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Research Submission

Anxiety, Depression, and Pain in Burning Mouth Syndrome: First Chicken or Egg?

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Background.—Burning mouth syndrome (BMS) is an idiopathic and chronic pain condition for which patients may experience high levels of pain, anxiety, and depression. So far, it has not yet been well investigated whether specific psychiatric features (anxious traits, personality disorder, or somatization) may play a role in the BMS pathogenesis or whether some BMS symptoms, or BMS itself, may cause secondary psychiatric symptoms.

Objective.—The aim of this study was to evaluate the relationship between pain, depression, and anxiety in BMS and healthy patients in order to hypothesize a possible underlying pathogenetic model.

Methods.—Fifty-three patients with BMS and 51 healthy volunteers matched for sex and age were enrolled. All patients underwent a physical examination, laboratory screening tests, and psychiatric assessment with the following instruments: Visual Analog Scale, the Hamilton Rating Scale for Depression, the State-Trait Anxiety Inventory Form Y 1-2 (STAI Y1-Y2), and the Symptom Checklist-90-Revised (SCL-90-R).

Results.—BMS patients and healthy volunteers showed a statistically significant difference in psychiatric features: Regression analysis showed that pain is affected by depression ($R = 0.373$; R^2 corrected = 0.123; $F = 8.563$; $P < .005$), and depression is affected by anxiety ($R = 0.512$; R^2 corrected = 0.248; $F = 18.519$; $P < .001$). BMS patients have statistically significant higher scores of anxiety (STAI Y1, $P = .026$ and STAI Y2, $P = .046$) and depression ($P < .001$), and higher SCL-90-R scores on somatization ($P = .036$) and hostility dimensions ($P = .028$) than the control group.

Conclusions.—We may hypothesize that anxiety could determine a secondary demoralization in BMS patients (depression) and depressive symptoms could contribute to pain, accordingly. Therefore, pain could be a somatic feature of depression. Our findings provide an example of a possible pathogenetic model for BMS.

Key words: anxiety, burning mouth syndrome, depression, hostility, pain, somatization

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Burning mouth syndrome (BMS) is an idiopathic and chronic pain condition that affects more than 1 million individuals in the United States alone.[1] The International Association for the Study of Pain and the International Headache Society define it as a "distinctive nosological entity," including all forms of burning sensation in the mouth and complaints described as stinging sensation or pain, in the absence of specific oral lesions and without alterations in blood tests and/or instrument findings.[2] The frequency in the Italian population is significant, as it is estimated that approximately 3.7%[3] of individuals in their fifth to seventh decade of life are affected by BMS. In general, the condition mostly affects women, with a relation of approximately 3:1; this gender difference could be probably explained by biological, psychological, and/or sociocultural factors.[4]

In almost all patients, BMS is characterized by sensory symptoms (burning, pain, foreign body sensation such as sand granularity, decrease of salivation, and itching) involving mostly the tip and the anterior two-thirds of the tongue. However, many other oral mucosa sites may be involved, such as the hard palate, lips and alveolar ridges, buccal mucosa, and floor of the mouth.[5] Pain can be particularly intense, but has a typically different quality than that occurring, for example, in a tooth. It tends to persist for at least 4-6 months, to be constant and bilateral, and to be relieved with food consumption. In addition, some patients may even report dysgeusia, and/or hyposmia and/or dysosmia.[6]

Therefore, BMS is difficult to describe and summarize in easily and objectively assessable symptoms or symptoms cluster.[7,8]

The pathogenesis of BMS remains poorly understood, although both physiological and psychological factors have been hypothesized to be involved. Several studies have shown a high prevalence of psychiatric symptoms and/or mental disorders in BMS. Indeed, Rojo et al[9] showed that 51% of patients with BMS had a diagnosis of at least another psychiatric illness (Diagnostic and Statistical Manual of Mental Disorders [DSM]-III-R), and Maina et al[10] demonstrated that the majority of BMS patients (71.6%) had a variety of other axis I psychiatric disorders, as well. In addition, Jerlang has suggested that somatic complaints due to unfavorable life experiences associated with chronic pain may influence both individual personality and mood changes.[11] Many BMS patients, in fact, report one or more adverse life events in their clinical/social history, such as difficult infancy, inadequate parenting, poor adaptation to school and work, family or marital strife, and financial problems.[12,13]

However, psychological problems are more common in patients with chronic pain and may be the result of pain rather than its cause.[14] They seem to be independent from symptom intensity, but appear to be mostly related to prolonged period of pain and a long history of unsuccessful treatment.[4,14] In addition, it has been demonstrated that BMS patients may experience higher levels of pain, anxiety, and depression, especially when oral cancer phobia occurs.[11,15] Based on the current data present in the literature, it is difficult to establish whether specific psychiatric features (anxious traits, personality disorder, or somatization) may play a role in the pathogenesis of BMS or determine whether some BMS symptoms, or whether BMS itself, like other chronic pain disorders, may lead to secondary psychiatric symptoms.[15]

The aim of this clinical study was to evaluate the relationship between pain, anxiety, and depression in BMS and control groups in order to hypothesize a possible underlying pathogenetic model, and the prevalence of anxiety and depression in both groups.

METHODS

Study Design.—This was a cross-sectional prospective controlled clinical study carried out from January 2008 to December 2009 at the Department of Neuroscience and the Oral Medicine Unit, Department of Odontostomatological and Maxillofacial Science, Federico II University of Naples.

All patients received written information and provided their written informed consent for the management of personal data before participating into the study. This study was approved by the local Ethical Committee and conducted according to the Helsinki Declaration.

Study Population.—The inclusion criteria for BMS patients were as follows: (1) both genders aged 18 or older; (2) presence of chronic pain in the oral mucosa in the absence of hard and soft tissue lesions of any

kind; and (3) pain lasting more than 6 months, continuous throughout the day, with no paroxysm and not following a unilateral nerve trajectory. Conversely, the exclusion criteria encompassed the following: (1) every organic conditions that could be considered a causative factor, such as diabetes, anemia, thyroid disease, hyposcialia related to systemic disorders, such as Sjögren's syndrome, contact allergies, psychotic illness, organic brain syndrome, or neurological disease; (2) abnormalities at the following laboratory investigations: salivary flow rates, laboratory tests, and eventually detection of candida; (3) actual substance use or abuse in the past 12 months before enrollment; and (4) use of antidepressants or benzodiazepines in the month prior to enrollment. 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.

The inclusion criteria for healthy patients were as follows: (1) both genders aged 18 or older; and (2) consultation at the department for the first time exclusively for dental disease (dental caries, periodontal disease). Conversely, the exclusion criteria encompassed the following: (1) oral mucosal lesions; (2) history of psychiatric disorder; (3) patients with unstable medical conditions or debilitating pathologies, such as cancer, osteonecrosis, pemphigus vulgaris; and (4) patients regularly treated with antidepressants, anticonvulsants, and/or psychotropic drugs.

BMS patients were selected consecutively from those ones consulting the Oral Medicine Unit of the Federico II University of Naples, whereas the control group was selected from patients attending different departments (ie, periodontology, prosthesis, restorative, orthodontics, endodontics, oral surgery) of the dental clinic of the same university for routine dental care. Both groups were enrolled during their first visit based on the inclusion/exclusion criteria. The control group was matched for sex, age, and educational level.

Psychiatric Evaluation Protocol.—Three oral medicine specialists (D.A., A.P., G.F.) were responsible for selecting BMS patients and healthy individuals as a control group, and for collecting all demographic and medical data of both groups. After screening, BMS patients and the control group were evaluated by a staff of 4 psychiatrists (V.S., M.R., F.K., M.P.) and one psychologist (G.V.) of the Department of Neuroscience of the same university hospital.

In order to evaluate the prevalence and association of psychiatric features (anxiety, depression) and pain in BMS patients versus a control group of healthy individuals, upon admission, every patient of both groups underwent a medical anamnesis (including history, clinical features, and treatment), a general medical examination, and an intra- and extraoral examination, followed by a psychiatric evaluation battery scale, including the Hamilton Rating Scale for Depression (HAM-D),[16,17] the State-Trait Anxiety Inventory Form Y 1-2 (STAI Y1-Y2),[18,19] the Symptom Checklist-90-Revised (SCL-90-R),[20] and the visual analog scale (VAS), to measure pain discomfort. This last scale ranged from 0 to 10 (0 = no discomfort and 10 = worst imaginable discomfort).

All these scales were reviewed for completeness before collection and were administrated in the standardized Italian versions.[21] Reliability of agreement among psychiatrists has been evaluated by Fleiss' kappa.

Statistical Analysis.—The reliability of agreement among psychiatrists was measured using Fleiss' kappa coefficient. One-way analysis of variance (ANOVA) for independent measures and chi-square analysis were used to compare demographic characteristics of BMS patients versus healthy controls. One-way ANOVA for independent measures was calculated for each scores obtained by the 2 groups. Pearson's correlation coefficients were used to verify relations among the psychiatric variables. Stepwise multiple regression analysis was run to examine interactions among variables.

RESULTS

Patients' Characteristics.—The study population consisted of 53 BMS patients (37 [69.8%] females and 16 [30.2%] males) with a mean age of 55.26 years (standard deviation [SD]: 11.50), and 51 healthy volunteers as a control group (34 [66.7%] females and 17 [33.3%] males) with a mean age of 54.02 years (SD: 13.28).

Table 1.—Demographic Characteristics of 53 BMS Patients and 51 Healthy Volunteers (Control Group)

	BMS Patients		Control Group			
Demographic	Mean	SD	Mean	SD	Test Value	*P* Value
Age	55.26	11.50	54.02	13.28	*F* 0.262	.610
Illness duration (years)	2.90	1.85	N/A	N/A	N/A	N/A
Educational level (years)	9.62	3.93	10.08	4.74	*F* 0.286	.594
Sex distribution (males /females)	16/37		17/34		χ^2 0.119	.731

BMS = burning mouth syndrome; *F* = Fisher's *F*; N/A = not applicable; SD = standard deviation; χ^2 = chi-square.

The general characteristics (age, illness duration, education level, gender frequency) of both groups are described in Table 1, along with the results of the one-way ANOVA and Pearson chi-square analyses. No statistically significant differences were found among all variables in the 2 groups, which appeared to be homogenous.

Psychiatric Evaluation.—The acquired data were checked for interrater agreement that was found to be excellent (Fleiss' $\kappa = 0.82$). The ANOVA tests run to evaluate differences between BMS patients and control participants yielded a significant statistical difference. Therefore, the null hypothesis was rejected.

The results of the single ANOVA tests showed statistically significant differences in 7 out of the 14 variables (Table 2). Indeed, on SCL-90-R scale, somatization, depression, anxiety, and hostility turned out to be statistically significant ($P = .036$; $P < .001$; $P = .002$; $P = .028$, respectively) comparing BMS patients versus the control group, as well as STAI Y1, STAI Y2, and HAM-D ($P = .026$; $P = .046$; $P < .001$, respectively).

Table 2.—Psychiatric Characteristics of BMS Patients and Control Group

	BMS Patients		Control Subject		ANOVA	
Variables	Mean	SD	Mean	SD	*F*	*P* Value
SCL-90-R						
Somatization	**1.21**	**0.76**	**0.90**	**0.73**	**4.540**	**.036**
Obsessive-compulsive	0.94	0.74	0.82	0.81	0.665	.417
Interpersonal sensitivity	0.76	0.57	0.67	0.60	0.530	.468
Depression	**1.35**	**0.85**	**0.76**	**0.74**	**13.994**	**<.001**
Anxiety	**1.16**	**0.85**	**0.67**	**0.68**	**10.397**	**.002**
Hostility	**0.90**	**0.76**	**0.58**	**0.70**	**4.992**	**.028**
Phobic anxiety	0.50	0.68	0.37	0.56	1.063	.305
Paranoid ideation	1.02	0.65	0.86	0.84	1.225	.271
Psychoticism	0.54	0.49	0.44	0.52	0.976	.326
STAI Y1	**48.73**	**11.65**	**44.49**	**6.80**	**5.078**	**.026**
STAI Y2	**47.46**	**10.70**	**43.61**	**8.57**	**4.093**	**.046**
HAM-D	**13.60**	**6.35**	**6.04**	**5.56**	**41.668**	**<.001**
VAS	5.53	2.84	N/A	N/A	N/A	N/A

Printed in bold are the variables associated with statistical significance level <.05.
ANOVA = analysis of variance; BMS = burning mouth syndrome; HAM-D = Hamilton Rating Scale for Depression; N/A = not applicable; SCL-90-R = Symptom Checklist-90-Revised; SD = standard deviation; STAI = State-Trait Anxiety Inventory (Form Y: 1 for "state"; 2 for "trait"); VAS = Visual Analog Scale.

Table 3.—Regression Analysis

Dependent Variables	Independent Variables	β	*T*	*P* Value
HAM-D	**STAI Y2**	**0.512**	**4.303**	**<.001**
	VAS	0.215	1.747	.087
	Somatization	0.176	1.263	.212
VAS	**HAM-D**	**0.373**	**2.926**	**.005**
	Somatization	0.172	1.246	.218
	STAI Y2	0.180	1.199	.236

Printed in bold are the variables associated with statistical significance level <.05.
HAM-D = Hamilton Rating Scale for Depression; STAI = State-Trait Anxiety Inventory (Form Y: 1 for "state"; 2 for "trait"); VAS = Visual Analog Scale.

A Pearson's correlation analysis, which preceded the regression analysis, was conducted for the variables of years of illness duration, pain (VAS), and the psychiatric evaluation battery scale scores (HAM-D, STAI Y1-Y2, SCL-90-R). Results showed that the somatization dimension on the SCL-90-R correlated with all variables; and that VAS correlated with the HAM-D ($r = 0.366$; $P = .007$) and STAI Y1 ($r = 0.355$; $P = .009$) and STAI Y2 ($r = 0.331$; $P = .016$) scores. VAS score did not correlate with illness duration.

Two different multiple regression analyses (stepwise method; criteria: probability of F to enter $\leq .05$, probability of F to remove $\geq .10$) were performed by evaluating the determining of these 2 dimensions, depression (HAM-D) and pain (VAS), independently of each other; so both depression and pain were dependent variables in each regression analysis. All other variables, including anxiety and somatization, were evaluated as independent variables (causes).

The regression analyses results showed that pain was affected only by depression ($R = 0.373$; R^2 corrected = 0.123; $F = 8.563$; $P < .005$) and that depression was affected only by anxiety ($R = 0.512$; R^2 corrected = 0.248; $F = 18.519$; $P < .001$) (Table 3).

DISCUSSION

Currently, there is still a controversy as to whether psychogenic factors are primary or secondary events in BMS patients because chronic pain conditions may affect and alter the subject's psychological profile. However, several studies have demonstrated that patients with BMS also suffer from a variety of psychological problems.[9-14,22]

Our results showed statistically significant differences in BMS patients versus healthy volunteers on many of the SCL-90-R dimensions, in HAM-D, and STAI Y1-Y2 scores, confirming the presence of psychiatric comorbidities. Indeed, BMS patients had higher scores for somatization (mean: 1.21; SD: 0.76) versus the control group (mean: 0.90; SD: 0.73), and for hostility dimensions (mean: 0.90; SD: 0.76) versus the control group (mean 0.58; SD: 0.70) of the SCL-90-R. Given that the 2 groups overlapped for all the demographic data, it is reasonable to hypothesize that the illness could be associated with the above-cited differences.

In a chronic idiopathic illness, one can rationally hypothesize that pain can contribute to, or determine, secondary psychiatric symptoms or disease illness. Moreover, an underestimated or misdiagnosed psychiatric condition can present with pain as its prevalent feature.[23]

Observations from several studies have highlighted an association between hostility and health,[24,25] with a higher prevalence and incidence of health problems in hostile individuals. It is also possible that psychosocial stress situations could be predictors of ineffective coping strategies, such as hostile reaction patterns.[26]

We therefore might wonder if chicken or egg comes first. The results of the regression analysis allowed us to hypothesize that anxiety could determine a form of secondary demoralization in BMS patients and that depressive symptoms could contribute to pain (pain as a function of depression).

However, despite regression analysis, we could argue that stress for coping with chronic pain could exacerbate preexisting characteristics, resulting eventually in psychopathological manifestations, for example, depression (diathesis–stress model[27]). Therefore, in this case, VAS, HAM-D, and STAI Y1-Y2 scores would correlate with illness duration, but in BMS patients VAS score does not correlate with illness duration. We could also claim that pain does not correlate with illness duration in other chronic pain disorders (chronic pelvic pain syndrome), probably due to a suggested adaptation to chronic pain.[28]

However, our results show that pain increases along with anxiety and depression, not with illness duration. Thus, pain could be a somatic feature of depression in people who are anxious and hostile, with somatization tendencies.

Nevertheless, this fascinating theory obviously presents several "leaks." First, although regression analyses suggested a cause–effect relation between pain, anxiety, and depression, BMS might be a more complex disorder that is not merely identifiable in somatic pain. Also, it cannot be denied that the constellation of BMS symptoms revolve around pain, which is the most studied and reproducible measure of the disease. Moreover, the fact that somatization could play a role in this illness does not automatically imply that "BMS is a somatoform disorder," although, according to DSM-IV criteria, BMS should be included in the category of somatoform disorders.[22]

Second, our study did not use specific scales to evaluate somatization, nor were BMS patients assessed from a psychodynamic perspective.

Third, this is a cross-sectional study. It would be preferable to have a longitudinal study done in order to confirm the causality assessment, but this would turn out to be ethically unacceptable, as BMS patients should not receive any kind of medical/psychological treatment for the entire duration of a study.

Last, but no less important, our study group was composed of a small sample size, although representative. It is interesting to note, however, that the suggested relation between psychiatric features (anxiety and depression) and pain can provide the rationale for the use of anxiolytic and antidepressants in the treatment of BMS, based not only on an *ex adjuvantibus* perspective.

In conclusion, we may hypothesize that anxiety could determine a form of secondary demoralization in people who are anxious and hostile, with somatization tendencies; depressive symptoms could contribute to pain that could be a somatic feature of depression in BMS patients. Although this new perspective clearly highlights the presence of psychiatric features (anxiety and depression) in BMS and their possible relationship with pain, further studies on a wider cohort of patients are warranted to demonstrate that sometimes "egg" may come first.

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