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Evaluation of *Candida albicans* prevalence in mouth and *Stafilococcus aureus* prevalence in eye and nose in patients with Sjögren's syndrome

Sjögren sendromu hastalarında göz ile burunda *Stafilococcus aureus* ve ağızda *Candida albicans* sıklığının araştırılması

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Abstract

Objective: Sjögren's syndrome (SS) is a chronic, progressive and autoimmune disease characterized by the lymphocytic infiltration of the exocrine glands leading to dry eyes and dry mouth. The present study investigates the prevalence of *Staphylococcus aureus (S. aureus)* in the ophthalmic and nasal mucosa and *Candida albicans* (*C. albicans*) in the oral mucosa of patients with primary SS. Previous studies in the literature have included only a limited number of cases, while the present study includes 100 patients with primary SS patients, contributing to the achievement of more reliable results. This study aimed to show that the frequency of *S. aureus* and *C. albicans* is high in patients with SS.

Methods: This study included patients diagnosed with primary SS based on the American-European Consensus Group criteria among those who presented to the outpatient Kayseri Training and Research Hospital, Clinic of Rheumatology between February 2016 and June 2016. Healthy volunteers without chronic diseases and without regular drug use among those who presented to the outpatient Kayseri Training and Research Hospital, Clinic of Internal Medicine were included in the study as a control group. Samples were collected from the nose (medial nasal mucosa of both nostrils), the mouth (buccal mucosa at the molar tooth level), and the conjunctival sac (with four swab rotations).

Results: *C. albicans* growths were identified in 37% (n=37) and 17% (n=17) of the patient and control groups, respectively, based on oral culture evaluations. The difference between the two groups was statistically significant (p=0.001). *S. aureus* growth was identified in 12% (n=12) and 1% (n=1) of the patient and control groups, respectively, based on nasal culture evaluations, and the difference between the two groups was statistically significant (p=0.002).

Öz

Amaç: Sjögren sendromu (SS) ağız ve göz kuruluğuna sebep olan, özellikle ekzokrin bezlerin lenfositik infiltrasyonu ile karakterize kronik, ilerleyici, otoimmün bir hastalıktır. SS'de ortaya çıkan ağız ve göz kuruluğuna bağlı olarak flora etkilenmekte ve bakterilerin kolonizasyonu artmaktadır. Çalışmamızda primer SS hastalarının göz ve burun kültürlerinde *Staphylococcus aureus (S. aureus)* ve ağız kültürlerinde *Candida albicans* (*C. albicans*) sıklığının sağlıklı gönüllülere göre fazla olduğunun gösterilmesi amaçlanmıştır.

Yöntem: Çalışmaya Şubat 2016-Haziran 2016 tarihleri arasında Kayseri Eğitim ve Araştırma Hastanesi, Romatoloji Polikliniği'ne başvuran Amerika-Avrupa Konsensus Grubu kriterlerine göre primer SS tanısı almış hastalar dahil edilmiştir. Kontrol grubu olarak ise Kayseri Eğitim ve Araştırma Hastanesi, İç Hastalıkları Polikliniği'ne başvuran sağlıklı gönüllüler alınmıştır. Örnekler burundan (her iki burun deliğinin medyal burun mukozası), ağızdan (molara yakın yanak mukozası) ve konjonktival kese (dört pamuklu çubuk dönüşü ile) alınmıştır.

Bulgular: Ağız kültürlerinin değerlendirilmesinde; hasta grubunun %37'sinde (n=37) ve kontrol grubunun %17'sinde (n=17) *C. albicans* üremesi tespit edildi. İki grup arasındaki farkın istatistiksel olarak anlamlı olduğu görüldü (p=0,001). Burun kültürlerinin değerlendirilmesinde hasta grubunun %12'sinde (n=12) ve kontol grubunun %1'inde (n=1) *S. aureus* üremesi saptanmıştır. İki grup arasındaki farkın istatistiksel olarak anlamlı olduğu görüldü (p=0,002).

Sonuç: Burunda *S. aureus* ve ağızda *C. albicans* görülme sıklığının SS'li hastalarda kontrol grubuna göre artmış olduğu tespit edildi. Elde edilen bu sonuçlar SS'de meydana gelen mukozal kuruluğun normal floranın değişmesine sebep olduğunu göstermektedir. Ancak normal floradaki bu değişikliğin hastalık oluşturup oluşturmadığı net olarak ortaya konamamıştır.

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Conclusion: Infections are among the main causes of morbidity and mortality in rheumatological diseases. The most common reason for hospital visits has been reported as infections associated with rheumatoid arthritis, systemic lupus erythematosus, and other rheumatological diseases. The involvement of SS in the exocrine glands leads to dysfunction and decreased secretions, resulting in dry mouth, dry eyes, and dry skin. As a result of these changes in SS, the colonization of both normal flora and unassociated pathogenic bacteria increases, contributing to a higher frequency of infections. In our study the prevalence of *S. aureus* in the nasal mucosa and *C. albicans* in the oral mucosa of primary SS patients was statistically significantly higher than in healthy controls.

Keywords: Primary Sjögren's syndrome, nasal *Staphylococcus aureus*, oral *Candida albicans*

Anahtar Kelimeler: Primer Sjögren sendromu, nazal *Stafilococcus aureus*, oral *Candida albicans*

Introduction

Sjögren's syndrome (SS) is a chronic, progressive, and autoimmune disease that characterized by the lymphocytic infiltration of the exocrine glands, leading to dry eyes and dry mouth.[1] The prevalence of SS is nine times greater in females than in males and occurs especially in the 4th and 5th decades, although it can be seen in all age groups.[2] The incidence of SS increases with age, being seven times more common in those aged 70 years or above than in those aged 40 years or above.[3] The most prominent involvement in SS is in the eye and oral mucosa, although nasal, pharyngeal, vulvar, gastric, sebaceous, sweat glands, and apocrine gland exocrine gland involvements may also be affected. Symptoms such as dry skin, dysphagia, and dyspareunia can be seen secondary to these involvements.[2] Among the extra-glandular involvements, the respiratory system may be affected on a spectrum ranging from dry cough to interstitial lung disease; musculoskeletal system involvements can vary from fatigue to myositis; and hematological system involvements can range from mild anemia to lymphoma. Additionaly, involvements of the kidneys, vessels, skin, and nerves can also be seen.[4] Symptoms depend on the affected organ and the severity of the involvement.

SS is referred to as primary when seen alone and secondary when it accompanies other connective tissue diseases, including systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, inflammatory muscle disease, autoimmune thyroiditis, and most commonly, rheumatoid arthritis.[5]

Atrophy and decreased secretion occur as a result of chronic inflammation in the exocrine glands. Protection from microorganisms diminishes as a result of the reduced exocrine gland secretions, leading to a predisposition to infections. A decreased prevalence of Candida, *Lactobacillus*, and *Streptococcus* mutans has been reported in the oral mucosa of patients with SS in previous studies.[6] In another study, the prevalence of oral candidiasis was reported as 74% and 23% were reported in patients with SS and healthy controls, respectively.[7]

The present study investigates the prevalence of *Staphylococcus aureus* (*S. aureus*) in the ophthalmic and nasal mucosa and *Candida albicans* (*C. albicans*) in the oral mucosa of patients with primary SS. Previous studies in the literature have included only a limited number of cases, while the present study includes 100 primary SS patients, contributing to more reliable results.

The prevalence of *S. aureus* is affected by factors such as age, antibiotic use, and hospitalization, although there are also variations based on the population being studied. The prevalence of *S. aureus* in the general population has been reported as 10-50%, and as high as 50-70% in healthcare professionals. Although S. aureus has been identified in the nasal mucosa of 34% of SS patients, there is a lack of studies reporting its prevalence in conjunctival cultures of SS patients to date.[8,9]

Materials and Methods

This cross-sectional study was approved by the Ethics Board of the University of Erciyes University Faculty of Medicine, and was carried out in compliance with the rules of the World Medical Association Declaration of Helsinki (approval number: 2015/581, date: 25.12.2015). Patients diagnosed with primary SS based on the American-European Consensus Group (AECG) criteria who presented the outpatient Kayseri Training and Research Hospital, Clinic of Rheumatology between February 2016 and June 2016 were included in the study.[10] Healthy volunteers without chronic diseases and without regular drug use who presented to the outpatient Kayseri Training and Research Hospital, Clinic of Internal Medicine were included as the control group.

Obtaining the Cultures

Samples were taken from the patients from the nose (medial nasal mucosa of both nostrils), the mouth (buccal

mucosa at the molar tooth level), and the conjunctival sac (with four swab rotations).

The conjunctival and nasal swab samples were harvested in a chromogenic culture medium, and the growing colonies were transported to the culture medium in accordance with a 0.5 McFarland standard with the addition of a cefoxitin disk. The samples were then identified as methicillin-resistant *staphylococcus aureus* (MRSA) and methicillin-sensitive *staphylococcus aureus* (MSSA), depending on the cefoxitin disk sensitivity after overnight incubation. The growing staphylococci were thus determined as MRSA or MSSA and recorded.

The growing *C. albicans* colonies were recorded after incubating the samples obtained from the oral mucosa in a chromogenic culture medium.

Statistical Analysis

IBM SPSS Statistics (Version 23.0. Armonk, NY: IBM Corp.) was used for the statistical analysis of the obtained data.The normality of the distribution of the cases was evaluated using a Shapiro-Wilk test and histograms. Continuous variables were expressed as mean ± standard deviation or as median and 25^{th}-75^{th} percentiles, while categorical variables were expressed as the number of cases and percentages (%). Categorical variables were analyzed using a Pearson chi-square test or Fisher's exact chi-square test. A Mann-Whitney U test was used for the comparison of nonparametric variables, with values expressed as median and 25^{th}-75^{th} percentiles. The results were accepted as statistically significant when $p<0.05$. Age-adjusted p-values were used due to the difference in the age distribution of the patient and control groups. A logistic regression analysis was used for the calculation of the p-value. The age variable was entered into the model when the effect of the group variable on the growth was explored, and age-adjusted p-values were calculated.

Results

A total of 100 patients [97 female (97%), 3 male (3%)], diagnosed based on the AECG criteria, and 100 healthy volunteers [95 female (95%), 5 male (5%)] ($p>0.05$), were included in the study. The age range of the patients was 20-76 years, with a mean age of 50.1±11.9 years, and the age range of the control group was 18-77 years with a mean age of 38.1±13.2 years ($p<0.001$).

C. albicans growths were identified in 37% (n=37) and 17% (n=17) of the patient and control groups, respectively, based on an oral cultures evaluations. The difference between the two groups was statistically significant (p=0.001). Age-adjusted p-values were used due to the difference in the age distribution of the patient and control groups (p=0.023). Among the positive cultures in the patient group, 35 were found to be *C. albicans* positive and two to be *C. albicans* negative; while the positive cultures in the control group included 11 *C. albicans* positive and six *C. albicans* negative cultures.

S. aureus growth was identified in 12% (n=12) and 1% (n=1) of the patient and control groups, respectively based on nasal cultures. The difference between the two groups was statistically significant (p=0.002). Age-adjusted p-values were used due to the difference in the age distribution of the patient and control groups (p=0.008). Only one of the growing microorganisms was MRSA among the growing microorganisms in the patient group, and the remaining 11 were MSSA, while one MSSA growth was identified in the control group.

No growths were detected in the cultures of the samples taken from the right eye.

Only one MSSA growth was detected in the patient group in the cultures swabbed from the left eye. No growth was seen in the control group (Table 1).

No statistically significant associations were found between *C. albicans* growths in the mouth and antinuclear antibody (ANA) positivity, anti-Sjögren's syndrome A (SSA)

Table 1. Results of the cultures

	Control group (n=100)	Patient group (n=100)	p	Adjusted p*
Positive *C. albicans* growth in the mouth	17% (n=17)	37% (n=37)	**0.001**	**0.008**
Positive ***S. aureus*** growth in the nose	1% (n=1)	12% (n=12)	**0.002**	**0.023**
Positive ***S. aureus*** growth in the right eye	0% (n=0)	0% (n=0)		
Positive ***S. aureus*** growth in the left eye	0% (n=0)	1% (n=1)		

**: P-value adjusted for age, S. aureus: Stafilococcus aureus, C. albicans: Candida albicans*

positivity, anti-Sjögren's syndrome B (SSB) positivity, and rheumatoid factor (RF) positivity (Table 2).

No statistically significant associations were found between S. aureus growth in the nose and ANA positivity, Anti-SSA positivity, Anti-SSB positivity and RF positivity (Table 3).

Discussion

All mucosal membranes in the human body have mucosal barriers and defense systems that prevent the entry of microorganisms. Among these systems, saliva and its contents, in addition to contributing to the chewing, swallowing, and speaking functions, help remove bacteria from the mouth and prevent bacterial localization.[11,12] The sweat and sebaceous gland secretions from the skin are antimicrobial, while specific cells and the mucus they secrete in the respiratory tract form a defense barrier. If this barrier is defective, it facilitates the entry of microorganisms into the body and the development of infection.

Infections are among the main causes of morbidity and mortality in rheumatological diseases. The most common reason for presentation to the hospital has been reported as infections associated with rheumatoid arthritis, systemic lupus erythematosus, and other rheumatological diseases.[13]

The involvement of SS in the exocrine glands leads to dysfunction and decreased secretions, resulting in dry mouth, dry eyes, and dry skin. As a result of these changes in SS, the colonization of both normal flora and unassociated pathogenic bacteria increases, contributing to a higher frequency of infections.

Candidiasis is the most common fungal infection in the oral cavity and generally develops due to an overgrowth of Candida in the normal flora. The most common causative agent is *C. albicans*, although non-albicans species such as C. glabrata, C. tropicalis, C. krusei, and C. parapsilosis are becoming more common. Host-specific factors such as immunosuppression, inadequate nutrition, endocrine system diseases (such as diabetes mellitus and hypothyroidism), certain drug use, cancer, presence of prosthesis, changes in the amount of saliva, changed epithelial cellular layer, carbohydrate-rich nutrition, age, and inadequate oral hygiene all increase the sensitivity of a person to oral candidiasis.[14]

Table 2. Association between Candida growths and features of patients

	With Candida growth	Without Candida growth	p
Smoker	36.4% (n=8)	63.6% (n=14)	0.944
Non-smoker	37.2% (n=29)	62.8% (n=49)	
ANA positive	37.4% (n=34)	62.6% (n=57)	0.811
ANA negative	33.3% (n=3)	66.7% (n=6)	
Anti-SSA positive	41.6% (n=16)	59% (n=23)	0.505
Anti-SSA negative	34.4% (n=21)	65.6% (n=40)	
Anti-SSB positive	33.3% (n=3)	66.7% (n=6)	0.811
Anti-SSB negative	37.4% (n=34)	62.6% (n=57)	
RF positive	42.1% (n=8)	57.9% (n=11)	0.609
RF negative	35.8% (n=29)	64.2% (n=52)	

ANA: Antinuclear antibody, Anti-SSA: Sjögren syndrome antibody-A, Anti-SSB: Sjögren syndrome antibody-B, RF: Rheumatoid factor

Table 3. Association between *Stafilococcus* growths and features of patients

	With *S. aureus* growth	Without *S. aureus* growth	p
Smoker	22.7% (n=5)	77.3% (n=17)	0.080
Non-smoker	9% (n=7)	91% (n=71)	
ANA positive	12.1% (n=11)	87.9% (n=80)	0.931
ANA negative	11.1% (n=1)	88.9% (n=8)	
Anti-SSA positive	5.1% (n=2)	94.9% (n=37)	0.091
Anti-SSA negative	16.4% (n=10)	83.6% (n=51)	
RF positive	15.8% (n=3)	84.2% (n=16)	0.572
RF negative	11.1% (n=9)	88.9% (n=72)	

ANA: Antinuclear antibody, Anti-SSA: Sjögren syndrome antibody-A, Anti-SSB: Sjögren syndrome antibody-B, RF: Rheumatoid factor, S. aureus: Stafilococcus aureus

The oral mucosal culture growths of 16 patients with primary SS, 12 patients with secondary SS, and 14 patients with xerostomia were compared, revealing prevalence rates of oral *Candida* of 81.25%, 66.7%, and 71.4% in the primary SS group, secondary SS group, and xerostomia group, respectively, with no statistically significant difference found between the groups.[15] That study reported that dry mouth for any reason increased the presence of oral candida, while in the present study, oral *Candida* was identified in 37% and 17% of the primary SS patient group and the control group, respectively. This significant difference was attributed to the decreased saliva secretion and to the opportunistic overgrowth of *Candida*, normally present in the oral mucosa, due to dry mouth.

There have been few studies to date on nasal *S. aureus* carriers with primary SS. In a study comparing 57 patients with SS and 79 healthy controls, the prevalence of *S. aureus* in the nasal cultures was reported to be 20% and 12% in the primary SS group and the control group, respectively.[9] In the present study, on the other hand, the prevalence of *S. aureus* in the nasal cultures of the primary SS patients was 12%, compared to 1% in the control group. The differences in the results of the two studies may be attributable to the different growth media used. The culture samples were incubated in eosin methylene blue agar and Sabouraud dextrose agar in the previous study, whereas in the present study, samples were incubated in chromogenic agar and evaluated accordingly. The significant difference in the frequency of *S. aureus* growth in the present study in the nasal mucosa of the patient and control groups was thought to result from nasal dryness associated with primary SS and the resulting damage to the mucosal barrier.

Study Limitations

Some limitations of our study include the age difference between the patient and control groups, as healthy volunteers were included in the control group and did not have any underlying diseases.The patients in the SS group did not have other diseases that cause dry mouth, such as Graft-Versus-Host Disease or Wegener's granulomatosis. However, the age of the patient group may be a contributing factor to the dry mouth.

It is known that patients did not receive immunosuppressive treatment. However, no questions were asked to the patients about oral and dental hygiene. Additionally, the initial aim of the study did not include a comparison of demographic characteristics between the patient and control groups. For this reason, it was thought that the differences we found in the study were due to SS.

Conclusion

In conclusion, the prevalence of *S. aureus* in the nasal mucosa and *C. albicans* in the oral mucosa of primary SS patients was statistically significantly greater than in the healthy controls. One limitation of this study is its single-center design, suggesting that multi-national studies involving larger patient groups are required to accurately determine the increased prevalence of these microorganisms in the mucosa of primary SS patients.

Ethics

Ethics Committee Approval: This cross-sectional study was approved by the Ethics Board of the University of Erciyes University Faculty of Medicine, and was carried out in compliance with the rules of the World Medical Association Declaration of Helsinki (approval number: 2015/581, date: 25.12.2015).

Informed Consent: An informed consent form was obtained from all participants in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.B., T.A., S.K., Concept: T.A., Design: T.A., Data Collection and Processing: İ.B., T.A., S.K., Analysis or Interpretation: İ.B., T.A., S.K., Literature Search: İ.B., Writing: İ.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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