Somatosensory Profiling of Patients with Burning Mouth Syndrome and Correlations with Psychologic Factors

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Aims: To compare somatosensory function profiles and psychologic factors in patients with primary burning mouth syndrome (BMS) and healthy controls and to evaluate correlations of subjective pain ratings with somatosensory and psychologic parameters. **Methods:** A quantitative sensory testing (QST) protocol—including cold detection threshold (CDT), warmth detection threshold (WDT), thermal sensory limen (TSL), paradoxical heat sensation (PHS), cold pain threshold (CPT), heat pain threshold (HPT), mechanical pain threshold (MPT), wind-up ratio (WUR), and pressure pain threshold (PPT)—was performed at the oral mucosa of the tongue, buccal, and palatal sites in 30 Chinese patients (25 women and 5 men, mean age 50.9 ± 9.2 years) with primary BMS and in 18 age- and gender-matched healthy controls (15 women and 3 men, mean age 53.2 ± 7.0 years). For each BMS patient, *z* scores and loss/gain scores were computed. Psychologic status was evaluated in both groups using the Self-Rating Anxiety Scale and Self-Rating Depression Scale. Correlations of BMS patients' subjective pain ratings with somatosensory and psychologic profiles were assessed with the use of Pearson or Spearman correlations and multiple linear regression. **Results:** In BMS patients, 53.3% had somatosensory abnormalities according to *z* scores vs 22.2% of healthy controls ($P = .033$). The abnormalities in BMS patients were somatosensory loss to thermal nonnoxious stimuli (TSL = 20.0%, CDT = 13.3%, WDT = 13.3%), mechanical pressure stimuli (PPT = 16.7%), pinprick stimuli (MPT = 6.7%), and thermal pain stimuli (CPT = 3.3%), and somatosensory gain to repetitive pinprick stimuli (WUR = 6.7%), pressure stimuli (PPT = 6.7%), and thermal pain stimuli (HPT = 3.3%). The most frequent loss/gain score was 13.3% for loss of thermal somatosensory function with no somatosensory gain; 13.3% for loss of thermal and mechanical somatosensory function with no somatosensory gain; and 13.3% for gain of mechanical somatosensory function with no somatosensory loss. Mild elevations in anxiety scores were seen in 30% of the BMS patients, and 50% and 36.7% had mild and moderate elevations, respectively, in depression scores. No anxiety or depression was detected in the control group. QST results, but not psychologic scores, were significantly correlated with patients' subjective pain ratings (PHS, Spearman coefficient −0.384, $P = .029$; CPT, Pearson coefficient −0.370, $P = .034$; MPT, Pearson coefficient −0.376, $P = .032$; PPT, Pearson coefficient 0.363, $P = .037$). **Conclusion:** The present findings documented distinct differences in somatosensory function in patients with primary BMS compared to controls, indicating a complex pathophysiology and interaction between impairments in nociceptive processing and psychologic functioning. *J Oral Facial Pain Headache 2019;33:278–286. doi: 10.11607/ofph.2358*

Keywords: *burning mouth syndrome, psychological changes, quantitative sensory testing, somatosensory profiles*

Burning mouth syndrome (BMS) is typically described by patients as a burning sensation of the oral mucosa in the absence of clinically apparent mucosal alterations. BMS mainly affects middle-aged women with psychologic disorders,[1,2] and the tongue is the most often affected site; however, the palate and other oral mucosal sites can also be involved.[3] So far, the pathogenesis is regarded as largely idiopathic.[3,4] In general, most studies concur that the etiology is multifactorial and will include local, systemic, and psychogenic factors.[3,4] Somatosensory function in BMS has been the focus of

several investigations[5–10]; however, so far, few studies have applied a comprehensive and standardized battery of quantitative sensory testing (QST) with a limited sample.[11]

Somatosensory sensitivity can be measured using QST and can be applied to the orofacial region.[12–19] There are several studies that have showed alterations in thermal sensory thresholds in BMS patients.[5,9,10,20] Most of these studies have revealed negative sensory signs using different test devices and methods. The German Research Network on Neuropathic Pain (DFNS) has established a standardized QST protocol for examination and data analysis that systematically evaluates thermal and mechanical somatosensory functions.[13,21] This standardized protocol has been applied in the assessment of somatosensory functions in BMS patients by Hartmann et al with a small sample size (n = 5).[11] More systematic evaluations using this standardized protocol to explore the somatosensory abnormalities of BMS patients are needed.

Due to the multifactorial etiology of BMS, the psychologic conditions of the patients have been widely evaluated, and increased levels of anxiety and depression have been reported in previous studies.[1,4,22]

The aims of this study were to evaluate somatosensory function at the oral mucosa according to a standardized QST protocol and to assess psychologic characteristics in BMS patients. Finally, associations of somatosensory function and psychologic features with perceived pain intensity in BMS patients were tested using correlation and regression analyses. It was hypothesized that there would be distinct somatosensory and psychologic differences between BMS patients and controls, as well as a significant correlation between these parameters and perceived pain intensity in BMS patients.

Materials and Methods

Participants

From 2014 to 2015, Chinese BMS patients were recruited from the Department of Oral Medicine, Peking University School and Hospital of Stomatology, Beijing, China. All the patients were investigated and diagnosed with primary BMS by one specialist in accordance with previously published criteria.[1,23] Inclusion criteria were intraoral burning or a dysesthesia sensation recurring daily for more than 2 hours per day for more than 3 months without clinically evident causative lesions. Exclusion criteria were oral infections; contact sensitivity to dental materials; food allergies; tongue injuries; various mucocutaneous diseases/disorders; Sjögren's syndrome; diabetes mellitus; hypothyroidism, iron or zinc deficiency, or vitamin B complex deficiency; and medications affecting the nervous system, such as tranquilizers, antihistamines, or pain medication. A total of 138 patients with burning symptoms from the Department of Oral Medicine, School and Hospital of Stomatology, Peking University, participated in the study. Eighteen age- and gender-matched healthy volunteers from the community participated in the study.

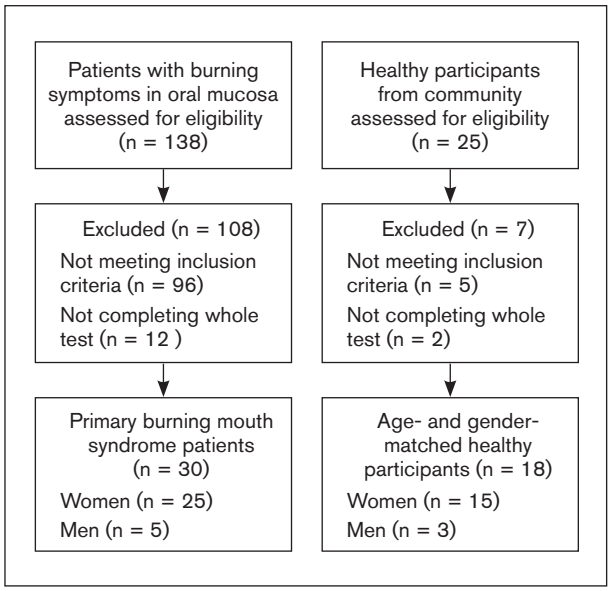

Fig 1 Flow diagram of participant enrollment.

Finally, 30 BMS patients were diagnosed with primary BMS (25 women and 5 men, mean age of 50.9 ± 9.2 years, mean pain history of 16.6 ± 22.2 months, mean pain intensity of 3.2 ± 1.5 on 0- to 10-cm visual analog scale [VAS]), and 108 patients were diagnosed with BMS due to secondary pathology. Eighteen controls (15 women and 3 men, mean age 53.2 ± 7.0 years) completed the QST and psychologic questionnaires (Fig 1). All participants gave written informed consent. The study adhered to the Declaration of Helsinki II and was approved by the local ethics committee in China (PKUSSIRB-201412029).

Quantitative Sensory Testing

Parameters from the standardized QST battery developed by DFNS[21] and modified for the intraoral region[14] were used in this study. All QST measures were performed in a quiet room with a temperature between 21° and 23°. The QST battery consisted of: cold detection threshold (CDT); warmth detection threshold (WDT); thermal sensory limen (TSL); paradoxical heat sensation (PHS); cold pain threshold (CPT); heat pain threshold (HPT); mechanical pain threshold (MPT); wind-up ratio (WUR); and pressure pain threshold (PPT). The investigator was carefully instructed and trained under supervision according

to the latest guidelines.[15] CDT, WDT, TSL, PHS, CPT, HPT, and PPT were investigated in three oral mucosal regions: the tongue region on the middle anterior dorsal surface of the tongue; the hard palate region on the junction point between the anterior first third and middle third of the hard palate; and the right buccal region, 1 cm from the angle of the mouth. The MPT and WUR were only tested in the right buccal and tongue sites, as the stimuli were delivered with a weighted pinprick that could not be applied to the hard palate.

Thermal Thresholds and TSL. Thermal testing was performed using the Medoc Pathway with intraoral thermode (6-mm–diameter round surface). CDT, WDT, TSL, PHS, CPT, and HPT were measured in triplicate, and the means were used for further analysis. For the TSL, the temperature first rose, and the participants pressed a button when they perceived a change in temperature. Then the temperature ramp changed direction and the thermode cooled down, and this was again reversed when the participants perceived a change in temperature and pressed the button.[16–19,21,24] The number of PHS during this procedure was recorded. Baseline temperature was set at 37°. For all thermal testing, ramped stimuli of 1°/second was used, and the procedure ended when the participants pressed a button. Temperature cutoffs were set at 0°C and 50°.[16–19,21,24]

Mechanical Pain Threshold. Weighted pinprick stimuli were delivered with seven custom-made punctate mechanical stimulators with fixed stimulus intensities (flat contact area of 0.2-mm diameter) that exerted forces of 8 to 512 mN to determine the MPT.[16–19,21,24] Contact time was 1 to 2 seconds. All pinprick tests were carried out with the stimulator perpendicular to the examination site. Five repeated threshold measurements were made, each through applying a series of ascending and descending stimulus intensities. The final threshold was the geometric mean of the five series of ascending and descending stimulus intensities.[16–19,21,24]

WUR for Repetitive Pinprick Stimuli. To measure the WUR for repetitive pinprick stimuli, the perceived magnitude of a train of 10 pinprick stimuli repeated at a rate of 1 Hz was divided by that of a single pinprick stimulus with the same force.[16–19,21,24] The custom-made pinprick stimulators used in the MPT determinations were used for WUR assessment. The instrument that delivered at a force that the participant perceived as "slightly painful" was chosen. The 128-mN stimulator was tried first[12,14,16-19,21,24,25]; if the response was 0 (not painful), the test was repeated with a stronger force,[12,14,16–19,21,24,25] and if the participant perceived the stimulus as intolerable, a weaker force was used. If a participant did not perceive the 512-mN stimulator to be painful, the test was abandoned.[12,14,16–19,21,24,25] The WUR test was repeated three times.

Pressure Pain Threshold. PPT was measured using a computerized pressure algometer (Medoc AlgoMed) with a probe covered with rubber with a surface area of 0.18 cm^2 and a constant application rate of 30 kPa/second. The probe was applied perpendicular to the examination site.[12,14,16–19,21,24,25] At the first painful sensation, the participants pressed a button to interrupt stimulation. The test was repeated three times.[12,14,16–19,21,24,25]

All participants received careful instructions and a training test to ensure compliance. The whole trial of tests took about 1 hour per participant. The participants kept their eyes closed throughout the QST procedure.[12,14,16-19,21,24,25]

Psychologic Assessment

The psychologic status of the patients and healthy controls was assessed with the Chinese version of the Zung Self-Rating Anxiety Scale (SAS)[26] and the Zung Self-Rating Depression Scale (SDS)[27] under instruction of one doctor. The two scales have high reliability and validity.[28] Each scale contains 20 questions, and the respondents were required to indicate the frequency they felt the emotions during the last week on a 4-point scale (1 = very little time or not at all; 4 = all the time). Scores ≤ 50 were considered normal, 50 < scores ≤ 60 were considered to indicate mild anxiety or depression, 60 < scores ≤ 70 were considered to indicate moderate anxiety or depression, and scores > 70 were considered to indicate severe anxiety or depression.[26,27]

Data Processing

All statistical calculations were performed using SPSS 13.0 software for Windows. The original threshold data were first transformed using log10(X) to get logarithmic data. The normality of all original and logarithmic data was investigated using the Kolmogorov-Smirnov method. Differences among groups and sites were analyzed using two-way analysis of variance (ANOVA). Data are presented as means ± standard deviations (SDs). $P < .05$ was considered statistically significant.

A *z* score transformation was performed for each QST variable.[13,19,25] The resulting *z* scores were adjusted in such a way that those > 0 indicated a gain of function, referring to a higher sensitivity compared to controls (hyperesthesia, hyperalgesia), while *z* scores < 0 indicated a loss of function, referring to a lower sensitivity (hypoesthesia, hypoalgesia).[13,25] A *z* score of 0 ± 1.96 represents the range that can be expected to include 95% of the control data.[13,25] To compare individual QST data of the BMS patients to the mean reference range of the same region in age- and

gender-matched controls, the patient data were *z* score transformed for each single variable in the same way using the transformation parameters of the reference group. The individual *z* scores were calculated in accordance with Rolke et al,[21] and *z* scores > 1.96 and < –1.96 indicate values outside of the 95% confidence interval (CI) of the reference group data (Fig 2).

For assessment of somatosensory loss and gain of function of the BMS patients and healthy participants, a loss/gain coding system was applied.[13,19] The loss/gain score combines a score of somatosensory loss of function (L0, L1, L2, or L3) with a score of somatosensory gain of function (G0, G1, G2, or G3).[13,19] The number after the letter L or G indicates whether the abnormality is related to the thermal modalities alone (1), the mechanical modalities alone (2), or mixed (3) (thermal and mechanical). If a *z* score of thermal and/or mechanical tests was < –1.96 on the three intraoral areas in comparison with the reference data (healthy participants), it was recorded as L1, L2, or L3.[13,19] Likewise, for somatosensory gain, thermal hyperalgesia (G1) was recorded if gain of function in cold or heat thresholds was found, mechanical hyperalgesia (G2) was recorded if gain of function in mechanical thresholds was found, and mixed hyperalgesia (G3) was recorded if hyperalgesia to both thermal and mechanical stimuli was found. L0 was scored if no loss of somatosensory function was present, and G0 if no gain of somatosensory function was detected.

The correlations of psychologic and somatosensory factors with participants' subjective pain ratings (0- to 10-cm VAS) were estimated using Pearson or Spearman correlation coefficients. A linear multiple regression mode analysis was also performed, with the patients' subjective pain ratings considered as the dependent variable γ and QST (CDT_{tongue}, CDT_{buccal}, CDT_{palate}, WDT_{tongue}, WDT_{buccal}, WDT_{palate}, TSL_{tongue}, TSL_{buccal}, TSL_{palate}, PHS_{tongue}, PHS_{buccal}, PHS_{palate},

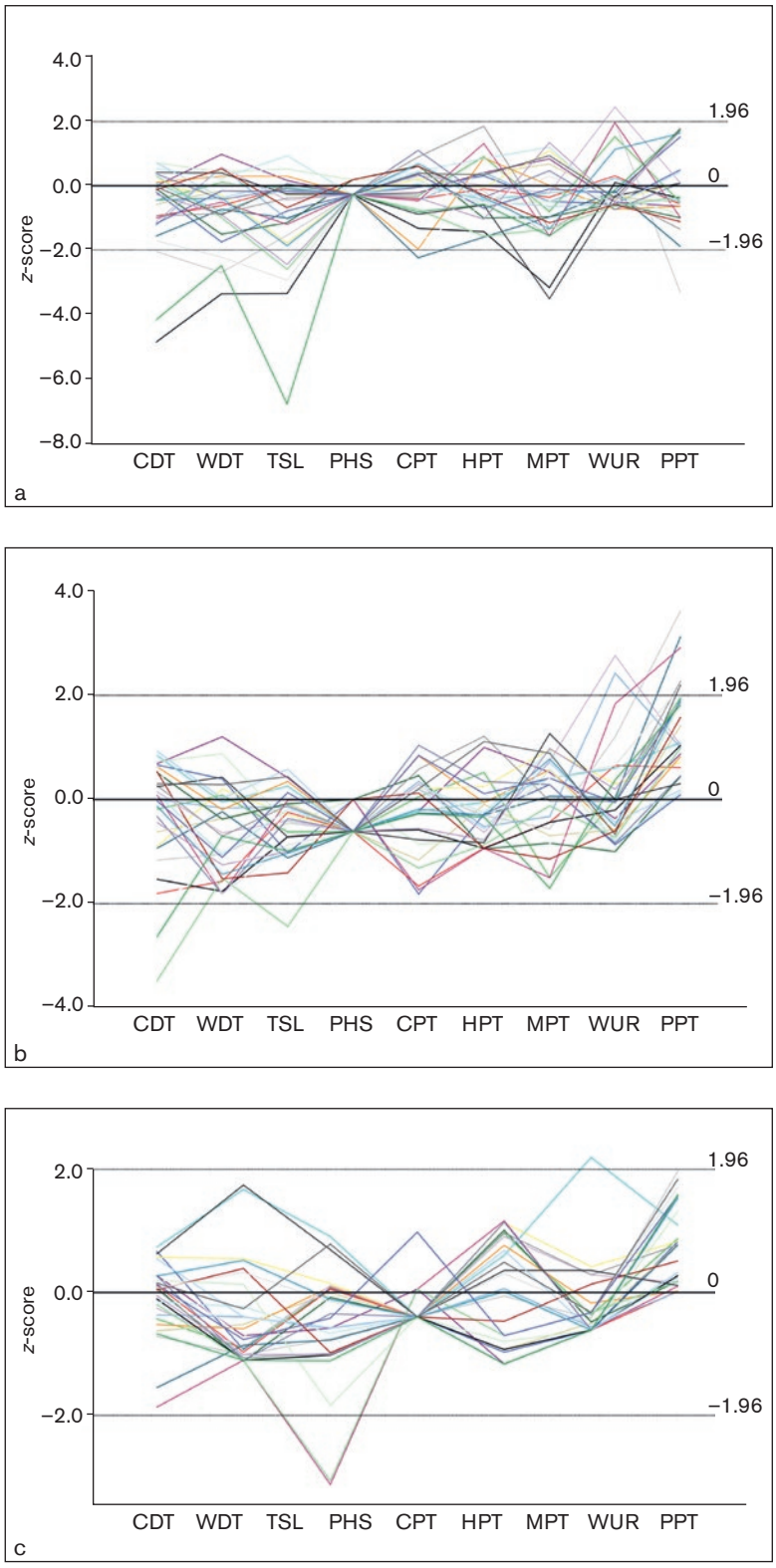

Fig 2 Somatosensory *z* score profiles of patients with primary burning mouth syndrome for quantitative sensory testing in the **(a)** tongue, **(b)** buccal region, and **(c)** hard palate, indicating abnormalities involving different peripheral or central pain mechanisms. The zone between the two lines (–1.96 < *z* < 1.96) is the normal range based on the control group. CDT = cold detection threshold; WDT = warmth detection threshold; TSL = thermal sensory limen; PHS = paradoxical heat sensation; CPT = cold pain threshold; HPT = heat pain threshold; MPT = mechanical pain threshold; WUR = wind-up ratio; PPT = pressure pain threshold.

Table 1 Quantitative Sensory Testing (QST) Parameters Before and After *z* Score Transformation

	Reference group (n = 18)						BMS patient group (n = 30)					
	Tongue	Buccal	Palate	*z* scores	< −1.96, n (%)	> 1.96, n (%)	Tongue	Buccal	Palate	*z* scores	< −1.96, n (%)	> 1.96, n (%)
CDT (ΔT, °C)	−4.4 (3.3)	−6.7 (3.9)	−9.0 (8.6)	0.00 (1.00)	1 (5.6)	0 (0.0)	−6.5 (4.1)	−7.6 (4.3)	−9.7 (5.0)	−0.31 (0.11)	4 (13.3)	0 (0.0)
WDT (ΔT, °C)	4.6 (2.5)	7.6 (3.1)	9.4 (3.3)	0.00 (1.00)	1 (5.6)	0 (0.0)	6.0 (2.6)	9.4 (2.5)	10.9 (2.5)	−0.54 (0.09)	4 (13.3)	0 (0.0)
TSL (°C)	10.4 (4.7)	16.4 (10.2)	19.0 (9.1)	0.00 (1.00)	2 (11.1)	0 (0.0)	14.7 (6.9)	20.8 (6.3)	23.3 (8.4)	−0.61 (0.11)	6 (20.0)	0 (0.0)
PHS (/3)	0.2 (0.7)	0.3 (0.6)	0.3 (0.7)	0.00 (1.00)	0 (0.0)	1 (5.6)	0.0 (0.1)	0.1 (0.1)	0.1 (0.2)	−0.35 (0.03)	0 (0.0)	0 (0.0)
CPT (°C)	21.4 (9.7)	20.8 (9.1)	13.6 (12.0)	0.00 (1.00)	2 (11.1)	0 (0.0)	20.0 (7.9)	19.4 (6.9)	12.0 (10.1)	−0.14 (0.08)	1 (3.3)	0 (0.0)
HPT (°C)	45.9 (2.6)	47.7 (2.5)	49.1 (1.6)	0.00 (1.00)	0 (0.0)	3 (16.7)	46.3 (2.1)	48.2 (1.6)	49.5 (0.9)	−0.22 (0.07)	0 (0.0)	1 (3.3)
MPT (mN)	97.4 (63.2)	109.0 (88.2)	—	0.00 (1.00)	1 (5.6)	0 (0.0)	134.8 (70.2)	112.4 (69.0)	—	−0.29 (0.13)	2 (6.7)	0 (0.0)
WUR	2.6 (1.8)	2.7 (1.6)	—	0.00 (1.00)	0 (0.0)	2 (11.1)	2.6 (1.6)	2.8 (1.5)	—	0.03 (0.11)	0 (0.0)	2 (6.7)
PPT (kPa)	191.8 (85.1)	248.1 (94.9)	423.4 (212.2)	0.00 (1.00)	2 (11.1)	0 (0.0)	203.7 (104.5)	293.6 (152.8)	418.3 (222.1)	0.23 (0.10)	5 (16.7)	2 (6.7)
All, mean n (%)					1.00 (5.6)	0.67 (3.7)					2.44 (8.1)	0.44 (1)

All data are reported as mean (standard deviation) unless otherwise indicated. *z* scores above 1.96 and below −1.96 indicate values outside of the 95% confidence interval (CI) of the reference group data. Such values were considered to be absolute abnormalities. BMS = burning mouth syndrome; CDT = cold detection threshold; WDT = warmth detection threshold; TSL = thermal sensory limen; PHS = paradoxical heat sensation; CPT = cold pain threshold; HPT = heat pain threshold; MPT = mechanical pain threshold; WUR = wind-up ratio; PPT = pressure pain threshold; ΔT = difference from the baseline temperature 37°C. MPT and WUR were tested only in the tongue and buccal regions.

Table 2 Somatosensory Differences (*P* values) Between Burning Mouth Syndrome Patients and Healthy Controls in the Tongue, Buccal, and Palate Regions for Nine Quantitative Sensory Testing Parameters

	CDT	WDT	TSL	PHS	CPT	HPT	MPT	WUR	PPT
Factor									
Group	NS	.001	.001	.003	NS	NS	NS	NS	NS
Site	.002	< .001	< .001	NS	< .001	< .001	NS	NS	< .001
Group × site	NS	NS	NS	NS	NS	NS	NS	NS	NS
Effect size									
Group	.014	.076	.071	.064	.005	.015	.019	.000	.005
Site	.089	.345	.176	.006	.123	.324	.001	.002	.267

Two-way analysis of variance was used. CDT = cold detection threshold; WDT = warmth detection threshold; TSL = thermal sensory limen; PHS = paradoxical heat sensation; CPT = cold pain threshold; HPT = heat pain threshold; MPT = mechanical pain threshold; WUR = wind-up ratio; PPT = pressure pain threshold; NS = no significant difference.

CPT_{tongue}, CPT_{buccal}, CPT_{palate}, HPT_{tongue}, HPT_{buccal}, HPT_{palate}, MPT_{tongue}, MPT_{buccal}, WUR_{tongue}, WUR_{buccal}, PPT_{tongue}, PPT_{buccal}, PPT_{palate}) and psychologic results (SAS scores, SDS scores) considered as the independent variables X. An adjusted R^2 was calculated.

Results

There were no significant age differences between the two groups (unpaired *t* test: *P* = .274). All QST data of both groups are shown in Table 1. CDT, WDT, TSL, MPT, and WUR results were normally distributed only after logarithmic transformation (Kolmogorov-Smirnov, *P* > .05).

Somatosensory Abnormalities of BMS Patients

Group Differences. BMS patients had higher mean WDT (lower sensitivity) (*P* = .001); higher mean TSL (lower sensitivity) (*P* = .001); and less PHS (higher accuracy) (*P* = .003) compared to controls (Table 2). There were no significant group differences with regard to mechanical parameters.

Abnormalities of QST z Scores in BMS Patients. The frequencies of abnormal values for each QST parameter in BMS patients and healthy controls are shown in Table 1. The most frequent somatosensory abnormalities in the BMS group were (in order of frequency): somatosensory gain with regard to PPT, WUR, and HPT; and somatosensory loss with regard

Table 3 Loss and Gain Distributions in the Oral Mucosa Region in Burning Mouth Syndrome (BMS) Patients and Healthy Controls

	Gain				
Loss	G0	G1	G2	G3	Total
BMS patients (n = 30)					
L0	14 (46.7)	1 (3.3)	4 (13.3)	0 (0.)	19 (63.3)
L1	4 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (13.3)
L2	3 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.0)
L3	4 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (13.3)
Total	25 (83.3)	1 (3.3)	4 (13.3)	0 (0.0)	30 (100)
Controls (n = 18)					
L0	14 (77.8)	0 (0)	0 (0.0)	0 (0.0)	14 (77.8)
L1	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)
L2	1 (5.6)	1 (5.6)	0 (0.0)	0 (0.0)	2 (11.1)
L3	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (5.6)
Total	16 (88.9)	1 (5.6)	1 (5.6)	0 (0.0)	18 (100)

All data are reported as n (%). Sensory abnormality coding system[13,19]: L1 = hypoesthesia to thermal stimuli (loss of function in cold or warm detection thresholds); L2 = hypoesthesia to mechanical stimuli (loss of function in mechanical or vibration detection thresholds); L3 = both thermal and mechanical hypoesthesia; G1 = hyperalgesia to thermal stimuli (gain of function in heat or cold pain thresholds); G2 = hyperalgesia to mechanical stimuli (gain of function in mechanical pain threshold or sensitivity, dynamic mechanical allodynia, or pressure pain threshold); G3 = both thermal and mechanical hyperalgesia. Normal values were coded as 0.

to TSL, PPT, CDT, WDT, MPT, and CPT. For all non-nociceptive detection thresholds (CDT, WDT, TSL, and PHS), only sensory loss was detected (13.3% to 20%). For nociceptive parameters (CPT, HPT, MPT, WUR, PPT), both sensory loss (hypoalgesia, 3.3% to 16.7%) and sensory gain (hyperalgesia, 3.3% to 6.7%) were found. The most frequent somatosensory abnormalities in the control group were (in order of frequency): somatosensory gain with regard to HPT, WUR, and PHS; and somatosensory loss with regard to PPT, CPT, TSL, CDT, WDT, and MPT.

Somatosensory Abnormalities of BMS Patients According to the Loss/Gain Coding System. The distribution of BMS patients according to the loss/gain coding system is shown in Table 3, with 46.7% of the patients having no somatosensory abnormalities (L0G0) compared to 77.8% of the control group (P = .033). L1G0 (loss of thermal somatosensory function with no somatosensory gain), L3G0 (loss of thermal and mechanical somatosensory function with no somatosensory gain), and L0G2 (gain of mechanical somatosensory function with no somatosensory loss) were the most frequent codings in the BMS group (all occurring in 13.3% of the BMS patients), which was not statistically significantly different from the control group (L1G0 = 5.6%, P = .371; L3G0 = 0%, P = .141; L0G2 = 0%, P = .141). The cumulative proportion of somatosensory loss with any gain (L1G0, L2G0, L3G0) was 36.7% in the BMS patients compared to 11.1% in the control group (P = .052) (Table 3). The cumulative proportion of BMS patients presenting with somatosensory gain without any loss (L0G1, L0G2, and L0G3) was 16.7%, compared to 0% in the control group (P = .083) (Table 3). The cumulative proportion of mixed loss and gain (L1G1, L1G2, L1G3, L2G1, L2G2, L2G3, L3G1, L3G2, and L3G3) was 0% in the BMS patients compared to 11.1% in the control group (P = .136) (Table 3).

Psychologic Profiles

According to the SAS, 30% (9 of 30 patients) of BMS patients had mild anxiety scores. According to the SDS, 50% of BMS patients had mild depression scores, and 36.67% had moderate depression scores. No healthy controls had elevated anxiety or depression scores. There were significant group differences with regard to anxiety (BMS: 45.3 ± 12.1; control: 27.9 ± 4.6; P < .001) and depression (BMS: 47.1 ± 14.8; control: 29.1 ± 6.6; P < .001) scores.

Correlation of Psychologic and Somatosensory Factors with Subjective Pain Ratings

Four QST parameters were significantly correlated with patients' subjective pain ratings (PHS_{tongue}, Spearman coefficient −0.384, P = .029; CPT_{tongue}, Pearson coefficient −0.370, P = .034; MPT_{buccal}, Pearson coefficient −0.376, P = .032; PPT_{palate} Pearson coefficient 0.363, P = .037) (Table 4). The regression results indicated: $\gamma = 3.361 - 3.583X_{PHS} - 0.023X_{CPT} - 0.007X_{MPT} + 0.003X_{PPT}$, R^2 = 0.426, P = .020, indicating that the dependent variable γ (patients' subjective pain rating) was explained by 42.6% through four selected independent variables (PHS, CPT, MPT, and PPT).

Discussion

The main finding of this study was that primary BMS patients had more somatosensory abnormalities than

Table 4 Correlations of Psychologic Variables and Quantitative Sensory Testing (QST) with Burning Mouth Syndrome Patients' Subjective Evaluations of Perceived Symptoms on a 0- to 10-cm Visual Analog Scale

Variables	Pearson or Spearman correlation coefficient	Significance (*P*)
SAS	−0.064[a]	NS
SDS	0.029[a]	NS
CDTtongue	−0.049[b]	NS
CDTbuccal	−0.165[b]	NS
CDTpalate	0.061[b]	NS
WDTtongue	0.041[b]	NS
WDTbuccal	−0.112b	NS
WDTpalate	0.037[b]	NS
TSLtongue	−0.194[b]	NS
TSLbuccal	−0.092[b]	NS
TSLpalate	−0.330[b]	NS
PHStongue	−0.384[a]	.029
PHSbuccal	−0.287[a]	NS
PHSpalate	−0.136[a]	NS
CPTtongue	−0.370[b]	.034
CPTbuccal	−0.219[b]	NS
CPTpalate	−0.311[b]	NS
HPTtongue	0.054[b]	NS
HPTbuccal	−0.280[b]	NS
HPTpalate	−0.028[b]	NS
MPTtongue	−0.270[b]	NS
MPTbuccal	−0.376[b]	.032
WURtongue	0.103[b]	NS
WURbuccal	0.166[b]	NS
PPTtongue	0.259[b]	NS
PPTbuccal	0.211[b]	NS
PPTpalate	0.363[b]	.037

Of the 27 correlation tests, 4 correlations were found to be significant, indicating that the higher the patients rated the perceived pain intensity, the lower the PHS, CPT, and MPT results, and the higher the PPT results.
SAS = Self-Rating Anxiety Scale; SDS = Self-Rating Depression Scale; CDT = cold detection threshold; WDT = warmth detection threshold; TSL = thermal sensory limen; PHS = paradoxical heat sensation; CPT = cold pain threshold; HPT = heat pain threshold; MPT = mechanical pain threshold; WUR = wind-up ratio; PPT = pressure pain threshold; NS = not significant.
[a]Spearman correlation coefficient.
[b]Pearson correlation coefficient.

healthy controls. BMS patients were also less sensitive to thermal stimuli than healthy controls, as determined with the WDT and TSL parameters. This study also highlighted significant inter-individual differences in somatosensory abnormalities in BMS patients with the use of *z* scores and the loss/gain coding system. In BMS patients, 30% had an increased anxiety score and 86.67% had an increased depression score, indicating anxiety and depression. However, QST parameters (PHS, CPT, MPT, PPT), rather than psychologic scores, had a significant correlation with BMS patients' subjective pain ratings.

Somatosensory Function Differences Between BMS Patients and Healthy Controls

In the overall group analysis, patients with BMS showed hypoesthesia to thermal stimuli, including thermal detection and paradoxical heat sensation, compared to controls. This result is partly in accordance with previous studies using different test methods.[5,6,8,9] Just et al investigated the effect of BMS on pain perception within the lingual nerve distribution and gustatory sensitivity using a capsaicin threshold test and regional taste tests.[6] Their results indicated that patients with BMS exhibited decreased gustatory and somatosensory perception compared to healthy controls.[6] Mo et al tested thermal and mechanical sensory and pain thresholds on 25 BMS patients and 19 matched controls in accordance with German Research Network for Neuropathic Pain guidelines.[5] The study concluded that BMS patients had a significant loss of thermal function but not mechanical function, which was similar to the present study.[5] There are several other studies showing that thermal sensory thresholds are altered in BMS patients.[8–10,20] Most of these studies have revealed negative sensory signs using different test devices and methods.

The present study assessed somatosensory changes in BMS patients using a standardized QST protocol following the latest guidelines. In addition to group comparisons, individualized data processing based on *z* scores and the loss/gain coding system was used.[29] The frequency of somatosensory abnormalities in every parameter was evaluated using *z* scores. The results indicated somatosensory loss was the most frequent abnormality (CDT, WDT, and TSL, Table 1). Mechanical somatosensory function abnormalities (MPT, WUR, and PPT, both loss and gain of function) were also detected in primary BMS patients, which indicates wider somatosensory changes for this group of patients. In addition, the use of *z* scores and the loss/gain coding system also allowed this study to highlight significant inter-individual differences in somatosensory abnormalities of BMS patients, indicating the need for individualized diagnosis and treatment for BMS patients.

Somatosensory function disorders of BMS patients may be associated with central or peripheral neuronal damage. Previous studies used positron emission tomography (PET) and demonstrated hypofunction of the nigrostriatal dopaminergic system in BMS patients.[30,31] A previous imaging study has shown that the dopaminergic system participates in the central regulation of pain.[32] Parkinson disease (PD) is caused by hypofunction of the dopamine system.[30] Pain is common in patients with PD and can precede the diagnosis of the disease.[30] Winter et al showed that 67.6% of the patients with PD had various types of pain symptoms.[33] Some studies found

low intraepidermal nerve fiber density and axonal degeneration in BMS patients compared to controls in tongue mucosal biopsies.[7,34,35] Similarly, Santos et al found low intraepidermal nerve fiber density in skin biopsy tissue in patients with lower limb dysesthesias.[36] All these findings suggest that primary BMS may have similarities to neuronal disorders. Nevertheless, at present, neurobiologic data may not explain the entire pathophysiology of pain in primary BMS patients, and other mechanisms may be involved.

Psychologic Differences Between BMS Patients and Healthy Controls

Of the BMS patients included in this study, 30% to 50% had symptoms of anxiety or depression. There is currently no consensus regarding the etiology or pathophysiology of BMS. Researchers point to a multifactorial background, and some believe that psychologic factors play a crucial role in the formation and maintenance of BMS sensations.[22,37] In order to identify psychologic or psychiatric deviation among patients with BMS and perform an adequate differentiated therapy, Kenchadze et al conducted clinical psychologic examinations in 39 BMS patients. As a result, depression, insomnia, cancer phobia, severe neurologic disorders, and phobic syndrome were revealed.[37]

The etiology of BMS is indeed complex and has been associated in the literature with menopause, trigger events, and even genetic factors.[3,4,37] Other studies have found central and peripheral nervous system impairments, supporting a neuropathic cause.[6–9,31] The findings of the present study indicate that a good proportion of BMS patients have both somatosensory abnormalities and psychologic disorders. The QST profiles, but not the psychologic scores, were associated with the patients' ratings of symptom intensity; ie, pain scores.

Chronic pain—for example, BMS—involves complex brain circuits, including sensory, emotional, cognitive, and interoceptive processing. The feed-forward interactions between physical and emotional states and the consequences of altered psychologic status on the expression of pain have made the evaluation and treatment of pain a challenge in the clinic. Chronic pain is associated with progressive changes and relentless decline in psychologic well-being paralleled by reward deficiency, pain sensitization, and cross-sensitization (depression, anxiety, addiction, etc) along with anti-reward (stress) allostatic neuroadaptations.[38] Negative affective states then substantially worsen pain conditions, further deteriorating psychologic outcomes.[38] Therefore, it will be mandatory to evaluate and consider both neurobiologic function (eg, somatosensory function) and psychologic well-being in patients with primary BMS.

Conclusions

The present findings documented distinct differences in somatosensory function and psychologic factors in patients with primary BMS compared to controls, indicating a complex pathophysiology and an interaction between impairments in nociceptive processing and psychologic functioning.

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