DOI:10.4274/tnd.2022.01947
Turk J Neurol 2023;29:24-29

Serum Levels of Neopterin, Galectin-3, Tissue Necrosis Factor Alpha, and Interleukin-10 During the Interictal and Attack Periods of Patients with Migraine

Migren Hastalarının İnteriktal ve Atak Dönemlerinde Neopterin, Galektin-3, Tümör Nekroz Faktörü Alfa ve İnterlökin-10 Serum Düzeyleri

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Abstract

Objective: This study aimed to determine the serum levels of neopterin, galectin-3, tissue necrosis factor alpha, and interleukin-10 (IL-10) during the interictal and attack periods of patients with migraine. It is hoped that the findings will contribute to the literature on the theory of neurogenic inflammation.

Materials and Methods: Eighty patients with migraine (40 attacks and 40 interictal periods) and 30 healthy volunteers were included in the study. Blood samples were taken from the people participating in the study, and serum was obtained under the appropriate conditions. The serum levels of all the parameters were determined using a ELISA kit (Coon Koon, Shanghai, China). The difference between the groups was evaluated using appropriate statistical analysis methods.

Results: Galectin-3 and neopterin levels were higher during the attack period compared with the interictal period, and IL-10 and galectin-3 levels were higher during the attack period than in the control group. There was no significant difference in any parameter between the control and interictal period groups. There was a correlation between galectin-3 and neopterin levels in all groups ($r = 0.598$, $P < 0.001$).

Conclusion: The levels of pro-inflammatory molecules, such as galectin-3 and neopterin, were found to be higher in patients with migraine during attacks, which is consistent with the theory of neurogenic inflammation. It is thought that the increase in IL-10 levels during the attack occurs to limit inflammation. Since the tetrahydrobiopterin pathway plays a role in inflammatory and neuropathic pain, it is thought that high neopterin levels during an attack may be associated with migraine headaches.

Keywords: Migraine, neopterin, galectin-3, TNF-α, IL-10

Öz

Amaç: Bu çalışmayla migren hastalarının interiktal ve atak dönemlerinde neopterin, galektin-3, tümör nekroz faktörü alfa ve interlökin-10 (IL-10) serum düzeylerinin belirlenmesi amaçlanmıştır. Böylece çalışma sonuçlarının nörojenik enflamasyon teorisi ile ilgili literatüre katkı sağlayacağı düşünülmüştür.

Gereç ve Yöntem: Çalışmaya 80 migren hastası (40 atak dönem ve 40 interiktal dönem) ve 30 sağlıklı gönüllü dahil edilmiştir. Çalışmaya katılan kişilerden kan örnekleri alınarak uygun koşullarda serum elde edilmiştir. Tüm parametrelerin serum seviyeleri ELISA yöntemiyle ticari kit (Coon Koon, Shanghai, China) kullanılarak gerçekleştirilmiştir. Gruplar arasındaki fark uygun istatistiksel analiz yöntemleri ile değerlendirilmiştir.

Bulgular: Galektin-3 ve neopterin seviyeleri interiktal döneme kıyasla atak dönemindeki migren hastalarında daha yüksekti. IL-10 ve galektin-3 seviyeleri kontrol grubuna kıyasla atak dönemindeki migren hastalarında daha yüksekti. Kontrol grubu ile interiktal dönem arasında hiçbir parametrede anlamlı farklılık tespit edilmedi. Tüm gruplarda galektin-3 ile neopterin seviyeleri arasında bir korelasyon olduğu görüldü ($r = 0,598$, $P < 0,001$).

Sonuç: Çalışmamızda nörojenik enflamasyon teorisi ile uyumlu olarak migren hastalarında atak sırasında galektin-3 ve neopterin gibi proenflamatuvar moleküllerin düzeyi daha yüksek bulunmuştur. Atak döneminde IL-10 düzeylerindeki artışın enflamasyonu sınırlamak amacıyla meydana geldiği düşünülmektedir. Tetrahidrobiopterin yolağının enflamatuvar ve nöropatik ağrıda rol oynaması nedeniyle atak sırasındaki yüksek neopterin düzeylerinin migren baş ağrısı ile ilişkili olabileceği düşünülmüştür. Ancak, bu konuda moleküler düzeyde daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Migren, neopterin, galektin-3, TNF-α, IL-10

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Received/Geliş Tarihi: 07.06.2022 **Accepted/Kabul Tarihi:** 02.09.2022

Introduction

Migraine is a chronic neurovascular disease characterized by episodic headaches that cause autonomic symptoms, and its pathogenesis has not been fully elucidated. It is 2–3 times more common in women than men and is genetically transmitted. The prevalence of migraine worldwide is between 2.6% and 21.7% in various studies, with an average of around 12% (1). According to the International Headache Society, migraine without aura is defined as a unilateral, throbbing headache that lasts between 4–72 hours, increases in intensity during routine physical activities, and can cause nausea, vomiting, photophobia, and phonophobia. Migraine with aura is characterized by the presence of visual, auditory, speech-related, or motor aura symptoms (2).

Various theories have been considered in studies on the pathology of migraine. These theories include neurogenic inflammation, contractile dysfunctions of cerebral blood vessels, and neurovascular events in which depression mechanisms originate from the cerebral cortex and spread. In some studies, cytokines, neuroinflammatory conditions, certain neuropeptides, and vasomotor changes have been implicated in the pathogenesis of migraine. One of the views put forward in the pathophysiology of migraine is sterile neurogenic inflammation. The accepted view in this theory is that inflammatory agents released into the innervation region of the sensory fibers in the meninges sensitize the nociceptors. The release of certain vasoactive neuropeptides, such as calcitonin gene-related peptide (CGRP), from the trigeminovascular system, initiates neurogenic inflammation, resulting in plasma extravasation, vasodilation, and the release of pro-inflammatory mediators, such as prostanoids and bradykinin (3,4).

Neopterin, galectin-3, and tissue necrosis factor alpha (TNF-α) are pro-inflammatory molecules, while interleukin-10 (IL-10) is an anti-inflammatory molecule. Neopterin is a catabolic product of guanosine triphosphate, a purine nucleotide, and is known as a biochemical marker associated with cell-mediated immunity produced by monocytes and macrophages activated by interferon-gamma (IFN-γ) (5). Galectin-3 is a β-galactoside-binding lectin, and studies have shown that galectins play a key role in the neuroinflammation and homeostasis of immune cells (6). TNF-α is a pro-inflammatory cytokine and stimulates the transcription of CGRP, which is thought to have an important role in the initiation of neurological inflammation in the pathogenesis of migraine (7). IL-10 is a potent inhibitor of pro-inflammatory cytokines and is known to support anti-nociception (8).

This study aimed to determine the serum levels of neopterin, galectin-3, and TNF-α, which may be an indicator of cellular immunity and the activation of inflammation, and IL-10, an anti-inflammatory and anti-nociceptive cytokine, during interictal and attack periods in patients with migraine. The study findings will contribute to the literature on the theory of neurogenic inflammation, which plays an important role in the pathogenesis of migraine.

Materials and Methods

Study Groups

The study was planned as a prospective randomized controlled clinical trial. All the patients included in the study had previously been diagnosed with migraine within the scope of the "International Classification of Headache Disorders 3rd Edition" (2). The study included 40 patients who visited the Emergency Department of Kahramanmaras Sutcu Imam University Faculty of Medicine Research and Application Hospital with an acute migraine attack and 40 patients with chronic migraine who came to the neurology outpatient clinic for a routine check-up without an acute migraine attack between June 2019 and December 2019. In addition, 30 healthy volunteers who did not have headache complaints and were similar in age and gender to the patient groups were included in the study as a control group. Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Kahramanmaras Sutcu Imam University Faculty of Medicine (approval no: 17, protocol code: 108, date: 03.04.2019). An informed consent form was signed by the volunteers who agreed to participate in the study. This study was financially supported by the Kahramanmaras Sutcu Imam University Faculty of Medicine Scientific Research Projects Unit (project protocol no: 2019/3-15 D).

The following patients were not included in the study: those who had additional diseases that may cause headaches other than migraine; those diagnosed with chronic diseases (hypertension, diabetes, chronic obstructive pulmonary disease, asthma, heart disease, or liver and kidney failure); those with acute or chronic inflammatory diseases (viral, bacterial, or autoimmune diseases); those with malignancies; and women who were pregnant.

Sample Collection

Blood was collected by experienced nurses from the healthy volunteers and patients after 12 hours of fasting, between 08:00 a.m. and 09:00 a.m. on the same day using 8 ml serum separating tubes (VACUETTE®, Greiner Bio-One, Frickenhausen, Germany) with gel separator but without anticoagulant. The samples were left to stand for 30 minutes to complete the coagulation and then centrifuged at 2.000 rpm for 20 minutes to obtain the serum. The serum samples were aliquoted and stored at -80°C until the study day.

Analysis of Neopterin, Galectin-3, Tissue Necrosis Factor Alpha, and Interleukin-10

The serum neopterin, IL-10, TNF-α, and galectin-3 levels were determined using commercial enzyme-linked immunosorbent assay kits (Coon Koon, Shanghai, China). A calibration curve was created using the calibrators included in each kit for measurements. Analyte concentrations in the serum samples were determined according to the calibration curve.

Statistical Analysis

Statistical analysis was performed using SPSS 20.0 (IBM Inc., Chicago, IL, USA). Descriptive statistics were presented as means (minimum–maximum) using tables. The conformity of the variables to the normal distribution was analyzed using Kolmogorov–Smirnov and Shapiro–Wilk tests. A Kruskal–Wallis test was used to compare the parameters that did not fit the normal distribution between the control, acute migraine attack, and chronic migraine groups. Post-hoc analysis was performed using the Mann–Whitney U test, in which *P* values obtained with Bonferroni correction were taken into account. The data of the two groups of patients with migraine as a whole were compared with

those of the control group using this test, and Spearman's rho was used to test the correlation. The efficiency of the parameters in the separation of the groups was evaluated using receiver operating characteristic (ROC) analysis, and the Youden index was used to determine the optimum cut-off value. A *P* value of ≤0.05 was considered statistically significant for all analyses.

Results

A total of 110 volunteers (30 controls, 40 patients with migraine in the attack period, and 40 patients with migraine in the interictal period) were included in the study. There was no statistical difference between the groups in terms of age variable (*P* = 0473), but with regard to gender, females were predominant in all three groups. The demographic data and laboratory results of the study groups are presented in Table 1.

The Kruskal–Wallis analysis showed that the IL-10, galectin-3, and neopterin levels of the three groups were different (Table 1). In the posthoc analysis, the IL-10 and galectin-3 levels were significantly higher in the attack period group compared to the control group (*P* < 0.001 and *P* = 0.027, respectively). No statistically significant difference was found in terms of the parameters between the interictal period and the control groups (*P* > 0.05). The galectin-3 and neopterin levels were found to be higher in the attack period group compared with the interictal period group (*P* < 0.001 and *P* = 0.008, respectively). The median levels of galectin-3 and neopterin of the three groups are shown in Figure 1.

The correlation between the parameters was evaluated using Spearman correlation analysis. There was a positive correlation between galectin-3 and neopterin (r = 0.598, *P* < 0.001). A moderate correlation was detected between IL-10 and galectin-3 (r = 0.390, *P* < 0.001) and IL-10 and neopterin (r = 0.337, *P* < 0.001) levels. While there was a correlation between TNF-α and galectin-3 (r = 0.621, *P* < 0.001) and between TNF-α and neopterin (r = 0.390, *P* < 0.001), there was no correlation between TNF-α and IL-10 (r = 0.024, *P* > 0.05).

The diagnostic efficiency of IL-10 in the distinction between the control and the attack period groups and galectin-3 and neopterin in the distinction between the attack period and interictal period groups was evaluated using ROC analysis. The Youden index was used to calculate the optimum cut-off. Accordingly, the area under the curve (AUC) value for IL-10 was calculated as 0.800 (*P* < 0.001) in distinguishing between the control group and the attack group. The specificity and sensitivity of IL-10 were 63% and 88%, respectively. The AUC value of galectin-3 was calculated as 0.747 (*P* < 0.001) and the AUC value of neopterin was 0.671 (*P* = 0.008) in distinguishing between the attack period and interictal period groups. The specificity of galectin-3 was 68%, and the sensitivity was 80%, whereas the specificity of neopterin was 38%, and the sensitivity was 93%. The ROC curves of IL-10, galectin-3, and neopterin are presented in Figure 2.

Discussion

Migraine refers to a complex disease that includes many pathophysiological mechanisms that distinguish it from a headache. The current study investigated the levels of pro-inflammatory (TNF-α, neopterin, and galectin-3) and anti-inflammatory (IL-10) molecules in the sera of patients with migraine in the acute attack and interictal periods, within the scope of neurogenic inflammation theory, which has an important place in the pathophysiology of migraine.

The results of this study indicated that the serum levels of IL-10 were higher in the attack period group compared to those in the healthy control group. IL-10 is an anti-inflammatory cytokine and can be produced by many cells, such as T-helper cells,

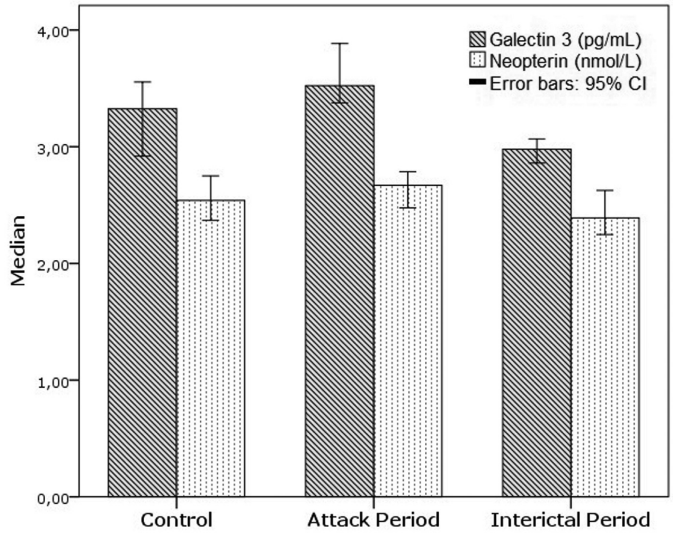

Figure 1. Galectin-3 and neopterin serum levels in the study groups
CI: Confidence interval

Table 1. The demographic data and laboratory results of the study groups[1,2]

	Control n = 30	Attack period n = 40	Interictal period n = 40	*P* value
Age (years)	37.1 (25–48)	37.1 (19–54)	33.00 (21–65)	0.473
Male/female	5/25	6/34	3/37	
Galectin-3 (pg/ml)	3.33 (1.34–7.24)	3.52 (2.69–62.27)	2.98 (1.68–39.25)	**<0.001**
Neopterin (nmol/l)	2.54 (1.92–3.82)	2.67 (2.17–27.21)	2.39 (1.12–32.46)	**0.027**
IL-10 (pg/ml)	23.93 (15.76–34.25)	27.69 (20.07–559.61)	25.77 (12.81–298.56)	**<0.001**
Tumor necrosis factor-alpha (TNF-α) (pg/ml)	47.00 (22.66–76.51)	40 .61 (26.54–633.55)	43.34 (23.80–676.68)	0.822

[1]Since the distribution was not normal, the results are given as median (minimum-maximum) for galectin-3, neopterin, IL-10, and TNF-α parameters. The results for the age parameter are given as means (minimum-maximum). [2]The *P* value is based on a Kruskal–Wallis test. TNF-α: Tumor necrosis factor-alpha, IL-10: Interleukin-10

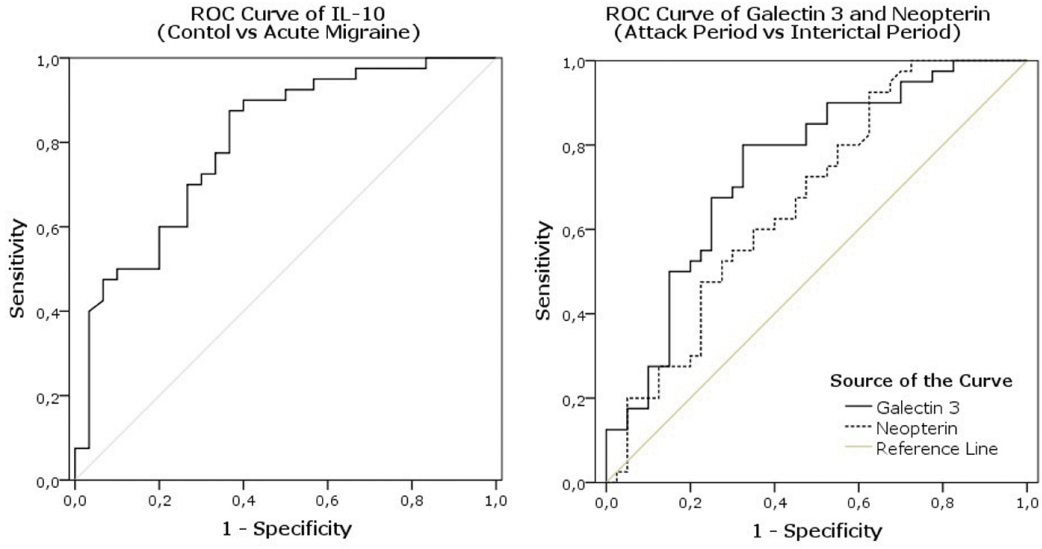

Figure 2. Receiver operating characteristic curves of IL-10, galectin-3, and neopterin
IL-10: Interleukin-10, ROC: Receiver operating characteristic

monocytes, macrophages, dendritic cells, cytotoxic T-lymphocytes, B-lymphocytes, keratinocytes, and epithelial cells. It is known to play a central role in limiting the response of the immune system to the inflammatory agent, thus maintaining tissue homeostasis and preventing tissue damage (9). Munno et al. (10) found that IL-10 level was higher in patients with migraine during the attack period compared to healthy controls and showed that IL-10 levels decreased in patients after they took sumatriptan, which functions as a serotonin receptor (5-HT1D/1B) analog in the treatment of migraine. Based on this finding, Munno et al. (10) maintained that IL-10-producing Th2 lymphocytes may have a role in the occurrence of migraine headaches. In another study conducted later, the fact that the levels of pro-inflammatory cytokines, such as IL-6, were found to be high in addition to the elevation of IL-10 during the attack period of patients with migraine suggested that the high level of IL-10 during the attack period may be due to the limitation of the emerging inflammation (11). In the current study, while IL-10 levels were high in the attack period group, there was no difference in IL-10 levels between the interictal period group and the control group. In two other studies, IL-10 levels during the interictal period were found to be undetectable (12,13). Considering that IL-10 is a potent anti-inflammatory cytokine, the results of the studies mentioned above and the present study strengthen the idea that IL-10 elevation occurs in response to inflammation in patients with migraine during an attack.

In the current study, there was no difference between the groups in terms of serum TNF-α levels. However, there was a positive correlation between TNF-α levels and galectin-3 and neopterin levels. The high levels of IL-10, which is an anti-inflammatory cytokine, in the attack period group may have caused the suppression of TNF-α and, thus, the lack of difference between the groups in terms of TNF-α levels.

Although the synthesis of galectin-3 in neurons is weak in the central nervous system (CNS), it has been shown *in vitro* that it is synthesized in oligodendrocytes and astrocytes, especially in microglia cells (14). After stimulation by IFN-γ, galectin-3 synthesis increases in glial cells. Moreover, galectin-3 itself increases the production of pro-inflammatory mediators such as TNF-α, IL-6, IL-1-beta, and IFN-γ via the Janus kinase-signal transducer of activators of transcription pathway in microglial cells (15). Galectin-3 plays a role in the CNS in conditions such as inflammation and brain damage. It has been shown that activated microglial cells synthesize galectin-3 during brain ischemia and that microglial cell activation is impaired in ischemic lesions and the number of microglial cells decreases in galectin-3 knock-out mice (16). Galectin-3, which is described as a harmful molecule because it activates microglia and macrophages that phagocytize myelin in experimental autoimmune encephalitis, is defined as beneficial in CNS damage for the same reason because phagocytosis of myelin residues is a requirement for post-injury regeneration (17).

A study on the effects of galectin-3 at the molecular level in patients with migraine was not found. However, Yucel et al. (18) reported that galectin-3 levels were higher in the serum of patients with migraine compared with healthy controls, but there was no difference in galectin-3 levels between patients in the attack period and those in the interictal period of migraine. In the current study, it was observed that galectin-3 levels increased in the patients with migraine during the attack period compared with both the control group and the interictal period group. Similarly, Gürger et al. (19) found galectin-3 levels were higher in patients with migraine during the attack period compared with a control group. In their study, the specificity and sensitivity of galectin-3 were calculated as 90% and 89%, respectively, in the distinction between patients during a migraine attack period and healthy controls (19). In the present study, the specificity and sensitivity of galectin-3 were found to be 68% and 80%, respectively, in distinguishing between the attack period and the interictal period of patients with migraine. Although there are some differences between the studies, the common finding of the current study and the two studies mentioned above is that galectin-3 levels increase during the attack period of

patients with migraine. Considering the role of galectin-3 in the inflammation process in the CNS and its pro-inflammatory effects as mentioned above, it is believed that neuroinflammation may play an important role in the formation of the attack period in patients with migraine.

Neopterin is a by-product of the tetrahydrobiopterin (BH4) synthesis pathway and is an important indicator of immune system activation, while 7,8-dihydroneopterin triphosphate is formed from gamma-glutamyl transpeptidase (GTP) by the enzyme GTP cyclohydrolase 1. The triphosphate part is cleaved by phosphatases to form 7,8-dihydroneopterin. Later, neopterin is formed by oxidation reactions (20). Thus, neopterin produced by monocytes and macrophages in response to IFN-γ stimulus is considered an indicator of both immune system activation and cellular immunity and oxidative stress. In this context, neopterin levels in biological fluids increase in acute and chronic conditions, such as viral infections, malignancies, allograft rejection, autoimmune diseases, and neurodegenerative diseases (21).

In the current study, neopterin levels were found to be higher in patients with migraine in the attack period compared with the interictal period. No other studies could be found measuring neopterin levels in the sera of patients with migraine. However, it has been shown that neopterin increases in cerebrospinal fluid (CSF) and plasma in various diseases with neuroinflammation. The higher concentration of neopterin in CSF compared with plasma, independent of the blood-brain barrier, indicated that neopterin production is present in the CNS, and studies on the cells that cause neopterin production in the CNS have shown the presence of neopterin production in glial cells, astrocytes, and even in some neurons (22,23). Moreover, it has been reported that the BH4 pathway is effective in the formation of neuropathic and inflammatory pain, and the inhibition of this pathway reduces pain (24). The fact that serum neopterin levels were found to be higher in the attack period compared with the interictal period in the present study is thus consistent with the current literature. The high neopterin levels detected during the attack period, especially when migraine headaches are present, suggest that neopterin and other possible intermediates in the BH4 pathway may play a role in the formation of headaches.

Study Limitations

The most important limitation of this study is the relatively small number of participants. Migraine classification could not be determined clearly because the necessary follow-up for the differential diagnosis of chronic migraine could not be performed with these patients. Another limitation is that the time elapsed between the onset of the migraine attack and the time of blood collection could not be standardized. In addition, the fact that the patients could not be followed up and that the difference between the attack period and interictal period of the same patients could not be observed is a limiting factor for the results of this study.

Conclusion

In conclusion, this study found the level of pro-inflammatory molecules, such as galectin-3 and neopterin, to be higher in patients with migraine during an attack, which supports neurogenic inflammation, an important theory in the pathogenesis of migraine. The increase of IL-10 levels during the attack period is thought to limit the inflammation, considering the increase of pro-inflammatory cytokines, such as galectin-3 and neopterin, during the attack period. Since the BH4 pathway is known to play a role in inflammatory and neuropathic pain, it is concluded that high neopterin levels may be associated with headaches in patients with migraine attacks. The study results should inform more detailed studies at the molecular level on the role of the BH4 pathway in the formation of migraine headaches.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Kahramanmaras Sutcu Imam University Faculty of Medicine (approval no: 17, protocol code: 108, date: 03.04.2019).

Informed Consent: Informed consent form was signed by the volunteers who agreed to participate in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.H., F.A.B., Design: A.H., F.A.B., Y.D., Data Collection or Processing: A.H., F.A.B., D.T.B., F.İ.T., Analysis or Interpretation: A.H., F.A.B., Y.D., D.T.B., F.İ.T., Literature Search: A.H., F.A.B., Y.D., Writing: A.H., Y.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was financially supported by the Kahramanmaras Sutcu Imam University Faculty of Medicine Scientific Research Projects Unit (project protocol no: 2019/3-15 D).

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