CLINICAL STUDY

AN EVALUATION OF THE NEED FOR MINOR SALIVA GLAND BIOPSY AND THE CLINICAL CORRELATION IN THE DIAGNOSIS OF PRIMARY SJOGREN SYNDROME

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SUMMARY

Aim: The aim of this study was to compare the rate of diagnostic contribution of the results of minor saliva gland biopsy taken for diagnosis of Sjögren syndrome (SS) and patient clinical findings and autoantibody test results.

Material and Methods: This retrospective study included patients who underwent serological tests with an initial diagnosis of SS and were referred to the Ear, Nose, and Throat Clinic for minor saliva gland biopsy. The demographic data, complaints, clinical findings, autoantibody test results and biopsy results of the patients were evaluated. The Chisholm-Mason classification was used to show lymphocyte infiltration in the saliva gland biopsy specimens. As all the cases were simple with a low complication risk, minor saliva gland biopsy was performed. Patients with secondary SS and those aged <18 years were excluded from the study.

Results: Saliva gland biopsy was performed on a total of 67 patients, comprising 58 (86.5%) females and 9 (13.5%) males with a mean age of 48.2 years (range, 21-78 years). In 3 cases the biopsies were unsuccessful, and of the 64 biopsies with successful sampling, 19 (29.6%) were reported as consistent with primary SS. The complaints of the patients were dry mouth (85.9%), dry eyes (73.4%), arthralgia (23.4%), and pain and swelling in the saliva gland (17.1%). Of the 19 (29.6%) patients with pathology reported as consistent with primary SS, positivity in at least one of the autoantibody tests (ANA, RF, SS-A, SS-B) was determined in 15 (23.4%) patients. The diagnosis of SS was made with saliva gland biopsy in 4 (6.2%) patients determined with negative autoantibody tests. Temporary marginal nerve paresis due to local anaesthesia was observed in only one patient, and no permanent complications developed in any patient.

Conclusion: Minor saliva gland biopsy is a method that can be safely and easily applied under office conditions. In the diagnosis of primary Sjögren syndrome, it is recommended that the diagnosis is confirmed with minor saliva gland biopsy when clinical findings are present.

Keywords: Chisholm-Mason classification, Minör saliva gland biopsy, minor saliva gland biopsy, Sjögren Syndrome

PRİMER SJÖGREN SENDROMU TANISINDA MİNÖR TÜKRÜK BEZİ BİYOPSİSİN GEREKLİLİĞİ VE KLİNİK KORELASYONUNUN DEĞERLENDİRİLMESİ

ÖZET

Amaç: Sjögren sendromu (SS) tanısı için alınan minör tükrük bezi biyopsi sonuçlarının, hasta klinik bulguları ve otoantikor test sonuçları ile birlikte tanıya katkı oranının karşılaştırılmasıdır.

Gereç ve Yöntem: Bu çalışma kapsamında SS ön tanısı ile serolojik testler uygulanan ve kulak burun boğaz kliniğine yönlendirilerek minör tükrük bezi biyopsisi yapılan hastalar retrospektif olarak çalışmaya dahil edildi. Hastaların demografik verileri, şikayetleri, klinik bulguları, otoantikor testleri ve biyopsi sonuçları değerlendirildi. Tükrük bezi biyopsi spesimen lenfosit infiltrasyonunu göstermek için Chisholm-Mason sınıflaması kullanıldı. Hastaların tümüne kolay ve komplikasyon riski düşük olması nedeniyle alt dudak minör tükrük bezi biyopsisi yapıldı. Sekonder SS olan hastalar ve 18 yaş altı hastalar çalışma dışı bırakıldı.

Bulgular: Tükrük bezi biyopsisi yapılan 9'u (%13.5) erkek, 58'i (%86.5) kadın ve yaş ortalaması 48.2 yıl (min-max; 21-78) olan toplam 67 hasta çalışmaya dahil edildi. Üç biyopsi tükrük bezi içermediğinden başarısız olarak kabul edildi, başarılı örnekleme yapılan 64 biyopsiden 19'u (%29.6) primer SS ile uyumlu olarak raporlandı. Hastaların şikayetleri ağız kuruluğu (%85.9), göz kuruluğu (%73.4), artralji (%23.4), tükrük bezi ağrısı ve şişmesi (%17.1) idi. Patolojisi primer SS ile uyumlu olarak raporlanan 19 (%29.6) hastanın 15'inde (%23.4) otoantikor testlerinin en az birinde (ANA, RF, SS-A, SS-B) pozitiflik saptandı. Otoantikor testleri negatif saptanan 4 (%6.2) hastaya tükrük bezi biyopsisi ile SS tanısı konuldu. Sadece bir hastada lokal anesteziye bağlı geçici marjinal sinir parezisi gözlenirken, 23 hiçbir hastada kalıcı komplikasyon gelişmedi.

Sonuç: Minör tükrük bezi biyopsisi ofis şartlarında güvenilir ve kolay uygulanabilir bir yöntemdir. Primer SS tanısında klinik bulgular varlığında minör tükürük bezi biyopsi ile tanının doğrulanması önerilmektedir.

Anahtar Sözcükler: Chisholm-Mason sınıflandırması, alt dudak tükrük bezi biyopsisi,minör tükrük bezi biyopsisi,Sjögren Sendromu

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INTRODUCTION

Sjögren syndrome (SS) is a chronic autoimmune disease that develops with the effect of environmental factors on the basis of genetic predisposition, is characterised by focal lymphocytic infiltrations mainly in the exocrine glands (tear glands and saliva glands), is less accompanied by systemic symptoms and leads to xerostomia and/or xerophthalmia[1]. An average of 5.8/100,000 diagnoses are made per year in the USA, and the majority of these are female (F/M: 9/1)[2]. There is no single clinical criterion or laboratory test that is sufficient alone for SS diagnosis. The 2002 American European Consensus Group (AECG) based SS classification criteria on the following: 1) dry eye symptoms, 2) dry mouth symptoms 3) dry eye findings (Abnormalities in the Schirmer test or Rose-Bengal test), 4) saliva gland function tests (abnormal flow rate, scintigraphy or sialogram), 5) minor saliva gland biopsy (focus score ≥1), 6) autoantibody positivity (anti-SS-A or anti-SS-B antibody). For SS classification of a patient, at least four of these six criteria must be positive. There must be one of the histopathological or serological criteria[3]. The classification criteria published by the American Rheumatology College (ACR) Sjögren International Clinics Collaboration Committee (SICCA) are based on objective findings. According to the 2012 ACR criteria based on the parameters of serological tests (anti-SSA and/or anti-SS-B, or positive rheumatoid factor, and ANA ≥1/320), ocular staining score ≥3, and focal lymphocytic sialadenitis (focus score ≥1/ 4 mm2), patients with at least two of these are classified as SS[4].

Despite the consensus on the methods used to show eye involvement in SS, consensus has not been achieved in the determination of dry mouth. Scintigraphy, sialography, saliva flow rate (stimulated/unstimulated), and minor saliva gland biopsy are the diagnostic tests used in the evaluation of saliva gland involvement.

Histopathological classification in SS was defined by Chisholm and Mason[5], as grading between 0 and 4. According to this classification, the grades are defined as 0: no inflammatory infiltration, 1: mild infiltration, 2: moderate level lymphocytic infiltration but no focus, 3: one focus, 4: more than one focus[5].

The aim of this study was to show the importance of minor saliva gland biopsy in SS diagnosis by evaluating the relationship between minor saliva gland biopsy results and serological characterstics in patients undergoing minor saliva gland biopsy with an initial diagnosis of SS.

MATERIAL and METHODS

Approval for this retrospective study was granted by the Local Ethics Committee (decision no: 2023-182, dated: 14/06/2023). The study included patients who underwent serological tests with an initial diagnosis of SS between November 2022 and May 2023, were referred from Rheumatology Clinic to the Ear, Nose, and Throat Clinic for minor salivary gland biopsy. The demographic data of age and gender, anti-nuclear antibody (ANA), rheumatoid factor (RF), anti-SS-A (Ro), and anti-SS-B (La) results were obtained from the hospital electronic records system. As all the cases were simple with a low complication risk, minor saliva gland biopsy was performed.

Under local anesthetic, a fish mouth incision, approximately 3cm in length, was made to the mucosal surface of the lower lip, parallel to the vermilion line and excision was performed including at least 10 minor saliva glands. Biopsies containing at least 4 lobules and in each area of 4mm2, the presence of at least two lymphoid aggregates containing 50 or more lymphocytes were accepted as histopathological diagnostic criteria for SS (Chisholm and Mason classification: 5). Cases not meeting these criteria, containing periductal and /or interlobular fibrosis and/or acinar atrophy together with lymphocytic/lymphoplasmocyte inflammatory cell infiltration at a generally mild level, were accepted as chronic non-specific sialadenitis. The results were evaluated by analyzing the demographic, clinical, histopathological, and serological characteristics of the patients. For the frequency of the clinical and laboratory findings, the percentage rates were examined.

Patients were excluded from the study if they had secondary SS, were aged <18 years, pathology results are not appropriate for diagnosis or had a condition that would make evaluation of the salivary gland biopsy difficult (head and neck radiation, hepatitis C infection,

HIV infection, sarcoidosis, amyloidosis and graft vs host disease).

Statistical Analysis Data obtained in the study were analyzed statistically using SPSS vn. 22.0 software (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA). Quantitative variables were stated as median, minimum and maximum values. The arithmetic mean and standard deviation values were used as the measure of central tendency according to the distribution characteristics of the variables.

RESULTS

Evaluations were made of 67 patients with suspected SS who were evaluated by a rheumatology specialist, underwent auto-antibody tests and were then referred to the Ear, Nose, and Throat Outpatient clinic for minor saliva gland biopsy. The patients comprised 58 (86.5%) females and 9 (13.5%) males with a mean age of 48.2 years (range, 21-78 years). In 3 cases the biopsies were unsuccessful, and of the 64 (95.5%) biopsies with successful sampling, 45 (70,3%) were reported as normal saliva gland pathology, 19 (29.6%) were reported as consistent with primary SS. Although minor salivary gland biopsy was negative in 12 (26%) of the remaining 45 (70.3%) patients, the diagnosis of SS was confirmed on the basis of positive serological tests. Of the 12 patients, 7 (15%) were positive for anti-SS-A, 3 (7%) were positive for anti-SS-B, and 2 (4%) were positive for both anti-SS-A and anti-SS-B. No patient with negative biopsy results exhibited positivity for RF. ANA positivity was observed in 17 patients, while positivity for anti-SS-A and anti-SS-B was noted in 5 (16%) of these patients. The complaints of the all patients were dry mouth (85.9%), dry eyes (73.4%), arthralgia (23.4%), and pain and swelling in the saliva gland (17.1%). Of the 19 (29.6%) patients with pathology reported as consistent with primary SS, positivity in the autoantibody tests (ANA, RF, SS-A, SS-B) was determined in 15 (23.4%) patients. ANA positivity was determined in 10 (52.6%), anti-SS-A positivity in 12 (63.1%), anti-SS-B positivity in 2 (10.5%), and RF autoantibody test positivity was not seen in any of these patients with a pathology result consistent with primary SS.

The diagnosis of SS was made with saliva gland biopsy in 4 (6.2%) patients determined with negative autoantibody tests (Table 1). All the patients with negative auto-antibody tests were aged <40 years. The Chisholm and Mason focal score was 3 in 2 of the patients with negative autoantibody tests and 2 in the other 2 patients. In the other 15 patients with positive pathology, the focal score was 1 in 4 patients, 3 in 2 patients, 2 in 8 patients, and 4 in 1 patient (Table 2). Temporary marginal nerve paresis due to local anesthesia was observed in only one patient, and no permanent complications developed in any patient.

Table 1: The postoperative focal activity scores of the patients with negative autoantibody tests (MSGB: minor saliva gland biopsy)

Patient	Age	Gender	Operation	POST-OP PAT. FOCAL SCORE	ANA	RF	RO/SS-A	LA/SS-B
1	36	F	MSGB	3	-	-	-	-
2	29	F	MSGB	2	-	-	-	-
3	34	F	MSGB	2	-	-	-	-
4	30	F	MSGB	3	-	-	-	-

Table 2: The postoperative focal activity scores of the patients with positive autoantibody tests (MSGB: minor saliva gland biopsy)

Patient	Age	Gender	Operation	POST-OP PAT. FOCAL SCOR	ANA	RF	RO/SS-A	LA/SS-B
1	48	F	MSGB	1	-	-	+	-
2	53	F	MSGB	2	+	-	-	-
3	55	F	MSGB	1	+	-	-	-
4	41	F	MSGB	3	+	-	+	-
5	39	F	MSGB	2	+	-	+	-
6	57	F	MSGB	2	+	-	+	-
7	37	F	MSGB	2	-	-	+	+
8	61	F	MSGB	3	+	-	+	-
9	43	F	MSGB	2	-	-	+	-
10	47	F	MSGB	4	-	-	+	-
11	46	F	MSGB	1	+	-	+	-
12	51	F	MSGB	2	-	-	+	-
13	38	F	MSGB	2	+	-	+	-
14	43	F	MSGB	1	+	-	-	-
15	48	F	MSGB	2	+	-	+	+

DISCUSSION

In this study that investigated the diagnostic benefit of minor saliva gland biopsy (MSGB), the biopsy samples taken from 95.6% of the patients with suspected primary SS were found to be sufficient for diagnostic purposes. The biopsy result of 29.6% of the patients were positive, and the auto-antibodies of 78.9% of these patients were also seen to be positive. In 6.2% of the patients who had auto-antibodies negativity, the diagnosis of primary SS was made at the rate of 100% with minor saliva gland biopsy. These findings indicate the clinical benefit of saliva gland biopsy in SS diagnosis with high sensitivity and good predictive value.

When this invasive procedure, which is diagnostically reliable, was examined in respect of complications, there was seen to be temporary numbness in 1.5% of the patients. This complaint, which was seen due to the local

anesthesia, completely recovered after 6-8 hours. No permanent local surgical complication was seen in any patient, which was consistent with similar studies conducted on MSGB complications[6].

In the diagnosis of primary SS, pancytopenia, increased sedimentation rate, and hypergammaglobulinemia may be seen in the laboratory tests. Of the SS autoimmune markers, ANA has been reported to be determined positive at the rate of 59-85%, RF at 36-74%, anti- SS-A at 33-74%, and anti-SS-B at 23-52%[7,8].

Significantly different from the data in literature, RF was not determined in any patients who were pathologically diagnosed with primary SS in current study. The positivity rates of ANA and anti-SS-A in the patients diagnosed in our center were found to be similar to the rates in previous studies, but anti-SS-B positivity (10.5%) was determined at a lower rate than in previous studies. In addition to these, the relationship between auto-antibody tests and pathological grade was not evaluated in the current study.

Many studies that have investigated the diagnostic benefit of MSGB have shown limited statistical significance and the number of patients has not been at a sufficient level. In a meta-analysis of 8 studies by Lee et al., MSGB was found to have 75.5% sensitivity and 90.7% specificity in groups of 583 patients and 627 control subjects[9]. Giovelli et al. evaluated 216 MSGBs in patients with glandular dysfunction and negative serology, and reported 86.57% sensitivity and 97.43% specificity[10]. In a study by Goel et al. of 47 patients with anti-SS- A negativity, the diagnosis of SS was made with MSGB in 31.9%[11]. When these studies are evaluated together, it can be seen that MSGB is a simple and reliable tool that is helpful in SS diagnosis, and to a great extent the findings are consistent with the current study.

Clinical suspicion and objective evaluation methods are used in the diagnosis of SS, which is the common view of the American European Consensus Group (AECG), and the ACR SICCA. The most important of these objective methods is MSGB.

In 4 of the 64 patients with negative serologic tests results in the current study, MSGB was performed and primary SS was diagnosed in 100%. This shows that this invasive procedure that requires an ENT clinical approach should be applied to patients with negative autoantibodies, especially those with dry mouth and dry eye symptoms.

The main symptoms in the clinical manifestations of SS are dryness of the eyes and mouth. In a study of 114 patients by Lee et al., dry mouth was determined in 94% and dry eyes in 92%[12]. In another study, dry mouth was determined at the rate of 100%, and dry eyes at 97.5%[13]. In the current study, dry mouth was found in 85.9% of cases and dry eyes in 73.4%.

When the 4 patients diagnosed with primary SS from MSGB were examined, all were female patients aged <40 years. Other common characteristics were the complaints of dry mouth and dry eyes. MSGB is a diagnostic method that can be comfortably performed under office conditions with a low complication expectation, especially for young female patients with complaints such as clinically evident dry mouth and dry eyes.

The incidence of lymphoma is increased in SS patients compared to the general population. Histopathological evaluation of salivary gland biopsies needs to be more detailed and careful with regard to lymphoma risk minor salivary gland biopsy, which allows determination of the presence and number of ectopic germinal centers, an important criterion for lymphoma, is a high-yield diagnostic method in this regard[14].

In a study, Jonsson et al. reported that the presence or absence of germinal center-like structures in the biopsy materials of patients diagnosed with primary SS could be used to determine the subgroups that could help determine the serological profiles of the patients and therefore predict the prognosis[14].

In the current study, only the focus scores were examined and the presence or absence of germinal center-like structures was not examined. It can be recommended that further more comprehensive, prospective studies are conducted on this subject.

Limitations of this study could be said to be the low number of patients diagnosed with primary SS from biopsy, and that no comparison was made between pathology and the titer values of the seroimmunological tests.

CONCLUSION

The results of this study showed that minor saliva gland biopsy is a reliable and easily applicable method, and especially in young patients with negativity determined in the autoimmune tests but with clinically suspected SS, the diagnosis should be confirmed with minor saliva gland biopsy.

REFERENCES

1. Ramos-Casals M, Tzioufas AG, Font J. Primary Sjögren's syndrome: new clinical and therapeutic concepts. Ann Rheum Dis. 2005;64(3):347-354.
2. Maciel G, Crowson CS, Matteson EL, Cornec D. Incidence and mortality of physician-diagnosed primary Sjögren syndrome: time trends over a 40-year period in a population-based US cohort. Mayo Clin Proc. 2017;92(5):734-743.
3. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N, Weisman MH; European Study Group on Classification Criteria for Sjögren's Syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002 Jun;61(6):554-8. doi: 10.1136/ard.61.6.554.
4. Shiboski SC, Shiboski CH, Criswell L, Baer A, Challacombe S, Lanfranchi H, Schiødt M, Umehara H, Vivino F, Zhao Y, Dong Y, Greenspan D, Heidenreich AM, Helin P, Kirkham B, Kitagawa K, Larkin G, Li M, Lietman T, Lindegaard J, McNamara N, Sack K, Shirlaw P, Sugai S, Vollenweider C, Whitcher J, Wu A, Zhang S, Zhang W, Greenspan J, Daniels T; Sjögren's International Collaborative Clinical Alliance (SICCA) Research Groups. 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 Apr;64(4):475-87. doi: 10.1002/acr.21591.
5. Chisholm DM, Mason DK. Labial salivary gland biopsy in Sjögren's disease. J Clin Pathol. 1968 Sep;21(5):656-60. doi: 10.1136/jcp.21.5.656.
6. Varoni EM, Villani G, Lombardi N, Pispero A, Lodi G, Sardella A, Uglietti D. Local complications associated with labial salivary gland biopsy for diagnosis of Sjögren's Syndrome: A retrospective cohort study. J Clin Exp Dent. 2020 Aug 1;12(8):e713- e718. doi: 10.4317/jced.56562.
7. Bournia V-K, Vlachoyiannopoulos PG. Subgroups of Sjögren syndrome patients according to serological profiles. Journal of autoimmunity. 2012;39(1-2):15-26.
8. Harley JB, Alexander EL, Bias WB, Fox OF, Provost TT, Reichlin M, Yamagata H, Arnett FC. Anti-Ro (SS-A) and anti-La (SS-B) in patients with Sjögren's syndrome. Arthritis Rheum. 1986 Feb;29(2):196-206. doi: 10.1002/art.1780290207.
9. Lee, Y.H. & Song, G.S. A Meta-analysis of the diagnostic value of minor salivary gland biopsy for primary Sjogren's syndrome. Ann Rheum Dis 74: 815.2-815, 2015
10. Giovelli RA, Santos MC, Serrano ÉV, Valim V. Clinical characteristics and biopsy accuracy in suspected cases of Sjögren's syndrome referred to labial salivary gland biopsy. BMC Musculoskelet Disord. 2015 Feb 15;16:30. doi: 10.1186/s12891-015- 0482-9.
11. Goel RR, Jeranko M, Jones L, Bishnoi A, Meysami A. Diagnostic Utility of Minor Salivary Gland Biopsy for Primary Sjögren Syndrome in Patients With Negative Anti-SSA Antibodies. Cureus. 2023 Sep 29;15(9):e46207. doi: 10.7759/cureus.46207.
12. Lee KA, Kim KW, Kim BM, Won JY, Kim HA, Moon HW, Kim HR, Lee SH. Clinical and diagnostic significance of serum immunoglobulin A rheumatoid factor in primary Sjogren's syndrome. Clin Oral Investig. 2019 Mar;23(3):1415-1423. doi: 10.1007/s00784-018-2545-4. Epub 2018 Jul 21.
13. Limon, M., Tezcan, D., Gülcemal, S., YILMAZ, S., & Akdam, N. (2019). Primer Sjögren sendromunda serolojik tetkiklerin tükrük bezi biyopsi derecesi ve klinik ilişkisinin değerlendirilmesi.Journal of Contemporary Medicine, 9(4), 391-394.
14. Theander E, Vasaitis L, Baecklund E, Nordmark G, Warfvinge G, Liedholm R, Brokstad K, Jonsson R, Jonsson MV. Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjögren's syndrome. Ann Rheum Dis. 2011 Aug;70(8):1363-8. doi: 10.1136/ard.2010.144782.