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Original scientific article

GDNF rs2910702, rs3096140, and rs3812047 POLYMORPHISMS IN OBSESSIVE COMPULSIVE DISORDER: PRELIMINARY STUDY

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The neurobiology of obsessive-compulsive disorder (OCD) is evidenced by a strong demonstration of malfunctions in the serotonergic and dopaminergic system. Recently, glial cell line-derived neurotrophic factor (*GDNF)* gene polymorphisms have been emphasized in psychiatric diseases and treatment strategies that have been tried to be developed in this regard. In the literature, there are several studies investigating the relationship between *GDNF* gene polymorphisms and psychiatric diseases excluding OCD. Therefore, this study aimed to compare the symptomatology and *GDNF* gene polymorphisms in early and late-onset OCD patients. For this purpose, patients diagnosed with OCD according to DSM-V diagnostic criteria in structured clinical interviews were grouped as early and late-onset based on the age of initiation. DNA was isolated from blood samples collected from 140 subjects (70 OCD and 70 healthy controls) in EDTA tubes, and rs2910702, rs3096140, and rs3812047 polymorphisms in *GDNF* gene were examined by Real-Time PCR. No significant correlation was detected between *GDNF* and the rs2910702, rs3096140, and rs3812047 polymorphisms in early and late-onset OCD subjects (P>0.05). Failure to detect correlations between OCD and *GDNF* gene polymorphisms might be due to the variable expression pattern of the *GDNF* gene in different tissues and pathologies. Therefore, future studies might be improved by including a larger group of patients and examining a wider range of tissues for the expression pattern of *GDNF*.

Key words: early-onset, *GDNF* gene, late-onset, Obsessive-compulsive disorder, single nucleotide polymorphism

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INTRODUCTION

Studies of obsessive-compulsive disorder (OCD) clusters and twins in families clearly demonstrate that genetics plays an important role in the etiology of the disease. Candidate gene studies have identified serotonergic, glutamatergic, and dopaminergic genes for OCD risk. Genetic linkage studies in OCD have linked chromosomes 9p24, 3q27-28, 14q23-32 and 1, 6, 7 and 15 with OCD. Genome-wide association studies (GWAS) of OCD have reported significant associations with the *RSPO4, DLGAP1, PTPRD, GRIK2, FAIM2, CDH20, MEF2BNB, MEF2B, MEF2BNB-MEF2B, BTBD3, ASB13* and *RFANK* genes. Polymorphism and methylation studies have shown the association of OCD with neurotrophic factor genes such as *BDNF* (PURTY *et al*., 2019, D'ADDARIO *et al.*, 2019).

Neurotrophic factors (NF) are families of molecules structurally and functionally related to neutrophin super family brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5)], including the family of glial cell line-derived neurotrophic factor (GDNF) (BARDE, 1990). Neurotrophic factors are a unique family of polypeptides that express important proteins for normal neuronal function, such as neurotransmitters and ion channels, and are effective in dendrite pruning and axon growth (HUANG *et al*., 2001). Since GDNF plays role in development and differentiation of dopaminergic neurons, it has a potential for Parkinson's disease therapy (GRANHOLM *et al.*, 2000). Also, disturbed *GDNF* expression was expected to be the reason for neuropsychiatric diseases such as depression and schizophrenia through impairment of dopaminergic neural circuitries and dysregulated synaptic plasticity (AIRAKSINEN *et al.*, 2002; HUDSON *et a*l., 1995). Conflicting results were obtained from the studies conducted on the expression levels of GNDF and depressive disorders. Patients with late-onset depression, major depression or bipolar disorder represented both increased and decreased levels of GDNF in their plasma (WANG *et a*l., 2011; ROSA *et al*., 2006; TSENG *et al*., 2013; DINIZ *et al*., 2012)

Modified epigenetic regulations in the *GDNF* promoter were hypothesized to help antidepressants and electroconvulsive therapy to increase the *GDNF* expression levels in rat hippocampal and human plasma (LIU *et al*., 2012; GOLAN *et a*l., 2011; ZHANG *et al*., 2010). Also, a post-mortem study on human brain samples revealed overexpressed GDNF protein levels in parietal cortex of patients with depression but not in basal ganglia and limbic areas (MICHEL *et al*., 2020). Interestingly, few genetic studies focused on the potential role of GDNF in etiopathology. First, GDNF involvement was suggested as a potential player in schizophrenia by a linkage study, which could not be verified by follow-up case-control studies that reported inconsistent findings (SUAREZ *et al*., 2006; LEE *et al*., 2001; MICHELATO *et a*l., 2004). As previously reported by WILLIAMS *et al*. (2007) who could not prove an involvement with schizophrenia after analyzing 9 single nucleotide polymorphisms (SNPs) and a poly-AGG repeat in 39 untranslated regions (WILLIAMS *et al.*, 2007). Other studies also failed to point a link between *GDNF* SNPs and attention deficit hyperactivity disorder (ADHD) (BOOR *et al*., 2002; SYED *et al*., 2007). The location on chromosome 5 where *GDNF* gene resides is continuously linked with Tourette syndrome (TS) in linkage studies (LAURIN *et al.*, 2009). Contrarily, expression of GDNF was observed in both gamma-aminobutyric acid (GABA)-ergic and cholinergic interneurons, which are known to be affected in TS (HIDALGO- FIGUEROA *et al.*, 2012). In addition to this, there is two serum study showing the relationship between OCD and

GDNF level and a *GDNF* polymorphism study associated with TS in OCD presence (FONTENELLE *et al*., 2012; TUNCA *et al*., 2015; HUARTES-FERNANDEZ *et al.,* 2015). However, these studies are insufficient and they do not reveal the role of *GDNF* in OCD. In this respect, this study was planned to understand the role of *GDNF* gene in early and late-onset OCD pathogenesis, to fill this gap in the literature, and to help guide future studies.

MATERIALS AND METHODS

Ethics

This study was conducted with the approval by the Institutional ethics committee of Aydin Adnan Menderes University in December 2016 (#2012\1010). Informed consent was obtained from all study participants and their families prior to the study.

Participants

The study group consisted of 70 patients diagnosed with OCD according to clinical interview scales and DSM-V diagnostic criteria. Patients with an onset of OCD before the age of 15 were considered as early-onset and after the age of 15 were considered as late-onset OCD. The control group included 70 people who were newly diagnosed with OCD and had no psychotropic medication or other drug use. Family histories were evaluated and those with a family history of psychiatric disease were recorded. Patients with schizophrenia, bipolar disorder, mental retardation and pervasive developmental disorders, major depression, posttraumatic stress disorder, panic disorder disease, smoking, alcohol use, and additional organic disease were excluded from the study. In both healthy control and OCD groups, people with a family history of schizophrenia and bipolar disorder that have high genetic transmission were excluded from the study.

Sample size

Sample size was determined by power analysis using G*Power software v3.1. Since a similar study could not be located in the literature related to this study, sample size was determined to be 64 patients considering the medium effect size with 0.05 type I error. Therefore, 70 OCD patients (early-onset OCD n=36; late-onset OCD n =34) were planned to be taken on the study. Additional 70 healthy control subjects were also included as control for comparison purpose.

Sociodemographic Data and Psychometrics Tests

Psychometric tests were administered by expert psychologists blind to the study. The sociodemographic data form was given to both groups. Also, both groups were evaluated by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS) and the DSM-III-R. Structured Clinical Interviews for DSM-II-(SCID-II) were performed to measure disease severity in OCD patients. Structured Clinical Interviews were evaluated for DSM-IV Axis I Disorders (SCID-I).

DNA Isolation

DNA was isolated from the blood samples of subjects according to the manufacturer's instructions with High Pure PCR Template Preparation Kit (Roche, Mannheim, Germany). DNA integrity and concentration was measured using Nano Drop 1000 Spectrophotometer V3.7 (Thermo Scientific, USA). DNA samples with a 260/280 optical density (OD) ratio between1.8 - 2.0 were considered suitable to work with. For Real-Time PCR analysis, 50 ng of DNA from each sample was amplified.

Genotyping

Genotyping in this study were performed according to CALISKAN *et al.* (2019) and DONDU *et al.* (2022). Single nucleotide polymorphisms (SNPs) were determined by Real-Time PCR on Light Cycler 480 (Roche, Berlin, Germany) using a panel of Light SNiP assay (TIBMOL BIOL GmbH, Berlin, Germany) based on Simple Probe® (Roche). The assay is able to distinguish single base mismatches allowing polymorphisms to be detected. A melting curve analysis was performed after Real-Time PCR to evaluate the functional variants rs2910702, rs3096140, and rs3812047 polymorphisms in *GDNF* gene.

Data Analysis

The data was analyzed by one-way ANOVA and Chi-Squared tests on SPSS-Windows 15 software (IBM).

RESULTS

Significant differences were present in age, education level, and marital status of the subjects between the study groups (P=0.005, 0.002, and 0.001, respectively). Gender distribution between the groups was similar (P=0.18). There was significant difference between the tic stories of the subjects in the groups (P=0.003). No significant differences were present in subjects' obsessions, compulsions, triggering life story, how to start, HDRS, HARS Y-BOCS Total, Y-BOCS-Obsess (Y-BOS obsessions) and Y-BOCS Comp (Y-BOS compulsion) scores between the study groups (P=0.19, 0.237, 0.67, 0.02, 0.867,0.756, 0.986, 0.889, and 0.766, respectively) (Table 1). Genotype distribution of *GDNF* rs2910702 gene polymorphisms was 50% AA, 28.2% AG, and 21.8% GG in the early-onset OCD group, 10% AA, 41.1%AG, and 48.9%GG in the late-onset OCD group, and 41% AA, 38.6% AG, and 20.4% GG in the control group. *GDNF* rs3096140 genotype distribution was 34.6%TT, 20.4%CT, and 45% CC in the early-onset OCD group, 47.4%TT, 47.6%CT, 5% CC in the late-onset OCD group, and 27.1% TT, 41.9% CT, and 31% CC in the control group. For *GDNF* rs3812047, it was 41% GG, 50%AG, and 9%AA in the early-onset OCD group, 36.2% GG, 15% AG, and 48.8 %AA in the late-onset OCD group, and 45.8%GG, 49.2% AG, 5% AG in the control group. Based on the genotypes, allelic frequencies were calculated as follows; 64.1% A, 35.9% G for rs2910702; 44.8% T, 55.2% C forrs3096140; and 66% G, 34% A forrs3812047 in the early-onset OCD group. Allele frequencies in the late-onset OCD were 31% A, 69% G for rs2910702; 71.2% T, 28.8% C for rs3096140; and 43.7% G, 56.3% A for rs3812047. Allele frequencies in the control group were 60.3% A, 39.7% G for rs2910702; 48% T, 52% C for rs3096140; and 70.4% G, 29.6% A for rs3812047. The chi-squared (χ^2) analysis of the genotype and allele distributions revealed no significant differences between the OCD groups and the control group (P>0.05) (Table 2).

Table 1. Sociodemographic and Clinical Comparisons of Groups
EOG: Early-onset group, LOG:Late-onset group,CG: control group,n: number, M: mean average, SD:standard deviation

	EOG	LOG	CG	
	n (%)	n (%)	n (%)	P value
Gender				
Female	27 (75)	30 (88)	40 (57)	0.18
Male	9 (25)	4 (12)	30 (43)	
Marital status				
Married	12 (33)	21 (62)	39 (56)	0.001*
Single	22 (61)	12 (35)	27 (39)	
Divorced	1 (3)	0 (0)	2 (3)	
Widow	1 (3)	1 (3)	2 (3)	
Tic story				
Yes	16 (44)	7 (21)	0 (0)	0.003*
No	20 (56)	27 (79)	50 (100)	
Triggered Life Event				
Yes	18 (50)	25 (74)		0.67
No	18 (50)	9 (26)		
How to start				
Sudden	8 (22)	10 (29)		0.02
Slow	28 (78)	24 (71)		
	n(%)	n(%)		P value
Obsessions				
Aggression	7 (19)	4 (12)		1.00
Contamination	14 (39)	22 (65)		0.09
Symmetry	11 (31)	11 (32)		1.00
Sexual	2 (6)	0 (0)		1.00
Religious	6 (17)	3 (9)		1.00
Somatic	3 (8)	2 (6)		0.11
Cleaning	10 (28)	14 (41)		0.54
Compulsions				
Cleaning	18 (50)	18 (53)		0.75
Ritualistic	2 (6)	3 (9)		0.10
Counting	10 (28)	1 (3)		0.09
Ordering/arranging	11 (31)	11 (32)		0.06
Hoarding	5 (14)	2 (6)		0.64
	M±SD	M±SD	M±SD	P value
Age	28.10±15.27	37.14±20.81	36.66±9.14	0.005*
Educational Level (year)	12.14±4.40	10.42±3.88	10.5±11.57	0.002*
HDRS	17.17±4.11	15.05±6.90	2.80±4.52	0.867
HARS	21.45±10.58	18.65±01.10	3.04±2.93	0.756
YBOCS TOTAL	25±8.14	22±7.79	0.0	0.986
YBOCS OBS	14.5±4.00	11.2±6.32	0.0	0.889
YBOCS COMP	12.3±9.59	12.1±4.55	0.0	0.766

Table 2. The genotype distributions and allele frequencies for GDNF polymorphisms in study groups.

Groups	rs2910702 polymorphism						
	Genotype (n/%)				Allele frequency (n/%)		
	AA	AG	GG	P value	A	G	P value
EOG (n=36)	18/50	10/28.2	8/21.8	0.307	23/64.1	13/35.9	0.670
LOG (n=34)	3/10	14/41.1	17/48.9		11/31	23/69	
CG (n=70)	27/40	25/36	18/26		40/57	30/43	
	rs3096140 polymorphism						
	Genotype (n/%)				Allele frequency (n/%)		
	TT	CT	CC	P value	T	C	P value
EOG (n=36)	13/34.6	7/20.4	16/45	0.318	16/44.8	20/55.2	0.890
LOG (n=34)	16/47.4	16/47.6	2/5		24/71.2	10/28.8	
CG (n=70)	21/30	29/41	20/29		34/49	36/51	
	rs3812047 polymorphism						
	Genotype (n/%)				Allele frequency (n/%)		
	GG	AG	AA	P value	G	A	P value
EOG (n=36)	15/41	18/50	3/9	0.259	24/66	12/34	0.433
LOG (n=34)	12/36.2	5/15	17/48.8		15/43.7	19/56.3	
CG (n=70)	30/43	32/46	8/11		45/64	25/36	

EOG: Early-onset group, LOG: Late-onset group, CG: control group, n: number

There were also no significant differences between gender, marital status, disease cycle, initiation, tic story, obsessions (aggression, symmetry, hoarding, contamination, sexual, religious, somatic), compulsions (cleaning, counting, hoarding, ritualistic, ordering/arranging), Y-BOCS Total, Y-BOCSObsess, Y-BOCS Comp, genotype, and allele distributions in the early and late-onset OCD patients (P>0.05).

DISCUSSION

This study is the first to investigate the relationship between early and late-onset OCD and *GDNF* gene polymorphisms in Turkish patients. In the study, no statistically significant relationship was detected between early and late-onset OCD patients and *GDNF* gene polymorphisms. Statistically significant difference was only detected in sociodemographic characteristics such as marital status, age, educational level, and tic stories of subjects with early and late-onset OCD.

OCD can be observed at 6-7 years of age with characteristic symptoms and disabilities, but may also occur for the first time in older ages. It typically begins in late adolescence or early adulthood. Age of onset usually corresponds to the early twenties (TUKEL *et al.*, 2004; LENSI *et al.*, 1996). Of the OCD adults, 30-50% reported that the onset was in childhood, and about two-thirds reported that the symptoms started before the age of 15 (RAPOPORT, 1990). According to this information in the literature, early and late-onset distinction in OCD was made before and after 15 years of age in the current study. It is thought that the disease starts at an earlier age in

men than women (NOSHIRVANI *et al*., 1991; TUKEL *et al*., 2005). Especially juvenile onset, often seen in males, has been associated with more familiality with tic disorder (EICHSTEDT *et al*., 2001). Similarly, in our study, OCD started earlier in men than in women, and this was thought to be associated with tics.

Early-onset of OCD is thought to be a distinctive feature. Differences have been reported in the number, distribution, and severity of symptoms among early and late-onset adult OCD patients (ROSARIO *et al*., 2001). In early-onset OCD patients, it has been shown that compulsions occur earlier than obsessions[33]the number of obsessions and compulsions was higher and the OCD symptom severity was higher; tic disorders and learning difficulties are more common; and treatment response was worse compared to the late-onset OCD (FONTENELLE *et al*., 2003; MILLET *et al*., 2004; MIGUEL *et al*., 2001). In one study, it was found that the time between the onset of OCD symptoms and the onset of the disorder in the early-onset group was shorter than that of the late-onset group (SOBIN *et al.*, 2000). In our study, similar to the literature, it was observed that the number of obsessions and compulsions were higher in early-onset OCD patients, compulsions were observed more than obsessions, and tic disorders were observed more frequently. In contrast to the literature, the onset time in early-onset OCD patients was found to be longer than the late-onset. Since the OCD patients in the study were not taking any medications, no response to treatment could be measured.

Based on the assumption that OCD is a neurodevelopmental disorder, it was hypothesized that the early-onset OCD may show a higher genetic transition and may be less related to environmental stressors. In late-onset OCD, stressful life events are thought to be effective in triggering the disease by using some genetic mechanisms. The neurobiology of OCD is characterized by a strong demonstration of dysfunction in the serotonergic and dopaminergic system. Family, twin, segregation, and linkage studies show that the genes related to serotonergic and dopaminergic system play a role in OCD (FRISCH *et al*., 2000). Recently, gene polymorphisms have been studied in psychiatric disease researches and treatment strategies are tried to be developed in this subject. Therefore, the relationship between *GDNF* gene polymorphisms and OCD was investigated in this study.

Neuronal growth, survival, and differentiation are regulated by neurotrophic factors expressed by the corpus striatum. Neurotrophic factors perform these functions through glutamate-dependent pathway as the neurodegenerative processes were shown to increase under dysregulated neurotrophic factors altering the glutamate signaling (MATTSON, 2008). Dopaminergic neurons located in the substantia nigra are also dependent on neurotrophic factors like BDNF and GDNF (HALL *et al*., 2003). The link between the *BDNF* and OCD was revealed, and *GDNF* currently may be linked to TS and ADHD as the *GDNF* locus on chromosome 5 was shown to be related with these diseases for more than one occasion (PASCUAL *et al.*, 2008; BARR *et al*., 1999; THE TOURETTE SYNDROME ASSOCIATION INTERNATIONAL CONSORTIUM FOR GENETICS, 2007) Concurrently, both striatal parvalbumin-positive(PV+)GABA-ergic and cholinergic interneurons express GDNF, both of which are known to be affected in TS (HIDALGO-FIGUEROA, *et al*., 2012). There is no study showing the direct relationship between OCD and *GDNF* in the literature. Limited studies are available. Two serum studies, on *GDNF* polymorphisms of OCD in combination with TS, and linkage study (FONTENELLE *et al*., 2012; TUNCA *et al*., 2015; HUARTES-FERNANDEZ *et al.*, 2015). In an association study of 6 target genes

(*GDNF*, *ITGA1*, *ISL1*, *FGF10*, *HCN1*, and *SLC1A3)* in the TS-linked region of chromosome 5 by LAURIN *et al.* (2009), no relation was found between TS and these 6 genes, GDNF being one of them. A significant relationship was found between the *GDNF* rs3096140 polymorphism and TS in a genotyping study that scanned 506 polymorphisms on 201 TS cases and 253 control subjects (HUARTES-FERNANDEZ *et al.*, 2015). In support of the results of LAURIN *et al*. (2009) no relationship between OCD and *GDNF* gene polymorphisms studied was found in the current study.

This study is the first to show that there is no relationship between early and late-onset OCD and *GDNF* gene polymorphisms in Turkish patients. Future studies with larger number of subjects and ethnic groups may be needed to further clear the association.

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GDNF rs2910702, rs3096140 i rs3812047 POLIMORFIZMI U OPESIVNO KOMPULZIVNOM POREMEĆAJU: PRELIMINARNA STUDIJA

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Izvod

O neurobiologiji opsesivno-kompulzivnog poremećaja (OCD) svedoči snažna demonstracija poremećaja u serotonergijskom i dopaminergičkom sistemu. Nedavno su u psihijatrijskim bolestima i strategijama lečenja koje se pokušalo razviti u tom pogledu naglašeni polimorfizmi gena neurotrofnog faktora (*GDNF*). U literaturi postoji nekoliko studija koje istražuju vezu između polimorfizama gena *GDNF* i psihijatrijskih bolesti isključujući OCD. Stoga je ovo istraživanje imalo za cilj upoređivanje simptomatologije i polimorfizma *GDNF* gena kod pacijenata sa ranim i kasnim OCD. U tu svrhu, pacijenti kojima je dijagnostikovan OCD prema dijagnostičkim kriterijima DSM-V u strukturiranim kliničkim intervjuima grupisani su rano i kasno na osnovu doba započinjanja. DNK je izolovana iz uzoraka krvi prikupljenih od 140 ispitanika (70 OCD i 70 zdravih kontrola) u EDTA epruvetama, a polimorfizmi rs2910702, rs3096140 i rs3812047 u *GDNF*-u ispitivani su PCR-om u stvarnom vremenu. Nije otkrivena značajna korelacija između *GDNF*-a i rs2910702, rs3096140 i rs3812047 polimorfizama u ispitanika s ranim i kasnim početkom OCD (P> 0,05). Neuspeh u otkrivanju korelacije između polimorfizama gena OCD i *GDNF* mogao bi biti posledica varijabilnog uzorka ekspresije gena *GDNF* u različitim tkivima i patologijama. Stoga bi se buduće studije mogle poboljšati uključivanjem veće grupe pacijenata i ispitivanjem šireg spektra tkiva radi ekspresijskog obrasca *GDNF*.

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