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Evaluation of chronic cough in an immunology and allergy clinic in the Black Sea region: Causes, prevalence and outcomes

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ABSTRACT

Aim: Chronic cough, one of the most common symptoms of respiratory diseases, is a condition that negatively affects patients' quality of life, prevents social activities, and is accompanied by a significant social burden. In addition, the causes of chronic cough may vary according to age and geographical location. Therefore, in this study, we wanted to examine the causes and frequency of chronic cough in the Black Sea region.

Methods: One hundred six patients age over 18 years with coughs lasting more than 8 weeks were examined retrospectively at the immunology and allergy polyclinic**.** Initial evaluations included details on ACE inhibitory use and smoking, allergy symptoms, reflux, chronic obstructive pulmonary disease, malignancy symptoms. Relevant diagnostic tests were performed if suspected. General tests included chest radiographs, pulmonary function tests, allergy prick tests, and neck ultrasounds.

Results: The most common causes are respectively asthma (28%), gastroesophageal reflux (26%), allergic respiratory diseases (16%), ACE inhibitor use (13%) and smoking (9.5%), Sjogren's syndrome (8.4%). The most common allergen detected in allergic respiratory diseases is house dust mite (82%).

Conclusion: Asthma is leading causes of chronic cough. Additionally, 56.7% of asthma cases were allergic asthma. Sjogren's syndrome also significantly contributes to chronic cough. This study is one of the first studies on the causes and treatment effects of chronic cough in the Black Sea Region of Türkiye.

Keywords: Chronic cough, asthma, gastroesophageal reflux, Sjogren's syndrome.

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1. Introduction

Cough protects the lungs from aspiration and can be a symptom of many diseases, varying in duration. Based on its duration, it can be classified into three categories: acute cough (≤ 3 weeks), subacute cough (3-8 weeks), and chronic cough (≥ 8 weeks) [1].

Chronic cough has many causes, and these causes differ between children and adults. Common causes identified in adults include asthma, chronic obstructive pulmonary disease (COPD), secondary cough after viral infections, gastroesophageal reflux disease (GERD)/laryngopharyngeal reflux disease, tobacco use, chest parenchymal disorders, angiotensin-converting enzyme (ACE) inhibitor use, eosinophilic bronchitis, and others. Apart from these, there may be a cough of psychogenic origin or an unknown cause. To determine its etiology, factors such as the development period of the cough, presence of dry or productive cough, characteristics of the sputum, severity, shortness of breath, and exposure to irritating substances or oral allergens need to be examined.

Despite extensive research, the cause may not be identified, and this condition is referred to as idiopathic chronic cough [2, 3]. Idiopathic chronic cough is thought to be a hypersensitivity disorder, typically characterized by cough triggered by low-level thermal, mechanical, or chemical exposure [4].

In practice, chronic cough persists for several years, sometimes decades, for a significant number of patients, despite extensive medical intervention [3]. In some cases, it can be excessive, uncomfortable, and prolonged. It is a common condition in the general population, affecting about 10% of adults [5]. The global prevalence of chronic cough is as high as 9.6%, while chronic cough is more prevalent in Europe (12.7% [95% CI 10.4–15.2%]) and America (11.0% [95% CI 7.8–14.4%]) than in Asia (4.4% [95% CI 1.8 – 7.4%]) [3]. Causes of chronic cough may vary depending on age and geography [6, 7]. In this study, we investigated the causes of chronic cough in the Black Sea region of Türkiye at the immunology and allergy clinic.

2. Materials and methods

Patients with chronic cough, referred by chest disease specialists, were studied retrospectively. Those over 18 years of age were included. Detailed histories focused on ACE inhibitor use, smoking, allergies, asthma, reflux, chronic obstructive pulmonary disease (COPD),

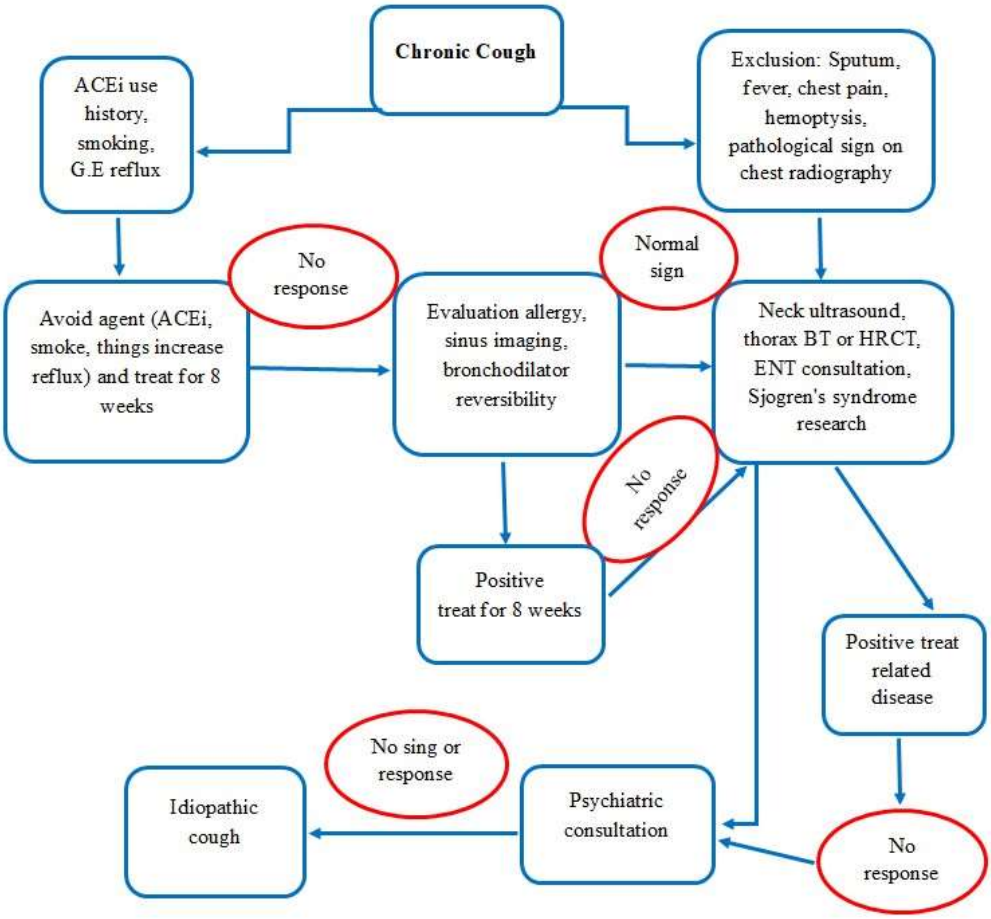

Figure 1. Chronic cough assessment algorithm in this study.

ACEi: Angiotensin-converting enzyme inhibitor, G.E: gastroesophageal, HRCT: High-resolution computed tomography; ENT: Ear, nose, and throat specialist, BT: Computed tomography,

pneumonia, and malignancy symptoms. Diagnostic tests were conducted as needed. If there was no guiding symptom or if the tests performed were normal, the following tests were conducted: chest radiograph, pulmonary function test with bronchodilator responsiveness prick test, neck ultrasonography, and, if necessary, chest computed tomography (CT).

Patients diagnosed with asthma were evaluated for eosinophils, total immunoglobulin E (IgE), allergy tests, and specific IgE, in addition to anamnesis for endotype classification. Ear, nose, and throat (ENT) specialist consultations were performed to evaluate upper respiratory tract-related diseases causing chronic cough. Patients with dry eye or mouth symptoms were evaluated for Sjogren's syndrome and salivary gland diseases. When Sjogren's syndrome was suspected, a rheumatologist consultation was arranged. Patients with suspected psychogenic cough were evaluated through psychiatric consultation. Those who did not respond to treatment and in whom no organic pathology was detected were considered to have idiopathic chronic cough.

After diagnosing the patients with one of the following conditions—reflux, cough due to smoking, asthma, allergic rhinitis, or post-infectious cough—treatment was given, and the patient was called for a follow-up check-up 8 weeks later. If there was no clinical improvement with treatment, other causes of chronic cough were investigated. The approach applied in our study is presented in Figure 1**.**

A total of 150 patients were referred. Lower and upper respiratory tract infections were detected in 38 patients, lung malignancy in 1 patient, and COPD in 11 patients, all of whom were excluded from the study. After excluding these cases, 106 patients were included in the study. The patients' information was recorded in Microsoft Excel, and analyses were made using the SPSS program. For this study, an application was made to the Ethics Committee of Samsun Training and Research Hospital on 09.07.2019, and approval was received with the decision number TUEK67-2019BADK/13-98. Informed consent was obtained from every patient, and their consent was recorded.

2.1. Statistics: 106 patients were studied after excluding those with infections, lung malignancy, and COPD. Data were recorded and analyzed using SPSS. Data were expressed as mean and +/- standard deviation (SD). Percentages of the variables were also analyzed via this program.

3. Results

Out of the 106 patients, 17 (16%) were male, and 89 (84%) were female. The average age of the patients was 49 ± 13.8 years (minimum: 21, maximum: 75), with no significant difference in the mean age between male and female patients. The most common causes of cough observed were asthma (28%), gastroesophageal reflux (24.5%), allergic respiratory diseases (16%), ACE inhibitor use (13%), smoking (9.5%), and Sjogren's syndrome (8.4%). Psychogenic cough was identified in 3 patients (2.8%), and idiopathic cough was identified in 2 patients (2%). Other less common causes included post-infection in 3 patients (2.8%), chronic angina in 2 (2%), bronchiectasis in 2 (2%), tracheal compression in 2 (2%), respiratory interstitial diseases in 1 (1%), cancer after radiotherapy in 1 (1%), and pulmonary arterial hypertension in 1 patient (1%). All identified causes were more frequently detected in female patients.

In the endotype evaluation of asthma among 30 patients, 18 (60%) exhibited dominant T-helper cell-2 (Th2) inflammation, while 12 (40%) did not. Among the patients with Th2 inflammation-dominant asthma, 17 (57%) had

Table 1. The causes of chronic cough.

The Causes of chronic cough	Number	Mean Age	Symptom Duration (Month/Years)
Asthma	30 (28%)	46±4	6± 2.8years
Allergic Asthma 14 house dut mite,1 grass mix,1 ragweed,1 aspergillus)	**17(16%)**		
Female	12		
Male	5		
Eosinophilic asthma	**1(1%)**		
Female	1		
Male			
Neutrophilic asthma	**12(11%)**		
Female	11		
Male	1		
Gastroesophageal Reflux	26(24.5%)	44±6	5 ±6.4years
Female	23		
Male	3		
ACE I	14 (13%)	65.3±5.8	2 ±1.4years
Perindopril	**9(8.4%)**		
Female	7		
Male	2		
Enalapryl	**5(4.7%)**		
Female	4		
Male	1		
Smoke	10(9.5%)	42±7.4	2.5±6.4years
Female	7		
Male	3		
Dry mouth secondary to collagen tissue diseases		52±4.6	8±7.4years
Sjogren's syndrome	9 (8.4%)		
Female	6		
Male	6		
Sjogren's syndrome secondary to Rheumatoid arthritis			
Female	1		
Male	1		
Mixed connective tissue			
Female	1		
Male	1		
Systemic scleroderma			
Female	1		
Male	1		
Post infections	3(2.8%)	51±3	3 ±3.8month
Female	3		
Male			
Psychological	3(2.8%)	42±5.2	4±4.8years
Female	3		
Male			
Chronic angina	2(2%)	53±4.2	5.5± 2.8years
Female	2		
Male			
Bronchiectasis	2(2%)	53.5±23.3	6.5±2.4years
Female	1	70	
Male	1	37	
Compressive causes (1guatr,1 paratracheal mass)		57±14	1 years±1.2years
Female	2(2%)		
Male	2		
Idiopathic(1 cold weather, 1 cold food trigger)		44±8.4years	20, 5±7years
Female	2 (2%)		
Male	2		
Others			
Respiratory interstitial Diseases	3(2.8%)	70	1 year
After cancer radiotherapy	1	63	10 years
Pulmonary Artery Hypertension	1	42	4 years
Female	1		
Male	3		
Mix		45	2 years
Allergic asthma + smoke	3(2.8%)		
Female	1		
Male	1	44.5±10.6	5.5±3, 8 years
Non-allergic Asthma+ reflux			
Female	2		
Male	2		

allergic asthma, and 1 had eosinophilic asthma. The most common allergen detected in allergic respiratory diseases was the house dust mite (82%). House dust mite sensitivity was found in 14 patients, grass mix in 1 patient, ragweed in 1 patient, and Aspergillus in 1 patient.

The condition with the longest duration of symptoms was Sjogren's syndrome, while the shortest-lasting symptoms were observed in post-infectious cough and cough due to ACE inhibitor use. The results are presented in Table 1**.**

4. Discussion

Chronic cough is a challenging condition for both physicians and patients. It significantly affects the patient's daily comfort and even impairs socialization. A detailed history and physical examination are essential for determining the cause of the cough. Despite thorough evaluations, the cause may not always be identified. Guidelines recommend staged empiric treatment following a comprehensive clinical history, physical examination, and focused diagnostic testing [8]. This study presents the causes of chronic cough identified in Turkey and the treatments applied.

Asthma is the second leading cause of death from chronic respiratory diseases [9]. In this study, asthma was also found to be the most common cause of chronic cough. The airway epithelium responds to external stimuli such as allergens, pollutants, and infectious agents (e.g., viruses) by stimulating the immune system. Asthma is classified according to the inflammatory response of the respiratory tract epithelium to these external stimuli. Asthma is divided into two endotypes: Type-2 inflammation dominant and low-type inflammation. Type-2 inflammation is defined as inflammation dominated by the release of interleukin (IL)-33, IL-25, thymic stromal lymphopoietin (TSLP) by epithelial cells, and IL-4, IL-5, IL-13 by the adaptive immune system [10, 11]. Type-2 inflammation is also characterized by elevated tissue and blood eosinophil infiltration and increased fractional exhaled nitric oxide (FeNO). In low-type-2 inflammation, there is a predominance of neutrophils. Type-2 inflammation predominates in allergic asthma and eosinophilic asthma, while low-type-2 inflammation may be considered neutrophilic asthma. Clinical factors that help classify asthma into these categories include the patient’s atopy history, allergy tests, eosinophil levels, FeNO, and total IgE values [11]. In our study, we found that 60% of asthma patients with predominant cough had Type-2 inflammation, while 40% had low-type-2 inflammation. Allergic rhinitis also causes postnasal drip, and asthma causes cough due to respiratory tract hyperreactivity. House dust mite is the most common allergen responsible for postnasal drip [12]. In our study, all allergic asthma patients also had allergic rhinitis, and 82% had house dust mite sensitization. Sensitization to pollen and Aspergillus was detected in only one patient each, which we did not consider clinically significant. All asthma patients were treated with inhaled long-acting beta2 agonists (LABA) and corticosteroids (ICS). Immunotherapy was initiated for patients with house dust mite and pollen sensitization. Immunotherapy is the only treatment option that affects the pathogenesis, causes remodeling, and corrects the disease in allergic respiratory diseases [13].

Gastroesophageal reflux (GERD) causes postnasal drip syndrome or cough due to stomach acid. It is one of the most common causes of chronic cough [14]. In our study, GERD was the second most common cause detected, and we observed a significant clinical response to treatment in a short period. However, the recurrence of cough can be prevented by emphasizing lifestyle changes in these patients.

The incidence of ACE inhibitor (ACEi)-related cough in the literature ranges from 3% to 35% [15]. In this study, ACEi-related cough was found in 13% of cases. This rate may be higher, as many patients may have been managed in internal medicine, chest diseases, and cardiology clinics rather than presenting to the allergy clinic. Perindopril (64.7%) and enalapril (36%) were the ACE inhibitors identified as causing cough. The frequency of ACEi-related cough varies by country and depends on drug usage patterns. A meta-analysis by Yiyun Hu et al. determined the frequency of cough associated with different ACE inhibitors: ramipril, fosinopril, lisinopril, perindopril, enalapril, trandolapril, and captopril [15]. In these patients, ACEi was discontinued, and treatment was switched to an angiotensin receptor blocker (ARB).

Neural C fibers and rapidly adapting receptors in the lungs and respiratory tract are stimulated by inhaling cigarette smoke [16], which is why it causes cough. In our study, 9.5% of patients had smoking-related cough. We explained to these patients that their cough would subside once they stopped smoking and called them for a follow-up. Afterward, both the patients and the researchers observed that the cough was indeed caused by smoking. These patients were assisted in quitting smoking.

Collagen tissue diseases are a group of rheumatic diseases that can cause dry mouth due to B lymphocyte infiltration in the salivary glands [17]. Rheumatoid arthritis, systemic lupus erythematosus, and scleroderma can lead to secondary Sjogren's syndrome, which causes dry mouth. These patients may develop cough, especially when swallowing, talking, and eating dry foods due to insufficient saliva secretion [18]. In this study, 8.5% of cough cases were attributed to Sjogren's syndrome. This rate is relatively high, highlighting the need to consider Sjogren's syndrome when evaluating chronic cough. Treatment included immunosuppressive therapy and salivation stimulation through chewing gum. For patients whose complaints persisted, pilocarpine (a parasympathomimetic) was prescribed.

Other causes of chronic cough included post-infection cough, bronchiectasis, external pressure, interstitial lung diseases, pulmonary hypertension, chronic angina, and psychological factors. If no cause can be identified after excluding these possibilities, chronic cough may be considered a condition of nervous dysregulation. These patients were classified as idiopathic. Two patients in this study had their cough triggered by cold weather and cold food. These patients were treated with LABA, ICS, montelukast, antihistamines, and were advised to avoid cold exposure. Although complete remission was not achieved, their symptoms significantly improved. Given the small number of patients, the clinical significance of these treatments is debatable. More studies are needed to fully understand the pathogenesis of idiopathic cough.

This study has several limitations, including its retrospective and single-center design. However, it may be of significant value in elucidating the cause and prevalence of chronic cough in the Black Sea region.

4.1. Conclusion: In this study, the most common causes of chronic cough were asthma, gastroesophageal reflux, allergic respiratory diseases, ACEi use, smoking, and Sjogren's syndrome. Chronic cough should be evaluated with a multidisciplinary approach involving internal medicine, pulmonology, otolaryngology, psychiatry, and allergy specialists. Studies employing this approach will help standardize the diagnosis and treatment of rare cases. This study has shown that, despite its rarity, Sjogren's syndrome has a significant incidence among the

causes of chronic cough. Further studies using a multidisciplinary approach are needed.

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