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The Association between GHRL and LEP Gene Polymorphisms and ADHD: Evidence from a Pediatric Cohort

GHRL ve LEP Gen Polimorfizmleri ile DEHB Arasındaki İlişki: Pediatrik Kohorttan Kanıtlar

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GRAPHICAL ABSTRACT

The rs34911341 polymorphism in the GHRL gene may influence ADHD risk and play a potential role in ADHD pathogenesis.

Attention Deficit Hyperactivity Disorder (ADHD) is characterized by changes in dopaminergic neurons. Ghrelin and leptin, with neurotrophic properties, play a crucial role in CNS regulation. This study aimed to investigate the association between ADHD and GHRL (rs34911341) and LEP (rs7799039) polymorphisms.

29 children diagnosed with ADHD and 24 healthy children were included. Genotyping was performed using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) method.

The genotype frequency of the GHRL gene rs34911341 polymorphism significantly differed between ADHD and healthy control groups (p=0.036), but allele frequencies did not (p=0.207). For LEP rs7799039 polymorphism, neither genotype nor allele frequencies differed between the groups.

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ABSTRACT

Aim: Dopaminergic neurons and dopamine transporters show variations in Attention Deficit Hyperactivity Disorder (ADHD). Furthermore, Ghrelin and leptin, hormones recognized for their neurotrophic effects, are significant in central nervous system regulation, influencing neuronal survival and development.

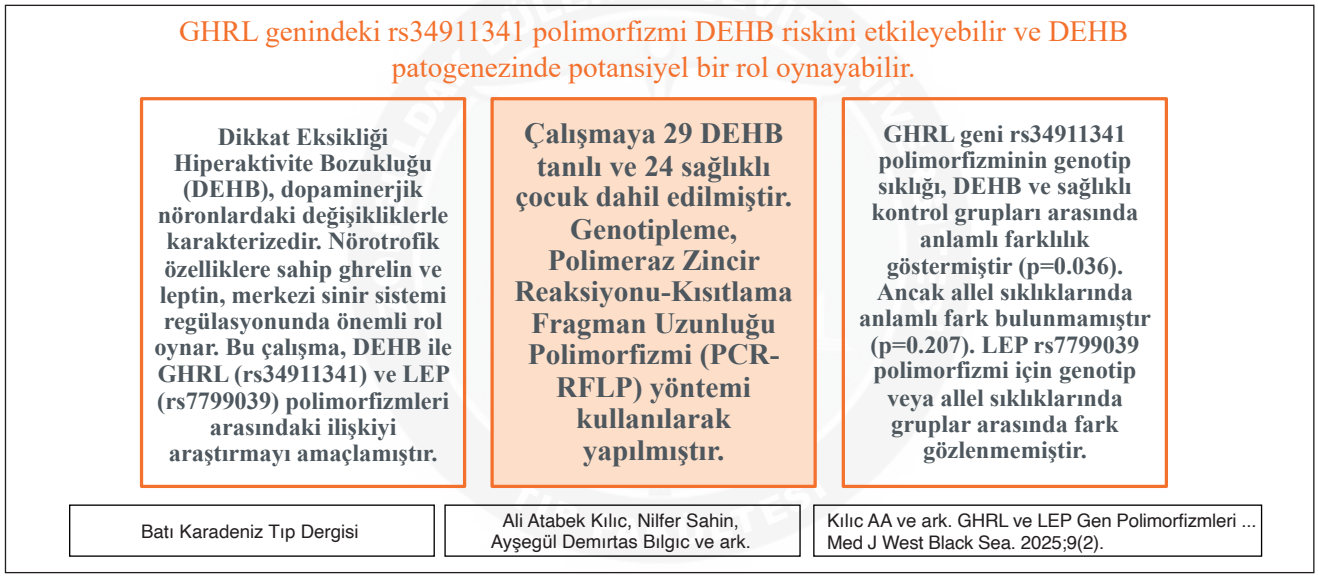
Material and Methods: This study aimed to examine the potential relationship between Attention Deficit Hyperactivity Disorder (ADHD) and polymorphisms in the GHRL (rs34911341) and LEP (rs7799039) genes. The research sample consisted of 29 children diagnosed with ADHD and 24 age-matched healthy controls. Genotypic analysis was conducted using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique.

Results: A significant difference in genotype distribution for the GHRL gene rs34911341 polymorphism was observed between the ADHD group and healthy controls ($p = 0.036$), whereas allele frequencies did not show a statistically significant difference ($p = 0.207$). In contrast, analysis of the LEP gene rs7799039 polymorphism revealed no significant differences in either genotype ($p = 0.579$) or allele frequencies ($p = 0.558$) between the two groups.

Conclusion: These findings suggest a potential role for the GHRL rs34911341 polymorphism in the development or presentation of ADHD. Further research is required to elucidate the mechanisms underlying this association.

Keywords: ADHD, development, GHRL, LEP, polymorphism

GRAFİKSEL ÖZET



ÖZ

Amaç: Dopaminerjik nöronlar ve dopamin taşıyıcıları Dikkat Eksikliği Hiperaktivite Bozukluğu'nda (DEHB) farklılıklar gösterir. Ayrıca, nörotrofik etkileriyle tanınan hormonlar olan Ghrelin ve leptin, nöronal sağ kalımı ve gelişimi etkileyerek merkezi sinir sistemi düzenlemesinde önemlidir.

Gereç ve Yöntemler: Bu çalışmanın amacı, DEHB ile GHRL (rs34911341) ve LEP (rs7799039) polimorfizmleri arasındaki ilişkiyi araştırmaktır. Çalışmaya DEHB tanısı almış 29 çocuk ve 24 sağlıklı çocuk dahil edildi. Genotipleme, PCR-RFLP (polimeraz zincir reaksiyonu-restriksiyon parça uzunluğu polimorfizmi) yöntemi aracılığıyla gerçekleştirildi.

Bulgular: GHRL geni rs34911341 polimorfizminin genotip sıklığı, DEHB ve sağlıklı kontrol grupları arasında önemli ölçüde farklılık gösterdi (p=0,036), ancak alel sıklıkları önemli ölçüde farklılık göstermedi (p=0,207). LEP rs7799039 polimorfizmi için, iki grup arasında ne genotip ne de alel frekansları farklı değildi (genotip frekansı için p=0,579; alel frekansı için p=0,558).

Sonuç: Bu bulgular, GHRL rs34911341 polimorfizminin DEHB'nin gelişiminde veya sunumunda potansiyel bir rolü olduğunu göstermektedir. Bu ilişkinin altında yatan mekanizmaları açıklamak için daha fazla araştırma gerekmektedir.

Anahtar Sözcükler: DEHB, gelişim, GHRL, LEP, polimorfizm

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a developmental problem that begins in childhood and manifests itself with symptoms such as difficulty in maintaining attention, sudden reactions and hyperactivity (1). Of paramount significance in the development and function of dopaminergic neurons is ghrelin. The GHRL gene, located on chromosome 3p25-26, encodes ghrelin, a hormone with roles in appetite, energy homeostasis, and importantly, dopamine signaling (2). The rs34911341 polymorphism in the GHRL gene has been implicated in studies of eating disorders and obesity, which sometimes have comorbidity with ADHD (3). The rs7799039 polymorphism in the LEP gene has been investigated in relation to stress and anxiety, which are also often related to ADHD (4). Longitudinal studies have underscored the persistence of ADHD symptoms into adolescence and adulthood (5). Individuals experiencing ADHD during their formative years face elevated risks of enduring challenges such as social impairment, delinquency, substance addiction, and accidents (6,7). Extensive research has illuminated a connection between ADHD and alterations in dopaminergic neurons and dopamine transporters (8,9). Insights from clinical brain imaging and genetic investigations have further solidified the link between ADHD and modifications within the dopaminergic system (10,11). Of paramount significance in the development and function of dopaminergic neurons is ghrelin. Deficiencies in ghrelin have been associated with dysregulation in dopaminergic neurodevelopment, mirroring ADHD-like behaviors. Notably, individuals with ghrelin deficiency exhibit conspicuous deficits in hyperactive locomotor activity and encounter learning and memory impairments akin to ADHD symptoms (12). Leptin, alongside ghrelin, also assumes a pivotal role in normal central nervous system regulation. Operating as a neurotrophic factor, leptin actively contributes to neuronal growth and survival (13). Its impact extends across both neuronal and glial cells, underscoring its sway over various nervous system facets (14,15). The notion of hyperactivity solely as a weight loss strategy has been expanded by studies on animal models, revealing a more intricate and multifaceted underlying mechanism (16). Although initially acknowledged for their roles in nutritional and appetite regulation, leptin and ghrelin have unfolded as vital players in brain physiology. They exert their influence on brain health through roles encompassing neuroprotection, neuroinflammation modulation, and metabolic regulation. Imbalances in metabolic equilibrium can lead to the erosion of neuroprotective pathways, while elevated leptin levels can exacerbate neuroinflammation, heightening susceptibility to neurodegenerative disorders (13). A plethora of investigations have linked leptin levels to a range of conditions, including depression, anxiety, behavioral disorders, sleep disturbances, and social isolation (17,18). We reported that the effect of the rs34911341 missense variant on protein stability and function is associated with pathogenic function (19). According to the Franklin database (https://franklin.genoox.com/), the G/A variation of the rs7799039 gene is located in the exon region of the LEP gene and is considered benign. The objective of this study is to investigate the potential link between ADHD and specific gene variants of GHRL (rs34911341) and LEP (rs7799039).

MATERIALS and METHODS

Study Population

The Faculty of Medicine's Medical Ethics Committee at Mugla Sitki Kocman University approved the study protocol (decision number: 16/I, dated 28/07/2021). All participants provided informed consent, confirming their voluntary participation. The study included 29 pediatric patients, aged 6 to 12, from the Department of Child and Adolescent Psychiatry at Mugla Sitki Kocman University's Faculty of Medicine. These patients were diagnosed with ADHD by a specialist child psychiatrist, using DSM-5 diagnostic criteria. Common comorbidities associated with ADHD, such as learning disorders, anxiety disorders, and oppositional defiant disorder, were also documented during the psychiatric evaluation. However, the study focused primarily on the ADHD diagnosis, and the influence of these comorbidities was not specifically analyzed. The control group comprised 24 healthy children without any psychiatric or chronic physical disorders. Children were selected for this group based on DSM-5-guided clinical interviews conducted by a child psychiatrist, confirming the absence of any chronic disease, ongoing medical treatment, or concurrent psychiatric disorder. Additionally, individuals with intellectual disabilities were excluded from the study. Sociodemographic data, including age, gender, and maternal and paternal ages, were recorded for all individuals in both the patient and control groups.

DNA Extractions and Genotyping

The spin column technique was employed to extract genomic DNA from peripheral blood samples, utilizing the Hibrigen Blood DNA Isolation Kit (MG-KDNA-02-250; Hibrigen Biotechnology R&D Industry and Trade Inc., Turkey). The LEP rs7799039 and GHRL rs34911341 polymorphisms were then genotyped using the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method. PCR amplification was performed in a 25 μL final reaction volume. Each reaction included 100 ng of template DNA and 2X Taq Master Mix (MG-TAQMX-01-80; Hibrigen Biotechnology R&D Industry and Trade Inc., Turkey). Thermal cycling was carried out using an automated thermal cycler (Thermo Fisher Scientific, USA). Table 1 provides the primer sequences and annealing temperatures used for amplification.

Post-PCR, amplification products were digested with specific restriction enzymes: SacI was used for rs34911341, and HhaI for rs7799039. Detailed digestion protocols, enzyme specifications, and expected fragment sizes are also provided in Table 1.

Electrophoresis of the PCR products was performed on 2. 5% agarose gels containing 0. 5 mg/mL ethidium bromide. To determine the size of the DNA fragments, a 100-bp DNA ladder (Thermo Scientific Gene Ruler, Catalog number: SM0241) was included in each lane.

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics software (version 22. 0; IBM Corp., Armonk, NY, USA). Depending on the data structure, categorical variables were analyzed using either Yates' corrected chi-square or Fisher Freeman-Halton tests. Quantitative variables were tested for normality using the Shapiro-Wilk test. Normally distributed data are presented as mean ± standard deviation (SD), and the independent samples t-test was used to compare groups. Non-normally distributed data are presented as median and interquartile range (IQR), and the Mann-Whitney U test was applied for group comparisons. Categorical data are shown as frequencies (n) and percentages (%). A p-value of less than 0. 05 was considered statistically significant.

RESULTS

DNA samples from 29 pediatric ADHD children and 24 healthy children were analyzed for GHRL gene rs34911341 and LEP gene rs7799039 polymorphisms. The patient's demographic features were shown in Table 2.

The control group's genotype distributions were consistent with Hardy-Weinberg equilibrium (p>0.05). Table 3 presents the genotype and allele frequencies observed for the GHRL rs34911341 and LEP rs7799039 polymorphisms. In the control group, the frequencies of the rs34911341 genotypes were: 58.3% for AA, 37.5% for AG, and 4.2% for GG. Conversely, the ADHD group displayed a different distribution, with 31.0% AA and 69.0% AG genotypes. This difference in genotype frequencies between the two groups was statistically significant (p=0.036), but there was no significant difference in allele frequencies for this polymorphism. Similarly, no significant differences were found in the genotype or allele distributions of the LEP rs7799039 polymorphism when comparing ADHD individuals with healthy controls (p > 0.05) (Figure 1).

DISCUSSION

ADHD stands as a prevalent and substantial neurodevelopmental condition characterized by the manifestation of attention deficits and/or hyperactivity/impulsivity symptoms (1). Within this investigation, we have delved into the potential impact of variations within the ghrelin and leptin genes on ADHD. Our findings unveil a significant relationship between the GHRL gene rs34911341 polymorphism and ADHD (p=0.036). In contrast, we did not find a significant association between the LEP rs7799039 polymorphism and ADHD. This could be due to several factors. Our sample size might have been insufficient to detect a small effect of this polymorphism. It's also possible that the LEP rs7799039 polymorphism does not have a direct effect on ADHD but rather interacts with other genes or environmental factors.

Table 1: Details of primer sequences, PCR-RFLP conditions, and PCR-product sizes

Gene	Polymorphism	Primers	Restriction Enzyme	Temperature of annealing	PCR -RFLP product sizes
GHRL	rs34911341	P1 P2	*Sac*I	64 °C	A allele : 618 bp G allele: 455 and 163 bp
LEP	rs7799039	P3		50°C	A allele: 242 bp G allele: 181 and 61 bp
		P4	*Hha*I		

P1: 5′-GCTGGGCTCCTACCTGAGC-3′ P2: 5′-GGACCCTGTTCACTGCCAC-3′
P3: 5′-TTCCTGTAATTTTCCCGTGAG-3' P4: 5′-AAAAGCAAAGACAGGCATAAA-3′

Table 2: Demographic data of the ADHD and control group

Clinical characteristics	ADHD (n=29)	Control (n=24)	p
Age (Mean±SD)	7.43 ± 1.39	7.16 ± 2.05	0.271
Gender, n(%)			
Male	24 (82.76)	17 (70.83)	0.341
Female	5 (17.24)	7 (29.17)	
Maternal Age (Mean±SD)	35.73 ± 4.38	35.96 ± 4.69	0.594
Paternal Age (Mean±SD)	39.94 ± 5.85	40.12 ± 5.56	0.553

Table 3: Genotype and allele frequency distribution of the GHRL rs34911341 and LEP rs7799039 polymorphism

	Control n (%)	ADHD n (%)	p
Genotype rs34911341			
AA	14 (58.3)	9 (31.0)	**0.036**
AG	9 (37.5)	20 (69.0)	
GG	1 (4.2)	0 (0.0)	
Allele rs34911341			0.207
A	37 (77.1)	38 (65.5)	
G	11 (22.9)	20 (34.5)	
Genotype rs7799039			
AA	5 (20.8)	10 (34.5)	0.579
AG	14 (58.3)	13 (44.8)	
GG	5 (20.8)	6 (20.7)	
Allele rs7799039			0.558
A	24 (50)	33 (56.9)	
G	24 (50)	25 (43.1)	

Table 4: Association Between rs34911341 and rs7799039 Polymorphisms and ADHD. Odds Ratio (OR) and 95% Confidence Intervals (CI)

SNP	To compare	OR	%95 GA
rs34911341	Genotype (AG vs AA)	3.46	1.10 – 10.91
	Allele (G vs A)	1.77	0.75 – 4.20
rs7799039	Genotype (AG vs AA)	0.46	0.12 – 1.72
	Allele (G vs A)	0.76	0.35 – 1.63

Table 5: Relationship Between rs34911341 and rs7799039 Polymorphisms and ADHD. Odds Ratios (OR) and their corresponding 95% Confidence Intervals (CI)

SNP	Karşılaştırma	OR	%95 GA
rs34911341	Genotype (AG vs AA)	3.46	1.09 – 10.91
	Allele (G vs A)	1.77	0.75 – 4.20
rs7799039	Genotype (AG vs AA)	0.46	0.12 – 1.72
	Allele (G vs A)	0.76	0.35 – 1.63

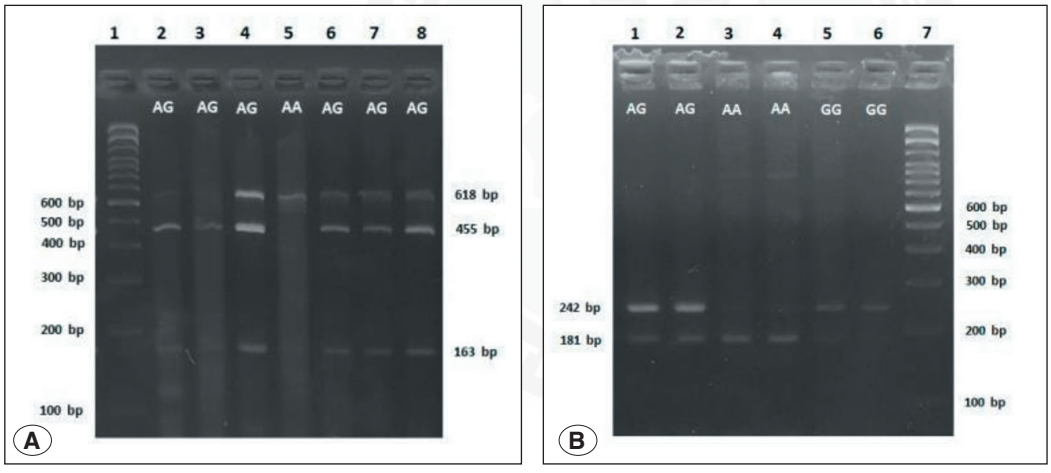


Figure 1: PCR-RFLP analysis for genotyping of GHRL rs34911341 polymorphism.

Ghrelin, an essential hormone predominantly synthesized in the stomach, holds a pivotal role in the regulation of both appetite and energy equilibrium. Investigative studies have drawn connections between variations within the ghrelin gene and various aspects of food consumption, eating disorders, and traits linked to obesity. These genetic deviations have the potential to influence either ghrelin production or its interaction with receptors, consequently impacting the intricate orchestration of appetite regulation and eating behaviors. Moreover, the genetic locus situated at 3p25-26, encompassing genes proximal to the ghrelin gene, has exhibited associations with metrics such as body fat percentage and cholesterol levels. While these genetic associations yield valuable insights into the genetic underpinnings of these traits, further research endeavors are indispensable to fathom the intricacies of their mechanisms, particularly their interplay with environmental factors (20). To further elucidate the potential role of ghrelin in ADHD, it's important to consider its distribution and function within the brain. Ghrelin receptors are found in several brain regions implicated in ADHD, including the hypothalamus, hippocampus, and ventral tegmental area (VTA) (21). In the VTA, ghrelin can modulate dopamine neurotransmission, a process that is known to be disrupted in ADHD (22). Polymorphisms in the GHRL gene could therefore influence dopamine signaling and contribute to the symptoms of hyperactivity, impulsivity, and inattention. For example, some studies suggest that ghrelin's influence on the mesolimbic dopamine pathway

may be related to impulsivity and reward-seeking behaviors, both of which are core features of ADHD (23). Delving into the interface of ghrelin with stress-induced anxiety, Asakawa et al. embarked on a study involving rodents. Their findings revealed that stress incites an elevation in ghrelin secretion, indicating a stress-responsive surge in ghrelin levels. Intriguingly, the administration of ghrelin subsequently elicited heightened anxiety-like behaviors in the rodents. This intriguing pattern suggests that ghrelin could potentially trigger anxiety under certain conditions. These observations thus furnish tangible evidence of ghrelin's involvement in the intricate web of stress responses and its plausible role in shaping anxiety-related behaviors. This underscores the nuanced interrelation between stress and the regulation of emotional states (24). The realm of psychiatric disorders, with a particular focus on impulsivity, ADHD, and eating disorders, has yielded intriguing connections to ghrelin. Notably, Anderberg et al. ventured into this domain, theorizing that ghrelin might heighten impulsivity owing to its appetite-stimulating effects. Their experimentation, involving the injection of ghrelin into the lateral ventricles of mice, resulted in observable increases in impulsive behaviors and impulsive decision-making, further supporting the notion of ghrelin's impact on impulsivity (25) In parallel, a study investigating the link between autism and ghrelin revealed lower serum ghrelin levels in children with ASD versus controls, given their similar pathophysiology to ADHD (26). Nonetheless, investigations by Vivenza et al. have indicated that polymorphisms within the ghrelin gene exhibit no discernible effects on overall ghrelin release, food intake regulation, energy equilibrium control, or endocrine functions (27). The Leu72Met polymorphism, while not introducing structural aberrations in mature ghrelin protein, does appear to impact mRNA stability, subsequently influencing ghrelin secretion or activity (28). Previous studies have explored the link between attention-deficit/hyperactivity disorder (ADHD) and the SYN III gene polymorphisms, specifically -631 C>G and -196 G>A. Kenar et al. reported an association between ADHD and the presence of the G allele at the -631 C>G site and the C allele at the -196 G>A site (29). Leptin, an adipose tissue-secreted hormone, was initially identified for its involvement in appetite regulation and maintaining energy balance. However, recent research indicates that leptin has broader effects on neuroendocrine and neuroprotective functions, extending beyond metabolic regulation and impacting multiple brain processes. There have been reports linking stress and anxiety disorders to the pathophysiology of ADHD (30). The study unveiled a positive correlation between elevated leptin levels and heightened levels of perceived stress in men (31). The selective deletion of leptin receptors in the adult hippocampus has been shown to induce behaviors associated with depression (32). The study conducted by Kraus et al. focused on investigating serum leptin levels in three separate groups: patients with schizophrenia, patients with depression, and a healthy control group. The remarkable finding of the study is that patients with schizophrenia exhibit significantly lower leptin levels than both the healthy control group and the group of individuals with depression. This observation suggests the possibility of a dysregulation of leptin signalling specifically associated with this psychiatric disorder (33). In 6-hydroxydopamine-induced Parkinson's disease animal models, leptin administration demonstrated the ability to ameliorate behavioral abnormalities and mitigate dopaminergic cell death (34). The association between leptin levels and the LEP gene rs3828942 polymorphism in anxiety disorders has been examined with attention to sex-specific differences. Findings indicated that women with the A allele had an increased risk of developing generalized anxiety disorder (GAD), whereas men with both GAD and the A allele exhibited reduced leptin levels (35).

Conclusion

This study investigated the potential link between ADHD and specific genetic variants, namely GHRL rs34911341 and LEP rs7799039. The findings indicated a significant association between rs34911341 polymorphism and ADHD susceptibility; individuals with the AG genotype were more frequently diagnosed with ADHD ($p = 0.036$). However, no significant association was found between the rs7799039 variant and ADHD risk.

It should be noted that the limited sample size poses a constraint on the broader applicability of these findings. Although the results contribute to understanding the potential role of ghrelin gene variants in ADHD, larger-scale studies are necessary to confirm these associations and clarify the underlying biological mechanisms.

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Author Contributions

Ali Atabek Kilic: Investigation, Writing-Original Draft, Visualization; **Nilfer Sahin:** Conceptualizaton, Resources, Investigation, Writing-Original Draft, Visualization; **Aysegul Demirtas BILGIC:** Investigation, Writing-Original Draft, Visualization; **Cilem Ozdemir:** Investigation, Writing-Original Draft, Visualization; **Murat Cenik:** Investigation, Writing-Original Draft, Visualization; **Tuba Gokdogan Edgunlu:** Conceptualizaton, Resources, Writing-Review and Editing, Supervision. All authors read and approved the final version of the manuscript.

Conflicts of Interest

Consent has been granted by all authors for the publication of this manuscript. The authors declare that they have no conflict of interest.

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Ethical Approval

The study protocol was approved by Muğla Sıtkı Koçman University Faculty of Medicine Medical Ethics Committee with the decision of 28/07/2021 and 16/I. The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Informed consent. Written informed consent was obtained from all patients prior to their participation in the study.

Review Process

Extremely and externally peer-reviewed.

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