REVIEW

DOI: http://dx.doi.org/10.15403/jgld-4245

Burning Mouth Syndrome Etiology: A Narrative Review

Michele Russo[1], Pellegrino Crafa[1], Simone Guglielmetti[2], Lorella Franzoni[1], Walter Fiore[3], Francesco Di Mario[1]

1) Department of Medicine and Surgery, University of Parma, Parma;
2) Department of Food, Environmental and Nutritional Sciences (DeFENS), Università degli Studi di Milano, Milan;
3) Sofar S.p.A., Trezzano Rosa, Italy

Address for correspondence:
Michele Russo,
Department of Medicine and Surgery, University of Parma, Parma, Italy
michele.russo@unipr.it

Received: 02.02.2022
Accepted: 21.04.2022

ABSTRACT

Burning mouth syndrome (BMS) is defined as "idiopathic orofacial pain with intraoral burning or dysesthesia recurring daily for more than 2 hours per day and more than 3 months, without any identifiable causative lesions, with or without somatosensory changes" in International Classification of Orofacial Pain, 2020. Worldwide prevalence of BMS was estimated to be 1.73% in population-based studies, while female and elderly are at higher risk of BMS. The aim of this narrative review is to clarify the main etiopathogenetic factors of BMS investigated so far in the scientific literature. There is growing evidence of an important role of peripheral neuropathology in BMS, supported by immunohistochemical studies which have demonstrated a significant loss of epithelial and subepithelial nerve fibers. Other possible etiopathogenetic factors emerging from literature are laryngopharyngeal reflux and hormonal and salivary changes related to aging and menopause. Finally, the role of the oral microbiota in BMS has not yet been thoroughly investigated. Further studies are necessary to investigate the probably multifactorial etiopathogenesis of primary BMS, a pathology which has a serious impact on the quality of life of our patients, a disease we find ourselves treating without the adequate therapy and the necessary knowledge.

Key words: burning mouth syndrome – etiology – pathogenesis – GERD – proton pump inhibitors – PPIs – microbiota – pepsin.

Abbreviations: BMS: burning mouth syndrome; BN: bulimia nervosa; BR: blink reflex; CB2: cannabinoid receptor type 2; GERD: gastroesophageal reflux disease; LPR: laryngopharyngeal reflux; NGF: nerve growth factor; QST: quantitative sensory tests; PPIs: proton pump inhibitor; TRPV1: transient receptor potential cation channel subfamily V member 1 ion channels.

INTRODUCTION

Burning mouth syndrome (BMS) is defined in the International Classification of Orofacial Pain, 2020 as "idiopathic orofacial pain with intraoral burning or dysesthesia recurring daily for more than 2 hours per day and more than 3 months, without any identifiable causative lesions, with or without somatosensory changes" [1]. Painful sensations of the oral mucosa that can be explained by local or systemic pathologies are defined as secondary BMS, as opposed to primary BMS, in which no cause or visible pathology can be linked to the typical symptoms [2]. Factors that are able to cause secondary BMS include deficiencies in vitamin B12, iron, zinc, or folic acid, the use of certain medications, the presence of systemic diseases such as diabetes and Sjögren's syndrome; the presence of erosive lesions, *Candida* infection and denture-induced damage [2]; for this reason, these factors must be excluded before making a diagnosis of primary BMS.

Regarding the prevalence of primary BMS, published data are sparse and highly variable. In an American population-based study, authors found the prevalence to be 0.11% in the general population. They also found that prevalence in women was significantly higher than men (0.17%), while the highest prevalence was in women aged between 70 and 79 years (0.53%) [3]. In Sweden, however, the reported prevalence is higher (3.7%) increasing to 8.7% in the elderly [4]. Similarly, in Taiwan prevalence proved to ranging from 2.24 (per 104) to 3.11 (per 104), while female and elderly seem to have an increased risk of developing BMS [5]. Finally, worldwide

prevalence of BMS was estimated to be 1.73% in population-based studies [6]. Subgroup analysis by continent showed that the prevalence in Asia (1.05%) is lower than in Europe (5.58%) and North America (1.10%). Again, the prevalence of female (1.15%) seems to be higher than male (0.38%) in the general population. Additionally, when comparing age categories, the prevalence seems to be higher for people over 50 (3.31%) than those under 50 (1.92%) [6].

Regarding symptomatology, the most common term patients use to describe BMS pain is "burning" [7], but allodynia, pricking pain, tingling, electrical discharges, numbness, and itching, have been described [8]. The most frequently affected area is the tongue, in particular symptoms are more constantly localized in the anterior two thirds of the tongue. Moreover, about half of the primary BMS patients reported the tongue to be the only affected area, followed by the hard palate and gums [7]. In typical cases, symptoms are bilateral and symmetrical [9], but unilateral localization is still possible while the symptomatology seems to have a circadian rhythm with burn/pain that tends to worsen during the day [10]. Most patients reported a long-lasting intermittent daily pain, but constant diurnal pain may also occur [8, 11]. Pain is generally spontaneous; however, in certain patients some foods, particularly spicy or acidic ones, may trigger it, while in other patients, local cold may alleviate pain [7]. Other reported symptoms are represented by oral paresthesia, subjective xerostomia, and altered taste (dysgeusia) [12]. In particular, dysgeusia and quantitative alterations of salivation are commonly reported in BMS, in fact, dysgeusia being present in about half of those patients [13]. Furthermore, the nature of those alterations in taste varies widely among primary BMS patients, it may involve all taste modalities, but metallic, bitter, or disgusting tastes are more commonly described [14].

Primary BMS should be considered a chronic disease poorly responsive to current therapies. In fact, a complete spontaneous remission was observed in less than 5% of the patients within 5 years after the onset of BMS, and less than a half of BMS patients improved their symptomatology significantly with therapy [15, 16]. The most common treatments reported include clonazepam, gabapentin and capsaicin [17]. In particular, the use of antidepressants has a major role in the treatment of primary BMS as demonstrated in the study from Rodríguez-de Rivera-Campillo et al. [16] where the concomitant use of clonazepam and psychotherapy significantly improved symptoms in 60% of patients.

Primary BMS can have a significant impact on the quality of life [18]. Indeed, 70% of BMS patients report mood changes and more than a half have changed their eating habits subsequently the onset of BMS. What is worse, is that nearly a quarter of BMS patients experience depression and a reduced desire to socialize [19], with a case of BMS leading to suicide also reported [20]. The diagnosis of primary BMS often occurs long after the onset of symptoms; at the base there could be a lack of knowledge of this disease by doctors and dentists. As a matter of fact, patients are visited, on average, by 3 doctors or dentists in approximately 3 years before receiving an adequate diagnosis [21]. Although different theories have been developed to describe the etiology of the disease, the true cause of BMS is still unknown, while a combination of numerous alterations has been proposed, suggesting a multifactorial etiology [22].

The purpose of this narrative review is to clarify the main etiopathogenetic factors of primary BMS investigated so far in the scientific literature in order to have a better framework of the disease and to understand the possible most promising fields for the development of future studies.

We searched relevant papers on Scopus, Pubmed and Cochrane databases. The research string comprised various combinations of "Burning mouth syndrome", "stomatodynia", "stomatopyrosis", "glossopyrosis", "glossodynia", "oral dysesthesia", "glossalgia", "etiology", "aetiology", "pathogenesis", "aetiopathogenesis" and "pathophysiology". Two authors searched databases independently. A third reviewer mediated any disagreements in the results of the two screeners. To be included, papers had to be focused on the etiology of primary burning mouth syndrome. All English-language papers from 1985 to December 2021, were eligible. Peer-reviewed, published literature, including narrative review papers, were eligible for inclusion. Studies involving animals, editorials, letters to the editor, and abstracts were excluded. Reference lists of included papers were hand-searched and included if the inclusion criteria were met. A total of 1,154 studies were analyzed, of which 25 were included after the application of the inclusion and exclusion criteria. The included papers were then organized and presented within the narrative review in specific sections based on their main etiological topic. Search strategy and a summary of the studies included in the review is available in the Supplementary file.

PERIPHERAL NEUROPATHOLOGY

Neurological Physiology of the Oral Cavity

To better understand the possible neurological role in the onset of typical BMS symptoms such as burning and dysgeusia, it is important to start from the physiology of the somatosensory innervation of the oral cavity. In particular, the chorda tympani nerve, a branch of the facial nerve, is responsible for taste sensation of the anterior two-thirds of the tongue. While taste sensation from the posterior third of the tongue is provided by the glossopharyngeal nerve. Taste receptors sited in the larynx are supplied by the superior laryngeal nerve, branch of the vagus nerve, and those sited on the soft palate are supplied by the greater superficial petrosal nerve [23]. The lingual nerve, a branch of the mandibular division of the trigeminal nerve, is responsible for mechanical and thermal sensations [13].

Neuropathology Role in Burning Mouth Syndrome

It was supposed that a damage in fibers responsible for taste sensation may drive a deregulation of central inhibitory system of the pain [24]. Moreover, there is growing evidence of an important role of peripheral neuropathology in BMS, supported by immunohistochemical studies which have demonstrated a significant loss of epithelial and subepithelial nerve fibers [25, 26] together with an increased expression in the surviving nerve fibers of BMS patients of nerve growth factor (NGF) [27], cannabinoid receptor type 2 (CB2) and transient receptor potential cation channel subfamily V member

1 (TRPV1) ion channels which have been associated with hypersensitivity and neuropathic pain [28, 29] The first evidence for trigeminal deficit in BMS dates back to 1997 and came from brainstem reflex recordings made in primary BMS patients [30]. Furthermore, about half of those patients show significant pain relief after lidocaine block of the lingual nerve, indicating a possible peripheral trigeminal neuropathic origin of the pain [31]. Svensson et al. [32] also found that BMS patients had pain and detection thresholds to argon laser stimuli significantly higher compared to healthy controls, while pain threshold was lower suggesting a perceptual deficit in those patients [32]. In order to gain further insight into the neural mechanisms of BMS pain, Forssell et al. [33] used quantitative sensory tests (QST) in addition to the blink reflex (BR) recordings, finding alterations in roughly 90% of primary BMS patients. Among those there was considerable heterogeneity, some patients had large fiber neuropathy, others small fiber neuropathy, while about 20% of the patients showed dysregulation in the trigeminal system, sometimes combined with thermal allodynia [33]. In patients with signs of trigeminal neuropathies, an analysis made by multimodal evoked potential recordings demonstrated specific preservation of C fibers responses and a loss in Aδ fibers responses [34]. This could be the mechanism underlying the burning pain of some patients with BMS, in which the stimulus conducted by the preserved C fibers to the nociceptors would no longer be inhibited by the afferents of the Aδ fibers [35]. Moreover, there is more evidence that links BMS with dysfunction in the central and peripheral nervous systems [36]. For example, Kishore at al. [37] analyzed serum levels of neuron-specific enolase, as a biomarker of peripheral neuronal injury, in patients with primary and secondary BMS, and found that primary BMS patients had significantly higher levels of neuron-specific enolase in comparison to secondary BMS patients and healthy controls. While the frequent report of dysgeusia and burning pain located to the tongue in BMS patients has also prompted the hypothesis that the hyperactivity of the somatosensory fibers of the trigeminal nerve could be a consequence of loss in central inhibition due to damage in taste fibers present in the chorda tympani or in the glossopharyngeal nerves [38]. In particular, some independent studies have reported chorda tympani hypofunction in BMS patients by means of electro-gustatory testing, which seemed to be also an useful tool capable of differentiating primary to secondary BMS [31, 39, 40].

LARINGOPHARYNGEAL REFLUX

Laryngopharyngeal reflux (LPR) is a condition in which gastroduodenal content travels up to the throat inducing inflammation and morphological changes in the upper aero-digestive tract [41]. To date, we know that the mediator of damage to the mucous membranes of the throat in LPR is represented by pepsin [42].

The first study that correlated LPR with the development of oral disorders dates back to 1971 [43]; from that date only a few studies have so far investigated the possible correlation between reflux and oral disorders [44-51]. Furthermore, between the aforementioned studies, authors reported discordant results, probably due to the application of non-uniform methodologies [51]. Indeed, in most of the papers the researchers used the diagnostic criteria of gastroesophageal reflux disease (GERD) and not those of the LPR [45, 46]. For example, Aframian et al [49] compared, using pH-metry, the oral pH of patients with GERD, bulimia nervosa (BN) and BMS, with that of a control group. The result showed a significantly lower pH in patients with BN and GERD, while the pH level of patients with BMS showed no significant differences with healthy individuals, although pH tended to be higher in the former [49]. In contrast, in a preliminary study, where the authors looked for a correlation between oral burning and episodes of LPR, it was found that half of the recruited patients had episodes of LPR, but no burning episodes were detected in correspondence of a drop in oropharyngeal pH [50]. Finally, in a recent paper authors evaluated pH levels and the presence of LPR episodes and GERD in patients with both primary BMS and typical symptoms of LPR, using pH-impedancemetry, gastrointestinal endoscopy and salivary pepsin measurements. Almost all patients showed at least one episode of LPR; similarly the pepsin test was positive in roughly 90% of cases. About one third of the analyzed patients suffered from LPR and GERD simultaneously [51]. As a consequence, saliva pepsin levels detection could be a useful instrument to investigate the potential involvement of LPR in primary BMS [52]. Another cause of discrepancy between older and current studies may lie in the focus of the former on low pH levels, but it has been well demonstrated that LPR as well as GERD are not exclusively acid in nature [53]. Lechien et al. [51] found that more than a half of primary BMS patients had non-acid or weakly acid LPR. In fact, since the nature of LPR is not always or exclusively acidic, proton pump inhibitors (PPIs) alone are not recommended as monotherapy in BMS patients presenting reflux [50]; a combination of PPIs, diet change and barrier drugs as alginate or magaldrate, showed more satisfactory performance, although still far from optimal, with an improvement in symptoms in 62.5% of cases, although this response could be due to a selection bias (symptoms reported by patients could exclude a primary BMS in most of them) [51]. For this reason, further studies with more stringent inclusion and exclusion criteria are needed in order to evaluate the role of LPR in primary BMS. Furthermore, it has been demonstrated that pepsin is able to produce intracellular damage on the oropharyngeal mucosa through endocytosis and consequent damage to the Golgi apparatus and mitochondria; mechanism on which PPIs have no effect [54]. Moreover, gastroduodenal enzymes not only may irritate the upper aerodigestive tract mucosa, but they may have an additional role on modifying the local microbiota [55]. Beyond possible speculations it is important to clarify that none of these factors have demonstrated that they are a causal factor of BMS.

OTHER POSSIBLE ETIOPATHOLOGICAL FACTORS

Gender, Age, and Hormones

In addition to peripheral nerve damage, dopaminergic dysregulation has also been reported in patients with primary BMS [56]. Furthermore, as described above, perimenopausal women are more frequently affected by BMS, a finding that

could be attributed to age-related reduction in estrogen and progesterone levels which can lead to dryness of the oral mucosa [57]. In order to better explain this concept, Woda et al. [58] suggested that the menopausal downregulation of neuroprotective hormones can lead to an irreversible degeneration of the small nerve fibers present in the oral mucosa and of those brain areas responsible for receiving oral somatic stimuli, ultimately this can result in typical BMS symptoms [58]. Finally, when the salivary hormone content of these patients was analyzed, elevated levels of estrogen and cortisol were found [59].

Psychiatric Diseases

Psychiatric disorders have long been regarded as a leading cause of BMS, but nowadays these disorders are considered a consequence of BMS itself or simply a concomitant factor [60]. In fact, although BMS patients often suffer from anxious-depressive disorders, these psychiatric manifestations arise after the onset of BMS [61]. Interestingly, there appears to be a correlation between the onset of psychological disorders in patients with BMS and normal oral nerve fibers density, although the reasons remain unknown [26].

Saliva Composition

Regarding saliva composition, in a recent study authors compared the proteomic profile of the saliva of BMS patients with that of healthy controls, using electrophoresis, demonstrating the higher presence, in BMS patients, of proteins associated with important signaling pathways such as those that regulate inflammation, stress and the immune system [62]. Using the same methodology other authors suggested that neurotrophin signaling pathway could be involved in the pathophysiology of BMS by increasing neural apoptosis within the oral mucosa [63]. In another study, saliva samples of post-menopausal women with BMS have been analyzed using infrared spectroscopy. Authors observed a decrease in the amount of salivary proteins, such as salivary α-amylase, which could change digestion capacity, and mucin, which has an antimicrobial and lubricant action. The authors also found an increased amount of nucleic acids in saliva, indicating a possible increased bacterial proliferation in the oral cavity [64].

Microbiota

Even if a thorough analysis of the oral microbiota has not been performed yet, it appears to be a correlation between the presence of *Helicobacter pylori* (*H. pylori*) in the oral cavity and halitosis and burning symptoms [65]. The presence of *H. pylori* could be explained by changes in the oral environment that would make the mouth a favorable habitat for the proliferation of this bacterium [66]. Gall-Troselj et al. [67] detected by PCR *H. pylori* DNA in tongue mucosa of about a fifth of the 268 BMS patients recruited; however, the authors were unable to find a causative link between the presence of the bacterium and the onset of the disease. In a subsequent study, *H. pylori* antibodies were found in the serum of 19 out of 150 (12.7%) patients with burning symptoms and healthy oral mucosa [67]. Notably, Bralio et al. [67] reported that burning symptoms resolved in a high percentage of these patients (79%) after *H. pylori* eradication therapy [67].

Concerning other microbial taxa, in an older article, authors found that the oral prevalence of Enterobacteriaceae and *Candida* species was higher in the BMS group compared with the controls; they also found that most frequently *Candida albicans*, *Enterobacter* spp. and *Klebsiella* spp. were the microorganisms involved [68]. In the study by Brailo et al. [67] mentioned above, colonies ascribable to *Candida albicans* were isolated from swabs of the oral mucosa of 38.6% of patients reporting burning symptoms and reported as "clinically invisible candidiasis". Accordingly, the authors concluded that in patients with symptoms of burning in the oral cavity and clinically healthy oral mucosa, candidal swab should be performed [67]. However, more recent studies were not able to find a significant correlation between the presence of *Candida* spp. and the onset of primary BMS [69, 70]. Indeed, Farah et al. [71] did not observe a statistically significant difference in the presence of Candida species in patients with BMS when compared with other oral diseases [71].

CONCLUSIONS

The possibility that small fiber sensory neuropathy is responsible for the onset of symptoms in BMS patients showed some solid evidence. However, the mechanisms underlying this peripheral neuropathy have yet to be elucidated. Another important pathogenetic mechanism seems to be represented by the presence of LPR, which not only may irritate the upper aerodigestive tract mucosa, but it may have an additional role on modifying the local microbiota. As regard to the bacterial flora, few studies have evaluated the oral microbiota in BMS and no study has thoroughly investigated it. However, studies currently available in literature identified a greater presence of *H. pylori*, *Candida* spp. and members of the Enterobacteriaceae family in BMS patients, although with conflicting results and without finding a significant correlation between the disease and the pathogens. Despite the lack of evidence, we think oral microbiota could represent a very promising field for further research. Finally, we must take into account that the prevalence of BMS is higher in post-menopausal women, and consequently, hormonal imbalances and aging could play a role in creating ideal conditions for the development of BMS. In conclusion, we believe that idiopathic BMS is defined as such only due to our inadequate knowledge of the underlying pathogenetic mechanisms. Further studies are necessary to investigate the multifactorial etiopathogenesis of primary BMS.

Conflicts of interest: None to declare.

Authors' contributions: M.R. and F.D.M. designed the research study. M.R., P.C. and L.F. collected data. M.R. and F.D.M. interpreted data and wrote the manuscript. W.F. interpreted the results and reviewed the manuscript. S.G. contributed with suggestions, reviewed and corrected the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/10.15403/jgld-4245.

REFERENCES

1. International Classification of Orofacial Pain, 1st edition (ICOP). Cephalalgia 2020;40:129-221. doi:10.1177/0333102419893823
2. Jääskeläinen SK, Woda A. Burning mouth syndrome. Cephalalgia 2017;37:627-647. doi:10.1177/0333102417694883
3. Kohorst JJ, Bruce AJ, Torgerson RR, Schenck LA, Davis MDP. The prevalence of burning mouth syndrome: a population-based study. Br J Dermatol 2015;172:1654-1656. doi:10.1111/bjd.13613
4. Bergdahl M, Bergdahl J. Burning mouth syndrome: prevalence and associated factors. J Oral Pathol Med 1999;28:350-354. doi:10.1111/j.1600-0714.1999.tb02052.x
5. Su NY, Wang YH, Chang YC. A nationwide register-based study of the prevalence of burning mouth syndrome in Taiwan from 2004 to 2013. J Dent Sci 2021;16:1074-1079. doi:10.1016/j.jds.2021.06.020
6. Wu S, Zhang W, Yan J, Noma N, Young A, Yan Z. Worldwide prevalence estimates of burning mouth syndrome: A systematic review and meta-analysis. Oral Dis 2021 Apr 5. doi:10.1111/odi.13868
7. Zilli C, Brooke RI, Lau CL, Merskey H. Screening for psychiatric illness in patients with oral dysesthesia by means of the General Health Questionnaire--twenty-eight item version (GHQ-28) and the Irritability, Depression and Anxiety Scale (IDA). Oral Surg Oral Med Oral Pathol 1989;67:384-389. doi:10.1016/0030-4220(89)90378-2
8. Braud A, Touré B, Agbo-Godeau S, Descroix V, Boucher Y. Characteristics of pain assessed with visual analog scale and questionnaire in burning mouth syndrome patients: a pilot study. J Orofac Pain 2013;27:235-242. doi:10.11607/jop.1038
9. van der Ploeg HM, van der Wal N, Eijkman MA, van der Waal I. Psychological aspects of patients with burning mouth syndrome. Oral Surg Oral Med Oral Pathol 1987;63:664-668. doi:10.1016/0030-4220(87)90366-5
10. Lopez-Jornet P, Molino Pagan D, Andujar Mateos P, Rodriguez Agudo C, Pons-Fuster A. Circadian rhythms variation of pain in burning mouth syndrome. Geriatr Gerontol Int 2015;15:490-495. doi:10.1111/ggi.12303
11. Forssell H, Teerijoki-Oksa T, Kotiranta U, et al. Pain and pain behavior in burning mouth syndrome: a pain diary study. J Orofac Pain 2012;26:117-125.
12. Zakrzewska J, Buchanan JA. Burning mouth syndrome. BMJ Clin Evid 2016;2016:1301.
13. Bartoshuk LM, Snyder DJ, Grushka M, Berger AM, Duffy VB, Kveton JF. Taste damage: previously unsuspected consequences. Chem Senses 2005;30 Suppl 1:i218-i219. doi:10.1093/chemse/bjh192
14. Scala A, Checchi L, Montevecchi M, Marini I, Giamberardino MA. Update on burning mouth syndrome: overview and patient management. Crit Rev Oral Biol Med 2003;14:275-291. doi:10.1177/154411130301400405
15. Sardella A, Lodi G, Demarosi F, Bez C, Cassano S, Carrassi A. Burning mouth syndrome: a retrospective study investigating spontaneous remission and response to treatments. Oral Dis 2006;12:152-155. doi:10.1111/j.1601-0825.2005.01174.x
16. Rodríguez-de Rivera-Campillo E, López-López J. Evaluation of the response to treatment and clinical evolution in patients with burning mouth syndrome. Med Oral Patol Oral Cir Bucal 2013;18:e403-e410. doi:10.4317/medoral.18142
17. De La Garza Aguiñaga M, Cruz Fierro N, Quintanilla Rodriguez LE, et al. Burning mouth syndrome: An overview and current update. Int J Appl Dent Sci 2021;7:252-256. doi:10.22271/oral.2021.v7.i4d.1380
18. López-Jornet P, Camacho-Alonso F, Lucero-Berdugo M. Quality of life in patients with burning mouth syndrome. J Oral Pathol Med 2008;37:389-394. doi:10.1111/j.1600-0714.2008.00672.x
19. Grushka M. Clinical features of burning mouth syndrome. Oral Surg Oral Med Oral Pathol 1987;63:30-36. doi:10.1016/0030-4220(87)90336-7
20. Fukushima Y, Kitamura T, Ikami E, et al. A case of burning mouth syndrome leading to suicide 10 days after self-cutting of tongue. Psychogeriatrics 2020;20:126-128. doi:10.1111/psyg.12449
21. Mignogna MD, Fedele S, Lo Russo L, Leuci S, Lo Muzio L. The diagnosis of burning mouth syndrome represents a challenge for clinicians. J Orofac Pain 2005;19:168-173.
22. Kamala KA, Sankethguddad S, Sujith SG, Tantradi P. Burning Mouth Syndrome. Indian J Palliat Care 2016;22:74-79. doi:10.4103/0973-1075.173942
23. Standring S, Gray H. Gray's anatomy: the anatomical basis of clinical practice. 40th ed. Edinburgh: Churchill Livingstone; 2008:499–525.
24. Grushka M, Epstein JB, Gorsky M. Burning mouth syndrome and other oral sensory disorders: a unifying hypothesis. Pain Res Manag 2003;8:133-135. doi:10.1155/2003/654735
25. Lauria G, Majorana A, Borgna M, et al. Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. Pain 2005;115:332-337. doi:10.1016/j.pain.2005.03.028
26. Penza P, Majorana A, Lombardi R, et al. "Burning tongue" and "burning tip": the diagnostic challenge of the burning mouth syndrome. Clin J Pain 2010;26:528-532. doi:10.1097/AJP.0b013e3181e15b83
27. Pezet S, McMahon SB. Neurotrophins: mediators and modulators of pain. Annu Rev Neurosci 2006;29:507-538. doi:10.1146/annurev.neuro.29.051605.112929
28. Jääskeläinen SK. Pathophysiology of primary burning mouth syndrome. Clin Neurophysiol 2012;123:71-77. doi:10.1016/j.clinph.2011.07.054
29. Forssell H, Jääskeläinen S, List T, Svensson P, Baad-Hansen L. An update on pathophysiological mechanisms related to idiopathic oro-facial pain conditions with implications for management. J Oral Rehabil 2015;42:300-322. doi:10.1111/joor.12256
30. Jääskeläinen SK, Forssell H, Tenovuo O. Abnormalities of the blink reflex in burning mouth syndrome. Pain 1997;73:455-460. doi:10.1016/S0304-3959(97)00140-1
31. Grémeau-Richard C, Dubray C, Aublet-Cuvelier B, Ughetto S, Woda A. Effect of lingual nerve block on burning mouth syndrome (stomatodynia): a randomized crossover trial. Pain 2010;149:27-32. doi:10.1016/j.pain.2009.11.016
32. Svensson P, Bjerring P, Arendt-Nielsen L, Kaaber S. Sensory and pain thresholds to orofacial argon laser stimulation in patients with chronic burning mouth syndrome. Clin J Pain 1993;9:207-215. doi:10.1097/00002508-199309000-00009
33. Forssell H, Jääskeläinen S, Tenovuo O, Hinkka S. Sensory dysfunction in burning mouth syndrome. Pain 2002;99:41-47. doi:10.1016/s0304-3959(02)00052-0
34. Galeotti F, Truini A, Cruccu G. Neurophysiological assessment of craniofacial pain. J Headache Pain 2006;7:61-69. doi:10.1007/s10194-006-0287-1
35. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 2002;3:655-666. doi:10.1038/nrn894
36. Valença MM, de Oliveira DA, Martins HA. Alice in Wonderland Syndrome, Burning Mouth Syndrome, Cold Stimulus Headache, and HaNDL: Narrative Review. Headache 2015;55:1233-1248. doi:10.1111/head.12688
37. Kishore J, Shaikh F, Zubairi AM, al. Evaluation of serum neuron specific enolase levels among patients with primary and secondary burning mouth syndrome. Cephalalgia 2022;42:119-127. doi:10.1177/03331024211046613

38. Yanagisawa K, Bartoshuk LM, Catalanotto FA, Karrer TA, Kveton JF. Anesthesia of the chorda tympani nerve and taste phantoms. Physiol Behav 1998;63:329-335. doi:10.1016/s0031-9384(97)00423-x
39. Just T, Steiner S, Pau HW. Oral pain perception and taste in burning mouth syndrome. J Oral Pathol Med 2010;39:22-27. doi:10.1111/j.1600-0714.2009.00824.x
40. Eliav E, Kamran B, Schaham R, Czerninski R, Gracely RH, Benoliel R. Evidence of chorda tympani dysfunction in patients with burning mouth syndrome. J Am Dent Assoc 2007;138:628-633. doi:10.14219/jada.archive.2007.0234
41. Lechien JR, Akst LM, Hamdan AL, et al. Evaluation and Management of Laryngopharyngeal Reflux Disease: State of the Art Review. Otolaryngol Head Neck Surg 2019;160:762-782. doi:10.1177/0194599819827488
42. Klimara MJ, Randall DR, Allen J, Figueredo E, Johnston N. Proximal reflux: biochemical mediators, markers, therapeutic targets, and clinical correlations. Ann N Y Acad Sci 2020;1481:127-138. doi:10.1111/nyas.14366
43. Howden GF. Erosion as the presenting symptom in hiatus hernia. A case report. Br Dent J 1971;131:455-456. doi:10.1038/sj.bdj.4802772
44. Hakeem A, Fitzpatrick SG, Bhattacharyya I, Islam MN, Cohen DM. Clinical characterization and treatment outcome of patients with burning mouth syndrome. Gen Dent 2018;66:41-47.
45. Cheung D, Trudgill N. Managing a patient with burning mouth syndrome. Frontline Gastroenterol 2015;6:218-222. doi:10.1136/flgastro-2014-100431
46. Preetha A, Sujatha D, Patil BA, Hegde S. Oral manifestations in gastroesophageal reflux disease. Gen Dent 2015;63:e27-e31.
47. Campisi G, Lo Russo L, Di Liberto C, et al. Saliva variations in gastro-oesophageal reflux disease. J Dent 2008;36:268-271. doi:10.1016/j.jdent.2008.01.003
48. Di Fede O, Di Liberto C, Occhipinti G, et al. Oral manifestations in patients with gastro-oesophageal reflux disease: a single-center case-control study. J Oral Pathol Med 2008;37:336-340. doi:10.1111/j.1600-0714.2008.00646.x
49. Aframian DJ, Ofir M, Benoliel R. Comparison of oral mucosal pH values in bulimia nervosa, GERD, BMS patients and healthy population. Oral Dis 2010;16:807-811. doi:10.1111/j.1601-0825.2010.01692.x
50. Becker S, Schmidt C, Berghaus A, Tschiesner U, Olzowy B, Reichel O. Does laryngopharyngeal reflux cause intraoral burning sensations? A preliminary study. Eur Arch Otorhinolaryngol 2011;268:1375-1381. doi:10.1007/s00405-011-1543-9
51. Lechien JR, Hans S, De Marrez LG, et al. Prevalence and Features of Laryngopharyngeal Reflux in Patients with Primary Burning Mouth Syndrome. Laryngoscope 2021;131:E2627-E2633. doi:10.1002/lary.29604
52. Lechien JR, Hans S, Bobin F, Calvo-Henriquez C, Saussez S, Karkos PD. Atypical Clinical Presentation of Laryngopharyngeal Reflux: A 5-Year Case Series. J Clin Med 2021;10:2439. doi:10.3390/jcm10112439
53. Ang D, Ang TL, Teo EK, et al. Is impedance pH monitoring superior to the conventional 24-h pH meter in the evaluation of patients with laryngorespiratory symptoms suspected to be due to gastroesophageal reflux disease? J Dig Dis 2011;12:341-348. doi:10.1111/j.1751-2980.2011.00519.x
54. Johnston N, Wells CW, Samuels TL, Blumin JH. Pepsin in nonacidic refluxate can damage hypopharyngeal epithelial cells. Ann Otol Rhinol Laryngol 2009;118:677-685. doi:10.1177/000348940911800913
55. Lechien JR, De Vos N, Everard A, Saussez S. Laryngopharyngeal reflux: The microbiota theory. Med Hypotheses 2021;146:110460. doi:10.1016/j.mehy.2020.110460
56. Jääskeläinen SK, Rinne JO, Forssell H, et al. Role of the dopaminergic system in chronic pain - a fluorodopa-PET study. Pain 2001;90:257-260. doi:10.1016/S0304-3959(00)00409-7
57. Liu YF, Kim Y, Yoo T, Han P, Inman JC. Burning mouth syndrome: a systematic review of treatments. Oral Dis 2018;24:325-334. doi:10.1111/odi.12660
58. Woda A, Dao T, Gremeau-Richard C. Steroid dysregulation and stomatodynia (burning mouth syndrome). J Orofac Pain 2009;23:202-210.
59. Kim HI, Kim YY, Chang JY, Ko JY, Kho HS. Salivary cortisol, 17β-estradiol, progesterone, dehydroepiandrosterone, and α-amylase in patients with burning mouth syndrome. Oral Dis 2012;18:613-620. doi:10.1111/j.1601-0825.2012.01937.x
60. Gurvits GE, Tan A. Burning muth syndrome. World J Gastroenterol 2013;19:665-672. doi:10.3748/wjg.v19.i5.665
61. Sikora M, Verzak Ž, Matijević M, et al. Anxiety and Depression Scores in Patients with Burning Mouth Syndrome. Psychiatr Danub 2018;30:466-470. doi:10.24869/psyd.2018.466
62. Castillo-Felipe C, Franco-Martínez L, Tvarijonaviciute A, Lopez-Jornet P, Lamy E. Proteomics-Based Identification of Salivary Changes in Patients with Burning Mouth Syndrome. Biology (Basel) 2021;10:392. doi:10.3390/biology10050392
63. Krief G, Haviv Y, Deutsch O, et al. Proteomic profiling of whole-saliva reveals correlation between Burning Mouth Syndrome and the neurotrophin signaling pathway. Sci Rep 2019;9:4794. doi:10.1038/s41598-019-41297-9
64. Rodrigues LM, Alva TDM, da Silva Martinho H, Almeida JD. Analysis of saliva composition in patients with burning mouth syndrome (BMS) by FTIR spectroscopy. Vibrational Spectroscopy 2019;100:195-201. doi:10.1016/j.vibspec.2018.12.002
65. Adler I, Denninghoff VC, Alvarez MI, Avagnina A, Yoshida R, Elsner B. Helicobacter pylori associated with glossitis and halitosis. Helicobacter 2005;10:312-317. doi:10.1111/j.1523-5378.2005.00322.x
66. Gall-Troselj K, Mravak-Stipetić M, Jurak I, Ragland WL, Pavelić J. Helicobacter pylori colonization of tongue mucosa--increased incidence in atrophic glossitis and burning mouth syndrome (BMS). J Oral Pathol Med 2001;30:560-563. doi:10.1034/j.1600-0714.2001.300909.x
67. Brailo V, Vuéiaeeviae-Boras V, Alajbeg IZ, Alajbeg I, Lukenda J, Aeurkoviae M. Oral burning symptoms and burning mouth syndrome-significance of different variables in 150 patients. Med Oral Patol Oral Cir Bucal 2006;11:E252-E255.
68. Samaranayake LP, Lamb AB, Lamey PJ, MacFarlane TW. Oral carriage of Candida species and coliforms in patients with burning mouth syndrome. J Oral Pathol Med 1989;18:233-235. doi:10.1111/j.1600-0714.1989.tb00769.x
69. Cavalcanti DR, Birman EG, Migliari DA, da Silveira FR. Burning mouth syndrome: clinical profile of Brazilian patients and oral carriage of Candida species. Braz Dent J 2007;18:341-345. doi:10.1590/s0103-64402007000400013
70. Sardella A, Lodi G, Demarosi F, Uglietti D, Carrassi A. Causative or precipitating aspects of burning mouth syndrome: a case-control study. J Oral Pathol Med 2006;35:466-471. doi:10.1111/j.1600-0714.2006.00438.x
71. Farah CS, Amos K, Leeson R, Porter S. Candida species in patients with oral dysesthesia: A comparison of carriage among oral disease states. J Oral Pathol Med 2018;47:281-285. doi:10.1111/jop.12675