

## Chronic Non-Productive Cough in Patients With Primary Sjögren's Syndrome

Gonca DOĞRU,<sup>1</sup> Ayşe BALKARLI,<sup>2</sup> Atalay DOĞRU<sup>3</sup>

<sup>1</sup>Department of Chest Diseases, Isparta State Hospital, Isparta, Turkey

<sup>2</sup>Department of Internal Medicine, Antalya Training and Research Hospital, Division of Rheumatology, Antalya, Turkey

<sup>3</sup>Department of Internal Medicine, Medical Faculty of Süleyman Demirel University, Division of Rheumatology, Isparta, Turkey

### ABSTRACT

**Objectives:** This study aims to evaluate the frequency of chronic cough due to dryness in the trachea and the relationship between depression and chronic cough in patients with primary Sjögren's syndrome (pSS).

**Patients and methods:** Eighty non-smoking patients (7 males, 73 females; mean age 47.6±9.2 years; range 18 to 70 years) with newly diagnosed pSS were included. All patients were evaluated clinically, radiologically, and physiologically. Patients with cough were assessed using the Leicester Cough Questionnaire and visual analog scale. Beck Depression Inventory was used to determine the risk of depression in patients with cough. Patients with asthma, rhinosinusitis, gastroesophageal reflux, and drug use which cause cough and pulmonary involvement in pSS were excluded.

**Results:** Non-productive cough was detected in 30 patients (37.5%). Fourteen patients (17.5%) were admitted to the hospital with cough at least once before the diagnosis of pSS. The median time between onset of symptoms and firm diagnosis was 24 months (25-75 interquartile ranges: 3-60 months). A significant difference was observed in the Beck Depression Inventory scores between patients with and without cough. There was a significant negative relationship between Leicester Cough Questionnaire and Beck Depression Inventory scores.

**Conclusion:** Patients with pSS often have symptoms for a long duration that mimic those of more commonly encountered non-specific pulmonary conditions. Xerotrachea should be considered in the differential diagnosis of chronic cough, especially in patients with normal pulmonary function tests and pulmonary imaging.

**Keywords:** Cough; Leicester Cough Questionnaire; primary Sjögren's syndrome; xerotrachea.

Sjögren's syndrome (SS) is a slowly progressive, chronic systemic autoimmune disease affecting 0.5-1% of the general adult population. It is characterized by lymphocytic infiltration of salivary and lacrimal glands.<sup>1</sup> Additionally, extraglandular organs including the lung, skin, kidney, heart, bone marrow, and neurological systems can also be affected. SS is seen up to nine times more often in females than in males. Disease onset is most common during the mid-50s.<sup>2</sup> SS can be subclassified into primary and secondary SS. Primary SS (pSS) occurs in the absence of a systemic autoimmune disease. However, secondary SS occurs in association with other underlying

rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and inflammatory myositis. Symptoms can range from mild to severe.<sup>3</sup>

Cough is a common symptom of many chronic respiratory diseases. Cough has a negative impact on patients' social life.<sup>4</sup> Pulmonary manifestation, an extraglandular complication, is seen in 10-20% of patients with pSS. Lung involvement plays a very important role in determining a patient's clinical outcome. pSS predominately affects airways and the interstitium, the space around the sacs of the lung. Respiratory complications include dry airways, interstitial lung disease (ILD),

**Received:** July 27, 2016 **Accepted:** November 21, 2016 **Published online:** April 05, 2017

**Correspondence:** Gonca Doğru, MD. Isparta Devlet Hastanesi Göğüs Hastalıkları Kliniği, 32100 Isparta, Turkey.

Tel: +90 216 - 578 48 59 e-mail: minan@yeditepe.edu.tr

©2017 Turkish League Against Rheumatism. All rights reserved.

non-Hodgkin's lymphoma, pleural effusion, and pulmonary embolism. ILD is the most common pulmonary manifestation of pSS.<sup>5</sup> ILD can be subclassified as nonspecific interstitial pneumonia, usual interstitial pneumonia, organizing pneumonia and lymphocytic interstitial pneumonia. Nonspecific interstitial pneumonia is the most common form of ILD.<sup>6</sup> Cough and dyspnea are the major causes for admission to hospital and dry cough without dyspnea is usually seen in disorders affecting the upper airways. Continuous dry cough disrupts daily activities and balance of human life and creates a significantly lower quality of life in 50% of patients with pSS.<sup>7</sup> Decreased tracheobronchial mucociliary clearance is higher in patients with pSS compared to normal. Histologically, atrophy of the submucosal glands in the nasopharynx, larynx, and trachea in association with lymphoid infiltration is seen.<sup>8</sup> Continuous dry cough, hoarseness, and nasal dryness due to mucosal dryness, mucus viscosity disorders, and impaired mucociliary clearance are the common complaints for which patients seek medical care. In this study, we aimed to evaluate the frequency of chronic cough due to dryness in the trachea and the relationship between depression and chronic cough in patients with pSS.

## PATIENTS AND METHODS

Eighty patients (7 males, 73 females; mean age  $47.6 \pm 9.2$  years; range 18 to 70 years) with newly diagnosed pSS according to the 2012 American College of Rheumatology classification criteria were included in this study, which was conducted at Antalya Training and Research Hospital and Süleyman Demirel University Research and Education Hospital between January 2016 and June 2016.<sup>9</sup> Patients with secondary SS, i.e. SS associated with other connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis, scleroderma, and mixed connective tissue disease were excluded. All patients were evaluated clinically, radiologically, and physiologically. A detailed pulmonary history was obtained. The patients' current and past history of medication were recorded, in addition, all patients underwent a detailed physical examination by a pulmonologist and a rheumatologist. Patients with drug use such as angiotensin converting enzyme inhibitors, inhaled

steroids, antibiotics, omeprazole, or pilocarpine were also excluded. Chest X-ray in standard posteroanterior projection, pulmonary function tests and an examination of the diffusing capacity of the lung for carbon monoxide were applied to all patients. Patients with lung involvement were excluded. Patients with other causes of cough such as bronchial asthma, rhinosinuitis, gastroesophageal reflux, heart failure, infection, hyperthyroidism, arrhythmia, or smoking were also excluded by clinical assessment and other laboratory investigations. We used three months as the cutoff for chronic cough. Patients with cough were assessed using the following scales: Leicester Cough Questionnaire (LCQ) and a cough visual analog scale (VAS). The cough VAS is a 100 mm scale on which patients indicate the severity of cough (0-30: mild, 40-60: moderate, 70-100: severe). LCQ is a health status measure for adults with chronic cough and VAS measures the severity of cough. In LCQ, a seven-point scale is used ranging from 1 to 7 and higher score shows better health status. LCQ is divided into three domains: physical, psychological, and social. The total score can range between 3 and 21 and is obtained by adding the scores from the individual domains.<sup>10</sup>

The patients' age, sex, educational level, socio-economic status, place of residence, marital status, and duration of illness were recorded on an information form that was developed by the authors of this study. Beck Depression Inventory (BDI) was used to determine the risk of depression in patients with cough. It contains 21 items and each item is scored from 0 to 3. The standard cut-off scores are as follows: 0-9 indicates normal, 10-18 indicates mild, 19-29 indicates moderate, and 30-63 indicates severe depression. Higher scores indicate more severe depressive symptoms. BDI was developed by Beck et al;<sup>11</sup> its adaptation, reliability, and validity studies for Turkey were performed by Hisli.<sup>12</sup>

Patients were evaluated for routine biochemical, hematological, and serological parameters. All patients included in the study tested positive for anti-nuclear antibody.

The study protocol was approved by the Antalya Training and Research Hospital Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of

**Table 1.** Demographic and laboratory data of primary Sjögren's syndrome patients

Parameter	Result				
	n	%	Mean±SD	Median	25-75 interquartile ranges
Age (year)			47.6±9.2		
Female	73	91.3			
Body mass index (kg/m <sup>2</sup> )				29.7	25.6-33.1
Fasting blood glucose (74-106 mg/dL)				95	89-103
Creatinine (0.66-1.09 mg/dL)				0.6	0.5-0.7
Alanine aransaminase (0-34 U/L)				18	13.2-24.5
Erythrocyte sedimentation rate (mm/h)			22.8±11.2		
C-reactive protein (0-3 mg/L)				0.1	0.05-0.3
Thyroid stimulating hormone (0.3-4.0 mU/mL)				1.72	1.2-2.7

SD: Standard deviation.

the Declaration of Helsinki. The registration number was 2016-059.

### Statistical analysis

Descriptive statistics are presented as frequency, percentage, mean, and standard deviation. Student's t-test was used in cases where the data distribution resembled normal distribution. The analysis of differences in continuous variables between the two groups was performed using the Mann-Whitney U test in cases where the data distribution was non-normal. Pearson's chi-squared test was applied to sets of categorical data. All statistical analyses were conducted using SPSS versiyon 13.0 (SPSS Inc., Chicago, IL, USA). A *p* value <0.05 was considered statistically significant.

## RESULTS

The median body mass index of the patients was 29.7 kg/m<sup>2</sup>. Biochemical parameters of patients with pSS are listed in Table 1. The

clinical complaints were distributed as follows: non-productive cough in 30 patients (37.5%), itching in 34 patients (42.5%), tooth decay in 31 patients (38.8%), hoarseness in 15 patients (18.8%), dryness of the nose in 38 patients (47.5%), taste disturbance in 13 patients (16.3%), and arthralgia in 35 patients (43.8%). Fourteen patients (17.5%) were admitted to the hospital with cough at least once before the diagnosis of pSS. The median time between onset of symptoms and firm diagnosis was 24 months (25-75 interquartile ranges: 3-60 months). The mean total score in the BDI was 11.8±8.5 (Table 2).

The LCQ, VAS, and BDI scores were 13.2±3.1, 47±18.5, and 15.2±9.2 in patients with cough, respectively (Table 3). A statistically significant difference was observed in the BDI scores between patients with and without cough (15.2±9.2 vs. 9.9±7.4, *p*=0.006). In addition, the delay in the diagnosis was significant between patients with and without cough (48 vs. 24 months, *p*=0.004) (Table 4). There was a significant negative relationship between LCQ

**Table 2.** Clinical features at diagnosis of primary Sjögren's syndrome

Parameter	Result (n=80)				
	n	%	Mean±SD	Median	25-75 interquartile ranges
Non-productive cough	30	37.5			
Itching	34	42.5			
Tooth decay	31	38.8			
Hoarseness	15	18.8			
Dryness of the nose	38	47.5			
Taste disturbance	13	16.3			
Arthralgia	35	43.8			
Hospital admission with cough	14	17.5			
Delay in the diagnosis, months				24	3-60
Beck Depression Inventory			11.8±8.5		

SD: Standard deviation.

**Table 3.** Scores of Leicester Cough Questionnaire, cough visual analog scale, and Beck Depression Inventory

Parameter	Result (n=30)	
	Mean±SD	Range
Leicester cough questionnaire	13.2±3.1	3-21
Cough visual analog scale	47±18.5	
Mild		0-30
Moderate		40-60
Severe		70-100
Beck Depression Inventory	15.2±9.2	
Normal		0-9
Mild		10-18
Moderate		19-29
Severe		30-63

SD: Standard deviation.

and BDI scores (Spearman correlation coefficient [Rho]=-0.534;  $p=0.002$ ). A significant negative correlation between LCQ and VAS (Rho=-0.852,  $p=0.001$ ) was also identified.

## DISCUSSION

In the current study, 37.5% of the patients had non-productive cough and of these patients, 46.6% were admitted to hospital with cough at least once before diagnosis of pSS. LCQ score was 13.2±3.1. LCQ is divided into three domains: physical, psychological, and social. There was no significant difference between domains of LCQ. Depression was more common in patients with chronic cough. Furthermore, there was a significant delay in the diagnosis of pSS in patients with chronic cough. This may have resulted from the nature of symptoms in these patients such as dryness of the mouth and eyes and cough. These complaints are relatively non-specific and the patients may consult with clinics that do not deal with rheumatological disorders.

Cough is an important symptom and is the main reason to seek medical attention for patients with lung diseases.<sup>13</sup> Chronic cough affects approximately 10% of the adult population and suffering from chronic cough can affect the quality of life negatively. The symptoms of chronic cough can be difficult to evaluate because cough has no specific disease pointers and can be caused by pulmonary and extrapulmonary diseases.<sup>14</sup> This may lead to failure in the diagnosis and treatment.<sup>15</sup>

Primary Sjögren's syndrome is a chronic systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands. Lung involvement varies depending on the methods used for detection. Clinically significant lung involvement is seen in 9-24% of patients with pSS.<sup>16</sup> However, in a study carried out by Uffmann et al.,<sup>17</sup> it was reported that pulmonary manifestations were estimated to occur in over 75% of patients with pSS when assessed with high resolution computed tomography and pulmonary function tests. In another study by Yazısız et al.,<sup>18</sup> including 123 patients with pSS, 24.4% of patients had pulmonary manifestations at the initial presentation or during the follow-up period. Continuous dry cough that can disrupt the quality of life is seen in 50% of patients with pSS. Xerotrachea, desiccation of the tracheobronchial tree, is one of the common causes of cough. Xerotrachea should be distinguished from ILD, which is usually accompanied by dyspnea, abnormal pulmonary function test, and diffusing capacity. Impairment in mucociliary clearance, as well as diminished or absent secretions of the mucous glands in the trachea, may lead to xerotrachea. An increase in the incidence of atelectasis, bronchiectasis, and respiratory infection are observed in patients with xerotrachea. It may be misdiagnosed as asthma or chronic

**Table 4.** Scores of Beck Depression Inventory and delay in diagnosis according to cough

Parameter	Patients with cough (n=30)			Patients without cough (n=50)			Range	p
	Mean±SD	Median	IQR	Mean±SD	Median	IQR		
Beck Depression Inventory	15.2±9.2			9.9±7.4				0.006
Normal							0-9	
Mild							10-16	
Moderate							17-29	
Severe							30-63	
Delay in the diagnosis (months)		48	12-96		24	0-51		0.004

SD: Standard deviation; IQR: 25-75 Interquartile range.

bronchitis.<sup>8,19,20</sup> More than 17.5% of the patients with non-pulmonary involvement sought medical care for cough at least once before the diagnosis of pSS. VAS and LCQ scale scores for cough were found to be moderately affected. Delay in the diagnosis of pSS was significant between patients with and without cough. When physicians keep a running list of likely diagnoses in mind for chronic cough, the diagnosis of xerotrachea due to pSS is rarely made since the cough may be symptomatic of other more common diseases such as asthma, gastroesophageal reflux or postnasal drip.

Cough can negatively affect patients' quality of life, leading to depression. Chronic cough can disrupt sleeping pattern and cause nausea, vomiting, and urinary incontinence. Fear of severe coughing in public places can cause social isolation. Chronic cough can also cause the deterioration of relationship with spouses and relatives. In our study, a significant difference was observed in the BDI scores between patients with and without cough and there was a significant negative correlation between LCQ and BDI similar to the literature. In clinical practice, while attention is paid to the physical symptoms of cough, the psychosocial effects are ignored.<sup>21</sup> In a study including 57 patients with chronic cough, 48% of patients were found to have moderate-high levels of anxiety and 16% of patients had depression.<sup>22</sup> Arıkan et al.<sup>23</sup> reported a significant correlation between the level of depression, quality of life and LCQ, similar to the findings of the current study. In another study that investigated the prevalence of depressive symptoms in patients with chronic cough, it was demonstrated that depression was common in patients with chronic cough and an improvement in cough score was associated with improvement in the depression score.<sup>24</sup>

The present study has some limitations that deserve to be mentioned. Firstly, since the study has a cross-sectional design, we cannot suggest a cause and effect relationship. Secondly, the number of patients are relatively low. However, patients with lung involvement were excluded. Thirdly, the diagnosis was based on clinical, radiologic, and physiologic evaluation. We did not perform bronchial biopsy or bronchoscopy. Thus no histopathological evaluation was carried out for the patients in our study.

In conclusion, cough due to dryness in the trachea in patients with pSS is seen more frequently than thought and can be the initial presentation of the disease. pSS, a common disease in the community, can be difficult to diagnose due to the heterogeneity of the symptoms. If physicians keep a running list of likely diagnoses in mind for chronic cough and the clinical approach is right, pSS can be easy to diagnose. Patients with pSS may be admitted to different clinics such as Pulmonary Medicine, Ophthalmology, Otolaryngology, and General Medicine depending on the patient's initial symptoms. In addition, xerotrachea does not feature prominently in the etiologies of chronic cough. For this reason, it may be misdiagnosed as asthma, chronic bronchitis, gastroesophageal reflux or postnasal drip. Delay in diagnosis may increase the incidence of depression. Thus, xerotrachea should be considered in the differential diagnosis of chronic cough, especially in patients with normal pulmonary function test and pulmonary imaging. When a patient has symptoms that appear to be unusual, physicians should include the trachea in the evaluation and carefully examine other symptoms of pSS.

#### **Declaration of conflicting interests**

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

#### **Funding**

The authors received no financial support for the research and/or authorship of this article.

## **REFERENCES**

1. Ramos-Casals M, Tzioufas AG, Font J. Primary Sjögren's syndrome: new clinical and therapeutic concepts. *Ann Rheum Dis* 2005;64:347-54.
2. Asmussen K, Andersen V, Bendixen G, Schiødt M, Oxholm P. A new model for classification of disease manifestations in primary Sjögren's syndrome: evaluation in a retrospective long-term study. *J Intern Med* 1996;239:475-82.
3. Blochowiak K, Olewicz-Gawlik A, Polanska A, Nowak-Gabryel M, Kociecki J, Witmanowski H, et al. Oral mucosal manifestations in primary and secondary Sjögren syndrome and dry mouth syndrome. *Postepy Dermatol Alergol* 2016;33:23-7.
4. Chung KF. Approach to chronic cough: the neuropathic basis for cough hypersensitivity syndrome. *J Thorac Dis* 2014;6:699-707.



5. Kreider M, Highland K. Pulmonary involvement in Sjögren syndrome. *Semin Respir Crit Care Med* 2014;35:255-64.
6. Reina D, Roig Vilaseca D, Torrente-Segarra V, Cerdà D, Castellví I, Díaz Torné C, et al. Sjögren's syndrome-associated interstitial lung disease: A multicenter study. *Reumatol Clin* 2016;12:201-5.
7. Stojan G, Baer AN, Danoff SK. Pulmonary manifestations of Sjögren's syndrome. *Curr Allergy Asthma Rep* 2013;13:354-60.
8. Mathieu A, Cauli A, Pala R, Satta L, Nurchis P, Loi GL, et al. Tracheo-bronchial mucociliary clearance in patients with primary and secondary Sjögren's syndrome. *Scand J Rheumatol* 1995;24:300-4.
9. Shiboski SC, Shiboski CH, Criswell L, Baer A, Challacombe S, Lanfranchi H, et al. American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance cohort. *Arthritis Care Res (Hoboken)* 2012;64:475-87.
10. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003;58:339-43.
11. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561-71.
12. Hisli N. Beck depression inventory for university students validity and reliability. *Turkish Journal of Psychology* 1989;7:3-13.
13. Cho SH, Lin HC, Ghoshal AG, Bin Abdul Muttalif AR, Thanaviratnanich S, Bagga S, et al. Respiratory disease in the Asia-Pacific region: Cough as a key symptom. *Allergy Asthma Proc* 2016;37:131-40.
14. Song WJ, Chang YS, Faruqi S, Kang MK, Kim JY, Kang MG, et al. Defining Chronic Cough: A Systematic Review of the Epidemiological Literature. *Allergy Asthma Immunol Res* 2016;8:146-55.
15. McGarvey LP. Does idiopathic cough exist? *Lung* 2008;186:78-81.
16. Palm O, Garen T, Berge Enger T, Jensen JL, Lund MB, Aaløkken TM, et al. Clinical pulmonary involvement in primary Sjogren's syndrome: prevalence, quality of life and mortality--a retrospective study based on registry data. *Rheumatology (Oxford)* 2013;52:173-9.
17. Uffmann M, Kiener HP, Bankier AA, Baldt MM, Zontsich T, Herold CJ. Lung manifestation in asymptomatic patients with primary Sjögren syndrome: assessment with high resolution CT and pulmonary function tests. *J Thorac Imaging* 2001;16:282-9.
18. Yazisiz V, Arslan G, Ozbudak IH, Turker S, Erbasan F, Avci AB, et al. Lung involvement in patients with primary Sjögren's syndrome: what are the predictors? *Rheumatol Int* 2010;30:1317-24.
19. Butnor KJ, Khoor A. Collagen vascular diseases and disorders of connective tissue. In: Tomaszefski Jr JF, editor. *Dail Hammar's Pulm. Pathol.* [Internet]. Springer New York; 2008 [cited 2013 Apr 4]. p. 722-59.
20. Turner RD, Bothamley GH. Chronic cough and a normal chest X-ray - a simple systematic approach to exclude common causes before referral to secondary care: a retrospective cohort study. *NPJ Prim Care Respir Med* 2016;26:15081.
21. Brignall K, Jayaraman B, Birring SS. Quality of life and psychosocial aspects of cough. *Lung* 2008;186:55-8.
22. McGarvey LP, Carton C, Gamble LA, Heaney LG, Shepherd R, Ennis M, et al. Prevalence of psychomorbidity among patients with chronic cough. *Cough* 2006;2:4.
23. Arikan H, Savci S, Calik-Kutukcu E, Vardar-Yagli N, Saglam M, Inal-Ince D, et al. The relationship between cough-specific quality of life and abdominal muscle endurance, fatigue, and depression in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2015;10:1829-35.
24. Dicipinigitis PV, Tso R, Banauch G. Prevalence of depressive symptoms among patients with chronic cough. *Chest* 2006;130:1839-43.