Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2023;48(1):29-36
DOI: 10.17826/cumj.1167916

RESEARCH

Use of methacoline challenge test to detect bronchial hyperresponsiveness in children with persistent rhinitis

Persistan rinitli çocuklarda bronş aşırı duyarlılığını saptamak için metakolin challenge testinin kullanımı

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Abstract

Purpose: The incidence of persistent rhinitis in childhood is increasing day by day. Since bronchial hyperreactivity (BHR) and asthma can also be seen in a significant proportion of patients with persistent rhinitis, the use of markers that may indicate the risk of developing asthma in these patients is very important in clinical follow-up. In this study, it was aimed to demonstrate the relationship between persistent rhinitis and asthma in childhood using the bronchial methacoline challenge test (BMCT) and to investigate other factors associated with the risk of developing asthma in patients with persistent rhinitis.

Materials and Methods: Patients aged 6-18 years who presented with findings of persistent rhinitis were evaluated with a detailed history, physical examination, and spirometry. Patients with normal examination findings and spirometry findings, and patients whose examination findings and nasal inflammation findings were compatible with moderate-to-severe rhinitis were included in the study, and their atopy status was evaluated by skin prick test, and their BHR was evaluated by BMCT.

Results: Seventy-three patients were included in the study. The mean age was 9±2.7years, 45.2% of the patients were male. 63% of the patients were allergic and family history of allergy was present in 45.2% of the patients. 82.2% of the patients had BHR detected with BMCT. The median blood eosinophil count (BEC) was 320/mm^3 and the IgE level was 160kU/L. Patients with atopy had statistically significantly higher IgE and BEC values compared with non-allergic patients. Patients with BHR were found to be younger, and had higher median BEC values. In multivariant analysis, it was observed that the patient's age<9 years, BEC values>300/mm^3, and IgE

Öz

Amaç: Çocukluk çağında persistan rinit sıklığı gün geçtikçe artmaktadır. Persistan rinitli hastaların önemli bir kısmında bronşial hiperrekativite (BHR) ve astım görülebildiğinden, bu hastalarda astım gelişme riskini gösterebilecek olan belirteçlerin kullanılması klinik takipte çok önemlidir. Bu çalışmada çocukluk çağındaki persistan rinit astım ilişkisinin bronşial methacoline challenge testi (BMCT) kullanılarak gösterilmesi ve persistan rinitli hastalarda astım gelişme riskiyle ilişkili diğer faktörlerin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Persistan rinit bulguları olan 6-18yaş arası hastalar ayrıntılı öykü, fizik muayene, spirometriyle değerlendirildi. Muayene bulguları ve spirometri bulguları normal olan hastalar ile muayene bulguları ve nazal inflamasyon bulguları orta-ağır rinitle uyumlu hastalar çalışmaya alındı ve cilt prik testiyle atopi durumları, BMCT yapılarak BHR'leri değerlendirildi.

Bulgular: Çalışmaya 73 hasta alındı. Yaş ortalaması 9±2,7yıl olarak bulundu. Hastaların %45,2'sinin erkek, %63'ü alerjik, %45,2'sinde ailede atopi öyküsü olduğu saptandı. BMCT ile hastaların %82,2Sinde BHR tespit edildi. BHR saptanan hastaların %24,7'sinde şiddetli; %32,9'unda orta, %24,7'sinde hafif derecede BHR olduğu gözlendi. Ortanca kan eosinofil sayısı (BEC) 320/mm^3; IgE düzeyi 160 kU/ltidi. Alerjik hastaların, alerjik olmayanlara kıyasla IgE, BEC değerleri istatistiksel olarak anlamlı düzeyde yüksekti. BHR olan hastaların başvuru yaşı daha küçük, BEC daha yüksekti. Çoklu değişkenli analizde hasta yaşının <9 yıl; BEC >300/mm^3 ve IgE düzeyinin >250IU/lt olması BMCT ile bronşial hiperreaktivite saptanma olasılığının arttığı gösterildi.

Sonuç: Persistan rinit yakınması olan her hasta BHR ve astım gelişme riski açısından mutlaka izlenmelidir. Bu

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Received: 31.08.2022 Accepted: 22.12.2022

levels>250IU/L increased the probability of detecting BHR with BMCT.
Conclusion: Care should be taken for every patient with persistent rhinitis because of the risk of BHR and asthma. Atopy examinations should be performed, but the possibility of developing BHR and asthma should not be overlooked even in the patients who are non- allergic.
Keywords:. Rhinitis, atopy, childhood, bronchial challenge test, bronchial hyperreactivity.

açıdan atopi tetkikleri yapılmalı ancak atopi saptanmasa da bu hastalaraki BHR ve astım gelişme olasılığı akılda tutulmalıdır.

Anahtar kelimeler: Rinit, atopi, bronş provakasyon testi, bronşial hiperreaktivite, çocukluk

INTRODUCTION

Rhinitis is described as inflammation of the nasal mucosa[1]. One or more of the following symptoms including runny nose, sneezing, nasal congestion, and/or itching are observed in patients. These symptoms are defined as persistent if they occur on two or more consecutive days, often lasting longer than 1 hour, and are observed for at least 12 weeks per year[2].

Although persistent rhinitis is frequently seen in childhood, it is especially common in adolescents[1]. Persistent rhinitis is classified as allergic (AR), infectious, non-allergic (NAR), non-infectious, and mixed-type rhinitis[2]. Asthma was reported in 10-40% of patients with rhinitis, and rhinitis was reported in 80% of patients with asthma[3]. Close follow-up of this patient group is required in terms of comorbid diseases such as asthma, rhinosinusitis, adenoid hypertrophy, and frequent otitis media[1].

In a recent systematic review, it was reported that single nucleotide polymorphisms in PTNP22 gene and CTLA-4 gene, serum total IgE level and history of parental atopy were among factors that were positively correlated with asthma in children with AR[4]. Bronchial hyperresponsiveness (BHR) which is characteristic for asthma can be detected in children with persistent rhinitis as both conditions share the common underlying pathophysiological mechanism[5]. Although the association between rhinitis and asthma in adults has been demonstrated using using bronchial methacoline challenge test (BMCT)[6], this test has been rarely used in children with allergic rhinitis in order to predict asthma development[7,8]. Early detection of BHR by using BMCT in children with persistent rhinitis may help to identify children particulary at risk for asthma.

In this study, we hypothesized that children with persistent rhinitis commonly have BHR and this can be detected by using BMCT. Herein, we aimed to evaluate the availability and usefullness of BMCT in children with persistent rhinitis in order to detect BHR and find out other clinical features and laboratory findings associated with asthma development.

MATERIALS AND METHODS

Patients who presented with findings of persistent rhinitis to the Pediatric Allergy Clinic, Faculty Hospital, Baskent University, were included in the study. An application was made to the Local Ethics Committee of Baskent University in order to conduct the study (KA1415/2009). Written informed consent was obtained from both parents at enrollment.

Patients

All patients aged 6-18 years who presented with nasal discharge, sneezing, itching in the nose and/or eyes, and cough were evaluated with a detailed history, physical examination, and pulmonary function test (PFT) between January and July. Among these, patients with normal examination findings and PFTs, and those with positive history for persistent rhinitis history and nasal inflammation findings consistent with moderate-severe persistent rhinitis whose parents gave consent for participation were included in the study.

Persistent rhinitis was defined as having symptoms more than 4 days per week and/or longer than 4 weeks per year. In addition, if the severity of the symptoms affects sleep and daily activities, disrupts work and school attendance, it is classified as moderate-severe persistent rhinitis[3].

According to the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline recommendations, patients with persistent rhinitis findings were questioned in terms of accompanying asthma findings[3] and skin prick tests (SPT) were performed. Written consent from the patients' parents and subjects was obtained for the study. We evaluated the family members of

patients for the presence of atopic diseases. In physical examinations, weight and height percentiles, signs of rhinitis, pulmonary auscultations, and any other positive findings were recorded.

Patients with neuromotor developmental retardation, growth retardation, smoking history, cardiac disease, bronchial asthma, any known other pulmonary and/or chronic diseases, those who could not cooperate in PFTs, and patients with signs of upper respiratory tract infection were excluded from the study.

Atopic patients

We evaluated the patients' atopy status using SPTs. Patients with a positive SPT were considered allergic, and patients without a positive SPT were considered non-allergic. Patients with allergies to a single allergen in SPTs and patients with multiple allergies in SPTs were separated. In addition, according to the results of SPTs, patients were divided into 2 groups including those with perennial allergies (house dust mites, furry animal epithelium, cockroaches, molds) and patients with pollen allergies. Serum immunoglobulin(Ig)-E levels and blood eosinophil counts(BEC) were measured in all patients.

Pulmonary function test

Pulmonary function tests were performed on all patients using spirometry. Patients whose spirometric values were not within normal limits or who did not cooperate with PFTs were excluded from the study. Bronchial methacholine challenge tests were planned for patients with normal spirometric values.

Before performing BMCTs, PFTs were performed in accordance with the guidelines of the American Thoracic Society and European Respiratory Society (ATC/ERS) using a Microplus Spirometer (Carefusion, Kent, UK). Spirometric values of forced vital capacity (FVC) and, forced expiratory volume in one second (FEV1) were recorded[9].

Bronchial Methacholine Challenge test

BMCTs were performed on all patients according to the protocol in the ATS guideline[9]. Briefly, doubling concentrations of fresh methacholine solutions were inhaled by using a dosimeter during a 2-minute tidal breathing period every 5 minutes, starting with 0.06 mg/mL up to 16 mg/mL or until a decrease in FEV 1 of at least 20% (PC 20) was obtained. A nebulizer (DeVilbiss model 646; DeVilbiss Co, Somerset, Pennsylvania) connected to an air compressor (Pulmo-Aid; DeVilbiss Co) with an output of 0.25 mL/min was used to produce the aerosols. A spirometer (Microplus Spirometer, Carefusion) was used to measure the FEV1 after each inhalation. BHR was expressed as the PC20. BHR to methacholine was defined as a PC20 ≤ 16 mg/mL. According to the BMCT results in the subjects were classified as severe BHR (PC20<1 mg/Ml); modarate BHR (PC20=1-4 mg/Ml); light BHR (PC=4-16 mg/mL); no BHR (PC>16 mg/mL). Children who had fever or acute respiratory symptoms within 1 week or whose predicted value of FEV1 was less than 70% were not asked to perform the BMCT.

Statistical analysis

IBM SPSS Statistics Version 17.0 package program (SPSS reference: IBM Corp. released 2011. IBM SPSS Statistics for Windows, version 20.0, Armonk, NY: IBM Corp.) was used for statistical analysis. Demographic variables were evaluated with descriptive statistics. Chi-square test was used for comparison of categorical measurements between groups. Mann-Whitney U and Student t test test was used to compare two groups of numerical variables according to distribution of variables. Firstly, univariate analyzes were performed to predict bronchial provocation test positivity. Then, multivariate logistic regression analysis was performed with variables having p value of <0.25 in the univariate analysis. All tests were 2-tailed, and a p value of <0.05 considered to be statistically significant.

RESULTS

Seventy-three patients who were diagnosed with persistent rhinitis were included in the study. The patients' mean age was 9 ± 2.7 years, 45.2% (n=33) were male, and 54.8% (n=40) were female. Atopy was detected in 63% (n=46) of the patients; 15.2% (n=7) of patients with atopy had single pollen sensitivity, 56.5% (n=26) had perennial atopy, and 28.3% (n=13) had both perennial and pollen sensitivity. Twenty-seven (58.7%) of the patients with atopy were sensitive to a single allergen. The family history of atopy was found in 45.2% (n=33) and BHR was detected in 82.2% (n=60) of the patients. Of the patients with BHR, 18 (24.7%) had severe BHR, 24 (32.9%) had moderate BHR, and 18 (24.7%) had mild BHR. The median FEV 1 value of the patients was

95 (89-97), FVC was 96% (92-98), the total IgE level was 160 kU/L (73-324), and BEC was 320 mm3 (150-530). The data on the clinical features of the patients are presented in detail in Table 1.

There was no statistically significant difference between the allergic or non-allergic groups in terms of age, gender, family history of atopy, BMCT results, BHR grade, FEV1 and FVC values. Total IgE values and BEC were found to be significantly higher in patients with atopy compared with patients without atopy (both $p < 0.001$). The details of the clinical features, PFT values, laboratory findings and BMCT results of the patients with respect to their atopic status are given in Table 2.

In comparison of patients with normal and abnormal BMCT results, no significant difference was detected according to gender, total IgE levels, atopy status, having an allergy to single perennial, single pollen or both allergen groups, the number of allergens to which the patient was sensitive (single or multiple), having atopic individuals in the family, and FEV1, FVC values. The age was significantly lower and BEC was significantly higher in patients with abnormal BMCT results ($p=0.033$ and $p=0.017$, respectively). The clinical, laboratory, and PFT findings according to normal and abnormal BMCT groups are given in Table 3.

When patients with normal and mildly positive BHRs and those with moderate-to-severe BHRs were compared, there were'nt important differences in the groups in terms of age, gender, familial atopy status, atopy status of the patient, having an allergy to a single perennial or single pollen or both allergen groups, the number of allergens (single or multiple), total IgE levels, and FEV1 and FVC values. We found BEC significantly higher in the moderate-to-severe BHR group compared to the normal and mild BHR group ($p=0.033$) (Table 4).

In multivariate analysis, the risk of BMCT positivity increased 10.989 times, [CI=95.1%; odds ratio (OR)=1.930-62.500; $p=0.007$] in patients <9 years, 12.242 times (CI=95%; OR=2.035-73.634; $p=0.006$) in patients who have BEC>300/mm^3, and 5.794 times (CI=95 %; OR=1,018-32.964; p= 0.048) in patients who have IgE levels >250 kU/L.

Table 1. Demographic characteristics and clinical and laboratory outcome measures of study population

Patients	Variables
Age, (year)*	9±2.7
FEV1 %, †	95 (89-97)
FVC %, †	96 (92-98)
Total IgE (kU/L) †	160 (73-324)
Blood Eosinophil count (mm^3) †	320 (150-530)
Gender, n, M/F (M %)	33/40 (45.2)
Atopy in family members,n (%)	33 (45.2)
The presence of atopy, n (%)	46 (63)
Positive result of BMCT ŧ ,n (%)	60 (82.2)
Degree of BHR §, n (%)	
>16	13 (17.8)
4-16	18 (24.7)
1-4	24 (32.9)
<1	18 (24.7)
The kind of alergen; perenial, polen n,(%)	
Perenial	26 (56.5)
Polen	7 (15.2)
Both polen and perenial	13 (28.3)
alergen index,n (%)	
Just one alergen	25 (58.7)
More than one alergen	19 (41.3)

*mean±SD; † median,interquarter range; ŧ BMCT; methacholine bronchial challenge tests; § BHR; bronchial hyperresponsiveness

Table 2. The demographic characteristics, clinical, laboratory outcomes and bronchial hyperresponsiveness to methacholine parameters of the two groups classified according to the presence of atopy.

Variable	Allergic Patients (n=46)	Non-allergic Patients (n=27)	P
Age (year)*	8.95(6.5-10.7)	6.5(10.7-11)	0.850
FEV 1 *	94.5(89-97)	89(97-97)	0.564
FVC *	96(92-98)	92(98-98)	0.828
Total IgE (kU/L)*	270(148-413)	148(134-413)	<0.001
Blood Eosinophil count (mm^3) *	480(320-630)	320(630-210)	<0.001
Gender, n, M/F(M %)	25/21 (54.3)	8/19 (29.6)	0.071
Atopy in family members,n (%)	24(52.2)	9(33.3)	0.188
Positivity of BMCT †, n, %	41(89.1)	19(70.4)	0,059
Degree of BHR ŧ, n (%)			0.016
N	5(10.9)	8(29.6)	
4-16	12(26.1)	6(22.2)	
1-4	13(28.3)	11(40.7)	
<1	16(34.8)	2(7.4)	

*Median (interquartile range); † BMCT; methacholine bronchial challenge tests; ŧ BHR, bronchial hyperresponsiveness

Table 3. The demographic characteristics, clinical, laboratory outcomes, and the presence of atopy of the two groups classified according to bronchial hyperresponsiveness to methacholine.

Results of BMCT*	Negative(n=13)	Positive (n=60)	p
Age, years †	11 (9-13)	8.3 (6.6-10.5)	0.033
Gender, n, M/F(M %)	6/7, (46.2)	27/33(45)	1.000
Atopy in family members, n (%)	3(23.1)	30(50)	0.144
Total IgE (kU/L) †	206(56-280)	157(77-348.5)	0.681
Blood Eosinophil count (mm^3) †	180(140-220)	420(183-585)	0.017
Atopy positive patiets, n(%)	5(38.5)	41(68.3)	0.059
Kind of alergen			1.000
Perennial	2(40)	24(58.5)	
Polen	1(20)	6(14.6)	
Both of them	2(40)	11(26.8)	
Alergen index, n,%			0.635
1	2(40)	25(61)	
>1	3(60)	16(39)	
FEV1 % †	96(92-97)	94,5(88-97)	0.098
FVC % †	96.5(93-98)	96(92-98)	0.552

* BMCT; methacholine bronchial challenge tests; † Median (interquartile range).

Table 4. The demographic characteristics, clinical, laboratory outcomes, and the presence of atopy of the two groups classified according to the degree of bronchial hyperresponsiveness.

Degree of BHR*	The patients without BHR and with Light BHR	The patients with Middle and Severe BHR	p
Age, years †	9.5(7-11,8)	8.3(6.5-10.5)	0.127
FEV1 % †	95(88-97)	95(89-97)	0.824
FVC % †	95(92-98)	96(92-98)	0.711
Total IgE, kU/L †	206(87-355)	151(53-312)	0.514
Blood Eosinophil count (mm3) †	220 (145-440)	430 (180-630)	0.033
Gender, n, M/F(M %)	11/20(35.5)	22/20(52.4)	0.232
Atopy in family members,n (%)	13(41.9)	20(47.6)	0.807
Atopy positive patiets, n(%)	17(54.8)	29(69)	0.318
Kind of alergen			0.782
Perennial	9(52.9)	17(58.6)	
Polen	3(17.6)	4(13.8)	
Both of them	5(29.4)	8(27.6)	
Alergen index, n,%			0.359
1	8(47.1)	19(65.5)	
>1	9(52.9)	10(34.5)	

*BHR: Bronchial hyperresponsiveness; † median, interquarter range.

DISCUSSION

It is known that AR is commonly associated with asthma and/or sometimes BHR[7]. Studies on adults and adolescents have shown an increased prevalence of asthma in subjects with allergic and non-allergic rhinitis[10,11]. Rhinitis has been shown to suggest an interaction between the upper and lower airways beyond allergy-associated inflammation[12,13]. In an international study including eight countries in Europe and Asia, it was observed that 76% of children had AR symptoms before the asthma was first diagnosed[1]. Rhinitis is a well known risk factor for adolescent and adult-onset asthma development[12].

Bronchial hyperreactivity is a key feature in asthma[14]. BMCT is a well-standardized and reliable method that has been used to detect BHR in adults and children since the 1970's[7,15,16]. BMCT correlates well with the presence and clinical severity of asthma[17]. However, BMCT has limitations in use in the diagnosis of asthma. The first of these limitations is that many subjects with BHR detected with BMCT are asymptomatic. Detection of BHR has high sensitivity but low specificity in the diagnosis of asthma[17]. The implementation of BMCT is costly and time-consuming[17]. Therefore, it is most often performed to exclude diagnosis of asthma. Furthermore, there is a limited number of studies using BMCT that provide preliminary information on this subject in the literature[7].

Karaatmaca et al. investigated the BHR status of children with AR and found BHR in 45% of patients with persistent AR. In addition, they found that patients with BHR had statistically significantly lower FEV1 and FEF25-75 values compared to those without BHR. They have shown the risk of developing BHR was higher in patients with longer duration of symptoms[7]. BHR was detected by using BMCT in 82.2% of the patients in our study. We found no significant difference in PFT findings of patients with and without BHR. BEC was significantly higher in patients with abnormal BMCT results. Lee et al reported that a high BEC was found to be associated with high prevalence of BHR[18]. Ahn et al. evaluated BHR in patients with AR including both adults and children and a treshold for BEC ≥ 320 cells/μL that could predict BHR was

determined[19]. Karaatmaca et al. suggested that BEC might be an alternative marker to predict BHR in patients with AR[7].

In the preschool children group, AR is a well-known risk factor for subsequent wheezing onset. In a cohort study, a previous diagnosis of AR was found in 41.5% of patients who were diagnosed with asthma at the age of 13 years. Therefore, the authors recommended early assessment of atopy status in preschool children with rhinitis in order to identify children at high risk of wheezing[12]. Atopy was shown as a factor directly affecting the BHR status of patients with rhinitis[11]. In our study, atopy was detected in 63% of our patients. While there was a slightly significant difference between our allergic and non-allergic patients in terms of BHR rates (p=0.059), there was a significant difference when compared in terms of BHR degrees (p=0.016). It was thought that this difference might be due to the higher frequency of severe BHR in the allergic group compared to the non-allergic group (34.8% and 7.4%, respectively). The prevalence of BHR to methacholine in children who had wheezing in the past 12 months was reported to differ widely from 25% in the United States to 60% in Turkey[14,20,21].

We revealed a statistically significant difference in terms of age being lower in patients with BHR compared to patients without BHR in our study. Therefore, BHR may be encountered more frequently in patients with early symptoms and an increase in asthma prevalence may be observed in these patients. In the multivariate analysis, it was found that patient age <9 years, BEC >300/mm3, and IgE levels >250 uK/L significantly increased the risk of BHR in our study. Karaatmaca et al. also reported that low age at onset of AR symptoms and high BEC values were associated with an increased risk of developing BHR[7].

Chawes et al. reported that the prevalence of asthma, IgE level, BEC values, and BHR rates were increased in patients with AR. They showed that only the prevalence of asthma increased in patients with NAR[11]. IgE levels and BEC were not found to be high in patients with NAR[11]. BEC is one of the most widely used predictive biomarkers of TH2-related allergic disease[7]. We compared IgE level, BEC, and BHR status in our patients with AR and non-allergic rhinitis IgE levels and BEC, in particular, were found to be signficantly higher in our AR group compared to non-allergic group.

Patients with rhinitis may report chronic cough due to stimulation of cough receptors in the nasal cavity, pharynx, and larynx, as well as postnasal discharge. These patients may be misdiagnosed as having asthma, and attention should be paid to this issue[1,22]. Our patients with moderate-to-severe persistent rhinitis were first questioned in terms of possible asthma in line with the recommendations of ARIA[3,11]. Exercise-related symptoms, prolonged nocturnal cough, recurrent cough not due to cold, night awakening symptoms, need for intermittent rescue use of inhaled β2-agonist, and the presence of response to 3-month inhaled corticosteroid treatment but relapse when treatment was stopped were questioned. In addition, according to the recommendations of ARIA, patients who are diagnosed as having AR whose BHR is not detected may develop asthma in the later stages of their lives, and these patients should be followed carefully.

Our study has several limitations. First, the small number of subjects were included. Second, due to the cross-sectional nature of the study, it would not be possible to know which patient will be diagnosed with asthma in the future. Third, it was not certain which patient was truly non-allergic since nasal provocation testwas not performed.

In conclusion, although BMCT provides valuable information in the selected patient group, it may not be the first option to be used in monitoring the possibility of asthma in patients with persistent rhinitis due to its invasiveness and cost-effectiveness. Every patient with persistent rhinitis should be followed up in terms of asthma risk, atopy examinations should be performed early in these patients, and the possibility of developing asthma should be considered even if the patients are non-allergic. Although further studies are needed, patient' BEC and IgE levels can be checked to predict BHR. In addition, it should be known that patients who are diagnosed as having early rhinitis are more likely to develop asthma in the future.

Yazar Katkıları: Çalışma konsepti/Tasarımı: SA, BUG; Veri toplama: BUG, SA; Veri analizi ve yorumlama: SA, BUG; Yazı taslağı: BUG; İçeriğin eleştirel incelenmesi: SA, BUG; Son onay ve sorumluluk: BUG, SA; Teknik ve malzeme desteği: BUG, SA; Süpervizyon: SA, BUG; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için Başkent Üniversitesi Tıp ve Sağlık Bilimleri Araştırma Kurulundan 17.12.2009 tarih ve 1415 sayılı proje onayı alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması olmadığını beyan etmişlerdir.
Finansal Destek: Yazarlar finansal destek almadıklarını beyan etmemişlerdir.
Author Contributions: Concept/Design : SA, BUG; Data acquisition: BUG, SA; Data analysis and interpretation: SA, BUG; Drafting

manuscript: BUG; Critical revision of manuscript: SA, BUG; Final approval and accountability: BUG, SA; Technical or material support: BUG, SA; Supervision: : SA, BUG; Securing funding (if available): n/a.
Ethical Approval: For this study, the project approval dated 17.12.2009 and numbered 1415 was obtained from the Başkent University Medical and Health Sciences Research Council.
Peer-review: Externally peer-reviewed.
Conflict of Interest: The authors have declared that there is no conflict of interest.
Financial Disclosure: The authors did not declare that they did not receive financial support.

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