Prevalence and Predictors of Sjögren's Syndrome in Patients with Burning Mouth Symptoms

Young Chan Lee, MD, PhD
Professor
Department of Otolaryngology-Head & Neck Surgery
Kyung Hee University
School of Medicine
Seoul, Republic of Korea

Ran Song, MD, PhD
Professor
Division of Rheumatology
Department of Internal Medicine
Kyung Hee University
School of Medicine
Seoul, Republic of Korea

You-Jung Yang, MD, PhD
Professor
Department of Nuclear Medicine
Kyung Hee University
School of Medicine
Seoul, Republic of Korea

Young-Gyu Eun, MD, PhD
Professor
Department of Otolaryngology-Head & Neck Surgery
Kyung Hee University
School of Medicine
Seoul, Republic of Korea

Correspondence to:
Dr Young-Gyu Eun
Department of Otolaryngology-Head and Neck Surgery
Kyung Hee University School of Medicine
Seoul, Korea
#1 Hoegi-dong, dongdaemun-gu
Seoul 130-702, Korea
Phone: 82-2-958-8471
Fax: 82-2-958-8470
Email: ygeun@hanmail.net

Aims: To investigate the prevalence and predictive factors of Sjögren's syndrome (SS) in a cohort of patients with burning mouth symptoms. **Methods:** A total of 125 patients with burning mouth symptoms were enrolled in a prospective study and assessed for the presence of SS. The severity of oral symptoms was evaluated by using questionnaires. Salivary flow rates and salivary scintigraphy were used to evaluate salivary function. Patient laboratory work-ups were reviewed, and SS was diagnosed by a rheumatologist based on the American-European Consensus Group criteria. The differences between the SS patient group and the non-SS patient group were analyzed with chi-square test or *t* test. **Results:** A total of 12 of the 125 enrolled patients (9.5%) had a positive autoimmune antibody test, and 6 (4.8% of the entire cohort) had SS (4 [3.2%] primary and 2 [1.6%] secondary). Patients with SS exhibited significantly decreased hemoglobin levels, an increased erythrocyte sedimentation rate, and an increased prevalence of autoantibody positive results compared to non-SS patients. Salivary scintigraphy showed that the uptake ratio of the submandibular gland in SS patients was decreased significantly. **Conclusion:** The prevalence of SS in patients with burning mouth symptoms was 4.8%. Therefore, clinicians who treat patients with burning mouth symptoms should evaluate laboratory findings and salivary functions to identify patients with SS. *J Oral Facial Pain Headache 2018;32:91–96. doi: 10.11607/ofph.1891*

Keywords: *autoantibodies, burning mouth syndrome, salivary gland, Sjögren's syndrome*

Burning mouth syndrome (BMS) is characterized by a burning sensation in clinically normal oral mucosa.[1] The International Headache Society defines primary BMS as "an intraoral burning sensation for which no medical or dental cause can be found."[2] The oral burning sensation may be primary or secondary to systemic or local factors. Some authors refer to secondary BMS as a burning sensation with an identifiable cause[3,4]; however, strictly speaking, it is important to distinguish secondary BMS from primary BMS. Furthermore, several local and systemic factors that can cause a burning sensation in the oral mucosa should be excluded. In addition, there are numerous conditions associated with BMS, including psychiatric, endocrine, immunologic, infectious, and iatrogenic causes, as well as autoimmune rheumatologic disorders, such as Sjögren's syndrome (SS) and systemic lupus erythematosus.[5]

SS is a well-known autoimmune disease characterized by focal lymphocytic infiltration and destruction of exocrine glands, resulting in sicca syndrome. When SS presents by itself, it is referred to as primary SS, and when it occurs simultaneously with other autoimmune diseases, it is referred to as secondary SS. SS has organ-specific characteristics, with xerostomia (subjective symptom) and salivary gland hypofunction (objective sign) two well-reported oral manifestations of SS.[6] Xerostomia is also a common symptom associated with BMS.[7,8] Several studies have suggested that decreased unstimulated salivary flow rate (SFR) is correlated with the etiopathogenesis of BMS in terms of decreased mucosal lubrication and protection and secondary fungal infection.[9,10] On the other hand, SS-associated neuropathies

Table 1 Demographics of Enrolled Patients with Burning Mouth Symptoms

Total no.	125
Age (y), mean ± SD	61.90 ± 12.73
Gender (M/F), n	30/95
HTN, n (%)	42 (33.6)
DM, n (%)	22 (17.6)
Antidepressant medication, n (%)	13 (10.4)
Current smoker, n (%)	15 (12.0)
Denture wearer, n (%)	21 (16.8)

SD = standard deviation; HTN = hypertension; DM = diabetes mellitus.

may also manifest as glossodynia and oral burning. Furthermore, the occurence of peripheral nervous system manifestations in SS is relatively common, ranging from 5% to 20%.[11] Therefore, early-stage SS can be misdiagnosed as BMS in practice. However, there have been no studies that have evaluated the prevalence of SS among patients complaining of burning mouth symptoms. Although SS is a benign and non–life-threatening disease, patients should be diagnosed and treated appropriately to improve quality of life (QoL) and prevent complications. Therefore, the aim of this study was to investigate the prevalence and predictive factors of SS in a cohort of patients with burning mouth symptoms.

Materials and Methods

The present study prospectively enrolled 125 consecutive Korean patients with oral burning symptoms who visited the School of Medicine's outpatient department from July 2013 to July 2016. The inclusion criteria of this study were based on the BMS definition by the International Classification of Headaches.[12] Patients presenting with burning pain who had other sources of intraoral mucosal lesions (eg, oral candidiasis, lichenoid lesion, or mucositis) or a history of previous head and neck cancer or radiotherapy were excluded. Patients with known histories of autoimmune disease, including SS, were also excluded. The study was approved by the Institutional Review Board of Kyung Hee University Hospital at Gangdong. Informed consent was obtained from all participants included in the study.

The intensity of oral pain–related symptoms (eg, hypoesthesia, dry mouth, oral pain, myalgia headache, tingling sensation, and hyposmia) in enrolled patients was assessed by the patients on a visual analog scale (VAS) ranging from 0 to 10, with 0 representing asymptomatic and 10 representing the most severe symptom. The 14-item Oral Health Impact Profile (OHIP-14) in Korean was used to evaluate the patients' QoL.

A medical history, including data related to underlying diseases, smoking history, use of dentures, and current medications, including antidepressants, were obtained for all patients. Patients also had a blood test assessing hemoglobin, glucose levels, serum iron and amylase, serum vitamin B12, serum folate, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and autoimmune antibodies (eg, antinuclear antibodies [ANA] and SSA/Ro and SSB/La antibodies). SFR was measured in all patients, and technetium (Tc)-99m pertechnetate salivary scintigraphy was performed for objective evaluation of salivary gland function.

SFRs for the unstimulated and stimulated states were evaluated with the methods for collecting saliva, as previously described.[13] Briefly, whole saliva was collected when patients were in a relaxed state at least 1 hour after a meal. In order to collect saliva, patients were asked to spit into a test tube for 5 minutes. To stimulate salivation, sugar-free, lemon-flavored candy was used.

For salivary scintigraphy, patients were administered 370 MBq Tc-99m sodium pertechnetate intravenously and then imaged with a variable angle dual head gamma camera (Philips Forte, Philips Medical Systems) using low-energy and high-sensitivity collimators. Images were acquired at 5, 15, and 30 minutes and again after administration of oral sialagogue and were digitally recorded in a 128 × 128 matrix. During the examination, the patient's head was fixed, and they were asked not to swallow.

To analyze scintigraphy images, regions of interest (ROI) were manually drawn around each of the four major salivary glands. The following functional parameters were calculated for both pairs of parotid and submandibular glands based on the ROI counts: uptake ratio (UR), maximum accumulation (MA), and maximum secretion (MS). UR was defined as the salivary gland count – the background count; MA (%) was calculated as (maximum activity before stimulation – initial activity 5 minutes after radiotracer injection) / maximum activity before stimulation × 100; and MS (%) was calculated as (maximum activity prior to stimulation – activity after stimulation) / peak activity before stimulation × 100.

The diagnosis of SS was made by a rheumatologist based on the American-European Consensus Group criteria.[14] All SS patients satisfied at least four of the six criteria (including objective criteria, oral symptoms, and ocular symptoms) and had either a positive anti 60-kD Ro test or positive pathologic test of the salivary gland.

Statistical Analysis

Statistical analysis was performed using PASW 18 (SPSS Inc). The differences between the SS patient group and non-SS patient group were analyzed with

Table 2 Comparison of Demographics and Laboratory Findings Between Patients With and Without Sjögren's Syndrome (SS)

	Range of normal values	SS patients (n = 6)	Non-SS patients (n = 119)	*P* value
Age (y), mean ± SD		68.17 ± 9.98	61.59 ± 12.81	.218
Gender (F), n (%)		6 (100)	89 (74.8%)	.334
Hemoglobin (g/dL), mean ± SD	12.0–16.0	11.73 ± 1.97	13.38 ± 1.36	.006
ESR (mm/h), mean ± SD	< 20	37.16 ± 18.14	17.04 ± 12.56	< .001
Glucose (mg/dL), mean ± SD	< 125	114.83 ± 26.58	115.28 ± 30.07	.972
CRP (mg/dL), mean ± SD	0–0.5	0.16 ± 0.12	0.13 ± 0.14	.610
Amylase (U/L), mean ± SD	22–80	71.33 ± 30.01	63.78 ± 26.43	.506
Iron (ug/dL), mean ± SD	60–180	79.83 ± 29.53	95.59 ± 51.03	.458
Vitamin B12 (pg/mL), mean ± SD	187–883	3,070.66 ± 6,288.10	920.06 ± 874.69	.441
Folate (ng/mL), mean ± SD	3.1–20.5	15.66 ± 5.00	15.16 ± 12.63	.923
ANA (+), n (%)	Negative	6 (100.0)	7 (5.8%)	< .001
Anti-SS-A/Ro (+), n (%)	Negative	3 (50.0)	0 (0.0%)	< .001
Anti-SS-B/La (+), n (%)	Negative	1 (16.6)	0 (0.0%)	.008

SD = standard deviation; F = female; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ANA = antinuclear antibodies.

Table 3 Comparison of Subjective Symptoms and Quality of Life Between Patients With and Without Sjögren's Syndrome (SS) as Determined by Mean ± Standard Deviation Score on 0–10 Visual Analog Scale (VAS) and OHIP-14 Questionnaire

	SS patients	Non-SS patients	*P* value
VAS			
Hypoesthesia	2.66 ± 3.66	3.17 ± 2.86	.679
Dry mouth	6.50 ± 3.61	4.90 ± 3.38	.263
Oral pain	5.50 ± 3.67	4.99 ± 3.13	.701
Myalgia	3.33 ± 3.01	2.72 ± 2.67	.592
Headache	2.50 ± 2.42	2.66 ± 2.70	.885
Tingling sensation	5.66 ± 4.08	3.26 ± 3.08	.070
Hyposmia	2.83 ± 3.06	2.37 ± 2.55	.673
OHIP-14 total (maximum total score = 56)	35.66 ± 7.39	38.58 ± 11.43	.539

OHIP = Oral Health Impact Profile.

the χ^2 test, and continuous variables were analyzed with *t* tests. Results were expressed as mean ± standard deviation (SD). *P* values < .05 were defined as statistically significant.

Results

The demographic characteristics of the 125 patients with symptoms of BMS who were enrolled in the prospective study are summarized in Table 1. The mean ± SD patient age was 61.90 ± 12.73 years. The majority (76.0%) of study participants were women, 10.4% were taking antidepressant medication, 12.0% were current smokers, and 16.8% used dentures. From the salivary scintigraphy and SFR tests, 6 patients (4.8%) were diagnosed as having SS. Of these 6 patients, 4 (3.2% of the whole sample) were considered to have primary SS and 2 (1.6% of the whole sample) secondary SS. One of these patients was also diagnosed with systemic lupus erythematous.

Table 2 shows the comparison of demographic and laboratory findings between the SS and non-SS patient groups. There was no significant difference in age or sex between the two groups. Hemoglobin (*P* = .006) and ESR (*P* < .001) values were significantly different between the two groups; specifically, hemoglobin values of SS patients were lower than those of non-SS patients, and ESR values of SS patients were higher than those of non-SS patients. Positive serum ANA (*P* < .001), anti-SS-A/Ro antibody (*P* < .001), and anti-SS-B/La antibody (*P* = .008) values were higher in the SS patient group. There were no significant differences between groups with respect to glucose, CRP, amylase, iron, vitamin B12, and folate levels. There were also no significant differences for all subjective symptom scores (VAS) or for total OHIP-14 score between the SS and non-SS patient groups (Table 3).

Finally, salivary function was assessed by SFR and salivary scintigraphy. There was no significant difference in mean unstimulated and stimulated

Table 4 Comparison of Salivary Function Assessed by Salivary Flow Rate (SFR) and Salivary Scintigraphy Between Patients With and Without Sjögren's Syndrome (SS)

	SS patients	Non-SS patients	*P* value
SFR			
Unstimulated (mL/min)	0.88 ± 0.75	1.31 ± 3.02	.749
Stimulated (mL/min)	3.74 ± 2.14	5.74 ± 4.09	.284
UR			
Parotid	1.15 ± 0.14	1.18 ± 0.19	.675
Submandibular	1.92 ± 0.14	2.43 ± 0.53	< .001
MA			
Parotid (%)	24.46 ± 5.74	22.33 ± 8.58	.589
Submandibular (%)	11.86 ± 8.96	14.07 ± 8.40	.579
MS			
Parotid (%)	35.66 ± 6.54	23.41 ± 14.33	.064
Submandibular (%)	25.55 ± 16.29	27.69 ± 11.52	.703

All data are reported as mean ± standard deviation. UR = uptake ratio; MA = maximum accumulation; MS = maximum secretion.

SFRs between the two groups (Table 4). According to the salivary function results of the parotid and submandibular glands as determined by scintigraphy, the UR of the submandibular glands in SS patients was significantly decreased compared to non-SS patients ($P < .001$), but there was no statistically significant difference between the two groups in the UR of the parotid, MA of the parotid and submandibular glands, or MS of the parotid and submandibular glands (Table 4).

Discussion

BMS is a complex disease entity associated with complaints of symptoms of burning, stinging, or pain in the oral cavity—including the tongue and lip mucosa—despite a normal mucosa. Although the etiology of BMS is unknown, multiple conditions of local, systemic, and psychological origins have been proposed.[5,7,8] BMS patients often have xerostomia, which is a subjective symptom. Although the relationship between BMS and hyposalivation (objectively decreased salivary function) is controversial, several studies have demonstrated a decreased unstimulated SFR in BMS patients.[10,15]

SS is an autoimmune disease that affects oral, ocular, and other extraglandular exocrine systems and often has a negative impact on patient QoL. Decreased salivary flow due to SS can cause xerostomia or sense of a burning mouth in individuals. Therefore, it is critical to perform diagnostic blood tests including autoantibodies (ANA, Anti-SSA/RO, and Anti-SSB/LA) to exclude SS as a cause of burning in the mouth. However, the prevalence of SS and clinical features suggestive of SS in patients with burning mouth symptoms have been unclear.

In this prospective study, the prevalence of SS in patients with burning mouth symptoms was 4.8%. In addition, patients with SS had decreased hemoglobin levels, an elevated ESR, and hypofunctional submandibular glands.

In general, the diagnosis of SS should be based on clinical and laboratory findings, but these are not specific for SS. As such, SS is difficult to diagnose due to the complexity of clinical symptoms and the possibility of concurrent symptoms from other autoimmune diseases in secondary SS. Indeed, several reports have described a frequent delay in the diagnosis of SS that can range from 3 to 11 years.[16,17] Although dry mouth is a characteristic symptom of SS, there is a wide range of variation in the initial clinical manifestation, which is often unspecific and vague, leading to delayed diagnosis.[16] In the present study, six patients with burning mouth symptoms were newly diagnosed with SS through blood tests and salivary scintigraphy.

Ramos-Casals et al analyzed the prevalence and characteristics of different hematologic features in a large cohort of Spanish patients with primary SS[18] and found hemocytopenia in one-third of the patients; anemia (22%), leukopenia (16%), and thrombocytopenia (13%) were the most common. Furthermore, hypergammaglobulinemia and an elevated ESR were found in 22% of the patients, which were closely associated with autoimmune markers such as rheumatoid factor, anti-Ro/SS-A, and anti-La/SS-B. These results are consistent with the present findings, where the mean value of hemoglobin was decreased and the ESR was elevated in patients with SS compared to patients without SS. Hemocytopenia is the most common anemia in chronic disease and is associated with systemic involvement and circulating antibodies, which may result in a condition of generalized inflammation rather than disease limited to glandular sites.[19] ESR correlates closely with the percentage of circulating gammaglobulins and is frequently elevated in primary SS, while serum CRP levels are usually

normal. Although ESR is a common and nonspecific laboratory test indirectly associated with systemic inflammation, an elevated ESR may nevertheless serve as a useful hematologic marker in primary SS related to circulating autoantibodies such as ANA, anti-Ro/SS-A, and anti-La/SS-B.[20]

The present study compared subjective xerostomia by using questionnaires and objective salivary function by using SFR and salivary scintigraphy. The results showed that SS patients had a decreased UR of the submandibular gland compared to non-SS patients, while there was no significant difference with respect to xerostomia symptoms, SFR, and parotid function. Previous studies have shown that salivary scans in patients with SS are more sensitive and specific for the submandibular glands than the parotid gland.[21,22] Consistently, submandibular glands were affected much more than parotid glands in the SS patients in the present study. This observed difference might be due to a difference in the respective functions of these two glands, as approximately 70% of unstimulated saliva is produced by the submandibular glands and sublingual glands.[23] Therefore, damage to the submandibular glands and subsequent decreased unstimulated/resting SFR appear to be major causes of xerostomia, leading to secondary mucosal damage and burning mouth symptoms. Because salivary gland hypofunction is one of the main characteristics of SS, evaluation of salivary function is often utilized as a diagnostic tool. Tensing et al evaluated salivary scintigraphy as a method to differentiate between SS patients and patients with sicca symptoms but without SS.[21] They concluded that differentiation between these two conditions is difficult, but that autoimmune markers and salivary scintigraphy can nevertheless be useful.

Interestingly, although the UR of the submandibular glands in SS patients was decreased compared to non-SS patients in the present study, there was no significant difference in the SFR or in subjective dry mouth symptoms between the SS and non-SS patient groups. This result could be due to the fact that symptoms of dry mouth emerge only when salivary flow is decreased to approximately half of normal flow.[24] Therefore, xerostomia may be absent during the early stages of SS, since the natural history of SS is accompanied by a progressive loss of salivary acinar tissue. In the present study, six patients who were newly diagnosed with SS (including secondary SS) complained of a burning sensation in their mouth rather than xerostomia at the time of the visit. It is also plausible that SS-associated neuropathies may manifest as oral burning. Consistent with this possibility, a recent study reported that the most common cranial neuropathy in SS is associated with trigeminal sensory neuropathy, which is characterized by facial numbness or paresthesia.[25]

Conclusions

In this prospective study, the prevalence of SS in patients with symptoms of BMS was 4.8%. Patients with SS had significantly decreased hemoglobin levels, increased ESR, and a higher prevalence of autoantibody positive results compared to non-SS patients. According to salivary scintigraphy, the function of the submandibular glands in SS patients was significantly decreased compared to that in non-SS patients. Therefore, clinicians who treat BMS should evaluate laboratory findings and salivary functions, which may identify patients with otherwise undetected SS.

Acknowledgments

This work was supported by a grant from Kyung Hee University in 2016 (KHU- 20160541). The authors report no conflicts of interest.

References

1. Zakrzewska JM, Forssell H, Glenny AM. Interventions for the treatment of burning mouth syndrome. Cochrane Database Syst Rev 2005;(1):CD002779.
2. Mock D, Chugh D. Burning mouth syndrome. Int J Oral Sci 2010;2:1–4.
3. Yilmaz Z, Renton T, Yiangou Y, et al. Burning mouth syndrome as a trigeminal small fibre neuropathy: Increased heat and capsaicin receptor TRPV1 in nerve fibres correlates with pain score. J Clin Neurosci 2007;14:864–871.
4. Rifkind JB. Burning mouth syndrome and "burning mouth syndrome." N Y State Dent J 2016;82:36–37.
5. Grushka M, Ching V, Epstein J. Burning mouth syndrome. Adv Otorhinolaryngol 2006;63:278–287.
6. Pinto A. Management of xerostomia and other complications of Sjögren's syndrome. Oral Maxillofac Surg Clin North Am 2014;26:63–73.
7. Sun A, Wu KM, Wang YP, Lin HP, Chen HM, Chiang CP. Burning mouth syndrome: A review and update. J Oral Pathol Med 2013;42:649–655.
8. Scala A, Checchi L, Montevecchi M, Marini I, Giamberardino MA. Update on burning mouth syndrome: Overview and patient management. Crit Rev Oral Biol Med 2003;14:275–291.
9. Soares MS, Chimenos-Küstner E, Subirá-Pifarrè C, Rodríguez de Rivera-Campillo ME, López-López J. Association of burning mouth syndrome with xerostomia and medicines. Med Oral Patol Oral Cir Bucal 2005;10:301–308.
10. Lee YC, Hong IK, Na SY, Eun YG. Evaluation of salivary function in patients with burning mouth syndrome. Oral Dis 2015;21:308–313.
11. Birnbaum J. Peripheral nervous system manifestations of Sjögren syndrome: Clinical patterns, diagnostic paradigms, etiopathogenesis, and therapeutic strategies. Neurologist 2010;16:287–297.
12. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629–808.
13. Navazesh M, Kumar SK. Measuring salivary flow: Challenges and opportunities. J Am Dent Assoc 2008;139(suppl):s35–s40.

14. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: A revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554–558.
15. Spadari F, Venesia P, Azzi L, et al. Low basal salivary flow and burning mouth syndrome: New evidence in this enigmatic pathology. J Oral Pathol Med 2015;44:229–233.
16. Al-Hashimi I, Khuder S, Haghighat N, Zipp M. Frequency and predictive value of the clinical manifestations in Sjögren's syndrome. J Oral Pathol Med 2001;30:1–6.
17. Mignogna MD, Fedele S, Lo Russo L, Lo Muzio L, Wolff A. Sjögren's syndrome: The diagnostic potential of early oral manifestations preceding hyposalivation/xerostomia. J Oral Pathol Med 2005;34:1–6.
18. Ramos-Casals M, Font J, Garcia-Carrasco M, et al. Primary Sjögren syndrome: Hematologic patterns of disease expression. Medicine (Baltimore) 2002;81:281–292.
19. Baimpa E, Dahabreh IJ, Voulgarelis M, Moutsopoulos HM. Hematologic manifestations and predictors of lymphoma development in primary Sjögren syndrome: Clinical and pathophysiologic aspects. Medicine (Baltimore) 2009;88:284–293.
20. Zheng L, Yu C, Yang C, Xie L, Shi H, Wang Z. The serological profiles of subgroup of primary Sjögren's syndrome correlation with the clinical features of parotid glands. J Craniomaxillofac Surg 2014;42:1260–1264.
21. Tensing EK, Nordström DC, Solovieva S, et al. Salivary gland scintigraphy in Sjögren's syndrome and patients with sicca symptoms but without Sjögren's syndrome: The psychological profiles and predictors for salivary gland dysfunction. Ann Rheum Dis 2003;62:964–968.
22. Vinagre F, Santos MJ, Prata A, da Silva JC, Santos AI. Assessment of salivary gland function in Sjögren's syndrome: The role of salivary gland scintigraphy. Autoimmun Rev 2009;8:672–676.
23. Chimenos-Kustner E, Marques-Soares MS. Burning mouth and saliva. Med Oral 2002;7:244–253.
24. Dawes C. Physiological factors affecting salivary flow rate, oral sugar clearance, and the sensation of dry mouth in man. J Dent Res 1987;66(spec no):648–653.
25. Klasser GD, Balasubramaniam R, Epstein J. Topical review—connective tissue diseases: Orofacial manifestations including pain. J Orofac Pain 2007;21:171–184.