Unexplained Somatic Comorbidities in Patients with Burning Mouth Syndrome: A Controlled Clinical Study

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Aims: *To evaluate the prevalence of unexplained extraoral symptoms in a group of patients with burning mouth syndrome (BMS) and compare the prevalence with that in patients with oral lichen planus (OLP) and age- and gender-matched controls.* ***Methods:*** *The occurrence of extraoral symptoms was analyzed in a group of 124 BMS patients, a group of 112 oral lichen planus (OLP) patients, and a group of 102 healthy patients. Oral symptoms were collected by a specialist in oral medicine and a general dentist, while data concerning unexplained extraoral symptoms were gathered by each specialist ward, ie, ophthalmology, gynecology, otolaryngology, gastroenterology, neurology, cardiology, internal medicine, and dermatology. A Fisher exact test ($\alpha = .05$) and Kruskal–Wallis test ($\alpha = .05$) were performed for statistical analysis.* ***Results:*** *In the BMS group, 98 (96.1%) patients reported unexplained extraoral symptoms, while 4 (3.9%) patients reported only oral symptoms. A painful symptomatology in different bodily regions was reported more frequently by BMS patients (83.3%) than by OLP patients (1.8%) and healthy patients (11.7%) ($P < .0001$). The differences in the overall unexplained extraoral symptoms between BMS (96.1%) and OLP patients (9.3%) ($P < .0001$) and between BMS (96.1%) and healthy patients (15.7%) ($P < .0001$) were statistically significant. The unexplained extraoral symptoms in BMS patients consisted of pain perceived in different bodily areas (odds ratio [OR]: 255; 95% confidence interval [CI]: 58.4–1112), ear-nose-throat symptoms (OR: 399.7; 95% CI: 89.2–1790), neurological symptoms (OR: 393; 95% CI: 23.8–6481), ophthalmological symptoms (OR: 232.3; 95% CI: 14.1–3823), gastrointestinal complaints (OR: 111.2; 95% CI: 42.2–293), skin/gland complaints (OR: 63.5; 95% CI: 3.8–1055), urogenital complaints (OR: 35; 95% CI: 12–101), and cardiopulmonary symptoms (OR: 19; 95% CI: 4.5–82).* ***Conclusion:*** *The great majority of BMS patients presented with several additional unexplained extraoral comorbidities, indicating that various medical disciplines should be involved in the BMS diagnostic process. Furthermore, the results suggest that BMS may be classified as a complex somatoform disorder rather than a neuropathic pain entity.* J OROFAC PAIN 2011;25:131–140

Key words: BMS, burning mouth syndrome, extraoral symptoms, somatic comorbidities

A relatively recent epidemiological study on the presence of medically unexplained symptoms carried out in seven specialities (dental, chest, rheumatology, cardiology, gastroenterology, neurology, and gynecology) showed that about one third of patients (26 out of 71) attending the dental clinic presented with medically unexplained symptoms.[1] Given the high prevalence of

medically unexplained symptoms in dental clinic patients, it is important to establish the prevalence of such symptoms in BMS patients. From the oral medicine point-of-view, the medically unexplained symptoms can be defined as unexplained extraoral symptoms.

BMS or oral dysesthesia covers all forms of burning sensation in the mouth, involving mainly the tongue and lips, followed by the hard palate, alveolar ridges, cheek, and floor of the mouth, which are not attributable to any known organic pathologies and are not supported by clinical findings.[2] BMS patients may sometimes describe oral mucosal pain, without detectable lesions and not related to tooth pain, as a burning sensation, a foreign body sensation such as sand granularity, a decrease in salivation, and itching, which ameliorates during meals. Some patients also report dysgeusia and/or decreased taste sensation.[3–5]

One million individuals in the United States are estimated to be affected by BMS,[6] with an estimated prevalence ranging from 0.7% to 4.6% in the general adult population.[5–7] It usually occurs in the fifth to seventh decade of life[5–8] and is more common in females than in males. About 10% to 40% of women attending centers for menopausal treatment suffer from BMS,[9] which is often associated with the presence of psychiatric disorders, such as anxiety, depression, and somatization.[4,10–12] An earlier study[13] has shown the co-occurrence of chronic orofacial pain and other chronic unexplained syndromes, such as chronic widespread pain, irritable bowel syndrome, and chronic fatigue, which are frequently found in the general population.

Therefore, the authors decided to conduct a controlled clinical study to evaluate the prevalence and association of unexplained extraoral symptoms in BMS patients in an outpatient clinic of a university hospital, including the principal medical specialties and using the same assessment across all settings. They considered that adequate control groups to evaluate the prevalence of oral and extraoral symptoms would consist of one made up of patients affected by organic oral pathology, such as oral lichen planus (OLP), and the second one made up of patients who commonly attended the authors' department for routine dental care. The primary endpoint was to evaluate the prevalence of unexplained extraoral symptoms in a group of patients with BMS and compare the prevalence with that in patients with OLP and age- and gender-matched controls. Only OLP patients were enrolled who had a reticular pattern, ie, white lesions that appear as a network of connecting and overlapping lines, papules, or plaque; did not report any symptoms[14]; and were not stressed by an unremitting oral burning associated with one or more unexplained bodily symptoms with a high rate of health-care seeking.

Materials and Methods

This was a prospective study carried out at the Oral Medicine Unit, Federico II University of Naples, between May 2009 and December 2009 and was designed as a controlled study for evaluating the prevalence of unexplained extraoral symptoms in BMS patients versus two control groups: OLP and healthy patients. The study design and the criteria for inclusion and exclusion were reviewed by a council of senior specialists in the same department of the university.

The three groups of patients were selected at the outpatient clinic during their first visit. At admission, every patient underwent a complete clinical interview and examination. Demographic information, past and present pathologies, oral and extraoral symptoms, and data concerning extraoral and oral symptoms were all recorded in clinical charts.

A dental specialist in oral medicine, with extensive experience with BMS and OLP patients, and a general dentist were responsible for selecting patients and collecting data. Each author saw the same number of patients (randomly assigned), ie, about 16 patients per group, for a total of about 48 patients, and always saw the same patients at each recall.

The patients diagnosed with BMS and OLP at the time of the enrollment were evaluated a second time by the same clinician after a period of 6 months to confirm the diagnosis.

The study population consisted of three samples: *(1)* BMS sample: 124 patients aged 18 or older (91 women, 33 men, mean age 57.4 [SD 11.9]) consecutively referred for the first time for outpatient treatment at the Oral Medicine Unit; *(2)* OLP sample: 112 patients aged 18 or older [80 women, 32 men, mean age 62.4 (SD 9.6)] consecutively admitted to the Oral Medicine Unit for dental care (caries, extraction of teeth, periodontal disease); and *(3)* healthy sample: 102 patients aged 18 or older (60 women, 42 men, mean age 57.2 [SD 16.5]) consecutively consulting the university dental clinic for routine dental care (caries, periodontal disease, tooth extraction). All of the participating patients received written information and gave written informed consent.

The inclusion criteria for BMS patients were: *(1)* both genders aged ≥ 18 years old; *(2)* the presence of chronic pain in the oral mucosa in the absence of hard and soft tissue lesions of any kind; *(3)* pain

lasting more than 6 months, continuous throughout the day, with no paroxysm and not following a unilateral nerve trajectory; and *(4)* absence of any abnormalities at the following laboratory investigations: salivary flow rates, laboratory tests (complete blood cell counts, blood glucose levels, serum iron, transferrin levels, folate levels, serum Vitamin B_{12} levels, immunological panel) and, eventually, detection of candida.[15] The exclusion criteria encompassed patients presenting with organic conditions that could be considered a causative factor, such as diabetes, anemia, contact allergies, psychotic illness or organic brain syndromes, or patients regularly treated with antidepressants, anticonvulsants, or psychotropic drugs. Patients who developed one of the above-mentioned conditions during the study were automatically excluded. In line with the literature, the diagnosis of BMS was established only after all other possible causes had been ruled out.[16]

The inclusion criteria for OLP patients were: *(1)* both genders aged ≥ 18 years old; *(2)* presence of characteristic bilateral clinical signs of mostly symmetrical, reticular/papular patterned lesions (Wickham's striae); *(3)* histological confirmation of clinical diagnosis via incisional biopsy exhibiting the histopathological finding of a well-defined bandlike zone of cellular infiltration confined to the superficial part of the connective tissue, consisting mainly of lymphocytes, a sign of "liquefaction degeneration" in the basal cell layer, and the absence of epithelial dysplasia.[17] The exclusion criteria were the presence of erosive and/or atrophic and/or bullous lesions, and painful symptomatology and/or treatment with antidepressants, anticonvulsants, or psychotropic drugs.

The inclusion criteria for healthy patients required both genders to be ≥ 18 years old, with no detectable oral mucosal lesions or unexplained oral symptoms, no history of psychiatric disorder, and consultation at the department for the first time exclusively for dental diseases (dental caries, periodontal disease). The exclusion criteria encompassed patients with unstable medical conditions or debilitating pathologies, such as cancer, osteonecrosis, and pemphigus, and patients regularly treated with antidepressants, anticonvulsants, or psychotropic drugs.

All patients who reported one or more extraoral symptoms during the first visit were referred to each single specialist area, ie, ophthalmology, gynecology, otolaryngology, gastroenterology, neurology, cardiology, internal medicine, and dermatology, to establish the exact etiology of the symptoms before any treatment was started. Each physician specialist gathered, recorded, and analyzed all extraoral symptoms in their own area and grouped them in either an "attributable to a medical condition/dysfunction" category or a "functional" category. Every patient who refused a speciality consultation after their first visit or reported having a medically-explained symptom was automatically excluded from the study.

All physician specialists made a diagnosis of "functional," based on what is currently reported in the literature, ie, functional or "medically unexplained" symptoms are defined as symptoms for which no appropriate medical diagnosis could be found after a physical examination and adequate laboratory and radiological investigations.[1]

All unexplained extraoral symptoms were collected by every single specialist, following a specific methodology in each single area, eg, the gastroenterologist used ROMA III consensus. Only the unexplained extraoral symptoms that had been present during the past 2 years in the same body region and had caused a significant impairment or required a medical consultation were investigated in the speciality consultation.

Therefore, the symptoms were classified as medically unexplained when a physician specialist reported a diagnosis of "functional" or, alternatively, the diagnosis was delayed because no abnormalities were detected 3 months after the initial appointment.[1] Likewise, in case of diagnostic controversy or symptoms lasting for less than 3 months, it was rated with a different code and excluded from the study analyses, eg, patients with an organic disease in which a clear alteration could be detected in laboratory and/or instrumental tests. All patients from all three groups who presented an extraoral symptom due to medical conditions were excluded from the study.

After receiving a definite diagnosis of BMS and ascertaining the presence or absence of any additional unexplained extraoral symptom by each single specialist area, all patients were treated with topical clonazepam[15] (0.5 mg, equivalent to five drops) as a mouthwash four times daily .

Statistical Analysis

Data concerning the somatic comorbidities for BMS subjects were compared to the OLP and the healthy control group. The prevalence of subjects with unexplained extraoral symptoms was calculated according to clinical symptoms, age, and gender. The association between variables was measured using the odds ratio (OR) and its 95% confidence interval (CI). The Fisher exact test ($\alpha = .05$) and Kruskal–Wallis test ($\alpha = .05$) were used to assess the probability of unexplained extraoral symptoms in patients with BMS versus OLP patients and healthy patients. Statistical analysis was performed using the Statistical Package for Social Sciences, version 16.0 (SPSS, IBM).

Table 1 Patients' Characteristics

Patient group	Patients with UES	Patients without UES	Patients with MES	Total patients	*P*
BMS					
Female	75	2	14	91	
Male	23	2	8	33	
No. of patients	98	4	22	124	
Mean age ± SD	57.2 ± 12.1	58.75 ± 17.7	60.6 ± 8.3	57.4 ± 11.9	
OLP					.0001
Female	8	64	8	80	
Male	4	26	2	32	
No. of patients	12	90	10	112	
Mean age ± SD	59.3 ± 11.8	61.9 ± 9.7	61.4 ± 8.2	62.4 ± 9.6	
Healthy					.0001
Female	10	38	12	60	
Male	6	28	8	42	
No. of patients	16	66	20	102	
Mean age ± SD	57.3 ± 14.4	54.7 ± 15.4	59.7 ± 9.5	57.2 ± 16.5	

MES = medically explained symptoms; UES = unexplained extraoral symptoms.

Results

During the period of the study from May 2009 to December 2009, 159 new BMS patients, 126 OLP patients, and 130 healthy patients attending the oral medicine unit were recruited. A total of 338 (81.6%) responses from patients was obtained. The response rate was 88.1% for BMS patients, 96.4% for OLP, and 78.4% for healthy patients. After clinical examination and laboratory and radiological investigations, 16 (10.1%) BMS and 6 (5.4%) OLP patients were excluded from the study because organic abnormalities were found, while 19 (11.9%) BMS patients and 4 (3.6%) OLP patients did not give permission for the processing of their personal data. All of the remaining 124 (77.9%) BMS patients, 112 (88.9%) OLP patients, and 102 (78.5%) healthy patients gave written consent to participate in the study. Demographic characteristics of the samples are shown in Table 1.

In line with the literature,[18] the oral symptoms in BMS patients were not homogeneous, but patients had a variety of complaints: 67 (54%) suffered from a diffuse oral burning combined with xerostomia, dysgeusia, and itching; 41 (33.1%) had a burning sensation localized only in specific sites of the mouth, frequently with xerostomia and dysgeusia; 16 (12.9%) did not report an oral burning sensation but only unexplained symptoms, such as xerostomia, sialorrhea, or dysgeusia (Table 2). Only four patients (3.2%) in the BMS group presented with an isolated oral mucosal complaint without unexplained extraoral symptoms. Almost all BMS patients (96.1%) had at least one of the 62 unexplained extraoral symptoms, whereas just 10.7% of OLP patients and 15.7% of the healthy patients reported one or two unexplained extraoral symptoms. These percentages (BMS versus OLP versus healthy patients) were statistically significant ($P < .0001$) (Table 1).

In agreement with previous studies[19–22] that have investigated these symptoms and/or syndromes individually, the study confirmed that the majority of unexplained extraoral symptoms increase in the middle-age range (46 to 55 years) (36 patients) and decrease in the younger and older age groups. The difference between the middle age group and second most numerous BMS age-range group (66 to 75 years, n = 25 patients) was significant ($P < .0005$).

One third of BMS patients reported 4 to 6 unexplained extraoral symptoms, one fourth reported 1 to 3 unexplained extraoral symptoms, one fifth reported 7 to 9 symptoms, and another one fifth reported 10 to 18 extraoral symptoms. The unexplained extraoral symptoms allocation is shown in Table 3. BMS patients reported 62 unexplained extraoral symptoms across eight medical specialties while the presence of the same symptoms in the control groups was very low (Table 3).

A painful symptomatology in different bodily regions was reported mainly by BMS patients (83.3%), whereas in OLP and healthy groups, painful sensations in different bodily areas were reported in 1.8% and 11.7%, respectively ($P < .0001$) (Table 3). As far as every single unexplained extraoral symptom

is concerned, a lump in the throat (33.3%) had the highest prevalence followed by tinnitus (28.4%) and ocular burning (25.5%), while skin/glands symptoms were present in 26.5% of BMS patients (Table 3). In all subgroups, females had a significantly higher prevalence of unexplained extraoral symptoms than males.

Among the unexplained extraoral symptoms in the BMS group, otorhinolaryngological (87.9%) and gastrointestinal symptoms (86.3%) had the highest prevalence followed by neurological symptoms (79%), urogenital symptoms (64.5%), ophthalmological symptoms (50.8%), skin/glands symptoms (26.5%), and cardiopulmonary symptoms (25.8%) (Table 4).

The relative frequencies of unexplained extraoral symptoms in relation to the total number of symptoms with their occurrence, along with the 95% CIs, ORs, and Fisher test ($\alpha = .05$), are reported in Tables 4 and 5. These data show that unexplained extraoral symptoms are more likely in BMS patients than in the two other groups, ie, OLP and healthy patients, who were affected by very low rates of unexplained extraoral symptoms. The underlying organic systemic diseases present in each group of patients are included in Table 6. No statistically significant difference was found between BMS versus OLP versus healthy patients for occurrence of systemic diseases ($P > .05$) (Table 6).

Table 2 Prevalence of Oral Symptoms in 124 BMS Patients

Other associated oral symptoms in BMS patients	No. of patients (%)	Total patients (%)
Diffuse oral burning		67 (54)
Diffuse burning + xerostomia	18 (14.5)	
Diffuse burning + dysgeusia + xerostomia	16 (12.9)	
Only diffused oral burning	14 (11.8)	
Diffuse burning + dysgeusia	12 (11.3)	
Diffuse burning + xerostomia + itching	4 (3.2)	
Diffuse burning + itching	3 (2.4)	
Localized oral burning		41 (33.1)
Burning of tongue	7 (5.6)	
Burning of tongue + xerostomia	4 (3.2)	
Burning of tongue + xerostomia + dysgeusia	4 (3.2)	
Burning of tongue and hard palate + dysgeusia	3 (2.4)	
Burning of tongue + dysgeusia	3 (2.4)	
Burning of tongue and cheeks + xerostomia	2 (1.6)	
Burning of lips	2 (1.6)	
Burning of cheeks and tongue + dysgeusia	2 (1.6)	
Burning of tongue and hard palate + xerostomia	2 (1.6)	
Burning of tongue and lips	2 (1.6)	
Burning of tongue and lips + xerostomia	2 (1.6)	
Burning of tongue and hard palate	2 (1.6)	
Burning of hard palate	2 (1.6)	
Burning of tongue and gums	2 (1.6)	
Burning of lips and gums + xerostomia	1 (0.8)	
Burning of tongue + xerostomia + dysgeusia	1 (0.8)	
Other oral symptoms without burning		16 (12.9)
Xerostomia	8 (6.5)	
Dysgeusia	4 (3.2)	
Sialorrhea	4 (3.2)	

Discussion

The present findings strongly indicate the co-occurrence of BMS and some unexplained extraoral symptoms showing that many patients who met the diagnostic criteria for BMS reported unexplained extraoral symptoms in different bodily regions at the same time. A high percentage of BMS patients (96.1%) presented one or multiple extraoral somatic comorbidities associated in different ways (clusters), and their co-occurrence was more likely in the BMS group than in the OLP and in the healthy control groups. The presence of unexplained extraoral symptoms in each single bodily region examined in the study was statistically significant when comparing BMS with OLP and healthy patients. Indeed, in the OLP and healthy groups, only a low percentage of patients reported from one to three unexplained extraoral symptoms and can be considered equivalent. Even though BMS and OLP are two pathologies that are manifested in a peculiar way in the mouth, it is evident that their nature is completely different. OLP physiopathology and clinical signs are well known, but conversely, BMS etiology and pathogenesis still remain a puzzle.

Currently, the presence of a number of symptoms is helpful in the formulation of a diagnosis and aids in defining a disease. Surprisingly, despite an increase in the number of unexplained extraoral symptoms, BMS patients did not report an increase in chances of reaching a biomedical diagnosis.

Table 3 Symptom Allocation in BMS, OLP, and Healthy Individuals

Symptoms/unexplained symptoms	No. symptoms in BMS (%)	No. symptoms in OLP (%)	No. symptoms in healthy (%)	BMS vs OLP	BMS vs healthy	BMS vs OLP vs healthy
Pain				$P < .001$	$P < .001$	$P < .0001$
Tension headache	15 (14.7)	0 (0)	4 (3.9)			
Muscular aches	7 (6.8)	0 (0)	3 (2.9)			
Back aches	23 (22.5)	1 (0.9)	0 (0)			
Pain arms/legs	8 (7.8)	0 (0)	0 (0)			
Abdominal pain	21 (20.5)	0 (0)	3 (2.9)			
Pains in joints	8 (7.8)	1 (0.9)	2 (1.9)			
Chest pain	6 (5.8)	0 (0)	0 (0)			
Headache, other	5 (4.9)	0 (0)	0 (0)			
Pain during sex	4 (3.9)	0 (0)	0 (0)			
Pain in rectum	3 (2.9)	0 (0)	0 (0)			
Pain during urination	2 (1.9)	0 (0)	0 (0)			
Ophthalmological				$P < .05$	$P < .05$	$P < .005$
Ocular burning	26 (25.5)	0 (0)	0 (0)			
Foreign body sensation	18 (17.6)	0 (0)	0 (0)			
Xerophthalmia	16 (15.7)	0 (0)	0 (0)			
Lacrimation	3 (2.9)	0 (0)	0 (0)			
Otorhinolaryngological				$P < .01$	$P < .01$	$P < .0002$
Lump in throat	34 (33.3)	0 (0)	0 (0)			
Tinnitus	29 (28.4)	1 (0.9)	1 (0.9)			
Dizziness	19 (18.6)	1 (0.9)	0 (0)			
Burning	10 (9.8)	0 (0)	1 (0.9)			
Hypoacusia	8 (7.8)	0 (0)	0 (0)			
Dysosmia	5 (4.9)	0 (0)	0 (0)			
Aphonia	2 (1.9)	0 (0)	0 (0)			
Dryness	2 (1.9)	0 (0)	0 (0)			
Gastrointestinal				$P < .001$	$P < .001$	$P < .0001$
Nausea	14 (13.7)	0 (0)	0 (0)			
Feeling bloated	7 (6.9)	3 (2.9)	3 (2.9)			
Bowel hyperactivity	11 (10.8)	3 (2.9)	1 (0.9)			
Burning epigastrium	9 (8.8)	0 (0)	2 (1.9)			
Regurgitation	12 (11.7)	0 (0)	0 (0)			
Bad taste in mouth	39 (38.2)	0 (0)	0 (0)			
Intolerance to foods	4 (3.9)	0 (0)	0 (0)			
Diarrhea	7 (6.9)	0 (0)	0 (0)			
Vomiting	11 (10.8)	0 (0)	0 (0)			
Aerophagia hiccup	3 (2.9)	0 (0)	0 (0)			
Fluid from anus	1 (0.9)	0 (0)	0 (0)			
Cardiopulmonary				$P < .01$	$P < .005$	$P < .006$
Palpitation	15 (14.7)	1 (0.9)	3 (2.9)			
Precordial discomfort	5 (4.9)	0 (0)	3 (2.9)			
Hyperventilation	7 (6.9)	0 (0)	3 (2.9)			
Dyspnea on exercise	4 (3.9)	1 (0.9)	1 (0.9)			
Breathless	11 (10.8)	0 (0)	1 (0.9)			

Table 3 (*continued*)

Symptoms/unexplained symptoms	No. symptoms in BMS (%)	No. symptoms in OLP (%)	No. symptoms in healthy (%)	BMS vs OLP	BMS vs healthy	BMS vs OLP vs healthy
Urogenital				*P* < .01	P < .001	*P* < .0005
Frequent urination	8 (7.8)	0 (0)	0 (0)			
Unusual vaginal discharge	6 (5.9)	0 (0)	0 (0)			
Unpleasant genital sensation	12 (11.8)	0 (0)	0 (0)			
Other urogenital complaints:						
Dryness	15 (14.7)	1 (0.9)	0 (0)			
Burning	14 (13.7)	1 (0.9)	0 (0)			
Itching	10 (9.8)	0 (0)	0 (0)			
Ejaculation dysfunction	5 (4.9)	2 (1.9)	3 (2.9)			
Neurological				*P* < .001	P < .001	*P* < .0001
Numbness/tingling	7 (6.8)	0 (0)	0 (0)			
Loss of memory	2 (1.9)	0 (0)	0 (0)			
Impaired coordination	14 (13.7)	0 (0)	0 (0)			
Localized weakness	23 (22.5)	0 (0)	0 (0)			
Fainting	1 (0.9)	0 (0)	0 (0)			
Loss of pain sensation	8 (6.9)	0 (0)	0 (0)			
Autonomic						
Hot/cold sweating	3 (2.9)	0 (0)	0 (0)			
Trembling/shaking	9 (8.8)	0 (0)	0 (0)			
Butterflies in stomach	7 (6.9)	0 (0)	0 (0)			
Dry mouth	25 (24.5)	0 (0)	0 (0)			
Flushing/blushing	12 (11.8)	0 (0)	0 (0)			
Skin/glands				*P* < .01	*P* < .05	*P* < .003
Excessive sweating	13 (12.7)	0 (0)	1 (0.9)			
Burning/itching	6 (5.9)	0 (0)	0 (0)			
Edema	1 (0.9)	0 (0)	0 (0)			
Blotchy skin	3 (2.9)	0 (0)	0 (0)			
Breast engorgement	4 (3.9)	0 (0)	0 (0)			

Table 4 Occurrence of the Unexplained Extraoral Symptoms in BMS, OPL, and Healthy Patients

	BMS		OLP		Healthy	
Symptoms	Relative frequency	95% CI	Relative frequency	95% CI	Relative frequency	95% CI
Pain	83.3%	73–94%	1.8%	0.8–3%	11.7%	10–13%
Ophthalmological	50.8%	40–61%	0%	0%	0%	0%
Otorhinolaryngological	87.9%	78–98%	1.8%	0.8–3%	1.9%	1–3%
Gastrointestinal	86.3%	76–95%	5.9%	4–6.9%	5.9%	4–7%
Cardiopulmonary	25.8%	16–37%	1.8%	0.8–3%	4.9%	3–6%
Urogenital	64.5%	54–75%	3.6%	3–5%	2.9%	2–4%
Neurological	79%	69–90%	0%	0%	0%	0%
Skin/glands	26.5%	17–38%	0%	0%	0.9%	0–2%

Table 5 OR of Unexplained Extraoral Symptoms Between BMS, OLP, and Healthy Patients

	BMS patients/OLP patients			BMS patients/healthy patients		
Symptoms	OR	95% CI	*P*	OR	95% CI	*P*
Pain	255	58.4–1,112	< .0001	34.7	16.3–74.2	< .0001
Ophthalmological	232.3	14.1–3,823	< .0001	211.7	12.8–3,485	< .0001
Otorhinolaryngological	399.7	89.2–1,790	< .0001	363.3	81–1,629	< .0001
Gastrointestinal	111.2	42.2–293	< .0001	100.7	38.1–265.9	< .0001
Cardiopulmonary	19	4.5–82	< .0001	6.7	2.5–18.1	< .0001
Urogenital	35	12–101	< .0001	72.2	21.3–245.2	< .0001
Neurological	393	23.8–6,481	< .0001	358.2	21.7–5,908	< .0001
Skin/glands	63.5	3.8–1,055	< .0001	28.1	3.7–211	< .0001

Table 6 Underlying Systemic Diseases

	BMS patients (%) n = 124	OLP patients (%) n = 112	Healthy patients (%) n = 102	BMS vs OLP vs healthy
Hypertension	19 (15.3)	12 (10.7)	19 (18.6)	*P* > .05
Hypertensive cardiopathy	13 (10.5)	1 (0.9)	4 (3.9)	
Ischemic cardiopathy	8 (6.5)	0 (0)	4 (3.9)	
Heart valve disease	4 (3.2)	0 (0)	3 (2.9)	
COPD	3 (2.4)	2 (1.8)	6 (5.8)	
Allergic asthma	1 (0.8)	0 (0)	4 (3.9)	
Hypothyroidism	11 (8.9)	8 (7.1)	5 (4.9)	
Osteoporosis	5 (4)	1 (0.9)	3 (2.9)	
Osteoarthritis	9 (7.3)	0 (0)	3 (2.9)	
Gastroduodenitis	1 (1.9)	0 (0)	0 (0)	
Gastritis	2 (1.3)	1 (0.9)	2 (1.9)	
SLE	1 (0.8)	0 (0)	0 (0)	
GERD	1 (0.8)	1 (0.9)	3 (2.9)	
Epilepsy	0 (0)	0 (0)	1 (0.9)	

COPD = chronic obstructive pulmonary disease; SLE = systemic lupus erythematosus; GERD = gastroesophageal reflux disorder.

A very low percentage of BMS patients (3.2%) reported an isolated oral complaint without unexplained extraoral symptoms. It is also evident that extraoral symptoms exist on a continuum of severity, ranging from patients with single, transient, and relatively mild symptoms to those with large numbers of chronic and extremely debilitating complaints.

As far as gender is concerned, females were more likely to report unexplained extraoral symptoms than males (female to male ratio, 3:1), and, in the literature, there are reported associated factors, such as psychiatric morbidity and sleep problems.[4,5,9,10,23–26] The association of BMS and unexplained ophthalmologic, otorhinolaryngological, neurologic, cardiologic, gastrointestinal, and dermatological symptoms was not previously reported in the literature. As far as irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome are concerned, their association with tempomandibular disorders (TMD)[27] and with chronic orofacial pain is well-known,[13] but not specifically with BMS. The present study has confirmed the association of BMS and vulvodynia in a subgroup of patients that has been described in a previous study.[28] Several lines of evidence reported multilocalized dynias mainly located in the vulva,[29] penis, and scrotum.[30] Thus, BMS may involve widespread parts of the body while control group patients have only sporadic involvement in the same region of the body.

As far as the etiology is concerned, it appears that BMS shares a double etiology: indeed, some investigations have hypothesized that it might be a manifestation of somatization,[4,10–12] while others have concluded that it might be a neuropathic pain rather than a somatoform chronic pain syndrome.[18,31–33] Likewise, this debate on a double nature of chronic pain has already been disputed in many chronic disorders, such as fibromyalgia, chronic fatigue, and itching.[34] Thus, the question of whether BMS should be considered a neuropathic disease or a somatoform pain disorder is trifling, as psychological disturbances and physical symptoms that affect BMS patients are likely to be considered expressions of the same pathological central nervous system (CNS) abnormalities.[35] There is a growing body of evidence, based on molecular and imaging techniques, that patients with unexplained chronic symptoms, traditionally classified as functional, psychosomatic, or medically unexplained, present with abnormalities of the central and/or peripheral nervous system. Therefore, psychological conditions and physical symptoms are likely to be considered expressions of the same pathological CNS abnormalities and the discussion of whether or not BMS should be considered a neuropathic disease or a somatoform pain disorder is losing its relevance.[35]

The pathophysiology of BMS is still unclear: some studies have suggested a dysfunction of the nigrostriatal dopaminergic pathway,[18,25,36] while another study has suggested an alteration of the taste system.[33] A further study on a small group of patients with BMS found a lower density of epithelial nerve fibers and axonal degeneration on biopsy in the anterior two thirds of the tongue, suggesting that BMS is caused by a trigeminal small fiber sensory neuropathy.[31] Neurophysiologic and imaging studies have suggested a dysfunction of the nigrostriatal and mesolimbic dopamine pathways in BMS patients similar to that found in patients with anxiety and other psychological distress. These studies revealed that a net brain hypoactivity may cause a loss of function in descending inhibitory serotoninergic and noradrenergic pathways and can cause, or at least contribute to, chronic pain.[32]

It cannot be concluded from the present findings that BMS is a discrete illness. A recent paper[37] included BMS in the dental functional somatic syndrome, along with TMD and atypical facial pain, since these diseases overlap with functional somatic syndromes in other organs, such as fibromyalgia and chronic fatigue syndrome. The present findings are in line with this research trend, although further studies, especially randomized controlled trials with long-term follow-up, are required to confirm these data. Nonetheless, the findings have some clinical implications. Indeed, until now, these coexisting symptoms have been ignored by oral health practitioners who focused only on areas of competence and usually interpreted BMS as an isolated manifestation. A more thorough clinical evaluation may reveal these coexisting symptoms for which BMS patients are not seeking help. The present data are consistent with the hypothesis that BMS is a complex, somatoform "syndrome" that might affect different targeted dynia areas. BMS patients with one or more somatic comorbidities might represent a separate BMS subgroup, which could be included in the category of "undifferentiated somatoform disorders."[38]

A multidisciplinary approach, along with a common language and an interchange of knowledge among all branches of medicine, is required for the management of these patients. Nonetheless, despite a multidisciplinary approach, unexplained extraoral symptoms-related management in BMS patients still remains a big challenge, as it is very complex for each of these clinical manifestations. Thus, it appears that there is a real need to have many medical disciplines involved within the BMS diagnostic process. All these disciplines need to have an awareness of BMS as a diagnostic entity in order to set an appropriate consultation among them.

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