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RESEARCH ARTICLE

Cognitive functions and childhood traumas in panic disorder

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ABSTRACT

Objective: The aim of this study was to evaluate neurocognitive function in patients with panic disorder (PD) in comparison with healthy individuals and to determine whether there was a relationship between neurocognitive function, childhood trauma, and clinical symptoms in PD patients.

Method: A total of 31 healthy individuals and 26 patients with PD were included in this study. The Psychology Experiment Building Language (PEBL)-Berg Card Sorting Test (BCST), PEBL-Victoria Stroop Test (VST), PEBL-Connections Test (PCT), and PEBL-Corsi Block Test (PCBT) were used to evaluate neurocognitive function. Childhood Trauma Questionnaire (CTQ), the Hamilton Anxiety Scale (HAM-A), and a sociodemographic data form were administered to all of the patients. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Severity Measure for PD Scale was used to assess the symptom severity of PD patients.

Results: The PD patients had poorer BCST results in comparison with the healthy controls. The two groups had similar results on the VST, PCT, and PCBT. There was no statistically significant correlation between neurocognitive test scores and the CTQ and HAM-A scores in the PD group. Logistic regression analysis indicated that the diagnosis of PD was associated only with the total number of correct responses on the BCST subtests.

Conclusion: The results demonstrated that PD patients may have impaired executive function, such as problem-solving, strategy determination, complex attention, and conceptualization, however executive function was not generally associated with childhood trauma or the severity of PD.

Keywords: Child abuse, cognitive dysfunction, panic disorder

INTRODUCTION

Panic disorder (PD) is characterized by recurrent, sudden-onset attacks that cause intense fear or distress. Maladaptive behavioral changes may occur as a result of constant anxiety related to new attacks and the possible consequences (1).

It can be difficult to determine temporal precedence in the presence of cognitive impairment and anxiety. In some studies examining the neurobiology of anxiety disorders, it has been reported that neuropsychological functionality may be affected: It has been reported in several studies that anxiety reduces cognitive flexibility, impairs working memory and planning skills, decreases information processing speed and response inhibition, and makes decision-making difficult (2-6). There are also data suggesting that deficiencies in high-level cognitive processes precede the development of anxiety

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pathology and may be a risk factor for anxiety (7,8). A limited number of studies evaluating neuropsychological function in patients with PD have reported cognitive function impairment in areas such as short-term memory, visuospatial memory, executive function, long-term memory, and working memory (9-11).

Psychiatric disorders such as anxiety and depression in adulthood can be associated with childhood trauma (CT) (12). According to the World Health Organization, CT refers to adverse events, including physical and emotional abuse, physical and emotional neglect, sexual abuse, a negative family environment, peer violence, and witnessing collective violence occurring before 18 years of age. Sexual trauma in childhood increases the risk of PD in adulthood; a history of sexual and physical trauma has been observed at a higher rate in PD patients than some other anxiety disorders (13,14).

CT has been found to be associated with impairment of cognitive function, such as working memory capacity (15,16), verbal recall, and attention (15), in both clinical and nonclinical samples. Therefore, CT may predispose an individual to anxiety and cognitive dysfunction. Physical neglect and emotional abuse may also be associated with memory loss in adulthood, which may constitute a risk factor for the development of psychopathology. It has been suggested that healthy adults who are more exposed to physical neglect and emotional abuse have higher error rates on a spatial working memory test. However, a pilot study found that while there may be an association, the relationship between physical neglect or emotional abuse and psychomotor speed and sustained attention did not reach the level of significance. The relationship between executive function, such as visual discrimination, sustained attention, reasoning and planning skills, was not significantly associated with CT (17). In a study of adolescents aged 12-17 years without a diagnosis of psychiatric disorder, it was reported that there was a significant relationship between physical abuse and neglect and perseverative errors, which may have been related to decreased cognitive flexibility (18).

Few studies have evaluated executive function in PD patients, and a literature review revealed no study of the relationship between CT and executive function. Therefore, neurocognitive function, especially executive function, was a focus of this study. The objective was to compare PD patients and healthy individuals in terms of neurocognitive function and CT, and to evaluate the association between neurocognitive functions, CT, and clinical symptoms in PD patients. A hypothesis of the study was that PD patients would demonstrate more executive dysfunction and more CT than healthy controls, and that there would be a significant relationship between executive function, CT, and clinical symptoms. The results of this study may provide new insight into factors that may be associated with executive dysfunction in PD patients.

METHOD

The patients and healthy controls were informed in detail about the study and enrolled after providing consent. Approval for the research was granted by the Pamukkale University Faculty of Medicine Ethics Committee on August 8, 2019 (no: 60116787-020/54430).

Participants

A total of 26 patients and 31 healthy individuals who presented at the Pamukkale University Faculty of Medicine psychiatry outpatient clinic between September 2019 and July 2020 and were diagnosed with PD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Volunteer hospital staff and their relatives with similar age and gender characteristics to the PD group were included in the healthy control group following a psychiatric examination and assessment of medical history.

The members of the patient group all met the DSM-5 diagnostic criteria for PD and the participants in the control group had no psychiatric disorder. Exclusion criteria for the patient group were a comorbid psychiatric disorder other than PD or agoraphobia according to the DSM-5 and use of psychopharmacological drugs in the previous 15 days. Those who had disease-related cognitive dysfunction (such as cerebrovascular disease, dementia, intellectual disability/mental development disorder) that could affect psychiatric assessments and scale results and those who were illiterate were also excluded.

Measures

Sociodemographic Data Form

An information form was prepared by the researchers to collect sociodemographic data and clinical characteristics of the participants. The form was completed during clinical interviews conducted with the patients and healthy individuals.

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Severity Measure for Panic Disorder - Panic Disorder Scale (PDS): The PDS is a 10-item self-assessment scale developed by the

American Psychiatric Association to evaluate the severity of PD in individuals aged 18 and over. A 5-point Likert-type scale (0: never, 4: always) is used to respond to each item (1). The total possible score is 0-40, and a higher score indicates more severe PD symptoms. The average total score is calculated by dividing the raw total score by number of items in the measure (i.e., 10). The average total score reduces the overall score to a 5-point scale, which allows the clinician to gauge the severity of the disorder. A Turkish validity and reliability study was performed by Balikci et al. (19). The average total score of the scale was used in this study.

Psychology Experiment Building Language (PEBL)-Berg Card Sorting Test (BCST): The BCST is the computer version of the Wisconsin Card Sorting Test (WCST) which is a neuropsychological test used to measure frontal lobe (especially dorsolateral prefrontal cortex) function and executive function (20). The test involves reasoning, learning, problem-solving and the ability to change strategy according to changing conditions and measures cognitive processes such as complex attention, feature identification, perseverance, working memory, executive function, conceptualization, and abstract thinking (21). Fox et al. (22) assessed the BCST and found that the results were similar to those of the WCST (22). The test score is calculated by the program at the end of the test. Karakas et al. (23) provided a standardized Turkish version as part of the Neuropsychological Test Battery of Cognitive Potentials (BILNOT Battery) project and the BILNOT Handbook. The number of completed categories, the total number of correct responses, the total number of incorrect responses, the number of perseverative responses, the number of perseverative errors, the number of non-perseverative errors, the number of conceptual level responses and the learning to learn scores of BCST were analyzed in this study.

PEBL-Victoria Stroop Test (VST): The VST examines 3 basic processes: selective attention, word reading, and color naming as a reflection of frontal cortical area activity. Performance measures the individual's cognitive rigidity-flexibility, information processing speed, ability to change goals in line with changing demands, parallel processing of stimuli, and the ability to resist automatic processes. The VST uses 3 conditions in which the participant must name the color of dots (D), neutral words (W), and words for a color (C) printed in another color. The respondent is asked to inhibit incongruent inferences, when, for example, the word "green" is printed in red ink. The responses are timed and scored automatically. The first and second parts of the test are used to measure cognitive speed, and the third part is used to measure response inhibition. The Stroop effect is the delay in reaction and processing (24–26). A longer response duration indicates impaired processing (24). A standardized Turkish version of the VST was provided Karakas et al. (25) as part of the BILNOT Battery Handbook (25). The total time and C-W time difference, W/D, and C/D time ratios were analyzed in this study.

PEBL-Connections Test (PCT): The PCT is a matrix-based trail-making test in which the participant's task is to click on the appropriate item on the computer screen form connections as quickly as possible in a specified order. A series of samples are used, which include numbers and letters. Errors are recorded automatically. In the single section of the PCT the participant is asked to connect letters or numbers in sequence. In the switch section of the test, the letters and numbers appearing on the screen must be connected as 1-A, 2-B, 3-C and so on, or A-1, B-2, C-3, etc. The PCT provides important data about executive functions such as psychomotor speed, visual-motor scanning, planning, cognitive flexibility and complex response and complex attention ability (27,28). This version of the test was designed to avoid some of the confounds of earlier versions. A norm determination and reliability study of a Turkish test for participants aged 20-49 years was conducted by Turkes et al. (28). It has been reported that the single-and switch sections are strongly correlated with each other, and that the switch section can be used to evaluate higher-level cognitive functions (29). The numbers of target click, total click and overclicks on the single and switch sections of the PCT and the differences between these results were evaluated in this study.

PEBL Corsi Block Test (PCBT): The CBT is a widely used assessment of visuospatial working memory, the capacity to temporarily store and process information, which depends on the integrity of the prefrontal cortex. The original test uses 9 cube-shaped blocks placed on a board. The test-taker is asked to repeat a demonstrated sequence in the same or reverse order. Random sequences of increasing length are provided and the participant must try to replicate the pattern (21,30). Several digital versions have been developed that have advantages in terms of simplified use, accuracy in timing, and automatic response times. In this study, the PCBT (21), a computer version of the CBT, was administered using the forward response option. The block span, total correct responses, and total score data were evaluated in this study.

Childhood Trauma Questionnaire (CTQ): The original CTQ was developed by Bernstein in 1994 and included 70 items. It was later reduced to 28 items by the same researcher (31,32). The Turkish validity and reliability study of the scale was performed by Sar et al. (33). A categorical evaluation of the scale was provided by Walker et al. (34). The CTQ total score is the sum of 5 subtest scores consisting of emotional abuse, physical abuse, physical neglect, emotional neglect, and sexual abuse. Each subscore can yield 5-25 points, and the total score is 25-125. Positive statements are reversed when calculating the score. There are also 3 items measuring denial of trauma despite positive statements. The CTQ total score was used for the analysis in this study.

Hamilton Anxiety Scale (HAM-A): The HAM-A was developed by Hamilton in 1959 to determine the level of anxiety and symptom distribution (35). This interview scale comprises 14 items examining mental and physical symptoms. Eight items constitute the somatic subscore and 6 items represent the psychic subscore. A total of the subscores of ≤17 points is graded as a reflection of mild anxiety, 18-24 points is considered moderate, and ≥25 points is scored as severe anxiety. The Turkish validity and reliability study was conducted by Yazici et al. in 1998 (36).

Statistical Analysis

The data were analyzed using IBM SPSS Statistics for Windows, Version 25.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean±standart deviation and categorical variables as numbers (percentages). A chi-squared test was used for the categorical variables of gender, education level, marital status, and family history of psychiatric disorder. After assessment for normal distribution, the differences between the continuous variables of normally distributed age, neurocognitive test scores, CTQ total, HAM-A subscales and total score were analyzed using Student's t-test. Pearson correlation analysis was used to analyze the correlation between the neurocognitive test scores and the CTQ and HAM-A total scores in the PD group. Logistic regression analysis was applied to identify relationship between executive functions and PD. Age, gender and the scores of executive function tests (number of categories completed, total number of correct responses, number of conceptual level responses) that revealed significant difference between PD and healthy control groups were used as independent variables in logistic regression analysis. $P<0.05$ was considered statistically significant in all of the analyses.

RESULTS

There was no statistically significant difference between the 2 groups (PD group: n=26; control group: n=31) in terms of the sociodemographic variables of age, gender education level, marital status, and family history of psychiatric disorder with the exception of employment status (Table 1). Student's t-test used to determine whether there was a difference between the PD and control groups in terms of BCST, VST, PCT, and PCBT scores. It was revealed that the number of categories completed, the total number of correct responses and the number of conceptual level responses in the PD group were significantly lower and that the total number of incorrect responses and the number of non-perseverative errors in BCST were higher than healthy controls. There was no statistically significant difference between groups in terms of VST C-W time difference, W/D and C/D time ratios. The number of target and total clicks in the single and switch sections of the PCT was significantly lower in the PD group than in the healthy control group, however the differences of the total and over click numbers between the single and switch sections were similar in PD and control groups. No significant differences between groups were seen in any section of the PCBT (Table 2).

The findings indicated that the PD group had significantly higher scores than the control group in the CTQ total, HAM-A total and HAM-A subscale scores (Table 3).

There was no significant correlation between the neurocognitive test scores and the total scores of CTQ and HAM-A ($p>0.05$). In addition, there was no significant correlation between the CTQ, HAM-A, and PDS total scores ($p>0.05$). PDS total score was correlated with the PCBT block span ($r=0.529$, $p=0.005$), total score ($r=0.623$, $p=0.001$), total correct number ($r=0.422$, $p=0.032$), memory span ($r=0.599$, $p=0.001$) and PBT overclick single connection ($r=0.526$, $p=0.006$) subtest scores.

In the logistic regression analysis PD was performed using the PD and control groups were taken as dependent variables and age, gender, number of completed categories, total number of correct responses, and number of conceptual level responses were taken as independent variables. Analysis using the enter method determined that the independent variables explained 37% of a diagnosis of PD, and only the BCST-total number of correct responses subtest was associated with the diagnosis of PD (Table 4).

Table 1: Comparison of healthy controls and panic disorder patients according to sociodemographic variables

	Healthy control group (n=31)		Panic disorder group (n=26)				
	Mean	**SD**	**Mean**	**SD**	**t**	**df**	**p**
Age (years)	28.1	6.6	27.3	8.5	0.420	55	0.676
	n	**%**	**n**	**%**	**χ^2**	**df**	**p**
Gender							
Female	15	48.4	16	61.5	0.986	1	0.321
Male	16	51.6	10	38.5			
Marital status							
Married	7	22.6	9	34.6	1.014	1	0.314
Single	24	77.4	17	65.4			
Education level							
Primary school	2	6.5	6	23.1	4.301	2	0.116
High school	13	41.9	12	46.2			
University	16	51.6	8	30.8			
Employment status							
Unemployed	0	0	10	38.5	18.442	3	<0.001
Employed	18	58.1	5	19.2			
Student	13	41.9	10	38.5			
Retired	0	0	1	3.8			
Family history of psychiatric disorder							
Yes	8	25.8	7	26.9	0.009	1	0.924
No	23	74.2	19	73.1			

SD: Standard deviation

DISCUSSION

In this study PD patients performed more poorly on the BCST than healthy individuals, but demonstrated similar results on the VST, PCT, and PCBT. A PD diagnosis predicted the total number of correct responses in the BCST, which represents executive function. This result supports the hypothesis that executive functions would be impaired in PD patients and suggests a relationship between executive functions and PD diagnosis. Although the scores related to executive functions, such as problem-solving, complex attention, conceptualization, and planning were lower in the PD patients than in the healthy individuals, visuospatial working memory results were similar. In addition, the assumption that childhood traumas would be more common in PD patients was confirmed, however there was no association between executive functions and childhood traumas and the severity of PD symptoms.

Executive functions have a strong association with the frontal cortical area. The neurobiological model of PD suggests subcortical hyperactivation and therefore cortical hypoactivation, especially in the frontal cortical area (37). Executive dysfunction in PD is an expected finding in this context, but there have also been reports with contrary results. In some studies evaluating WCST performance, no significant difference was found between PD patients and healthy controls (9,27). The fact that no correlation was found between BCST scores and the severity of PD symptoms and anxiety in the PD group in this study suggests that executive functions were not affected by PD severity or general anxiety. The results of previous studies have also supported these findings that state and trait anxiety did not have a significant effect on executive functions, memory, or verbal learning (10). While high-level anxiety impairs cognitive function, low-level anxiety can also affect cognitive function negatively (38). Therefore, since there appears to be no linear relationship between anxiety level and attention, memory, and executive function, it was not surprising to find that there was no correlation between executive function and PD severity or anxiety.

Table 2: Comparison of BCST, VST, PCT, and PCBT scores between groups

	Healthy control group (n=31)		Panic disorder group (n=26)				
	Mean	SD	Mean	SD	t	df	p
BCST-Number of categories completed	4.1	1.1	3.0	1.4	3.107	55	0.003
BCST-Total number of correct answers	51.8	4.7	46.3	6.2	3.814	55	<0.001
BCST-Total number of incorrect answers	12.2	4.7	17.7	6.2	-3.814	55	<0.001
BCST-Perseverative response number	19.5	3.2	19.3	7.8	0.151	32.297	0.881
BCST-Perseverative error count	7.5	2.8	9.0	5.2	-1.336	55	0.187
BCST-Non-perseverative error count	4.6	3.1	8.3	7.5	-2.359	32.093	0.025
BCST-Conceptual level response number	47.8	6.4	41.7	11.7	2.499	55	0.015
BCST-Learning to learn score	1.5	4.1	2.9	6.8	-0.894	32.345	0.378
VST-Part D	51.7	15.5	58.3	18.5	-1.453	55	0.152
VST-Part W	39.2	11.6	47.2	18.0	-1.956	41.344	0.057
VST-Part C	49.6	15.7	59.3	24.3	-1.735	41.326	0.090
VST-C-W difference	10.4	10.9	12.0	11.4	-0.533	55	0.596
VST-W/D ratio	0.7	0.1	0.8	0.1	-0.905	55	0.369
VST-C/D ratio	0.9	0.3	1.0	0.2	-0.342	55	0.734
PCT-Target single connection	19.9	6.4	16.9	4.3	2.051	52.583	0.045
PCT-Click total single connection	21.3	6.3	17.6	5.8	2.276	55	0.027
PCT-Overclick single connection	3.9	2.7	6.1	5.5	-1.860	35.122	0.071
PCT-Target switch connection	16.8	5.3	14.3	3.2	2.041	55	0.046
PCT-Click total switch connection	18.4	5.2	14.8	4.4	2.705	55	0.009
PCT-Overclick switch connection	5.3	4.1	6.1	8.0	-0.477	55	0.635
PCT-Target switch-single difference	3.1	2.4	2.6	2.0	0.797	55	0.429
PCT-Click total switch-single difference	2.9	2.7	2.7	5.4	0.153	55	0.879
PCT-Overclick switch-single difference	-1.4	4.1	-0.1	6.6	-0.987	55	0.328
PCBT-Block span	5.7	1.2	5.4	0.9	0.846	55	0.401
PCBT-Total time	48.4	17.4	45.3	18.1	0.663	55	0.510
PCBT-Total	8.1	1.5	8.2	2.1	-0.076	55	0.940
PCBT-Memory span	5.1	0.7	5.0	0.8	0.274	55	0.785

BCST: Berg card sorting test, PCBT: PEBL-Corsi block test, PCT: PEBL-Connections test, PEBL: Psychology experiment building language, VST: Victoria stroop test, SD: Standard deviation

Table 3: Inter-group comparison of CTQ and HAM-A subscale scores

	Healthy control group (n=31)		Panic disorder group (n=26)				
	Mean	SD	Mean	SD	t	df	p
CTQ	31.8	6.5	38.5	12.1	-2.535	37.055	0.016
HAM-A total	2.0	2.6	18.3	4.8	-15.225	37.286	<0.001
HAM-A psychic	1.3	1.7	8.9	2.5	-12.792	42.817	<0.001
HAM-A somatic	0.7	1.1	9.0	3.4	-11.710	29.935	<0.001

CTQ: Childhood Trauma Questionnaire, HAM-A: Hamilton Anxiety Scale, SD: Standard deviation

Similar to the PCT results of this study, it was reported that there was no difference between healthy controls and PD patients in some studies using a trail-making test (TMT) (27,39). In another study, it was reported that the results of the first part of TMT, which evaluates psychomotor speed, were similar to those of

Table 4: Logistic regression analysis of neurocognitive functions predicting panic disorder

	Cox & Snell R^2	Nagelkerke R^2	Wald value	df	P	Odds ratio	95% Confidence Interval	
							Lower	Upper
Model	0.281	0.375						
Age			0.768	1	0.381	0.961	1.135	1.167
Gender			1.942	1	0.163	2.538	2.039	1.073
Number of completed categories			0.002	1	0.964	1.022	0.937	1.067
Total number of correct responses			6.386	1	0.012	0.679	0.982	1.064
Number of conceptual level responses			1.693	1	0.193	1.110	0.948	1.300
Constant			7.474	1	0.006	2457429		

Dependent variables: Panic disorder and healthy control groups. Independent variables: age, gender, number of completed categories, total number of correct responses, number of conceptual level responses. Exp (B): Odds ratio; df: Degrees of freedom

other studies and that performance in the second part, which evaluates cognitive flexibility, were lower in PD patients, but the difference was eliminated when the effect of comorbid psychiatric disorders was controlled (5).

The similar performance of PD patients and healthy individuals in the VST seen in this study support these results. However, BCST results evaluating functions related to the frontal cortical area suggest that executive function problems may occur in PD patients independently of the level of anxiety. These difficulties may be due to cortical hypoactivation in the frontal cortical area in PD patients (37). To our knowledge, there has not yet been a report of a significant etiological factor that leads to executive function impairment in PD patients. Kurt et al. (27) reported that there was no significant difference between healthy controls and PD patients in terms of executive functions. In addition, PD has not been associated with poor performance in the cognitive functions of selective attention, information processing speed, ability to change targets, parallel processing of stimuli with and without attention, and the ability to resist the interference of automated processes. PCBT performance evaluating visuospatial memory of PD patients were found to be similar to those of healthy individuals. In a meta-analysis study, it was reported that while there was some evidence of neurocognitive impairment in PD, further study was needed to draw meaningful conclusions (40). It has been reported that the PCBT performance of PD patients was lower than that of healthy controls and that the visuospatial working memory learning process was poor (9,41). In another study, it was noted that the PCBT performance of PD patients was significantly better than that of healthy controls (10,42). Inconsistent results regarding executive function in PD patients may be related to study characteristics such as age and education level, sample size, methodological differences (neurocognitive tests used), and comorbid psychiatric disorders. The small number of meta-analyses of studies with sufficiently similar conditions makes it difficult to reach a clear conclusion.

In this study, a history of CT was more prevalent in the PD patients than in the healthy patients. It has been reported that sexual trauma in childhood increases the risk of PD in adulthood, and a history of sexual and physical trauma in the past has been observed at a higher rate in PD patients than other anxiety disorders (13,14). It has also been observed that PD patients have a more frequent history of trauma, especially emotional abuse, compared with a healthy control group (43). Many studies have noted that CT exposure was associated with impaired cognitive functioning in adulthood. In a review, it was stated that poor performance in working memory tasks was observed in the presence of CT; there was a significant effect on visuospatial working memory functions, and CT negatively affected working memory performance in individuals with and without a psychiatric disorder (16). Majer et al. (17) also found that healthy adults exposed to emotional abuse and physical neglect had a higher error rate in tests related to spatial working memory. The lack of a relationship between neurocognitive performance and CT in PD patients in this study suggests that CT may not be associated with executive function, despite being more common in the PD patients. There is no study yet in the literature examining the relationship between executive function and CT in patients with PD. Based on all the findings of this study, it was concluded that there was no significant relationship between CT and

executive functions such as working memory, psychomotor speed, or attention in PD.

One of the limitations of this study is that the presence of a comorbidity in PD patients was not evaluated with a structured interview, but the participants were assessed with a clinical interview conducted by a psychiatrist. The level of depression, for example, which may affect the results related to neurocognitive function, was not evaluated. The fact that the PD patients included in the study did not use medication and that patients with other psychiatric disorders were not included in the study contribute to the value of the results of this study.

In conclusion, we found that a history of CT was higher in PD patients and that they may have problems related to executive functions such as problem-solving, complex attention, conceptualization, and abstract thinking.

Contribution Categories		Author Initials
Category 1	Concept/Design	N.K.O., D.B.
	Data acquisition	D.B.
	Data analysis/Interpretation	N.K.O., D.B., B.Y.
Category 2	Drafting manuscript	D.B., B.Y.
	Critical revision of manuscript	N.K.O., B.Y.
Category 3	Final approval and accountability	N.K.O., B.Y.
Other	Technical or material support	D.B., N.K.O.
	Supervision	N.K.O.

Ethics Committee Approval: Approval for the research was granted by the Pamukkale University Faculty of Medicine Ethics Committee on August 8, 2019 (no: 60116787-020/54430).

Informed Consent: The patients and healthy controls were informed in detail about the study and enrolled after providing consent.

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