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Sicca Symptoms and Its Relationship with Primary Sjögren's Syndrome in Geriatric Patients

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Abstract

Objective: Sicca symptoms are frequently observed in geriatric patients, and Sjögren's syndrome is a prototypic disease associated with sicca symptoms. This study aimed to determine the frequency of sicca symptoms and its relationship with primary Sjögren's syndrome (pSS) in geriatric patients in comparison with young patients.

Materials and Methods: This study included 477 patients, with the geriatric group comprising 277 patients aged ≥65 years who were compared to the 200 young patients in the control group. All the subjects were asked questions for the evaluation of sicca symptoms. The Schirmer's and unstimulated whole salivary flow tests were conducted on all the subjects. The diagnosis of pSS was based on the American-European Consensus Group criteria.

Results: The symptoms of dry mouth (33.9% vs. 2%) (p<0.001) and eyes (20.9% vs. 2.5%) (p<0.001) were significantly higher in the geriatric group. Thirteen patients in the geriatric group (13/277, 4.69%) and one patient in the control group (1/200, 0.5%) were diagnosed with pSS (p=0.010). The rate of pSS was 6.89% (12/174) for elderly females and 0.97% (1/103) for males (p=0.036).

Conclusion: The prevalence of pSS is considerably higher in geriatric patients. Every geriatric patient, especially elderly women, should be routinely assessed for sicca symptoms and objective tests should be performed in the presence of sicca symptoms.

Keywords: Dry eyes, dry mouth, geriatric, primary Sjögren's syndrome, sicca symptoms

Introduction

Sicca symptoms are frequent complaints in geriatric patients. Often, both the patients and their attending physicians consider these complaints as a component of aging or as a side-effect of medications. Therefore, these symptoms are mostly ignored and eventually causing the patients to stop mentioning about them (1,2). Also, age-related cognitive deterioration prevents many symptoms such as dry mouth and dry eye from being noticed. Besides medications, acute or chronic parotitis, graft-versus-host disease, hepatitis C, head and neck radiotherapy, SS and sarcoidosis are among the causes of sicca symptoms (3). In large studies focusing on the sicca symptoms in geriatric patients, affirmation with objective tests was only made when subjective complaints of dry mouth and dry eye were present. Thus, the sensitivity of the tests decreased with cognitive impairment.

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease, where the exocrine glands are mainly affected. Permanent dry mouth and dry eye occur due to functional and structural impairment of salivary and tear glands. According to the European League Against Rheumatism (EULAR)- SS task force, sicca symptoms are the most common manifestation of SS, with up to 98% of cases (4). The frequency of dry mouth

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and dry eye increases with age (5). pSS can occur in patients of all ages, it mainly manifests in the fourth and fifth decade of life. The prevalence of pSS ranges between 0.01-5% (6). The difference in the prevalence ratios is generally due to the age of the studied population, the differences in sample sizes, and the use of different classification criteria for pSS. Precise data could not be obtained both because of the small number of prevalence studies in geriatric population and the implementation of different classification criteria. However, the prevalence in the geriatric population is higher than the young (7,8). There are no previous studies concerning the prevalence of pSS in the geriatric population of Turkey.

This study aims to investigate the rate of sicca symptoms and its relation to pSS in geriatric patients and compare with the young patients. pSS diagnosis was based on the AECG criteria. The most widely accepted current classification criteria for pSS are the AECG criteria (9). The American College of Rheumatology (ACR)/EULAR classification criteria have been published in 2016 (10). The population described by both criteria is very similar (11). The diagnosis of pSS was also evaluated according to the 2016 ACR/EULAR classification criteria in this study.

Materials and Methods

This study was designed as an observational cross-sectional study.

Study population

A total of 477 patients were included in this study. 277 patients ≥65 years who received outpatient treatment in the Geriatrics Clinic of Ankara University Faculty of Medicine within 6-months period constituted the study group. Two hundred patients ≥18 years who received outpatient treatment in the General Internal Medicine Clinic of Ankara University Faculty of Medicine between the same dates constituted the control group.

Ethic

The protocol of this study was approved by the Ankara University Faculty of Medicine Medical Research Ethics Committee as dated 24.9.2012 and numbered 13-247. The study conforms to the provisions of the World Medical Association's Declaration of Helsinki. All of the patients signed the informed consent forms.

Exclusion criteria

The patients who were previously diagnosed with a systemic autoimmune disease, acute or chronic parotitis, graft-versus-host disease, hepatitis C, acquired immunodeficiency disease, lymphoma, sarcoidosis, who had a medical history of head and neck radiotherapy, who had uncontrolled diabetes mellitus, who used anticholinergic drugs, who had a general condition disorders that impair their ability to make the Schirmer's test or the unstimulated whole salivary flow test, who refused to participate in the study were excluded from the study.

Investigation of sicca symptoms

All patients were asked questions evaluating sicca symptoms. Patients who gave a positive answer to at least one of the following questions were considered to have dry eye symptom; 1. Have you had daily, persistent, troublesome dry eyes for more than 3 months? 2. Do you have a recurrent sensation of sand or gravel in the eyes? 3. Do you use tear substitutes more than 3 times a day? Patients who gave a positive answer to at least one of the following questions were considered to have dry mouth symptom; 1. Have you had a daily feeling of dry mouth for more than 3 months? 2. Have you had recurrently or persistently swollen salivary glands as an adult? 3. Do you frequently drink liquids to aid in swallowing dry food? These questions are those used in revised version of the European criteria proposed by the AECG to detect sicca symptoms (9).

Demonstration of dry mouth and dry eye with objective tests

All participants in the study, no matter whether they had dry mouth and dry eye or not, were subjected to the unstimulated whole salivary flow test and the Schirmer's test.

In the Schirmer test, sterilized standard Schirmer strips were carefully placed on the lower lid margins of both eyes. The strips remained in position for 5 min. After 5 min, the wetting levels of the strips were recorded in units of millimetres. If the Schirmer test result was ≤5 mm in at least one eye, the test was considered positive (12).

The unstimulated whole salivary flow test was used for the evaluation of salivary hypofunction. The volume of saliva that the participant accumulated within 15 min was measured and the result of the test was considered to be positive in the presence of a collection ≤1.5 mL (the unstimulated whole saliva flow rate ≤0.1 mL/minute) (13).

Diagnosis of pSS

The pSS diagnosis was based on the American-European Consensus Group (AECG) criteria. All patients who had objective dry mouth and/or dry eye were reevaluated for pSS by a rheumatology specialist. The blood samples were collected from these patients to test for anti-Ro [Sjögren's syndrome antigen A (SSA)] and anti-La [Sjögren's syndrome antigen B (SSB)] autoantibodies (by enzyme-linked immunosorbent assay test). The patients with objective dry mouth and/or dry eye and having either anti-SSA/Ro or anti-SSB/La antibody positivity were diagnosed as pSS. A minor salivary gland biopsy was performed to the patients who had dry mouth and/or dry eye but negative anti-SSA/Ro or anti-SSB/La antibodies by the rheumatology specialist. The patients who were found to have a focus score of ≥1 were diagnosed with pSS. Additionally, the diagnosis of pSS was evaluated according to the 2016 ACR/EULAR classification

criteria. The compatibility between the two diagnostic criteria was checked.

Histological examination of minor salivary gland biopsy

Salivary gland samples were obtained from the mucosa of the lower lip that appeared normal. The biopsy was evaluated using focus scoring according to the American-European criteria by an expert histopathologist. Focus is defined as an aggregate of 50 or more mononuclear cells per 4 mm^2. The biopsy was accepted as positive when the focus score was ≥1 (14).

Statistics

SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA) was used to statistically analyse all data. Variables are presented as mean ± standard deviation or frequency. The data had previously been subjected to a normal distribution test (Kolmogorov-Smirnov). To compare quantitative variables, Student's t-test was used for the normally distributed variables, and Mann-Whitney U test was used for variables that were not normally distributed. For the comparison of qualitative data, the chi-squared test was used. Fisher's Exact test was used where cell values are expected to be smaller than 5 exceeded 20% percentage. All tests were two tailed, and p-values <0.05 were considered to indicate statistical significance.

Results

The geriatric group and the control group are compared terms of sicca symptoms and clinical features (Table 1). According to the revised AECG criteria, 13 patients in the geriatric group (13/277, 4.69%) and 1 patient in the control group (1/200, 0.5%) received a pSS diagnosis (p=0.010). Twelve of geriatric cases and the young case were females (F/M=13/1). The rate of pSS according to gender is shown in Table 2. Considering all patients included in the study, the rate of pSS was determined as 2.93% (14/477). When evaluated with the 2016 ACR/EULAR classification criteria, the same patients were diagnosed with pSS.

From the patients with objective dry mouth and/or dry eye and having either anti-SSA/Ro or anti-SSB/La antibody positivity, 4 patients (3 patients from the geriatric group and 1 patient from the control group) were diagnosed as pSS. Four cases had only anti-SSA/Ro positivity. Minor salivary gland biopsy was performed to 14 patients who did not have positive antibodies. Ten patients were found to have a focus score of ≥1 and these patients were diagnosed with pSS.

Although there were no complaints of dry mouth or dry eye, dryness was detected by objective tests in two geriatric patients. One of these patients was diagnosed with anti-SSA/Ro autoantibody positivity and the other was diagnosed with pSS by salivary gland biopsy.

The patients diagnosed with pSS and not diagnosed with pSS in the study group compared in terms of dry mouth and dry eye symptoms and clinical features (Table 3).

Discussion

In our study to determine the rate of sicca symptoms and its relation to pSS in geriatric individuals and compare with the young patients, both sicca symptoms and pSS were found to be significantly more common in geriatric individuals.

The prevalence of sicca symptoms in people ≥65 years of age is reported by up to 30% (2,15). In a population-based study with 2481 subjects aged between 65-84 years, dry mouth or dry eye was present in approximately 27% of the community, and they

Table 1. Comparison of the groups in terms of sicca symptoms and clinical features

Parameters	Study group (n=277)	Control group (n=200)	p
Age (mean)	74.08±6.52	39.25±10.69	**<0.001**
Gender (female/male)	174/103	126/74	0.956
Number of chronic diseases	2.76±1.65	1.17±0.87	**<0.001**
Number of drugs used	3.35±1.38	1.60±1.08	**<0.001**
Presence of dry mouth symptom (%)	122 (44.0)	13 (6.5)	**<0.001**
Presence of objective dry mouth (%)	94 (33.9)	4 (2)	**<0.001**
Swollen salivary glands (parotid or submandibular) (%)	14 (5.1)	0	**<0.001**
Presence dry eye symptom (%)	85 (30.7)	8 (4)	**<0.001**
Presence of objective dry eye (%)	58 (20.9)	5 (2.5)	**<0.001**
Presence of both dry mouth and dry eye symptom (%)	51 (18.4)	1 (0.5)	**<0.001**
Simultaneous positivity of saliva test and Schirmer's test (%)	17 (6.1)	0	**<0.001**
Use of artificial eye drops (%)	37 (13.4)	2 (1)	**<0.001**
Diagnosis of pSS	13 (4.69)	1 (0.50)	**0.010**

pSS: Primer Sjögren's syndrome

Table 2. The rate of primary Sjögren's syndrome according to gender

Group	Patient with primary Sjögren's syndrome		
	Female	Male	p
Geriatric (%)	12 (12/174-6.89%)	1 (1/103-0.97%)	**0.036**
Control (%)	1 (1/126-0.8%)	0 (0/74-0%)	1.000
Total (%)	13 (13/301-4.32%)	1 (1/176-0.56%)	**0.023**

Table 3. Comparison of patients diagnosed with pSS and not diagnosed with pSS in the study group in terms of sicca symptoms

Parameters	pSS (n=13)	No pSS (n=264)	p
Age (mean)	72.85±6.29	74.14±6.53	0.486
Presence of dry mouth symptom (%)	8 (61.5)	114 (43.2)	0.309
Presence of objective dry mouth (%)	10 (76.9)	84 (31.8)	**0.002**
Presence dry eye symptom (%)	7 (53.8)	78 (29.5)	0.122
Presence of objective dry eye (%)	8 (61.5)	50 (18.9)	**<0.001**
Presence of both dry mouth and dry eye symptom (%)	6 (46.1)	45 (17.0)	**0.022**
Simultaneous positivity of saliva test and Schirmer's test (%)	6 (46.1)	19 (7.2)	<0.001

pSS: Primer Sjögren's syndrome

were simultaneously present in 4.4% of the population (16). However, the patients with sicca symptoms were not examined by a rheumatologist for the presence of SS. In our study, the complaints of dry mouth and dry eye in geriatric patients were 44% and 30.7%, respectively. These rates were higher than the literature. This result may be related to the fact that the patients included in the study were selected from the patients who were admitted to the hospital, not from the society. In our study, all subjects, whether or not they had the complaints of dry mouth and/or dry eye, were evaluated by objective tests (the unstimulated whole salivary flow test and the Schirmer's test). Thus, the patients who do not feel dry mouth or dry eye or who could not report dry mouth and dry eye due to cognitive deficiency were also identified. By the objective tests, dry mouth rate as 33.9%, and dry eye rate as 20.9% was determined in geriatric patients. Cases that were positive for one or both objective tests were further evaluated by a rheumatologist for the presence of pSS according to the AECG and ACR/EULAR classification criteria.

Estimates of the prevalence of pSS vary widely, depending upon the specific classification criteria, study design, and the population examined (17,18). By Kabasakal et al. (19) in a study of women in Turkey have investigated the prevalence of pSS. According to the revised European criteria and AECG criteria, the prevalence of pSS was found to be 1.56% and 0.72%, respectively. In a prevalence study conducted by Birlik et al. (20) on both male and female subjects, the prevalence of pSS was reported as 0.21% according to the AECG criteria, which is actually surprisingly lower than the predicted mean value for the general population. There are no previous studies concerning the prevalence of pSS in the older adults of Turkey. In our study, considering all patients included in the study, the rate of pSS was determined as 2.72%. A small group of patients diagnosed with pSS could have primarily extraglandular manifestations without significantly demonstrating dry mouth or dry eye (21). Since the rate of such patients is quite low, we did not evaluate our patients in this respect, considering that it would not affect our study results.

According to the "1993 European Community criteria," Thomas et al. (22) predicted the prevalence of pSS in geriatrics as 3-4%. Botsios et al. (23) reported the pSS prevalence as 6% by using "1996 Revised European Classification Criteria". These studies were conducted according to the European study criteria identified in 1993 and 1996, which are less strict than the 2002 "AECG Criteria". Haugen et al. (24) have evaluated two different populations with an age range of 40-44 and 70-74, according to the 1993 European criteria and 1996 revised European criteria. In the group aged between 40-44, the prevalence of pSS according to the 1993 and 1996 rules was found to be 0.44% and 0.22% respectively; whereas in the second group aged between 71-74, it was reported as 3.39% and 1.4%, respectively. Drosos et al. (25) have diagnosed 8 out of 62 elderlies from a public nursing home with pSS through biopsy, all of whom were asymptomatic. Among 103 older adults women, Strickland et al. (26) have identified dry mouth in 39% and dry eye (with the Schirmer's test) in 24% of the patients. Two of these 103 women were diagnosed with pSS, and 12% were evaluated as possible pSS. In our study, the rate of pSS in older adults subjects was 4.7% (6.9% for older adults females and 0.9% for males). SS affects primarily middle-aged women. The female/male ratio ranges from 9/1 to 14/1 (27,28). Our results are also compatible with the literature (female/male ratio: 12/1).

Unlike the 2002 AECG criteria, in the ACR/EULAR classification criteria, positive serology for anti-SSB/La in the absence of anti-SSA/Ro is no longer considered a criteria item. Nevertheless, in this study, all patients diagnosed with pSS according to 2002 AECG Criteria were anti-SSA/Ro antibody positive while anti-SSB/La negative. Therefore, when the patients were evaluated with the 2016 ACR/EULAR classification criteria, the same patients who were diagnosed with pSS according to the AECG criteria were diagnosed with pSS. We found that both sets of criteria were compatible with each other and we think that any of them could be used in geriatric patients, depending on the clinician's preference. In our study, only 4 (1 young and

3 geriatric patients) patients having dry mouth and/or dry eye were diagnosed through anti-SSA/Ro antibody positivity. Older patients with SS have lower frequency of serologic abnormalities, such as anti-SSA, anti-SSB, rheumatoid factor, and hyperglobulinemia, than a young one (29-31). In addition, biopsy was positive in 10 of 14 patients who underwent salivary gland biopsy.

In our study, two geriatric patients who did not complain of dry mouth or dry eye were diagnosed with pSS. This is a remarkable finding and it demonstrates that the presence of dry mouth and dry eye could be detected through objective tests, even though the patients do not mention them as a result of possible cognitive impairment or other reasons (32,33).

Study Limitations

The study has some limitations. Firstly, this study was conducted with outpatients. This is not a community survey. Therefore, only the pSS ratio was determined. pSS prevalence information was not available. Secondly, because our study aimed not only to determine the rate of sicca symptoms, but also to determine the relationship between sicca symptoms and pSS, patients with a condition other than pSS that would cause sicca symptoms were excluded from the study. Therefore, the rate of sicca symptoms in geriatric patients may be higher than that shown in our study. However, our study is the only study in Turkey to determine the rate of sicca symptoms and pSS in geriatric patients. Finally, the control group in the study consisted of young patients. Considering that comparisons with young patients would not be made, the results of the comprehensive geriatric evaluation of the geriatric patients were not recorded during the study. For this reason, comprehensive geriatric evaluation results of geriatric patients could not be given.

Conclusion

In our study, the rate of pSS in the older adults was found 4.69%, despite the use of the revised AECG and ACR/EULAR Classification Criteria, which are much conservative than the previous measures. This ratio quite high and is worth attention. Sicca symptoms are the cardinal symptoms in pSS. These symptoms are non-specific and can occur with many other conditions. Also, these have a profound effect on the quality of life of patients with pSS. In the geriatric age group, sicca symptoms are not commonly mentioned complaints in doctor visits. On the other hand, most of the patients with sicca symptoms do not have Sjögren syndrome. In our study, especially in geriatric patients with dry mouth and dry eye symptoms, pSS detection rate was significantly higher. Therefore, patients with sicca symptoms should be carefully interviewed by geriatrics, and objective tests should be conducted in order not to miss pSS. Early diagnosis and treatment will have a positive effect on the quality of life of patients with pSS. Awareness should be raised for morbidity in these patients and the possible lymphoproliferative diseases that can develop in further years.

Ethics

Ethics Committee Approval: The protocol of this study was approved by the Ankara University Faculty of Medicine Medical Research Ethics Committee as dated 24.9.2012 and numbered 13-247. The study conforms to the provisions of the World Medical Association's Declaration of Helsinki.

Informed Consent: All of the patients signed the informed consent forms.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.K.C., O.K., A.Ş., Concept: Ö.K.C., O.K., A.Ş., N.T., T.A., Design: Ö.K.C., O.K., A.Ş., N.T., T.A., Data Collection or Processing: Ö.K.C., O.K., A.Ş., Analysis or Interpretation: Ö.K.C., O.K., A.Ş., Literature Search: Ö.K.C., O.K., A.Ş., N.T., T.A., Writing: Ö.K.C., O.K., A.Ş., N.T., T.A.

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