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Potential Biomarkers for an Evidence-Based Diagnosis of Burning Mouth Syndrome

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Burning mouth syndrome (BMS), a chronic pain disorder with an unclear etiology, is characterized by a burning sensation in the oral cavity. The absence of objective diagnostic methods for this condition complicates its diagnosis and treatment. Recently, efforts have been ongoing to find biomarkers for the diagnosis and evaluation of patients with BMS. Several studies have reported hematological changes, differences in salivary protein composition, and peripheral neuropathy in the affected oral tissues. This review summarizes the research regarding the objective changes observed in patients with BMS to identify potential diagnostic approaches.

Keywords: Biomarkers; Burning mouth syndrome; Diagnosis

INTRODUCTION

Burning mouth syndrome (BMS) is predominantly observed in middle- and old-aged women. It has unknown causes and is characterized by burning pain without associated pathological findings in the oral mucosa [1]. Burning pain can occur anywhere in the oral mucosa; however, it is most common in the anterior one-third of the tongue. Changes in taste sensation (abnormal taste, decreased taste, etc.) are also common [1-4].

Despite the unclear pathophysiology of BMS, several factors are considered to interact in a complex manner to produce these outcomes [1,2,5]. Local factors that irritate the mucous membrane and systemic and emotional factors have been suggested as causes of BMS [1,2,6]. Recent studies have reported BMS as an instance of neuropathic pain [7,8]. Peripheral neurodegeneration such as changes in the peripheral or oral sensory nerves caused by various stimuli and abnormalities in the central nervous system related to pain control have been suggested as related to BMS [7-9].

The unclear pathophysiology of BMS and the absence of objective lesions make treatment of BMS difficult for clinicians [1,10]. In the absence of objective measurements, treatment outcome is only assessed based on the patient's subjective experience of pain [9,11]. Treatment is focused on relieving symptoms rather than eliminating BMS, and drug treatment for neuropathic pain control is regarded as the best method [2,3,12].

As previously mentioned, the diagnosis and treatment of BMS pose considerable challenges, and clinical experience most often serves as the source of guidance [9,12]. Current diagnosis and treatment methods include repeated trial and error and vary among patients. Chronic orofacial pain, such as BMS, may be aggravated by misdiagnosis and inappropriate drug selection caused by a missed treatment period [13]. Thus, a set of objective criteria for the diagnosis and evaluation of BMS is critical to the development of new BMS treatment protocols. Accordingly, efforts are ongoing

to find biomarkers for the diagnosis and evaluation of patients with BMS [9,11,14-16]. However, more studies on the predictive factors that can suggest treatment outcomes and monitor disease severity during treatment are needed.

In this study, we aimed to identify potential biomarkers that could be used in the diagnosis of BMS. Only studies that included primary BMS with laboratory tests were summarized. Several potential biomarkers and hematological test results related to the diagnosis and follow-up of BMS were also investigated.

DIAGNOSTIC CRITERIA

The international classification of orofacial pain (ICOP) has suggested the following criteria [17] for BMS: (1) persistent burning sensation in the oral mucosa (2) that recurs daily for at least 2 hours, for at least 3 months, (3) with no other identifiable cause and (4) no clinical signs of inflammation or neuropathy. The ICOP criteria are widely used to diagnose and manage BMS. As these criteria emphasize, a clinician must quickly rule out any local or systemic cause that may contribute to the burning pain in the oral mucosa.

Collecting information such as the patient's pain history and medical history and conducting a clinical and laboratory examination can help in evaluating the underlying causes of BMS [10]. Despite these steps, patients with BMS are on average diagnosed after 12-13 months owing to the lack of objective clinical or laboratory examination criteria for BMS diagnosis [18,19]. Therefore, objective and evidence-based diagnostic criteria must be established for the effective diagnosis and treatment of BMS.

BMS-ASSOCIATED BIOMARKERS

1. BMS-Associated Serum Parameters

Various hematological abnormalities have been associated with oral burning pain. A previous study reported associations with systemic diseases such as diabetes, hypothyroidism, and nutritional deficiencies [20]. This section will explore serum parameters in patients with primary BMS without these systemic diseases.

das Neves de Araújo Lima et al. [21] compared psychological, hormonal, and genetic factors between BMS and secondary oral burning (SOB) to identify any differences between them. The BMS group had higher levels of anxiety and depression than the SOB group. However, no significant differences in hormonal levels were found between the two groups. In addition, genetic analysis revealed that compared with the SOB group, the BMS group had higher levels of specific genetic markers associated with chronic pain. Overall, the study suggested that BMS might have a stronger genetic component than SOB, and psychological factors might play a role in BMS development. Barry et al. [22] analyzed the plasma cytokines and chemokines in both the BMS and control groups. They also analyzed psychological factors using the 16-item Quick Inventory of Depressive Symptomatology questionnaire. In BMS, the plasma expression level of interleukin (IL)-8 was high, and IL-8 showed significant correlations with both depression and oral pain. An increase in depression symptoms in the BMS group compared with that in the healthy control group was reported; however, no significant differences were noted in other cytokines and chemokines [22].

According to Lee et al. [23], the antidiuretic hormone (ADH) levels in men with BMS were significantly higher than those in the control group. They suggested that the high ADH levels in the BMS group may contribute to the dry mouth sensation and altered taste perception, which are commonly associated with BMS. However, more studies are needed to confirm these findings and determine the exact role of ADH in BMS development.

Other studies have examined the serum parameters related to immunity, neurodegeneration, and stress and considered their possible role as the cause of BMS [24-26]. Several studies that have identified specific biomarkers in the serum have also reported that they are potentially very useful in the diagnosis of BMS. For instance, Koike et al. [24] found that patients with BMS had low plasma adrenaline levels and a high $CD4^+/CD8^+$ ratio. Similarly, Kishore et al. [25] reported that neuron-specific enolase was elevated in the blood of patients with primary BMS. Kho et al. [26] also confirmed that in patients with BMS, the MUC1 transcript was significantly highly expressed, and their blood contained higher IL-6 levels, raising the possibility of an objective diagnostic criterion for BMS.

2. BMS-Associated Salivary Parameters

Research is ongoing into salivary biomarkers that can be used for the diagnosis of BMS. Saliva represents a multifaceted biological fluid that contains diverse biomolecules, including DNA, RNA, proteins, metabolites, and microbiota [27]. Saliva-based diagnosis is regarded as a useful method that allows for early diagnosis, can provide symptomatic improvement and posttreatment monitoring, and has the potential to replace blood as the primary medium for fluid biopsy [15,27]. Moreover, since saliva is easy to collect noninvasively, it is easy to use in clinical practice. Finally, the pain-inducing and saliva-existing areas coincide. Of course, these features are only useful if appropriate biomarkers are found in the saliva [16].

Several studies have reported increased salivary biomarkers in patients with BMS in response to inflammation, peripheral nerve damage, and stress [28-32]. According to Nosratzehi et al. [28], the BMS group had significantly higher levels of salivary cortisol and α-amylase than the control group, indicating increased stress levels. Kim et al. [29] analyzed the levels of salivary cortisol, 17β-estradiol, progesterone, dehydroepiandrosterone, and α-amylase in patients with BMS and observed significantly high levels of salivary cortisol and 17β-estradiol in these patients.

Total saliva protein analysis revealed a significant difference in the protein composition ratio in the BMS group compared with the control group [30-32]. Specifically, Ji et al. [30] identified approximately 50 distinct differences in proteins in the saliva of patients with BMS. Among them, proteins such as α-enolase, IL-18, and kallikrein-13, which show the greatest change, were further quantitatively analyzed, and α-enolase and IL-18 were found to be highly applicable in the diagnosis of patients with BMS. Krief et al. [31] also conducted a proteomic analysis of whole saliva from patients with BMS and found upregulated expression levels of certain proteins involved in the neurotrophin signaling pathway, which is responsible for regulating neuron growth and survival. This result suggests that these altered protein levels may play a role in the pathogenesis of BMS. Another proteomics study of the acid-soluble fraction of whole saliva in patients with BMS revealed altered expression levels of cystatin SN in the saliva, which is involved in inflammation and oxidative stress [32].

3. Quantitative Somatosensory Assessment in BMS

Although the pathophysiology of BMS remains unclear, it is considered a neuropathic pain disorder. The persistent burning pain is believed to be related to peripheral neuropathy or alterations in pain modulation centrally. Quantitative sensory testing (QST) is a means of objectively quantifying the degree of peripheral nerve abnormalities. Several studies have attempted to objectively assess sensory abnormalities in patients with BMS [33-37].

Altered pain thresholds, tolerance, and sensory perception have been observed in patients with BMS. In addition, patients with BMS often report accompanying sensory abnormalities, including dysgeusia, and oral burning pain [35-37]. Yilmaz et al. [33] discussed how BMS and iatrogenic lingual nerve injuries (ILNI) often exhibit similar symptoms, such as burning or tingling sensations. This similarity can make their differential diagnosis difficult. They assessed QST results in patients with BMS and ILNI and found that the BMS group was more sensitive to capsaicin than the control group. Moreover, the BMS group was more sensitive to cold and had a lower warm-detection threshold, whereas the ILNI group showed decreased sensitivity to cool and warm stimuli. They concluded that QST can help differentiate diseases by measuring thermal and mechanical thresholds in the affected area. Watanabe et al. [34] investigated the association between somatosensory dysfunction and symptom duration in BMS. Their study participants were patients with BMS who presented with symptoms of varying durations. QST was employed to evaluate the somatosensory function in the oral mucosa, and the findings demonstrated a positive correlation between longer symptom duration and increased somatosensory dysfunction, indicating a progressive impairment in sensory perception over time. These results suggest that symptom duration may contribute to the development and severity of somatosensory dysfunction.

Peripheral small-fiber neuropathy and abnormal QST results have been reported, supporting a peripheral pathophysiology. Although studies have assessed sensory abnormalities using QST in patients with BMS, most were conducted on only a small number of patients. To establish a diagnostic method for BMS using QST, further studies are necessary.

4. Biopsy Results

Numerous studies have utilized tissue biopsies to investigate BMS. The findings from tissue biopsies also suggest the presence of peripheral small-fiber neuropathy in patients with BMS. Lauria et al. [38] concluded that BMS is caused by damage to the peripheral nerve fibers in the tongue. They performed tongue tissue biopsies on 12 patients with BMS and found a significantly reduced density in the peripheral nerve distribution in the tongue of this group compared with those of the healthy control group. Puhakka et al. [8] evaluated intraepithelial nerve fiber density in the tongue biopsies of patients with BMS and observed significantly less density in their fibers. Penza et al. [39] classified patients with BMS based on the distribution of epithelial nerve innervation observed on tongue biopsies. Among the group with significantly reduced innervation, patients reported burning pain in multiple areas of the oral cavity. By contrast, patients with BMS and normal innervation experienced a burning pain localized to the tip of the tongue and exhibited significantly higher levels of depression. This finding suggests that in diagnosing BMS, a tongue biopsy may serve as a valuable tool in guiding the selection of treatment for patients with BMS.

Tissue biopsy can also reveal alterations in transient receptor potential vanilloid 1 (TRPV1), associated with burning pain. Yilmaz et al. [40] found that the heat and capsaicin receptor TRPV1 and nerve growth factors (NGF) were higher in the BMS group than in the control group. They observed a correlation between the pain intensity and the presence of these factors in the BMS group. Moreover, they found that the high levels of the TRPV1 receptor in nerve fibers correlated with higher pain scores in the BMS group. Treldal et al. [41] divided their participants into three groups based on their responses to local anesthesia. They found that TRPV1, NGF, NGF receptors, and IL-17 were slightly stronger in the effect group than in the no-effect group; however, the difference was not statistically significant. Borsani et al. [42] discovered modified levels of TRPV1 and cannabinoid receptors (CB) type 1 and 2 within the epithelial cells of the tongue in patients with BMS. In patients with BMS, tongue epithelial cells exhibited high expression levels of TRPV1and CB2, and low expression levels of CB2. Kho et al. [26] evaluated MUC1 and Toll like Receptor 2 (TLR-2) expression levels in patients with BMS and revealed noteworthy elevations in MUC1 transcripts in the BMS group when compared with both the OLP and control groups. However, they did not observe a significant disparity in TLR-2 expression across the groups. These research findings not only contribute to our understanding of the pathophysiology of BMS but also demonstrate its diagnostic potential.

CONCLUSION

Despite efforts at the establishment of objective diagnostic criteria for BMS, no conclusive outcome has been reached. Existing research results allow us to infer that BMS is a neuropathic disease, contributes to our understanding of the pathophysiology of BMS, assists us in classifying patients with BMS, and improves our ability to identify appropriate treatment approaches. The accumulation of objective data related to BMS brings us ever closer to establishing objective testing methods and diagnostic criteria. Owing to the insufficient number of studies focusing on a larger cohort of patients with BMS, more extensive research is needed in the future. The establishment of a systematic means of testing and diagnosing BMS may shed light on the pathophysiology of the disease and aid in the discovery of a complete treatment method.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets used in this study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualization: WJ, KEL. Formal analysis: KEL. Methodology: WJ. Project administration: KEL. Writing - original draft: WJ, KEL. Writing - review & editing: WJ, KEL.

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