


Evaluation of Approach and Etiology in Patients with Chronic Cough in Trakya University Hospital

Trakya Üniversitesi Hastanesi'nde Kronik Öksürüklü Hastalarda Yaklaşım ve Etiyolojinin Değerlendirilmesi

 İlker YILMAM

 Tuncay ÇAĞLAR

 Ebru ÇAKIR EDİS

¹Department of Chest Diseases, Trakya University Faculty of Medicine, Edirne, Türkiye

²Department of Chest Diseases, Ekol Hospital, Edirne, Türkiye

ORCID ID

İY : 0000-0003-4349-5771

TÇ : 0000-0002-1862-9259

EÇE : 0000-0002-8791-5144



ABSTRACT

Objective: In this study, we aimed to determine the most common etiological causes in patients with chronic cough and to evaluate the effectiveness of empirical treatment approach model in patients with chronic cough.

Material and Methods: Patients who presented to the chest diseases outpatient clinic with a cough complaint for more than 8 weeks within a period of 15 months and who had not been diagnosed with this symptom before were included in the study.

Results: Ninety patients with cough complaint for at least 8 weeks who applied to the chest diseases outpatient clinic with this complaint were included in the study. Sixty-four of the patients (71.1%) were female and 26 of them (28.9%) were male. The mean age of the patients was 46 (17–79). In their respiratory system examinations, physical examination findings were not found in 69 patients (76.6%). As the most common cause of chronic cough, asthma alone was found in 22 patients (24.6%). The second most common etiological cause was found to be gastroesophageal reflux (21.1%). In 13 patients (14.4%), more than one etiological cause was found.

Conclusion: Although asthma, reflux, and upper airway cough syndrome are found among the most common causes in patients with chronic cough, it should be considered that more than one etiological cause may coexist in some patients.

Keywords: Asthma, chronic cough, empirical approach, gastroesophageal reflux, upper airway cough syndrome.

ÖZ

Amaç: Çalışmanın amacı, kronik öksürüklü hastalarda en sık görülen etiyolojik nedenleri belirlemek ve kronik öksürüklü hastalarda ampirik tedavi yaklaşım modelinin etkinliğini değerlendirmektir.

Gereç ve Yöntemler: Göğüs hastalıkları polikliniğine 15 aylık süre içinde, sekiz haftanın üzerinde öksürük yakınması ile başvuran daha önce bu semptomla yönelik herhangi bir tanı konulmamış hastalar dahil edildi.

Cite this article as: Yılmaz İ, Çağlar T, Çakır Edis E. Evaluation of Approach and Etiology in Patients with Chronic Cough in Trakya University Hospital. Journal of Izmir Chest Hospital 2023;37(1):22–27.

Received (Geliş): September 29, 2022 **Revised (Revize):** March 07, 2023 **Accepted (Kabul):** March 10, 2023 **Online (Çevrimiçi):** April 18, 2023

Correspondence author (Sorumlu yazar): İlker YILMAM, MD. Trakya Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Edirne, Türkiye.

Tel: +90 533 571 79 22 **e-mail:** drilkeryilmam@gmail.com

© Copyright 2023 by Journal of Izmir Chest Hospital - Available online at www.ighdergisi.org

Bulgular: Araştırmaya en az sekiz hafta öksürük yakınması olup göğüs hastalıkları polikliniğine bu şikâyet ile başvuran 90 hasta dahil edildi. Hastaların 64'ü (%71,1) kadın, 26'sı (%28,9) erkek idi. Hastaların yaş ortalaması 46 yıl (17-79) idi. Solunum sistemi muayenelerinde; 69 (%76,6) hastada fizik muayene bulgusu saptanmadı. En sık kronik öksürük nedeni olarak, 22 (%24,6) hastamızda tek başına astım saptandı. İkinci sıklıkla saptadığımız etiyolojik neden gastroözefageal reflü idi (%21,1). On üç (%14,4) hastamızda ise birden fazla etiyolojik neden bulundu.

Sonuç: Kronik öksürüklü hastalarda astım, reflü ve üst hava yolu öksürük sendromu en sık nedenler arasında saptanmasına rağmen, bazı hastalarda birden fazla etiyolojik nedenin bir arada bulunabileceği göz önünde bulundurulmalıdır.

Anahtar kelimeler: Astım, kronik öksürük, ampirik yaklaşım, gastroözefageal reflü, üst hava yolu öksürük sendromu.

INTRODUCTION

Cough is a physiological response to mechanical and chemical stimuli due to irritation of cough receptors located mainly in the epithelium of the upper and lower respiratory tracts, pericardium, esophagus, diaphragm, and stomach.^[1]

Cough is one of the most common respiratory symptoms to result in outpatient clinical referral. It causes deterioration in quality of life, loss of school and workforce, and increases health-care costs due to unnecessary drug use. The initial assessment aims to classify duration and severity of the clinical presentation with guidelines from the American College of Chest Physicians (ACCP). Three categories are listed based on duration: acute cough, lasting <3 weeks; subacute cough, lasting between 3 and 8 weeks; and chronic cough, lasting more than 8 weeks.^[2–4]

It is difficult to reveal the etiology of chronic cough. Over the past decade, international guidelines have been developed to help physicians in clinical practice to diagnose, assess the severity of, and manage cough – particularly chronic cough.^[3,5] These guidelines recommend identifying the potential causes of chronic cough and then suggest specific treatments for any underlying disease. Moreover, they address the treatment of cough in patients whose underlying disease remains unknown.

In our study, we aimed to demonstrate our algorithmic approach to diagnosis and treatment of patients who presented to our outpatient clinic with chronic cough and the etiological reasons in those patients.

MATERIAL AND METHODS

Patients who presented to our outpatient clinic with a chronic cough within a period of 15 months were included in our study. The anamnesis of the patients was taken and they were physically examined. Their smoking habits and medications were asked. Respiratory function tests were performed in terms of asthma, consultations were requested for patients considered necessary from the otorhinolaryngology, and internal medicine outpatient clinics. All patients who had a cough for 8 weeks and who had not been diagnosed with this symptom before were included in the study due to chronic cough. Patients with previously diagnosed asthma bronchiale and chronic obstructive pulmonary disease and 8-week cough were not included in the study.

Anamnesis-based empirical treatment approach was mostly applied instead of a diagnosis model that confirmed the diagnosis of the disease in terms of the upper airway cough syndrome (UACS), gas-

troesophageal reflux disease (GERD), and eosinophilic bronchitis. Invasive procedures and advanced imaging methods (endoscopy, fine-needle aspiration biopsy [FNAB], thoracoscopic biopsy, pleural biopsy, and ultrasonography) were applied to our patients who were examined with a pre-diagnosis of malignancy.

Statistical Methods

Statistical analyses were performed using the SPSS Version 23.0 (IBM Corp 2015, Armonk, NY, and USA). The data of the patients were calculated using descriptive statistical methods (mean and standard deviation) and frequency analysis was performed.

RESULTS

Ninety patients with cough complaint for at least 8 weeks who presented to the chest diseases outpatient clinic with this complaint were included in the study. Sixty-four of the patients (71.1%) were female and 26 of them (28.9%) were male. The mean age of the patients was 46.24±15.42 (17–79). The mean cough duration was 17.29±30.49 (2–180) months.

Seventy patients (77.8%) had a dry cough, ten patients (11.1%) had sputum purulence together with cough, and ten patients (11.1%) had white sputum. Sixteen patients (17.8%) had chest pain together with cough, and 34 patients (37.8%) had wheeze complaint. The complaints of the patients accompanying the cough are given in Table 1.

While there was no seasonal relationship with cough in the questioning of 74 (82.2%) patients, cough was found to increase in relation to spring months in eight patients (8.9%), winter months in six patients (6.6%), and autumn season in two patients (2.2%). Only seven patients (7.8%) stated that related to meals, their coughs increase after eating.

Our eight patients (8.9%) had a cough lasting for at least 2 years, 3 months per year. While no relationship was found between cough and time in 39 patients (43.3%), it was more common in 35 patients (38.9%) at night and in 16 patients during daytime (17.8%).

In the questioning of smoking, 33 of our patients (36.7%) had a history of smoking and nine of them were smoker and 24 were ex-smoker.

Our 11 patients (12.2%) were taking angiotensin-converting enzyme inhibitor (ACE- inhibitors). No additional disease was found in 48 patients (53.3%). Hypertension in 20 patients (22%), coronary artery disease and cardiac arrhythmia in five patients (5.5%), diabetes mellitus in five patients (5.5%), gastritis and stomach ulcer in four patients (4.5%), hepatitis virus carriage in four patients (4.5%),

Table 1: Symptoms accompanying cough

Symptom	n	%
Wheeze	34	37.8
Retrosternal burning	28	31.1
Regurgitation	23	25.6
Postnasal drip	21	23.3
Chest pain	16	17.8
Shortness of breath	13	14.4

Table 2: PA chest radiological findings

Finding	n	%
No pathology	71	79
Infiltration	4	4.5
Sequela lesions	3	3.3
Cardiomegaly	3	3.3
Pleural effusion	2	2.2
Interstitial pattern	1	1.1
Atelectasis	1	1.1
Widening of mediastinum	1	1.1
Mass	1	1.1
Not scanned	3	3.3
Total	90	100

PA: Postero-anterior.

hypothyroidism in three patients (3.3%), tuberculosis history in two patients (2.2%), and extrapulmonary malignancy history in two patients (2.2%) were present.

In their respiratory system examinations, physical examination findings were not found in 69 patients (76.6%). Eight patients (8.9%) had rale, six patients (6.7%) had expiratory length, five patients (5.6%) had rhonchus, and two patients (2.2%) had a decrease in respiratory sounds in one hemithorax.

As imaging method, 87 patients (96.6%) had PA chest X-ray, 11 patients (12.2%) had thorax computed tomography (CT), and six patients (6.7%) had high resolution CT. PA chest radiological findings of the patients are given in Table 2. Our three patients did not have a radiological scanning because they mostly had upper airway symptoms and did not want to have a PA chest X-ray.

Complete blood count was performed in 80 patients (88.9%). The results of 68 of these patients were within normal limits.

Department of Otorhinolaryngology (ENT) consultations were asked for 35 patients. Seventy-eight patients (86.6%) were tested for pulmonary function. In 22 of those patients (24.4%) early reversibility tests were evaluated as positive, whereas 5 patients (5.6%) had positive results in late reversibility tests.

Sputum was examined in eight patients (8.9%). Acid-resistant bacteria (ARB) in sputum were requested from three patients (3.3%),

Table 3: Causes of chronic cough in patients

Cause	n	%
Asthma	22	24.6
GERD	19	21.1
UACS	8	8.9
Asthma+GERD	7	7.7
ACE-inhibitors	6	6.7
Post-infection	5	5.5
NAEB/Asthma	4	4.5
Lung cancer	3	3.3
DILD	3	3.3
Bronchiectasis	2	2.2
Asthma/NAEB+GERD	2	2.2
Pneumonia+sinusitis	1	1.1
Pulmonary tuberculosis	1	1.1
Sarcoidosis	1	1.1
GERD+UACS	1	1.1
Due to radiotherapy	1	1.1
Tracheal external compression	1	1.1
Ace-inhibitors+GERD	1	1.1
Asthma+UACS	1	1.1
Idiopathic	1	1.1
Total	90	100

GERD: Gastroesophageal reflux disease, UACS: Upper airway cough syndrome, ACE-inhibitors: Angiotensin converting enzyme inhibitor, NAEB: Non-asthmatic eosinophilic bronchitis, DILD: Diffuse interstitial lung disease.

sputum cytology from two patients (2.2%), aerobic culture in sputum from one patient (1.1%), cytology in bronchial lavage and ARB from one patient (1.1%), and aerobic culture in sputum, ARB and fungal culture from one patient (1.1%).

Invasive intervention was performed during the diagnosis process in our ten patients (11.1%). Gastroscopy was performed in four patients (4.5%), bronchoscopy in two patients (2.2%), bronchoscopy and thoracoscopic biopsy in one patient (1.1%), pleural biopsy in one patient (1.1%), FNAB in one patient, and bronchoscopy and FNAB in one patient (1.1%).

Four patients (4.4%) were admitted to the chest diseases service for examination and treatment. Eighty-six patients (95.6%) were followed up in the outpatient clinic. Two (2.2%) of the hospitalized patients were hospitalized due to pleural effusion, 1 (1.1%) due to mass, and 1 (1.1%) due to diffuse interstitial lung disease.

During treatment, 29 patients (32.2%) were given inhaled steroids with the pre-diagnosis of asthma bronchiale, 18 patients (20%) were given empirical proton-pump inhibitor considering GERD, and seven patients' (7.8%) drugs were replaced considering ACE-induced cough. More than one etiological cause for cough was found in 13 patients (14.4%). Eight of them (8.9%) were associated with non-asthmatic eosinophilic bronchitis (NAEB) and GERD. The etiological reasons we found in our patients are given in Table 3.

Among the less common causes of cough that we found in our study, there were causes such as cough that developed after radiotherapy, sarcoidosis, lung neoplasm, tuberculosis, bronchiectasis, tracheal compression, ACE-inhibitors, and GERD association. One patient could not be diagnosed and evaluated as idiopathic cough.

DISCUSSION

About 10–38% of the admissions to the chest diseases outpatient clinic are due to chronic cough.^[6] The prevalence of chronic cough has been estimated at up to 13% of the general population and may be associated with significant impairment of quality of life, together with anxiety and depression.^[7,8] This is especially common in patients who undergo numerous consultations and/or unsuccessful therapeutic trials before getting the diagnosis unexplained chronic cough or chronic refractory cough (CRC). Therefore, there is increasing interest in understanding possible mechanisms for these clinical conditions.

The two most influential guidelines for the management of cough, and particularly CRC, are: 1) those developed (4) and updated (2) by the ACCP, and 2) those developed by the ERS (3). The definitions, classification, diagnosis and differential diagnosis, assessment of severity, and management (non-pharmacologic and pharmacologic) are similar in these guidelines.

Systematic evaluation of chronic cough was first introduced in 1977 by Irwin et al.^[9] with the definition of “anatomical diagnostic protocol.” This systematic evaluation includes patient history, physical examination, and laboratory evaluations.

A patient with chronic cough should definitely have chest radiography scan. A finding in the scan can completely change the approach to the patient. The approach to be followed after this stage should be planned by considering the cough severity and expectations of the patient, the facilities of the clinic and the benefit-cost evaluations. There are two different models in approaching the patient with chronic cough. In general, the chance of controlling cough is higher in cases where the cause of chronic cough is fully revealed and specific treatment is given.^[4,10,11] This situation constitutes the main basis of the “cause-based treatment model.” In the cause-specific treatment model, the etiology should be revealed before the specific treatment. In addition to this, comprehensive study also includes revealing the potential cause by lung radiography, pulmonary function testing (PFT), reversibility test, bronchial provocation test, sputum cytology, 24-h esophageal pH monitoring, lung and paranasal tomography, bronchoscopy and similar tests and finally confirming, or excluding the diagnosis by checking the specific treatment response.^[12] This approach is the most expensive but the shortest route.

Another approach in chronic cough is the “empirical treatment model.” Empirical treatment means starting treatment based on clinical findings against one or more of the possible factors in chronic cough etiology even in the absence of objective laboratory data. It aims to reveal the causes of chronic cough according to the treatment response and/or to eliminate the cough. This approach can be considered as an alternative to the diagnosis-based treatment model because it is simple, fast, and inexpensive. It especially gains importance in centers with limited laboratory facilities and patients who

do not accept further examination. In our study, empirical treatment model was used in the treatment approach to patients.

In the majority of cases, a number of associated conditions are identified,^[13] most commonly UACS (formerly named postnasal drip), asthma bronchiale, gastroesophageal reflux, eosinophilic bronchitis, and intolerance to drugs such as ACE inhibitors. While UACS is generally in the first place in the studies, asthma took the first place in our study. This may be related to the fact that when patients with cough first present to the ENT outpatient clinic, patients with the diagnosis of UACS do not come to the chest diseases outpatient clinic after being properly evaluated and treated there, and patients who are considered suffering from asthma or other causes are sent to our clinic or the prevalence of asthma is high in our region. However, there have been no recent studies showing a higher prevalence of asthma in our region (Thrace) than the other regions of our country.

In our 22 patients (24.6%), the sole cause of cough was found as asthma bronchiale. In four patients (4.5%), whose pulmonary function tests were normal and who reaped the benefit of inhaled steroids treatment, no definite distinction could be made between NAEB and asthma. NAEB was first described in 1989 by Gibson et al.^[14] The diagnosis is established when the eosinophil rate in induced sputum is more than 3% and PFT values are normal. All patients were diagnosed with asthma by pulmonary function test (early reversibility-late reversibility) and the primary complaint of all patients was cough. BPT was not performed in any of our patients. The diagnosis of NAEB was not proven by induced sputum examination in any of our patients, and it remained a preliminary diagnosis.

The second most common etiological cause we faced was GERD. In 19 patients (21.1%), it was found as the sole cause of chronic cough. Most of the patients were diagnosed with empirical treatment approach. The detection of GERD-related findings in laryngoscopic evaluation of the patients was one of the factors that made the empirical treatment decision easier. In four patients (4.5%), peptic ulcer was considered in the gastroenterology clinic and gastroscopy was performed, and GERD-related findings were found in 3 (3.3%) of them. In the treatment of GERD, lansoprol 30 mg/pantoprazole 40 mg was given our patients twice a day, and treatment-resistant GERD was not found.

A striking point in many studies in the literature is that the chronic cough symptom is 2–3 times higher in women (especially the middle age group). In the study of Kaynar et al.^[15] between 2000 and 2002 in Erzurum in our country, 33 (73.3%) of 45 patients were female. In our study, similarly, 71.1% of our patients were female. This is usually explained by the increased sensitivity of the cough reflex in women.

Although some of the patients report that persistent coughs start after an infection, there is no information specifically linking previous viral infections to ongoing persistent cough. Viral infections are known to increase cough reflex sensitivity.^[16] In our study, 28 patients (31.1%) described flu infection before cough.

It is also known that sleep suppresses the cough reflex. In patients describing lung disease and cough at night, spontaneous cough almost completely disappears in the deep sleep parts of sleeping.^[17] Cough decreasing at night may be associated with GER due to the closure of the lower esophageal sphincter. While

39 of our patients (43.3%) did not describe a time relationship, 35 patients (38.9%) stated that cough was more at night and 16 patients (17.8%) during daytime.

Cough that occurs in patients using ACE-inhibitors was first reported with captopril in 1985.^[18] This is its pharmacological effect, and its incidence can reach up to 16%. The dose is not associated, and the time of occurrence may be some hours or more than a year after the initiation of treatment.^[19] The cough is predominantly seen in females and non-smokers.^[20] ACE-inhibitors are associated with increased sensitivity of the cough reflex, so it may worsen the cough due to other causes.^[21] The average time for stopping cough is 26 days, but it may last up to 40 weeks in some patients.^[22] In our study, 11 patients (12.2%) were taking ACE-inhibitors. ACE-inhibitors were replaced in all of these patients. Response assessment was performed after 1 month for cough due to ACE-inhibitor use. While ACE-inhibitors use was found to be the sole cause of chronic cough in only six patients (6.7%), the association of ACE-inhibitors and GERD was evaluated as the cause of chronic cough in one patient (1.1%).

Up to 20% of patients with cough cannot be diagnosed after extensive research and treatment trials.^[23] Another remarkable issue in patients with chronic cough is that there may be more than one etiological cause. The number of these reasons can even be up to 4. In some studies, the rate of more than one cause may be clearer than a single cause.^[24] Therefore, all systems should be reviewed in patients with chronic cough, not based on a single cause. In our study, more than one etiological cause was found in 13 patients (14.4%).

The disadvantage of empirical treatment is that the etiology of cough has not been established, even if the treatment is successful. This is especially true when effective treatment is initiated for two or more causes. Another disadvantage is the possibility of focusing on common causes and overlooking rare causes. Therefore, the empirical treatment process should be limited to a certain stage. Treatment trials of 1–2 weeks in UACS, asthma bronchiale, and NAEB are usually sufficient to give an idea of treatment response. For GERD- and ACE-inhibitor-induced cough, at least 4 weeks may be required.^[25–27] If the cough improves, the current treatment is continued. If there is no adequate response to the initial treatment, specific treatment for other causes should be initiated.

Our study was conducted before the COVID-19 pandemic. Along with the pandemic period, post-viral infections have become an important cause for chronic cough. Long COVID is a multisystemic condition comprising often severe symptoms that follow a severe acute respiratory syndrome coronavirus 2 infection. Shortness of breath and cough, which persisted for at least 7 months in 40% and 20% of patients with long COVID, respectively, are the most common respiratory symptoms.^[28]

CONCLUSION

The most important step in treating chronic cough that negatively affects the quality of life of the person is to be able to establish a correct diagnosis. In our study, a diagnosis and treatment algorithm starting from cheap and non-invasive methods was applied to the patients who presented to our clinic. It should be taken into account that more than one etiological cause may coexist in patients with treatment-resistant chronic cough.

Disclosures

Ethics Committee Approval: The study was approved by The Trakya University Faculty of Medicine Ethics Committee (date: 15.02.2007, number: 2007/15).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – İ.Y., T.Ç., E.Ç.E.; Design – İ.Y., T.Ç., E.Ç.E.; Supervision – İ.Y., T.Ç., E.Ç.E.; Fundings – İ.Y.; Materials – İ.Y.; Data Collection and/or Processing – İ.Y., T.Ç., E.Ç.E.; Analysis and/or Interpretation – İ.Y.; Literature Search – İ.Y.; Writing – İ.Y.; Critical Reviews – İ.Y., T.Ç., E.Ç.E.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

- McGarvey L, Gibson PG. What is chronic cough? terminology. *J Allergy Clin Immunol Pract* 2019;7:1711–4.
- Irwin RS, French CL, Chang AB, Altman KW; CHEST Expert Cough Panel*. Classification of cough as a symptom in adults and management algorithms: CHEST guideline and expert panel report. *Chest* 2018;153:196–209.
- Morice AH, Millqvist E, Bieksiene K, Birring SS, Diczpinigaitis P, Domingo Ribas C, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J* 2020;55:1901136.
- Irwin RS, Baumann MH, Bolser DC, Boulet LP, Braman SS, Brightling CE, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129(Suppl 1):1S–23S.
- Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS, et al. Treatment of unexplained chronic cough: CHEST guideline and expert panel report. *Chest* 2016;149:27–44.
- Doğan Mülazimoğlu D, Kayacan O. Kronik öksürüğe yaklaşım. *Tuberik Toraks* 2017;65:227–36.
- Song WJ, Chang YS, Faruqi S, Kim JY, Kang MG, Kim S, et al. The global epidemiology of chronic cough in adults: A systematic review and meta-analysis. *Eur Respir J* 2015;45:1479–81.
- Chamberlain SA, Garrod R, Douiri A, Masefield S, Powell P, Bücher C, et al. The impact of chronic cough: A cross-sectional European survey. *Lung* 2015;193:401–8.
- Irwin RS, Boulet LP, Cloutier MM, Fuller R, Gold PM, Hoffstein V, et al. Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians. *Chest* 1998;114(Suppl 2):133S–81S.
- Morice AH, Fontana GA, Sovijarvi AR, Pistolesi M, Chung KF, Widdicombe J, et al. The diagnosis and management of chronic cough. *Eur Respir J* 2004;24:481–92.
- Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Am Rev Respir Dis* 1990;141:640–7.
- Irwin RS, Madison JM. The persistently troublesome cough. *Am J Respir Crit Care Med* 2002;165:1469–74.
- Song WJ, Chang YS, Morice AH. Changing the paradigm for cough: Does 'cough hypersensitivity' aid our understanding? *Asia Pac Allergy* 2014;4:3–13.
- Gibson PG, Fujimura M, Niimi A. Eosinophilic bronchitis: Clinical manifestations and implications for treatment. *Thorax* 2002;57:178–82.

15. Kaynar H, Yılmaz N, Akgün M, Meral M, Sağlam L, Görgüner M ve ark. Sigara içmeyenlerde kronik öksürük etyolojisi. *Toraks Derg* 2005;6:8–12.
16. O'Connell F, Thomas VE, Studham JM, Pride NB, Fuller RW. Capsaicin cough sensitivity increases during upper respiratory infection. *Respir Med* 1996;90:279–86.
17. Power JT, Stewart IC, Connaughton JJ, Brash HM, Shapiro CM, Flenley DC, et al. Nocturnal cough in patients with chronic bronchitis and emphysema. *Am Rev Respir Dis* 1984;130:999–1001.
18. Sesoko S, Kaneko Y. Cough associated with the use of captopril. *Arch Intern Med* 1985;145:1524.
19. Yeo WW, Foster G, Ramsay LE. Prevalence of persistent cough during long-term enalapril treatment: Controlled study versus nifedipine. *Q J Med* 1991;80:763–70.
20. Alharbi FF, Kholod AAV, Souverein PC, Meyboom RH, de Groot MCH, de Boer A, et al. The impact of age and sex on the reporting of cough and angioedema with renin-angiotensin system inhibitors: A case/noncase study in VigiBase. *Fundam Clin Pharmacol* 2017;31:676–84.
21. Morice AH, Lowry R, Brown MJ, Higenbottam T. Angiotensin-converting enzyme and the cough reflex. *Lancet* 1987;2:1116–8.
22. Ojoo JC, Kastelik JA, Morice AH. Duration of angiotensin converting enzyme inhibitor (ACEI) induced cough. *Thorax* 2001;56:iii72.
23. Haque RA, Usmani OS, Barnes PJ. Chronic idiopathic cough: A discrete clinical entity? *Chest* 2005;127:1710–3.
24. Palombini BC, Villanova CA, Araújo E, Gastal OL, Alt DC, Stolz DP, et al. A pathogenic triad in chronic cough: Asthma, postnasal drip syndrome, and gastroesophageal reflux disease. *Chest* 1999;116:279–84.
25. Pavord ID, Chung KF. Management of chronic cough. *Lancet* 2008;371:1375–84.
26. Chummun D, Lü H, Qiu Z. Empiric treatment of chronic cough in adults. *Allergy Asthma Proc* 2011;32:193–7.
27. Goldsobel AB, Kelkar PS. The adult with chronic cough. *J Allergy Clin Immunol* 2012;130:825–825.e6.
28. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine* 2021;38:101019.