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Original article

Burning mouth syndrome and Reflux Disease: relationship and clinical implications

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Abstract. *Background and aim:* An association between reflux and burning mouth syndrome (BMS) has been proposed for a long time, although there is little evidence of a connection. Aims of this study were threefold: 1) to investigate the frequency of BMS in a sample of GERD patients showing both typical and atypical symptoms; 2) to measure a non-invasive marker of GERD, i.e. serum Gastrin 17, in a sample of BMS patients; 3) to assess the efficacy of different therapeutical schedules for GERD in BMS patients. *Methods:* We divided the study in 3 main steps. In step one, we selected 500 consecutive GERD patients to analyze type and frequency of extraesophageal manifestations of reflux disease, including BMS. In step two, we selected 124 consecutive BMS patients and collected data about symptoms presentation and serum gastrin 17 levels. In step three, we performed a follow-up evaluating the efficacy of 3 different drugs on BMS. *Results:* In step one, 204 patients complained heartburn; 31 pharyngeal globus; 52 chronic cough; 54 pharyngitis; 31 postnasal drip; 56 burning mouth symptoms; 34 noncardiac chest pain; 17 asthma and 21 sleep apnea. In step two, 29 patients had gastrin-17 ≤ 1 pg/L; 64 patients between 1 and 3; and 31 patients ≥ 3. In step three, 49 patients reported slight benefit with PPI, 75 no benefit. 61 patients reported slight benefit with sodium alginate and sodium bicarbonate, 63 no benefit. 23 reported an almost complete remission with HYCHSA, 26 slight benefits, 33 no benefit. *Conclusions:* Prevalence of BMS in GERD patients was similar to that reported for chronic chough and pharyngitis. Low levels of Gastrin 17 were found in the majority of BMS patients. Finally, we observed a greater benefit from barrier drugs therapy than from PPI therapy in BMS patients. (www.actabiomedica.it)

Key words: Stomatodynia, glossodynia, burning mouth syndrome, gerd, reflux, gastroesophageal reflux disease

Introduction

Burning mouth syndrome (BMS) is defined in the International Classification of Orofacial Pain (ICOP) as an intraoral burning or dysaesthetic sensation, recurring daily for more than two hours per day for more than three months, without evident causative lesions on clinical examination and investigation (1). BMS was previously classified as secondary, when related to local causes or systemic conditions now coded to these disorders, and primary when such conditions were excluded. Nowadays, the latest available classification distinguishes between BMS with or without somatosensory changes based on quantitative sensory testing (1). The tongue appears to be the most affected area and the involvement is usually bilateral and symmetrical. The pain, described as a burning sensation or dysesthesia, tends to worsen during the day in most cases (2). The global prevalence of BMS was estimated to be 1.73% in population studies, albeit with wide differences between geographic areas, with a prevalence in Asia (1.05%) lower than that of Europe (5.58%) and

North America (1.10%). There are also differences between genders and ages with the prevalence in female (1.15%) higher than in male (0.38%) and a higher prevalence for people over 50 (3.31%) than for people under 50 (1.92%) (3).

Regarding the etiology of BMS, it is still considered idiopathic, although there is some evidence of a neuropathic damage whose primary cause has not yet been defined, many factors could in fact be involved such as hormonal changes, reflux, microbiota, aging. But nothing has been proven yet (4).

An association between reflux and BMS has been proposed for a long time, although there is little evidence of a connection. In particular, a study by Lechien and colleagues, showed a higher prevalence of BMS in patients with laryngopharyngeal reflux (LPR). According to the same authors, a combination of diet, PPIs, and alginate/magaldrate demonstrated to be effective in relieving symptoms in patients with BMS; however, they did not investigate separately the effectiveness of the single components of the therapy (5).

Aim

For these reasons, aims of this study were to evaluate the effectiveness of different drugs, usually used to treat reflux diseases, on the relief of BMS symptoms; to evaluate symptomatic characteristics and clinical presentation of patients with BMS referred to the gastroenterologist for reflux disease and to assess the frequency of extraesophageal manifestations of gastroesophageal reflux disease (GERD) in a sample of consecutive patients referred to a second level center.

Methods

We divided the study in 3 main steps. During first step we selected 500 consecutive patients (234 F, mean age 49 yrs, range 22-71) with endoscopically proved diagnosis of esophagitis or with a pH-impedance or pH-metry suggestive of reflux referred to a second level center to analyze type and frequency of extraesophageal manifestations of reflux disease with a particular focus on BMS-type symptoms. In the second phase of the study, we selected 124 consecutive patients (73 F, mean age 53 years, range 22-71) with a diagnosis of BMS according to the International Classification of Orofacial Pain, 1st edition (ICOP) diagnostic criteria (1), (Table 1).

During this step we orally questioned the patients about demographics, information about dietary and life-style habits, presence and severity of BMS symptoms, previous therapies performed, as well as tests performed for GERD diagnosis. In the attempt of characterize BMS from a pathophysiological point of view, we measured fasting serum levels of Gastrin 17, as non-invasive marker of GERD (6,7), by using an ELISA method (Biohit Helinki, Finland). Finally, we performed a follow-up (mean follow-up time: 3 months, range: 2-6 months), of these patients evaluating the efficacy of 3 different types of drugs on the relief of oral BMS symptoms: proton pump inhibitors (PPI); a melt-in-mouth medical device composed by an oral combination of hyaluronic acid, chondroitin sulfate and aluminum (HYCHSA: 1100 mg, GERD-OFF© SOFAR S.p.A., Trezzano Rosa, Italy); tablets of sodium alginate and sodium bicarbonate. Clinical outcome of therapy was assessed by means of two tools: visual analogue scale (VAS ranging from 0-10 where 10 represents the worst bearable pain and symptomatic score (S.S.) which attributes three different scores to each of the four considered symptoms (oral burning, dysgeusia, xerostomia, dysesthesia). The sample was collected in a unique gastroenterological center located in North-east of Italy.

Table 1. Diagnostic criteria for BMS according to the International Classification of Orofacial Pain, 1st edition (ICOP).

Diagnostic criteria for BMS:
A. Oral pain fulfilling criteria B and C
B. Recurring daily for >2 hours per day for >3 months1
C. Pain has both of the following characteristics: 1. burning quality 2. felt superficially in the oral mucosa
D. Oral mucosa is of normal appearance, and local or systemic causes have been excluded
E. Not better accounted for by another ICOP or ICHD-3 diagnosis

This is a prospective, open label, not randomized monocentric study.

During this phase, after signing the informed consent, patients underwent base-line visit, with collection of demographics, information about dietary and life-style habits, previous therapy taken as well as presence and severity of BMS symptoms. Severity was graduated as follows: 0= absence of symptoms, 1= occasional, 2= continuous, with symptomatic score ranging from 0 to 8 altogether. Both VAS and S.S. were collected in a semi structured way at baseline (T0) and after the period of follow-up on therapy (T1) (Figure 1).

Statistical analysis

Continuous variables were reported as mean, standard deviation (SD), range; 95% confidence interval was provided for mean, when applicable. Changes from baseline for VAS and G.S.S. were evaluated by a Student test for pair data. All statistical analysis were performed using SPSS 28.0 statistics software.

Statement of Ethics

This study was performed in accordance with the declaration of Helsinki, following approval from ethical committee of S. Bortolo Hospital Vicenza (Vi), Italy, approval number: 92687, with informed consent form from the patients being waived off.

Results

First phase

500 consecutive patients (234 F, mean age 49 yrs, range 22-71) with endoscopically proved diagnosis of esophagitis or with a pH-impedance or pH-metry suggestive of reflux were enrolled, of those 204 (95 F, mean age 47 yrs) complained heartburn as main symptom; 31 (24 F, mean age 51 yrs) pharyngeal globus; 52 (18 F, mean age 48 yrs) cough; 54 (22 F, mean age 54 yrs) pharyngitis; 31 (14 F, mean age 50 yrs) postnasal drip; in 56 patients (41 F, mean age 51 yrs) burning

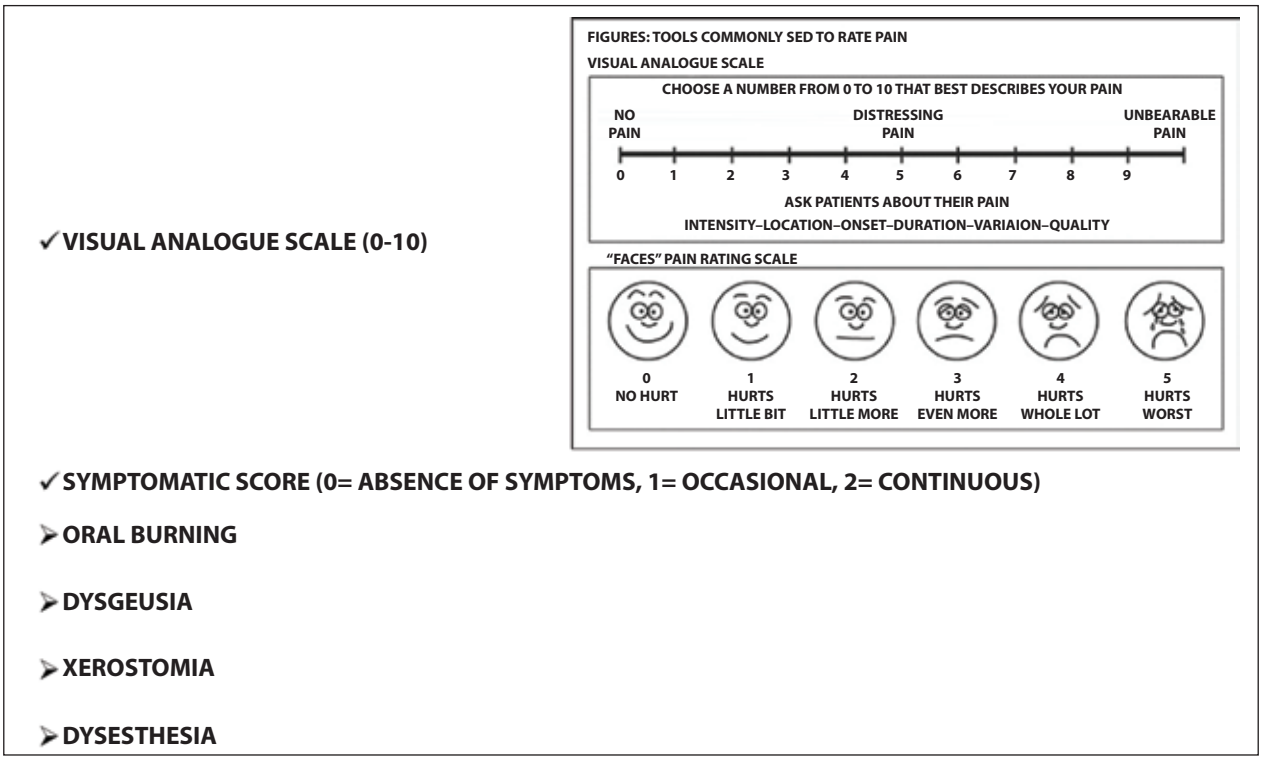

Figure 1. Visual Analogue Scale and Symptomatic Score for clinical outcome assessment.

mouth symptoms were prevalent; 34 (5 F, mean age 53 yrs) with noncardiac chest pain (NCCP); 17 (12 F, mean age 33 yrs) with asthma and 21 patients (3 F, mean age 58 yrs) who mainly complained sleep apnea.

Second phase

During this phase we selected 124 BMS patients (73 F, mean age 53 yrs, range 22-71), among those 54 underwent esophagogastroduodenoscopy (EGD): 9 patients had a diagnosis of esophagitis, while 45 had non-erosive reflux disease (NERD). All patients underwent serum gastrin-17 analysis: 29 patients had a value of gastrin-17 ≤ 1 pg/L; 64 patients between 1 and 3 pg/L; and 31 patients had a value of gastrin-17 ≥ 3 pg/L. Regarding symptoms, 41 patients had burning pain localized to the tongue, while 83 had it spread to the entire oral cavity. All patients also complained a certain degree of dysgeusia, with 53 of them reporting a feeling of acid in the mouth, 44 a feeling of bitter, while 27 patients reported a feeling of sweetish in the mouth.

Third phase

All 124 BMS underwent PPI therapy continuously for at least 2 months. 49 reported slight benefit on oral symptoms (VAS at T0=7, T1=4, p<0.1; S.S. at T0=8, T1=4, p<0.1) while 75 patients reported no benefits (VAS at T0=6, T1=6 p=n.s.; S.S. at T0=7, T1=6, p=n.s.). After this first step the same patients took tablets of sodium alginate and sodium bicarbonate three times a day (after breakfast, after lunch, at bedtime) off-therapy from PPI for at least two weeks. Sixty-one patients reported slight benefit (VAS at T0=6, T1=3, p<0.1; S.S. at T0=7, T1=3, p<0.1) while 63 reported no benefit on oral symptoms (VAS at T0=7, T1=6, p=n.s.; S.S. at T0=6, T1=7, p=n.s.). Finally 82 patients (48 F, mean age 51 yrs, range: 22-71) underwent therapy with HYCHSA 1100 mg (GERD-OFF©), three times a day (after breakfast, after lunch, at bedtime), of those 23 reported an almost complete remission of oral symptoms (VAS at T0=7, T1=2, p<0.01; S.S. at T0=8, T1=3, p<0.01), 26 a slight benefit (VAS at T0=6, T1=3, p<0.1; S.S. at T0=7, T1=4, p<0.1) while 33 patients reported no benefit on BMS symptoms (VAS at T0=7, T1=6, p=n.s.; S.S. at T0=6, T1=5, p=n.s.). Table 2 summarizes the overall results.

Discussion

The first important finding that emerges from this study is that 11.2% of the 500 GERD patients enrolled had burning mouth as their main symptom. A much

Table 2. Efficacy of different drugs on relief symptoms in BMS patients.

PPI (124 pts)		**Sodium alginate ad sodium bicatbonate (124 pts)**		**HYCSA (82 pts)**	
49 pts (slight benefit)		61 pts (slight benefit)		23 pts (almost complete remission)	
T0	**T1**	**T0**	**T1**	**T0**	**T1**
VAS 7	**VAS 4**	**VAS 6**	**VAS 3**	**VAS 7**	**VAS 2**
SS8	**SS4**	**SS7**	**SS3**	**SS8**	**SS3**
75 pts (no benefit)		63 pts (no benefit)		26 pts (slight benefit)	
T0	**T1**	**T0**	**T1**	**T0**	**T1**
VAS 6	**VAS 6**	**VAS 7**	**VAS 6**	**VAS 6**	**VAS 3**
SS7	**SS6**	**SS6**	**SS7**	**SS7**	**SS4**
				33 pts (no benefit)	
				T0	**T1**
				VAS 7	**VAS 6**
				SS6	**SS5**

higher prevalence than that estimated for the general population in Europe (3). However, it is not possible to establish a causal relationship between reflux and BMS given the observational nature of the data. On the other hand, the grater prevalence of burning mouth symptom in woman seems confirmed even in the presence of GERD (41 females out of 56 patients) (3). Notably, this percentage is similar to that found for a chronic cough and pharyngitis, to well-known atypical symptoms of GERD.

During the second phase of the study serum Gastrin-17 was evaluated as a marker of gastric acid secretion due to the negative feedback between acid secretion and this hormone (6,7).

Among the 124 BMS patients, 29 (23.4 %) had G-17 level lower than 1 pg/L, suggestive of high acid production and GERD. Therefore, other 64 pts (51.6%) reported Gastrin 17 levels < 3pg/L, suggesting a possible reflux of both acid and bile, opposite to 31 pts (25.0%), showing gastrin 17 values > 3 pg/L. This data support, from a pathophysiological point of view, a possible relationship between BMS and GERD. However, at the end of the last step of the study, 60.5% of patients reported no benefit with PPI, while 49.2% reported slight benefit with sodium alginate and sodium bicarbonate, 31.7% reported slight benefit with HYCHSA 1100 mg and interestingly 28% of the patients showed an almost complete remission of the symptoms with the same drug. This could indicate a minor role of gastric acid output in BMS etiology, while other components could be involved and thus explain the efficacy of barrier drugs in alleviate the symptomatology. For example, Pepsin has been suggested as one possible factor (5), but further studies are required in order to clarify BMS etiology.

Strengthen of the study are represented by: A) large sample of enrolled GERD patients, B) large sample of BMS patients, C) comparison between patients under PPIs and subjects treated with sodium alginate plus sodium bicarbonate and HYCHSA, 1100 mg, D) duration of follow-up: three months as mean time, E) evaluation of early relapse of symptoms using every patient as its own control.

Weakness of the study: A) open study lacking a standardized randomization, B) no count pills in order to monitoring compliance, C) no evaluation of quality of life using SF36 or similar questionnaires, but only VAS, D) during the third phase of the study GERD diagnosis was made with gastroscopy and G-17 levels and not with the gold standard i.e., pH-impedance E) PPI efficacy was evaluated retrospectively.

Conclusions

We demonstrated a higher prevalence of burning mouth symptoms in GERD patients compared to the general population and similar to the percentage of other atypical symptoms of GERD, like chronic cough and pharyngitis. We also demonstrated a higher prevalence of GERD, assessed by a non-invasive marker such as gastrin 17, in BMS subjects compared to the general population. Finally, we observed a greater benefit from barrier drugs therapy than from PPI therapy, suggesting that gastric acidity is not the key factor in the etiopathogenesis of BMS, although further studies are required.

Conflicts of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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