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ORIGINAL ARTICLE

Somesthetic, gustatory, olfactory function and salivary flow in patients with neuropathic trigeminal pain

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OBJECTIVES: To determine somesthetic, olfactory, gustative and salivary abnormalities in patients with burning mouth syndrome (BMS), idiopathic trigeminal neuralgia (ITN) and trigeminal postherpetic neuralgia (PHN).

SUBJECTS AND METHODS: Twenty patients from each group (BMS, ITN, PHN) and 60 healthy controls were evaluated with a systematized quantitative approach of thermal (cold and warm), mechanical, pain, gustation, olfaction and salivary flow; data were analyzed with ANOVA, Tukey, Kruskal–Wallis and Dunn tests with a level of significance of 5%.

RESULTS: There were no salivary differences among the groups with matched ages; the cold perception was abnormal only at the mandibular branch of PHN ($P = 0.001$) and warm was abnormal in all trigeminal branches of PHN and BMS; mechanical sensitivity was altered at the mandibular branch of PHN and in all trigeminal branches of BMS. The salty, sweet and olfactory thresholds were higher in all studied groups; the sour threshold was lower and there were no differences of bitter.

CONCLUSION: All groups showed abnormal thresholds of gustation and olfaction; somesthetic findings were discrete in ITN and more common in PHN and BMS; central mechanisms of balance of sensorial inputs might be underlying these observations.

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Keywords: sensorial interaction; facial sensibility; orofacial pain; trigeminal nerve; taste; olfactory threshold; gustation; neuropathic pain; quantitative sensory testing

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Introduction

Trigeminal postherpetic neuralgia (PHN), idiopathic trigeminal neuralgia (ITN) and burning mouth syndrome (BMS) are the most common neuropathic pain syndromes that affect the facial region. Neuropathic pain is associated to abnormalities in the peripheral (PNS) and/or central nervous system (CNS) (Kost and Straus, 1996), such as neuroplastic changes, cellular death, facilitation and long term potentiation of synapses, which may cause sensorial abnormalities (Watson *et al*, 1991). At the trigeminal area, the taste and smell perception are involved in the sensorial input of the oral and nasal cavity.

Besides somesthetic abnormalities, altered gustation has been identified in trigeminal neuropathic pain (Grushka and Sessle, 1988; Grushka *et al*, 2003; Femiano *et al*, 2008). However, in the current scientific literature, it was not possible to find controlled comparative studies with complete sensorial evaluation of these patients including the olfaction and salivary flow, which are important parts of taste perception. These findings can essentially contribute to the understanding of physiopathological mechanisms of these diseases. Thus, the objective of this study was to determine the somesthetic, olfactory, gustative and salivary flow abnormalities in patients with BMS, ITN and PHN compared with controls.

Material and methods

This research was approved by the Ethics Committee of Hospital das Clinicas, Medical School, University of Sao Paulo (HC-FMUSP), and all patients signed the informed consent. Sixty ($n = 60$) consecutive patients diagnosed as BMS ($n = 20$), ITN ($n = 20$) and PHN ($n = 20$) according to the International Association for the Study of Pain (IASP) criteria (Merskey and Bogduk, 1994) were evaluated at the Orofacial Pain Team of HC-FMUSP between August 2007 and January 2008 and compared with 60 healthy subjects divided into two groups according to the ages: CG1 ($n = 30$): 18–50

years old; and CG2 (n = 30): 51–85 years old. This division was made to match the controls to the study groups considering that ages can affect the sensorial perception.

Inclusion criteria
Absence of oral infection or injury at the oral mucosa, agreement in participating of the study, diagnosis by IASP, normal cognitive function that would allow the psychophysics tests and the understanding of the protocol were the inclusion criteria.

Exclusion criteria
Infection or inflammation of the superior airways in the last 15 days before the examination, daily smoking of drinking habits, systemic disease that could cause pain (e.g. fibromyalgia, diabetes mellitus, rheumatoid arthritis), alter the salivary flow (e.g. Sjögren Syndrome) or alter the sensorial function (e.g. Hansen's disease) were the exclusion criteria.

Mean pain intensity by the Visual Analogue Scale was 8.9 (range 6–10), and all patients had more than 2 years of disease (mean 6.9, range 2–15). The affected branches of ITN were: V3 (9 patients), V2-3 (8), V2 (1), V1 (1), V1-2-3 (1); the affected branches of PHN were: V1 (14 patients), V2 (2), V2-3 (2), V1-2-3 (1), V1-2 (1). All patients with BMS had burning at the tongue and palate.

Initially, it was checked if the patients were fasting during the last 2 h, and did not have had any medication within the last 48 h to start with the protocol. The medication for PHN (amytriptiline) and ITN (carbamazepine) was not suspended previously because of ethical concerns. All the patients were evaluated between 1 and 4 PM to avoid the variation of the salivary flow and sensorial perception because of the circadian cycle.

Salivary flow
The evaluation started with the quantitative non-stimulated salivary flow analysis by the following method: two pieces of cotton were placed into a plastic device and weighed in a calibrated balance of accuracy (Acculab® V1200, Sartorius AG, Germany). The patient was oriented to swallow the saliva inside the mouth, and the cotton was placed and kept during 5 min below the tongue of the patient, which was oriented to do not swallow during this period of time. After that, the cotton was removed and placed again in the plastic device, weighed and the difference of weight (before and after the evaluation) was divided into five to calculate the salivary flow (g min^{-1}) (Pupo *et al*, 2002).

Sensorial evaluation
After the evaluation of salivary flow, all subjects underwent a standardized protocol of superficial facial perception, which was applied in distinct areas of the face (bilateral trigeminal branches in the following order); in the intraoral area, only pain thresholds were evaluated (superior and inferior arches: bilateral vestibular gingiva) (Siqueira *et al*, 2006):

1 Thermal perception – cold and warm perception (Electrical device designed at the Functional Neurosurgery Division – HC-FMUSP).
2 Mechanical/tactile perception – microfilaments of vonFrey.
3 Pain perception – superficial algometry (Micromar®; Diadema, São Paulo, Brazil).

Each thermal and mechanical stimulae was applied three times, and the threshold would be identified if the subject had recognized at least two of the three applications; if not, the next stimulae in crescent order would be applied, to avoid tolerance effect. The algometry was performed with a superficial device and a disposable needle of 0.7 × 15 mm.

4 Gustative thresholds in the following molar concentrations (Bartoshuk, 1989; Davidson and Murphy, 1997):

Sweet (glucose): 0.01; 0.032; 0.1; 0.32; 1.0
Sour (citric acid): 0.01; 0.032; 0.1; 0.32; 1.0
Salty (Sodium chlorate): 0.01; 0,032; 0.1; 0.32; 1.0
Bitter (urea): 0.01; 0.032; 0.1; 0.32; 1.0

A single drop for each concentration was applied and swallowed by the patient, compared with a single drop of distillate water; if not felt, the next concentration would be applied. Between different taste modalities, the patient had the mouth washed with distillate water.

5 Olfactory threshold with isopropanol solutions (9.9; 15; 23.3; 32; 48; 53; 70%; Cain, 1989; Davidson and Murphy, 1997). Each concentration and a bottle of water were together offered to the patient, whom should choose the one with the substance for three times; if the correct one was chosen all times, the threshold was identified. If not, the next concentration was offered with the bottle of water.

All subjects evaluated were in the sitting position, with the head resting in a flat surface and Frankfurt line parallel to the soil and in a silent room with acoustic protection at the walls and the door closed. Only the patient and the researcher were at the room. All patients were evaluated by the same researcher. The patients and controls received the same instructions after been positioned, which were: to keep the eyes closed during the exam, and that stimulus would be applied at their face and mouth and they should identify and report if they felt and what they felt (by saying 'yes' or 'no' and 'which was the stimulus'). Only the researcher knew the order of the stimuli. Finally, all findings were tabled and statistically analyzed.

Statistical analysis
All data were tabled and the frequencies, means, standard deviations and ranges were compared among the groups with the statistical tests: demographic characteristics, algometry, olfaction, gustation and salivary flow were analyzed with ANOVA 1 factor and Tukey test; Kruskall–Wallis and Dunn tests were used for warm, cold and tactile perceptions. The level of significance was 5%.

Table 1 Demographic characteristics of the study and control groups: the controls were divided into two groups according to the ages in order to match with the patients ($n = 120$)

Groups (n)	*Gender*		*Ages (years), mean (±s.d.)*	*Matching* (P = *0.33*)*
	Female	*Male*		
PHN (20)	12	8	71.33 (±8.16)	A
ITN (20)	10	10	61.50 (±8.97)	B
BMS (20)	16	4	60.95 (±12.21)	B
CG1 (30)	15	15	41.60 (±6.68)	B
CG2 (30)	21	9	70.60 (±10.45)	A

PHN, trigeminal postherpetic neuralgia; ITN, idiopathic trigeminal neuralgia; BMS, burning mouth syndrome; CG, control group.
*Statistical significance – ANOVA 1 factor and Tukey test.

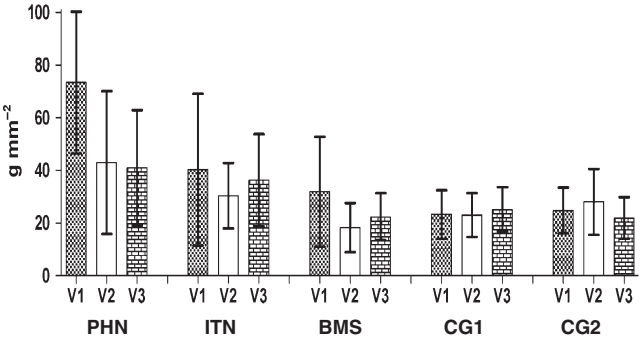

Figure 1 Columns of algometry thresholds: means and standard deviations; the higher pain threshold was at the ophthalmic branch of PHN (g mm^{-2}; $n = 120$). PHN, trigeminal postherpetic neuralgia; ITN, idiopathic trigeminal neuralgia; BMS, burning mouth syndrome; CG, control group

Results

Demographic characteristics

The demographic characteristics and the homogeneity of gender and ages among the groups can be observed in Table 1.

Salivary flow

Table 2 shows the means and standard deviations of salivary flow (g min^{-1}) of the study and control groups; we can observe that PHN was similar to the older controls, and different from other subjects.

Table 2 Means and standard deviations of salivary flow (g min^{-1}) ($n = 120$)

Groups	*Salivary flow* (P = *0.001**)
PHN	0.1436 (±1.32) A
ITN	0.2881 (±0.02) B
BMS	0.2958 (±0.00) B
CG1	0.3131 (±0.01) B
CG2	0.1629 (±0.00) A

PHN, trigeminal postherpetic neuralgia; ITN, idiopathic trigeminal neuralgia; BMS, burning mouth syndrome; CG, control group.
*Statistical significance – ANOVA 1 factor and Tukey test.

Sensorial evaluation

Somesthesia (thermal, mechanical and pain evaluation). We can observe in Table 3 the results of thermal and mechanical perception tests analyzed by Kruskall–Wallis. The cold perception was only abnormal at the mandibular branch of PHN; ITN had no thermal or mechanical abnormality. Algometry showed higher thresholds at the ophthalmic branch of the PHN patients (Figure 1). There were no intraoral differences of thresholds in the sensorial evaluation ($P = 0.87$; Table 4).

There were significant differences in three of the four basic flavors (sweet $P = 0.001$; salty $P = 0.004$; sour $P = 0.0001$) by the Kruskall–Wallis and Dunn tests; the sweet and salty thresholds were higher and the sour threshold was lower than the control groups (Figure 2). There were no statistical differences in the bitter threshold ($P = 0.1694$) in the study groups. The olfaction thresholds were higher in all patients when compared with controls ($P = 0.0389$; Figure 2).

Discussion

The quantitative sensory testing allows the measurement of the sensitive perception for the comprehension of sensorial interaction in humans with neuropathic pain.

Table 3 Thermal and mechanical evaluation of study and controls at all trigeminal branches; only PHN had abnormal cold perception and ITN had no thermal or mechanical abnormalities ($n = 120$)

	Cold			*Warm*			*Mechanical/tactile*		
	V1 (P = *0.46*)	*V2* (P = *0.79*)	*V3* (P = *0.001*)	*V1* (P = *0.001*)	*V2* (P = *0.001*)	*V3* (P = *0.001*)	*V1* (P = *0.001*)	*V2* (P = *0.004*)	*V3* (P = *0.001*)
PHN	5	4	11*	7*	4*	7*	3	1	10*
ITN	3	3	3	2	3	2	4	3	3
BMS	5	6	5	5*	6*	6*	8*	8*	8*
CG1	6	7	7	0	0	0	3	1	4
CG2	3	8	8	0	0	0	1	1	1

PHN, trigeminal postherpetic neuralgia; ITN, idiopathic trigeminal neuralgia; BMS, burning mouth syndrome; CG, control group; *V*1, ophthalmic branch; *V*2, maxillary branch; *V*3, mandibular branch.
*Statistical significance – Kruskall–Wallis test ($P < 0.05$).

Table 4 Pain thresholds in the intraoral region (superior and inferior vestibular gingiva)

	*V*2	*V*3
PHN	18.89 ± 19.06	26.10 ± 23.80
ITN	21.50 ± 22.77	18.00 ± 18.23
BMS	21.00 ± 19.17	21.00 ± 19.17
CG1	27.00 ± 26.59	27.00 ± 26.59
CG2	28.67 ± 28.49	28.67 ± 28.49

There were no statistical differences among the groups ($P = 0.87$; $n = 120$).
PHN, trigeminal postherpetic neuralgia; ITN, idiopathic trigeminal neuralgia; BMS, burning mouth syndrome; CG, control group; *V*2, maxillary branch; *V*3, mandibular branch.
*No statistical significance – ANOVA 1 factor and Tukey test ($P = 0.87$).

In facial pain, it is not possible to evaluate sensation without the inclusion of the perception of taste, characterized by the association of olfaction and gustation. In our study, we could observe abnormalities in almost all sensorial modalities that were studied, which shows evidence of neuropathic mechanisms involved in these diseases. Currently, among the accepted theories for trigeminal neuropathic pain with undetermined cause, such as BMS, the sensorial unbalance between the gustatory and trigeminal inputs seems to be involved in the physiopathology (Grushka *et al*, 2006). In this study, we included the salivary flow analysis because it is known that saliva has an important role in the transduction of the signals at the oral cavity, not only gustative but also somesthetic, mediated by the trigeminal nerve (Hershkovich and Nagler, 2004). Thus, by this standardized methodology and the comparison of patients with three of the most commons neuropathic pain syndromes of the trigeminal system with matched controls, we presented a standardized protocol for the analysis of sensorial abnormalities that are involved in trigeminal neuropathic pain, and the main findings and hypothesis.

Salivary flow and sensitivity

The objective of investigating the salivary flow was to identify possible abnormalities that could underlie the sensorial findings of our results, and in this sample, matching the patients with the controls by the ages, we could observe that there were no differences. In BMS, it has already been described that patients do not have salivary flow abnormalities and that xerostomia should be a diagnostic of exclusion; our data also showed the same results than previous analysis (Grushka and Sessle, 1988; Bergdahl and Bergdahl, 1999). However, it is the first study that investigated the salivary flow of patients with ITN and trigeminal PHN, and we can also see that there were no differences in these other trigeminal neuropathic pains about the salivary flow. Thus, by these findings, salivary flow does not play a role in the sensorial findings at the oral cavity in these patients.

Gustative and olfactory findings

All the patients presented gustative and olfactory abnormalities which were similar among the study groups and support unspecific central mechanisms in all diseases. Taste complaints are common in other pain patients (Kamath *et al*, 1983; Perros *et al*, 1996). It is interesting to observe that the bitter taste was normal in all groups, and a possible reason for that is the mediation of this sensation by the glossopharyngeal nerve with different central pathways than the interaction of the trigeminal and chorda-tympani afferents. Other interesting finding is the lower threshold of sour; the acid radicals are also involved in the pain perception, and it is possible that, in these patients with central sensitization, pain fibers to be sensitized to these radicals.

Idiopathic trigeminal neuralgia

Our anterior results show that trigeminal somesthetic abnormalities can be evidenced in ITN, although discrete (Siqueira *et al*, 2006), similar to other findings in the same patients (Synai *et al*, 2003). In this controlled sample, we could observe that among trigeminal abnormalities, ITN had the most discrete findings and that only the pain thresholds were increased. Patients with clinical symptoms of ITN can present vascular compression of the trigeminal root at the entry zone, which needs to be excluded as a primary cause, and abnormal myelin findings can be associated or not to that compression, resulting in nerve damage at this area. It is known that the compression is not present in all patients, and that there are normal subjects that may have vascular compression with no pain (Peker *et al*, 2009). This study supports that central mechanisms are more important in the physiopathology of

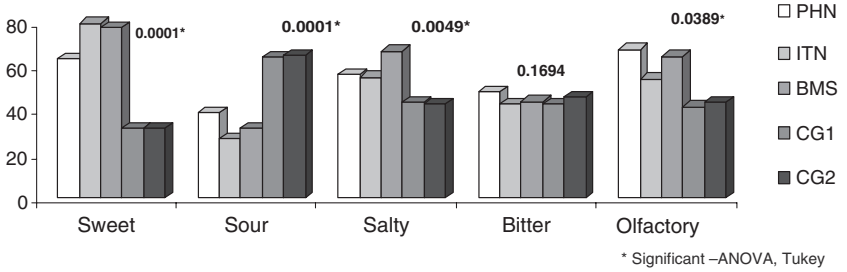

Figure 2 Columns of gustation (molar concentrations) and olfaction (percentages) thresholds: means and standard deviations. The sweet, salty and olfactory thresholds were higher and the sour threshold was lower in the studied groups ($n = 120$). PHN, trigeminal postherpetic neuralgia; ITN, idiopathic trigeminal neuralgia; BMS, burning mouth syndrome; CG, control group

ITN than the peripheral damage by the compression itself. The paroxysmal shock-like component is associated with the observed preserved function of tactile large fibers, in the same circumstances than in allodynia, and the central inhibition of pain fibers due to activation of the descendent system is probably responsible for the higher pain thresholds that were the only trigeminal evidence, supporting the central theory of this disease.

Trigeminal postherpetic neuralgia

Among the three studied syndromes, PHN showed higher algometry thresholds, especially at the ophthalmic branch similar to our previous data (Alvarez *et al*, 2007), and it was the only one that had differences in the cold perception, besides the abnormalities in all trigeminal branches for warm perception. On the other hand, interestingly, the mandibular branch was affected in all sensorial modalities despite the prevalence of the disease at the ophthalmic branch. PHN is characterized by intense allodynia and non-paroxysmal pain associated to sharpening episodes triggered by light stimuli (Kost and Straus, 1996); our results show that the peripheral tactile fibers are preserved and involved in the allodynia of trigeminal PHN mainly at the ophthalmic branch, and that the pain fibers at the peripheral system are also centrally inhibited such as ITN hypothesis. The preservation of small peripheral fibers is also supported by the preference of the virus about infecting large fibers (Nordenboos, 1959; Insinga *et al*, 2005) and the hypoalgesia and thermal abnormalities that occurred only in trigeminal branches not affected by the infection (maxillary and mandibular). The sensorial findings at the mandibular and maxillary branches are more due to central plastic changes with the progression of the disease after the healing of the infection, therefore studies with a long-term follow up of these patients would elucidate if these abnormalities occur only with the progression of the disease or if they are present close to the period of infection.

On the other hand, it is interesting to observe that PHN and BMS, both having non-paroxysmal pain and burning complaints, had all trigeminal branches with higher warm thresholds. It is possible to hypothesize that the abnormal function of warm afferences could be responsible for the burning complaint in these patients, mediating the perceived neuropathic pain as evidenced in other studies.

Burning mouth syndrome

Burning mouth syndrome is the most studied disease about its sensorial abnormalities (Jaaskelainen *et al*, 2005; Grushka *et al*, 2006) and as expected showed tactile abnormalities, which possibly are associated with peripheral nerve losses as observed in other studies of biopsies of peripheral tissues of the tongue (Eliav *et al*, 2007). Among the studied diseases, it was the only one that has been studied about peripheral mechanisms, and signs of peripheral degeneration have been demonstrated. These data and the previous findings support that these mechanisms are important only in BMS, among the studied diseases, but that the gustatory abnormalities are not exclusive of this one, possibly more a consequence than a cause of the chronic neuropathic pain, the same for the olfactory abnormalities. Our theory is that the peripheral abnormalities can underlie this disease, by peripheral large fibers degeneration, and that the gustative, olfactory, warm and pain findings are consequences of central plastic changes after chronification, causing the burning sensation by the abnormal warm perception. For the understanding if the peripheral degeneration is the start of the disease or if it is idiopathic, new cohort studies within the population are necessary.

By our results, we suggest that central neuroplastic phenomena are involved in all patients by the abnormal thresholds of gustation and olfaction. One hypothesis is the unbalance of the inputs arriving at the CNS, which is underlying it by the dysfunction of some modalities of sensation resulting in the regulatory function of the other modalities, considering the sensory system as a unique form of consciousness of the interacted sensations. Limitations are the fact that psychophysics are subjective and depend on the collaboration of the patient and on a range of quantity of stimuli, but human subjects can be well analyzed by this methodology, and some neuropathic painful diseases such as the idiopathic ones do not have good animal models. It is important to state a limitation of the study, which was the impossibility of suspending the medication of the patients before 48 h of evaluation due to ethical issues. Medication can also influence salivary flow and perception, and the 48 h of interval without medication could only partially wash out the drugs.

Some of the important contributions of this study are the investigation of olfactory threshold besides the gustative evaluation, and the salivary flow evaluation. Gustatory and olfactory abnormalities could be a cause or a consequence and it was not the objective of this study.

In the intraoral evaluation, the pain thresholds were similar among the studied groups, and it can be supported but the similarities that the pain thresholds presented in the extraoral maxillary and mandibular branches.

In conclusion, all groups showed abnormal thresholds of gustation and olfaction; somesthetic findings were discrete in ITN and more common in PHN and BMS; central mechanisms of balance of sensorial inputs might be underlying these observations.

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