

Pitfalls for diagnosis of burning mouth-like syndrome

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ABSTRACT

This research gives a scientific framework for burning mouth syndrome (BMS) etiology and diagnostic approach in clinical dental and medical practice. BMS-like symptoms can be induced by systemic diseases such as diabetes, gastrointestinal, endocrine disorders, allergy etc or by local oral cavity conditions as candidiasis or geographic tongue or odontogenic causes. Because the etiology of BMS is multifactorial, treatment can only be distinctive, and is aimed at relieving symptoms. The complexity of BMS symptoms and associated psychosocial infirmities, anxiety and depression raise the need for a multidisciplinary and individualised approach.

Keywords: burning mouth syndrome, oral mucosa, burning mucosa, oral dysesthesia

INTRODUCTION

The World Health Organization has defined burning mouth syndrome (BMS) as a "chronic orofacial pain with an intraoral burning or dysaesthetic sensation that recurs for more than 2 hours per day on 50% of the days over more than 3 months, without evident causative lesions on clinical investigation and examination" [1]. It has a multifactorial etiology and is associated with psychological distress such as anxiety, depression, rage/ frustration. The diagnosis is established by exclusion of other diseases that would better explain the symptoms [1].

In the literature there are four types of classification for BMS. For a uniform reporting, the oral medicine specialists and dental practitioners use mainly the first one, which is based on the evolution of BMS symptoms. The second classification refers also to the clinical criteria, mainly the associated symptoms. The third classification divides BMS in subclinical neuropathies and the fourth is based on etiology.

Based on symptoms evolution BMS is classified in three types [2,3]. In BMS type 1 the symptoms are not present on waking up, but appear and increase in severity as the day progresses, without preventing the patient from falling asleep; according to the authors, this type is observed in approximately 35% of BMS patients. In BMS type 2 symptoms are present continuously, all day after waking up; this type is encountered in approximately 55% BMS patients. Type 2 BMS patients are the most difficult to treat successfully, because a large proportion have chronic anxiety, which is the most recalcitrant obstacle to cure. In BMS type 3, patients have asymptomatic days and may experience symptoms in unusual oral sites, such as the floor of the mouth, oral mucosa, and throat. 10% of BMS patients have this history, which in the past has been reported as "atypical" heartburn. A study of type 3 BMS patients determined that their main precipitating factors were emotional instability and allergic factors [4].

The second classification is based on the presence of associated oral symptoms and divides BMS

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as follows: (1) complete BMS (oral mucosal pain, dysgeusia, and xerostomia), (2) oligosymptomatic BMS (pain and dysgeusia, or pain and xerostomia), and (3) monosymptomatic pain) [5]. In addition, the authors introduced a distinction in theory symptomatic criteria and additional symptomatic criteria.

The third classification is based on subclinical neuropathies associated with BMS [6]. It divides BMS patients in a subgroup characterized by peripheral neuropathy with small diameter fibers of the oral mucosa and a subgroup that fits the concept of central pain. The two types can overlap in some cases. Individuals with the peripheral type of BMS respond better to local treatments, while the central type does not respond to local treatments and is often associated with psychiatric comorbidity, such as depression, anxiety, and cancerphobia [7]. Lately another subclinical neuropathic subtype was added to the previously mentioned types. This BMS type includes patients with lingual, mandibular or trigeminal subclinical pathology, which will be determined after careful neurophysiological examination and is clinically indistinguishable from previous groups [7].

The etiological classification [8] recognize three subtypes of BMS that support the suspected etiology: BMS type 1 caused by systemic factors, including side effects of medications; BMS type 2 produced by neurological imbalance, during which the symptoms are caused by central or peripheral neurological dysfunctions that affect, in particular, the taste path; BMS type 3 by idiopathic cause.

The International Headache Society (IHS) in the third edition of Classification of Headache Disorders stated that BMS is a matter of debate in patients with general diseases or local factors [9]. In the diagnostic criteria of BMS, IHS included the presence of symptoms for >2 hours/day for >3 months with burning or dysaesthetic sensation involving the superficial oral mucosa [9].

A variety of local and systemic diseases, including allergies and side effects of medications, can cause burning sensations in the mucosa. Their symptoms are not usually very different from those of BMS. These cases mimic BMS and were previously named secondary BMS or secondary to other conditions by Scala [10]. Secondary BMS cases are different from “primary” or “idiopathic” BMS in which a distinct etiology cannot be determined. The idiopathic BMS is a diagnosis of exclusion of all possible general and local causes for burning sensation. From the first consultation and suspicion of BMS, a complete set of laboratory investigations is recommended. These tests include a complete haematological evaluation (complete blood count, hemoglobin, serum iron, zinc, ferritin, vitamin B1, B2, B6, B12, and folic acid), serum glucose, thyroid panel,

antibodies to *Helicobacter pylori*, etc. In patients with diagnosed systemic disease, a medical consultation for its treatment is recommended.

BURNING MOUTH LIKE-SYNDROME AND SYSTEMIC DISEASES

Gastrointestinal disorders

In a large number of BMS patients (37.5% of 884) were detected the presence of serum gastric parietal cell antibody, thyroglobulin antibody, thyroglobulin antibody positivity. Further studies are needed to determine if gastric parietal cell autoantibodies are detected in BMS patients which can be thus diagnosed with autoimmune atrophic gastritis [11]. Also gastroesophageal reflux disease may be involved in the development of BMS. The use of appropriate treatment given the reflux characteristics was associated with an improvement in symptoms [12]. In BMS patients with gastric disorders, a gastroenterologist evaluation is needed.

There are several reports in the literature in which celiac disease is associated with BMS-like symptoms. Such a case of an elderly woman suffering from a burning tongue may not meet the diagnostic criteria for BMS, it has been reported. Complete relief of symptoms was observed 10 weeks after initiating a gluten-free diet [13].

Allergy

In rare cases of BMS-like symptoms, patients may experience allergies, for example to peppermint oil, chewing gum, toothpaste, mouthwash and lipstick. Although this subtype may be associated with dental allergens, several food, cosmetic and pharmaceutical products have also been identified as allergens related to the occurrence of this “atypical” BMS or BMS type [14].

Blood disorders

A series of blood disorders associate the burning sensation of the oral mucosa and particularly the tongue.

In the general population it has been estimated that a few percent of older men and probably 10-20% of older women suffer from iron deficiency anemia [10]. Oral findings suggesting the presence of iron deficiency include cracks or fissures of the labial commissures, a pallor colour of the oral mucosa, and a smooth, red, painful dorsal tongue mucosa with papillary atrophy. These signs and symptoms actually rule out a diagnosis of BMS [16].

Another type of anaemia which can mimic BMS is pernicious anemia. This is a megaloblastic anemia caused by a lack of vitamin B12, which is due to a deficiency of the intrinsic factor responsible for

the resorption of vitamin B12. In this disease, oral symptoms may include a burning or itching sensation of the oral mucosa, taste disturbances, intolerance to wearing prostheses, and occasionally dry mouth. The clinical examination can reveal atrophy of the papillae of the dorsum tongue. In advanced cases, the tongue may have a smooth, bright red surface, as reported in a single case report [17].

In BMS cases with deficiencies of zinc levels, the replacement therapy improved the symptoms but did not remit it completely [18].

Vitamin deficiencies other than B12

In a study among 70 BMS cases, without clinically mucosal changes, levels of a number of serum vitamins has been determined. In 28 cases (40%) a reduction of vitamins B1, B2, B6 or a combination of these vitamins was found and no case was anaemic or iron deficient. None of the 70 BMS cases showed a scarcity in vitamins A, C, D or E. In a control group rhyming subjects without complaints of oral burning, vitamins reduced level was detected in only 7%. The vitamin-deficient BMS group of 28 cases was given proper remedy. The non-vitamin-deficient BMS cases were given identical vitamin regimens. Of the 28 vitamin-deficient cases, a remarkable 24 cases were asymptomatic after 1 month and remained so after 3 months. No remission was reported in any of the non-vitamin-deficient cases after 1 month or after 3 months [16].

Diabetes mellitus

Diabetes has been connected to BMS based on the underlying mechanism of peripheral neuropathy (as burning feet) which it induces in time. Some authors consider that this comorbidity in untreated or poorly controlled can mimic the BMS and it was noticed that a better control of the main disease does improve the pain [7]. Another possible connection with diabetes is the experience of salivary dysfunction, which can lead to a decrease in salivary flow and change in saliva composition. Many studies have detected impaired salivary function in adults with diabetes, the universal prevalence of xerostomia in diabetic patients varies between 34% and 51% [19]. Xerostomia can lead to many problems, such as difficulty eating, swallowing and speaking and can favour oral candidiasis. It may have a negative effect on patients' quality of life. The etiology is a mystery, but may be related to polyuria, neuropathy and microvascular changes and also changes in the salivary glands.

There is also a significant relationship between xerostomia and glucose levels in saliva, and the highest level of salivary dysfunction is observed in cases with poor glycemic control [19]. There is a correlation between immune factors related to BMS

and increased sedimentation rate and increased salivary IgA encountered in diabetes patients [20].

Endocrine disorders

Gonadal hormones

Despite the unspecified etiology of this discomfort, the experiments confirmed the influence of the underlying hormonal factors [21].

Inconstant psychoendocrinological interactions may affect the oral mucosa and the severity of oral burning sensation in patients with postmenopausal BMS [22]. This is explained by the changes in the sensory pathway caused by decrease of estrogen levels [7]. Although the response of the vaginal epithelium to estrogen, examined by exfoliative cytology and using an immunohistochemical test, is quite distinct and the response of the oral epithelium is minimal [22].

It has been appreciated that BMS is triggered by a nervous system damage induced by neurotoxic factors on small fibers and basal ganglia in an environment of decreased neuroprotective gonadal hormones and increased levels of stress hormones, typical of menopause. It mainly affects women, especially after menopause, when its prevalence can be between 18% and 33% [23]. In postmenopausal women, BMS typically occurs without significant oral lesions, normal laboratory findings, and in association with psychological factors such as depression, which may be due to a range of factors, such as hormonal factors. In addition, neuropathic changes, oral phantom pain, and nerve inflammation may be predisposing factors for BMS [24].

Hashimoto 's thyroiditis

Hashimoto's thyroiditis is an immune thyroid disease that accounts for 30% of aggressive thyroid disease. It is more common in women (about 5-10%) and in patients with other types of self-aggressive diseases [25]. Both genetics and environmental factors contribute to the etiological causes of this disease.

In untreated patients with Hashimoto's thyroiditis, the levels of TSH in hypothyroidism, Anti-TPO, Anti-TG, Free T3, Free T4 modified indices were associated with BMS-like symptoms. Therefore, it seems the levels of various hormones, especially in hypothyroidism, is among the factors affecting BMS. Besides, the increased levels of Anti-TPO, Free T3, and TSH indices was associated with the BMS intensity [26].

Hypothalamic-pituitary-adrenal axis

Circadian rhythm dysfunction has been speculated to underlie anxiety, depression, sleep disturbances, hypothalamic-pituitary-adrenal axis dysfunction, and chronic pain experienced by patients

with BMS [27]. Disruptions in the circadian rhythm affect pain perception, mood and it may affect hypothalamic-pituitary-adrenal axis [28].

Side effects of medications

In the literature there are case reports of BMS considered to be caused by drug intake. The angiotensin-converting enzyme inhibitors are the most commonly reported but the pathogenic mechanism is not yet fully determined [29,30,31]. Some authors incriminate the inflammatory reaction induced by bradykinin increased level. Other drugs reported to favor BMS-like symptoms are antipsychotics, antiretrovirals, and benzodiazepines [29]. This association between BMS and other drugs is controversial as it may be connected with the dose, the pharmacology, other psychogenic factors and the changes related to age [29].

Psychiatric disorders

Psychogenic factors frequently associated with BMS symptoms are anxiety, depression, or personality disorders. This pathogenic mechanism may be related to dopaminergic hypofunction. Analyzing the history of psychiatric disorders, some authors noticed that the onset of BMS was preceded by major depression, generalized anxiety disorder, and painful conditions other than orofacial disorders in almost 80% of cases [32]. When compared to controls, in BMS patients the sleep quality is reduced [33].

BURNING MOUTH LIKE-SYNDROME AND ORAL MUCOSA RELATED CONDITIONS

Although the symptoms of BMS are diagnosed by a complete and minacious anamnesis, a thorough examination of the oral cavity and, in particular, of the oral mucosa, is mandatory in the diagnostic procedure. Oral examination requires an adequate light source. Partial or complete dentures must be removed. For a proper examination of the tongue, the patient will be asked to extend the tongue and to move it through the oral cavity in order to permit the visual examination of all the mucosa [34]. Some oral benign conditions can be observed in BMS patients.

Oral candidiasis

Oral candidiasis can be developed by many predisposing factors, including xerostomia. Salivary dysfunction in these patients may contribute to the increased transport of fungi. Candida-related lesions include pseudomembranous and atrophic mucosal areas, angular cheilitis and median rhomboid glossitis. In at least a quarter of the population *C. albicans* is present in the normal oral flora without causing visible mucosal clinical changes. Can-

did growth can be enhanced by several local and general factors, resulting in penetration into the upper layers of the epithelium. Candidiasis is more common in smokers, in diabetic patients with poor glycemic control, in dentures wearers, in patients who use local and general steroids and antibiotics [35,36,37]. The diagnosis of oral candidiasis is established by clinical criteria and mycological confirmation. The treatment is mainly topical with antifungal agents.

Atrophy of the oral mucosa

A study of 20 BMS patients and 20 healthy control subjects analyzed oral smears collected from the normal clinical appearance mucosa in order to detect cytological and cytomorphometric techniques. The authors concluded that these changes are likely to be associated with epithelial atrophy and unregulated maturation process of the oral mucosa that may contribute to oral symptoms [38].

The fungiform papillae of the anterior dorsal tongue can become inflamed ('lingual papillitis'), producing a reddish aspect of the tongue surface and often accompanied by burning sensations which resemble BMS symptoms but disappear in a short period [39].

Anatomical variants of the tongue

Self-observation of oral mucosal conditions may increase the patient's attention on this area and aggravate pre existing symptoms with or without objective causes.

Geographical tongue, also called erythema migrans, is a benign condition of unknown etiology, characterized by recurrent atrophic areas on the dorsum and lateral edges of the tongue [40]. Fissured tongue is another normal variant of the dorsal tongue. Both clinical entities require no treatment and are unanimously accepted as benign conditions which carry no risk.

Median rhomboid glossitis is a condition of the dorsal tongue mucosa located on the midline, anterior to the foramen caecum. The areas are red flat or slightly prominent or nodular, rhomboid or oval shape [34].

Lingual tonsil is a benign hyperplastic lymphoid tissue ("lymphoid hyperplasia") located in the posterior margin of the tongue. It is most frequently bilaterally and increases in volume if dental foci are present or in case of mechanical dental injury of the areas.

ODONTOGENIC CAUSES

In BMS patients any dental treatment that is not really indicated should be avoided until a certain diagnosis. Some of the local causes of BMS can be allergy to dental materials, galvanism, dental treat-

ment, etc. Oral galvanism refers to an electrochemical reaction between different dental metal restorations in the presence of a conductive solution, such as saliva. The size of the currents can be calculated after measuring the potentials and polarizations of the metal restorations.

Prosthesis or dentures problems related to occlusion, stability and temporomandibular joint are considered to be a cause observed in 50% of BMS patients. In almost all patients, complete resolution of symptoms was obtained after removal of the prosthesis defects [41].

CONCLUSIONS

BMS is a complex disease that affects not only one organ or structure, but the body as a whole. The clinician should be prepared for establishing differential diagnosis and know the difference between primary BMS and BMS-like symptoms.

There are symptoms that mimic BMS in systemic diseases such as diabetes, Hashimoto 's thyroiditis

and also circadian rhythm dysfunction, in malfunction of hypothalamic-pituitary-adrenal axis, allergies, etc.

In addition, the local factors should be taken into consideration and the oral mucosa be evaluated for unusual features, candidiasis or recent dental treatment, galvanism.

Most affected cases are over 50 years old with a frequency higher in women than in men. Because the etiology of BMS is multifactorial, treatment can only be distinctive, and is aimed at relieving symptoms. The complexity of BMS symptoms and associated psychosocial infirmities, anxiety and depression raise the need for a multidisciplinary and individualised approach.

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