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Causative or precipitating aspects of burning mouth syndrome: a case–control study

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BACKGROUND: On causative or precipitating causes of burning mouth syndrome (BMS), there is a lack of consensus. In this prospective case–control study, we compared clinical features and laboratory aspects to evaluate the association of the proposed causative/precipitating factors of BMS.

METHODS: A total of 61 BMS patients and 54 control subjects underwent several evaluations: rest and stimulated salivary flow rates measurements, laboratory tests, isolation of *Candida* species, assessment of parafunctional activities, detection of anxiety and depression by means of the Hospital Anxiety and Depression Scale. Odds ratio and 95% confidence interval were calculated to compare the variables.

RESULTS: No statistically significant differences were found with regard to the tested variables except for anxiety and depression.

CONCLUSIONS: The results of this study seem not to support a role for the usually reported causative or precipitating factors of BMS and efforts should be addressed towards different aetiologies including possible neuropathic mechanisms of BMS.

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Introduction

The complaint of a localized or widespread burning sensation in the mouth can be a symptom of other disease or a syndrome in its own right of unknown aetiology. In this case, if no underlying oral or systemic causes are identified and no oral signs are found the term *burning mouth syndrome* (BMS) should be used (1, 2). The International Association for the Study of Pain defines glossodynia and sore mouth (BMS) as a burning pain in the tongue or other oral mucosa but it does not draw the distinction between burning as a symptom and burning as a part of a syndrome (3). The International Headache Society (4) defines BMS as an intraoral burning sensation for which no medical or dental cause can be found.

The word syndrome seems to be justified because many of the patients will also have other subjective symptoms (i.e. xerostomia, oral paraesthesia and altered taste) or other associated symptoms (i.e. headache, insomnia) (5). Furthermore, some of the patients show anxiety, depression, cancerphobia and personality disorders (2). Recently, several papers have suggested peripheral alterations in the function of the sensory trigeminal system with the presence of abnormal reflex (i.e. blink reflex) (6–10) and/or a disturbed autonomous innervation of oral cavity (11–13) as noteworthy possible mechanisms.

Despite these aspects, which seem to be accepted by many authors, there is a lack of consensus on causative or precipitating causes of BMS. As a consequence, medical literature claims that efforts should be directed at defining BMS aetiology and pathogenesis and at suggesting effective forms of treatment for patients suffering from this chronic condition (1). Historically, several causative or precipitating aspects of BMS have been suggested, including systemic factors (i.e. nutritional deficiencies or menopause) (14, 15) local factors (i.e. decrease in salivary output, presence of *Candida* species, parafunctional habits) (16–18), psychological factors (19–21). However, little objective data substantiate these aspects and risk factors and risk patients have not been identified.

The aim of this prospective case–control study was to compare clinical features and laboratory aspects of subjects suffering from BMS and of control subjects to evaluate the association, if one, of the proposed causative or precipitating factors of BMS.

Patients and methods

Protocol and consent forms of this prospective case–control study were evaluated and approved by the University of Milan Ethics Committee. Subjects referred

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to the Unit of Oral Pathology and Medicine during the period from January 2000 to December 2003 were considered for the study.

A total of 67 patients who reported a history of oral complaint (burning and/or pain) for at least 6 months (22) and who demonstrated absence of oral signs and of underlying causes (1, 2) received a clinical diagnosis of BMS. As six patients refused to enter the study, only 61 were considered for the study.

A total of 54 patients, matched for age and gender, and with a histopathological diagnosis of oral traumatic fibroma (39 subjects), oral mucosal benign pigmentations (eight subjects) and oral leukoplakia (seven subjects) served as controls.

Demographic and medical questionnaires with information related to the presence of current systemic diseases and on-going medications were administered to patients suffering from BMS and patients of the control group. In addition, the two groups underwent several evaluations. They included laboratory tests (complete blood cell counts, blood glucose levels, serum iron and trasferrin levels, serum vitamin B_{12} and folic acid levels) (Table 1), and isolation of *Candida* species from oral mucosal scrapes (Saboraud's medium incubated at 37°C for 48 h). The flow rates of unstimulated and stimulated whole saliva were determined using the draining or spit method (23). Whole unstimulated saliva was collected for 5 min and saliva stimulated by chewing a standardized piece of paraffin was collected for 3 min into a graded glass tube. Parafunctional activities were also clinically evaluated (24). In particular, subjects were asked if they clenched or bruxed their teeth, if they awaken with an awareness of their jaw or have sore muscles from 'biting' their teeth, if they have habits as lip sucking or licking and mouth breath. Moreover, the evaluation of the tooth or denture excessive wear was performed with an accurate examination to assess minimal wear on the tip of the cusp or occluding planes, or on the incisal edges, flattening of cusps or grooves, partial or total loss of contour or dentin exposure when identifiable.

Furthermore, for the purpose of the study and to detect anxiety and depression, both in BMS patients and in control group patients, the Hospital Anxiety and Depression (HAD) Scale was applied. The HAD Scale is a self-assessment scale that was designed to detect mood disorders in non-psychiatric populations (25, 26) and has been proposed in the evaluation of BMS patients in previous studies (27). It is divided into two subscales relating to anxiety and depression and each subscale contains seven items pertaining to mood disorder (28). In analysing the HAD scales, scores of greater than 10 indicate the probable presence of anxiety or depression, scores of 7 or less no significant anxiety or depression, and scores of 8–10 are of borderline significance.

Table 1 Table of reference value (normal ranges) for the laboratory tests performed in the present study (39)

	SI units	*Conventional units*
Ferritin, serum		
M	15–400 μg/l	15–400 ng/ml
F	10–200 μg/l	10–200 ng/ml
Iron, serum	5.4–28.7 μmol/l	30–160 μg/dl
Glucose (fasting), plasma	4.2–6.4 mmol/l	75–115 mg/dl
Vitamin B12, serum		
Normal	185 pmol/l	>250 pg/ml
Borderline	92–185 pmol/l	125–250 pg/ml
Deficient	<92 pmol/l	<125 pg/ml
Folic acid, serum		
Normal	7.0–39.7 nmol/l	3.1–17.5 ng/ml
Borderline	5.0–6.8 nmol/l	2.2–3.0 ng/ml
Deficient	<5.0 nmol/l	<2.2 ng/ml

In BMS patients, pain history and characteristics related to its onset were also recorded. Burning sensation intensity was collected with a visual analogue scale (VAS) (29) from 0 to 10 (no pain–extreme pain). Attention was also paid to the BMS patients' descriptions of their life histories (i.e. stressful life events) and their mouth disease to consider cancerphobic or hypochodriacal tendencies, self-reported anxiety or depression. In particular, cancerphobia, anxiety and depression were discussed with the patient during the first visit using close questions (with binomial answer yes/no), as 'Are you afraid of having cancer in the mouth?', 'Do you feel depressed or anxious?'.

No patient was lost at the follow-up visits or dropped out the study even though some laboratory/clinical data were not available in some patients.

Data were processed and analysed using Excel 2000. As all outcomes were binomial or were transformed in binomial values, odds ratio (OR) and 95% confidence interval (CI) were calculated to compare the variables between the BMS group and the control group. Moreover, the between-group differences in age, demographic and medical aspects were statistically evaluated by the Student's *t*-test.

Results

The study group (BMS) was composed of 57 women (median age, 62.7 years, SD 7.1) and four men (median age, 62 years, SD 2.1). All patients had a history of oral complaint for more than 6 months (average: 25.0 ± 15.7 months; range: 6–58 months). Among BMS patients a similar pain pattern was observed and oral symptoms usually began by early afternoon (65% of patients) and maximum discomfort was reached by evening (80% of patients). Burning sensation, referred by 97% of the patients, was associated with other symptoms. Frequently, patients complained of dry mouth (36%), pricking and/or tingling sensations (32%), altered taste perception or persistent metallic/bitter taste (16%). In 77% of BMS subjects, the oral symptoms occurred at more than one oral site – the tongue (97%), the mucosal surface of the lower lip (60%) and the anterior hard palate (36%) being the most frequently affected. On the VAS, the mean score of the pain reported by patients was 7.0 (max 10, min 4.1, SD 1.4, SEM 0.18).

The control group was composed of 49 women (median age, 62.3 years, SD 7.1) and five men (median age, 51.3 years, SD 3.0).

Table 2 Laboratory variables with statistical differences between BMS and control groups. (NS, not statistically significant)

	BMS patients		*Control subjects*		
	Normal value	*Abnormal value*	*Normal value*	*Abnormal value*	*OR (95% CI)*
Glucose (fasting), plasma	45/53 (85%)	8/53 (15%)	47/51 (92%)	4/51 (8%)	2.089 (0.620–6.980), NS
Iron, serum	46/54 (85%)	8/54 (15%)	44/50 (88%)	6/50 (12%)	1.275 (0.425–3.817), NS
Ferritin, serum	50/55 (91%)	5/55 (9%)	44/48 (48%)	4/48 (85%)	1.100 (0.299–4.034), NS
Vitamin B12, serum	49/55 (89%)	6/55 (11%)	46/49 (94%)	3/49 (6%)	1.878 (0.481–7.248), NS
Folic acid, serum	49/56 (87.5%)	7/56 (12.5%)	46/50 (92%)	4/50 (8%)	1.643 (0.478–5.608), NS
RFR (resting flow rate)	47/54 (87%)	7/54 (13%)	46/50 (92%)	4/50 (8%)	1.713 (0.497–5.855), NS
SFR (stimulated flow rate	48/54 (89%)	6/54 (11%)	46/50 (92%)	4/50 (8%)	1.438 (0.406–5.061), NS
Candida	Positive smears 14/53 (26.5%)	Negative smears 39/53 (73.5%)	Positive smears 12/46 (26%)	Negative smears 34/46 (74%)	1.017 (0.420–2.463), NS

The difference between the median age of the two groups (BMS patient 62.7 years versus control subjects 61.3 years) was not statistically significant ($P > 0.05$).

Demographic and medical aspects
Differences in demographic aspects were recorded between groups regarding employment. A greater number of control subjects were employed (control group: 23 subjects employed, 13 retired, 18 housewives; BMS group: five subjects employed, 14 retired, 42 housewives). No significant differences were observed in the education level. Furthermore, no differences were found in the prevalence of medical conditions sometimes linked to BMS (i.e. diabetes, connective diseases for a possible iatrogenic immunodeficiency that make the patients more prone to mucosal infections or gastrointestinal disorders).

Salivary flow rate
Data were not available in seven BMS patients and in four control group subjects. No significant differences were detected in the assumption of xerogenic drugs between case and control subjects. Despite the fact that 36% of BMS patients reported xerostomia, a lower number of them showed a reduction both in resting flow rate (RFR <0.1 ml/min) and in stimulated flow rate (SFR <0.5 ml/min) (30). No significant differences were found between BMS and control subjects in salivary flow rates (Table 2).

Systemic deficiencies
The haematological examination revealed deficiency problems in only a few of the BMS patients. In particular, 15% of BMS patients revealed abnormally high glucose levels versus near 8% of the control group patients. Among BMS patients, nearly 15% were possibly iron deficient and nearly the same findings (12%) were detected in the control group. In the BMS group, folic acid and vitamin B12 deficiencies were present in 11–12.5% of the patients, whereas in the control group folic acid and vitamin B12 deficiencies were present in 6–8% of the subjects. No significant differences were found between BMS and control subjects regarding glucose, iron, ferritin, folic acid and vitamin B12 (Table 2).

Candida
Data were not available in eight BMS patients and in eight control group subjects. No signs of clinical candidiasis were observed in BMS patients nor in control group subjects. Smear for *Candida* was positive in 26.5% of BMS patients and the same percentage was detected in control group subjects. No significant differences were found between BMS and control subjects (Table 2).

Menopausal state
Data were not available for four BMS women and five control group women. No significant differences were found between the BMS and control group women in the prevalence of oestrogen replacement therapy taken after menopause (BMS, 12%; control group 10%) (Table 3).

Parafunctional habits
Data were not available in 12 BMS patients and in 11 control group subjects. Parafunctional activities as lip

Table 3 Clinical variables with statistical differences between BMS and control groups

	BMS patients		*Control subjects*		
	Presence	*Absence*	*Presence*	*Absence*	*OR (95% CI)*
Parafunctional habits	10/49 (20.5%)	39/49 (79.5%)	9/43 (21%)	34/43 (79%)	0.969 (0.360–2.604), NS
Anxiety (as self-reported)	47/51 (92%)	4/51 (8%)	21/46 (45.5%)	25/46 (54.5%)	13.988 (4.472–43.189)*
Depression (as self-reported)	32/51 (63%)	19/51 (37%)	8/46 (17%)	38/46 (83%)	8.0 (3.129–20.379)*
Cancerphobia (as self-reported)	23/51 (45%)	28/51 (55%)	12/46 (26%)	34/46 (74%)	2.237 (0.994–5.438), NS
Menopausal state	51/53 women (96%)	2/53 women (4%)	41/44 women (93%)	3/44 women (7%)	1.866 (0.353–9.778), NS
Hormone replacement therapy	6/51 menopausal women (12%)	45/51 menopausal women (88%)	4/41 menopausal women (10%)	37/41 menopausal women (90%)	1.233 (0.345–4.385), NS

*Statistically significant. NS, not statistically significant.

Table 4 HAD Scale results in BMS and control groups

	BMS patients		*Control subjects*		
	Probably presence	*Probably absence + borderline*	*Probably presence*	*Probably absence + borderline*	*OR (95% CI)*
Anxiety (HAD Scale)	28/53 (53%)	25/53 (47%)	10/48 (21%)	38/48 (79%)	4.256 (1.780–10.148)*
Depression (HAD Scale)	23/53 (43%)	30/53 (57%)	8/48 (16%)	40/48 (84%)	3.833 (1.528–9.572)*

*Statistically significant.

sucking or licking, occlusal or denture excessive wear, mouth breathing were observed in an equal percentage of BMS patients and control group patients (20%) (Table 3).

HAD Scale

Data were not available in eight BMS patients and in six control group subjects. Anxiety scores were significantly higher in BMS patients (probably because of the presence of anxiety in 53% , with borderline scores in 32%) compared with the control group (probably because of the presence of anxiety in 21%, with borderline scores in 16.5%). Also depression scores were significantly higher in BMS patients (probably because of the presence of depression in 43%, with borderline scores in 23%) compared with the control group (probably because of the presence of depression in 16.5%, with borderline scores in 16.5%).

Significant differences were found between BMS and control subjects regarding self-reported descriptions of anxiety and depression. No significant differences were found between BMS and control subjects regarding cancerphobia (Table 4).

Discussion

Burning mouth syndrome remains a poorly understood disease in oral medicine even though new evidence for a possible neuropathic pathogenesis is emerging (6–13). The aetiology of BMS has generated considerable debate in the medical literature and several factors and different concepts have been proposed (22). Probably, the most relevant aspect is whether BMS should be considered either as a 'distinctive entity' or as a 'symptom disruption', as reported in a recent review (31). Following the latter hypothesis, research has been addressed to the identification of causative or precipitating factors in BMS. Unfortunately, most of the studies investigating local or systemic aspects were not methodologically sound and failed to support any aetiopathogenetic hypothesis.

The aim of this prospective case–control study was to compare clinical features and laboratory aspects of subjects suffering from BMS and of control subjects to evaluate a possible association of the proposed causative or precipitating factors of BMS. Our control group was selected among patients with oral conditions not related to the variables studied. In fact we considered this group the best control group available, being the most representative of the population at risk of becoming cases, defined by Schulz and Grimes as 'these individuals who would have been selected as cases had they developed the disease' (32).

Grushka in 1987 (33) considered 72 BMS patients and 43 volunteers who served as age- and sex-matched controls. The haematological values for the BMS patients were compared with normal values characteristic of the general populations and some aspects were detected with a questionnaire. The study revealed no significant differences in medical conditions, in the menopausal state and in the prevalence of oestrogen replacement therapy, in *Candida* smears, in the nutritional status (i.e. iron or folate deficiency). In comparison with control subjects, the BMS patients reported a significantly higher prevalence of dry mouth (subjective report). The author concluded that the study provided little evidence for considering the investigated factors as important causative agents in BMS. Browning et al. in 1987 (34) considered 25 BMS patients and 25 patients with chronic painful oral conditions. No differences were detected between BMS patients and control group regarding serum ferritin, vitamin B12, folate and glucose levels. The results of this controlled study show that a significantly higher proportion of BMS patients had a psychiatric disorder (mixed anxiety and depressive symptoms) when compared with the control group (44% versus 16%). Maresky et al. in 1993 (35) detected only three variables (self-medication, xerostomia and other salivary disturbances) as significantly different between 85 BMS patients and 156 patients with oral conditions. Furthermore, a statistically significant association was found only between BMS and anaemic women. In 2001, Vucicevic-Boras et al. (36) studied the serum levels of iron, vitamin B12, folic acid, calcium and magnesium in 41 patients suffering from BMS and in 35 matched controls. Only statistically significant lowered vitamin B12 levels were found in patients with BMS and the authors concluded that serum deficiencies of iron, folic acid, calcium and magnesium are not aetiological factors in BMS. Recently, Nagler and Hershkovich (37) performed salivary analysis in subjects with oral sensory complaints including BMS. In this study, the mean salivary flow rate values (spit method) in the BMS group (82 subjects) were lower than that of control group (84 subjects) although the difference was not statistically significant.

Thus, besides the described paper (33–37), no other evaluations has ever investigated in the same group of subjects with all the variables considered in this controlled clinical evaluation.

The analysis of the results indicate no differences in the investigated variables in BMS patients and controls except for anxiety and depression, as revealed by HAD Scale. The HAD Scale has proved to be a reliable and valid tool for identifying patients with emotional disorders who could probably benefit from a more precise psychiatric evaluation (25). Emotional distress, mood complaint or even psychiatric disorders are often described in patients suffering from BMS with anxiety and depression as the most important ones (19–21). Nevertheless, it is necessary to emphasize that there is an increasing controversy as to whether depression and anxiety are primary or secondary events. It is noteworthy that prolonged stress such as chronic pain conditions as found in BMS patients may affect and alter the subject's psychological profile. As a consequence, authors' opinion is that evidence of a causal relationship between BMS and psychogenic factors is difficult to prove. Benefits from psychological treatment (i.e. cognitive therapy) (38) in BMS patients are probably related to a better ability to cope with their suffering and emotional distress.

Our opinion is that, considering the results of this study and the existing literature, the clinical and laboratory aspects investigated might no longer be considered as causative or precipitating factors of BMS. During the diagnostic process these variables could be merely evaluated to exclude dental or medical cause of an oral burning sensation and to differentiate patients suffering from idiopathic BMS. As a consequence, efforts should be addressed towards different pathogenesis including possible neuropathic mechanisms of BMS.

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