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Burning Mouth Syndrome: A Brief Review

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Abstract: *Burning mouth syndrome (BMS), a chronic and intractable orofacial pain syndrome is characterized by the presence of burning sensation of the oral mucosa in the absence of specific oral lesion. In addition to burning sensation, patient with BMS also complains of oral mucosal pain, altered taste sensation, and dry mouth. It is observed principally in middle-aged patients and postmenopausal women. Its pathophysiology has not been fully elucidated and involves peripheral and central neuropathic pathways. Various local, systemic and psychological factors are associated with BMS, but its etiology is not fully understood, Its largely multifactorial, and associated medical conditions may include gastrointestinal, urogenital, psychiatric, neurologic and metabolic disorders, Clinical diagnosis relies on careful history taking, physical examination and laboratory analysis. Treatment is often tedious and is aimed at correction of underlying medical conditions, supportive therapy, and behavioral feedback. An interdisciplinary and systematic approach is required for better patient management, Short term follow up data is promising, however, long term prognosis with treatment is lacking. The purpose of this article is to present a brief review of epidemiology, classification, pathophysiology, etiology, clinical features, differential diagnosis, diagnosis, treatment and prognosis of burning mouth syndrome.*

Keyword: *Burning mouth syndrome, review, diagnosis, treatment*.

I. Introduction

Burning mouth syndrome (BMS) is a chronic pain disorder characterized by burning, stinging, and/or itching of the oral cavity in the absence of any organic disease. It lasts at least 4 to 6 mo and most often involves the tongue with or without extension to the lips and oral mucosa (1). Patient complaining of burning sensation of the oral cavity present one of the difficult task to the oral health care professionals. This condition gets even worsened if it is accompanied by pain. Pain is the frequent cause of suffering and disability that seriously impairs the quality of a human life.(2). The pathophysiology of BMS is not yet fully established. Several studies have shown significant differences in thermal nociception and the limits of patients with BMS compared with controls, (3,4) demonstrating that there may be neuropathic changes involved. However, it is not known if the dysfunction is peripheral or central. Scala et al proposed that the BMS be classified into two clinical types (5): primary or essential/idiopathic BMS, for which local or systemic causes cannot be identified, and secondary BMS, which is due to organic causes, such as oral infections, autoimmune diseases of the oral mucosa (lichen planus), nutritional/vitamin deficiencies, allergies, irritation caused by reflux, candidiasis, diabetesmellitus, or administration of certain drugs (6,7).

The diagnosis and treatment for primary BMS are controversial. There are no specific, well-established laboratory tests or diagnostic criteria, and the diagnosis is made by
exclusion of all other possible disorders (8).

Epidemiology:

The prevalence of burning mouth symptoms reported from international studies ranges from 0.7% to 4.6% (5). The considerable variation in prevalence among these studies may be because of different definitions of BMS leading to different criteria for the selection of the populations (9). BMS is basically a disorder of middle aged and elderly individuals with an age range of 38-78 years (10) This condition is extremely rare in patients under 30 years and never been reported in children and adolescence (11). It seems that their prevalence increases with age in both males and females. BMS exhibits significant female predilection and the ratio between females and males varies from 3:1 to 16:1 in various literature studies (12) Even though it is not yet defined, these gender differences were explained in the context of biological, psychological, and sociocultural factors. Epidemiological studies reveal that this condition is particularly common among periand postmenopausal women where their prevalence increases up to 12-18% (13).

Classifications:

There have been several proposed classification schemes to better characterize and define BMS. One of the proposed classification is based on daily fluctuations of the symptoms (14,15)

a) Type 1: Characterized by progressive pain, patients wake up without pain, which then increases throughout the day, affects approximately 35% of patients. This type may be associated with systemic diseases, such as nutritional deficiencies.
b) Type 2: Symptoms are constant throughout the day and patients find it difficult to get to sleep, represents 55%. These patients usually present associated psychological
c) disorders.
d) Type 3: Symptoms are intermittent, with atypical location and pain. Constitutes 10% of patients. It seems that contact with oral allergens could play an important etiologic role in this group.

Scala et al. classified BMS into two categories: 'Primary or essential/idiopathic' BMS, in which local or ystemic causes cannot be identified, and involving peripheral or central neuropathological pathways. "Secondary" BMS, resulting from local, systemic or psychological factors (5) Thus, these idiopathic and secondary criteria form two different subgroups of the same pathology (9).

Pathophysiology:

The pathophysiology of BMS has not been fully elucidated. Various studies have shown significant differences in thermal and nociception thresholds of patient with BMS compared to control subjects (3). Thus, a neuropathic mechanism for BMS is currently favored. However, controversy remains over whether a peripheral or central dysfunction is responsible for BMS. Evidence in the literature links BMS to a peripheral neuropathy. Superficial biopsies of the anterolateral tongue from BMS patients showed a significantly lower density of epithelial and subpapillary nerve fibers than controls. Morphologic changes were consistent with axonal degeneration. This supports a trigeminal small fiber sensory neuropathy or axonopathy (16). Moreover, Borelli et al (17) found increased levels of nerve growth factor, a neuropeptide vital to nociceptive function in adults, in the saliva of BMS subjects. Other histopathologic studies of patients with BMS have shown increased density of TRPV1 ion channels and P2X3 receptors on scattered nerve fibers, a finding previously linked to hypersensitivity and neuropathic pain symptoms in various models of human pain conditions (18). Additionally, dysfunction of the chorda tympani branch of the facial nerve may be involved in the pathogenesis of BMS. Patients with BMS will report improved symptoms with eating, suggesting that stimulation of the gustatory system decreases pain sensation. Finally, increased excitability or inhibition of the trigeminal system has been implicated as patients with BMS have greater alterations in blink reflexes compared to normal

Subjects (19). Central neuropathic mechanisms have been demonstrated following thermal stimulation of the trigeminal nerve in patients with BMS. Patients with BMS show patterns of cerebral activity similar to those that appear in other neuropathic pain disorders, suggesting that the cerebral hypoactivity could be an important element in the pathogenesis of BMS (2)

Etiology: The etiology of BMS is poorly understood. Most support a multi-factorial syndrome involving the interaction of biological and psychological systems. A number of etiologies have been proposed suggesting BMS involves alterations in both central and peripheral nervous systems (20). The various factors related with the etiopathogenesis of this syndrome have been divided into local, systemic and psychological.(9) (Table 1)

Local Factors: One should consider physical, chemical or biological (some bacteria or fungi) factors which have a direct irritant effect on the oral mucosa and are able to set off the burning symptoms (21). A mechanical factor to consider is the use of poorly fitting prostheses that produce microtrauma or local erythema. Local allergic reactions, due principally to high levels of residual monomers should also be considered. Infection by Candida albicans has been considered one of the most frequent factors in the production of BMS (22). Xerostomia is a concomitant symptom in patients with BMS, prevalence varying between 34 and 39% (23). In recent years investigations have been carried out into the alterations in taste perception and tolerance to pain as a possible cause of the burning sensation (9).

Systemic factors

Systemic factors implicated in BMS; many of these are deficiencies, such as vitamin deficiencies (in particular low levels of vitamin B12, and others such as vitamin B6, folic acid and vitamin C), and anemias. Furthermore, some studies suggest that BMS is associated with low serum levels of zinc. Hormonal changes (reduced plasma estrogens), diabetes mellitus, thyroid dysfunction (hypothyroidism) and immunological diseases have also been described. Many medications are intimately related with burning mouth; among which are found antihistamines, neuroleptics, some antihypertensives, antiarrhythmics and benzodiazepines. Antihypertensives are among the most frequently implicated medicines, principally those that act on the renin-angiotensin system (captopril, enalapril and lisinopril)(24).

Psychological factors

Studies exist that suggest that psychopathologic factors may play an important role in BMS and support the multifactorial etiology, in which physical changes may interact with psychological factors (25, 21). Many of these patients have symptoms of anxiety, depression and personality disorders, and it has been demonstrated that patients with burning mouth syndrome have a greater tendency towards somatization and other psychiatric symptoms. Cancerphobia can be present in up to 20-30% of these patients. A lower level of socialization and higher levels of somatic anxiety have been observed, as well as muscular tension, a higher tendency to worry about health and greater sadness. BMS is considered a chronic pain disorder that adversely affects quality of life (23, 26).

ETIOLOGIC FACTORS (21)
LOCAL Poorly fitting prosthesis Dental treatment Parafunctional habits- Clenching, Bruxism, Allergic contact stomatitis Taste Alterations Infection- Bacterial, Fungal, Viral Xerostomia
SYSTEMIC Endocrine- Hypothyroidism, Menopause, Diabetes Deficiencies- Iron, Vitamin B complex, Zinc Anemia Medications Sjogren's Syndrome Esophageal reflux
PSYCHOLOGIC Anxiety Depression Compulsive disorders Cancerphobia
IDIOPATHIC FACTORS

Clinical features

Oral burning pain remains the chief symptom of BMS. Most individual describes this symptom as burning, tingling, scalding, annoying, tender, or numb feeling of the oral mucosa, most commonly involving the anterior 2/3 of the tongue, followed by dorsum, lateral borders of tongue, anterior portion of hard palate, and labial mucosa (2). Other, less frequent locations are the oral mucosa, floor of the mouth, soft and hard palate, and oropharynx (24). The onset of pain is spontaneous, bilateral with no identifiable precipitating factors. Pain may be felt deep within the mucosa, continuous for at least 46 months, with moderate to severe intensity that may vary during the day. The location of pain is not pathognomonic, often involving more than one site. Some may even experience burning sensation involving extra oral mucosa including the anogenital region. In some, pain alters the sleep pattern that leads to poor. quality of life, anxiety, depression, decrease desire to socialize and/or somatization (5).

The oral burning sensation usually increases progressively during the day, reaching a maximum intensity at the end of the afternoon / early evening, pain being absent during the night in the majority of patients. Patients do not normally awaken during the night, but do find it difficult to get to sleep. These patients often present mood changes, including irritability, anxiety and depression. The majority of studies describe the coexistence of oral burning with other symptoms, such as dry mouth, dysgeusias, metallic taste, bitter taste or combinations thereof, and/or changes in intensity of taste perception. In addition, dysphagia and atypical facial or dental pain may appear (24). The feeling or evidence of dry mouth in these individuals is more likely due to the side effects of anticholinergics, psychotropic drugs, antihistamines and or diuretics (27). There have been several studies that have shown clear alterations in the quality and quantity of saliva in BMS affected individual (2). And this may be due to the disturbance of sensory modalities of small diameter afferent fibers. Approximately, 2/3 of the patient complains of dry mouth (2). Finally, parafunctional habits such as lip and cheek biting, bruxism, tooth grinding and clenching, tongue thrusting, and lip licking are observed with BMS (5). Physical examination and laboratory analysis are classically unremarkable in primary BMS. However, they can be abnormal in secondary BMS. Oral findings potentially include areas of erythema, geographic tongue, candidiasis, atrophic glossitis, lichen planus, and xerostomia (28).

Differential diagnosis

The mimickers of BMS may include stomatitis, atypical facial pain, atypical odontalgia, idiopathic facial arthromyalgia, pemphigoid, pemphigus, neoplastic lesions in the oral cavity, acoustic neuroma, denture design or tooth restoration failures, herpes simplex or herpes zoster, trauma to lingual or mandibular nerves after dental surgery (5, 29). Other systemic diseases that can manifest symptoms similar to BMS should be considered: Sjögren´s syndrome, diabetes, candidiasis, deficiencies of iron, folate, zinc or group B. vitamins (24). Detailed history and physical exam is crucial to differentiate above medical conditions (28).

Diagnosis

The diagnosis of BMS remains challenging as diagnostic criteria are not sufficiently defined or universally accepted, several confounding diagnoses exist, and the clinical picture is often variable (28). taking a thorough and comprehensive history is the key to diagnosis of BMS. Important information to be ascertained by the practitioner relates to the past and current symptoms (pain, dry mouth, taste), their duration, intensity, character, location, onset, and factors that improve or worsen the pain and its course. A numeric or visual analog scale measuring the patient's pain intensity and dry mouth should be used (9).

Scala et al (5) proposed the following fundamental criteria: (1) daily and deep bilateral burning sensation of the oral mucosa; (2) burning sensation for at least 4 to 6 mo; (3) constant intensity, or increasing intensity during the day; (4) no worsening but possible improvement on eating or drinking; and (5) no interference with sleep. Additional supportive criteria are, (1) dysgeusia and/or xerostomia; (2) sensory or chemosensory alterations; and (3) mood changes or psychopathological alterations. Since primary BMS is a diagnosis of exclusion, thorough investigation for local and systemic factors associated with secondary BMS is essential. Careful review of recent mood disturbances, dietary habits, history of dental procedures, use of dental prosthetics, nutritional deficiencies, and changes in medication is necessary in the evaluation of BMS. Physical examination primarily consists of detailed study of the oral cavity, including dental inspection. Laboratory analyses must include hematological assessment of nutritional deficiencies, blood glucose levels, autoimmune markers, estrogen and progesterone concentrations, patch testing for specific allergies (5). Measurement of salivary flow rates should be employed (30).

Additional studies may warrant oral cultures and scrapings to evaluate for a bacterial or fungal origin of symptoms. Tongue biopsy is not required if the tongue appears normal on clinical exam and is only indicated when a particular lesion is visualized. In general, the diagnosis of BMS remains a major challenge, requiring extensive clinical and laboratory evaluation with a particular attention to details of patient's history and physical exam (28).

Treatment

The complex and multifactorial etiology of BMS necessitates systematic and interdisciplinary approach for the proper management of these patients. Although many drugs, treatment methods have been proposed for the management of BMS, none of them proves to be a gold standard one and are not satisfactory. Treatment planning should be custom made to each patient. Obtaining the correct clinical diagnosis of BMS is of paramount importance for the management (2). Acquiring patient trust and reassurance is of paramount in the management of BMS, and it is crucial that the patient understands and accept the diagnosis and has a realistic understanding of the likelihood of being cured. These have a great impact on patient's attitude and may often results in longterm beneficial effects (31). The investigator should have a detailed review of patient's personal/familiar/medical/dental/personal histories and a careful interpretation of data obtained from various physical and laboratory investigations. If any local, systemic or psychological factors are evident, attempt should be made to treat or eliminate these factors. A thorough clinical examination of the oral mucosa is crucial in these patients. The lack of oral mucosal pathology is mandatory for the diagnosis of BMS. Details regarding the quality, onset, persistence, intensity, occurrence, duration, relieving factors, evolution, site(s) involved in pain symptoms are essential. This information will give a vital clue in differentiating the BMS from other chronic orofacial pain disorders. Because BMS is a multifactorial disease, none of a single drug or treatment procedure can result in complete remission of all symptoms. Management of BMS can be broadly discussed under three topics namely topical medications, systemic medications and behavioral interactions. Medications used for BMS include antidepressants, analgesics, antiepileptics, antifungals, antibacterials, sialagogues, antihistamines, anxiolytics, antipsychotics and vitamin, mineral, and hormonal replacements (2). Topical application of capsaicin (0.025% cream) has been used in BMS as a desensitizing agent and is thought to inhibit substance P. Reduced patient tolerance and increased toxicity limits its use in some patients (32). Trials have also been made on rinsing with 0.15% benzydamine hydrochloride, 3 times a day, having an analgesic, anesthetic, and anti-inflammatory effect, but with inconsistent results (33). Some other gets relieved from pain by using mouth rinse made of Tabasco sauce with water (34) or alternatively one made of hot pepper and water in a dilution between 1:2 and 1:1.(23). The topical application of clonazepam (by sucking a tablet of 1 mg), an

agonist of gamma amino butyric acid receptors, 3 times a day for 14 days found some success in some (35). The most commonly used local anesthetic agent, lidocaine was tried by few and they have not been shown as an effective treatment due to their short duration of analgesic action. Topical application of 0.5 ml Aloe vera gel at 70%, 3 times a day combined with tongue protector is found to be effective for reducing the burning and pain sensation of tongue (36). Topical lactoperoxidase (biotene mouthwash) and 5% doxepin were attempted and found to be ineffective (37). Studies have been made to evaluate the efficacy and tolerance of amisulpiride (50 mg/day) and selective serotonin inhibitors: paroxetine (20 mg/day) and sertraline (50 mg/day) in the treatment of BMS, over eight weeks, with a reasonably high efficacy (around 70%). However, the effect of amisulpiride manifests early, after one week of treatment. No serious adverse effects are referred in any of the three groups. Serotonin reuptake inhibitors are effective, above all with an associated depression, being better tolerated for the absence of anti-cholinergic effects, particularly in dry mouth. According to the results obtained with gabapentin, it seems to have little or no effect in patients with BMS. The medication was administered at an initial dose of 300 mg/day, increasing by 300 mg/day every two days to a maximum of 2,400 mg/day. The efficacy of oral clonazepam (0.25 mg/day increasing to a maximum of 3 mg/day) has also been evaluated with variable results, or by topical application (0.5 mg to 1 mg two or three times a day) with better results (24). Systemic capsaicin has been used (0.25%, three times a day, for 30 days) with a significant reduction in pain intensity compared with a placebo group. However, its use is not recommended for extended treatment, since 32% of patients experience gastric pain after four weeks of treatment (24).

Hormone replacement therapy (HRT) has also been used, finding that women with symptoms of burning and estrogen receptors in the oral mucosa respond to hormone replacement, while this does not occur in patients without these receptors; however it cannot be guaranteed that HRT could be an effective treatment for the oral symptomatology (24). Several studies suggest that alpha lipoic acid can improve the symptoms in BMS, showing that at two months, 97% of the patients treated with alpha lipoic acid (200 mg, three times a day) experienced an improvement in the symptoms. This improvement is maintained during the first year in 70% of the patients. In other studies, the combination of psychotherapy (2 one-hour sessions weekly for two months) and alpha lipoic acid (600 mg/day for two months), was significantly more beneficial than psychoanalysis alone or alpha lipoic acid alone. The results suggest that alpha lipoic acid could complement psychotherapy and be an acceptable alternative to psychoactive medication. However, in studies that compare with a placebo the efficacy is limited (38). Studies on the effect of cognitive therapy on resistant BMS shows a statistically significant reduction in pain intensity for those receiving cognitive therapy compared with placebo immediately following the therapy and a further reduction at the 6-month follow up (31). Another study showed some improvement of BMS resulting from psychotherapy treatment over 2 months, with significant improvement when combined with alpha-lipoic acid therapy (ALA) (600 mg/d) (39). It seems from these studies that the practitioner may consider the involvement of a behavioral medicine practitioner as part of a multidisciplinary approach when managing patients who have BMS.

Prognosis:

Although the short term follow up studies may show potential symptomatic improvement with treatment in patients with BMS, the longterm outcomes for BMS remain unclear. Early observational report by Gilpin (40) in 1936 may provide a closer look at the natural history of the disease that follows a "rule of 3's": up to one third of cases would enter spontaneous remission, another third would show moderate improvement, and finally the last third would show no improvement or even worsening of the symptoms. Prospective clinical and pharmaceutical advances may have significantly changed the landscape of BMS, as recent study showed nearly 10% of spontaneous remission, 26% of moderate improvement, 37% of no significant change, and finally 26% of worsening of symptoms in patients receiving no therapy with an estimated follow up of at least 18 mo. Therapy may be effective in 29% of the patients, with 56% reporting no changes, and 15% admitting worsening of the pain (30). In perspective, complete understanding of the etiology and pathogenesis is imperative to the development of novel and efficacious therapeutic strategies, and will guide overall prognosis of the disease in the future (28).

II. Conclusion

Burning mouth syndrome is a painful and often frustrating condition to the patients. Its pathogenesis relates to complex interlay of central and/or peripheral neural pain pathways. The etiopathogenesis of BMS seems to be complex and multifactorial. Diagnosis and management of BMS is not an easy task for oral health care professionals. Furthermore, the lack of understanding the cause and mechanism behind the syndrome adds to the difficulty in finding a therapeutic management program. Although there are various forms of pharmacologic treatment for idiopathic BMS, there are no well-defined data and studies to formulate a consensus on this syndrome. A thorough understanding of the etiology and psychological impact of this disorder, combined with novel pharmacological interventions is required for better management.

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