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BURNING MOUTH SYNDROME IN POST MENOPAUSAL FEMALES: AN UPDATE ON THIS ENIGMATIC PATHOLOGY

Dental Science

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ABSTRACT

Burning mouth syndrome (BMS) is a challenging enigmatic condition characterized by burning pain in the oral mucosa without any identifiable cause. This is a condition predominantly affecting 18-30% of the peri-/post-menopausal women. The diagnosis is based on exclusion as by definition it will not have an identifiable cause. The pathophysiological mechanisms for the symptoms are poorly understood and therefore the management of this condition remains empirical and at times arbitrary and often ineffective even till date. Further the challenges faced in its diagnosis and management has a significant emotional impact on patients. This article is an effort to review and update various pathophysiological mechanisms and effective treatment modalities of BMS in post menopausal females.

KEYWORDS

Burning Mouth Syndrome, causes, Post menopausal stage, diagnosis, management

INTRODUCTION

Burning mouth syndrome (also sometimes referred as BMS, BMD, Stomatopyrosis, Glossopyrosis, Stomatodynia, Glossodynia, Sore Mouth, Sore Tongue, Scalded Mouth Syndrome and Oral Dysesthesia) is a chronic pain syndrome characterized by burning in the oral soft tissues with clinically normal, healthy oral mucosa in which a medical or local dental cause has been excluded."(1-3) The term BMS clinically describes a prolonged burning sensation of the oral mucosa, commonly on anterior part of the tongue, that often increase in intensity at the end of each day, and that seldom interferes with sleep. Full blown syndrome is commonly observed inpost menopausal women.(3,4) The onset is generally insidious and without any recognizable precipitating factors. The mean severity of burning or BMS pain has been assessed at about 5-8 cm on a 10 cm Visual Analogue Scale (VAS), where 10 cm corresponds to worst possible pain. Other symptoms commonly associated with this syndrome are dysgeusia, xerostomia, sensory anamolies and psychological disorders.[3,5-7]

This condition is typically observed in middle aged and elderly subjects with an age range from 38—78 years with female to male ratio of about 7:1.(1,3,7) Based on the makeup of most studies published to date, oral burning appears to be most prevalent in post menopausal women. They report pain onset ranging from 3 years before to 12 years after menopause.The tip of the tongue is the most common location (71%) for burning, followed by the lips (50%), lateral border of the tongue (46%), dorsum of the tongue (46%) and palate (46%).(3,7,8,9) Because of the variability in criteria used to diagnose BMS, the true prevalence is uncertain. Approximately 90% of women who attend healthcare clinics for their BMS symptoms are peri/postmenopausal women. Likewise, 18%-33% of menopausal women exhibit BMS symptoms.[3,9,10]

Thus the first step in diagnosis is to look for a possible cause to explain the burning sensation. When none is found and when the mucosa appears absolutely healthy, a tentative diagnosis of BMS is made. The search for a possible cause continues even as empirical treatment begins.However the treatment is often ineffective in alleviating symptoms.Patients are often referred from one health care professional to another without effective management. Thus, BMS represents a disorder with a very poor prognosis in terms of quality of life.[3]

By definition the etiopathogenesis of BMS is uncertain. However some workers have tried to develop hypothesis and models to explain its etiopathogenesis. Some workers have also suggested that BMS is probably of multifactorial origin.Its pathogenesis remains largely enigmatic.[3]

Many researchers believe that patients diagnosed with BMS have symptoms characteristic of trigeminal nerve disorders (alterations in pain perception and neuron transmission, and increased excitability of the trigeminal vascular system), in turn suggesting that underlying basis of the syndrome is neuropathic.(10,11,12) Studies have shown the presence of alterations in the small-diameter nerve fibers (C fibers) in patients with BMS. Some patients show neuropathic signs affecting both larger- and smaller-diameter nerve fibers. It therefore may be postulated that BMS is a consequence of both generalized alterations and disorders at different levels of the trigeminal system.(10,11,12) Similarly, the existence of an enhanced blink reflex in some patients with BMS points to a central nervous system alteration correlated to dopaminergic system dysfunction.[13]

Other authors have suggested that BMS behaves as a form of oral phantom pain.Some alteration in taste function would allow stimulation of the taste nerve endings to generate both excitatory and inhibitory signals.(10) Data suggests that individuals who suffer from BMS are likely to be "supertasters" and have large number of fungiform papillae that are innervated mostly (75%) by trigeminal nerve and partly (25%) by chorda tympani nerve. BMS may result from hyperactivity of the sensory component of the trigeminal nerve following loss of central inhibition as a result of damage to the chorda tympani.[14,15]

Also hormonal causes have been identified as we know that the prevalence of BMS is greater among post menopausal females. Since both BMS and vulvodynia occur more frequently in menopausal women, estrogen deficiency could be considered as a common pathological mechanism of these clinical conditions.(16) Estrogen receptors are also identified in both the tongue and the vaginal mucosa

besides having microscopic similarity.(16) There are also strong views expressed against the psychogenic nature of BMS at menopause in view of the dramatic drop in sex steroid levels at the menopausal transition.(16)Physiological levels of estrogens are neuroprotective in the nigrostriatal dopaminergic system so that their decline with menopause may also partly explain the age and gender predilection of this disorder. Moreover recent findings suggests that estrogen receptors found in trigeminal neurons modulate nociceptive responses and may offer a valuable link in explaining the female preponderance observed in BMS patients population.[14]

Interestingly, Recent studies using videocapillaroscopic examination with a capillaroscope with a fiber-optic probe at a magnification of x200 provided important diagnostic results regarding alterations of the local microcirculation in subjects with BMS when compared with healthy subjects.(17) They found significant increase in the diameter of the capillary ansae, afferent ansae and efferent ansae in subjects with BMS compared with normal individuals.[17]

Also Psychological disorders such as depression and anxiety play an important role in the modulation of pain perception, being able to increase or decrease nerve transmission from the peripheral pain receptors, and modifying individual pain perception - reducing the pain threshold and thus causing normal stimuli to be perceived as painful.(18-20) The classical description of depression and anxiety concomitant to BMS suggested an association between the latter and psychological problems. In addition, improvements in BMS have been observed as a result of cognitive-behavioral therapy and the use of anxiolytic drugs.(14)This indicates that psychological disorders may predispose to the development of BMS, though the way in which they might influence its pathophysiology remains unclear. However, there is increasing controversy as to whether depression and anxiety are primary or secondary events to the oral pain.[19-21]

ROLE OF ORAL PHYSICIAN IN ESTABLISHING DIAGNOSIS

Burning in the mouth may arise from a variety of disorders.(22-24) This can be best assessed by an Oral physician , a specialist in Oral Medicine which is a specialty of dentistry concerned with the care of oral diseases .

The first responsibility is to rule out other causes of chronic burning sensation in the oral cavity with an identifiable cause . (22-24) The next is to ascertain if the patient is mistaking a normal mucosal variation as a mucosal pathology and is perceiving a burning sensation due to a psychogenic cause.

Drug history is important. Among the drugs reported to induce manifestations similar to those of BMS, mention should be made of efavirenz, an anti retroviral agent and antihypertensive agents.(25) Curiously, the only types of antihypertensive drugs associated with BMS-compatible symptoms are those compounds that act upon the angiotensin-renin system, i.e., ACEIs (captopril, enalapril and lisinopril) and ARAII drugs (eprosartan and candesartan). BMS may result from an anomaly of renin angiotensin system that blocks angiotensin II activity.[25]

We have developed an algorithm for the evaluation of BMS by an oral physician(FLOWCHART 1). The presence of underlying psychological disorders can be revealed by appropriate structured interviews.[3]

MANAGEMENT

Once the diagnosis of BMS is established, we must reassure the patient that the tissues are clinically healthy and their condition is not serious. We must also understand that the burning sensation is real and that we have not been able to unearth a course in the light of current medical knowledge. They should be offered regular follow-up from two to four times a month during the symptomatic period. Each evaluation should include an analysis of pain levels, personality, psychological functioning, and quality of life. A personal interpretation of the evolving nature of the syndrome should be included in a patient diary. The protocol for BMS management is complex. Patientswith Secondary BMS can fall into specific sub-categories accordingto the identified disorder(s) ("patient stratification"), and,subsequently, they undergo appropriate therapy based on identified etiologies.(3) The remaining cases (Primary BMS) will undergo proper pain control(3) (FLOWCHART 2).

Although a large variety of drugs, medications, and miscellaneous treatments has been proposed in BMS, the treatment management of this syndrome is still not satisfactory, and there is no definitive cure.[9,26,27]

Initially, it is important to provide patients with informationon the nature of their condition and give reassurance. Precautionary measures, such as abstaining from specific food allergens, should also be suggested. Drugs able to induce either BMS or xerostomiashould be avoided as well. A proper interactive counseling often results in term beneficialeffects.

Proper administration of conjugated estrogens and medoxyprogesterone acetate may relieve oral symptoms in per/ post menopausal females.(28) However, HRTs has not been found useful in majority of patients.(28) No RCTs of sufficient quality is present in comparing HRT versus placebo in treatment of BMS. Only one study showed Tibolone (2.5 mg daily) to be more effective than Oryzanol (30 mg 3 times a day) plus Vitamin E (100 mg 3 times a day) at improving symptoms in post menopausal women with BMS.(28) Thus, well designed clinical studies are required for evaluating the usefulness of HRT in BMS treatment.

Many pharmacological agents administered topically or systemically,have been proposed to overcome the burning issues in BMS.(26,27)Topical therapies that has been tried are clonazepam (1 mg tablet to be dissolved and hold in mouth), capsaicin (0.025% cream), Benzydamine hydrochloride (0.15% oral rinse) and lidocaine (2% gel). On the other hand, systemic agents used are amitriptyline (10-75 mg/day), paroxetine (20 mg/day), amisulpride (50 mg/day), sertraline (50mg/day), meclobemide (150 mg 2 times daily), levosulpiride (100 mg/daily), olanzapine (2.5 mg/day), clonazepam (0.25-2mg/day), gabapentin (300-2400 mg/day), alpha lipoic acid (200 mg tid) and capsaicin (0.025% capsules tid).[9,14,26,27]

At present evidence based management of BMS based on published randomized clinical trials suggests use of topical clonazepam, systemic SSRIs, amisulpride, alpha lipoic acid. While widespread clinical practice would support topical therapies such as lidocaine or capsaicin and systemic therapies like tricyclic antidepressants and anticonvulsants.[9,14]

Studies are few as it is difficult to conduct randomized controlled trials (RCTs) with or without blinding. Further, subjectivity of pain is another confounding factor.

Tammiala-Salonen et al(29) evaluated trazodone (100 mg) in a randomized double blind group and placebo controlled trials with a duration of 8 weeks but did not observed any significant difference between the two.Maina et al(30) compared the efficacy and tolerability of amisulpride (50 mg/day), paroxetine (20mg/day) and sertraline (50mg/day) in the treatment of BMS with a duration of 8 weeks and found an efficacy of about 70% with effect of amisulpride manifested earliest, after a single week of therapy. Pekiner FN in 2008 (31) assessed the efficacy of meclobemide (150 mg 2 times daily) for 3 months on the burning pain and psychologic status in ninety-four patients with BMS and 94 matched control subjects. Here, thirty-seven patients reported well to very good improvement while 44 reported satisfactory improvement without any adverse reactions.

Demarosi F et al in 2007 (32) evaluated the efficacy of the systemic administration of levosulpiride (100 mg/daily) for 8 weeks in 39 patients where 28 patients reported at least some improvement, and these patients had oral symptoms for significantly less. Another drug Olanzapine was evaluated by Ueda N in 2008 (33) who treated two cases of burning mouth syndrome with olanzapine (2.5 mg/day). One case was a 54-year-old female with BMS in whom olanzapine brought about dramatic improvement in the symptoms while the other case was of a 51-year-old male with BMS who failed to respond to paroxetine treatment but when Olanzapine (2.5 mg/day) was added to the treatment regimen and was increased to 5.0 mg/day the following week, the patient noted a reduction in symptoms and continued to live normally thereafter without experiencing severe symptoms.

Dysfunction of the dopaminergic system would justify systemic administration of the antiepileptic drugs gabapentin and clonazepam in BMS patients, which act upon the gabaergic system - enhancing its activity in an attempt to counter dysfunction of the dopaminergic

system.(14,26) Heckmann et al, (34) conducted an open study of 15 patients treated with gabapentin (300 mg every 48 hours to a maximum of 2400 mg/day) but did not find any significant reduction in their burning sensation. Grushkaet al(35) tested clonazepam via the oral route (starting dose was 0.25 mg/day, and was increased at a rate of 0.25 mg/day to a maximum of 3 mg/day) in a group of 30 patients with BMS and found that 43% experienced slight improvement.Woda et al (41) evaluated topical clonazepam in an open label study (0.5-1 mg, 2 to 3 times a day, to retain in saliva for three minutes followed by expulsion) with 25 patients and found that 40% reported complete symptoms remission.

Capsaicin 0.25% via the oral route was evaluated by Petruzzietal (36,37) in a randomized triple blind and placebo controlled study in 25 patients where 83% improved after the treatment. However progressive cases of gastric pain were documented in the treated group thus limiting systemic use of capsaicin in prolonged treatments.

Femiano et al (39) evaluated antioxidant Alfa LipoicAcid at a dose of 600 mg/day, in a parallel group and placebo controlled study. In the treated group, 5 patients experienced slight improvement, and 15 patients should resolution of their BMS.However a recent study failed to support the role for ALA in the treatment of BMS.[9,38]

Benzydamine hydrochloride is a non steroidal drug with analgesic, anti-inflammatory and antimicrobial properties.(26)Sardella et al (42) carried out a randomized, double blind study to assess the efficacy and safety of benzydamine hydrochloride (0.15% as a rinse for one minute) three times a day during four weeks where only 10% show partial improvement and thus this modality was proved ineffective in BMS patients.

Similarly, a single open label not blinded RCT indicated topical lactoperoxidase in oral solution (Biotene mouthwash) 5-6 times daily for 60 days is not effective at improving burning symptoms among patients with BMS.[9]

Sucralfate (20% suspension of sucralfate four times a day) for 3 weeks was selected by Campisi et al(43) in management of BMS on grounds that it protects the digestive mucosa. It strongly adheres to the ulcer. It precipitates surface proteins at ulcer base and act as a physical barrier for preventing acid, pepsin and bile from coming in contact with the ulcer base.(26) However, no significant results were obtained even in this study.

Therapy resistant BMS has been associated with underlying pschycological distress and these patients may particularly benefit from Cognitive Behavioral Therapy.[14]

A single RCT study demonstrating benefit when compared to placebo suggests that cognitive therapy sessions of one hour per week over 12 to 15 weeks have beneficial effects on reducing BMS pain intensity for upto 6 months. CBT has also been successfully supplemented with alpha lipoic acid.[9,14,45]

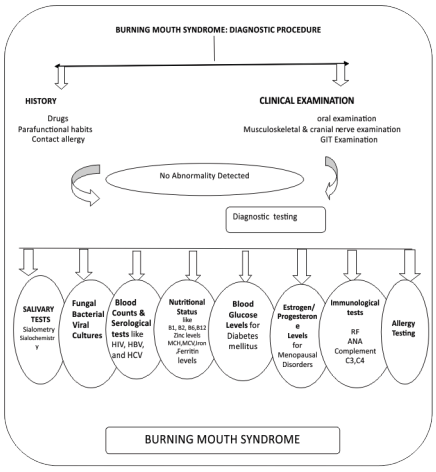
Ayurveda has shown promise with the use Daruhalad, a type of Turmeric, which is used in paste form in combination with honey for topical application. Homeopathy also suggests use of Acid Nitricum or Merc Sol for BMS, both 200 potency, depending on the patients clinical findings and history. Herbal medicine tends to treat specific causes of pain and burning. Sardella A et al in 2008 evaluated the effects of systemic Hypericumperforatum extract (300-mg capsules containing either H. perforatum extract (hypericin 0.31% and hyperforin 3.0%) three times a day for 12 weeks in 43 patients with BMS but did not found successful results.(46)

CONCLUSION

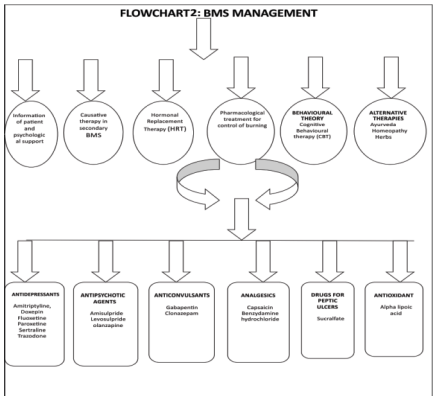
Post- menopausal women may suffer from Burning Mouth Syndrome which is a poorly understood condition affecting the mouth. BMS is a diagnosis of exclusion as establishing its diagnosis requires exclusion of all possible causes that may lead to burning sensation in the oral cavity.Thus it needs a specialist in oral medicine for an appropriate diagnosis. The approaches for evaluation and management of BMS are still not standardized and well designed clinical studies are required in this field.

Topical therapies such as lidocaine ,capsaicin and topical clonazepam, systemic therapies like SSRIs, tricyclic antidepressants, anticonvulsants, amisulpride, alpha lipoic acid and CBT are currently employed though none have been uniformly effective. Doctors treating women should be aware of this condition as it has a bearing on the quality of life of the patient. It may also be related to other symptoms of the patient. An integrated approach in patient care will lead to more effective treatment strategies the field of medicine.

FLOWCHART 1: BMS DIAGNOSIS



FLOW CHART 2: BMS MANAGEMENT



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