Is Burning Mouth Syndrome a Neuropathic Pain Disorder? A Systematic Review

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Aims: To conduct a systematic review compiling an update on the pathophysiology of burning mouth syndrome (BMS) by reviewing the theories and studies published in the last 5 years that consider BMS a neuropathic disease. **Methods:** A literature review was carried out in April 2020 on the PubMed database by using the following MeSH terms: "(burning mouth OR burning mouth syndrome OR burning mouth pain OR sore mouth OR burning tongue OR oral neuropathic pain OR glossodynia OR stomatopyrosis) AND (etiopathogenesis OR etiopathological factors OR etiology)." **Results:** The research carried out according to the methodology found 19 case-control studies (1 of which was in vivo) and 1 RCT. Of the 19 included studies, 8 showed an evidence score of 2–; 8 showed 2+; another 2 showed 2++; and 1 showed 1+. Quality studies on this topic are insufficient and heterogenous. **Conclusion:** In the pathogenesis of BMS, both peripheral and central neuropathies appear to play a pivotal role. Nevertheless, the balance between them varies from case to case and tends to overlap. BMS does not seem to be a result of direct damage to the somatosensory nervous system, but a dysfunction in it and in the brain network. *J Oral Facial Pain Headache 2021;35:218–229. doi: 10.11607/ofph.2861*

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Burning mouth syndrome (BMS) is a chronic orofacial pain disorder[1] mainly found in middle-aged or elderly women,[2] with a mean age of 60 years.[3] It is characterized by stomatopyrosis (burning mouth sensation or stomatodynia) in patients with a clinically normal oral mucosa and without any particular disease.[4,5] However, burning mouth symptoms are usually comorbid with nutritional deficiencies and/or psychologic disorders, such as anxiety, depression, and even stress.[5,6]

BMS is associated with several symptoms, such as altered perception of taste (dysgeusia), paresthesia, dysesthesia, dry mouth sensation (xerostomia), and painful tongue (glossodynia), despite an often normal salivary secretion.[3,6] Burning sensation is the most representative symptom, usually of moderate to severe intensity and appearing bilaterally symmetrical. It usually takes place on the tip of the tongue, but can also be noted at the lateral border of the tongue, lips, and hard palate.[1,7] Symptoms are aggravated when eating very hot or spicy food, and some patients relate that their symptoms are relieved by consuming very cold food or drinks.[4]

Recent studies do not consider BMS a secondary disease.[1,5] BMS is referred to as a burning symptom that is not attributable to local or systemic causes after excluding such conditions.[5,8,9] Thus, to properly diagnose a patient with BMS, local factors such as allergic reactions, fungal infections, viral diseases, atrophic candidiasis, microtrauma, and decreased quality and/or quantity of salivary secretion should be considered and distinguished, since these factors can also produce oral burning sensations due to irritation of the oral mucosal tissues.[5,10]

Also, systemic factors such as nutritional deficiencies (low serum vitamin B12, folic acid, ferritin, zinc, and magnesium levels); hormonal changes; systemic diseases (anemia, diabetes mellitus, thyroid diseases, and immunologic diseases); and medications (antihistamines, neuroleptics, antihypertensives, and benzodiazepines) must be ruled out as well.[3,5,8]

More frequently, studies suggest that the main cause of BMS seems to be neuropathy in the central and peripheral mechanisms related to

Table 1 All Reviewed Articles, Level of Evidence According to SIGN Criteria, and Conclusions

Study, y, country	Evidence level	Type of study/aspects	Most relevant conclusions
Treldal et al, 2016, Denmark[3]	1+	RCT (randomized, experimental, double-blinded, crossover, and placebo-controlled). Aimed to evaluate the effect of a bupivacaine lozenge on oral mucosal pain, xerostomia, and taste alterations in patients with BMS, characterizing inflammatory and neurogenic profiles and oral symptomatology. Twenty-one women with BMS (mean age 57.5 [38–71] y) vs 10 age-matched women as control group (mean age 59 [55–65] y); all were healthy blood donors. The BMS patients were divided according to their response to a local anesthetic lozenge on oral pain (effect [n = 13], no effect [n = 8]).	Effect of a local anesthetic indicates a peripheral neuropathology involving lack of estrogen and upregulation of estrogen receptors, and no effect indicates a systemic inflammation-induced mechanism leading to increased levels of plasma cytokines. Patients in the effect group displayed a more intense immunoreactivity to the estrogen receptor in their buccal mucosa, whereas the no-effect group tended to have elevated plasma levels of the proinflammatory cytokines than the effect group and control group.
Shinoda and Noma, 2017, Japan[14]	2–	Case-control and in vivo study. An assessment of the mRNA expression of Artn in the tongue mucosa of patients with BMS was conducted first: 9 BMS patients (n = 9 women, 71.6 ± 7.7 [58–80] y) and 9 controls (4 men and 5 women, 75 ± 12.9: [51–85] y). And last, a mouse model of BMS by application of 2,4,6-trinitrobenzene sulfonic acid diluted with 50% ethanol to the dorsum of the tongue.	There was no significant difference in the health history between patients with BMS and control subjects. The mRNA expression of Artn in the tongue mucosa of patients with BMS was significantly higher than that of control subjects. Findings in the mouse model suggest that upregulation of TRPV1 in trigeminal neurons innervating the tongue, by GFRa3-mediated signaling, facilitate the transmission of nociceptive information, contributing to the resulting heat hypersensitivity observed in BMS. Artn-GFRa3 signaling may be a therapeutic target for treating tongue pain associated with BMS.

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a trigeminal dysfunction.[2,6,7] Thus, in some patients, psychogenic factors appear to have an important role in BMS aggravation.[5,6] Many authors wonder whether psychologic factors are responsible for the cause of BMS or whether the daily presence of symptoms is the triggering factor of the psychopathology.[4]

The link between psychogenic factors and BMS pain may be induced by a mechanism that can either potentiate or suppress spinal nociceptive signals without peripheral input. This may be carried out by pain-modulating neural pathways descending from the cortex, hypothalamus, midbrain, and medulla to the spinal cord and may be influenced by emotional states (such as excitement, stress, anxiety, or depression).[7]

The present article aimed to conduct a systematic review compiling an update on the pathophysiology of BMS, reviewing the theories and studies published in the last 5 years that consider BMS as a neuropathic disease.

Materials and Methods

Literature Search Strategy

A literature review was carried out in April 2020 in the PubMed database using the following MeSH terms: "(burning mouth OR burning mouth syndrome OR burning mouth pain OR sore mouth OR burning tongue OR oral neuropathic pain OR glossodynia OR stomatopyrosis) AND (etiopathogenesis OR etiopathological factors OR etiology)." Additionally, reference journals were hand searched to source additional relevant publications.

Selection and Inclusion Criteria

Articles were selected according to the following criteria: papers written in English or Spanish; prospective and retrospective studies, cross-sectional studies, and case reports and case series. Article selection and analysis were carried out by two authors (I.C.H. and J.C.S.).

Articles published before January 2015 and articles that did not evaluate the link between BMS and a neuropathic origin were excluded. Titles and abstracts were screened by the two reviewers, and papers that did not mention a neurogenic topic regarding BMS were excluded. Finally, after reading the full texts, all articles that did not review/analyze the neuropathic perspective of BMS were excluded. Discrepancies were solved by consultation with a third reviewer (J.L.L.).

The major findings of each study are summarized in Table 1 (compiled by I.C.H., J.C.S., and J.L.L.).

Table 1 All Reviewed Articles, Level of Evidence According to SIGN Criteria, and Conclusions *(continued)*

Study, y, country	Evidence level	Type of study/aspects	Most relevant conclusions
Barry et al, 2018, Ireland[15]	2–	Case-control, pilot study. Explored the impact of BMS on the plasma expression profiles of 10 individual cytokines/chemokines and related this plasma signature to clinical symptoms, including pain and depression using pro-inflammatory 10-plex assays. Ten BMS patients (mean age: 57.6 ± 3.79 [36–75] y) and 10 healthy volunteers (mean age: 52.9 ± 1.2, 49–59 y). Both groups were women.	Proinflammatory cytokines/chemokines are commonly linked with nociceptive signaling and are elevated in neuropathic pain disorders, and it was found for the first time that IL-8 proinflammatory chemokine is enhanced in the plasma of BMS patients, is correlated with pain levels and symptoms of depression in individuals with BMS, and could even be a new biomarker. A reduction in average plasma IL-10 protein expression (anti-inflammatory) was determined in BMS samples. 50% of the BMS patients reported the occurrence of a major life event (death/illness in family). 70% of BMS patients referred mild-moderate depression. The total score was blindly generated for patients and healthy control participants, producing a quantitative result corresponding to depression severity.
Mo et al, 2015, China[16]	2+	Case-control study. Aimed to compare thermal and mechanical sensory and pain thresholds in BMS patients and their age- and gender-matched controls to investigate a probable neuropathic basis of BMS. Also, to perform explorative correlation analyses between QST variables and clinical characteristics. Twenty-five BMS patients (8 men, 17 women; mean age 49.5 ± 11.4 y) and 19 age- and gender-matched healthy controls (12 women, 7 men).	BMS patients had lower cold detection and pain thresholds (less sensitivity) and higher warm detection and pain thresholds (less sensitivity) at the tongue and lip than healthy participants. They also found a localized loss of thermal function in the BMS patients. These findings further support the hypothesis that BMS could be a neuropathic pain condition with involvement of peripheral and/or central pain mechanisms. The present study did not find any localized loss of mechanical function in BMS patients, indicating that the small-fiber neuropathy may only, or predominantly, involve the small C and A-δ nerve fibers in BMS patients.
López-Jornet et al, 2017, Spain[17]	2++	Case-control study. Aimed to identify the neuropathic component of pain experienced by BMS patients evaluated using PD-Q and neuropathic pain questionnaire. Sixty-four patients; 33 BMS (5 men and 28 women, mean age 66.6 ± 10.6 y) and 31 controls suffering nociceptive pain (7 men and 24 women, mean age 63.8 ± 13.5; 19 OLP, 2 oral candidiasis, 5 traumatic ulcers, and 5 recurrent aphthous stomatitis). The average duration of experiencing BMS in the sample was 3.16 years.	Almost a third of BMS patients present neuropathic pain, which is strongly associated with the intensity of pain measured using a VAS. The use of simple routing diagnostic methods (as PD-Q) could help identify patients suffering neuropathic pain and facilitate individualized management of BMS.
Heo et al, 2015, Republic of Korea[18]	2++	Case-control study. Aimed to compare the PDQ-DN4 and DN4i neuropathic pain questionnaires for primary BMS and to analyze their differences and similarities. Patients (N = 81) were divided into 2 groups: 42 BMS (35 women and 7 men, mean age 62.4 y [62.30 ± 10.08]) and 39 nociceptive pain (32 women and 7 men, mean age 61.58 y [61.58 ± 12.06]).	Using these neuropathic pain questionnaires, the present study identified a substantial proportion of neuropathic pain components in BMS patients.

Artn = artemin; BMS = burning mouth syndrome; CG = cingulate gyrus; COMT val158met = polymorphism altering catechol-O-methyltransferase; DFNS = German Research Network on Neuropathic Pain; DRD2 = dopamine D2 receptor; DFNS = German Research Network on Neuropathic Pain; EGMt = electrogustatometry thresholds; fMRI = functional magnetic resonance imaging; GFRa3 = GDNF family receptor alpha 3; GMC = gray matter concentraion; MRI = magnetic resonance imaging; MTS = mechanical temporal summation; PD-Q = painDETECT questionnaire; QST = quantitative sensory testing; TRPV1 = transient receptor potential vanilloid 1; VAS = visual analog scale; VBM = voxel-based morphometry.

Table 1 All Reviewed Articles, Level of Evidence According to SIGN Criteria, and Conclusions *(continued)*

Study, y, country	Evidence level	Type of study/aspects	Most relevant conclusions
Zavoreo et al, 2017, Croatia[19]	2–	Case-control study. Brain parenchyma at midbrain level (axial section) was analyzed in 20 BMS patients and 20 controls with transcranial ultrasonography. Twenty BMS patients (women, mean age 64.7 y [64.7 ± 12.3]) and 20 controls with chronic lumbrosacral pain (women, mean age 61.5 y [61.5 ± 15]).	In BMS patients, significant differences were reported in hypoechogenicity of the substantia nigra and midbrain nuclei, as well as hyperechogenicity of the brain nucleus. It seems that BMS could be analyzed as an oral variant of restless legs syndrome. Transcranial ultrasonography is a noninvasive, reproducible method that enables visualization and evaluation of stem structures and their environment in the brain of BMS patients.
Kolkka et al, 2019, Finland[22]	2+	Case-control study. Using a rigorously controlled design, aimed to confirm earlier findings in BMS by comparing the findings in blink reflex and thermal QST studies to age- and sex-matched healthy controls and to test whether DRD2 gene 957C>T or COMT val158met polymorphisms influence pain sensitivity or experience in BMS. Forty-five BMS patients (43 women, 2 men, mean age 62.5 y [45–82]) and 32 healthy controls (30 women and 2 men, mean age 64.8 y [48–84]).	BMS patients showed thermal hypoesthesia within lingual nerve distribution compatible with small-fiber neuropathy. The DRD2 957C>T genotype influences perception and experience of BMS pain. This confirms earlier findings of neuropathic pain in BMS. However, the pre-pain range was significantly narrower in BMS patients because of the thermal hypoesthesia reflected in a high warmth detection threshold.
Watanabe et al, 2019, Japan[24]	2+	Case-control study. Assessed the association between somatosensory dysfunction and disease duration in patients with BMS using a standardized battery of QST developed by the DFNS. Twenty-nine BMS patients, all women from 30 to 74 years old (54.8 ± 12.1 y) and 29 healthy controls (49.9 ± 6.9 y).	There was no significant difference in the number of patients who had attained menopause between the subchronic and chronic BMS groups, which revealed evidence of a lack of relationship between menopause and chronicity of BMS. Past and present data show that BMS duration is positively associated with the likelihood of exaggerated pain response.
Nasri-Heir C et al, 2017, USA[25]	2–	Case-control, pilot study. Aimed to review the literature on primary BMS diagnosis, mechanisms, and treatment, focusing on pain modulation and conducted a pilot study presenting preliminary data that suggests a link between primary BMS and a faulty inhibitory pain system. Ten cases (women with primary BMS with an age range of 36–71 y) and 15 healthy controls (15 women with an age range of 34–70 y).	Painful mechanical stimulus (in the arm): There was no significant difference in MTS between control and primary BMS groups. Painful heat stimulus: the conditioning stimulus (immersion of the nondominant forearm in the 46°C water bath) had a significant effect on the resulting sensation in response to a heat stimulation applied to the dominant forearm in the controls, but not in the BMS group (like in chronic pain conditions, they may present an inefficient inhibitory pain system). The various possible underlying mechanisms involve the peripheral and central nervous system and may be associated with a less efficient modulation of pain.
Sinding et al, 2016, Germany[26]	2+	Case-control study. Investigated the change of GMC in subjects with BMS using VBM. Patients (N = 42) divided into 3 groups: 12 BMS (7 women, mean age 59.4 ± 12.1 y [35–72]); 17 dysgeusia (11 women, mean age 58.4 ± 8.1 y [42–73]); and 13 healthy controls (10 women, mean age 59 ± 3.4 y [50–73]).	BMS presents modification of GMC mostly in pain regions, while dysgeusia shows these changes in areas associated with emotions, motor anticipation, and somesthesia. Therefore, BMS and dysgeusia are driven by different brain mechanisms, which does not support the theory of a similar etiology. If the pain does not come from the periphery, the brain itself may drive it. In the BMS group, a decrease of GMC was found in areas normally acting as antinociceptive areas (anterior and posterior CG, cerebellum, and inferior temporal gyrus), which supports the hypothesis of a central pain. This is the first time that significant changes in GMC have been identified in several areas of BMS patients. These changes may be the result of the chronification process.

Table 1 All Reviewed Articles, Level of Evidence According to SIGN Criteria, and Conclusions *(continued)*

Study, y, country	Evidence level	Type of study/aspects	Most relevant conclusions
Wada et al, 2017, Japan[27]	2+	Case-control study. Aimed to calculate structural connectivity and to evaluate the brain network at local and global connectivity by 1.5T MRI. Fourteen BMS patients (mean age 50.9 y [42–63], women) and 14 healthy age-matched controls (mean age 50.2 [42–65], women).	Strengthened connections between several brain regions belonging to the medial system were detected, as well as between the medial system and thalamus, basal ganglia, and brainstem, which exhibits an emotional aspect of BMS and chronic pain. Alteration of the connectivity of the medial system to the brainstem in this investigation may reflect the disruption of descending pain modulation function in BMS.
Shinozaki et al, 2016, Japan[28]	2–	Case-control study. Aimed to test whether peripheral neuropathic changes contribute to central excitation in BMS by investigating the roles of the central and peripheral nervous systems with a thermal stimulus deliberating a warm and noxious heat stimulation evaluated with fMRI. Compared spatial and temporal brain responses to painful thermal stimuli in women with BMS and with pain-free sex- and age-matched volunteers. Sixteen right-handed women < 65 y of age with BMS (mean age 51.1 ± 9.1 y) and 15 age-matched right-handed healthy women controls (mean age 49 ± 8.4 y).	There was a significant reduction in pain perception after repeated tonic heat stimulation applied at the lower lip in controls. In BMS patients, the same stimulation suppressed brain activity in the cingulate cortex without reducing perceived pain sensation. The response of the parahippocampal area differed in BMS patients and controls when the same repeated thermal sequence was applied at the palm. The prefrontal cortex and cingulate cortex are involved in pain modulation and suppressed activity in these brain areas impairs suppression of pain perception in BMS patients. BMS patients show specific brain responses due to impaired function of the central and peripheral nervous systems.
Yoshino et al, 2017, Japan[29]	2+	Case-control study. Examined activation of brain regions with fMRI in response to intraoral tactile stimuli when modulated by angry facial expressions. Twenty-seven BMS patients (21 women, mean age 44.8 ± 12 y) and 21 age-matched healthy controls (18 women, mean age 46.3 ± 10.7 y).	Neural responses in the post-central gyrus are more strongly affected by angry facial expressions in BMS patients, which may reflect one possible mechanism underlying impaired somatosensory system function in this disorder. The pain-related VAS scores in daily life were positively correlated with changes in post-central gyrus activation during tactile stimuli in the angry condition for BMS patients. Clinical characteristics in BMS patients may be linked to hypersensitivity of the intraoral sensory perception associated with the angry emotional condition.
Kohashi et al, 2020, Japan[39]	2–	Case-control study. Examined temporal brain responses in fMRI to an ongoing hot stimulus to investigate the pain-modulating system in patients with BMS and differences in response to the central nervous system. Fifteen right-handed women (52.6 ± 6.3 years) who were diagnosed with BMS and 15 age- and gender-matched, right-handed controls (49.0 ± 8.4 y).	These findings suggest that the brain in patients with BMS is highly sensitized to pain signals originating from the trigeminal system. In patients with BMS, it is known that small nerve fiber atrophy is observed in the oral mucous epithelium, and such a peripheral pathology may be involved in sensitization of the brain in BMS.
Hartmann et al, 2017, Germany[40]	2+	Case-control study. Analyzed intraoral neurophysiologic changes in patients with unilateral lingual nerve lesions as well as patients with BMS by applying a standardized QST protocol. Four patients suffering from a peripheral lesion of the lingual nerve (women, mean age 50.5 y [39–72]); 5 from BMS (4 women and 1 man, mean age 51.8 y [37–70]); and 8 healthy controls (women, mean age 56.9 y [37–69]).	Patients with BMS revealed significant deficiencies, indicating a cold/warmth hypoesthesia and consecutively a small-fiber loss. Mechanical test thresholds revealed pinprick hypoalgesia, indicating an impaired function in small fibers, which is a typical finding in patients suffering from peripheral nerve damage. The results indicate that patients with LNI suffer from a peripheral neuropathy. BMS could be seen as neuropathy with variable central and peripheral contributions among individuals, resulting in chronic pain.

Table 1 All Reviewed Articles, Level of Evidence According to SIGN Criteria, and Conclusions *(continued)*

Study, y, country	Evidence level	Type of study/aspects	Most relevant conclusions
Puhakka et al, 2016, Finland[41]	2–	Case-control study. Aimed to investigate the mucosal innervation of the tongue in a clinically and neurophysiologically meticulously characterized group of patients with primary BMS compared to appropriately age- and sex-matched controls. Ten BMS patients (67.9 y, 60–77.5) and 10 healthy controls (67.4 y, 58.4–75.9); all women.	Nine out of 10 patients with BMS showed neurophysiologic or psychophysical signs of a more generalized peripheral nervous system dysfunction. Pure focal small-fiber neuropathy of the oral mucosa has a role in the pathophysiology of BMS. BMS may be related to a more generalized yet subclinical peripheral neuropathy. The present results imply that with adequately sensitive tools, widespread alterations in nervous system function can be confirmed in the majority of patients with primary BMS.
Braud et al, 2017, France[43]	2–	Case-control study. Aimed to explore taste function in primary BMS patients and paired controls using EGMt recordings within fungiform and foliate taste bud fields. Twenty-one BMS (19 women, 2 men, mean age 58.5 ± 11.7 y) and 21 matched controls (19 women, 2 men, mean age 58.9 ± 11.5 y).	A proportion of 22.2% of BMS patients described taste complaints, such as persistent sour or salty taste and ageusia. Highest mean EGMt were recorded on both sides of the dorsum of the tongue; significant differences in EGMt were observed between smokers (n = 39) and nonsmokers (n = 3). Mean EGMt were significantly increased in BMS group compared to control group for the right side of the dorsum tongue and right lateral side of the tongue. The results evidenced gustatory dysfunction within fungiform papillae located at the right side of the dorsum of the tongue in BMS patients. Therefore, the present taste detection decay within fungiform tastebud fields may relate to chorda tympani dysfunction. Present unilateral elevated thresholds within foliate papillae taste fields in the BMS group point toward the glossopharyngeal nerve as a result of nerve damage.
O'Neill, 2019, UK[44]	2+	Case-control study. Aimed to assess the utility of corneal confocal microscopy in identifying small-fiber damage in patients with BMS. Seventeen patients with BMS (15 women and 2 men, mean age 61.7 ± 6.5 y) and 14 healthy controls (7 women and 7 men, mean age 59.3 ± 8.68 y).	Corneal confocal microscopy identified corneal small-fiber damage in BMS patients, which confirms the presence of a small-fiber neuropathy (this could previously be shown through a reduction in epidermal nerve fiber density in tongue biopsies). This technique is a rapid, noninvasive imaging method that accurately and reproducibly quantifies small-fiber damage in a range of peripheral neuropathies. A significant increase in corneal Langerhans cells density in BMS patients was also shown, which is suggestive of immune alterations in BMS.

Artn = artemin; BMS = burning mouth syndrome; CG = cingulate gyrus; COMT val158met = polymorphism altering catechol-O-methyltransferase; DFNS = German Research Network on Neuropathic Pain; DRD2 = dopamine D2 receptor; DFNS = German Research Network on Neuropathic Pain; EGMt = electrogustatometry thresholds; fMRI = functional magnetic resonance imaging; GFRa3 = GDNF family receptor alpha 3; GMC = gray matter concentraion; MRI = magnetic resonance imaging; MTS = mechanical temporal summation; PD-Q = painDETECT questionnaire; QST = quantitative sensory testing; TRPV1 = transient receptor potential vanilloid 1; VAS = visual analog scale; VBM = voxel-based morphometry.

Assessment of Quality

All 19 selected articles were read in their entirety by all authors, who came to a consensus about their level of evidence. The Scottish Intercollegiate Guidelines Network (SIGN) criteria were used to assess the level of evidence (Table 2).[11]

Results/Discussion

A total of 622 studies resulted from the electronic research. After screening the titles and excluding duplicates, the remaining number of articles was 34. After abstract screening, 21 more studies were excluded,

Table 2 Levels of Evidence According to The Scottish Intercollegiate Guidelines Network (SIGN)[11]

Evidence level	Type of studies
1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2++	High-quality systematic reviews of case-control, or cohort studies or high-quality case-control or cohort studies, with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a high probability that the relationship is causal.
2–	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3	Non-analytic studies; eg, case reports and case series.
4	Expert opinion.

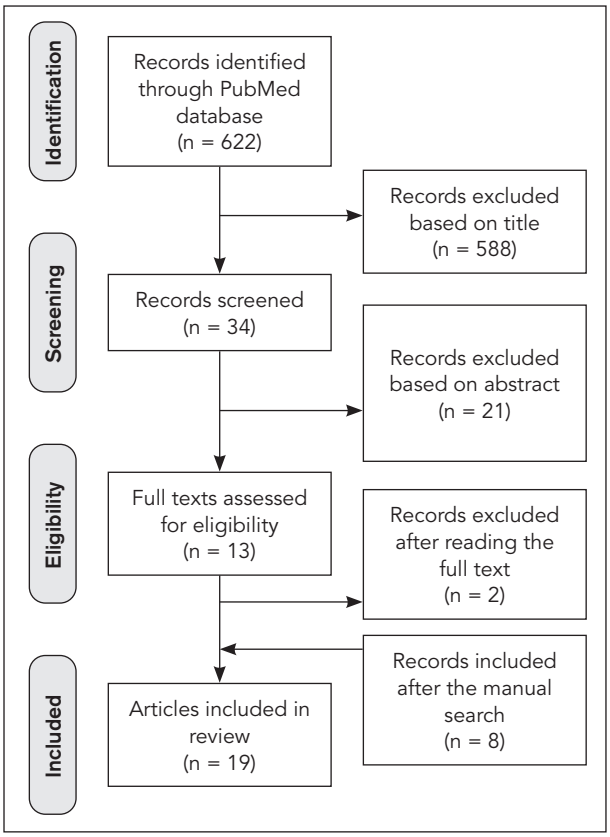

Fig 1 PRISMA flow diagram showing article selection.

and after reading the full texts, 2 more articles were excluded, resulting in 11 included articles. Eight additional articles were included manually for presenting content relevant to the topic; these 8 studies were selected by reading the references of the included articles and complying with the exclusion criteria. Th search process is summarized in Fig 1.

A total of 19 studies were included; 18 case-control studies (1 of which was also an in vivo animal study) and 1 randomized controlled trial. Eight of the 19 studies included showed an evidence of 2–; 8 showed 2+; another 2 showed 2++; and 1 more showed 1+. Table 1 shows all the reviewed studies, their most relevant aspects, and their level of evidence according to the SIGN criteria.[11]

The main finding of this systematic review is that patients with BMS seem to have substantial differences compared to healthy controls owing to the fact that they could present both peripheral and central neuropathies.

BMS patients can be classified into three subgroups according to pathophysiology: *(1)* BMS with a central pain pattern that can be attributed to hypofunction of the central dopaminergic system in the basal ganglia or to dysfunction of serotoninergic pathways (20% to 40%); *(2)* BMS related to a peripheral small-diameter fiber neuropathy of the intraoral mucosa (50% to 60%); or *(3)* BMS with a subclinical lingual, mandibular, or trigeminal system pathology (20% to 25%).[8,12,13]

The last subgroup will not be discussed in this article, since it is a subclinical trigeminal neuropathy and not primary BMS. Unfortunately, it is clinically indistinguishable from the other two subgroups, although it can be dissected with careful neurophysiologic examination.[8] This subgroup is compatible with the poor diagnostic sensitivity of clinical sensory examination, most notably in the chronic phase after nerve injury.[5,13]

Orofacial Pain Mechanisms

Regarding orofacial pain mechanisms, recent studies have indicated that plastic changes following orofacial inflammation and trigeminal nerve injury occur. These changes take place in trigeminal neurons, satellite glial cells in the trigeminal ganglion, secondary neurons, microglia, and astrocytes in the trigeminal spinal subnucleus. It requires therapeutic intervention, since myofascial pain syndrome, BMS, and trigeminal neuralgia play no part in the defensive mechanisms of the body.[14] Barry et al reported for the first time that in the plasma of BMS patients, IL-8 proinflammatory chemokine is enhanced, and there is a reduction of IL-10 anti-inflammatory chemokine, which correlates with pain levels and symptoms of depression in individuals with BMS and could even be a new biomarker.[15]

Identifying Neuropathic Pain Components in BMS Patients

According to the most recent literature, BMS is diagnosed as a neuropathy with no possible cause after ruling out all other possible causes mentioned above. In the case of a concrete cause, the BMS is considered secondary rather than primary and is therefore not a neuropathy. The findings of another case-control study by Mo et al support the hypothesis that primary BMS is a neuropathic pain condition with involvement of peripheral and/or central pain mechanisms.[16] The most common methods for assessing these features to achieve individual management are: *(1)* painDETECT and visual analog scale (VAS) questionnaires (López-Jornet et al found that almost one-third of BMS patients present neuropathic pain, which is strongly associated with the intensity of pain measured using the VAS, and that the use of simple routing diagnostic methods facilitate an individualized management of BMS[17]); and *(2)* neuropathic pain questionnaires (Heo et al identified a substantial proportion of neuropathic pain components in BMS using such a questionnaire[18]).

Central Nervous System in BMS (Nigrostriatal Dopaminergic System)

In the pathogenesis of BMS, central sensitization is characterized by a structural and functional neural plasticity that results in increased excitability and tonic activity of central nociceptive neurons.[7] These abnormalities are connected to painful syndromes, since dopaminergic neurons originate in the midbrain and control descending pain inhibition pathways.[19]

An impaired endogenous dopamine system has been found in many BMS patients. This observation has led to the understanding that downregulation of central dopaminergic pain-inhibitory pathways plays a role in BMS pathogenesis. This happens especially in patients with anxiety or depression. These conditions are both associated with dysregulation of the central mood-mediating dopaminergic pathways[7,20]; however, Sikora et al found that BMS patients were more frequently associated with an anxious and depressed state when compared to the control group, reporting that such symptoms began after the BMS symptoms first occurred.[21] The variation of the dopamine receptor D2 (DRD2), a gene 957C>T polymorphism in BMS patients, contributes to experimental pain perception influencing sleep disturbances, pain sensitivity, and the experience of pain in BMS patients.[22] In 2017, a multicenter study confirmed the comorbidity of sleep disturbances and mood disorders in patients with BMS, suggesting that both aspects are a common and aggravating factor in BMS.[20,23]

Diagnosis of BMS with a central pain pattern.

A faulty inhibitory pain system.

Past and present data show that BMS duration is positively associated with the likelihood of an exaggerated pain response.[24] Deficient inhibitory top-down pain modulation via the striatal dopamine loop may be a risk factor for the development of chronic neuropathic orofacial pain and may be associated with less efficient modulation of pain. This may be linked to BMS, as it was reported after applying a painful stimulus and assessing the pain scale.[25]

No relief after peripheral treatment.

Central neuropathy seems to be the dominant mechanism in causing pain in patients with BMS who experience anxiety or depression and who do not have immediate relief after local anesthetic regional nerve block or topical treatment with capsaicin or clonazepam.[7] As Sinding et al suggest, if the pain does not come from the periphery, it may be driven by the brain itself.[26]

Brain imaging and blood flow.

Only five of the articles (26.32%) included in this review found statistically significant differences related to brain imaging and blood flow between BMS patients and controls:

- Magnetic resonance imaging (MRI): In anatomical structure imaging, Wada et al showed an alteration of the connectivity of the medial system to the brainstem that may reflect the descending pain modulation function in BMS.[27] Similarly, Sinding et al found a reduction of gray matter concentration of the pain matrix in BMS patients, mostly in the pain regions, while patients with dysgeusia presented modifications in areas associated with emotions, motor anticipation, and somesthesia.[26]
- Functional MRI (fMRI): Patients with BMS showed a singular response to painful hot stimuli, showing less volumetric brain activation when assessed with imaging methods by means of fMRI (imaging of metabolic function). This event occurs especially in the bilateral thalamus, resembling functional brain imaging findings in other neuropathic pain conditions due to differentiation of the somatosensory pathways.[13]
- Transcranial ultrasonography: BMS patients show hypoechogenicity of the substantia nigra and midbrain nuclei, as well as hyperechogenicity of the brain nucleus. These patients also present an alteration of the brain parenchyma, midbrain raphe, and brain nucleus.[19] In fact, Shinozaki et al found that BMS patients show specific imaging brain responses due to impaired function of the central and peripheral nervous systems.[28] Also, neural responses in the postcentral gyrus are more strongly affected by angry facial expressions in BMS patients, which may reflect one possible mechanism underlying impaired somatosensory system function.[29]

- SPECT/CT: Depression in patients with BMS may be associated with lower regional cerebral blood flow in the left temporal and left parietal lobes.[26]

Treatment for central involvement in BMS

Neuropathic pain is a common and difficult health problem to manage since it is complicated to apply a single, standardized approach to treat such disease.[30] Central-type BMS appears to improve with the use of first-choice drugs for neuropathic pain. The most recommended drugs are tricyclic antidepressants (nortriptyline and amitriptyline), serotonin-noradrenaline reuptake inhibitors (duloxetine and milnacipran), and antiepileptic (gabapentin and pregabalin) and antipsychotic drugs (amisulpride).[2,31]

Other treatment options are currently being studied and seem to be promising. In a study of five patients with BMS, Ito et al showed no effective results with antidepressants, but pregabalin relieved pain considerably. In view of these results, the authors affirm that pregabalin could also become a treatment option for BMS patients who are not responsive or who are resistant to SNRIs.[32]

Also, activation of the endogenous opioid system seems to relieve pain in BMS patients. This can be achieved by applying repetitive transcranial magnetic stimulation, which initially releases dopamine in the striatum and thereby activates the endogenous opioid system.[13]

Furthermore, for successful management of BMS symptoms, the psychologic status of the patients should be evaluated and managed accordingly.[5] Some authors support the application of vasodilator drugs to improve regional cerebral blood flow.[12]

Peripheral Nervous System in BMS (Sensory C and/or Trigeminal Nerve Fibers)

Approximately 20% of patients with BMS showing the typical clinical symptoms and brainstem reflex recordings mediated via large myelinated Aß afferents have shown signs of damage in the trigeminal nerve or its brainstem circuits.[13]

Higher density of fungiform papillae

There is evidence reporting a higher density of fungiform papillae in BMS patients, which suggests that this could be a risk factor. The innervation of the anterior two-thirds of the tongue comes from chorda tympani nerve fibers of the lingual nerve. Coincidentally, this area is the most typically affected by BMS, has a large number of taste buds in the fungiform papillae, and has several neuronal dysfunctions linked to BMS pain.

Trigeminal small-fiber neuropathy

In the peripheral mechanisms associated with atrophy of small nerve fibers, neuroprotective steroids and glial cell line–derived neurotrophic factor family ligands may have fundamental roles.[1] The pathogenesis of BMS starts with a decrease in the number of small-diameter nerve fibers in the lingual mucosa (C-fiber reduction). Then, the remaining fibers show upregulation of the transient receptor potential vanilloid 1 (TRPV1) ion channel, TRP cation channel subfamily M (melastatin) member 8 (TRPM8), P2X3 receptors, and nerve growth factor (NGF). TRPV1 channels respond to heat and chemical irritants like capsaicin. TRPM8 are cold-activated channels that also respond to menthol. In the trigeminal nervous system, P2X3 ion channel receptors are expressed by a subpopulation of small-diameter primary nociceptors, and when activated by adenosine triphosphate (ATP), they can evoke a sensation of burning pain.[7,33,34]

Along with this, Shinoda et al found that there is an increase in peripheral artemin (Artn) signaling in the tongue mucosa of BMS patients. In their results, mRNA expression of Artn was significantly higher than in control subjects. With this knowledge, they created a mouse model of BMS by application of 2,4,6-trinitrobenzene sulfonic acid diluted with 50% ethanol to the dorsum of the tongue, inducing a persistent, week-long, noninflammatory tongue pain. With this, they found a significant increase in Artn expression, a marked tongue heat hyperalgesia, and an increase in the number of glial cell line–derived neurotrophic factor family receptor α3 (GFR α3)–positive and TRPV1-positive trigeminal ganglion neurons innervating the tongue.[35]

Although the cause of these neuropathic changes remains unknown, there have been hypotheses based on repeated epithelial nerve fiber trauma, and some studies have suggested a neuroactive steroid depletion.[5] An RCT by Treldal et al reported epithelial atrophy in BMS patients and a local anesthetic effect in 13 of the 21 BMS patients, which indicates a peripheral neuropathology involving lack of estrogen and upregulation of estrogen receptors, while no effect indicates a systemic inflammation–induced mechanism leading to increased levels of plasma cytokines.[3]

Diagnosis of BMS with a peripheral pain pattern

Immediate relief with certain treatments.

Peripheral pain can be indicated by immediate relief after local anesthetic regional nerve block or topical treatment with capsaicin or with clonazepam.[7]

Saliva changes.

BMS may also lead to the deterioration of salivary condition with a lower flow rate of saliva, antioxidant capacity, secreted amount of secretory immunoglobulin A (SIgA) per minute, and higher spinnability. The lower antioxidant capacity in the patient's serum suggests that it can be used as a diagnostic variable for BMS.[36] Lower salivary flow rates could only be at-

tributed to a greater impact of systemic disease and medication, since Acharya et al could not find any difference in gland function but observed a significant decrease in unstimulated salivary flow rate.[37] On the other hand, another study found that skin diseases and xerostomia, but not parafunctional habits, were strongly associated with BMS. Another reason that could explain the dry mouth sensation may be via an altered composition of salivary moisturizing properties. These are mainly based on mucins secreted by minor salivary glands.[38]

Quantitative sensory testing.

Denervation of chorda tympani nerve fibers that innervate fungiform buds leads to alternative trigeminal innervation, which results in dysgeusia and burning pain when eating hot foods.[1] This may occur because this nerve contains not only gustatory afferents, but also thermal and mechanosensitive sensory afferents.[39] By applying a standardized QST protocol, intraoral neurophysiologic changes[16,40] and the likelihood of an exaggerated pain response can be found.[24] There is a thermal hypoesthesia and cold/warmth hypoalgesia compatible with pure focal small-fiber loss and neuropathy.[5,22,40,41] A preferential involvement of the A∂ fibers compared to the C fiber system in the lingual nerve distribution, leading to a constant hypoesthesia to cooling, has been demonstrated. Also, the C fiber dysfunction (warm hypoesthesia), when present, is restricted to the trigeminal distribution.[41] Mo et al did not find any localized loss of mechanical function, but did find a localized loss of thermal function in BMS patients, indicating that the small-fiber neuropathy may only, or predominantly, involve the small C and A-δ nerve fibers in BMS patients.[16]

Dysgeusia and electrogustatometry.

The pathophysiologic process shows abnormalities in electrogustometry (EGM) involving small A∂ taste afferents.[13] Dysgeusia and phantom tastes are frequent symptoms found in BMS patients[1]; it has been reported that 45% of BMS patients suffer from these symptoms.[42] This may be led by the deterioration of the salivary condition.[36] In a case-control study by Braud et al, 22.2% of the BMS patients described taste complaints, such as persistent sour or salty taste and ageusia.[43] Imura et al reported a higher threshold only for sourness in BMS patients, while other tastes did not differ from healthy patients.[36] The most common phantom tastes reported in BMS patients are "bitter" and "metallic" tastes. This may result from disinhibition of the glossopharyngeal nerve after damage to the chorda tympani nerve.[1] Several studies that measured the EGM thresholds (EGMt) for taste perception have consistently demonstrated hypofunction of the chorda tympani.[39] Damage in the chorda tympani nerve could be the cause of the gustatory dysfunction in fungiform papillae found in these patients, although an elevated threshold within unilateral foliate papillae fields points toward glossopharyngeal nerve damage. Nevertheless, dual innervation of foliate papillae by glossopharyngeal and chorda tympani afferents may occur.[43] However, Sinding et al suggest that BMS and dysgeusia are driven by different brain mechanisms, which does not support the theory of a similar etiology.[26]

Corneal confocal microscopy.

This technique is a rapid, noninvasive imaging method that is very useful for monitoring disease progression, response to treatment, and differentiating disease subtypes, if possible. It has identified corneal small-fiber damage in BMS patients and a significant increase in corneal Langerhans cell density, which is suggestive of immune alterations in BMS.[44]

Treatment for peripheral involvement in BMS

Drug treatment in BMS with peripheral origin can consist of topical clonazepam,[2] which is a benzodiazepine applied topically to mucosa and is thought to decrease excitability of peripheral sensory nerve fibers. As it is an agonist of gamma aminobutyric acid (GABA) receptor, it activates pain-inhibitory pathways in the spinal cord and in peripheral nociceptors. Moreover, when given systemically, it has central sedative, anxiolytic, and analgesic effects. The use of both topical and systemic clonazepam has been reported to reduce the intensity of BMS pain.[7] Topical capsaicin is limited by its side effects,[6] but has the capacity to bind to the TRPV1 ion channels of small-diameter peripheral sensory nerve fibers, mediating desensitization of afferent nociceptors. This process leads to reversible degeneration of peripheral sensory nerve endings and therefore reduces the burning pain sensation in BMS.[7]

Overlap of Central and Peripheral Pain Patterns

As a matter of fact, central involvement has also been reported in the pain-taste alteration. Through trigeminal afferents, there are two pathways that conduct nociceptive signals to the brainstem. First, trigeminal afferents extend along the trigeminal spinal tract to reach the trigeminal spinal nuclei. Second, a certain portion of trigeminal afferents reach the nucleus tractus solitarii directly.[1]

In a situation of persistent peripheral neuropathy, there is a release of excitatory biologic mediators, which can activate postsynaptic N-methyl-D-aspartate (NMDA) receptors by the central afferent nociceptor terminals in the dorsal horn of the spinal cord, thereby causing central sensitization with increased excitability. There may also be a reduction in the functional activity of the GABA-mediated pain-inhibitory interneuron circuits in the dorsal horn of the spinal cord,

which under physiologic circumstances inhibit glutamate/NMDA-mediated central sensitization, possibly contributing to the neuropathic pain of BMS.[7]

Limitations

As limitations, it must be mentioned that, given the enormous heterogeneity of the studies found, a meta-analysis could not be performed. This systematic review took the literature published in the last 5 years that evaluated BMS as a neuropathic origin syndrome in consideration. All of the studies found present results that demonstrate several aspects connecting this disease to a neuropathic origin.

Conclusions

These findings suggest that, in the pathogenesis of BMS, both peripheral and central neuropathies appear to play a pivotal role. Nevertheless, the balance between them varies from case to case and tends to overlap. It does not seem to be a result of direct damage to the somatosensory nervous system, but a dysfunction in it and in the brain network. BMS remains a clinical therapeutic dilemma that needs further research about its etiology and pathophysiology. Maybe in the future, this syndrome could be considered as a neuropathic pain condition.

Highlights

- Investigators previously thought that BMS was purely psychogenic in origin; nowadays, new studies are proving that it is a complex condition involving the peripheral and central nervous systems, psychometrics, and perhaps a genetic involvement.
- The mechanism of neuropathic pain in BMS may not be due to direct damage to the somatosensory nervous system, but to dysfunction in the somatosensory nervous system and the brain network. Laboratory investigations and brain imaging have indicated changes in the central and peripheral nervous systems.
- There is further evidence for small-fiber damage in BMS, with the potential utility for monitoring disease progression and/or response and differentiating disease subtypes.
- Treatment can be with local or systemic medications, focused on the relief of symptoms and improving patients' quality of life.

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