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RECENT ADVANCEMENT IN DIAGNOSTICS AND THERAPEUTICS IN OVERCOMING BURNING MOUTH SYNDROME

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ABSTRACT

Oral health is an integral part of primary health and quality of life, most of the elderly population complains about prolonged irritation of the oral mucosa which should receive special consideration until effective and complete cure. Burning mouth syndrome (BMS) is of multifactorial origin the etiopathogenesis of BMS seems to be complex with local, systemic, and/or psychological factors are involved in stimulation of painful burning sensation symptoms. Otherwise BMS has been found to be associated with either peripheral nerve damage or dopaminergic system disorders. Extensive clinical examination is required to the start of the treatment for BMS, because elimination of unlikely factors usually results in a significant clinical improvement of oral burning and pain symptoms.

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INTRODUCTION

Burning mouth syndrome (BMS) is an idiopathic condition characterized by a continuous burning sensation of mucosa of the mouth typically involving tongue with bilateral, symmetric distribution accompanied by gustatory disturbance, Xerostomia…etc (Milkov *et al*., 2013). BMS are common among post-menopausal elderly women occurring at 7:1 ratio in comparison to elderly adult male population. Clinical manifestation of BMS includes sensation of burning or irritation, pain or numbness and patients may also suffer from dry mouth, dry lips and persistent metallic taste. Clinically BMS has been classified based on the pain and etiology broadly into Primary BMS which occurs due to neuropathological abnormalities whereas secondary BMS are related to a number of variable localized and systematic causes such as microbial infection, Lichen planus, allergies, hormonal imbalance, nutritional deficiencies, smoking, alcoholism, diabetes mellitus, autoimmune disorder, Sjogren's syndrome, fibromyalgia, stress, anxiety, medication, cancer treatment. The diagnosis is often misleading and delayed due to lack of understanding of the nature of the entity, in addition to the patients taking up many other irrelevant health resources, deviating from appropriate therapy (Milkov *et al*., 2013; Mitsikostas, 2017). Till now there is no satisfactory treatment for BMS as exact reason for the condition is difficult to be diagnosed. In this review, we discuss the essentials in understanding the etiology for accurate diagnosis and contribute the critical views on the advanced therapy for BMS.

Challenges in characterizing the etiology: Extensive physiological and lab tests The need for the differential

diagnosis is emphasized in order to give thorough check up about the exact etiology as the treatment is primarily based on the etiology and then about the symptoms. Clinical examination plays a keys role in differential diagnosis in identifying the salient features such as atrophies, erythema, leukoplakia, ulceration, geographic tongue, benign migratory glossitis, enamel damage (sleep bruxism), malocculusion, palpation of the jaw & thyroid, any nutritional deficiencies, Scleroderma, stomatitis, patient social behavior with smoking, alcohol consumption and mental disorders and so on. BMS occurs more frequently in menopausal women as estrogen receptors are also been identified in the tongue and the vaginal mucosa. A complex battery of laboratory test are to be done are as follows CBC count, Serum B vitamin levels, Serum folate, Serum ferritin, Serum blood glucose, Urine analysis for glucose, TSH, T4, Thyroid binding globulin, Antithyroperoxidase antibodies, Antithyroglobulin antibodies, Antimicrosomal antibodies, LH, FSH, Sialochemistry, ESR, Anti SS-A, Anti SS-Ro, Anti SS-B, Anti SS-La antibodies, RF, ANA as the etiology has to be defined for effective treatment (Heir, 2005; Kuten-Shorrer *et al*., 2014).

CRITERIA DEVELOPED BY SCALA FOR THE DIAGNOSIS OF BURNING MOUTH SYNDROME (Mari, 2011)

FUNDAMENTAL INCLUSION CRITERIA

- Daily deep burning sensation of oral mucosa
- Burning sensation for at least 4 to 6 months
- Constant intensity, or increasing intensity throughout the day
- No worsening on eating or drinking
- No interference with sleep

ADDITIONAL INCLUSION CRTITERIA

- Dysgeusia and / or Xerostomia
- Sensory or Chemosensory alterations
- Mood changes or psychopathological alterations

Functional and psychological specific techniques can be used to test for taste disturbance and salivary function. Electrogustometric thresholds (EGMt) were recorded in 21 BMS patients and 21 paired-matched controls at nine loci of the tongue assessing fungiform and foliate gustatory papillae function. Mean EGMt were significantly increased with BMS for right side of the dorsum of the tongue and right lateral side of the tongue. These data depicted impaired taste sensitivity in BMS patients within fungiform and foliate taste bud fields and support potent gustatory/nociceptive interaction in BMS (Howard *et al*., 2002). Immunohistochemical studies shown that C -small diameter nerve fibers alterations evidenced in patients with BMS. It has also been suggested that BMS originate from neurological alterations occur in peripheral level. This hypothesis is supported by the observed local oral mucosal receptor effects of clonazepam, which to date has been found to be the most effective treatment for the symptoms of BMS. Other authors have suggested that BMS behaves 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.

Transcranial sonography

In order to diagnose neuronal pain the use of transcranial sonography of the brain parenchyma, *substantia nigra*, midbrain raphe and brain nucleus were evaluated in 20 patients with BMS (64.7±12.3 years) and 20 controls with chronic pain in the lumbosacral region (61.5±15) have shown hypo echogenicity of the *substantia nigra* and *midbrain raphe* as well as hyper echogenicity of the *brain nucleus* in BMS patients as compared to controls revealing the neuronal involvement of BMS (Maina *et al*., 2002).

Pain DETECT

Establishing the nature of the pain experienced by BMS patients is essential to providing a treatment that effectively relieves and manages orofacial pain. In this context, painDETECT (PD-Q) is a simple, patient-reported questionnaire designed to screen and identify neuropathic pain, often an element of BMS. In the present study, pain DETECT identified statistically significant differences between the two groups for burning ($P < 0.010$), prickling ($P = 0.001$), electric shock-like sensation ($P = 0.046$), thermal sensation ($P < 0.001$), numbness ($P = 0.002$)—useful information, although other authors claim that the questionnaire cannot replace clinical judgment (Mari, 2011; Lopez-Jornet *et al*., 2017).

Proteomics

Use of ACE inhibitors and angiotensin receptor blockers are perhaps the most commonly associated cause of BMS which is probably due to the increase in the bradykinin resulting in angiodema releasing Kallikrein resulting in burning sensation. Other common antiretrovirals and Topirimate for trigeminal neuralgia, has been reported to cause BMS-like symptoms. The clinician should be aware of neurotoxin poisoning as a possible cause of symptoms of burning mouth, especially among patients who have recently traveled to a tropical area. The average concentration of opiorphin in BMS patients significantly higher shown importance of the patient health history and medication do play a crucial role in preventing contraindicative treatment (Ji, Diep *et al*., 2017). In a study conducted by Eoon HJ *et al* in estimating 1130 saliva protein using liquid chromatography - tandem mass spectrometry 50 proteins were significantly changed in the BMS patients when compared to the healthy control subjects (39 up-regulated and 11 down-regulated). Alpha-enolase, interleukin-18 (IL-18), kallikrein-13 (KLK13), and cathepsin G, were selected for further validation. The fold changes for alpha-enolase, IL-18, and KLK13 were determined as 3.6, 2.9 and 2.2 (burning mouth syndrome vs. control) and corresponding receiver operating characteristic values were determined as 0.78, 0.83 and 0.68 respectively. These findings indicate that testing of the identified protein biomarkers in saliva might be a valuable clinical tool for BMS detection (Zavoreo *et al*., 2017).

Treatment for primary and secondary BMS

For BMS there is no definitive therapy is available, different strategies for specific treatments works successfully only for some individuals. The physician experimenting combinations of therapies may be appropriate as in cognitive therapy being synergistic with other agents.With appropriate empirical treatment that causes secondary burning mouth syndrome (BMS) based on the nature of symptoms or exam findings would benefit the patient effectively. Hormone replacement therapy (HRT) has not been majorly found to be useful though

estrogen deficiency is generally not accepted as entire causal. Opposingly, reduced steroid levels at the menopausal transition are clear evidence. Current and routine treatment for BMS includes discontinuation of medications leading to xerostomia, burning sensation such as anticholinergics or psychotropics, Adjustment of levothyroxine dosing, oral nystatin, abstinence from smoking, tobacco use, adjustment of dentures chewing sorbitol-containing gum to stimulate saliva, Pyridostigmine, Pilocarpine, or other sialogogues, B vitamin supplementation, iron supplementation, folate supplementation, neuropathic analgesics. Newer descriptive ailments are necessitated for empirical treatment of BMS.

Local treatment

More recent studies with topical 0.02% capsaicin also showed slight improvement, but with few significant results as capsaicin, a chief component of peppermint capable of binding TRPV1 (Transient Receptor Potential Vanilloid 1), a potent calcium receptor. When inactive, neuronal responses are linked to heat, thus prolonged exposure to capsaicin can deplete the TRPV1 in peripheral tissues, contributing to the long-term desensitization of peripheral nociceptors and consequently alleviate symptoms. Clonazepam is a benzodiazepine that has an inhibitory effect on the central nervous system has shown promising results for relief of symptoms. A literature review by Miziara *et al* of treatment studies suggested that topical clonazepam, although not a cure, offers short-term improvement of burning mouth syndrome, with studies on alpha-lipoic acid and cognitive therapy showing their effectiveness as well. The long-term efficacy of high venlafaxine doses combined with systemic and topical administered clonazepam in a particular subgroup of BMS patients who do not respond to current clinical management[2]. Topical clonazepam has been shown to be an effective treatment for BMS with peripheral nervous system alteration, but not central nervous system alteration. BMS patients with central nervous system alteration present more comorbid psychiatric problems such as depression and anxiety [8].

Systemic treatment

Various medications such as selective serotonin reuptake inhibitor antidepressants like sertraline (50 mg/day), paroxetine (20 mg/day) for 8 weeks, and duloxetine at a dose of 30-60 mg/day, a dual action antidepressants that inhibit both serotonin and noradrenaline resulted in a significant improvement of oral burning sensation. Antipsychotics such as amisulpride, levosulpiride at a dose of 50 mg/day for 24 weeks proved to be effective and shows a better patient compliance when used in short duration. Alpha-lipoic acid (ALA) at a dose of 600 mg/day, either alone or in combination for 2 months, acts as an antioxidant and a powerful neuroprotective agent that prevents nerve damage by free radicals, regenerating other antioxidants such as vitamin C and E, able to increase the intracellular levels of glutathione, thereby significantly reduces the symptoms in patients with idiopathic dysgeusia. In a double blinded study duloxetine was administered to 77 patients diagnosed with BMS or atypical odontalgia for 12 weeks. The initial dose of duloxetine was established as 20 mg/d and was increased to 40 mg/d after week 2. Visual analog scale scores (VAS) were significantly lower 12 weeks after than at the start of the administration of duloxetine. Several studies have demonstrated the efficacy of botulinum toxins types A and B in treating several neuropathic pain disorders by prolonged duration of action.

Conclusion

Though BMS is an incompletely understood enigma and being fantasized with numerous etiologies in its causal a proper diagnosis and timed therapy would be the first choice of ailment facing the challenges by the clinicians and should be updated with novel finding. Pharmacogenomics, stem cell therapy, Nano-based therapy and many more possible outsources are promising venture in future to rapid and sensitive diagnosis and therapy of BMS.

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