelli M, Bocchio-Chiavetto L. Serum levels of brain-derived neurotrophic factor in drug-naive obsessive-compulsive patients: a case-control study. J Affect Disord 2010; 122:174-178.*