

REVIEW

Burning mouth syndrome

Ağız yanması sendromu

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Burning mouth syndrome (BMS) is characterized by oral burning or similar pain in the absence of detectable oral mucosa changes. This condition is more common among middle-aged and elderly women. Although various local, systemic, and psychological factors are considered to be possible causes of BMS, it is still a challenge in the field of oral medicine. The aim of this review is to discuss several aspects of BMS, update current knowledge, and provide guidelines for patient management.

Key Words: Burning mouth syndrome/etiology/therapy.

Ağız yanması sendromu, herhangi bir patolojik değişikliğin saptanamadığı, oral yanma veya benzer ağrılar ile karakterize bir hastalıktır. Bu durum, orta yaş ve üstü kadınlar arasında daha sık görülür. Çeşitli lokal, sistemik ve psikolojik faktörler ağız yanması sendromunun olası nedenleri olarak kabul edilse de, ağız hastalıkları alanında hala tam olarak açıklığa kavuşturulamamış bir durumdur. Bu derlemede, ağız yanması sendromu çeşitli açılardan ele alınmış, sendromla ilgili en son bilgilere yer verilmiş ve tedavi seçenekleri sunulmuştur.

Anahtar Sözcükler: Ağız yanması sendromu/etyoloji/tedavi.

Burning mouth syndrome (BMS) is a distinctive nosological entity characterized by unrelieved oral burning or similar pain in the absence of detectable oral mucosa changes.^[1]

Terms previously used to describe what is now called BMS include stomatodynia, stomatopyrosis, glossodynia, glossopyrosis, sore tongue, sore mouth, and oral dysaesthesia to emphasize the quality and/or the location of pain in the oral cavity.^[2,3]

EPIDEMIOLOGY

The prevalence of BMS has been reported in epidemiological studies from different countries and cultures.^[4]

Burning mouth syndrome is believed to be more common among middle-aged and elderly women. In a survey among randomly selected men and women of ages 20-69 years in Northern Sweden,

the prevalence of BMS increased from 0.7% to 3.6% in men and from 0.6% to 12.2% in women with increasing age.^[5] In another study comprising 6,103 elderly men and women recruited from a group of pensioners in Sweden, BMS was reported in 2.4% of men and 8.5% of women. The occurrence of BMS was unaffected by age in both sexes.^[6] Similarly, Hakeberg et al.^[7] reported the prevalence of BMS as 4.6% among a representative population of Swedish middle-aged and elderly women, but they found no association between age and BMS.

In a retrospective study of 140 BMS cases among a sample of Catalan population, most cases (46.3%) were located in the age group of 65 to 74 years, with 44.2% of this group being females.^[8] In a large-scale survey of reported orofacial pain among adults in the USA, the estimated prevalence of burning mouth pain was 0.7%.^[9] In a representative sample of gener-

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al adult population of Finland, Tammiala-Salonen et al.^[10] estimated the prevalence of BMS as 7.9%, with a significant female preponderance. Basker et al.^[11] investigated the UK population attending general dental practices and found the BMS frequency as 5.1%, with women comprising the majority (4.2%).

ETIOLOGY

Though the cause-effect relationship between the possible etiological factors and BMS has not been established, its etiology is considered to be multifactorial and is often classified into three groups:^[12,13]

1. Local factors
2. Systemic factors
3. Psychological factors

A. Local factors

Local factors leading to burning sensations of the oral mucosa include the following:

Helicobacter pylori: Study results do not confirm the causative role of *H. pylori* in BMS. Gall-Troselj et al.^[14] collected samples by the cytobrush technique from the dorsal tongue mucosa of a group of 144 BMS patients and *H. pylori* was found in 25 patients.

Poor oral hygiene: Plaque and tartar accumulation is an irritating factor of gingiva and oral mucosa for many oral diseases including BMS. In a preliminary study of 30 BMS cases, nearly half of the patients presented with great deficiencies in oral hygiene.^[15]

Oral candidiasis: Subclinical *Candida* infection has been suggested as one of the etiological factors in patients with BMS. Chen and Samaranayake^[16] collected parotid saliva samples and found that *Candida glabrata* tended to grow better in the saliva of BMS patients than that of the controls. Vitkov et al.^[17] examined 72 native Upper-Austrians with burning mouth sensations and took smears for *Candida* estimation from the sites of sensations. Microbiological examination showed an increased candidal density in 53% of patients with burning sensations. Gorsky et al.^[18] reported that, of BMS patients with no clinical signs of candidiasis, 86% improved after using antifungal lozenges and 13% had complete elimination of their symptoms.

Oral parafunctional habits: Several studies reported parafunctional habits in patients with BMS.^[19,20] This parafunctional activity (tongue thrusting, bruxism, clenching) is significantly related to anxiety.^[20] Since

several studies have provided evidence for some neurological alterations in BMS, it is conceivable that the parafunctional habits might result in neuropathic changes that ultimately lead to BMS symptoms.^[21]

Allergic reactions: Hypersensitivity to some materials has been reported, but their precise role in the symptoms of BMS is not clear.^[22] Virgili et al.^[23] performed patch testing with the Italian standard series, preservatives, and dental series. The number of BMS patients with a positive reaction to patch testing was six out of 15, while the number of allergic patients in the control group was three out of 12. Though contact allergy in BMS does not seem to play a primary role, it is advisable to perform patch tests to identify a possible etiological agent. Purello-D'Ambrosio et al.^[24] reported a female denture wearer who was referred to their service due to burning of the lips and tongue but with no visible oral lesions. Patch tests gave a positive result only to a 2% petrolatum cadmium sulfate, which was present in the denture. Removal of the denture resulted in relief of oral symptoms in three days. Hypersensitivity to mercury was found to be one of the most common medical diagnoses associated with BMS.^[25] Pigatto et al.^[26] reported a case in which BMS was associated with a strong allergy to mercury. The symptoms disappeared after the mercury tooth filling had been removed.

Galvanism: Electrochemical reactions between different metallic restorations may resemble the symptoms of BMS.^[3] Production of electrical currents can cause a sharp or burning sensation with or without an associated metallic taste.^[22]

Ill-fitting dentures: Denture aspects in BMS etiology are controversial. In a preliminary study of 30 BMS cases, 45% of the patients wore inadequate dentures.^[15] Although ill-fitting dentures were implicated as the single greatest contributor to BMS by some authors,^[27] the persistency of BMS symptoms was reported in the majority of patients whose denture abnormalities were adequately corrected.^[28]

Malignancies: Carcinomas of the oral cavity can also present as itching or burning.^[3]

Neuropathies: The facial nerve innervates taste buds in the filiform and fungiform papillae on the anterior tongue, glandula sublingualis and glandula submandibularis via the chorda tympani which joins the lingual branches of the mandibular division of the trigeminal nerve. Lingual branches of the

glossopharyngeal nerve innervate taste buds in the circumvallate and foliate papillae on the posterior tongue. Damage to related nerves can cause oral burning, dysgeusia (taste disturbances), xerostomia, and oral mucosal sensory changes.^[29-33] Since oral burning and associated symptoms show a pattern similar to the symptoms of some inflammatory neural conditions or regional nerve trauma, a possible neuropathic basis for BMS has been suggested.^[21,29] Lauria et al.^[29] obtained superficial (3 mm) punch biopsies of the lateral aspect of the anterior two-thirds of the tongue to investigate the innervation of the epithelium and demonstrated that patients with persistent BMS had a trigeminal small-fiber sensory neuropathy affecting the tongue, characterized by a significant loss of epithelial and subpapillary nerve fibers. Furthermore, duration of symptoms and decrease in the density of epithelial nerve fibers showed a trend toward correlation in BMS patients.

Salivary gland dysfunction: In patients with BMS, saliva and salivary flow may play an important role in the initiation and maintenance of the symptoms. From a physiological perspective, saliva is a dispersing medium for substances that transmit stimuli to the oral mucosa. An alteration in the concentration of organic and inorganic salivary components, determined by the type of secretion or by the amount of saliva secreted might possibly influence stimulus capture and reception and alter oral mucosal perception. Foamy and highly viscous saliva would produce a discontinuous and thinner residual film, thus, more easily inducing dry mouth sensations. Likewise, the tongue receptors would be continuously more exposed to stimuli.^[34] Some investigators pointed to dry mouth as an important factor in the etiology of BMS and described a significant association with decreased whole salivary flow.^[5,19,35] However, studies that analyzed salivary gland function in the pathogenesis of BMS showed divergent findings.^[13] Some investigators reported no differences in either whole saliva flow rates or parotid gland flow rates.^[13,36,37] The disparities between these studies may be attributable to the different saliva collection techniques employed.^[37]

B. Systemic factors

Nocturia: Nocturia is the increased frequency of voiding at night due to the alteration in the regular pattern of urine excretion.^[38] An increase in the occurrence of BMS could be expected in parallel with

increased nocturnal micturition episodes, as BMS increases in association with oral dryness and oral dryness increases in association with nocturia.^[5,39] In a study comprising 6,103 elderly men and women, Asplund^[6] found that nocturnal thirst and drinking were twice as more common in women than in men and showed significant increases in both men and women with BMS. The occurrence of BMS increased in parallel with increased nocturnal micturition episodes in women. This study reported that negative fluid balance as a consequence of nocturnal polyuria was an overlooked pathogenetic mechanism in the genesis of BMS in the elderly.

Temporal arteritis: Temporal arteritis is a systemic granulomatous disease that predominantly affects branches of the carotid artery. A painful burning tongue may develop during temporal arteritis or be the initial presenting symptom.^[40]

Malignancies: Multiple myeloma is a malignant disease that is characterized by multifocal proliferation of atypical plasma cells and the presence of monoclonal gamma globulins and/or their subunits in the serum. Vucicevic-Boras et al.^[41] reported a case with burning symptoms in the whole oral cavity as the initial sign of multiple myeloma despite clinically healthy appearance of the mucosa. In multiple myeloma, BMS can result from sensory neuropathy occurring due to damage to axons and myelin in nerves caused by antinerve antibody properties of monoclonal anomalous protein, even when radiological examination fails to reveal bony defects.^[42]

Tumor markers: Vucicevic-Boras et al.^[43] found that evaluation of tumor markers (CEA, CA 19-9, AFP, CYFRA 21-1) in patients with BMS did not indicate an underlying malignancy as a cause of burning mouth, obviating the use of routine screening of tumor markers in patients with BMS.

Neurotoxin poisoning: Heir^[44] presented a case of ciguatera neurotoxin poisoning, in which the chief complaints were intra- and perioral burning and a sense of cold in the throat. Thus, neurotoxin poisoning should be known as a possible cause for symptoms of burning mouth, especially in patients who have recently traveled to, or eaten fish imported from, the tropical areas where ciguatera is endemic.

Diabetes mellitus: It has been reported that type II diabetes mellitus plays a role in BMS development.^[11,15,19,45,46] Diabetic neuropathy (DN) occurs in approximately

50% of diabetic patients and symptoms consistent with BMS may occur secondary to DN.^[46] Gibson et al.^[45] reported that the symptoms of BMS in diabetic patients improved after glycemic control. However, some investigators reported that oral burning complaints were caused by oral candidiasis in diabetic patients who were more prone to oral infections.^[17,47]

Gastroesophageal reflux: Burning mouth syndrome is occasionally associated with gastroesophageal reflux and, more specifically, the symptomatology relates to oropharyngeal areas and the base of the tongue.^[48,49]

Nutritional deficiencies: Deficiencies of vitamins C, B2, B3, B6, B12, folic acid; iron; fats and water may cause oral burning complaints.^[19,25,50,51] Lamey et al.^[52] reported that replacement therapy of vitamin B1, B2 and B6 was effective in treating BMS in 88% of patients. However, Hugoson and Thorstensson^[53] found that vitamin B1, B2, B6 replacement therapy was ineffective for the relief of burning sensations. Vucicevic-Boras et al.^[54] reported that there were no statistically significant differences in serum levels of iron, folic acid, calcium, and magnesium between patients with BMS and controls other than significantly decreased vitamin B12 levels in patients with BMS.

Menopausal hormonal changes: Hormonal changes are considered to be an important factor in BMS,^[55] because approximately 90% of women with BMS have been found peri/postmenopausal, with the greatest frequency of BMS onset falling between three years before and 12 years after menopause.^[18,19,27,51,56] The efficacy of hormone replacement therapy (HRT) is controversial.^[11,57-60] Response to HRT varied based on the presence or absence of the expression of nuclear estrogen receptors in oral mucosa, demonstrated by immunohistochemical identification of estrogen receptors in incisional biopsy samples of patients with primary BMS. Estrogen receptors were found in oral epithelium in most patients who responded to replacement therapy, whereas estrogen receptors were not detected in unresponsive patients.^[57,58]

Thyroid abnormalities: One of the less common causes of BMS is thyroid abnormalities.^[61] Goss^[62] found that BMS was associated with hypothyroidism or over-treatment of hyperthyroidism.

Medication: Every drug can produce untoward consequences, even when used according to standard or recommended methods of administration. Adverse drug reactions can affect the mouth and associated

structures.^[63] Angiotensin-converting enzyme inhibitors (ACEIs) are extensively prescribed in medical practice for the management of hypertension and chronic cardiac failure.^[64] Case reports have linked BMS to the use of ACEIs. Once these medications were reduced or discontinued, oral burning was found to remit within several weeks.^[65-69] However, Castells et al.^[70] did not favor the theory of ACEI-induced effect and reported that this adverse effect appeared only in patients with some predisposing conditions. Culhane and Hodle^[71] reported a case of clonazepam-induced BMS, which is the first published report describing BMS with a benzodiazepine. Levenson^[72] presented a case in which BMS was seen as a side effect of selective serotonin reuptake inhibitors. Another study reported that medication with L-thyroxins was the most important pharmacological factor for BMS.^[5] Furthermore, many medications cause xerostomia and may lead to burning mouth.^[61,73] In a preliminary study of 30 BMS cases, 56.6% of the patients used xerostomia-inducer medications, principally antihypertensives, antidepressants, and anxiolytics.^[15] Soares et al.^[13] and Hakeberg et al.^[7] observed that, among the different drug categories that were taken by patients with BMS, only the antihypertensives and diuretics presented a risk factor for BMS. On the other hand, Pajukoski et al.^[74] showed psychotropics and anticoagulants as risk factors for BMS.

Neuropathies: Animal studies have indicated that nigrostriatal dopaminergic system is involved in central pain modulation; hence, hypofunction of this system may play a role in the pathophysiology of BMS, which is a chronic pain state.^[75,76] Furthermore, burning mouth patients exhibit abnormalities in the excitability of the blink reflex,^[77,78] which is a brainstem reflex under inhibitory dopaminergic control.^[79] Forssell et al.^[77] assessed the blink reflex of patients with BMS in response to an electrical stimulus applied to the area of the trigeminal nerve and showed abnormalities in the blink reflex in most cases, possibly representing subclinical changes in the trigeminal system and abnormal sensory thresholds in the other patients that may indicate thin fiber dysfunction. Of 46 patients, 33 showed signs of hypoesthesia. Thus, thin fiber dysfunction and trigeminal neuropathy were suggested as mechanisms of neuropathy in BMS.

C. Psychological factors

Personality and mood changes have been consistently demonstrated in patients with BMS, suggesting

that somatic symptoms can be symbolic representations of psychological suffering. Depression, masked depression, anxiety, cancerophobia, and emotional states are counted among the psychological factors related to BMS.^[5,8,80-83] However, there is controversy as to whether psychological dysfunctions are primary or secondary events. Because psychological dysfunctions are common among patients with chronic pain, these disorders may be a result of BMS rather than its cause.^[84,85]

CLINICAL FEATURES

Common clinical features of BMS are summarized below:

- There are no signs of lesions or other detectable changes in the oral mucosa, even in the painful areas.^[1]
- Burning sensations are generally spontaneous and occur continuously for at least 4 to 6 months.^[1]
- Pain level may vary from mild to severe, but moderate pain is the most frequent presentation.^[21,56]
- Oral pain is generally bilateral and more than one oral site may be affected. The sites of predilection for pain are the tongue (especially the tip or anterior two-thirds), lips, hard palate, gingiva, buccal mucosa, and the floor of the mouth, respectively.^[3,49,56]
- Burning sensations are accompanied by oral dryness and taste abnormalities (dysgeusia) in at least 50% of cases.^[5,18,27,51,56]
- Oral mucosal sensory abnormalities may occur.^[21,29]

• Symptoms may be present in three different patterns:^[12,86]

- *Type 1 BMS* is characterized by a pain-free waking, with gradual increase in severity as the day progresses.
- *Type 2 BMS* consists of continuous symptoms throughout the day and the night.
- *Type 3 BMS* is characterized by intermittent symptoms which follow no specific pattern with pain-free periods during the day.

CLASSIFICATION

The clinical forms of BMS are:^[21]

1. *Primary BMS*: If no causes can be identified by clinical/laboratory examinations, it is called “primary”, “essential”, or “idiopathic” BMS.
2. *Secondary BMS*: If the clinical/laboratory examinations determine a pathological condition that causes burning sensation, it is called “secondary” or “associated” BMS.

MANAGEMENT

Initially, patients should be informed on the nature of their condition and the things that should be taken care of. They should also be made aware that the treatment will be prolonged and that not all the symptoms will definitely disappear.^[21,34,87] Patients should:

- provide good oral hygiene;
- have regular, healthy diet;

TABLE I
POSSIBLE CAUSES OF SECONDARY BMS AND ITS MANAGEMENT

Condition	Treatment
Oral candidiasis	Antifungal medication (Nystatin, clotrimazole, ketoconazole, fluconazole, itraconazole, etc.)
Oral parafunctional habits	Biteguard, physiotherapy, consultation with psychologist/psychiatrist
Neuropathies	Consultation with neurologist, alpha lipoic acid (ala) therapy
Salivary gland dysfunction	Systemic agents: sialogogues (pilocarpine, cevimeline, etc.) Topical agents: salivary substitutes
Diabetes mellitus	Consultation with endocrinologist, glycemic control
Gastroesophageal reflux	Consultation with gastroenterologist
Nutritional deficiencies	Consultation with internist, replacement therapy
Menopausal hormonal changes	Consultation with gynecologist, hormone replacement therapy
Medications	Consultation with the physician for drug substitution or lowering the dose of the drug, if possible
Psychological disorders	Consultation with psychologist or psychiatrist

- avoid consumption of tobacco, alcohol, and beverages containing large amounts of caffeine;
- avoid habitual ingestion of very hot or very spicy foods;
- avoid habitual ingestion of beverages and foods that contain strong acids;
- avoid the use of mouthrinses containing alcohol or potent detergents.

Since the underlying cause can be determined in secondary BMS, treatment should be directed toward the elimination of identified etiological conditions (Table I).^[21,22,49,88]

Since the diagnostic workup fails to identify a clinical or laboratory abnormality in primary BMS, it is inappropriate to design a definitive therapy for this condition. Many pharmacological agents, administered topically or systemically, have been proposed to overcome the symptoms in BMS:

- *Low dose of benzodiazepines*: Daily topical use of clonazepam (tablet, 3 times daily for sucking) showed partial-to-complete pain relief in most patients with primary BMS.^[89-91] Alternatively, chlordiazepoxide may be prescribed.^[92]
- *Low dose of antidepressants*: At low dosages, tricyclic antidepressants (amitriptyline) show analgesic action, independent of their antidepressive effect.^[93,94] Amisulpride, paroxetine, and sertraline are other antidepressants reported to be well-tolerated and effective in BMS.^[95,96]
- *Capsaicin*: Systemic or topical administration of capsaicin is therapeutically effective for the short-term treatment of BMS, but side-effects (C-fiber degeneration, gastric pain) may threaten its usage.^[97-99]
- *Low dose of anticonvulsants*: Gabapentin can provide symptomatic relief in BMS patients.^[88]

CONCLUSION

Burning mouth syndrome is still an interesting and complicated condition in the field of oral medicine because of the multifactorial causes and the absence of visible abnormalities. Thus, the key to achieve the most effective treatment is to identify causative factors and to adopt a multidisciplinary approach.

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