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Burning Mouth Syndrome – An Enigma

Síndrome de Boca Urente - Un Enigma

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ABSTRACT: Burning mouth syndrome (BMS) is an enigmatic condition because the intensity of symptoms rarely corresponds to the clinical signs of the disease. Symptoms include oral burning, dry mouth, pain, changes in eating habits, severe menopausal symptoms, and non specific health problems etc. BMS is most prevalent in postmenopausal women with female: male ratio of 7:1. The etiology of BMS is multifactorial such as hormonal changes (menopause), nutritional deficiencies and taste disturbances to name a few. BMS is a challenge to diagnose and manage. The present article discusses some of the recent understanding of etiopathogenesis of BMS as well as the role of pharmacotherapeutic management in this disorder.

KEY WORDS: burning mouth syndrome, glossopyrosis, glossodynia.

INTRODUCTION

The Burning mouth syndrome is defined as a chronic orofacial pain syndrome, without evidence of mucosal lesions and clinical signs of disease or laboratory abnormalities (Guidice, 2008). Strictly speaking the term “burning mouth syndrome” should only be used when a definite cause has not been found (ADA, 2005).

Various synonyms are used interchangeably to describe BMS – such as somatopyrosis, glossopyrosis, stomatodynia, glossodynia, sore mouth, sore tongue and oral dysesthesia (Charland *et al*., 2009).

To date, despite a large body of knowledge, the BMS etiology remains largely enigmatic and presents challenge for both researchers and clinicians.

Epidemiology. Based on the information of most studies published to date, oral burning appears to be the most prevalent in post menopausal women (Grushka *et al.,* 2002). It has been reported in the 10-40 percent of women presenting for treatment of post menopausal symptoms (Grushka *et al*.). We usually see 10 women for every man who has BMS. The most commonly reported range has been 0.7 to 4.6 percent (Charland *et al*.).

Pathophysiology. The pathophysiology of BMS is in ambiguity.The BMS follows the pathway of chronic intraoral pain disorder (Guidice). The receptors present in the oral cavity are excited by a stimulus and the impulse is transmitted via Ad and specifically via type C to trigeminal sensory ganglion, from here fibers ascend as special trigeminal tract to dorsal horn of spinal cord. Then second order neurons of spinothalmic tract are excited which passes upward through brainstem to intralaminar and ventrolateral nuclei of thalamus. Finally fibers relay to somatosensory cortex and the impulse is preceived as burning pain causing distress to patient (Greenberg & Glick *et al*., 2003).

The recent studies demonstrated that patients with BMS have a trigeminal small-fiber sensory neuropathy affecting the tongue, characterized by a significant loss of epithelial and sub-papillary nerve fibers. These findings resemble the picture of the “burning feet syndrome” associated with loss of epidermal nerve fibers. Similarly, BMS patients showed a decreased density of unmyelinated nerve fibers within the epithelium as well as diffuse axonal derangement demonstrated by histochemical studies. The distribution and quality of sensory symptoms involving the anterior two- thirds of the tongue bilaterally and the sparing of

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the remaining territories innervated by the trigeminal nerve even in patients with long standing disease, suggest that BMS is caused by a primary axonopathy rather than a neuronopathy. Nevertheless, selective degeneration of small-diameter sensory neurons cannot be excluded (Lauria *et al.,* 2005).

The epithelial nerve fibers of papilla are naked axons with no Schwann cell ensheathment and have synaptic contacts with the taste buds of fungiform papilla. Hence, their stimulation can induce a burning sensation and affect the gustatory perception. Moreover, ongoing axonal degeneration could induce nerve fiber sensitization and account for persistent hyperalgesia (Lauria *et al*., 2005).

Symptoms. There are many symptoms associated with BMS which generally do not conform to anatomic boundaries. The tip of the tongue is the most common location (71%), followed by lips (50%), lateral border of tongue (46%) and palate (46%) (Miyamoto & Zicardi, 1998).

Lamb *et al*. developed a classification system to group the varied course of symptoms (Miyamoto & Zicardi):

BMS Type 1: is defined as absence of symptoms on awakening, with gradual increase in symptoms as day progresses.
BMS Type 2: describes the burning as present day and night.
BMS Type 3: patients are characterized as those with days of remission which follows no specific pattern.

The most common symptoms of BMS are pain and burning in oral mucosa, xerostomia (dry mouth), dysgeusia (taste alteration). Other associated symptoms are changes in eating habits, sleep disturbances, headache, severe menopausal symptoms, mood changes, irritability, anxiety, depression and decreased desire to socialize (Kanchan *et al.*, 2008).

Etiological Factors. Possible casual factors for BMS are classified in four categories (de Moura *et al.,* 2007):
1. Local Factors
2. Systemic Factors
3. Psychogenic Factors
4. Neurogenic Factors

1. Local factors. Although many predisposing factors have been attributed to BMS, all are controversial. Main and Basker found ill fitting denture to be the single greatest contributor in their patient population. However in majority of patients in whom denture abnormalities were adequately corrected, burning mouth symptoms persisted (Miyamoto & Ziccardi). The chemical irritation, allergic reaction to dental materials, parafunctional habits, galvanic current have not be found to be important causes of BMS (Kanchan *et al*.).

Salivary Dysfunction. The salivary alteration observed in the patients with BMS, such as lower expression of low molecular weight proteins (<13 k D) may contribute to changes in lubricating function of saliva and in the perception of oral mucosa. Thus elevated salivary viscosity may result in thin and discontinuous salivary film covering the oral mucosa that triggers the sensation of dry mouth and causes lingual receptors to be more exposed to stimuli for e.g. vanilloid receptors(VRI) in the memory affluent neurons. The identification of low molecular weight proteins as well as excitation of VRI receptors may contribute to understanding of BMS pathogenesis (de Moura *et al*.).

Taste Disturbances. Patients with BMS often report with dysguesia and phantom tastes (Femiano *et al*., 2006). Tie *et al*. found that there are central inhibitory interactions between the taste and oral pain- taste normally inhibiting oral pain (Femiano *et al*.; Grushka *et al*., 2006).

Taste receptors for bitter taste are smallest and most vulnerable to injury than others. The damage to *chorda tympani* or taste buds releases the inhibition in the glossopharyngeal nerve (so phantom taste) or trigeminal nerve (touch and pain changes). So BMS thus might be considered as phantom pain (Femiano *et al*.).

It has been suggested that supertasters have genetic ability to taste 6- n-propyl thiouracyl (PROP) who report most bitter sensation from PROP (Grushka *et al*.). Supertasters are persons with enhanced ability to detect taste. Non-tasters usually have 5 or less taste buds and supertasters have more than equal to 30 taste buds per 6 mm. The patients with BMS are primarily supertasters and intensity of oral pain was found to correlate with density of fungiform papillae (Grushka *et al*.).

GABA is known to be an inhibitory neurotransmitter found in taste system, if taste damage produces loss of inhibition, replacement of GABA agonist such as clonazepam relieves the loss of inhibition and relieves pain in BMS (Grushka *et al*.).

Ulcerative and Erosive Lesions, Candidiasis. It is of no surprise that intestinal microbes are found in mouth. *H. pylori* found in the gastric ulcers are also found in mucosal ulcers of the mouth.In the study *H. pylori* was found in 16 % of BMS cases (Gall-Troselj *et al.*, 2006).

Pseudo membranous and erythomatous candidiases are also associated with BMS. Grosky *et al.* reported that in patients with BMS with no clinical signs of candidiases, 86% improved after using antifungal lozenges. We can differentiate the tongue pain associated with candidiases and BMS, as in candidiases there is a functional pain but in BMS tongue pain disappears on eating (Terai & Shimahara, 2007).

2) Systemic Factors

Hormonal Changes. Approximately 90% of women in BMS in studies have been post menopausal, with the greatest frequency of onset reported from 3 years before to 12 years after menopause (Kanchan *et al*.). Neither systemic nor topical hormonal replacement therapy has been shown to be effective. In a recent study hormone replacement therapy was found to be efficacious in BMS patients who had demonstrated nuclear estrogen receptors on the immuno-histochemical assay and ineffective in those who did not have receptors (Miyamoto & Ziccardi). Estrogen replacement therapy alleviates psychological distress in post menopausal women (Kanchan *et al*.).

Diabetes Mellitus. The Diabetes mellitus has been linked to BMS with an evidence to 10% to 37% (Miyamoto & Ziccardi). As diabetes predisposes to oral candidiases which causes mucosal irritation and thus results in oral burning (Kanchan *et al*.). In addition to diabetes, prolonged exposure to glucose can lead to deterioration of nerve endings. Poor circulation is also the adverse effect of diabetes and thereby lowers the pain threshold as these factor can easily disrupt functions at the ends of v2 or v3 branches of trigeminal nerve.

Viral Infection. A possible association between BMS and herpes viral damage was evaluated in a recent study on the basis of a view that herpes virus can lead to neuropathies. But further studies are required to distinguish active or post viral infection in BMS (Grushka *et al.*).

Anaemias, Nutritional and Hematological Disorders. Metabolism and integrity of oral mucosal lining is sensitive to deficiencies of vitamins and minerals (Kanchan *et al*.). Vitamins and mineral deficiencies have been reported to be important in the etiology of BMS with their prevalence ranging from 2% to 85% (de Moura *et al*.). However definite role of vitamin B1, B2, and B6 remains unclear.

Hypothyroidism. Recent Studies show correlation between BMS, taste and hypothyroidism. Thyroid hormone is essential for maturation of taste buds. In hypothyroidism, there is a decreased level of T3, T4 and TSH level is increased. So patients with hypothyroidism manifest with aguesia or dysguesia (Femiano *et al*.).

Drugs. Medications are reported to cause BMS. Angiotensin converting enzyme inhibitors are most frequent. Angiotensin receptor blocker (losartan), anticoagulants, antiretrovirals (efevirenz), anticholinergics, metoclorpramide etc., also causes BMS. Switching to an alternative drug may be required (Guidice; Grushka *et al*.).

3) Psychogenic Factors. Several studies have suggested that patients with BMS have depression, mood and anxiety disorders. Successful life may sometimes play a role in onset of this disorder (Bogetto *et al.,* 1998). Stress leads to production of free radicals and increased cortisol levels which can degrade ordinary T 3 to form reverse T3 that has action opposite to that of T 3 required for taste function (Femiano *et al.*).

Lack of soreness during sleep and increase in symptoms during day are just indicators that syndrome may have psychological genesis.

4) Neurogenic Factors. Recent Studies have pointed to dysfunction of various cranial nerves associated with taste sensation as possible cause of BMS (Kanshan *et al*.). Abnormal perception of intensity of pain range, alteration in neuronal transmission and disturbances of neurovascular microcirculatory system approves the neuropathic view on BMS (Grushka *et al*.). Serum levels of IL6, a neuroprotective cytokine is found low in BMS patients. The neuroprotective actions of IL6 on trigeminal nociceptive pathway might be weakened because of low levels of IL6 in BMS patients which could aggravate hyperalgesia in these patients (Chen *et al.*, 2002).

Diagnosis. History taking is the key to diagnosis of BMS. The diagnosis is based on clinical characteristics

including either a sudden or intermittent onset of pain, bilateral presentation, a progressive increase in pain during day and remission of pain with eating and sleeping. Normal laboratory findings are found in BMS patients. Alternate causes of oral burning pain should be ruled out before a diagnosis of BMS is entertained.

Management. Treatment of BMS focuses on symptomatic relief and psychological management. Since the etiology is complex treatment remains symptomatic. Relief is usually provided by topical application of dyclonine- 0.5%, aq diphenhydramine 0.5%, lidocaine and other analgesics.

Therapy for BMS involves the use of centrally acting medications as for other neuropathic pain conditions. Studies generally support the usage of low doses of benzodiazepines, anticonvulsants and tricyclic antidepressants. Studies support the use of low dose (0.25-0.75 mg) clonazepam or tricyclic antidepressants (10-40 mg), including amitryptyline, desipramine, nortryptaline, imipramine and clomipramine. Clonazepam is a benzodiazepine used either topically or systemically which appears to have excellent efficacy in BMS. The beneficial effects of tricyclic antidepressants in decreasing chronic pain indicate that in low doses these agents may act as analgesics (Grushka *et al*.).

Studies suggest the use of combination of medications in treatment of BMS rather than higher doses of single medication, especially with regard to controlling adverse effects. Grushka believes that best treatment for BMS consists of a combination of clonazepam, gaapentine and baclofen (Charland *et al.*). If indicated, nutritional or estrogen therapy should be initiated.

Recently, Femiano *et al.* have shown the use of alpha lipoic acid in management of BMS (Femiano & Scully, 2002). 96% of patients had shown significant improvement in their symptoms. It is a potent antioxidant and neuroprotective agent. It has been tried in diabetic neuropathy. It increases intracellular glutathione level and helps in elimination of free radicals. These results support the theory that BMS has a neuropathic origin.

A study conducted by Ohio State University has shown the use of capsaicin for desensitization. Hot pepper sauce commonly found in grocery stores is a good source of capsaicin. Hot pepper sauce in water is used in ratio of 1:2. Swish in mouth for 45 seconds and spit. It acts by depletion of substance p so results in decreased peripheral burning (Allen & Kalmer, 2010).

Cognitive behavioral therapy was shown to be effective even when used independently. Specifically, Dr Leong suggested that showing empathy and reassuring the patient that the disorder is real can significantly lower the perception of pain. Patient should be reassured that it is not fatal nor is it cancerous and will eventually resolve (Charland *et al*.).

Finally, to conclude with multiple etiological factors are included under the umbrella of BMS. So it becomes a challenge to diagnose and manage. So special concern and repeated reassurance should be given to the patients of BMS.

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RESUMEN: El síndrome de boca urente (SBU) es una condición enigmática porque la intensidad de los síntomas rara vez se corresponde con los signos clínicos de la enfermedad. Los síntomas incluyen ardor bucal, boca seca, dolor, cambios en los hábitos alimenticios, graves síntomas de la menopausia, y problemas no específicos de salud, entre otros. SBU es más frecuente en las mujeres posmenopáusicas con relación mujer/hombre de 7:1. La etiología del SBU es multifactorial, como los cambios hormonales (menopausia), las carencias nutricionales y alteraciones del gusto por nombrar algunos. SBU es un reto con respecto al diagnostico y al manejo. El presente artículo analiza algunos de los acuerdos recientes de la etiopatogenia de SBU, así como el papel de la gestión farmacoterapeutica en este trastorno.

PALABRAS CLAVE: síndrome de boca urente, glosopirosis, glosodinia.

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