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5-Year Experience at a Single Center: Retrospective Analysis of 38 Patients with Hereditary Angioedema: A Descriptive Study

Tek Merkez 5 Yıllık Deneyimimiz: 38 Herediter Anjiyoödem Hastasının Retrospektif Analizi: Tanımlayıcı Bir Araştırma

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ABSTRACT Objective: Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by recurrent angioedema attacks, without itching or urticaria. With this study, we aimed to increase the awareness of HAE by presenting the characteristics of these patients who applied to the emergency department and allergy immunology clinic. **Material and Methods:** A total of 38 patients, 25 (65.8%) female and 13 (34.2%) male, were included. **Results:** The mean age was 40.90±12.66, mean age at the onset of symptoms was 13.5 (1-56), mean age at HAE diagnosis was 24.61±13.78, and the diagnostic delay was 8.84±8.97 years. Of all cases, 18 (47.4%) were followed-up with Type I HEA and 20 (52.6%) were followed up with Type II HAE. A family history of HAE was present in 89.5% and a family history of death due to HAE was present in 31.6% of the patients. Mean age at diagnosis differed significantly between those with or without a family history of death due to HAE (18.0±7.24 vs. 27.65±15.08 years; p=0.043). The episodes were triggered by stress in 20 (52.6%) patients. The symptoms at first presentation included swelling in extremities in 18 (47.4%) patients. **Conclusion: A**lthough HAE is a rare disorder associated with variable clinical presentations complicating the diagnostic process, it may also be associated with mortality. Periodic reporting of clinical experience from centers dealing with HAE patients bears significance not only for increasing awareness among medical professionals and preventing diagnostic delays but also for improving the life quality of patients as well as for decreasing the morbidity and mortality.

Keywords: Hereditary angioedema; C1 esterase inhibitor; laryngeal diseases

ÖZET Amaç: Herediter anjiyoödem (HAÖ), ürtiker ve kaşıntının eşlik etmediği, tekrarlayan anjiyoödem atakları ile karakterize, otozomal dominant geçişli nadir bir bozukluktur. Biz, bu çalışma ile HAÖ farkındalığını artırmak için acil servise ve alerji immünoloji kliniğine başvuran HAÖ hastalarının genel özelliklerini sunmayı amaçladık. **Gereç ve Yöntemler:** Toplam 38 [kadın: 25 (%65,8), erkek: 13 (%34,2)] hastanın verileri incelendi. **Bulgular:** Hastaların yaş ortalaması 40,90±12,66 yıl, ilk şikâyetlerin başlama yaşı 13,5 (1-56), HAÖ tanı yaşları 24,61±13,78 yaş ve tanıda gecikme 8,84±8,97 yıl idi. On sekiz (%47,4) hasta Tip I HAÖ, 20 (%52,6) hasta Tip II HAÖ olarak takip edilmekteydi. Hastaların %89,5'inin akrabalarında HAÖ tanısı, %31,6'sında ise HAÖ ilişkili akraba ölümü hikâyesi mevcuttu. Ailesinde HAÖ sebebiyle mortalite öyküsü olanlarda tanı yaşı 18,0±7,24; mortalite öyküsü olmayanlarda ise 27,65±15,08 olmak üzere anlamlı fark vardı (p=0,043). Yirmi (%52,6) hastada stres atakları tetiklerken; 18 (%47,4) hastada hastaların başlangıç şikâyeti ekstremitelerde şişlik şeklindeydi. **Sonuç:** HAÖ, farklı klinik prezantasyonları sebebiyle tanınması zor, nadir ama ölümcül olabilen bir hastalıktır. Hem hekimlerin bu konuda farkındalığının artırılması hem hastalara gecikmeden tanı konulması ve hastaların tedavilerinin gecikmeden başlanması açısından, HAÖ ile ilgilenen merkezlerin belli aralıklar klinik tecrübelerini paylaşması, hastaların yaşam kalitesinin artırılması ve hastalığa bağlı mortalite ve morbiditenin azaltılması açısından oldukça önemlidir.

Anahtar Kelimeler: Herediter anjiyoödem; C1 esteraz inhibitörü; larinks hastalıkları

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by recurrent angioedema attacks, without itching or urticaria. This rare condition results from absent or dysfunctional C1 esterase-inhibitor due to mutations involving the SERPING1 gene, leading to excessive production of

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bradykinin with resultant vasodilation, edema, and episodes of angioedema.[1] Angioedema attacks often involve the skin, upper respiratory tract mucosa, and gastrointestinal system mucosa.[2,3] Although angioedema attacks are self-limiting and angioedema may resolve within 2 to 5 days without treatment, there is a risk of fetal asphyxia due to laryngeal attacks. Therefore, World Allergy Organization guidelines emphasize the importance of rapid diagnosis and treatment.[4] Furthermore, many other conditions may mimic HAE. It should also be noted that angioedema associated with bradykinin is pathogenetically different from histamine-induced angioedema. Therefore, HAE patients do not get benefit from epinephrine, antihistamines and corticosteroids, and instead, require C1 esterase inhibitor protein replacement or prevention of bradykinin production or function.[3] A high level of awareness on clinical characteristics of this rare condition is therefore of utmost importance, particularly for emergency physicians, in order to avoid diagnostic and therapeutic delays as well as to differentiate other conditions that may mimic HAE.[5] Thus we believe that periodic reporting of clinical experience on HAE patients will provide significant contributions in this regard.

MATERIAL AND METHODS

PATIENTS

This study was carried out in the tertiary university hospital, Necmettin Erbakan University Meram Faculty of Medicine Hospital, an important center for HAE in Turkey and we retrospectively analyzed 38 [female: 25, male: 13] patients who had adequate data in their medical records by examing 5-year data (15 patients were not included in the study because they did not come for regular follow-up and there was not enough information in their files). In our follow-ups, we investigated demographic parameters (such the current age, gender, age at complaints start and age at diagnosis, consanguinity, frequency of angioedema attacks, the origin of the complaints, whether there is death in the family due to HAE or another patient diagnosed with HAE, the treatments it received before the diagnosis of HAE, causes of HAE attacks, the effect of interventional procedures on attack frequency such as tooth extraction or surgery, the effects of menstruation, pregnancy, and delivery on female patients, treatments applied in the emergency department) and laboratory parameters (such C4 levels, C1 esterase inhibitor level, and activity) of the patients. Diagnosis of HAE was based on the presence of positive family history, low C4, and C1 inhibitor (C1INH) deficiency (Type I), or on identification of C1INH dysfunction (Type II), as proposed by international guidelines.[4] The study protocol was approved by the Ethics Committee of Necmettin Erbakan University (Date: 21.11.2018, Number: 14567952-050/2351). This study was carried out in accordance with the Principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

BIOCHEMICAL ANALYSES

Complete blood counts were performed with an Abbott Cell Dyn 3700 device using Sheath reagents (Illinois, United States). Serum C4 levels were measured with Siemens Advia 2400 Clinical Chemistry System with colorimetric methods (New York, United States). Serum C1 esterase inhibitor levels were measured with Siemens BN II/ BN ProSpec system, using a nephelometric assay (New York, United States); serum C1 esterase inhibitor functions were measured with the chromogenic method using a Stago Compact Max device (New Jersey, United States).

STATISTICAL ANALYSES

Statistical analysis was performed with IBM SPSS Statistics version 22 software package. Normally distributed parameters were presented as mean±standard deviation and skewed parameters were expressed as median (interquartile range: minimum-maximum). Descriptive data were presented as frequencies and percentages and compared using chi-square test. Comparisons between baseline characteristics were performed by independent Student t, Mann-Whitney rank-sum, Fisher exact or chi-square tests where appropriate. A p value of less than 0.05 was considered statistically significant.

RESULTS

Medical records of 38 (female=25, 65.8%; male=13, 34.2%) patients with adequate data in patient files were examined. The mean age was 40.90±12.66 years. The mean age at the onset of symptoms was 13.5 (1-56) years. HAE was diagnosed at a mean age of 24.61±13.78 years. The duration of diagnostic delay was 8.84±8.97 years. Table 1 summarizes the demographic, clinic, and laboratory characteristics of the patients. Mean age at diagnosis differed significantly between those with or without a family history of death due to HAE (i.e. 18.0±7.24 vs. 27.65±15.08 years, respectively; p=0.043). Although the diagnostic delay in those with a family history of death due to HAE was shorter than those without such history (7.67±5.81 years vs. 9.39±10.17 years, respectively), the difference was insignificant (p=0.590).

Eighteen (47.4%) patients were diagnosed with Type I and 20 (52.6%) were diagnosed with Type II HAE. The median C4 was 0.06 (0.01-2.08) g/L (range: 0.01-0.2), median C1 esterase inhibitor was 24 (3-94) mg/dL (range 18-32 mg/dL), median C1 esterase inhibitor activity was 13.5% (3-171%) (range: 70-130%).

TABLE 1: Demographic, clinical and laboratory properties of patients with HAE.

	Total (n=38)
Current age	40.90±12.66
Age at diagnosis	24.61±13.78
Diagnostic delay, years	8.84±8.97
C4, g/L	0.06 (0.01-2.08)
C1 esterase inhibitor, mg/dL	24 (3-94)
C1 esterase inhibitor activity, %	13.5 (3-171)
HAE Type I, n (%)	18 (47.4)
HAE Type II, n (%)	20 (52.6)
Family history, n (%)	34 (89.5)
Death in the family due to HAE, n (%)	12 (31.6)
First complaint/attack zone	
• Extremities	18 (47.4)
• Abdominal	6 (15.8)
• Head and neck area	9 (23.7)
Attack involvement zones	
• Extremities	36 (94.7)
• Abdominal	29 (76.3)
• Head and neck area	25 (65.8)
• Genital area	14 (36.8)

HAE: Hereditary angioedema; C: Compleman.

Family history of HAE and death due to HAE was present in 89.5% and 31.6% of the participants, respectively.

The symptoms at first presentation included swelling in extremities in 18 (47.4%) patients, angioedema in face/neck and tongue in 9 (23.7%), and abdominal pain in 6 (15.8%). In 5 (13.1%) patients, the presenting symptoms involved all three systems.

During the course of the illness, angioedema episodes involved the extremities in 36 (94.7%) patients, abdomen in 29 (76.3%) patients, head and neck in 25 (65.8%) patients, and genital area in 14 (36.8%) patients, with no significant differences between the site of involvement (p=0.295, 0.122, 0.078, and 0.391, respectively). The attack frequency ranged between an episode per week and an episode per year.

Stress was the triggering factor for attacks in 20 (52.6%) patients, while it was fatigue in 18 (47.4%), trauma in 16 (42.1%), prolonged standing in 12 (31.6%), and sorrow in 11 (28.9%).

Three (7.9%) patients reported development of a HAE attack after surgery, while 17 (44.7%) reported an attack after dental treatment. Seven of the 24 (29.2%) female patients described increased HAE attack frequency during the menstrual period, while 17 (70.8%) reported no such changes in attack frequency. Again, 6 of the 18 (33.3%) female patients observed increased attack frequency during pregnancy, while 8 (44.4%) patients had no change, and 4 (22.2%) had reduced attack frequency. Among 17 female patients who had a history of delivery prior to study 11 had normal vaginal delivery (64.7%), while 6 (35.3%) had a caesarean section (one of the 18 patients with a history of pregnancy had an abortion). None of the patients with normal delivery had an attack after birth, as compared to occurrence of an HAE attack in 33.4% (2 out of 6 patients) of those who had a caesarean section.

Fifteen (39.5%) patients reported no symptoms prior to attacks, while 12 (31.6%) had fatigue and loss of energy, 10 (26.3%) patients had nervousness.

Before the diagnosis of HAE, thirty-two (84.2%) patients visited an emergency room due to an an-

gioedema attack, while 15 (39.5%) patients were not referred to any specific clinics, 9 (23.7%) patients were referred to an allergy and immunology unit, 4 (10.5%) patients were referred to dermatology, and 4 (10.5%) to internal medicine. While 21 (65.6%) of 32 patients who applied to the emergency department did not benefit from treatment, 10 (31.3%) patients stated that they rarely benefit. It was understood that all of these patients were treated with anti-histamine and steroid treatment because of the HAE attacks, and 10 (31.3%) patients received adrenaline injection. No patients were receiving ecallantide at the time of study, as this medicine is not currently available in our country. All patients receiving long-term prophylactic treatment were being treated with attenuated androgen, with no patients having tranexamic acid treatment. Also, all patients were being treated with plasma-derived C1 esterase inhibitor on an on-demand basis. Additional icatibant was prescribed to those with a family history of mortality due to HAE or to those with marked laryngeal abdominal symptoms. Nineteen (50%) patients were receiving on-demand therapy with C1 esterase inhibitor and icatibant, while 14 (36.8%) received only C1 esterase inhibitor as an on-demand treatment. Four (10.5%) patients were having on-demand treatment with attenuated androgen as well as with C1 esterase inhibitor and icatibant. There was only 1 (2.6%) patient who had on-demand treatment with attenuated androgen for prophylaxis plus C1 esterase inhibitor. Table 2 summarizes the detailed demographic, clinic, and laboratory characteristics of the patients.

DISCUSSION

HAE is a rare autosomal dominant disorder characterized by angioedema episodes that may lead to death. Although angioedema attacks may resolve spontaneously within 2 to 5 days, the reported rate of death due to asphyxia in studies from previous decades was up to 30% due to the absence of effective treatments.[6]

Diagnostic delay is common in HAE patients.[7] According to Zanichelli et al.'s study, the time elapsed from symptom onset and diagnosis was 1.4 to 8.5 years.[8] Gómez-Traseira et al. explained these diagnostic delays on the basis of the rare occurrence of the condition as well as inadequate awareness among healthcare professionals.[9] On the other hand, as indicated by Bork et al., delayed diagnosis may be associated with an increased risk of asphyxia-related mortality in undiagnosed patients.[10] In another report, the duration between symptom onset and diagnosis was 17.7±12.6 years.[8] As explained above, this might be related with the low awareness of both patients and physicians regarding the life-threatening nature of the HAE episodes. Another disadvantage of late diagnosis relates to the fact that many patients receive unnecessary treatments, sometimes leading to increased risk of death.[7] Furthermore, failure to diagnose or late diagnosis may have adverse consequences in terms of the life quality of patients.[8] In the current study, the duration of diagnostic delay was 8.84±8.97 years, again probably resulting from low level of awareness among physicians. In support of this view, only 26.3% of the patients in this study attending to an emergency unit due to HAE episodes were referred to an immunology and allergy unit, while others were either referred to inappropriate specialties or not referred at all. Additionally, the diagnostic delay was longer among our patients without a family history of HAE-related mortality than those with such a history.

Attacks of HAE frequently involve 3 main anatomic sites, namely the skin (cutaneous attacks), gastrointestinal tract (abdominal attacks), and upper respiratory tract (laryngeal/pharyngeal attacks).[7] In Gómez-Traseira et al.'s study, extremities were affected in 36.4% of the cases, while abdomen was affected in 18.7%, and facial edema occurred in 17.75% as the first site of involvement.[9] In general, extremities represent the most frequent site of involvement. In the study by Bork et al., skin attacks occurred in 221 out of 975 HAE patients.[11,12] Again, episodes involving the skin were reported in 87.1% of the cases in another study.[13] Abdominal attacks of HAE represent significant diagnostic challenges for the physician, as these frequently mimic acute abdomen and may be the first symptom in up to 25% of the patients. Attacks may be accompanied by gastrointestinal colic, nausea, vomiting and/or diarrhea due to edema of the gastric and intestinal walls.[11] Nearly 70% of the patients experience abdominal at-

TABLE 2: Detailed demographic, clinical, laboratory analysis of the patients with HAE.

P	G	Age at first symptoms	Age at diagnosis	Diagnostic delay	First symptoms	Localization of attacks				Precipitating factors	Family History	Death in the family due to HAE	HAE Type
						Extremites	Abdominal	Facial	Genital				
1	F	7	9	2	Extremity	+	+	+	-	Stress, fatigue, long standing, trauma, dental procedure	+	+	Type I
2	F	37	37	-	Head-neck region	-	-	+	-	Fatigue, trauma	+	-	Type II
3	F	1	10	9	Head-neck region	+	+	+	+	Stress, cold weather, fatigue, long standing, trauma	+	+	Type II
4	M	16	25	9	Head-neck region	+	-	+	+	Stress, sadness, fatigue, cold weather, trauma	+	+	Type I
5	M	56	57	1	Extremity	+	-	+	-	Stress, sadness, fatigue, long standing, trauma	+	-	Type I
6	F	16	19	3	Abdominal	+	+	-	-	Stress	+	-	Type I
7	F	17	25	8	Extremity	+	-	-	-	Trauma, long standing	-	-	Type I
8	F	27	30	3	Extremity	+	+	+	+	Sadness	+	-	Type I
9	F	11	15	4	Abdominal	-	+	-	-	-	+	-	Type II
10	F	18	23	5	Extremity/abdominal	+	+	-	-	Stress, cold weather, fatigue	+	+	Type II
11	F	20	34	14	Extremity	+	+	-	-	Stress	+	-	Type I
12	F	20	50	30	Extremity	+	-	-	-	-	+	-	Type I
13	F	17	17	-	Abdominal	+	+	+	+	Stress, sadness	+	-	Type I
14	F	16	22	6	Extremity	+	+	+	+	Sadness, cold weather, fatigue, long standing, trauma, menses, dental procedure	+	+	Type II
15	M	17	20	3	Abdominal	+	+	+	-	Stress, fatigue, trauma	+	-	Type II
16	M	7	27	20	Extremity	+	-	-	-	Trauma	+	-	Type I
17	M	46	49	3	Extremity	+	-	+	-	Stress	+	-	Type II
18	F	7	16	9	Head-neck region	+	+	+	+	Stress, fatigue, cold weather, trauma, long standing, menses, dental procedure	+	+	Type II
19	F	10	31	21	Extremity	+	+	-	-	Stress, sadness, fatigue, trauma, long standing	+	+	Type II
20	M	10	26	16	Extremity	+	-	+	+	Stress, sadness, menses, dental procedure, long standing	+	-	Type II
21	F	16	21	5	Extremity/abdominal	+	+	-	-	Cold weather, fatigue, trauma, dental procedure	+	+	Type II
22	F	6	40	34	Extremity	+	-	-	-	Dental procedure	+	-	Type II
23	F	13	19	6	Extremity	+	+	+	-	Stress, fatigue, menses, dental procedure	-	-	Type II
24	F	36	48	12	Extremity	+	+	+	+	Cold weather, dental procedure	+	-	Type II
25	M	7	10	3	Head-neck region	+	+	-	-	Sadness, dental procedure	+	-	Type II
26	F	4	15	11	Extremity	+	+	+	+	Fatigue, trauma, menses	+	-	Type I
27	F	12	33	21	Head-neck region	+	+	-	-	Fatigue, menses, dental procedure	+	-	Type I
28	M	20	30	10	Extremity/abdominal	+	+	+	-	-	-	-	Type II

HAE: Hereditary angioedema; P: Patient; G: Gender; M: Male; F: Female.

continued...→

TABLE 2: Detailed demographic, clinical, laboratory analysis of the patients with HAE *(continue)*.

P	G	Age at first symptoms	Age at diagnosis	Diagnostic delay	First symptoms	Localization of attacks				Precipitating factors	Family History	Death in the family due to HAE	HAE Type
						Extremities	Abdominal	Facial	Genital				
29	M	26	57	31	Abdominal/head-neck region	+	+	+	-	Dental procedure	+	-	Type I
30	M	5	8	3	Extremity	+	+	+	+	Stress, sadness, long standing, trauma, dental procedure	+	+	Type I
31	F	7	23	16	Head-neck region	+	+	+	-	Stress, long standing	+	+	Type II
32	M	14	15	1	Extremity	+	+	+	-	Stress , menses, dental procedure	+	+	Type I
33	F	2	3	1	Head-neck region	+	+	+	+	Stress, sadness, fatigue, dental procedure, trauma	+	-	Type II
34	M	7	13	6	Extremity/abdominal	+	+	+	+	Fatigue, trauma, long standing, dental procedure	+	+	Type I
35	F	12	15	3	Extremity	+	+	+	+	Stress, sadness, fatigue, long standing, trauma	+	-	Type I
36	F	12	16	4	Head-neck region	+	+	+	-	Dental procedure	+	-	Type II
37	M	9	12	3	Abdominal	+	+	+	+	Cold weather, fatigue, sadness, trauma	+	-	Type I
38	F	15	15	-	Abdominal	+	+	-	-	Stress, sadness, dental procedure, menses, long standing	-	-	Type II

HAE: Hereditary angioedema; P: Patient; G: Gender; M: Male; F: Female.

tacks.[12] In this study, this corresponding figure was 76.3%, while it was 74.3% in the study by Kesim et al.[13]

From clinical viewpoint, the most dreaded complication of HAE is the laryngeal involvement. Approximately half of all patients experience at least one laryngeal attack during their lifetime, although recurrent attacks affect only less than 1%.[11,12] In one study, facial and laryngeal edema were found to occur in 65% and 55.7% of the patients, respectively.[13] In the current report, 65.8% of the patients had angioedema in the head and neck region. In our opinion, medical centers dealing with HAE patients should share their clinical experience regarding this rare entity, as this condition is associated with an increased risk of asphyxia and unnecessary laparatomies, particularly due to poor overall awareness of the abdominal symptoms.[14]

Most patients experience prodromal symptoms before attacks. Also, many triggering factors for attacks have been described, such as emotional changes, sleep disorders, trauma, prolonged standing or sitting, drugs, menstruation, and surgical interventions.[7,14-16] It should be noted that attack triggers are different from histamine-mediated angioedema in this patient group. In a study from Turkey, the most common triggering factors were trauma (28%) and stress (14.3%).[13]

Dental extraction is a medical intervention that requires special attention due to its potential to initiate HAE episodes. In the study by Bork et al., 25% of the patients who did not receive prophylactic treatment before dental extraction had life-threatening facial swelling and laryngeal edema.[17] In female patients, variable effects of hormonal changes (e.g. pregnancy and menstruation) have been reported.[18,19] In the study by Kesim et al., 6 of 42 (14.3%) female patients reported an increase in attacks during menstruations.[13] Bouillet et al. reported that 35% of the attacks were related with perimenstrual and menstrual period in their patients.[18] In the same study, it

was reported that 38% of patients had increased HAE attacks during pregnancy and 32% of patients had decreased HAE attacks.[18]

Although it may be assumed that stress associated with labor as well as the surgical interventions may trigger an HAE attack, labor has not been associated with triggering of attacks in many women. Chinniah et al. reported that 89% of the female patients did not require prophylactic treatments during delivery, and the attack frequency during delivery and the following 2 day period was 6%.[19] On the other hand, prophylaxis with plasma-derived C1 esterase inhibitor concentrate has been recommended by Caballero et al. for deliveries involving forceps use, vacuum extraction, and caesarean section.[20]

The objectives of treatment in HAE include protection from attacks and prevention of recurrence, reduction of morbidity and mortality, and improvement in patients' quality of life.[7] The two main therapeutic approaches used for that purpose involve prophylaxis, either short or long-term, and on-demand treatments. World Allergy Organization strongly recommends the use of C1 esterase inhibitor concentrates, icatibant, and ecallantide for the prevention of HAE attacks, while tranexamic acid and attenuated androgens are effective for long term prophylaxis.[7] Since acute attacks may occur even in patients receiving prophylactic treatments, there should be an action plan in place for each patient directed toward acute attacks.[4]

CONCLUSION

In conclusion, HAE is a rare but potentially life-threatening disease that presents significant diagnostic challenges due to variable clinical presentations. Emergency physicians should also consider the diagnosis of HAE, especially in cases of urticaria angioedema that does not benefit from antihistamine treatments, severe abdominal pain mimicking acute abdomen, and treatment-resistant larynx edema. Interclinical collaborations, periodic reporting of clinical experiences from centers dealing with HAE patients, as well as education on HAE are bears significance not only for increasing awareness among medical professionals and preventing diagnostic delays but also for improving the life quality of patients, as well as decreasing morbidity and mortality.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Gökhan Aytekin,* ***Design:*** *Nazire Belgin Akıllı, Ahmet Zafer Çalışkaner;* ***Control/Supervision:*** *Gökhan Aytekin, Şevket Arslan, Eray Yıldız, Fatih Çölkesen;* ***Data Collection and/or Processing:*** *Gökhan Aytekin, Eray Yıldız, Fatih Çölkesen;* ***Analysis and/or Interpretation:*** *Gökhan Aytekin, Şevket Arslan, Ahmet Zafer Çalışkaner;* ***Literature Review:*** *Gökhan Aytekin-Nazire Belgin Akıllı;* ***Writing the Article:*** *Gökhan Aytekin, Ahmet Zafer Çalışkaner;* ***Critical Review:*** *Gökhan Aytekin, Ahmet Zafer Çalışkaner;* ***References and Fundings:*** *Gökhan Aytekin, Ahmet Zafer Çalışkaner;* ***Materials:*** *Gökhan Aytekin, Eray Yıldız, Fatih Çölkesen.*

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