The assessment and management of chronic cough in children according to the British Thoracic Society guidelines: descriptive, prospective, clinical trial

Belgin Usta Guc¹, Suna Asilsoy² and Cemile Durmaz³

¹ Department of Pediatric Allergy, Konya Education and Research Hospital, Konya, Turkey
² Department of Pediatric Allergy, Faculty of Medicine, Adana Education and Research Hospital, Baskent University, Adana, Turkey
³ Adana Numune Education and Research Hospital, Adana, Turkey

Abstract

Background: Chronic cough is a common problem of various etiologies. While diagnosis may relatively be easy in the presence of some specific findings, it tends to be rather difficult when there are no clear symptoms. Therefore, practical guidelines are needed for management of patients with chronic cough. We aimed to evaluate assessment and management of chronic cough in children according to the British Thoracic Society guidelines published in 2008.

Methods: Patients with chronic cough lasting longer than 8 weeks between 5 and 16 years old were evaluated. Pulmonary function test and chest radiography were performed on all patients. Further workup was conducted on those requiring further investigation. Patients were re-evaluated at 2- to 4-week intervals, and we followed our patients for 18 months until cough resolved.

Results: One hundred fifty six patients (52.5% female) aged 5–16 (8.4 ± 2.6) years were included. Of the 156 patients, 19.2% (n = 30) were diagnosed with postnasal drip syndrome plus asthma; 18.6% (n = 29) with postnasal drip syndrome; 12.2% (n = 19) with asthma; 12.2% (n = 19) with protracted bacterial bronchitis; and 11.5% (n = 18) with nonspecific isolated cough, 9.6% (n = 15) with cough variant asthma, 5.7% (n = 9) with psychogenic cough and 3.2% (n = 5) with gastroesophageal reflux disease.

Conclusions: Postnasal drip syndrome and asthma was the most common cause of chronic cough. Asthma-associated findings were found in some of the patients diagnosed with postnasal drip syndrome. It has been observed that there could be more than one particular cause for cough concerning some patients. The gastroesophageal reflux disease was not a common primary cause of chronic cough in children.


Key words
chronic cough – cough variant asthma – nonspecific isolated cough – postnasal drip syndrome plus asthma

Correspondence
Belgin Usta Guc, MD, Konya Education and Research Hospital, Department of Pediatric Allergy, 42040 Meram/Konya, Turkey.
Tel: +00 90 332 444 06 42/5313
Fax: +00 90 332 323 67 23
email: defneusta@hotmail.com

Received: 14 June 2013
Revision requested: 22 October 2013
Accepted: 20 November 2013
DOI:10.1111/crj.12076

Authorship and contributorship
Belgin USTA GUC and Suna ASILSOY were involved in designing the study, and collecting and analyzing the data. Cemile DURMAZ was involved in collecting the data. Belgin USTA GUC and Suna ASILSOY wrote the first draft of the paper and read the manuscript and approved its submission.

Ethics
The Local Ethics Committee of Baskent University approved the study. The patients were informed of the nature and purpose of the study and oral as well as written informed consent was obtained.

Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Introduction

Chronic cough is a very common problem and is one of the most frequent reasons for many doctor visits in childhood. Chronic cough is not a disease in itself; rather, it is a symptom of an underlying condition. Diagnosis may be easy in the presence of some specific findings, while it is very difficult in the absence of such findings (1, 2).

Several guidelines have been developed to diagnose and treat chronic cough in children. One set of guidelines was developed by The American College of Chest...
Physicians (ACCP), where chronic cough is defined as lasting longer than 4 weeks. In the British Thoracic Society (BTS) guidelines published in 2008, chronic cough is defined as lasting longer than 8 weeks (3, 4). In 2008, a research paper based on the ACCP Guideline was published about a study on patients of 5 years of age and older with chronic cough (5). However, literature reveals no studies conducted with 2008 BTS guidelines to evaluate chronic cough in children according to 2008 BTS guidelines. Although these guidelines have similar features, they differ as to duration of cough, terminology used in diagnosis and period of treatments. This study aimed to evaluate the assessment and management of children over 5 years of age with chronic cough in accordance with the 2008 BTS guidelines.

Researchers have recently begun discussing ‘nonspecific isolated cough’ in childhood. The term has been used to describe that children who have a persistent dry cough are otherwise well and have a normal chest radiograph. In the BTS guidelines, the concept of nonspecific isolated cough has been debated in detail (4). We also discussed the evaluation of children older than 5 years with nonspecific isolated cough in this study.

Materials and methods

This study included patients presenting with chronic cough at the Department of Pediatric Allergy and Immunology, Adana Research and Training Hospital, Faculty of Medicine, Baskent University. Prior to the study, written approval was obtained from the Local Ethics Committee of Baskent University.

Patients

The patients with chronic cough were evaluated between September 2009 and September 2010. These written consents of the patients’ parents were obtained for the study. The duration of cough, characteristics of cough (dry, wet or both), prognosis of cough during the day (daytime, night or both), accompanying findings, active and passive smoking habits or exposure, presence of atopic diseases (asthma, allergic rhinitis, atopic dermatitis in parents or siblings), symptoms like heartburn, and/or bad taste in the mouth were all evaluated through a detailed history of the patients. On physical examination, weight and height percentiles, pulmonary auscultations as well as other findings (which might be associated with a specific disease) were recorded.

Patients with a history of premature birth, neuro-motor development retardation, development-growth retardation, chest wall deformity, a smoking habit, clubbing, cardiac disease, any known chronic disease and/or a pulmonary disease, and those who could not cooperate in pulmonary function test (PFT) were all excluded from the study.

Study design

The guidelines recommended by BTS were taken as a basis in this study. During their first visit, chest radiography and PFT were performed on all the patients who were evaluated at 2- to 4-week intervals until cough resolved. If needed, PFT and chest radiography were repeated. Depending on history and physical examination results, skin prick test (SPT), tuberculin skin test, gastroesophageal reflux (GER) scintigraphy, serum immunoglobulin levels, sweat chloride test, high-resolution chest tomography (HRCT) were also performed. We followed our patients for 18 months until their cough had resolved.

Definitions

(i) Asthma: Patients with a forced expiratory volume in 1 s value under 85% at PFT and a recovery rate of ≥12% following bronchodilator responsiveness test [15 min after the administration of three puffs (100 mcg/puff) albuterol via mask] and whose cough resolves following with treatment of inhaled corticosteroid (ICS) such as budesonide 400 μg/day (4, 6).

(ii) Cough variant asthma (CVA): Isolated dry cough (no wheezing). Cough responds rapidly to anti-asthma medication but relapses when stopped (4, 6).

(iii) Protracted bacterial bronchitis (PBB): Presence of isolated chronic productive cough that resolves with antibiotic therapy within 2 weeks after other underlying conditions excluded (clarithromycin, 15 mg/kg/day, 2 weeks) (4, 7).

(iv) GER disease (GERD): A clinical manifestation of the excessive reflux of gastric contents into the esophagus causing various symptoms (heartburn, regurgitation, dysphagia, pulmonary and laryngo-pharyngeal symptoms) that is confirmed with GER scintigraphy and resolves with antireflux treatment [lansoprazol (15 mg/day), domperidone (1 mg/kg/day)].

(v) Postnasal drip syndrome (PNDS): This term includes postnasal drip because of sinusitis, allergic and nonallergic rhinitis. A medical history matching the detection of postnasal discharge during physical examination, nasal mucosal edema, hyperemia, pallor, response to antihistamines, allergen avoidance, nasal
saline solution, antibiotic therapy and/or nasal steroid therapy (4, 6, 8).
(vi) Bronchiectasis: Chronic irreversible dilatation of diseased bronchi confirmed on thorax HRCT in patients with wet cough.
(vii) Psychogenic/habitual cough: A disruptive bizarre honking cough in a child who exhibits 'la belle indifference' is suggestive of a psychogenic cough that is usually observed to cease when the patient sleeps or focuses attention somewhere else.
(viii) Tuberculosis infection: Positive tuberculin skin test in patients with normal chest examination and radiography.
(ix) Nonspecific isolated cough: Dry cough without any complaints in patients who are generally healthy and have normal physical examination, chest radiography and PFT (4).

Statistical analysis

Descriptive analyses were made using a statistical software package (SPSS, version 14.0; SPSS; Chicago, IL, USA). The data were presented as the mean ± standard deviation.

Results

The study included 156 patients aged 5–15.5 (8.42 ± 2.6) years. Of these patients, 82 (52.5%) were females and 74 (47.5%) males; 89 (57%) had dry cough, 42 (26.9%) wet cough and 25 (16%) both dry and wet cough; 61 (39%) were exposed to parental smoking; 56 (35.8%) had an atopic disease in family history; and 65 (41.6%) had cough at night, 30 (19.2%) had cough at daytime, and 61 (39.1%) at both daytime and nighttime (Table 1). Table 2 illustrates diagnostic distribution of the patients in the first examination.

Asthma

At the first evaluation, 21 patients received diagnosis of asthma based on physical examination and PFT findings; ICS treatment was administered to these patients. No recovery was observed in two patients despite ICS treatment. In the eighth week of observation, GER scintigraphy was performed on these two patients, and they were diagnosed with reflux. In addition to the ICS treatment, these patients were given antireflux treatment, and cough resolved following this treatment. Atopy was detected in 17 (80.9%) of these patients by SPT. Figure 1 shows the evaluation of the patients in accordance with BTS guidelines.

PNDS

During initial assessment, PNDS was detected in 62 patients. Figure 2 illustrates the evaluation of patients with PNDS.
- Sinusitis: 29 patients with diagnosis of sinusitis were treated with amoxicillin-clavulanate and nasal saline solution. Cough resolved in 16 patients. In the remaining 13, cough persisted. PFT was repeated in 13 patients. Reversibility was demonstrated in 10. After ICS treatment was administered to 10 patients with positive reversibility, their cough resolved. At the end of the follow-up, 10 patients with positive reversibility were diagnosed as asthma plus PNDS. GER scintigraphy was performed on three patients who had normal PFTs. These patients were defined as GERD (Fig. 2).
- Rhinitis (allergic and nonallergic): Of the 62 patients with PNDS, 33 underwent antihistaminic and/or nasal steroid treatment following diagnosis of rhinitis. In 20 out of the 33 patients diagnosed as rhinitis, cough

Table 1. Demographic characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>156</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>82 (52.5)</td>
</tr>
<tr>
<td>Mean age (year)</td>
<td>8.42 ± 2.6</td>
</tr>
<tr>
<td>Mean length of cough (month)</td>
<td>3.99 ± 3.21</td>
</tr>
<tr>
<td>Presence of family atopic disease, n (%)</td>
<td>56 (35.8)</td>
</tr>
<tr>
<td>Passive smoking, n (%)</td>
<td>61 (39)</td>
</tr>
<tr>
<td>Cough type, n (%)</td>
<td></td>
</tr>
<tr>
<td>Dry</td>
<td>89 (57)</td>
</tr>
<tr>
<td>Wet</td>
<td>42 (26.9)</td>
</tr>
<tr>
<td>Dry + wet</td>
<td>25 (16)</td>
</tr>
<tr>
<td>Cough timing, n (%)</td>
<td></td>
</tr>
<tr>
<td>Night</td>
<td>65 (41.6)</td>
</tr>
<tr>
<td>Daytime</td>
<td>30 (19.2)</td>
</tr>
<tr>
<td>Night + daytime</td>
<td>61 (39.1)</td>
</tr>
</tbody>
</table>

Table 2. Diagnostic distribution of the patients in the first examination

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Values, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postnasal drip syndrome</td>
<td>62 (39.7)</td>
</tr>
<tr>
<td>Nonspecific isolated cough</td>
<td>36 (23.0)</td>
</tr>
<tr>
<td>Protracted bacterial bronchitis</td>
<td>23 (14.7)</td>
</tr>
<tr>
<td>Asthma</td>
<td>21 (13.4)</td>
</tr>
<tr>
<td>Psychogenic cough</td>
<td>9 (5.8)</td>
</tr>
<tr>
<td>GERD</td>
<td>5 (3.2)</td>
</tr>
</tbody>
</table>

GERD, gastroesophageal reflux disease.
Persisted. Because reversibility test in repeated PFT was positive, ICS was added to the treatment. At the end of the follow-up, 20 patients with positive reversibility were diagnosed with asthma plus rhinitis. SPT was performed on all the patients with rhinitis. Atopy was observed in 25 patients (Fig. 2).

**Nonspecific isolated cough**

In the physical examination and chest radiography, 36 patients had normal findings. In the first evaluation, these patients formed the nonspecific isolated cough group. They were recommended to avoid exposure to parental smoking (if any). The cough resolved spontaneously in four patients 2 weeks later. ICS treatment was administered to 32 patients. Twenty-four patients responded to the therapy, and the therapy was stopped at the end of 4 weeks. Nevertheless, after cessation of the treatment, cough recurred in 15 of 24 patients. Thus, further ICS treatment was given, and consequently, cough resolved. These 15 patients were considered to have cough-variant asthma. SPT was performed on all the patients with CV A. Atopy was detected in nine patients. ICS treatment of the patients without atopy was continued for 12 weeks, and cough did not recur after cessation of the therapy. GERD was diagnosed in three of the eight unresponsive patients to ICS treatment, and cough resolved following antireflux treatment. Five of the eight unresponsive patients recovered spontaneously during the follow-up (Fig. 1).

**PBB**

Clarithromycin was administered to 23 patients who suffered from wet cough and were diagnosed by
normal physical examination and chest radiography. Two weeks later, the cough of 19 patients resolved, and these patients were accepted as PBB. The remaining four patients’ cough exacerbated; therefore, PFT were repeated, and HRCT and tuberculin skin test were performed. Two patients had positive reversibility on PFT, tuberculin skin test >15 mm and normal HRCT. Acid-resistant bacteria and tuberculosis culture were studied from sputum of two patients, and the results were negative. These patients received diagnoses of tuberculosis infection and bronchial hyperreactivity. Isoniazide (10 mg/kg/d) and ICS treatments were administered to these patients, and the results resolved 3 weeks later. Bronchiectasis was detected on HRCT in other two patients. In order to evaluate the etiology of bronchiectasis, immunoglobulin A (IgA), IgG, IgM, IgE and IgG subgroups, sweat chloride, and nasal saccharine tests were performed. IgG2 deficiency was found in one patient.

Psychogenic/habitual cough
Nine patients, in their history, reported that their cough resolved particularly during sleep and worsened when others’ attention was on them. These patients had normal physical examinations, chest radiographies, PFTs and GER scintigraphies. According to their history, they were diagnosed with psychogenic/habitual cough. Then, we transferred the patients to Child and Adolescent Psychiatry Department.

GER
GER scintigraphy was performed on five patients with symptoms suggestive of GER. These patients had normal PFT and chest radiography. Based on scintigraphy results, reflux extending to the upper esophagus was detected. Antireflux treatment and measures against GER were administered. Their complaints resolved 4 weeks later.

To sum up, distribution of the diagnosis of the patients with chronic cough was 19.2% (n = 30) with PNDS plus asthma, 18.6% (n = 29) with PNDS, 12.2% (n = 19) with asthma, 12.2% (n = 19) with PBB, 11.5% (n = 18) with nonspecific isolated cough, 9.6% (n = 15) with CVA, 5.76% (n = 9) with psychogenic/habitual cough, 3.2% (n = 5) with GERD, 1.9% (n = 3) with PNDS plus GERD, 1.9% (n = 3) with nonspecific isolated cough plus GERD, 1.3% (n = 2) with asthma plus GERD, 1.3% (n = 2) with tuberculosis infection...
plus bronchial hyperreactivity, 0.6% (n = 1) with bronchiectasis plus immune deficiency, and 0.6% (n = 1) with bronchiectasis. Table 3 illustrates diagnostic distribution of the patients at the end of monitoring for 18 months.

Discussion

Asthma is a chronic disease characterized with reversible obstruction of airways. It has been reported in several studies that it is the most common cause of chronic cough (4, 5, 9). Its diagnosis is easier in the presence of typical findings (such as auscultation findings and detection of reversibility in PFTs). However, children with asthma may present at clinics with a cough complaint only (4, 9). In such cases, bronchial provocation test may help with diagnosis, and when the test is negative, diagnosis may be eradicated; yet, when it is positive, diagnosis is not definite. Another method of diagnosis is through response to treatment. ICS treatment can be recommended for such patients but only after a thorough evaluation of other causes potentially responsible for chronic cough. If the child has responded to anti-asthma therapy and the treatment has subsequently been stopped, CVA is suggested by an early relapse that again responds to treatment (4). When patients do not respond to treatment, the type of the treatment should be questioned, and comorbid situations (such as allergic rhinitis, sinusitis and GERD) or an alternative diagnosis should be considered. Two of our patients, unresponsive to ICS, were diagnosed as GERD. During the first evaluation in our study, based on findings of auscultation and reversibility in PFTs, 21 patients received a diagnosis of asthma. However, later, a further observation revealed 34 of our patients were defined as asthma eventually.

The second most common cause of chronic cough in our study was PNDS, a term comprising postnasal drip because of allergy, nonallergic rhinitis and sinusitis (6). PNDS was defined in ACCP guidelines as ‘upper airway cough syndrome’. The term upper airway cough syndrome has a clearer definition in the ACCP guidelines compared with BTS. Potential connection between PNDS, asthma and GERD was defined in children (10–12). It is believed that direct effect of nasopharyngeal reflux in mucosa leads to inflammatory response, and thus, mucociliary clearance is interrupted (12). In our study, despite the administration of appropriate treatment, cough was persistent in 53% (n = 33) of the patients with PNDS. We detected GERD in three patients with no response to the PNDS treatment. Thirty patients who did not respond to the PNDS treatment sufficiently were administered with ICS treatment based on clinical findings and PFTs, and all such patients responded to the ICS treatment subsequently. Eventually, these 30 patients were also diagnosed with PNDS plus asthma. The results of our study support the argument that asthma and rhinitis are associated and may be manifestations of a single disease entity. This finding necessitates careful observation of PNDS and its close link to asthma (13).

PBB has been reported to be the most common cause of chronic cough, particularly in children aged under 2 years (7, 14). For wet cough, a 2-week antibiotic therapy, or more precisely, bronchoalveolar lavage fluid analysis ( neutrophilic inflammation and isolation of microorganism), and an absence of pointers suggesting alternative diagnoses are used for diagnosis (7, 15). Detailed evaluation is recommended for patients who suffer from wet cough and do not respond to antibiotic therapy. PBB was reported to be one of the common causes of chronic cough in a study whose subjects were at similar ages to the ages of ours (5). In our study, 19 patients (12.2%) were treated with antibiotic therapy because of PBB diagnosis.

Nonspecific isolated cough, based on BTS guidelines, was found to be one of the common causes of chronic cough in our study. The term ‘nonspecific isolated cough’ corresponds to dry cough in the ACCP guideline. Clinical trials and epidemiological studies have revealed that significant number of children suffer from nonspecific isolated cough (4, 16, 17). These children are healthy and have normal physical examination, PFT and chest radiographies. Their only symptom is dry cough. In fact, nonspecific isolated cough is not a diagnosis but a term. It is stated that

Table 3. Diagnostic distribution of the patients at the end of monitoring for 18 months

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Values, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postnasal drip syndrome plus asthma</td>
<td>30 (19.2)</td>
</tr>
<tr>
<td>Postnasal drip syndrome</td>
<td>29 (18.6)</td>
</tr>
<tr>
<td>Asthma</td>
<td>19 (12.2)</td>
</tr>
<tr>
<td>Protracted bacterial bronchitis</td>
<td>19 (12.2)</td>
</tr>
<tr>
<td>Nonspecific isolated cough</td>
<td>18 (11.5)</td>
</tr>
<tr>
<td>Cough variant asthma</td>
<td>15 (9.6)</td>
</tr>
<tr>
<td>Psychogenic cough</td>
<td>9 (5.76)</td>
</tr>
<tr>
<td>GERD</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Postnasal drip syndrome + GERD</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Nonspecific isolated cough + GERD</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Asthma + GERD</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>TB infection</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Bronchiectasis + immune deficiency</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

GERD, gastroesophageal reflux disease; TB, tuberculosis.
The management of chronic cough in children

Usta Guc et al.

asthma may develop in some of these children and that short-term ICS administration may be used to confirm diagnosis of CVA (3, 4). In children, asymptomatic acid and nonacid GER has been reported as one of the causes of unexplained chronic cough (18). In our study, 24 out of 32 patients treated with ICS responded to the therapy. After cessation of the treatment, cough recurred in 15 of the 24 patients. ICS treatment was given again, and consequently, cough resolved. Eventually, we believed that these 15 patients had CVA.

In the first examination, 36 of our patients were appeared to have nonspecific isolated cough; however, at the end of monitoring for 18 months, we were convinced that 41.7% (n = 15) of these 36 patients had CVA and 8.3% had GERD (n = 3). There is no any study in the literature evaluating nonspecific isolated cough in children according to 2008 BTS guidelines. So we cannot compare our results with patients with non-specific isolated cough.

One of the common causes of chronic cough is post-infectious cough. Frequently, respiratory syncytial virus, Mycoplasma pneumoniae, Chlamydia pneumoniae and Bordetella pertussis are among factors known to cause protracted post-infectious cough (6, 19, 20). The persistent airway inflammation and temporary sensitivity of airways, which developed following the infection, are accountable for protracted cough. It is known that post-infectious cough may last 3–8 weeks. At the first stage of our study, there were no patients who, we thought, could be suffering from post-infectious cough, as only patients with a cough of ≥8 weeks were included in the study. However, in retrospect, we think that some of our patients could have been suffering from post-infectious cough.

GERD has been reported as one of the most common causes of chronic cough in adults (21–23). In children, this is controversial (5, 24). Although it is known that reflux and cough trigger each other, the relation between them is not exactly known (25–27). It has been reported that reflux causes isolated cough (28). At initial evaluation, we demonstrated reflux as main diagnosis in five patients (3.2%), all of whom responded to GERD treatment. However, when we re-evaluated the treatment-unresponsive patients who were diagnosed as asthma and/or PNDS, we found reflux comorbidity in five additional patients. These results have shown that GERD rarely causes cough by itself in children, yet it frequently accompanies other diagnoses.

Our study has some limitations. We did not have the opportunity for 24-h pH-monitoring study, which is the gold standard for diagnosis of GER. In our study, episodes of GER were evaluated by scintigraphy in patients who have symptoms like heartburn and/or bad taste in the mouth. Second, we were not able to evaluate nonacid reflux episodes.

Psychogenic/habitual cough also needs to be taken into consideration as one potential cause of chronic cough. Of our patients, 5.7% (n = 9) were diagnosed with psychogenic/habitual cough. A typical feature of these patients who had normal physical examination, chest radiography and PFT was that they did not cough during sleep or when their attention was distracted. Their cough was psychogenic and of a ‘la belle indifference’ nature (4, 29). Their cough worsened in others’ presence, such as parents or teachers yet decreased in frequency and/or severity with pleasurable social activities or exercise (4).

Passive exposure to smoking is another factor that deteriorates cough (4, 6). In some studies, chronic cough was diagnosed in 50% of children (<11 years) whose both parents smoked (6). Although parents stated that they did not smoke in the presence of their children, it was determined in our study that 39% (n = 61) of parents did in fact smoke. Despite the fact that it does play an important part in the formation and/or increase of cough, it is controversial to state whether passive exposure to smoking does indeed cause chronic cough by itself only (30).

In conclusion, PNDS plus asthma, PNDS, asthma and PBB were found to be the most common causes of chronic cough. It has been observed that there could be more than one particular cause for cough concerning some patients. We conclude that the BTS guidelines for the management of chronic cough are effective and can be successfully used. Thus, before patients’ re-evaluation at 2- to 4-week intervals, clues for specific diseases should be evaluated, and then depending on findings of the evaluation, further investigations should be carried out if and when necessary.

Acknowledgements

Belgin USTA GUC and Suna ASILSOY were involved in designing the study, and collecting and analyzing the data. Cemile DURMAZ was involved in collecting the data. Belgin USTA GUC and Suna ASILSOY wrote the first draft of the paper and read the manuscript and approved its submission. The authors thank Safak Ugur for the English revision.

References


