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ORIGINAL ARTICLE

Burning mouth syndrome: Analysis of diagnostic delay in 500 patients

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Abstract

Objectives: To assess the diagnostic delay, the number and type of referrals and the clinical and psychological profile in a wide sample of patients with Burning Mouth Syndrome (BMS).

Materials and Methods: Data on the disease onset, oral symptoms, type and number of practitioners consulted, misdiagnoses, and the presence of medically unexplained extraoral physical symptoms were recorded in 500 BMS patients. Potential predictors of diagnostic delay were also evaluated.

Results: The mean diagnostic delay was 29.71 ± 47.19 months. An average of 2.61 ± 1.65 practitioners were consulted by each patient, the most frequent being the general physicians (287; 57.4%), maxillofacial surgeons (111; 22.2%), and otolaryngologists (104; 20.8%). The mean number of misdiagnoses was 3.54 ± 1.85. Nonspecific stomatitis, candidiasis, and gastroesophageal reflux were the most common misdiagnoses. Higher age, low education, the presence of dysgeusia, and a previous history of psychiatric illness were predictors of a longer diagnostic delay (*p*-value: 0.028, 0.050, 0.007, 0.034, respectively).

Conclusions: The lack of knowledge among specialists, the high rate of misdiagnosis, and the diagnostic delay of BMS highlight the need to introduce educational interventions in all medical specialties in order to promote an early and appropriate diagnosis, thereby improving the prognosis and quality of life of the patients.

KEYWORDS
burning mouth syndrome, diagnostic delay, medically unexplained physical symptoms, misdiagnosis, psychological profile

Daniela Adamo and Elena Calabria have contributed equally to this work and share first authorship.

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1 | INTRODUCTION

Burning mouth syndrome (BMS) is a chronic orofacial pain condition characterized by a burning/pain or dysesthetic sensation affecting the oral mucosa and lasting for at least 3 months without any clinical evidence (International Classification of Orofacial Pain, 1st edition (ICOP), 2020). The overall worldwide prevalence of BMS is 1.73% in the general population and 7.72% in clinical patients, with the highest prevalence in Europe (5.58%) and in females over 50 years (Wu et al., 2022). The symptomatology is very complex because the patients often report several oral and extraoral symptoms in addition to the burning/pain. Subjective salivary alterations such as xerostomia, sialorrhea, taste disturbance, intraoral foreign body sensation, globus and itching are the most frequently associated oral symptoms (Adamo et al., 2020, 2021; Moisset et al., 2016) while ophthalmodynia, vulvodynia, gastrointestinal complaints and skin burning have been reported as more common medically unexplained extraoral physical symptoms (UEPS; Mignogna et al., 2011).

Growing evidence has suggested that BMS is a multifactorial disease in which a central and peripheral neuropathy is involved in the etiopathogenesis (Lopez-Jornet et al., 2017); in addition, mood disorders, sleep disturbance, and cognitive impairment are frequently associated (Canfora et al., 2021), reducing the quality of life of the affected patients (Canfora et al., 2022; Jedel et al., 2020).

Although several treatments have been suggested for the improvement of the burning/pain, and psychological distress, the knowledge about this disease has not significantly improved among healthcare providers over time (Reyad et al., 2020). This is suggested by the lengthy delays frequently reported between the onset of the symptoms and the definitive diagnosis of BMS (Freilich et al., 2020). Considerable evidence has suggested that healthcare providers find it difficult to distinguish between different types of orofacial pain and consequently to diagnose and manage these conditions. Thereby, they effectively abandon the patients, leave them without a proper diagnosis and force them to consult several specialty doctors, so starting their "healthcare journey" (Beecroft et al., 2013; Peters et al., 2015).

This delay in diagnosis may have a serious individual and social impact, creating a heavy burden on healthcare systems resulting in higher socioeconomic costs. Meanwhile, the patients tend to get lost in a circuit of doctors, being transferred from one specialist to another (Pereira et al., 2021).

In 2005, in a retrospective study on 59 BMS patients, Mignogna et al. (2005) reported an average diagnostic delay of about 34 months. In addition, most patients received several misdiagnoses and consulted at least three doctors prior to receiving a correct diagnosis of BMS. Similarly, in a retrospective study on 49 BMS patients, Klasser et al. (2011) reported an average delay of 20 months until a definitive diagnosis, while in two recent studies on 50 and 102 BMS patients, a shorter diagnostic delay of 13 and 12 months has been, respectively, reported (Freilich et al., 2020; Ni Riordain et al., 2019).

In light of the heterogeneity of the findings present in the literature, the aim of the present study was to investigate and better characterize the occurrence of diagnostic delay and of the related factors in a wide sample of 500 BMS patients in the South of Italy. To the best of our knowledge, this is the first study having performed this analysis in such a large sample of BMS patients.

The primary endpoint of the current study has been to investigate:

1. the diagnostic delay, analyzing the time from the onset of the symptoms to the definitive diagnosis, the number and type of specialists consulted, and the number and type of misdiagnoses made.

The secondary endpoints have been to evaluate:

1. the psychological profile (anxiety, depression and sleep disturbance), any systemic comorbidities and drug consumption, and the intensity and quality of pain in the BMS patients, with a careful analysis of both the additional oral symptoms and UEPS.
2. to identify the potential predictors of diagnostic delay in BMS patients, taking into account the sociodemographic profile, risk factors, systemic comorbidities, drug consumption, pain evaluation and symptomatology, psychological factors and UEPS.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This is an observational cross-sectional study which has been conducted at the Oral Medicine Department of the University of Naples "Federico II" in accordance with the ethical principles of the World Medical Association Declaration of Helsinki, after approval by the Ethical Committee of the University (Approval Number: 251/19: February 20, 2019). The adopted methods conformed with the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies (von Elm et al., 2014).

The study was conducted between January 2020 and January 2022. All newly diagnosed patients with BMS were invited to participate in the study and a written informed consent was obtained from each of them; no payment was provided for participation. Initially, 590 BMS patients of either gender and aged >18 years were screened and prospectively recruited for the study. However, 500 individuals met the inclusion criteria (Figure 1: flow chart).

In accordance with the definition of the International Classification of Orofacial Pain (ICOP, 2020), the inclusion criteria for the BMS patients were the presence of an intraoral burning or dysesthetic sensation, recurring daily for more than 2 h per day for more than 3 months, without any evident causative lesions on clinical examination and investigation, including an analysis of laboratory findings. The exclusion criteria were patients suffering from diseases that could be recognized as a causative factor of BMS;

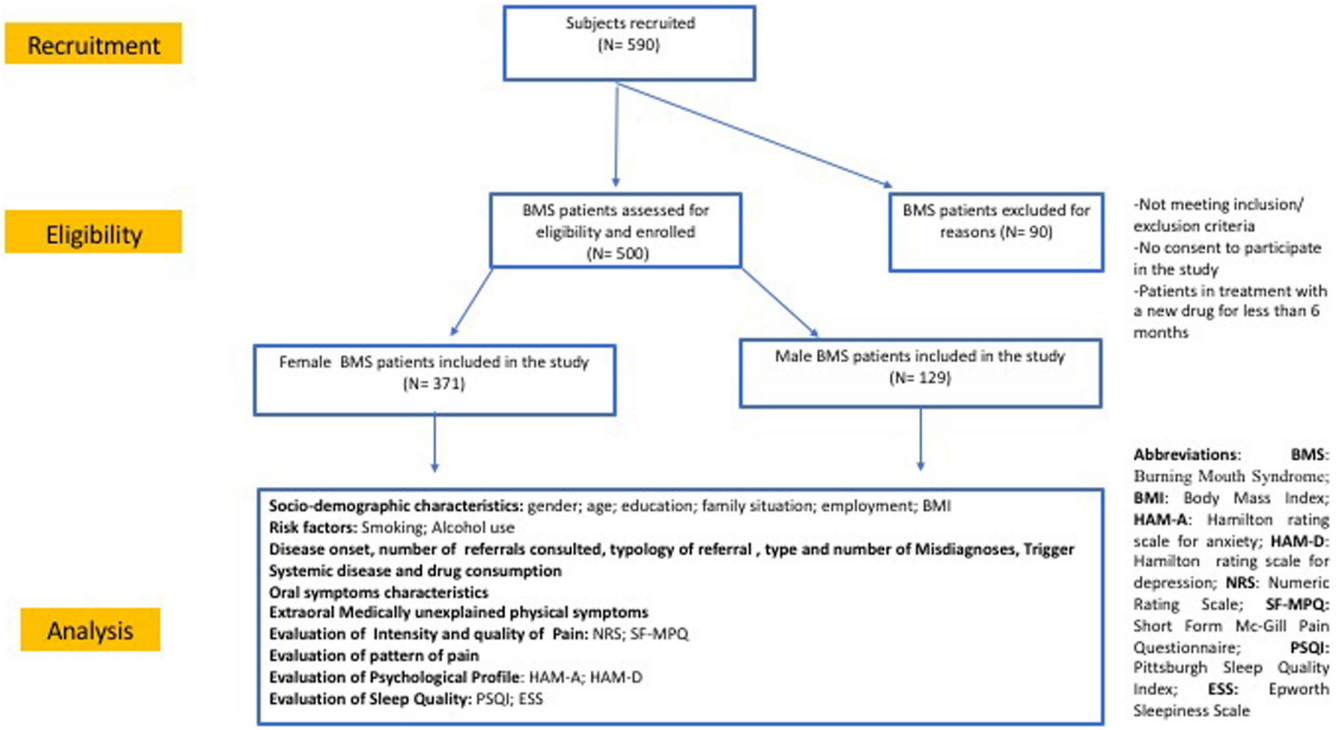

FIGURE 1 Flow chart of the study.

patients aged under 18; patients having a history of alcohol or substance abuse and patients unable to understand or complete the questionnaires. In addition, patients who had been on medication for at least 6 months before the onset of the oral burning symptoms were admitted, while patients whose chronic therapies had been modified within 6 months prior to the onset of BMS were excluded. The challenge–dechallenge–rechallenge test was used in all subjects with a suspicion of an adverse drug reaction.

2.2 | Procedure, data collection, and outcomes of interest

Each patient underwent an intraoral and extraoral screening by an oral medicine specialist (DA) and data were obtained by means of face-to-face questionnaires addressing the sociodemographic profile (age, years of education, family situation, and job status), body mass index (BMI), risk factors (smoking status and alcohol consumption), systemic comorbidities, drug consumption, oral symptoms, and sites involved. Also, the diurnal pattern of the symptoms (same in the morning/afternoon/evening, worse in the afternoon/evening, worse in the morning, continuous or intermittent), any improvements reported during eating and the worst symptom reported by the patients were recorded.

The outcome evaluated for the primary objective of the present study was the diagnostic delay, measured as the time (in months) between the onset of the oral symptoms and the definitive diagnosis of BMS. To better characterize all the factors related to the diagnostic delay, data on the number of medical and healthcare providers consulted, the number and type of misdiagnoses before the definitive BMS diagnosis, and the cause of the disease attributed by the patients were also collected. Additionally, the extraoral physical symptoms were recorded and considered as UEPS after a careful evaluation of the patient's medical records relating to previous consultations with clinicians specialized in the specific area of the symptoms (ophthalmologists, otolaryngologists, gastroenterologists, gynecologists, dermatologists, cardiologists, specialists in internal medicine, rheumatologists, and neurologists).

2.3 | Pain, psychological profile, and sleep assessment

The following battery scale was administered to all the BMS patients:

1. the Numeric Rating Scale (NRS) and the Short Form McGill Pain Questionnaire (SF-MPQ) to evaluate the intensity and quality of the pain/burning (Hjermstad et al., 2011; Melzack, 1987);
2. the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A) to evaluate the level of anxiety and depression (Hamilton, 1959, 1960);
3. the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS) to evaluate the sleep quality (Curcio et al., 2013; Vignatelli et al., 2003).

Questions about the history of previous and/or the familiarity of mood disorders were addressed to all the participants. Moreover, the number of patients suffering from insomnia prior to the BMS

diagnosis was recorded and the onset of insomnia (in months) prior to the BMS diagnosis and the sleep duration (in hours) were calculated.

2.4 | Statistical analysis

The R software (v. 4.1 2; Team Rcore, 2016) was used to carry out the statistical analyses. Descriptive statistics, including means, standard deviations (SD), medians and interquartile ranges (IQR), were used to summarize all the variables. The Spearman's correlation and Wilcoxon–Mann–Whitney test were computed to analyze the correlation between the above quantitative and qualitative predictors and the disease onset, respectively. The age, years of education, BMI, NRS, SF-MPQ, HAM-A, HAM-D, PSQI, ESS have been considered as quantitative predictors and gender, marital status, employment, menopause, smoking, alcohol use, the most common oral symptoms reported by patients, location of pain, diurnal pattern of symptomatology, the most common comorbidities and UEPS, the presence of previous history of psychiatric illness and the onset of sleep disorders prior to BMS have been considered as qualitative predictors. *p*-values <0.05 or 0.01 were considered moderately or strongly significant, respectively.

3 | RESULTS

Table 1 summarizes the socio-demographic profile, BMI and risk factors, comorbidities and drug consumption in the sample of patients. A total of 500 BMS patients (129 males and 371 females; M:F 1:3) were enrolled. With respect to the female participants, 324 (87.3%) were in menopause. The mean age of the patients was 64.5 ± 12.94 years. The majority of the patients were married (381, 76.2%), unemployed (217; 43.4%), non-smokers (370; 74%) and non-consumers of alcohol (426: 85.2%). 420 (84%) BMS and 348 (69.6%) patients were affected by at least one systemic comorbidity and were taking at least one drug, respectively. Hypertension (249; 49.8%) and hypercholesterolemia (193: 38.6%) were the most common medical comorbidities of the BMS patients. Therefore, with regard to the drug consumption, a high prevalence of the BMS patients were taking antihypertensives, statins, and antiplatelets.

The onset of the disease, the number of consultations prior to the diagnosis, the type of the referrals, and the type and number of misdiagnoses are shown in Table 2. The mean delay from the onset of the symptoms to the correct BMS diagnosis was 29.71 ± 47.19 months. Each patient consulted on average 2.61 ± 1.65 practitioners. Physicians (287; 57.4%), maxillofacial surgeons (111; 22.2%), and otolaryngologists (104; 20.8%) were the specialists most frequently consulted while only 82 (16.4%) of the BMS patients had been examined by a dentist in relation to their symptoms before consulting the Oral Medicine Unit. The mean number of misdiagnoses was 3.54 ± 1.85; nonspecific stomatitis (223: 44.6%), candidiasis (200: 40%), and gastroesophageal reflux disease (GERD; 180:36%) were the most common misdiagnoses made. Figure 2 shows the

TABLE 1 Sociodemographic profile, risk factors, systemic comorbidities, and drugs consumption in the 500 BMS patients.

Demographic variables	BMS patients
Gender	Frequency (%)
Male	129 (25.8)
Female	371 (74.2)
Age (in years)	Mean ± SD 64.5 ± 12.94
Education (in years)	Mean ± SD 9.2 ± 4.55
Family situation	Frequency (%)
Single	37 (7.4)
Married	381 (76.2)
Divorced	24 (4.8)
Widowed	58 (11.6)
Employment	Frequency (%)
Employed	119 (23.8)
Unemployed	217 (43.4)
Retired	164 (32.8)
Body mass index	Mean ± SD 26.76 ± 3.51
Risk factors	**Frequency (%)**
Smoking	
Never	370 (74)
<5 cigarettes	21 (4.2)
5–10 cigarettes	20 (4)
10–15 cigarettes	40 (8)
>15 cigarettes	49 (9.8)
Alcohol use	
Never	426 (85.2)
Yes (1–2 units/week)	51 (10.2)
Yes (2–3)	17 (3.4)
Yes (>3)	6 (1.2)
Systemic comorbidities	**Frequency (%)**
Yes	420 (84)
No	80(16)
Hypertension	249 (49.8)
Hypercholesterolemia	193 (38.6)
Previous myocardial infarction	20 (4)
Other cardiovascular diseases	41 (8.2)
Asthma	30 (6.2)
Gastroesophageal reflux disease	90 (18)
Endocrine diseases	7 (1.4)
Benign prostatic hypertrophy	26 (5.2)
Hypothyroidism	68 (13.6)
Hyperthyroidism	5 (1)
HCV infection	9(1.8)
HBV infection	3(0.6)

TABLE 1 (Continued)

Systemic comorbidities	Frequency (%)
Neoplastic disease	30 (6)
Others	96 (19.2)
Drugs consumption	**Frequency (%)**
Yes	348 (69.6)
No	152 (30.4)
ACE-inhibitors	62 (12.4)
Calcium channel blockers	45 (9)
Angiotensin II receptor antagonists (ARBs)	84 (16.8)
Thiazide diuretics	63 (12.6)
Beta blockers	80 (16)
Statins	137 (27.4)
Ezetimibe	10 (2)
Antiplatelets	145 (29)
Blood thinners	25 (5)
Bisphosphonates	11 (2.2)
Levothyroxin sodium	58 (11.6)
Steroids	12 (2.4)
Proton pump inhibitors	121 (24.2)
Others	66 (13.2)

Abbreviations: BMS, burning mouth syndrome; SD, standard deviations.

main type of misdiagnoses made by the different specialists before the appropriate BMS diagnosis. All the BMS patients had undergone at least one diagnostic test, such as a swab for oral candidiasis (210; 42%) and/or gastroscopy (120; 24%), and had received unsuccessful empirical treatment with antifungals (400; 80%), antiseptics mouthwash (450; 90%), vitamins (180; 36%), proton pump inhibitors (175; 35%), or topical steroids (50; 10%).

The prevalence of the oral symptoms and oral sites involved is shown in Table 3. Intraoral foreign body sensation (394; 78.8%), xerostomia (308; 61.6%), and dysgeusia (225; 45%) were, respectively, the most frequent oral symptoms reported in addition to the burning. In the majority of patients, the burning/ pain (272; 54%) was localized in one or more sites of the oral mucosa, with the tongue (456; 91.2%) and lips (311; 62.2%) the most common oral sites involved.

Table 4 summarizes the intensity, quality, and pattern of the pain, any improvement during eating and the worst symptom in the sample of patients. The median and IQR of the NRS and SF-MPQ were 10;9–10 and 10;7–12, respectively, suggesting that the patients with BMS suffered from a high level of intensity of pain/ burning. Considering the quality of the pain, the most common attributes used by the patients with respect to the burning/heat were heavy, tiring/exhausting, and sickening. In the majority of the patients (274; 54.8%), no difference in the pattern of the symptoms was reported during the day and an improvement in the symptoms during meals was reported only in 123 (24.6%) BMS patients. In addition, burning was considered the worst symptom in the majority of patients (417: 83.4%).

TABLE 2 Diagnostic delay, number of consultations prior to the diagnosis, type of referral and number and type of misdiagnoses.

Diagnostic delay (months)	Mean ± SD
	29.71 ± 47.19
Number of doctors consulted prior to diagnosis of BMS	**Mean ± SD**
	2.61 ± 1.65
Referrals	**Frequency (%)**
Physician	287 (57.4)
Maxillofacial Surgeon	111 (22.2)
Otolaryngologist	104 (20.8)
Gastroenterologist	85 (17)
Dentist	82 (16.4)
Dermatologist	36 (7.2)
Neurologist	35 (7)
Psychiatrist	27 (5.4)
Misdiagnosis	**Mean ± SD**
Number of misdiagnoses	3.54 ± 1.85
Type of misdiagnosis	**Frequency (%)**
Aspecific stomatitis	223 (44.6)
Candidiasis	200 (40)
Gastroesophageal reflux	180 (36)
Hypoavitaminosis	54 (10.8)
Trigeminal neuralgia	45 (9)
Allergic reaction	38 (7.6)
Sjogren's syndrome	25 (5)

Abbreviations: BMS, burning mouth syndrome; SD, standard deviations.

The psychological profile, sleep evaluation, and causes of disease attributed by the patients are summarized in Table 5. The median and IQR of the HAM-A and HAM-D were 17 [15–20] and 17 [14–20], respectively, suggesting that, generally, patients with BMS suffer from mild anxiety and mild depression. In addition, 148 (29.6%) and 16 (3.2%) BMS patients reported a previous history of mood disorders and the presence of first degree relatives affected by mood disorders, respectively. Poor sleep (PSQI>5) was reported in 451(90.2%) BMS patients and the onset of insomnia anticipated the onset of BMS by on average 4 [3–7] years in 53.8% (269) of the patients. Surprisingly, only 46 (9.2%) patients reported the occurrence of the disease after dental treatment while the majority of the patients (405;81%) were unable to attribute the onset of the disease to any known cause.

The prevalence and type of the UEPS reported by the patients are summarized in Table 6. UEPS were detected in 169 (33.8%) patients with a mean of 2.8 ± 1.50 symptoms for each patient. Irritable bowel syndrome (48; 9.6%), fibromyalgia (36; 7.2%), and tinnitus (32; 6.4%) were the most common UEPS reported.

Tables 7 and 8 show the relationships between the diagnostic delay and quantitative and qualitative predictors. Higher age and lower educational level (in years) as well as the presence of dysgeusia

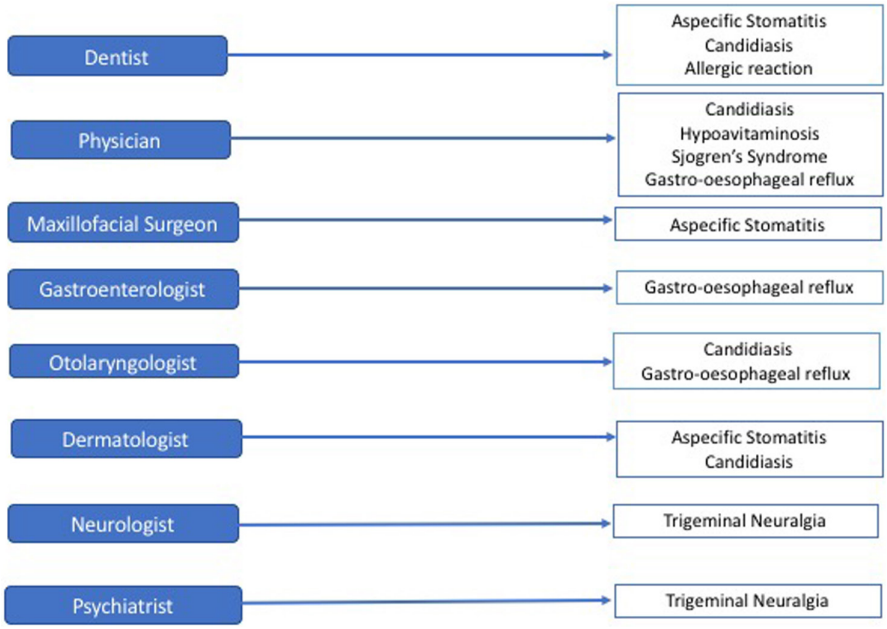

FIGURE 2 Main types of misdiagnoses made by different clinicians before appropriate BMS diagnosis.

and of a previous history of psychiatric illness were strongly correlated with the diagnostic delay (*p*-values: 0.028, 0.050, 0.007, 0.034, respectively).

4 | DISCUSSION

Knowledge of chronic orofacial pain conditions, mainly BMS, continues to be very limited among healthcare providers and dentists (Beecroft et al., 2013; Ni Riordain et al., 2019), as suggested by the lengthy delays from the onset of the symptoms until the proper diagnosis observed in this study. The diagnostic delay has a mean of 29.7 months (SD: 47.19) although some patients reported a symptomatology without diagnosis also for 6 years. The average number of doctors consulted prior to the BMS diagnosis was 2.6 (SD: 1.65).

The diagnostic delay found in this study is higher compared with the previous studies where the average duration from the onset of symptoms to diagnosis was 20, 13, and 12 months, respectively (Freilich et al., 2020; Klasser et al., 2011; Ni Riordain et al., 2019).

It was slightly lower compared with the findings of the study of Mignogna et al. (2005) where the appropriate BMS diagnosis was made on average after 34 months and the number of doctors consulted was 3.1. As suggested by the results of this study, the diagnostic delay could be related to a failure to recognize the symptomatology by the first-line healthcare providers consulted, generally physicians, maxillofacial surgeons, and otolaryngologists. Surprisingly, despite the oral cavity being the main site of the symptomatology, only 16.4% (82) of patients had consulted a dentist prior to receiving a BMS diagnosis.

These results may be attributed to the misinformation that the BMS patients received in the Italian language by searching on the Internet and/or to the difficulty in performing proper research possibly due to the older age and low educational level. Indeed, both factors were correlated with a longer diagnostic delay. In addition, when checking "oral burning" or "burning tongue" on Google, an allergic reaction, gastroesophageal reflux, stress, and vitamin deficiency are the most common misdiagnoses offered in Italy to the patient while a diagnosis of BMS is only in fifth or sixth place in the list. Instead, as reported by the study of Alnafea et al., (2017), the same research in English offers BMS as the first diagnosis. Therefore, adequate information may contribute to shift patients toward an oral medicine specialist, probably reducing the diagnostic delay in other countries. This suggests that not only the poor knowledge of the clinicians but also cultural differences around the world may impact on this delay.

In this context, it seems obvious that all the patients had received at least one misdiagnosis (on average 3.54) and that they had undergone several unnecessary diagnostic tests and unsuccessful empirical treatments. There were several differences in the prevalence of the misdiagnoses made by the different specialists. Indeed, nonspecific stomatitis, candidiasis, and GERD were the most common first diagnoses made by physicians, maxillofacial surgeons, and otolaryngologists, respectively. In particular, a positive fungal culture was one of the most important confounding factors for clinicians and for patients, even if a positive candida swab in the absence of clinical lesions may represent candida carriage rather than an active infection (Freilich et al., 2020; Patel, 2022). Therefore, it is plausible that, in the first line, antifungals are one of the most frequently prescribed empirical treatments by clinicians also more than once over time. Another frequent misdiagnosis was GERD (36%) with the result that a significant number of the BMS patients had undergone a stressful invasive procedure such as gastroscopy (24%), which may further complicate the communication with the patient about the proper neuropathic etiopathogenesis of the disease. Surprisingly, despite their knowledge about somatic symptom

TABLE 3 Prevalence of oral symptoms and location in the 500 BMS patients.

Oral symptoms	Frequency (%)
Burning	500 (100)
Intraoral foreign body sensation	394 (78.8)
Xerostomia	308 (61.6)
Dysgeusia	225 (45)
Globus pharyngeus	183 (36.6)
Subjective change in tongue morphology	108 (21,6)
Sialorrhea	107 (21.4)
Itching	61 (12.2)
Tingling sensation	57 (11.4)
Occlusal dysesthesia	41 (8.2)
Oral dyskinesia	39 (7.8)
Dysosmia	25 (5)
Subjective halitosis	30 (6)
Location of pain/burning	**Frequency (%)**
Burning/pain diffuse to entire oral mucosa	228 (45.6)
Burning/pain localized in one or more sites of oral mucosa	272 (54.4)
Tongue	456 (91.2)
Lips	311 (62.2)
Palate	305 (61)
Gums	295 (59)
Cheeks	265 (53)
Floor of the mouth	242 (48.4)
Trigone	1 (0.2)

Abbreviation: BMS, burning mouth syndrome.

TABLE 4 Intensity, quality and pattern of pain, improvement during eating and worst symptom in the 500 BMS patients.

	BMS
Pain	**Median; IQR**
NRS	10 [9–10]
SF-MPQ	10 [7–12]
Diurnal pattern of symptoms	**Frequency (%)**
Same in the morning/afternoon/evening	274 (54.8)
Worse in the afternoon/evening	207 (41.4)
Worse in the morning	19 (3.8)
Continuous	313 (62.6)
Intermittent	187 (37.4)
Improvement during eating	**Frequency (%)**
Yes	123 (24.6)
No	377 (75.4)
Worst symptom	**Frequency (%)**
Burning	417 (83.4)
Change in tongue morphology	20 (4)
Dysgeusia	14 (2.8)
Xerostomia	24 (4.8)
Globus	3 (0.6)
Sialorrhea	5 (1)
Intraoral foreign body sensation	5 (1)
Occlusal Dysesthesia	10 (2)
Oral Dyskinesia	2 (0.4)

Abbreviations: BMS, burning mouth syndrome; IQR, interquartile range; NRS, Numeric Rating Scale; SF-MPQ, Short-form McGill Pain Questionnaire.

disorders, trigeminal neuralgia was the only diagnosis made by all neurologists and psychiatrics consulted (62; 12.4%), suggesting a limited knowledge of BMS also in psychiatric and neurological settings. On this regard, interestingly, a longer delay in BMS diagnosis was associated with the presence of a previous history of psychiatric illness, possibly because patients who have experienced mood disorders in their life may be more likely to interpret their oral symptoms as manifestation of an oral or gastrointestinal diseases rather than as somatic symptoms, this leading to many time-consuming consultations and treatments.

The delay in the diagnosis may be related not only to a limited knowledge about the disease and to misinformation but also to the complexity of the symptoms, the high prevalence of systemic comorbidities and the presence of mood disorders often identified in these patients. Regarding the symptomatology, despite oral burning being reported by all the patients and being considered the worst symptom (83.4%), the presence of additional symptoms may delay the proper diagnosis by healthcare providers who have a familiarity only with the burning symptom. Indeed, the most frequent additional symptoms reported by patients, such as the intraoral foreign body sensation (78.8%) xerostomia (61.6%), and dysgeusia (45%), may be associated with other systemic diseases and may represent confounding factors for clinicians. Specifically, intraoral foreign body sensation, also defined as oral cenesthopathy, is a very complex symptom because the definition includes not only the specific and strong conviction of the patients that they have a foreign body in their mouths but also all complaints of unusual oral sensations, such as slime sensations on the gums or on the tongue, excessive mucous secretion, or other bizarre oral sensations. In the Diagnostic and Statistical Manual of Mental Disorders (DSM V), cenesthopathy is categorized as a delusional disorder, somatic type (DDST). However, as suggested by Umezaky Y, this symptom may be better considered as an oral perceptual dysfunction that may be related to an asymmetrical regional cerebral blood flow between the right and left side that in turn may cause an impairment in the descending sensory pathway (Umezaki et al., 2018). Furthermore, a change in the sensory perception of the amount of saliva in the mouth, reported by patients as xerostomia could lead to a confusion of this disease with the oral manifestation of a systemic disease such as Sjogren's syndrome and/or as a sign of an adverse drug reaction (Jacob et al., 2022) and so further delay the proper diagnosis of BMS by clinicians. In addition, the multimorbidity and polypharmacy of older BMS patients may

TABLE 5 Psychological profile, sleep evaluation and cause of disease attributed by the BMS patients.

Psychological profile	Median; IQR
HAM-A	17 [15–20]
HAM-D	17 [14–20]
History of previous mood disorders	**Frequency (%)**
Yes	148 (29.6)
Familiarity of mood disorders	**Frequency (%)**
Yes	16 (3.2)
Sleep evaluation	**Frequency (%)**
Poor sleep (PSQI > 5)	451 (90.2)
Insomnia onset prior to BMS diagnosis	269 (53.8)
	Median; IQR
Sleep duration (in hours)	5 [5–6]
Insomnia onset prior to BMS diagnosis (in years)	4 [3–7]
PSQI	8 [7.75–10]
ESS	7 [5–9]
Cause of disease attributed by the patient	**Frequency (%)**
Dental treatment	46 (9.2)
Stressful life event	124 (24.8)
Not attributed	405 (81)

Abbreviations: BMS, burning mouth syndrome; ESS, Epworth Sleepiness Scale; HAM-A Hamilton Anxiety; HAM-D Hamilton Depression; IQR, interquartile range; PSQI, Pittsburgh Sleep Quality Index.

TABLE 6 Medically unexplained extraoral physical symptoms reported by the 500 BMS patients.

Medically unexplained extraoral physical symptoms	Frequency (%)
Yes	169 (33.8)
No	331 (66.2)
Number of symptoms	**Mean ± SD**
	2.8 ± 1.50
Type	**Frequency (%)**
Irritable bowel syndrome	48 (9.6)
Fibromyalgia	36 (7.2)
Tinnitus	32 (6.4)
Ophthalmodynia	24 (4.8)
Skin burning/itching	23 (4.6)
Vulvodynia	21 (4.2)
Functional dyspepsia	18 (3.6)
Tension Headache	16 (3.2)
Dizziness	10 (2)
Restless legs syndrome	7 (1.4)
Ear itching	5 (1)
Nasal itching/Burning	4 (0.8)
Low Back pain	3 (0.6)
Myofascial pain	3 (0.6)
Anal itching	3 (0.6)
Asthenia	2 (0.4)
Premature Ejaculation	2 (0.4)

Abbreviation: BMS, burning mouth syndrome.

additionally complicate the evaluation of a correct diagnosis. Indeed, in this study, the majority of BMS patients with xerostomia had reported changing and/or replacing many medications, predominantly antihypertensives, with unsuccessful results on their symptomatology, causing additional distress and a worsening of the disease.

Finally, among other additional symptoms, dysgeusia has been found to be strongly correlated to a longer diagnostic delay, further suggesting that a more complex symptomatology may complicate the early diagnosis especially for clinicians with little knowledge of this disease. Indeed, dysgeusia has been defined as a persistent, unpleasant, abnormal, or altered taste sensation, sometimes described as metallic in nature; it has been attributed to various neurologic, nutritional, and metabolic disorders, a large number of medications, and aging. Moreover, dysgeusia, regardless to the etiology, has been strongly correlated with mood disorders. For instance, Deems et al. in their study on 750 patients found that 28.5% of patients with dysgeusia exhibited mild-to-severe depression, while in another Mizoguchi et al. reported a case of dysgeusia successfully treated with sertraline (Deems et al., 1991; Mizoguchi et al., 2012). Nevertheless, there is also evidence that taste disorders in BMS patients may be interpreted as oral phantom sensation resulting by regional oral sensory nerve damage. Indeed, according to the oral inhibition model, all the tasting sensory nerves of the mouth (for instance the chorda tympani, the lingual branch of the trigeminal nerve, the glossopharyngeal nerve, the greater superficial petrosal nerve) can mutually inhibit one another, so that if one nerve is damaged, it leads to the disinhibition of the others. In this respect, the literature suggests that in many cases, idiopathic BMS is an oral pain phantom caused by the loss of chorda tympani function and subsequent trigeminal disinhibition (Snyder & Bartoshuk, 2016).

Another confounding factor causing a late diagnosis may be related to the pattern of the symptomatology. Indeed, in contrast with several other studies (Forssell et al., 2012; Lopez-Jornet et al., 2015; Tu et al., 2019) in the majority of patients (274; 54.8%), the symptoms were present all day, without any improvement while eating (377; 75.4%). This result may explain the worsening of the disease over a lengthy period before the diagnosis and treatment. Interestingly, in this sample, only 46 (9.2%) BMS patients reported the onset of the symptomatology after dental treatment.

In agreement with previous studies (Adamo et al., 2020, 2021; Galli et al., 2017; Schiavone et al., 2012) in this research, the BMS patients suffered from mild anxiety and mild depression with a high prevalence of sleep disturbances (90.2%) in addition to the high level of pain/burning, suggesting that as well as the pain assessment a psychological assessment is mandatory in this group of patients. It is known that pain and mood disorders are closely interconnected in a

TABLE 7 Correlation of diagnostic delay and quantitative predictors in 500 BMS patients.

Demographic characteristics	ρ	*p*-value
Age	0.098	0.028*
Years of education	−0.088	0.050*
BMI	−0.025	0.578
Clinical parameters	ρ	***p*-Value**
NRS	0.002	0.969
SF-MPQ	0.028	0.531
HAM-A	0.019	0.666
HAM-D	0.043	0.338
PSQI	−0.023	0.608
ESS	−0.044	0.331

Note: ρ is Spearman's correlation coefficient. *p*-Value: *Moderately significant $0.01 < p \leq 0.05$.

Abbreviations: BMI, body mass index; BMS, burning mouth syndrome; ESS, Epworth sleepiness scale; HAM-A Hamilton Anxiety; HAM-D Hamilton depression; NRS, numeric rating scale; PSQI, Pittsburgh sleep quality index; SF-MPQ, Short-form McGill Pain Questionnaire.

bidirectional relationship. Indeed, in this context, the several clinical consultations and the diagnostic delay of 29 months may increase the fear of the patients that they have a serious disease, also amplifying the psychological distress. Moreover, the high prevalence of mood disorders may contribute to a high prevalence of UEPS (33.8%) which may further aggravate the disease.

4.1 | Limitations

First, these results may underestimate the delay in the diagnosis of BMS because the recruitment of the participants was undertaken in an Oral Medicine Unit and, therefore, may not represent a true analysis of all Italian patients affected by BMS. Moreover, due to the cross-sectional design of the study, the real onset of anxiety and depression has been not evaluated and, therefore, it is not possible to understand which condition manifested itself first. Further studies are needed to clarify this point.

5 | CONCLUSIONS

The delay in the diagnosis of BMS continues to be very high, on average 29 months, in the South of Italy, suggesting that the knowledge of BMS remains limited and underrecognized among healthcare providers. The multiple consultations, the high rate of misdiagnosis, and the long delay in receiving a BMS diagnosis may contribute to a heavy burden not only on health systems, with an increase in socioeconomic costs, but also on patients, predominantly emotional, with a worsening of the disease and psychological distress, which in turn may negatively affect their quality of life. Therefore, there is an urgent need to introduce educational interventions in all medical

TABLE 8 Dependence analysis of diagnostic delay and qualitative predictors in 500 BMS patients.

	Disease onset median [IQR]	*p*-value
Gender		
Male	12 [12–24]	0.955
Female	12 [12–24]	
Marital status		
Yes	12 [12–24]	0.902
No	12 [12–24]	
Employment		
Yes	12 [12–24]	0.639
No	12 [12–24]	
Menopause		
Yes	12 [12–36]	0.543
No	12 [12–24]	
Smoking		
Yes	12 [12–24]	0.463
No	12 [12–24]	
Alcohol use		
Yes	15 [12–36]	0.270
No	12 [12–24]	
Burning		
Yes	12 [12–24]	–
Intraoral Foreign body sensation		
Yes	12 [12–36]	0.163
No	12 [12–24]	
Xerostomia		
Yes	12 [12–36]	0.488
No	12 [12–24]	
Dysgeusia		
Yes	12 [8–24]	**0.007****
No	12 [12–36]	
Globus		
Yes	12 [12–30]	0.829
No	12 [12–24]	
Subjective change in tongue morphology		
Yes	12 [12–36]	
No	12 [12–24]	0.407
Globus		
Yes	12 [12–30]	0.829
No	12 [12–24]	
Location of pain/burning		
Localized in one or more sites	12 [12–24]	0.570
Diffuse	12 [12–36]	
Worse in the morning		
Yes	12 [6–24]	0.821
No	12 [12–24]	

(Continues)

TABLE 8 (Continued)

	Disease onset median [IQR]	*p*-value
Worse in the afternoon/evening		
Yes	12 [12–24]	0.801
No	12 [12–24]	
Same morning/afternoon/evening		
Yes	12 [12–24]	0.350
No	12 [12–24]	
Continuous		
Yes	12 [12–24]	0.928
No	12 [12–24]	
Intermittent		
Yes	12 [12–24]	0.938
No	12 [12–24]	
Improvement during eating		
Yes	13 [12–24]	0.558
No	12 [12–24]	
Hypertension		
Yes	12 [12–24]	0.582
No	12 [12–24]	
Hypercholesterolemia		
Yes	12 [12–24]	0.738
No	12 [12–24]	
Previous myocardial infarction		
Yes	21 [10.5–24]	0.944
No	12 [12–24]	
Other cardiovascular diseases		
Yes	24 [12–48]	0.071
No	12 [12–24]	
Gastroesophageal reflux disease		
Yes	12 [6–24]	0.054
No	12 [12–24]	
Hypothyroidism		
Yes	12 [12–27]	0.815
No	12 [12–24]	
Fibromyalgia		
Yes	24 [12–36]	0.122
No	12 [12–24]	
Irritable bowel syndrome		
Yes	12 [6–24]	0.287
No	12 [12–24]	
Tinnitus		
Yes	12 [12–36]	0.995
No	12 [12–24]	
Sleep disorder prior to BMS		
Yes	15[12–36]	0.710
No	12[12–24]	
Previous history of psychiatric illness		
Yes	12[12–24]	0.034*
No	12[12–24]	

Note: A significant difference between medians was measured by the Mann–Whitney test. *p*-Value: *Moderately significant $0.01 < p \leq 0.05$. **Strongly significant $p \leq 0.01$.

Abbreviations: BMS, burning mouth syndrome; IQR, interquartile range.

specialties in order to promote an early and appropriate diagnosis, avoiding doctor shopping and improving the prognosis and quality of life of BMS patients. This educational input should be better focused on both additional intraoral and extraoral symptoms, and also on the systemic comorbidities associated with the burning which may complicate the diagnosis. Moreover, in this context, it seems essential both to establish a gold standard assessment for the BMS diagnosis through a validation of diagnostic pathways for patients and to identify specialized orofacial pain centers in order to improve the assessment and the management of this complex disease.

AUTHOR CONTRIBUTIONS

Daniela Adamo and Elena Calabria contributed to the conceptualization of the study, the methodology, the data collection and curation, and the drafting of the paper. Federica Canfora contributed to the methodology, the data collection and curation and to the writing of the paper. Massimo Aria and Luca D'Aniello analyzed the data and contributed to the writing of the manuscript. All the other authors were involved in the data collection and the review of the article. Stefania Leuci and Michele Davide Mignogna were in addition involved in the supervision of all the study.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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