

Burning mouth syndrome: a discussion about possible etiological factors and treatment modalities

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Abstract

Although several studies discuss the contributing factors associated with the burning mouth syndrome (BMS), there is still controversy with regard to its etiology. Therefore, in the majority of cases, the establishment of an adequate diagnosis and consequently the best treatment modality is complicated. In order to assist the clinician in the establishment of the correct diagnosis and management of BMS, this article reviews the literature, providing a discussion on the various etiologic factors involved in BMS, as well as the best treatment modalities for this condition that have showed to be the most effective ones in randomized clinical trials. In addition, the authors discuss some clinical characteristics in the differential diagnosis of BMS and other oral diseases. It is important for the clinician to understand that BMS should be diagnosed only after all other possible causes for the symptoms have been ruled out.

Keywords: burning mouth syndrome, xerostomia, mouth diseases.

Introduction

Several diseases of the oral mucosa may have burning as a symptom, such as herpes simplex virus, oral lichen planus (under its clinical forms: erosive, atrophic and ulcerative), aphthous stomatitis, candidiasis (mainly under its acute form) and xerostomia. However, patients who refer a burning sensation if the oral mucosa or a chronic pain without any visible alteration of the oral tissues might be diagnosed as having burning mouth syndrome (BMS)¹.

It is very important for clinicians to be able to distinguish a burning mouth symptom caused by a specific disease besides BMS. BMS is considered to be a pain or burning sensation affecting the clinically normal oral tissues, for which local and systemic causes have been excluded. The term "syndrome", in this case, is justified because of the simultaneous presence of several subjective symptoms, including feeling of dryness (subjective xerostomia), altered taste, and burning sensation of the oral tissues, comprising or not the tongue^{2,3}.

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Literature review

Definition

BMS is referred as a chronic orofacial pain or burning sensation in the oral mucosa or tissues without any clinically significant lesion or alteration. According to the International Headache Society, BMS is an intraoral burning sensation for which no dental or medical cause is found⁴. The BMS pain may be described as a burning sensation that is often qualitatively compared to a toothache. A wide variety of terms have been reported in the literature to describe BMS, which include glossodynia/stomatodynia, glossopyrosis/stomatopyrosis, oral dysesthesia and sore mouth^{5,6}.

Epidemiology

BMS may occur in any tissue inside the oral cavity, although most often it is found on the two thirds of the anterior and on the tip of the tongue¹. This disease has a prevalence that varies from 0.7 to 15% in the general population⁷⁻¹⁰ and has an average duration of two to three years¹¹. It predominantly affects middle-aged women in the postmenopausal phase and in a ratio of 7:1 when compared to men^{12,13}.

Few studies have mentioned the presence of BMS in earlier ages^{7,12,14}, which indicates that its prevalence increases with age⁴.

According to Lamey and Lamb¹⁵, the symptomatology associated with BMS may be classified in three types^{16,17}, as shown in **Table 1**.

Pathogenesis and etiology

The pathogenesis and etiology of the BMS are not completely understood yet. Some authors have suggested that there is a multifactorial etiology: local, systemic and psychological factors (**Table 2**)^{14,18-24}. The local factors may include temporomandibular disorders (TMD), oral candidiasis, parafunctional habits (clenching and bruxism), xerostomia (**Figure 1**), salivary glands dysfunction, hypersensitivity reactions (**Figure 2**) and misfitted and poorly designed dentures. However, the literature is sometimes conflicting and unclear, because the diagnosis of BMS should be confirmed after ruling out other causes to the burning sensation, such as oral candidiasis or TMD.

Special attention must be given to the dentures, since it has been demonstrated that there is a possible correlation between the problems related to oral dentures (adjustment, design) and the BMS for both may cause central and/or peripheral changes in the sensory nerve function, causing atypical oral pains^{25,26}.

Table 1. Classification of the symptomatology associated with burning mouth syndrome (BMS)

Types	BMS symptomatology according to Lamey and Lamb ¹⁵	Factors associated with BMS in each type ^{16,17}
1	Symptoms are not present when the patient wakes up, but they will appear and increase during the day.	Moderate anxiety disorders.
2	Symptoms are present all day and night and strongly associated with anxiety.	Severe psychiatric disorders.
3	Symptoms are not present during some days and are associated with emotional instability or a hypersensitivity reaction to some foods.	Emotional instability or allergic reactions.

Table 2. Factors associated with the etiology of burning mouth sensation

Local	Systemic	Psychological	Neuropathic
Temporomandibular disorders	Nutritional deficiencies	Depression	Neurogenic abnormalities
Oral candidiasis	<i>Diabetes mellitus</i>	Anxiety	-
Parafunctional habits	Hormonal disturbances	Psychopathologic distress	-
Xerostomia	Immunomediated diseases	-	-
Salivary glands dysfunction	Systemic drugs	-	-
Hypersensitiveness reactions	-	-	-
Misfitted or poorly designed dentures	-	-	-



Figure 1. Patient with xerostomia.



Figure 2. Patient with hypersensitivity reaction.

Concerning hypersensitivity reaction, Mott et al.²⁶ mentioned not only allergy to denture base acrylic resins and contouring or fabrication errors, but also the presence of parafunctional habits as important factors in the development of BMS. Furthermore, Gao et al.²⁴ have found that oral parafunctional habits are causative agents in BMS, specially tongue thrusting and lip sucking.

Xerostomia has been identified in almost 65% of the patients with BMS^{7,14,27-29}, which demonstrates that these patients are significantly more susceptible to this condition. Marques-Soares et al.³⁰ have investigated the function of the salivary gland in BMS pathogenesis and found divergent results, concluding that it is still not clear whether hyposalivation is a typical sign of this syndrome. Those authors have also evaluated the salivary flow rate and found no statistically significant differences. Furthermore, it is known that the administration of certain medications as diuretics, anti-hypertensive drugs and mainly psychotropics may influence salivary gland function³¹.

Radiotherapy on head and neck regions may produce severe and irreversible damages to the salivary glands, leading to a severe condition of permanent xerostomia, which have to be identified during the clinical interview³².

Bergdahl and Bergdahl³² have stated that psychological factors have an influence on xerostomia, sometimes without hyposalivation, and that they could be intimately related to depression, anxiety and use of antidepressants. In a case-control study that investigated anxiety and salivary cortisol levels in patients with BMS, Amenábar et al.³³ found that 50% of these patients presented a worse level of anxiety than those without BMS. These authors associated this BMS-anxiety relationship with the salivary cortisol level that is presented in a higher level in patients with these two disorders.

Cavalcanti et al.¹³ have found no difference in the presence of *Candida albicans* between BMS and control patients. Thus, candidiasis has not been confirmed as an associate etiological factor for BMS.

Some systemic factors might also be associated with BMS, such as nutritional deficiencies as pernicious anaemia, iron deficiency, vitamin B complex deficiency, folate deficiency and vitamin C deficiency³⁴. Yet, systemic diseases, such as *diabetes mellitus*, hormonal disturbs, immunomediated diseases and psychological disorders could be associated factors^{21,35}.

Some authors have pointed out a possible relationship between *diabetes mellitus* and BMS, since this syndrome is found in 2 to 10% of diabetic patients^{15,34,36,37}. Although Sardella et al.³⁸ did not find this relationship, burning sensation could be a symptom of an undiagnosed *diabetes mellitus*³⁹ and perhaps the control of diabetes leads to the improvement or cure of BMS⁶. Deficiency disorders have always been referred as cause of BMS. Nutritional deficiencies have been claimed to cause BMS in 2 to 33% of patients⁴⁰. However, other studies did not find a high prevalence of nutritional deficiency in patients with BMS^{15,36}.

BMS may also change the individual's general and psychological well being, reducing the quality of life, even though it is not clear if psychopathologic distress is related to this syndrome or if it is a result of the chronic symptoms that these patients passed through¹⁸. Some studies have reported that people with BMS experience ad-

verse life events more frequently than people without BMS, which may be a risk factor for developing BMS^{24,41}.

There is evidence of a possible relationship between BMS and psychogenic factors, as shown by Sardella et al.³⁸. More recently, several authors have investigated the trigeminal somatosensory system in order to detect neurogenic abnormalities⁴²⁻⁴⁷. These studies suggest peripheral alterations in the function of this system with the presence of abnormal reflex, for example, the blink reflex⁴⁴.

Calcitonin gene-related peptide (CGRP) is one of the neurotransmitters found in the nerve fibers of the nervous system that is involved in salivary secretion and plays an important role in the development of pain and hyperalgesia⁴⁸. Supporting this interpretation, some studies showed that the use of neuroprotective/neurotropic drugs improved the symptoms in patients with BMS^{19,49}. However, Zidverc-Trajkovic et al.⁵⁰ found no elevated levels of CGRP in the saliva of patients with BMS, which seems to demonstrate the trigeminal nerve degeneration in this syndrome.

Psychiatric disorders could be associated with more than 50% of the cases of BMS⁵¹. Several studies in psychiatric literature have associated anxiety and depression with BMS symptomatology^{14,42,52,53}. Gao et al.²⁴ found anxiety, depression and somatization symptoms to be the most common psychological problems in BMS. Bergdahl et al.¹⁶ demonstrated that patients with BMS exhibited low levels of socialization and high levels of anxiety and health status concern when compared to a Control Group.

Marques-Soares et al.³⁰ identified medications that could have a preventive role with regard to BMS, such as systemic drugs for vascular and digestive disorders, analgesics and psychotropic drugs. Hugosson and Thorstenson⁵³, in a study involving patients with BMS and a control group, have observed that 87.5% of the patients with the syndrome were usually taking one or more drugs; 44% were psychotropic drugs, 25% were digestive disorder drugs, 25% were respiratory disorder drugs and 6.2% were vitamins⁵⁴. According to Bergdahl and Bergdahl⁷, the chronic use of systemic drugs may be a significant factor for BMS. In a study that investigated the clinical basis of this syndrome and a possible association with the oral carriage of *Candida* species, Cavalcanti et al.¹³ found that 80.6% of the patients with BMS were chronic users of systemic drugs, among which 35.5% were benzodiazepines, 19.35% were other antidepressants and 38.7% were antihypertensive drugs. Some drugs, like antihypertensive agents, are frequently associated with the beginning of symptoms compatible with BMS. Antihypertensive drugs that act in the renin-angiotensin system are more frequently related to the occurrence of BMS⁵⁵.

According to Drage and Rogers¹¹, over 37% of the patients exhibit more than one factor contributing to oral pain sensation (burning), which must be identified and treated. In contrast, there are cases of spontaneous remission in approximately half of patients with BMS, as reported elsewhere^{5,28,56}.

Sardella et al.³⁸ evaluated a group of patients with BMS who received the definitive diagnosis after being submitted to a clinical examination, standard set of examinations (salivary flow rate), lab tests (complete blood cell count, blood glucose levels, serum iron level, transferrin level, serum vitamin B level and folic acid level) and isolation of *Candida* spe-

cies from oral mucosa scraping. Tests were performed for contact allergy as a means of excluding this possibility. After analysis and 18 months of follow-up, spontaneous remission cases occurred in the patients who had not received any type of treatment. Therefore, the findings of this study suggest that a spontaneous remission may be expected only in a small portion of patients within five years after the onset of BMS. Alcohol consumption and smoking must be abolished during the treatment of BMS.

Treatment

Bogetto et al.⁵⁷, in a randomized clinical trial (RCT), compared amisulpride, paroxetine, clordemetildiazepam and amitriptyline to a placebo and found a statistically significant reduction from baseline in BMS symptoms and depression for patients receiving 50 mg/day amisulpride. In a 60-day RCT, Femiano et al.⁵⁸ compared alpha-lipoic acid to cellulose (placebo). The results showed that 97% of the patients receiving the treatment had some level of improvement, and only 40% of those receiving placebo had a slight improvement. In a 14-day RCT⁵⁹ with six months of follow-up, clonazepam was compared to placebo. At the end of the treatment period, a statistically significant difference in the mean decrease in pain intensity was observed among the patients who used clonazepam.

Cognitive behavioral therapy is another type of treatment that showed to be of great value in the management of BMS. Bergdahl et al.⁵⁹, in a previous RCT, found a statistically significant difference in the reduction of pain intensity for those receiving this type of therapy in comparison to a placebo attention program immediately following the therapy and after six months of follow-up.

Oral lafutidine showed a significant effect in reducing the intensity of oral burning sensation and may be a viable option for the treatment of BMS⁶⁰. Yamazaki et al.⁶¹ observed that the use of paroxetine for the treatment of BMS reduced the pain in about 80% of patients with BMS with minor transient side effects.

There is no consensus in the literature concerning the best treatment approach. Conservative management, such as low doses of tricyclic antidepressants, benzodiazepines or doxepins and topical clonazepam or gabapentin are some options that have been evaluated^{32,62,63}. However, Heckmann et al.⁶⁴ demonstrated that gabapentin presents few or no effect in BMS.

There is insufficient evidence to understand the real cause and to provide clear guidance for an effective treatment of BMS. Most studies are small, uncontrolled investigations, and there are no reports of longitudinal cohort studies. Further research is therefore needed.

The importance of assessing whether burning mouth is a symptom of other disease or a real distinct syndrome must be highlighted. Clinicians should identify the BMS and its situation and also be able to give a reliable explanation about this condition and its benign nature to the patient. Additionally, an individual approach concerning the assessment and treatment of patients with BMS is necessary. In order to reduce patient's suffering, psychological methods may be helpful for patients to cope with BMS symptoms.

Especially in clinical situations in which there is no consensus about the best treatment approach to be adopted, to be as conserva-

tive as possible is a wise choice. In the authors' experience, the use of combined treatment, such as behavioral modification and psychotherapy associated with the use of gabapentin and/or clonazepam, has been successful. BMS could be a kind of neuropathic pain and could respond positively to treatment with gabapentin and other drugs used to manage this condition.

Definitive diagnosis of BMS must be preceded by a thorough clinical examination focusing on the presence of signs such as erythema, candidiasis, xerostomia or any mucosa abnormalities, in addition to review of medical history in a detailed clinical interview. The BMS diagnosis will be defined only after excluding all possibilities of oral mucosa diseases, contact allergy reactions and all other possible causes of referred pain or burning sensation. Special attention must be given to the prescription of drugs to these patients because most medication can induce xerostomia, which may aggravate BMS. Due to the multifactorial etiology of this condition (local, systemic, psychogenic and neuropathic), clinicians should better opt for an integrated treatment adequately carried out by a multiprofessional team in order to manage all symptoms and alterations related to BMS. Furthermore, it is important to have in mind that, in most patients, the disease is self-limiting, not exceeding three years, regardless of the treatment modality used.

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