The role of sensory input of the chorda tympani nerve and the number of fungiform papillae in burning mouth syndrome

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**Objective.** The aim of this study was to evaluate patients suffering from burning mouth syndrome (BMS) and control subjects by means of sensory testing and fungiform papillae count.

**Study design.** The left and right anterior two-thirds of the tongue of 25 BMS subjects and 20 healthy control subjects were evaluated for electric taste and electric detection threshold. The number of fungiform papillae/cm² was evaluated by using close-up digital photography.

**Results.** The electric taste/tingling detection threshold ratio was significantly higher in BMS compared with control subjects (P = .041). No difference was found between the number of fungiform papillae/cm² in the BMS compared with the control subjects (P = .277). Patients suffering from BMS for a prolonged period of time presented with a significantly elevated electric taste/tingling detection threshold ratio (P = .031).

**Conclusions.** BMS may be a neurodegenerative process with chorda tympani nerve hypofunction potentially playing a role in the pathophysiology of this disorder. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:65-72)

According to the International Association for the Study of Pain, burning mouth syndrome (BMS) is defined as a burning pain of the tongue and/or other oral mucous membrane in the absence of clinical signs or laboratory findings.¹ This condition affects predominantly middle-aged women in the postmenopausal period. Occurrence before the age of 30 years is rare, and the female-to-male ratio is approximately 7:1.²⁻⁴ Multiple oral sites may be involved, but the anterior two-thirds of the tongue are the most commonly affected, followed by the palate.⁵⁻⁶

Anatomically, the taste sensation of the anterior two-thirds of the tongue is supplied by the chorda tympani nerve, a branch of the facial nerve, and other modalities, such as pain, mechanical, and thermal sensations, are supplied by the lingual nerve, a branch of the mandibular division of the trigeminal nerve.

Unfortunately, to date, there are no defined diagnostic criteria for BMS, which is usually diagnosed by the exclusion of other conditions that could cause an intraoral burning sensation. The prognosis is poor, and the burning sensation can last for many years. A complete spontaneous remission is rare and may occur in only 3% of the patients, ~5 years after the onset.⁷⁻⁸

Although recent literature presents a growing body of evidence suggesting that BMS has a neuropathic origin, its etiology is still unknown and presents a challenge for both researchers and clinicians.⁹⁻¹² However, evidence exists that strongly suggest an association between BMS and the gustatory system. First, the presence of dysgeusia or phantom taste (which is a disorder of the gustatory system where the patient perceives a persistent taste in the absence of stimulation) occurs in ~70% of the BMS patients.⁴⁻¹³ The most common “phantom taste” reported in BMS patients are “bitter” and “metallic,” which are believed to be the result of disinhibition of the glossopharyngeal nerve after damage to the chorda tympani.¹⁴

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The mediation of taste involves inhibitory interactions among taste nerves. Halpern and Nelson (1965)\textsuperscript{15} showed early evidence for central inhibitory connections between the chorda tympani and glossopharyngeal nerves and suggested that input via the chorda tympani might inhibit units of the solitary nucleus that receive input from both the chorda tympani and the glossopharyngeal nerves. After anesthesia of the chorda tympani nerve, this inhibition was released and glossopharyngeal nerve responses were intensified. Yanagisawa et al.'s (1998)\textsuperscript{16} findings also support Halpern and Nelson's theory.

Moreover, links between taste and oral pain in the central nervous system have been demonstrated. Formaker and Frank (2008),\textsuperscript{17} after evaluating 57 BMS patients for taste function, found that identification of NaCl as “salty” and citric acid as “sour” was particularly difficult for women with BMS compared with the control group. They concluded that pain pathway activation may affect neural and behavioral taste function. Anseloni et al. (2005)\textsuperscript{18} investigated the central pathways by which taste stimuli involve neural antinociceptive mechanisms. They demonstrated that intraoral sucrose activates neurons in the periaqueductal gray and nucleus raphe magnus, 2 key brainstem sites critically involved in descending pain modulation.

Furthermore, BMS patients report relief of their burning sensation when they eat, suggesting that the stimulation of the gustatory system might be involved in the decrease of pain.\textsuperscript{8} In fact, clinical experience has shown that BMS patients report that they often eat a piece of candy or chew gum to help relieve their burning sensation during the day.

Finally, it is noteworthy that the largest number of taste buds are located on the anterior two-thirds of the tongue, which is the area most commonly affected site in BMS.\textsuperscript{19,20} An interesting hypothesis regarding BMS etiology was suggested by Grushka and Bartoshuk (2000).\textsuperscript{21} They suggested that BMS occurs after damage of the gustatory system and that this damage could occur in any nerve that carries taste, i.e., the glossopharyngeal, vagus, chorda tympani, and greater petrosal nerve. Those authors also suggested that the chorda tympani and the lingual nerve exert mutual inhibitory mechanisms by which taste input inhibits the area of the brain receiving input from the trigeminal nerve. Therefore, damage to the chorda tympani nerve might release the inhibition, leading to intensification of trigeminal sensations, such as pain, which is then perceived by the patient as a constant oral burning sensation (Fig. 1).

Based on these data, the purpose of the present study was to evaluate chorda tympani and lingual nerve function in BMS patients by sensory assessment of current perception threshold (CPT). A similar approach was used by Eliav et al. (2007).\textsuperscript{22} Quantitative sensory testing as a CPT procedure is based on the traditional neurologic examination of sensory function, psychophysical procedures, and an array of stimulus modalities that assess the functional capacity of primary afferent fibers.\textsuperscript{23} Although the gustatory stimuli are not fully understood, the fibers accessed in the present study were mostly A-delta fibers which carry gustatory and nociceptive information from the tongue.\textsuperscript{24} Increasing evidence from several studies indicates that altered CPT reflects changes in sensory perception that may result from injuries to any part of the nervous system.\textsuperscript{25} Partial nerve damage may be followed by either hypo- or hypersensitivity accompanied by neuropathic pain. CPT can both assess peripheral nerve function and mechanisms of central sensitization in painful conditions.\textsuperscript{23}

CPT in the present study was aimed to evaluate the function of the lingual and chorda tympani nerves in BMS subjects and evaluate BMS group by means of sensory testing. Electric detection threshold (tingling sensation) was used to assess lingual nerve function and electric taste detection threshold (electrogustatory test) was used to assess the chorda tympani nerve function. Recent literature also suggests that individuals genetically endowed with a large number of fungiform papillae might be more predisposed to develop BMS.\textsuperscript{21} The predisposition would be due to the greater innervation of that area and, therefore, the greater potential of loss of inhibition in case damage to the chorda

![Fig. 1. Proposed mechanism: ongoing equilibrium disruption induced by chorda tympani hypofunction leads to lingual nerve disinhibition and may generate central sensitization.\textsuperscript{21}](image-url)
tympani occurs. Based on those data, the purpose of the present study was also to evaluate the number of fungiform papillae/cm² in a group of patients suffering from BMS.

METHODS

This study was conducted at the Orofacial Pain Center, New Jersey Dental School, University of Medicine and Dentistry of New Jersey (UMDNJ), where treatment of BMS patients is provided on a regular basis. The Institutional Review Board at UMDNJ approved this study, which includes 2 different groups. Patients suffering from other chronic orofacial pain conditions, with burning pain due to surgery or trauma, <18 years old, or who were pregnant were excluded from the study.

BMS group

The BMS group included patients with a complaint of oral burning sensation for ≥3 months in an absence of any local or systemic causes that could explain the burning sensation. These patients underwent a complete clinical examination comprising a history of the present condition, a review of medical history, and physical examination including an intraoral examination. Also, to identify any underlying diseases as a source of intraoral burning symptoms, patients were referred for serologic screening, which included a basic metabolic panel, fasting glucose serum level, iron serum levels/ferritin, vitamin B₁₂ and folate levels, antinuclear antibodies anti–Ro/SS-A (SSA), anti–Ro/SS-B, and rheumatoid factor, thyroid-stimulating hormone, thyroxine, triiodothyronine, and complete blood count. Gastroesophageal reflux disease was ruled out by history, and sialometry was performed to rule out salivary hypofunction. Negative findings of the serologic results, combined with the history of the present symptoms, review of medical history, intraoral examination, and sialometry allowed a diagnosis of BMS to be made.

Control group

The control group included healthy subjects with no dental or oral pathologies and no oral pain or discomfort. Subjects in this group were matched with the BMS group for age and gender.

Data collection

Informed consent was obtained from each study participant. The subjects from the BMS and control groups underwent fungiform papillae count and evaluation of chorda tympani and lingual nerve function. In addition, the BMS group was also evaluated by means of sensory testing. The examinations were consistently performed at the same location by a calibrated examiner.

Fungiform papillae count. The photographic method to measure the density of fungiform papillae is a validated method reported in previous studies. The photograph of the tongue was taken with a closeup intraoral digital camera (Sony Cybershot 5.0 Mega Pixels Digit with Slave Ring Flash RF-5.0). A millimeter rule was placed in the photo. The image was transferred to a computer where a grid was superimposed on it. The grid was stretched to coincide with 1 cm markings on the ruler, thus creating boxes of 1 cm². Two squares were assessed bilaterally and the papillae contained within each representative square were counted, summed, and divided by 2, giving the average number of papillae/cm² (Fig. 2).

The pictures were randomly selected regardless of the group, and the number of fungiform papillae were independently counted by 2 calibrated investigators who were blinded to the diagnosis. The mean of the 2 results was calculated and used for data analysis.

Sensory assessment—current perception threshold. The sensory assessment of the chorda tympani and lingual nerves was performed through the electric detection thresholds. The lingual nerve function was assessed by using electric detection (tingling) threshold, and the chorda tympani nerve function was assessed by using electric taste detection threshold (electrogustatory test). Although the use of the electrogustatory test has generated controversy, it is considered to be a well-established and reliable clinical tool. Subjects under medications or medical conditions that could potentially alter the electric taste detection threshold results were excluded from the study.

A neurometer (Nervscan Analyzer) was used to induce electric current stimulus. The mental nerve territory (the lower lip area) was evaluated bilaterally for electric detection threshold (tingling sensation) as cal-
ibration and control. The left and right anterior two-thirds of the tongue were evaluated for electric taste and electric detection threshold (tingling sensation). A small amount of hypoallergenic conductive electrode gel was applied to the surface electrodes before placement (on the skin but not on the mucosa). A nonconductive soft white adhesive strip (Softape Neurotron) was used to hold Goldtrodes electrodes in place during extraoral stimulation. During tongue stimulation, the area was dried and isolated.

For the electric detection threshold, a train of constant-current electric stimulus was delivered to the skin or mucosa through 8-mm-diameter spherical disposable gold-plated electrodes. The electric detection and taste thresholds were evaluated via an ascending method of limits, and the stimulus frequency was 250 Hz.

Normally, electric stimulation of the tongue can provoke 2 different sensations. One is described as a tingling and the other as taste. The electric taste threshold in the tongue is easily recognized as a sensation often described as a “battery-like” or sour taste. The taste sensation is conducted via the chorda tympani and the tingling sensation via the lingual nerve. Therefore, electric detection threshold of the anterior two-thirds of the tongue can distinguish between the chorda tympani and lingual nerve functions.

The means by which electric taste stimulation occurs is not fully understood; however, besides affecting receptor cells bypassing the stimulus receptor, electric current may influence taste sensation by changes in the salivary pH. Hydrogen ions are discharged from the anode as a result of electric current, inducing a reduction in the pH of saliva. Consequently, ionic receptors are activated by acidic saliva, leading to a perception of sour taste.

The tongue tests were performed separately for taste and tingling sensations. The series for taste sensation was performed first. To determine the CPT value for the test series, the machine automatically determined the numbers of replicates (which were on average 3 or 4 trials). Once that was determined, the machine displayed the results as a range (maximum and minimum values of taste threshold). The mean value of the range for each site was calculated and used for data analysis.

The same procedure was performed for the series of tingling sensation. The CPT test was performed by 1 calibrated examiner. The automated design of the CPT testing procedure assured that neither the patient nor the operator could influence the test outcome based on subjective impressions. Even though the examiner was not blinded, the results could not be changed, because they were computerized. During the CPT determination procedure, neither the tester nor the subject was aware of the output parameters of the device throughout the testing session. The test was performed by 1 calibrated examiner.

Statistics

Statistical analyses were performed with StatView (1992-98; SAS Institute, Cary, NC). Unpaired Student t test was used to analyze the sensory assessment and number of fungiform papillae/cm² between BMS and control groups. Alpha level for significance was set at .05.

The electric test (taste and tingling) was compared based on the raw data of each side, and because of known interpatient variability of electric stimulation, the results were expressed as ratios (taste/tingling) as well. Normal range of the ratios and the reliability of this method were already validated in previous studies. The mental nerve territory was evaluated bilaterally for electric detection threshold as calibration and control. In the intraoral site, the left and right anterior two-thirds of the tongue were evaluated for electric taste and electric tingling detection thresholds. Taste/tingling ratios were performed for each side separately and then combined.

Because there is no literature describing the normal values for the number of fungiform papillae/cm², a normal range was considered to be within the range of ±2 SD of the mean calculated from the control group. Scores above (or below) were considered to be abnormal.

One-way analysis of variance (ANOVA) followed by Fisher protected least significant difference (PLSD test) was used to analyze differences in sensory assessment and duration of complaint.

RESULTS

A total of 45 subjects were included in this study: 25 subjects diagnosed with BMS and 20 healthy control subjects (control group). Women represented 80% of the subjects in the BMS group and in the control group. The mean age of the groups was BMS 58.0 ± 12.4 years (range 39-83 years) and control group 54.2 ± 7.2 years (range 44-71 years).

Sensory assessment was performed in the mental nerve territory (lower lip) for calibration. Electric detection thresholds obtained for the control subjects in the mental area of the right side (BMS 28.750 ± 4.507 μA, control 30.250 ± 4.953 μA; unpaired Student t test: \( P = .823 \)) and left side (BMS 31.875 ± 3.647 μA, control 34.500 ± 5.870 μA; unpaired Student t test: \( P = .696 \)) did not differ significantly from those of the BMS subjects.

The electric taste threshold mediated through the chorda tympani on the right side (BMS 232.800 ± 42.797 μA, control 80.333 ± 11.736 μA; unpaired
Student t test: \( P = .010 \) and left side (BMS 203.000 ± 41.875 \( \mu \)A, control 74.333 ± 11.607 \( \mu \)A; unpaired Student t test: \( P = .024 \); Fig. 3) was significantly elevated in BMS compared with healthy control subjects.

The electric taste/tingling detection threshold ratio was significantly higher in BMS subjects (mean ratio ± SEM: BMS 3.837 ± 0.797, control 1.610 ± 0.265; unpaired Student t test: \( P = .041 \); Fig. 4) compared with the control group.

There was no significant difference between the number of fungiform papillae/cm\(^2\) in the BMS subjects compared with the control group (BMS 27.554 ± 2.122, control 31.575 ± 3.112; unpaired Student t test: \( P = .277 \); Fig. 5).

In line with the objectives of this study to evaluate BMS subjects by means of sensory testing, an overall significant difference was observed in electric taste/tingling detection thresholds ratio between different duration of symptoms in BMS subjects. The electric taste/tingling detection thresholds ratio was significantly elevated in patients who had the onset of their symptoms for ≥41 months (1-way ANOVA: \( P = .031 \); Fig. 6). Values ranged from 2.732 ± 0.923 to 6.521 ± 1.631. Fisher PLSD pairwise comparisons showed that the differences were between the groups 3-20 months (\( n = 10 \)) and ≥41 months (\( n = 9 \); \( P = .024 \)) and between the groups 21-40 months (\( n = 6 \)) and ≥41 months (\( n = 9 \); \( P = .022 \)).

**DISCUSSION**

The results of this study confirm the findings of Eliav et al. (2007).\(^{22}\) The fact that the electric taste/tingling detection threshold ratio was significantly elevated in the BMS group compared with control subjects demonstrated hypofunction of the chorda tympani and supports the hypothesis that BMS is related to malfunction of the gustatory system. However, whether it is a cause or a result of this condition requires further investigation.

It is known that one of the major problems in BMS is the lack of concrete elements to make a precise diagnosis. Currently, there are no defined diagnostic criteria for BMS, which is usually reached by exclusion of other diseases, leading to misdiagnoses and presenting an obstacle to successful treatment. Therefore, there is a potential for clinicians to use an elevated taste/tingling ratio to support a diagnosis of BMS. Further
studies are necessary to validate this method as a diagnostic tool.

The fact that the electric taste detection threshold ratio was enhanced in the BMS group demonstrated that more stimulus was necessary to obtain a response from the chorda tympani compared with the control group, indicating, therefore, the malfunction (hypofunction) of the chorda tympani in BMS patients. Higher thresholds in BMS patients using electrogustometry test have been reported in the literature.38,39 These are further confirmed by the electric taste threshold, which was also elevated in BMS compared with control subjects. Additionally, the fact that there was no difference in the mental nerve territory on the electric tingling detection threshold between the BMS and control groups confirms the consistency of the data.

Damage to the chorda tympani is believed to occur after viral or respiratory infections, otitis media, head trauma, or the use of medications, which can affect both women and men. Damage to the chorda tympani is also believed to occur owing to loss of estrogen at the time of menopause, which could explain the higher prevalence of BMS in postmenopausal women.40

The interactions between the cranial nerves that mediate taste and the trigeminal nerve have been demonstrated; therefore, an investigation to determine if damage to other cranial nerves that mediate taste plays a role in BMS would be of interest.16,17

The electrogustatory test has a number of limitations that has to be considered. Even though the tongue was dried and isolated at the time of the examination, it is known that variations in salivary composition and quantity could alter electric taste thresholds. In addition, electrode size, composition/material, and distance between the electrodes may also affect electric taste.41,42 Furthermore, older individuals present a high resistance to the flow of electric current owing to their skin; therefore, to minimize intersubject variability, earlier studies expressed results as a ratio for each tested area (the electric detection threshold of the affected side divided by the electric detection threshold of the contralateral side).43-46 Nevertheless, in BMS the use of side-to-side ratios for the tongue has no value, because this is often a bilateral condition; however, because the innervation of anterior two-thirds of the tongue is supplied by 2 sensory nerves (chorda tympani for taste and lingual nerve for other sensations), the electric taste/tingling detection thresholds ratio may be a repeatable and reliable measure.24

The recent literature also has hypothesized that individuals genetically endowed with a larger number of fungiform papillae would be more susceptible to develop BMS owing to the increased innervation of that area; therefore, they would be “superperceivers” presenting a larger potential of loss of inhibition if they incur damage to the chorda tympani.21,26 Contrary to what was hypothesized, in the present study the number of fungiform papillae was not significantly increased in BMS compared with control subjects; however, this result cannot discard the role of fungiform papillae in BMS.

Importantly, we found that patients suffering from BMS for a prolonged period of time had increased electric taste/tingling detection threshold ratio. A possible explanation for this finding could be the presence of a degenerative process involving nerve damage. Lauria et al. (2005)47 reported that, compared with control subjects, BMS patients demonstrated significantly lower density of epithelial nerve fibers, which tended to correlate with the duration of symptoms.
Moreover, epithelial and subepithelial nerve fibers showed dispersed structural changes suggesting axonal degeneration.

Neuropathic pain syndromes are sensory disorders that occur from changes after damage or dysfunction of the peripheral or central neural pathways. Several types of injury to primary afferents can cause persistent pain and destruction by metabolic, chemical, or infective (virus) diseases leading to neurodegeneration. Recently, Woda et al. (2009) proposed the neurodegeneration associated with the drastic decline of neurosteroids after the concomitant falls of gonadal and adrenal steroids as a possible mechanism for BMS. Further studies are necessary to clarify this finding.

CONCLUSIONS

The results of the present study confirm earlier findings demonstrating chorda tympani hypofunction in BMS subjects. The elevated electric taste detection threshold and the elevated electric taste/tingling detection threshold ratio are potentially useful tools to support clinicians in the diagnosis of BMS. Future studies are necessary to validate this method as a diagnostic tool.

In addition, patients suffering from BMS did not present with more fungiform papillae/cm² per area on the dorsum of the tongue compared with control subjects. However, this result cannot rule out the role of fungiform papillae in the pathophysiology of BMS.

In the BMS group, subjects with a complaint of longer duration presented with a significantly elevated tingling/taste detection threshold ratio, indicating a possible neurodegenerative process involving BMS. Nevertheless more studies are necessary to clarify this finding.

REFERENCES


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