MCBU SBED
MANİSA CELAL BAYAR ÜNİVERSİTESİ SAĞLIK BİLİMLERİ ENSTİTÜSÜ DERGİSİ
MANISA CELAL BAYAR UNIVERSITY JOURNAL OF INSTITUTE OF HEALTH SCIENCE
ISSN: 2147-9607

DERLEME
REVIEW
MCBU-SBED, 2017, 4(2): 597-603

AN UPDATE ON BURNING MOUTH SYNDROME

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Gönderim Tarihi / Received: 21.02.2017
Kabul Tarihi / Accepted: 13.06.2017
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ÖZ

Yanan ağız sendromu belirli medikal veya dental patoloji olmaksızın ağız içi yanma hissi olarak tanımlanmaktadır. Sıklıkla orta yaşlı ve yaşlı kadınlarda görülen kronik bir durumdur. Sıklıkla idiopatik olup patofizyolojisinden pekçok faktörün sorumlu olduğu bilinmektedir; ancak henüz etyopatogenezi tam aydınlatılamamıştır. Yanan ağız sendromunun tedavisi hem hekimler hem de hasta açısından genellikle çok başarılı değildir. Bu hastaların tedavisinde multidisipliner ve sistemik yaklaşım gereklidir. Bu derlemede yanan ağız sendromunun epidemiyolojisi, etyolojisi, patofizyolojisi, tanı ve tedavi modaliteleri özetlenmiştir.

Anahtar Kelimeler: *Yanan ağız sendromu, Glossodini*

ABSTRACT

Burning mouth syndrome (BMS) is defined as an intraoral burning sensation without any identifiable medical or dental pathology. BMS is a chronic condition that is most commonly seen in middle-aged and elderly women. This condition is often idiopathic, pathophysiology is most probably of multifactorial origin; but yet, its etiopathogenesis remains unclear. The management of BMS is usually unsatisfactory for both physician and patients. Interdisciplinary and systemic approach is necessary for the management of patients with BMS. In this review article epidemiology, etiology, pathophysiology, diagnosis and treatment modalities of BMS have been summarized.

Keywords: *Burning mouth syndrome, Glossodynia*

INTRODUCTION

Burning mouth syndrome (BMS) is a chronic clinical entity manifested as a burning type pain or a burning sensation in mouth without being accompanied by abnormal clinical or laboratory results (1). There are variety of names applied to this presentation including, but not limited to, BMS (the most widely accepted), stomatodynia, stomatopyrosis, glossopyrosis, glossodynia, sore mouth, sore tongue and oral dysesthesia (2).

Burning sensation in mouth may be an accompanying symptom of oral lesions, it also can be observed in individuals with healthy oral tissues. BMS has a multifactorial ethiology, therefore to diagnose BMS as an "idiopathic BMS" all pathologies associated with BMS must be ruled out.

BMS is first described in the twentieth century by Butlin and Oppenheim as glossodynia and Headache Classification Subcommitte of the International Headache Society classifies the disease under "central causes of facial pain".

EPIDEMIOLOGY

The prevalance of BMS was reported in various international studies between 0.6% to 15% (3). BMS is a disease that is usually seen in postmenopausal women, mostly over 55 years of age. There are also cases diagnosed in early adulthood (between 20-40 years). There is a gender difference with a female predominance; and BMS is rarely diagnosed in men.

ETIOLOGY

The etiology is unknown, but it is believed to be multifactorial. Patients with BMS often have anxiety and clinical depression (4). Psychogenic factors such as depression, anxiety and fear of cancer have been implicated in BMS, although it is pretty reasonable that these conditions could be the result of the chronic pain rather than its cause (5).

Based on the definition provided by the International Headache Society, which presumes that BMS is of idiopathic nature, attempts have been made to identify the risk factors and possible role of these risk factors in etiopathology of the syndrome. Therefore, we can classify the etiopathogenesis of BMS as primary, idiopathic and secondary forms, and identifiable risk factors as local or systemic (1).

Oral candidiasis is not an uncommon condition in this patient population. Similarly, viral diseases such as herpes simplex or zoster can result in similar symptoms that can be interpred as a burning sensation. Although the pain of post herpetic neuralgia is usually much more severe, occasionally it also can present solely as a burning sensation on the oral mucosa (2).

BMS is eventually associated with reduced salivary flow and abnormal saliva composition

(increasing concentreations of K+, Na+, Cl-, Ca+2, Immunglobulin A, amylase). Even in the absence of hyposalivation, patients may complain of xerostomia and dry mouth and loss of taste and smell (6,7). On the other hand, several reports suggested that subjective feeling of dry mouth in BMS patients is more likely due to idiosyncratic side effects from an extensive abuse of anticholinergics, such as pyschotropic drug, antihistaminic and diuretics. Lee et al. found that the subjective symptoms and quality of life in patients with BMS were not correlated with salivary function. The resting salivary flow was significantly lower compared to healthy controls. In contrast, there was no difference in stimulated salivary flow rate between the BMS group and the control group. Furthermore, in patients with BMS, there is also no difference in terms of salivary gland function between patients with and without hyposalivation (8).

Allergic reactions against dietary allergens have been demonstrated in patients with BMS. These allergens include sorbic acid, cinnamon, nicotinic acid, propylene glycol, and benzoic acid. Other allergens identified by patch testing are dental metals such as zinc, cobalt, mercury, gold and palladium. Sodium lauryl sulfate, a detergant in toothpaste known to cause dry mouth, may also be involved in the etiopathogenesis of BMS (9).

According to Wardrop et al. depression and anxiety can be the product of a common factor, an endocrinological disorder could be the cause of these alterations in women following menopause (10). Forabosco et al. attributed the relief of oral discomfort following hormone therapy, to the presence of estrogen receptors on the oral mucosa (11). On the other hand, Tarkkila et al. evaluated the association between oral discomfort and menopause in 3173 patients, and demonstrated that 8% of these women exhibited burning sensations of the oral tissues. Nevertheless, hormone replacement therapy did not prevent the occurence of symptoms (12).

A potential association between smoking and development of BMS has been reported in a recent study (estimated odds ratio of 12.6) (9). Cases of drug-induced BMS (topiramate, carbidopa/levodopa) have been reported in the last years. Although these cases may not truly represent primary BMS, it may be important to recognize drug-induced BMS and other causative factors of oral burning sensations (13). Etiologic factors of BMS have been summarized on Table 1.

CLASSIFICATION

Scala et al. previously introduced the concepts of ‘primary’ (idiopathic) and ‘secondary’ (resulting from identified precipitating factors) BMS to allow a more systematic approach to patient management. In primary BMS, organic or local causes cannot be identified and a neuropathologic origin is likely (14). Secondary BMS is a variant that is associated with local or systemic factors. Local factors include xerostomia, oral candidiasis, oral submucous fibrosis, poorly fitting prosthesis, bad oral habits (such as tongue thrusting and bruxism), etc. Systemic factors include nutritional deficiencies (such as thiamin, riboflavin, niacin, vitamin B12, folic asid and iron deficiencies), endocrine disorders (like estrogen deficiency, diabetes mellitus and hypothyroidism). Sjogren’s syndrome, anxiety, psychosocial stress, depression, Parkinson’s disease and others (15).

PATHOPHYSIOLOGY

BMS is a complex disease and may be of neuropathic etiology, with reduced pain and sensory thresholds (16). Furthermore, a recent article proposes a hypothesis focused on a neurodegenerative cause of BMS: chronic anxiety or post-traumatic stress, associated to menopause, leads to dysregulation of the adrenal production of steroids. One consequence is decreased or modified production of some major precursors for the neuroactive steroid synthesis occuring in the skin, mucosa and nervous system. This results in neurodegenerative alterations of small nerves fibers of the oral mucosa and /or some brain areas involved in oral somatic sensations (17). Oral mucosa biopsies of patients with BMS demonstrated decreased density of epithelial nerve fibers as well as axonal dearrangement, indicating a potential role for peripheral small-fiber sensory neuropathy (18). These neuropathic changes in nerve fibers become irreversible and precipitate the burning pain, dysgeusia and xerostomia associated with somatodynia (17). In addition to the neuropathic theory of BMS Siviero et al. demonstrated central involvement of the olfactory pathways as well as somatosensory and gustative pathways in pathophysiology of BMS (19). Moreover, Borelli et al. found increased levels of nerve growth factor, a neuropeptide vital to nociceptive function, in the saliva of patients with BMS (20).

Interestingly, polymorphism in pro-inflammatory interleukin (IL)-1β has been shown in patients with BMS, suggesting that regulation of IL-1β methabolism may be a therapeutic target in patients with BMS. Indeed, recent studies showed that pro-inflammatory citokines such as IL-6 are also increased in the saliva of patients with BMS, suggesting, neuroinflammatory processes may play role in the disease (16).

Tatullo et al. demonstrated a significant correlation between “oxidative stress” and “BMS” in female patients. Female patients with BMS show significantly different d-ROMS (total oxidant capacity) and BAP (biological antioxidant potential as iron- reducing activity) levels, compatible with an oxidative stress condition (17).

CLINICAL MANIFESTATIONS

The diagnosis of BMS remains challenging as 1) diagnostic criteria are not sufficiently defined or universally accepted; 2) several confounding diagnoses exist, and 3) the clinical picture is often variable. Scala et al (14) proposed the following fundamental criteria: (1) Daily and deep bilateral burning sensation of the oral mucosa; (2) burning sensation for at least in the last 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 effect of sleeping on discomfort.

Most of the time, patient found difficulty in describing the sensations they perceive (3). Burning sensation in the oral mucosa is the most frequent description of patients but BMS might manifest as an itching sensation, numbness, alterations in taste (the BMS patients reported ageusia for bitter/acid/spicy substances or metallic taste), dry mouth, burning pain, oral stinging, etc (21). The location of pain is not pathognomonic, but often involving more than one site (3). The burning sensation generally involves the tongue, especially at its tip and edges, and can be extended to any area of the mouth (4). Additionaly, some patients may even experience burning sensation in extra oral mucosa including the anogenital region (3).

Patients usually report that the burning sensation presents its lowest intensity upon waking up, but reappears after the first meal of the day. Once begun, it is continuous, reaching the maximum intensity by late evening. Burning mouth also often co-exists with other chronic pain disorders (22).

MANAGEMENT

There are no effective standard treatment protocols for all BMS patients. Therapy options are pharmacological treatments (local or systemic) and alternative (psychiatric, acupuncture, electro-convulsive therapy, etc.) methods. It is of utmost importance to differentiate the primary and secondary BMS, as in secondary BMS, the goal of therapy is to treate the underlying pathology (21).

Treatment of BMS is usually symptomatic; However, when local factors that could increase the sensation of oral burning are present, they should be eliminated. Food with irritative effect on mucosa like alcohol, spicy foods and acid drinks should be avoided (23).

A multimodal treatment regimen is often recommended. In general, patients with BMS may have a response to pharmacological treatments with anxiolytics, anticonvulsants, antidepressants, atypical antipsychotics, histamine receptor antagonists, and dopamine agonists. Evidence of effective treatment is available for clonazepam, the herbal supplementation of catuama, tongue protectors with aloe vera, alpha lipoic acid in combination with gabapentin, capsaicin rinse (which induces desensitization to thermal, chemical, and mechanical stimuli through depletion of substance P), acupuncture, and negatively for alpha lipoic acid alone (3, 18).

Some studies relate to the topical use of capsaicin to control neuropathic pain, as this drug acts on the sensory afferent neuron and can be used an analgezic. However, capsaicin increases the burning sensation at the beginning of the treatment and thus, may have a limited compliance. Topical anaesthetics such as lidocain (2%) are used as a symptomatic treatment to reduce the pain (23).

Systemic capsaicin has been shown to reduce pain however there is a significant number of side effects, and frequently patients suffer particularly from gastric pain (2).

Gremeau-Richard et al. categorized patients with BMS into central and peripheral groups and reported that patients with predominantly peripheral stomatodynia tended to have better response to topical clonazepam than those in the central group (24).

When neural damage is suspected, alpha lipoic acid (ALA) can be employed in patients with BMS due to its neuro-protective effect. Patients treated with antipsychotics and those who received 200 mg of ALA three times a day, for at least 2 months, experienced significant symptomatic improvement. The most impressive results were obtained in the group treated with ALA and antipsychotics simultaneously (23).

Gabapentin and alpha lipoic acid may be used alone or in combination for reducing the symptoms in patients with BMS. The most effective results were obtained with the combination therapy (4).

Iron, vitamin B12 and folic acid are related to the health of oral epithelium. Long-term dry mouth and iron, vitamin B12 or folic acid deficiency may cause at least partial atrophy of the oral epithelium in patients with BMS. Sun et al. found significantly higher prevalence of vitamin B12, iron and folic acid deficiencies and abnormally elevated blood homocysteine level in patients with either primary or secondary BMS compared to healthy controls. Supplementation of vitamin B12, folic acid and vitamin B6 can lower the higher serum homocysteine level to normal level. Therefore, it is interesting to know whether different vitamin-supplement treatments may decrease the abnormally higher blood homocysteine level to normal level and reduce oral symptoms in patients with either primary or secondary BMS (15).

Recent advances from behavioral, pyschophysiological, and neuroimaging methods demonstrate that the placebo effect is a ‘real’ neurobiological phenomenon and that the altered pain experience during placebo analgesia results from active inhibition of nociceptive activity (18). In their seminal study, Petrovic et al. (25) used PET to compare the functional anatomy of placebo analgesia with that opioid treatment and demonstrated a shared neural network underlying both placebo and opioid analgesia involving the rostral anterior cingulate cortex and brainstem.

Cognitive- behavioral (CB) therapy is a proven and effective for pain reduction in BMS patients. The beneficial effects of group CB intervention is probably mediated by modulating the psychological pathways, especially the pain perception (26).

Further improvement has been noted when cognitive behavioral therapy is combined with pharmacological management. Alpha-lipoic acid has been shown to result

in significant symptom reduction in combination with CB therapy (26).
Glossodynia is considered as a pain disorder among somatoform disorders (27). Antidepressants are widely used in the treatment of BMS28. Because of side effects of tricyclic antidepressants, new-generation antidepressants-selective serotonin reuptake inhibitors(SSRI) and serotonin-noradrenalin reuptake inhibitors (SNRI) which are associated with less frequent and milder side effects, have recently been increasingly used in consideration with role of serotonin in pain perception (27, 28).

Recently it was suggested that acupuncture might be effective in patients with BMS. Brailo et al. reported that the average decrease in burning symptoms after the acupuncture treatment was 55.2%. All patients experienced a decrease in burning symptoms that was reflected in the lower VAS (visual analogue scale) scores (29).

ECT (Electroconvulsive therapy) may be considered in severe and refractory cases of idiopathic BMS (30). Momota et al. reported that high wattage pulsed stellate ganglion near-infrared irradiation (SGR), which is considered to correct abnormalities in the autonomic nervous system was safe and effective for the treatment of BMS (31).

The sense of taste is mediated through the salivary zinc-dependent polypeptide, gustin. Low salivary zinc concentration leads to reduction in taste and appetite. Previous studies have shown that treatment with exogenous zinc can increase the salivary gustin level and improve the taste function (15). Therefore, zinc administration may potentially be helpful to treat taste disorders, by stimulating feeding (32).

In addition to well-defined analgesic properties, cannabinoids actively target many pathopshysiological mechanisms contributing to neuropathic orofacial pain disorders, therefore, cannabinoids may represent a bona fide therapeutic strategy for these conditions (16).

ALA, clonazepam, capsaicin and psychotherapy showed modest benefit in the first two months at least in some studies and for some outcomes. Evidence for longer term outcomes was more limited. Catauma, tongue-protectors and clonazepam also showed promise. However, these conclusions are limited by short follow-up periods, marked variability in study methods and quality, and low participant numbers in individual studies. To date, the best available evidence is for ALA, capsaicin and clonazepam with equal efficacy for local or systemic forms when these alternatives are available. Given the side effects of systemic capsaicin, mouth washes and oral analogues such as lafutidine should be considered. In individual studies, catauma, tongue-protectors and more formal individual psychotherapy may show promise (33).

The main treatment modalities used in BMS have been summarized on Table 2.

PROGNOSIS

Prospective clinical and pharmaceutical advances may have significantly changed the landscape of BMS, as recent study showed nearly 10% spontaneous remission, 26% moderate improvement, however; 37% showed no significant change, and finally 26% showed worsening of symptoms in 18 months followup. Therapy may be effective in 29% of patients, with 56% reporting no changes, and 15% admitting worsening of the pain (9).

Individuals with chronic pain have a higher prevalance of depression, anxiety, alcohol and drug abuse, or dependence than those without pain. In a recent review, it was reported that chronic pain was associated with increased risk of suicide and that the rates of suicidal ideation were higher in individuals with pain than those without (34).

CONCLUSION

Burning sensation in the mouth, is a clinical condition called burning mouth. When any etiologic factor identified, patients where these symptoms are included in the burning mouth syndrome group. In patients admitted with complaints of burning sensation in the mouth, detailed anamnesis, careful examination of the oral mucosa and laboratory tests are utmost importance to exclude the secondary BMS and to guide the therapy. The etiology of the disease remains unrevealed and there is no accepted treatment algorithm. A multidisciplinary approach is required in treatment (endocrinologists, dentists, neurologists, psychiatrists, etc). Despite attempts with various treatment modalities, there is no effective treatment which enhances quality of life of patients with BMS.

TABLES

Table 1. Local and systemic factors responsible from BMS

1. Local factors	**2. Systemic factors**
○ Dry mouth (salivary gland disorders, drugs, radioteraphy) ○ İnfections (bacterial, fungal or viral) ○ Trauma ○ Alcohol ○ Smoking ○ Repetitive oral habits (bruxism, tongue motor tics) ○ Allergic contact (dental material, allergenic foods, hygienic/ cosmetic products, etc.) ○ Mucosal disorders (lichen planus, geographic tongue, fissured tongue)	○ Nutritional deficiencies (Vitamin B1, B2, B6, B12, niacin, folic acid, iron, zinc) ○ Endocrine disorders (diabetes, thyroid disease, menopause) ○ Autoimmune diseases (Sjogren's syndrome, Sicca syndrome) ○ Drugs (angiotensin converting enzyme inhibitors, antihyperglycemics, chemotherapeutic agents, benzodiazepines, neuroleptics, antihistamines) ○ Gastrointestinal disorders (helicobacter pylori) ○ Psychiatric disorders (depression, anxiety, obsessive-compulsive disorder, somatoform disorders) ○ Peripheral or central neuropathy

Table 2. The main treatment modalities used in BMS

Topical Treatments	○ Lidocaine ○ Benzydamine hydrochloride ○ Topical antifungals ○ Sucralfate ○ Capsaicin ○ Clonozepam
Systemic Treatments	○ Antidepressants ○ Antihistamines ○ Benzodiazepines ○ Antipsychotics ○ Iron ○ Vit B12/ Folate ○ Vit. B1, B2, B6, Zinc ○ Estrogen ○ Neuroleptics ○ Alpha lipoic acid
Alternative Treatments	○ Cognitive behavioral therapy ○ Hypnosis ○ ECT (Electroconvulsive therapy) ○ Acupuncture ○ Cannabinoids ○ SGR (stellate ganglion near-infrared irradiation)

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