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Current international consensus on burning mouth syndrome ; systematic review of recent review articles

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ABSTRACT : Burning mouth syndrome (BMS) is a type of chronic orofacial pain, which is difficult to diagnose and treat. Patients suffer from BMS worldwide. The pathophysiology of this disorder is not fully understood. This study looked at recent review articles about the classifications, diagnosis and pathophysiology of BMS. PubMed/MEDLINE and WEB of SCIENCE® databases were reviewed to identify articles about BMS, written in English from 2010 to May 2017. Eighteen review articles about BMS were identified, including six systematic reviews, 11 narrative reviews, and one meta-analysis. The most frequently cited classification system for BMS was the International Classification of Headache Disorders (ICHD). Fourteen of the 18 articles (78%) subtyped BMS as primary and secondary BMS, and 16 (89%) of the 18 articles revealed that the main pathophysiology of BMS was pain of neuropathic origin. A review and meta-analysis clearly demonstrated significant relationships between psychological factors and BMS. BMS is most frequently subtyped as primary and secondary. Pain in BMS is regarded as of neuropathic origin, although its etiology may be multifactorial. This paper will discuss these findings and a summary of the reviews will be presented.

Key Words : burning mouth syndrome, neuropathic pain, neuropathy, psychological factor

Introduction

Burning mouth syndrome (BMS) is a type of chronic orofacial pain that is challenging to diagnose and treat[1]. BMS is characterized by a burning sensation, accompanied by pain and/or itching, which may occur in any area of the mouth, including the tongue, palate, lips, and gums[2]. Its etiology has not yet been determined[2]. Patients with BMS have a reduced quality of life compared with controls[3-5]. In addition, patients with BMS frequently complain of taste alteration (dysgeusia, hypoguesia) or dry mouth (xerostomia)[6]. The oral burning or pain seldom interferes with sleep and never worsens, but may be relieved by eating and drinking[5]. A variety of health professionals may be consulted, including dentists, general practitioners, oral medicine physicians, and dermatologists[7].

In Japan, BMS is considered a type of dental psychosomatic disease. Psychogenic causes have been causally linked to the "wastebasket diagnosis" of BMS[6]. Alternative terms for BMS include glossalgia, stomatodynia, glossopyrosis[1], glossodynia, stomaropyrosis, sore tongue, oral dysesthesia[3, 7, 8], persistent idiopathic orofacial pain[6], and scaled mouth syndrome, although BMS remains the most popular term, both in Japan and worldwide[9].

Little is known about the epidemiology of BMS, due in part to a lack of universal diagnostic criteria[3]. BMS mostly affects postmenopausal women and rarely affects individuals under age 30 years[1]. Prevalence rates may vary, and generally range from 0.1% to 18% in the general population, but may be as high as 40%[1-3, 6, 10, 11].

Scala *et al*.[6, 12] classified BMS into two clinical forms,

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primary and secondary BMS. Primary BMS is regarded as caused by unidentified organic systemic/local factors ; whereas secondary BMS is caused by systemic, local, and psychological factors[6].

Although the pathophysiology of primary BMS is not fully understood, pain in BMS was identified as neuropathic[1, 4, 5]. This study reviewed recent review articles about the classifications, diagnosis and pathophysiology of BMS.

Materials and methods

Review

The databases of PubMed/MEDLINE and the WEB of SCIENCE® were systematically reviewed, using the search terms, "burning mouth syndrome", "BMS" and "review", for review articles written in English from 2010 to May 2017. "Letters to the editor", "Case report", and "original articles" were excluded.

Review protocol

Factors recorded included type of the review articles, year of publication, country of the first author, department of the first author, and impact factor of the journal. Articles describing the classification and diagnosis of BMS and the pathophysiology of BMS were selected.

Results

Selected reviews

Our review identified 18 review articles on BMS[1-8, 10, 13-21], including six systematic review[3, 5, 14, 15, 18, 21], 11 literature or narrative review[1, 2, 4, 6-8, 10, 12, 17, 19, 20], and one meta-analysis[18]. One of the systematic review articles included a meta-analysis[5].

Two articles were published in 2010[8, 17], one in 2012[6], three in 2013[1, 10, 12], three in 2015[2, 4, 19], seven in 2016[3, 7, 14-16, 18, 20], and two in 2017[5, 21].

The countries of the first author are listed in Table 1. The first authors of four articles were from United States of America[1, 10, 17, 21], with other first authors spread throughout countries in Europe, South America, and Asia.

The first authors of nine articles were from department of dentistry[3, 7, 8, 12, 15, 17-20]. Three first authors were from department of otolaryngology[2, 10, 21], three from department of neurology[1, 4, 16], and one each from department of clinical neurophysiology[6], health science[5], and psychiatry[14].

Table 1. Country distribution of the first authors

United States of America : 4 articles
Brazil : 2 articles
United Kingdom : 2 articles
Finland : 2 articles
Italy : 2 articles
Australia : 1 article
China : 1 article
France : 1 article
Saudi Arabia : 1 article
Spain : 1 article
Taiwan : 1 article

Thirteen of the 18 articles were published in journals with impact factors in 2015 ranging from 1.087 to 6.103[1, 3-8, 12, 14, 16, 18, 19, 21]. The remaining five articles were published in journals without impact factors[2, 15, 17, 20] (Incites™ Journal Citation Reports®).

Classification of the BMS

Although known for more than a century, BMS was not formally categorized as a distinct disorder until 2004, when the International Headache Society (IHS) included BMS in the International Classification of Headache Disorders-II (ICHD-II)[14]. The International Association for the Study of Pain (IASP) defined BMS as "distinctive nosological entity characterized by unremitting oral burning or similar pain in the absence of detectable oral mucosa changes"[3, 22].

The ICHD-III-β re-defined BMS as "intraoral burning or dysaesthetic sensation that recurs daily for more than two hours per day over more than three months in the absence of clinically evident causative lesions[15] (Table 2). Of the 18 articles, five used the ICHD-II classification (2004)[1, 8, 10, 14, 20], four[3-5, 20] used the of ICHD-III-β classification (2013), and two used the IASP classification (1994)[3, 10].

Table 2. ICDH-3β ; Diagnostic of burning mouth syndrome[5]

(a) Oral pain fulfilling criteria B and C
(b) Recurring daily for > 2 hours per day for > 3 months
(c) Pain has both of the following characteristics ; 1-burning quality 2-felt superficially in the oral mucosa
(d) Oral mucosa is of normal appearance and clinical examination including sensory testing is normal
(e) Not better accounted for by another ICHD-3 diagnosis

Subtypes of BMS

1. Primary and secondary (Scala et al; 2013)[12, 13]

BMS can be classified into two clinical form, primary and secondary BMS[12, 13]. Secondary causes must be ruled out to classify patients as having primary BMS[1] (Tables 3, 4 and 5). Secondary causes can include the side effects of medication, nutritional and vitamin disorders, allergies, oral lichen planus, oral mucosa diseases, candidiasis, autoimmune type connective tissue diseases, trigeminal neuralgia, multiple sclerosis, Parkinson's disease, gastrointestinal reflux, diabetes mellitus, thyroid and other endocrine disorders, and psychological disorders or factors[1, 23, 24]. In the present study, 14 of the 18 articles (78%) used the classification of primary and secondary BMS[1-5, 8, 10, 12, 15-20].

2. Muzyka and De Rossi classification (1999)

The Muzyka and De Rossi classification system classified BMS into three types. In type1, patients are pain-free on waking, but experience increasing symptoms during the day. This type affects approximately 35% of patients and is linked to systemic disorders, including nutritional deficiencies and auto-immune conditions. In type 2, patients have continuous pain throughout the day. This type occurs in about 55% of patients, and is usually associated with psychological disorders. In type 3, patients have intermittent symptoms. This type occurs in 10% of patient is associated with allergic reaction[4, 14, 25]. Of the 18 articles in this study, five described patients using the Muzyka and De Rossi classification system[8, 10, 12, 14, 20].

Table 3. Local factors related to secondary burning mouth syndrome[4, 8, 10]

Local factors
Poorly fitting dentures
Parafunctional habits (e.g. clenching, bruxism, tongue posturing)
Dental anomalies (trauma) Dental treatment
Taste alterations and disorders
Xerostomia
Mechanical or chemical irritants, Galvanism
Infection (e.g. fungal, viral, bacterial,enterobacter, and klebsiella)
Oral mucosal lesions (e.g. lichen planus, benign migratory glossitis, scalloped and/or fissured tongue)
Allergic contact stomatitis related to dental restorations, Denture materials, oral care products, food, preservatives, additives, flavorings
Hyposalivationdue to radiation therapy, disorders of salivary glands, medications
Myofascialpain

Table 4. Systemic factors related to secondary burning mouth syndrome[4, 8, 10]

Systemic factors
Endocrine alterations (e.g. hypothyroidism, diabetes mellitus, menopause)
Chronic medical conditions (e.g. gastrointestinal, urogenital diseases)
Deficiencies (Fe, vitB complex,B1, B2, B6, B12, zinc, folic acid)
Anemia
Medication
Hyposalivationdue to connective tissue disease
Autoimmune disorders (e.g. Sjögrensyndrome)
Parkinson's disease
Multiple sclerosis
Globus pharynges, lupus erythematous
Dietary antigen, smoking,
Esophageal reflex
Neuropathy and neuralgia

Table 5. Psychological factors related to secondary burning mouth syndrome[4, 8, 10]

Psychological factors
Anxiety
Depression
Personality disorders, pain attacks
Cancer phobia
Psychosocial stress
Compulsive disorders
Somatoform disorders

3. Lamey and Lewis classification (1989)

The Lamey and Lewis classification system also classifies BMS into three types. In type 1, patients experience progressive pain throughout the day ; in type 2, patients experience constant pain throughout the day ; and type 3, symptoms are intermittent and patients have some symptom-free days[10]. Type 1 is not linked to psychiatric disorders ; type 2 is linked to psychiatric disorders, particularly chronic anxiety ; and type 3 is associated with contact stomatitis, reaction to food additives, and unspecified psychiatric disorders[5, 26]. Of the 18 articles in this study, only one described this classification system.

Diagnosis and pathophysiology of BMS

Of the 18 articles in this study, 16 reported that the main pathophysiology of BMS pain was considered as "neuropathic pain"[1-4, 6-8, 10, 12, 15-21]. Only two studies did not refer to a relationship between BMS pain and neuropathic pain[5, 14]. Although the pathophysiology of BMS is not fully understood, neurophysiological studies suggest that the central and/or peripheral nervous systems are implicated in BMS[8]. The results of superficial biopsy and immunohistochemical staining for markers of pathological changes in tongue mucosa suggest peripheral small fiber neuropathy[21]. Twelve (67%) of the 18 articles in this study reported the involvement of peripheral small-fiber and subclinical trigeminal neuropathy (67%)[1, 3, 4, 7, 8, 10, 12, 16, 17, 19-21], and 11 (61%) reported that central nervous system (CNS) pathology is involved in the pathophysiology of BMS (61%)[3, 4, 7, 8, 10, 12, 16, 17-20]. The positron emission tomography (PET) studies have shown a decline in striatal endogenous dopamine levels in patients with BMS, accompanied by defects in dopamine-mediated top-down pain modulation[19, 27], findings similar to those reported in patients with early Parkinson's disease[19]. Seven of the 18 articles (39%) reported that the central dopamine system was involved in the pathophysiology of BMS[3, 7, 10, 12, 19-21].

Three articles in this study[1, 12, 19] cited new subtypes of primary BMS with neuropathy[6]. Based on their neuropathic patterns, patients with BMS could be divided into three distinct subgroups. The first group, constituting 50-65% of patients, is characterized by peripheral small-diameter fiber neuropathy of the intraoral mucosa. The second group, constituting 20-25% of patients, is characterized by subclinical lingual, mandibular or trigeminal system pathology. The third group, constituting 20-40% of patients, is characterized by central pain that may be related to hypofunction of dopamine[6, 19].

While taste disturbances frequently accompany pain in patients with BMS, interactions between taste and pain may be involved in the pathophysiology of BMS[19]. Taste input may normally inhibit trigeminal input centrally[19]. It has been hypothesized that chorda tympani nerve hypofunction leads to loss of central inhibition, inducing a burning sensation of the tongue[3]. Of the 18 articles in this study, 10 (56%) indicated that taste disturbances and chorda tympani nerve problems were involved in the pathophysiology of BMS[1, 3, 4, 8, 16-21].

Psychological factors and BMS

BMS was initially classified as a psychological disorder[15], as rates of anxiety and depression are higher in BMS patients than in controls[1, 3-5, 8, 17]. Of the 18 articles included in this study, 12 (67%) showed relationships between BMS and psychological factors[1, 3-5, 7, 8, 10, 12, 15, 17, 20, 21].

At present, however, BMS is no longer considered a psychological disorder, with psychiatric disorders considered comorbid or secondary conditions, not causally related to BMS pain[19]. One review article reported that BMS is not due to psychological factors alone but may be a form of neuropathic pain that can have psychological effects[15]. Only one of the 18 articles included in this

study emphasized the significant role of psychological factors in BMS[5]. That article was a systematic review and meta-analysis of 14 studies, published from 2000 to 2016, examining the psychological of 14 studies published included in that meta-analysis, 13, psychiatric, and/or personality factors linked to BMS[5]. Of the 14 studies included in that meta-analysis, 13 reported evidence for the involvement of psychological factors in BMS, and 11 found that psychological and/or psychiatric factors played a role in BMS[5].

Discussion

The present review enabled an understanding of the current international consensus of BMS. Regarding the classification of the BMS, IHS classification (ICHD-II ; 2004) is evaluated as the first distinct description that BMS is a chronic orofacial pain syndrome. Now, the classification of ICHD-III-β (2013) is the newest version of the BMS classification.

Clinically, the concept of "primary" and "secondary" BMS is broadly accepted and is the most frequently used classification of BMS[6]. Secondary BMS has distinct causes for patient symptoms, with treatment or elimination of local, systemic and psychological factors usually resulting in significant clinical improvement[12]. In contrast, diagnosis of primary BMS is based on exclusion[3] and the performance of examinations to rule out all possible factors related to secondary BMS. Thus, the costs and time involved in the diagnostic process are very high and may differ markedly, as tests performed by different institutions may vary. Moreover, the term "secondary BMS" has been reported to be confusing and misleading[9]. Rather, oral symptoms caused by specific local and/or systemic factors should be simply classified as manifestations of the corresponding diseases, not as "secondary BMS"[9]. As for the Lamey and Lewis classification, the finding of causes of type 1 and 3 (systemic disease and oral allergy, respectively) suggest that they should not be classified as BMS.

Recent reviews about BMS were written by researchers and clinicians throughout the world. Moreover, these authors belonged not only to departments of dentistry, including those of oral surgery and oral medicine, but to medical departments, including departments of oropharyngeal, neurology, psychiatry, and health science. This finding indicated the need for many types of healthcare professionals, including dentists, oral medicine doctors, oral surgeons, medical doctors, dental hygienists, and nurses, to know current information about BMS.

Pathophysiology

The pathophysiology of BMS is not yet fully understood. Several studies have shown significant differences between BMS patients and controls in thermal nociception and limits[2, 29, 30], suggesting the involvement of neuropathic change. However, it is not known if the dysfunction is peripheral or central[2]. BMS has a multifactorial etiology with enigmatic pathophysiology[4]. Possible dysfunction in both the peripheral and central neuronal systems has been observed in patients with BMS. These include ; (A) changes in thermal and nociception thresholds, suggesting neuropathy ; (B) a lower density of epithelial and subpapillary nerve fibers, consistent with axonal degeneration (trigeminal small-fiber sensory neuropathy) ; (C) a central deficiency in dopaminergic neurons ; (D) high levels of neural growth factors in saliva ; (E) changes in TRPV1 ion brain activation in response to heat stimuli, as revealed by functional-MRI, and (F) increased excitability or inhibition of the trigeminal system, as shown by alterations in blink reflexes[4, 6, 31, 32].

Although, CNS pathology has been implicated in the pathophysiology of BMS[3, 4, 7, 8, 10, 12, 16, 18-20], few studies have focused on the central mechanisms of BMS pain. Moreover, the relative roles of peripheral and central nervous system dysfunction in BMS pain pathophysiology are not yet fully understood[19]. Involvement of the CNS in BMS has been indicated only by imaging modalities, such as PET and functional MRI[7]. The relative involvement of peripheral and central nervous systems in BMS pathophysiology is likely directly related to treatment methods and outcomes[19].

Psychological factors

Many BMS patients show evidence of anxiety, depression and/or personal disorders[1, 3, 4, 7, 20]. Psychological and psychiatric disorders have been observed in up to 85% of patients with BMS, depression, hypochondria, cancerphobia, and insomnia being the most common diagnoses[1]. Because 17 of the 18 articles included in this study did not treat psychological and psychiatric factors in patients with BMS, psychological and psychiatric disorders are likely not necessary and sufficient conditions for diagnosis of BMS. Moreover, three of the 18[8, 10, 20] included psychological disorders and factors as

causes of secondary BMS. In contrast, a meta-analysis reported that psychological factors lay a crucial role in BMS, with significant relationships between anxiety or depression and BMS[5]. Thus, psychological factors cannot be excluded as being associated with BMS.

This review had several limitations. As this was the first attempt to evaluate review articles published in international journals, we do not know whether our methodology was the most appropriate. We do not have the tools to evaluate the bias and quality of the review articles. Of the review articles assessed, only six were systematic review, whereas 11 were literature and narrative reviews. Thirteen of the 18 articles were published in journals with published impact factors. However, we do not think that impact factor alone reflects the quality of an article, because impact factor is based on evaluation of the journal, not the individual article.

Conclusion

This review of recent review articles enabled a determination of current clinical consensus regarding BMS, with this disease currently classified using the ICHD-III-β (2013) classification system. BMS may be regarded as primary or secondary. Although BMS pain is most frequently as of neuropathic origin, its etiology is multifactorial.

Conflict of interest

None of the authors of this manuscript has any financial relationships with any organization regarding this study, and none has any conflicts of interest.

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