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MINIREVIEWS

Burning mouth syndrome

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Abstract

Burning mouth syndrome is a debilitating medical condition affecting nearly 1.3 million of Americans. Its common features include a burning painful sensation in the mouth, often associated with dysgeusia and xerostomia, despite normal salivation. Classically, symptoms are better in the morning, worsen during the day and typically subside at night. Its etiology is largely multifactorial, and associated medical conditions may include gastrointestinal, urogenital, psychiatric, neurologic and metabolic disorders, as well as drug reactions. BMS has clear predisposition to peri-/post menopausal females. Its pathophysiology has not been fully elucidated and involves peripheral and central neuropathic pathways. 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. Drug therapy with alpha lipoic acid, clonazepam, capsaicin, and antidepressants may provide symptom relief. Psychotherapy may be helpful. Short term follow up data is promising, however, long term prognosis with treatment is lacking. BMS remains an important medical condition which often places a recognizable burden on the patient and health care system and requires appropriate recognition and treatment.

Key words: Burning mouth syndrome; Glossodynia; Glossopyrosis; Burning tongue

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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[1,2]. BMS can be accompanied by dysgeusia (distortion in sense of taste) and subjective xerostomia (dry mouth). Its onset is spontaneous and the syndrome has a clear predisposition to peri-/postmenopausal women. Its secondary form has been associated with a variety of conditions including thyroid disease, psychiatric illnesses, oral infections, drug use, dental treatment, vitamin/mineral deficiencies, and others[3,4].

First described in mid nineteenth century, this condition was further characterized in the early twentieth century by Butlin and Oppenheim as glossodynia[5]. Over the ensuing years, BMS has been referred to as glossopyrosis, oral dysesthesia, sore tongue, stomatodynia, and stomatopyrosis[6]. It was first categorized as a distinct disease in 2004 by the International Headache Society, which defined primary BMS as "an intraoral burning sensation for which no medical or dental cause can be found." Current diagnostic criteria consist of daily persistent pain in the mouth with normal oral mucosa after exclusion of local and systemic diseases[7]. Its etiology is thought to be multifactorial, involving various local, sys-

temic, and/or psychogenic causes. Female gender, perimenopause, depression and anxiety, Parkinson's disease, and chronic medical conditions including gastrointestinal and urogenital diseases are risk factors for developing BMS[1,8-11].

BMS is an important clinical condition with aggravating symptoms, directly and indirectly impacting the quality of life, which often places a recognizable burden on the patient and health care system. Clinical consultations with a practicing gastroenterologist are common practice in today's medicine for the patients with BMS. This review focuses on various aspects of BMS, including its epidemiology, pathophysiology, etiology, clinical presentation, differential diagnosis, classification, clinical diagnosis, current treatment, and general prognosis.

EPIDEMIOLOGY

The estimated prevalence of BMS in the general population varies widely in the literature. Tammiala-Salonen *et al*[12] reported a rate of 15% of burning mouth symptoms in Finnish adult population, though half of the patients had visible oral mucosal lesions. In a cross-sectional analysis of over 1000 randomly selected Swedish patients from Public Dental Health Service registers, 3.7% of subjects were diagnosed with BMS after reporting burning mouth symptoms and undergoing a subsequent physical examination[8]. In contrast, Lipton *et al*[13] reported a prevalence of 0.7% based solely on self-reported symptoms from over 45 000 American households. Haberland *et al*[14] noted that 10% of new patients observed in his practice were diagnosed with BMS. Most recently, a large retrospective study of over 3000 Brazilian patients referred to an oral pathology service reported a prevalence of about 1%[1]. These highly variable rates are attributed to the wide age disparities of the examined population (typically, prevalence of BMS dramatically increases with age) as well as previous lack of universally accepted diagnostic criteria for BMS. Although further studies are needed with satisfactory criteria to determine the true prevalence of BMS, this data illustrates that the disease is an important medical condition that may be often encountered in the clinical practice.

BMS has a clear predisposition to gender and age. Women are 2.5 to 7 times more commonly affected than men[1,8,10]. Furthermore, up to 90% of female patients with BMS are perimenopausal women with typical onset from 3 prior- to 12 years post- the beginning of menopause[9]. BMS may affect any age group, with patients age ranging from 27 to 87 years of age, and a reported mean age of 61 years. Recent analysis by the same group showed an increased likelihood of gastrointestinal and urogenital disease in patients with BMS, with estimated odds ratio of 3.5 and 2.9, respectively, compared to control subjects. Patients with BMS had a statistically higher intake of medications for gastric disease compared to control group as well[1].

ANATOMY

The oral cavity is primary responsible for the ingestion and mastication of food. Its anatomical boundaries include the lips anteriorly, the cheeks laterally, the oropharynx posteriorly, the palate superiorly, and the floor of the mouth inferiorly[15]. The oral cavity contains several structures, including upper and lower dentition, the tongue, salivary glands, and mucosal glands[16]. It is lined by non-keratinized stratified squamous epithelium, which is moistened by secretions from various salivary glands[17].

The neuroanatomy of the oral cavity, particularly somatosensory innervation, has been implicated in the pathophysiology of BMS. The maxillary (V2) and mandibular (V3) branches of the trigeminal nerve supply most of the somatosensory innervation in the oral cavity, with some contribution from the glossopharyngeal nerve (cranial nerve Ⅸ). In regards to the tongue, the most commonly affected area in BMS, the lingual branch of V3 innervates the anterior two-thirds of the tongue while the glossopharyngeal nerve innervates the posterior third of the tongue. Together, they innervate the receptors on the papillae of the tongue, which are sensitive to mechanical, thermal, and tactile stimuli[17].

Alterations in taste and quantity of salivation are commonly reported in BMS. The chorda tympani branch of the facial nerve (Ⅶ) supplies chemoreceptors for taste in the anterior two-thirds of the tongue. The glossopharyngeal nerve (Ⅸ) provides taste sensation for the posterior third of the tongue. There are also taste receptors on the soft palate supplied by the greater superficial petrosal nerve branch of Ⅶ and on the larynx from the superior laryngeal nerve of the vagus nerve (Ⅹ). The salivary reflex begins with afferent inputs from taste and mechanoreceptors in the mouth that reach the brainstem salivatory centers. Parasympathetic and sympathetic fibers then supply the efferent fibers that act on the salivary glands[15].

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[18,19]. 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[20]. Moreover, Borelli *et al*[21] 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 $P2X_3$ receptors on scattered nerve fibers, a finding previously linked to hypersensitivity and neuropathic pain symptoms in various models of human pain conditions[22]. 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[23-28].

However, recent evidence indicates that dysfunction in the central nervous system can also cause BMS. Albuquerque *et al*[29] showed that BMS patients process thermal and pain stimulation in the brain differently than pain-free individuals as demonstrated by functional magnetic resonance imaging of the thalamus. Additionally, the dysregulation of the nigrostriatal dopaminergic system has been implicated in BMS[30]. Patients with Parkinson's disease are reportedly five times more likely to have BMS than the general population[31]. Finally, hospital anxiety and depression scores were significantly higher in the patients with central BMS[22].

As evident from these studies, the pathophysiology of BMS is highly complex, likely involving neural pathways at different levels of neuraxis. A recent double blind, randomized cross-over study of postmenopausal women showed heterogeneity of the response of BMS symptoms to lingual nerve block with lidocaine. If fact, it may lead to an effective increase, decrease, or an unchanged burning pain in patients, an effect attributed to variation in central, peripheral, or combined neurological pathways in pathogenesis of BMS[32]. The symptoms of BMS can result from subclinical insults at various points in the nervous system, presenting with instant or gradual bilateral distribution. Recent classification suggests a possible overlap of three distinct subclasses in BMS: a peripheral oral small fiber neuropathy (50%-60% of cases), subclinical major trigeminal neuropathy (20%-25%), and central deficiency in dopaminergic top-down inhibition (20%-40%)[23].

ETIOLOGY

The exact etiology of BMS remains imprecise and is likely multifactorial, including neuropsychiatric, endocrine, immunologic, nutritional, infectious, and iatrogenic causes. The disorder has been associated with several psychiatric diseases[9,33-35]. Depression or anxiety occurs in more than 50% of BMS patients, with depression predominating[34]. Personality disorders are also linked to BMS, affecting 86% of sufferers compared to 24% of normal individuals, with significant predilection to Cluster A disorders[36]. Most recently, a cross-sectional controlled study showed that BMS patients have a significantly higher frequency of past or present major depressive disorder, general anxiety disorder, hypochondria, and cancerophobia[37]. Although psychiatric disease was initially considered as a primary cause of BMS, it is now considered a concurrent or secondary factor as there is no definite correlation between the onset of BMS and stressful events and many other causes of BMS have been identified[9,33,35,38,39].

As described previously, BMS most commonly affects perimenopausal women, a finding that is attributed to dryness of mucosal membranes from age-related reduction in estrogen and progesterone levels and increased frequency of psychological disorders in middle-aged and elderly women[40]. Woda *et al*[41] has suggested that the fall in neuroprotective gonadal and adrenal steroids during menopause leads to a concomitant decrease in neuroactive steroids, leading to degeneration of oral mucosal small nerve fibers and brain areas involved in oral somatic sensations. These changes can become irreversible, resulting in burning pain and associated symptoms. Gao *et al*[42] showed that peri-/post-menopausal patients suffering from BMS may have lower levels of estradiol and increased levels of follicle stimulating hormone compared to healthy controls. Other endocrine conditions implicated in BMS may include diabetes mellitus and hypothyroidism[8].

Evidence also exists for an immunologic etiology. Allergic reactions have been demonstrated in BMS patients to dietary antigens. These include sorbic acid, cinnamon, nicotinic acid, propylene glycol, and benzoic acid[43,44]. Other allergens identified by patch testing are dental metals such as zinc, cobalt, mercury, gold, and palladium[45]. Sodium lauryl sulfate, a detergent in toothpaste known to cause dry mouth, may also be involved in the development of BMS[46]. Finally, autoimmune connective tissue disorders such as Sjogren's syndrome and systemic lupus erythematosus, are also associated with BMS[47].

BMS has also been linked to nutritional deficiencies including vitamins B1, B2, B6 and B12 as well as folic acid[2]. Most recently, zinc deficiency was shown to be a possible cause of BMS, with patients reporting improved symptoms after zinc replacement therapy[48].

A potential relationship between smoking and development of BMS has been described, with an estimated odd ratio of 12.6 in a recent study[43].

Certain oral infections have been implicated in BMS, particularly candidiasis. Patients with BMS have a higher intraoral prevalence of *Candida* species and coliforms like *Enterobacter* and *Klebsiella*[49,50]. Although this finding may be related to xerostomia and prosthetic dental wearing, a possible infectious origin of BMS is suggested by reports of remission after oral antifungal therapy[18].

Drug-associated BMS has also been reported in the literature. ACE inhibitors and angiotensin receptor blockers may trigger development of BMS, possibly due to increased levels of kallikrein in the saliva of BMS patients leading to increased inflammation in the oral cavity[9,51-53]. Nevirapine and efavirenz have been reported to cause BMS *via* an unknown mechanism[54,55]. Levodopa may play a role in the development of BMS in patients with Parkinson disease[31]. Finally, a case report of topiramate causing burning mouth-like symptoms has been de-

scribed, with symptom resolution upon discontinuation of the medication[56].

CLINICAL PRESENTATION

A typical patient with BMS is a peri- or post-menopausal woman with various medical comorbidities who complains of the classic triad of unremitting oral mucosal burning pain associated with dysgeusia and xerostomia in nearly two thirds of the cases with no visible disease in the oral mucosa for 4-6 mo duration. Clinical presentations may vary as some patients can be oligosymptomatic (pain and dysgeusia or xerostomia) or monosymptomatic (pain only)[10]. In general, 63% of patients report accompanying dry mouth, 60% bitter/metallic taste, and 35% altered taste perception[9]. The pain is described as burning, scalding, tingling, or numbness. It is of moderate to severe intensity and can decrease during eating. It is commonly bilateral and most often involves the tongue followed by the palate and lower lip. In contrast, the buccal mucosa and floor of the mouth are rarely affected[9]. The onset is spontaneous, though some BMS patients report antecedent dental procedures, initiation of medications, or other illnesses[10,57]. Xerostomia may be subjective however some patients have demonstrated alterations in saliva quantity and quality[10]. Vertical visual analogue scale (VAS, 0-10 cm)[58] is commonly used to describe pain intensity in BMS.

Review of systems may be remarkable for headache, chronic fatigue, gastrointestinal and urogenital symptoms, insomnia, mood changes, irritability, anxiety, and depression[4,57]. Other observed clinical conditions may include gastroesophageal reflux disease, hypertension, hematological disorders, nutritional deficiencies, diabetes mellitus, thyroid disorders, Parkinson's disease, Sjogren's syndrome and other autoimmune diseases[51,59]. Finally, parafunctional habits such as lip and cheek biting, bruxism, tooth grinding and clenching, tongue thrusting, and lip licking are observed with BMS[10].

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. Laboratory evaluation may reveal positive fungal oral cultures, elevated fasting blood sugar, decreased levels of vitamin B1, B2, B6, B12, folate, iron, and zinc, abnormal thyroid function studies, and positive serum autoantibodies[4,49].

MIMICKERS OF BMS

BMS presents with a main complaint of an intraoral sensation of burning, tingling, or stinging and sometimes accompanied by taste disturbances or dry mouth. 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[10,57]. Detailed history and physical exam is crucial to differentiate above medical conditions.

CLASSIFICATION

Two classification schemes have been proposed based on either etiology or clinical symptoms. When classifying by etiology, primary BMS is the idiopathic form for which organic causes cannot be identified while secondary BMS results from local or systemic pathological conditions[10]. The other scheme divides BMS cases into three types based on diurnal fluctuations of symptoms. Patients with type 1 BMS (35%) are symptom-free upon awakening with worsening symptoms throughout the day and variable symptoms at night. Type 2 BMS (55%) is defined by continuous symptoms in the day but none at night. Patients with type 3 BMS (10%) have intermittent symptoms interspersed with symptom-free days[34,60]. Type 1 BMS is linked to nutritional deficiencies and diabetes, type 2 to chronic anxiety, and type 3 to dietary or prosthetic allergies[2,18,44,61].

CLINICAL 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. Scala *et al*[10] 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[10]. Measurement of salivary flow rates should be employed[62].

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 atten-

tion to details of patient's history and physical exam.

TREATMENT

The first step in management is contingent on the specific type of BMS, primary versus secondary. The goal of therapy for secondary BMS should initially be directed at treating the causative local or systemic disease and withdrawing offending medications (such as ACE inhibitors). This etiology-directed therapy typically yields a good response. The cure for primary BMS, however, remains elusive despite attempts with different classes of medication. The variable response rate to medical therapy is likely due to the multifactorial pathophysiology of idiopathic BMS, including irreversible processes. Treatment is aimed at management this disease as a type of chronic neuropathy. Investigated strategies include benzodiazepines, antidepressants, topical capsaicin, alpha-lipoic acid, hormone replacement therapy, anticonvulsants, biofeedback technique to modify parafunctional habits, and psychosocial therapies.

Early studies by Italian researchers supported the use of alpha lipoic acid (ALA, a potent antioxidant) in 600 mg daily dose over two months in patients with BMS[63]. This data was not replicated by subsequent analysis in Brazilian patients[64], possibly due to the multivitamin compound of the ALA supplements or longer duration of the original therapy. Interestingly, same group suggested added benefit of ALA in patients with thyroid disease[65].

Recent randomized double blind placebo controlled trial showed that use of gabapentin alone (300 mg daily) or in combination with ALA (600 mg daily) was beneficial in reducing symptoms in 50% and 70% of patients with BMS, respectively, compared to placebo (15%)[66]. In line with the observed predisposition of BMS to peri-/post- menopausal women, a hormone replacement therapy may be intuitive, but short of initial promise with local oral administration, it is largely not effective when given systemically[67] possibly due to the irreversible nature of the neuropathic changes.

Clonazepam lozenges (oral dissolution of 1-mg tablets for 3 min with subsequent expectoration three times a day) are beneficial in patients with predominantly peripheral BMS. A double blind, randomized controlled study of topical clonazepam reported a reduction in pain intensity in 66% of patients after 2 wk and 29% after 6 mo[68]. Similar clinical benefit was replicated in follow up studies[33].

Short term use of oral Chlordiazepoxide (5-10 mg three times a day) to treat BMS has been reported, however, its long term effects were not significant[69].

Efficacy of capsaicin, a desensitizer of receptors for neurogenic inflammation, has been evaluated in several studies. Systemic capsaicin 0.25% capsules three times daily showed dramatic improvement (93%) in patients with severe BMS (VAS scale 8-10) at 1 mo[70]. Side effects including gastric pains in 32% of the patients were cumulative, and may preclude long term use of this medication. Local capsaicin rinse may be beneficial in treating BMS, with reported improvement of symptoms in over 75% of the patients after 8 wk of therapy without significant side effects[71].

Use of proton pump inhibitors (PPI), although clearly increased in the patients with BMS[1], may not necessarily be of benefit. Recent study measuring oropharyngeal pH found no significant correlation between laryngopharyngeal reflux and intraoral burning sensation in the examined population[72]. Anecdotal evidence exists in case reports of symptom relief with twice daily omeprazole in patients with endoscopy proven gastroesophageal reflux disease[73]. Whether there is a casual relationship between use of PPI and clinical primary BMS, an observation phenomenon, a true response, or simply a failed therapy remains to be established. Treatment of secondary BMS in the setting of gastroesophageal reflux disease is, however, warranted. Larger studies are needed to address potential benefit (or lack of it) of PPI in treatment of BMS.

Medical management of BMS may also include antidepressants and antipsychotics. In a prospective, open-label, noncomparative study of selective serotonin reuptake inhibitor (SSRI) paroxetine, 80% of patients experienced overall pain reduction including 36% of patients who reported complete remission after 12 wk of incremental treatment. Both treatment effects and adverse events were found to be dose dependent[74]. However, prophylactic use of domperidone for nausea in selected study patients may have had a potential confounding effect on the results. Another single-blinded non-placebo controlled study comparing paroxetine (20 mg daily), sertraline (50 mg daily), and an atypical antipsychotic amisulpride (50 mg daily) demonstrated a nearly 70% improvement in VAS score after 8 wk of therapy in each of the three groups[75]. A group from Spain reported complete remission in all female patients after 8 wk of amisulpride use, an effect lasting up to 24 wk with continuous administration of the medication[76].

Additionally, modifications of parafunctional habits may offer some symptom relief. Tongue protectors (worn 15 min three times a day) were shown to significantly improve pain scales in BMS patients after two months of treatment, however sample sizes were small and placebo effect could have been introduced[77].

Finally, psychiatric interventions show great promise in treating patients with BMS. Weekly one-hour sessions of cognitive behavioral therapy lasting for 12-15 wk significantly reduced BMS symptoms in all study patients compared to placebo control group, with an estimated 27% of patients remaining symptom-free at 6 mo follow up (none in placebo group)[78]. Weekly group psychotherapy administered for three consecutive months achieved symptom improvement in 70% of the patients[52]. Femiano *et al*[79] noted a statistically significant symptom improvement with cognitive psychotherapy (40%), alpha lipoic acid (81%), combination therapy (90%) compared to pill placebo control group (13%) of patients with BMS.

Anecdotal use of diphenhydramine/pectin swish and spit elixir[18] as well as oral pramipexole in BMS patients with Parkinson's disease have been reported[57].

Perceived variation in the results of the published data may stem from lack of effective differentiation between predominantly peripheral and predominantly central pathways in the pathogenesis of BMS. Therefore, improvement in future clinical diagnosis and discrimination between such groups of patients may improve clinical response rate to targeted local and systemic therapies.

For now, BMS remains a challenging medical condition to treat, and further research is required to determine the true efficacy of current management strategies for patients with this disorder. Future blinded randomized control trials with large sample size are necessary to provide new insight for use of various treatment modalities in BMS.

PROGNOSIS

Although the short term follow up studies may show potential symptomatic improvement with treatment in patients with BMS, the long-term outcomes for BMS remain unclear. Early observational report by Gilpin[5] 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[62]. 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.

CONCLUSION

BMS is a relatively common chronic intraoral pain disorder classically characterized by intractable burning that may be associated with dysgeusia and xerostomia. Its pathogenesis relates to complex interlay of central and/or peripheral neural pain pathways. Etiology of BMS is multifactorial and a secondary form of BMS should be diligently sought for and treated. Multidisciplinary approach, including medical and psychosocial therapy may be effective in symptom relief in patients with BMS, however, further studies are necessary to establish long term prognosis. BMS remains an important medical condition which often places a significant burden on the patient and health care system, and requires diligent recognition and treatment.

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