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ORIGINAL ARTICLE

The association between burning mouth syndrome and urologic chronic pelvic pain syndrome: A case-control study

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Abstract

Background: The overlap between some painful conditions is widespread. The aim of this study was to evaluate the overlap between burning mouth syndrome (BMS) and urological chronic pelvic pain syndrome (UCPPS) in an outpatient clinic of a university hospital.

Methods: A controlled clinical study was performed. BMS patients and healthy controls were enrolled in the study. Patients were screened through laboratory test and a complete urological examination. Two validated questionnaires were submitted to all the patients: National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) and International Prostatic Symptom Score (IPSS).

Results: A total of 50 BMS patients and 50 healthy controls were enrolled in the study. Statistically significant differences between the two groups regarding the items of the IPSS questionnaire of Incomplete Emptying ($U = 750$, $P < .001$), Intermittency ($U = 768.5$, $P < .001$), QoL ($U = 848$, $P < .002$), and Total Symptom score ($U = 1040$, $P = .05$) were found. Moreover, the responses of NIH-CPSI showed statistically significant differences regarding Pain subscale ($U = 714$, $P < .001$), QoL Impact subscale ($U = 1016.500$, $P = .05$), and NIH-CPSI total score ($U = 953.500$, $P = .002$).

Conclusion: To the best our knowledge, the reported data demonstrate for the first time an association between BMS and UCPPS. Further studies with a larger sample are needed to confirm the co-occurrence of urological symptoms in patients with burning mouth syndrome.

KEYWORDS

burning mouth syndrome, chronic pelvic pain syndrome, LUTS, overlap syndrome, quality of life

1 | INTRODUCTION

Functional somatic syndromes are a complex group of chronic diseases where symptoms are not correlated with structural alterations and/or organic cause. Irritable bowel syndrome (IBS), chronic fatigue syndrome, fibromyalgia (FM), non-specific chest pain, tension headache, temporomandibular disorders (TMD), atypical facial pain, hyperventilation syndrome, chronic pelvic

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pain, and interstitial cystitis represent the most common pathologies in a large group of entities.[1] This list is constantly evolving and represents an emerging medical issue.[2] Chronic pain is one of the most common reasons why people consult physicians for assistance[3] with a high prevalence of pain-related syndromes that represent the main cause of disability and disease burden globally.[4] Through the World Health Organization's (WHO) World Mental Health Survey instrument in ten developed countries, it has been estimated that about 37% of adults had chronic pain interfering with multiple aspects of the individual's life.[5] Data from epidemiological studies on the prevalence of chronic pain show that pain sites are often multiple and coexistent in the same patient.[6] The coexistence of different somatic syndromes varies between from 10% to 50%, showing a high degree of overlap and a low percentage of pure type.[7,8] The high degree of overlapping of many chronic painful disorders has also been recognized by the National Institute of Health and the U.S. Congress defining them as chronic overlapping pain conditions (COPCs) that include TMD, FM, IBS, vulvodynia, myalgic encephalomyelitis/chronic fatigue syndrome, interstitial cystitis/painful bladder syndrome, endometriosis, chronic tension-type headache, migraine headache, and chronic lower back pain.[9] The management is a challenge for clinicians, and the overlapping of multiple somatic syndromes complicates the treatment option, protocols, and follow-up.[10] This suggests a multidisciplinary treatment for a satisfactory patient management. Given the high prevalence of multiple symptoms, published data and ongoing clinical studies are crucial to better understand the best clinical algorithm in term of prevention and successful therapeutic management.

While the overlap between some conditions is well documented in the literature, such as neck pain, headache, low back pain, and jaw/face pain,[11] few data are presented on the relationship between burning mouth syndrome (BMS) and urologic chronic pelvic pain syndrome (UCPPS), a clinical syndrome characterized, principally, by the presence of pain and discomfort in the pelvic, genital, and perineal region, associated with urinary and sexual disfunction in the absence of a diagnosable cause.[12] This condition, which encompasses both interstitial cystitis/bladder pain syndrome (IC/BPS)[13] and chronic prostatitis/chronic pelvic pain syndrome (CP/CPSS),[14] is frequently associated with irritable bowel syndrome, chronic fatigue syndrome, TMDs, vulvodynia, and fibromyalgia.[15-17]

On these bases, the aim of this controlled clinical study was to evaluate the comorbidity between BMS and UCPPS in an outpatient clinic of a university hospital through the investigation of the presence of urinary and oral symptoms.

2 | MATERIAL AND METHODS

This project was a prospective, observational, and descriptive case-control study carried out at the Oral Medicine Unit and Urology & Andrology Unit, Federico II University of Naples, between October 2019 and February 2020. The study protocol was approved by the local Ethics Committee (No. 125/19). It was conducted according to the guidelines of the World Medical Association Declaration of Helsinki (World Medical Association, 2013) and follows STROBE guidelines for the reporting of observational studies. BMS patients and healthy controls, matched by age and gender, were consecutively enrolled during their first visit with an oral medicine specialist and a general dentist, respectively, based on the following inclusion criteria: (a) male/female, over 18 years old; (b) diagnosis of BMS according to the International Classification of OroFacial Pain criteria[18] for the study group, no oral mucosal lesions or unexplained oral symptoms for the control group; and (c) no abnormalities in laboratory (routine blood and urine tests) and imaging findings (abdomen ultrasound scan). On the other hand, the exclusion criteria for both groups were: (a) pediatric patients (<18 years); (b) systemic disorders or laboratory abnormalities known to be potentially associated with orofacial and urological symptoms; (c) comorbidities such as hypertension, diabetes mellitus, cerebrovascular diseases, neurodegenerative diseases, psychiatric disorder, urinary infection or other genitourinary diseases, inflammatory bowel disease; and (d) recent (<1 month) systemic antibiotic therapies.

Once enlisted, every patient was subjected to a complete clinical interview, a conventional oral inspection, and laboratory tests. In addition, two validated questionnaires were administered to all patients: *National Institutes of Health Chronic Prostatitis Symptom Index* (NIH-CPSI) and *International Prostate Symptom Score* (IPSS) (Table 1).

The patients who reported genitourinary pain and low urinary tract symptoms (LUTS) have been subjected to a complete urological

TABLE 1 National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) and International Prostate Symptom Score (IPSS) questionnaires

Domain	Score range
NIH-CPSI	
Pain	0-21
Urinary Symptoms	0-10
Quality of Life	0-12
Total score range	0-42[a]
IPSS	
Incomplete emptying	0-5
Frequency	0-5
Intermittency	0-5
Urgency	0-5
Weak stream	0-5
Straining	0-5
Nocturia	0-5
Total score range	0-35[b]

[a] The Genitourinary Pain Index (GUPI) is the female version of this questionnaire with a total score range from 0 to 45.

[b] 0-7: mild symptoms; 8-19: moderate symptoms; 20-35: severe symptoms.

examination, and only patients whose urological symptoms were defined by the specialist as "medically unexplained" were included.

All data were collected and were subjected to statistical analysis performed with SPSS software (version 25, SPSS Inc.). Descriptive statistics of the two cohorts were obtained using t test for independent samples for continuous variables, reporting means and standard deviation, while Fisher exact test was used for categorical variables, reporting absolute numbers and percentages. We successively used one-tailed Mann-Whitney U test on individual domains and total scores of the two compiled questionnaires in order to verify an eventual increase in urinary symptoms in BMS patients versus healthy controls. Statistical significance was assumed for $P < .05$.

3 | RESULTS

A total of 50 BMS patients and 50 healthy controls were recruited, and the descriptive statistics of the two cohorts of patients are reported in the following table (Table 2). All patients successfully completed both questionnaires autonomously. One-tailed Mann-Whitney U test performed on the responses of the IPSS questionnaire showed statistically significant differences between the two groups regarding the items of Incomplete Emptying ($U = 750$, $P < .001$), Intermittency ($U = 768.5$, $P < .001$), QoL ($U = 848$, $P < .002$), and Total Symptom score ($U = 1040$, $P = .05$) (Fig. 1), while no statistically significant difference was reported on items regarding Frequency ($U = 1066.5$, $P = .96$), Urgency ($U = 1154.5$, $P = .238$), Weak Stream ($U = 1156$, $P = .243$), Straining ($U = 1206$, $P = .368$), and Nocturia ($U = 1183$, $P = .309$). Overall, 44% of BMS patients reported moderate/severe symptoms ($P = .05$) and not satisfied/unhappy QoL ($P < .002$) at IPSS questionnaire versus, respectively, 28% and 16% of healthy controls. Similarly, one-tailed Mann-Whitney U test performed on the responses of NIH-CPSI for male and female (GUPI) showed statistically significant differences regarding Pain subscale ($U = 714$, $P < .001$), QoL Impact subscale ($U = 1016.500$, $P = .05$), and NIH-CPSI total score ($U = 953.500$, $P = .002$) (Fig. 2), while no statistically significant difference was reported regarding Urinary Symptoms subscale ($U = 1180$, $P = .314$). Overall, mean score of Pain subscale was 9.20 ± 6 for BMS patients vs 5.50 ± 3.3 for healthy controls ($P < .001$); similarly, mean score of QoL impact subscale was 4.7 ± 3 for BMS patients vs 3.94 ± 2.7 for healthy controls ($P = .05$) and, finally, mean total score of the entire NIH-CPSI questionnaire was 16.7 ± 10.6 for BMS patients vs 13.06 ± 7.7 for healthy controls ($P = .002$).

4 | DISCUSSION

Burning mouth syndrome is defined as "an intraoral burning sensation or dysesthesia, recurring every day for more than 2 hours a day for more than 3 months, without clinically evident causal lesions," and it is now included in the large group of "painful cranial neuropathies".[18] The current knowledge concerning the pathophysiology of BMS indicates that it is the final result of multiple alterations between central and peripheral nervous system, hormone balance, and psychological factors.[19] The referred symptoms are multifarious including burning, xerostomia, sialorrhea, taste disturbances, itching, and coating tongue, and the most common affected sites are tongue, palate, gingivae, and lower lips.[20] While the association with sleep disturbances and psychological disorders is widely documented,[21] few data are presented on other somatic comorbidities. Moisset et al. reported rare co-occurrence of pain and BMS, often represented by headache, TMDs, atypical facial pain, trigeminal neuralgia, post-herpetic facial pain, back pain, fibromyalgia, joint pain, abdominal pain, rectal pain, or vulvodynia.[22] A previous study highlighted the coexistence between BMS and other dynias such as carotidynia, orchidynia, and coccygodynia.[23] More evidence is presented on the overlapping between BMS and fibromyalgia/muscular pain.[24] Recently, Mignogna et al. noted high percentage of BMS patients with one or multiple extraoral somatic comorbidities including ocular, otorhinolaryngological, neurological, cardiological, gastrointestinal, and dermatological symptoms with a highest prevalence of ocular and gastrointestinal symptoms.[25] In the same study, the prevalence of UCPPS was estimated at 64.5%, including frequent urination, ejaculation dysfunction, and unpleasant genital sensations. The first step for the diagnosis of UCPPS is the assessment of symptoms through NIH-CPSI questionnaire followed by a complete examination of genitalia, perineum, prostate, and abdomen to rule out other causes that could be responsible for painful symptoms. An additional evaluation with microbiological analysis and urodynamic studies may be considered according to the clinical profile and prevalent symptoms.[26]

Considering that the presence of a COPC increases the probability of incurring, in the same individual, in another similar conditions,[27] it is possible, in our opinion, that patients affected by BMS

TABLE 2 Descriptive statistics of the two cohorts

	Patients with burning mouth syndrome	Healthy controls	*P* value
Female (%)	36 (72)	36 (72)	.588
Male (%)	14 (28)	14 (28)	.588
Mean age ± SD	50.38 ± 10.787	48.98 ± 12.438	.549
Smokers (%)	29 (58)	23 (46)	.317
Alcohol consumption (%)	19 (38)	19 (38)	.582

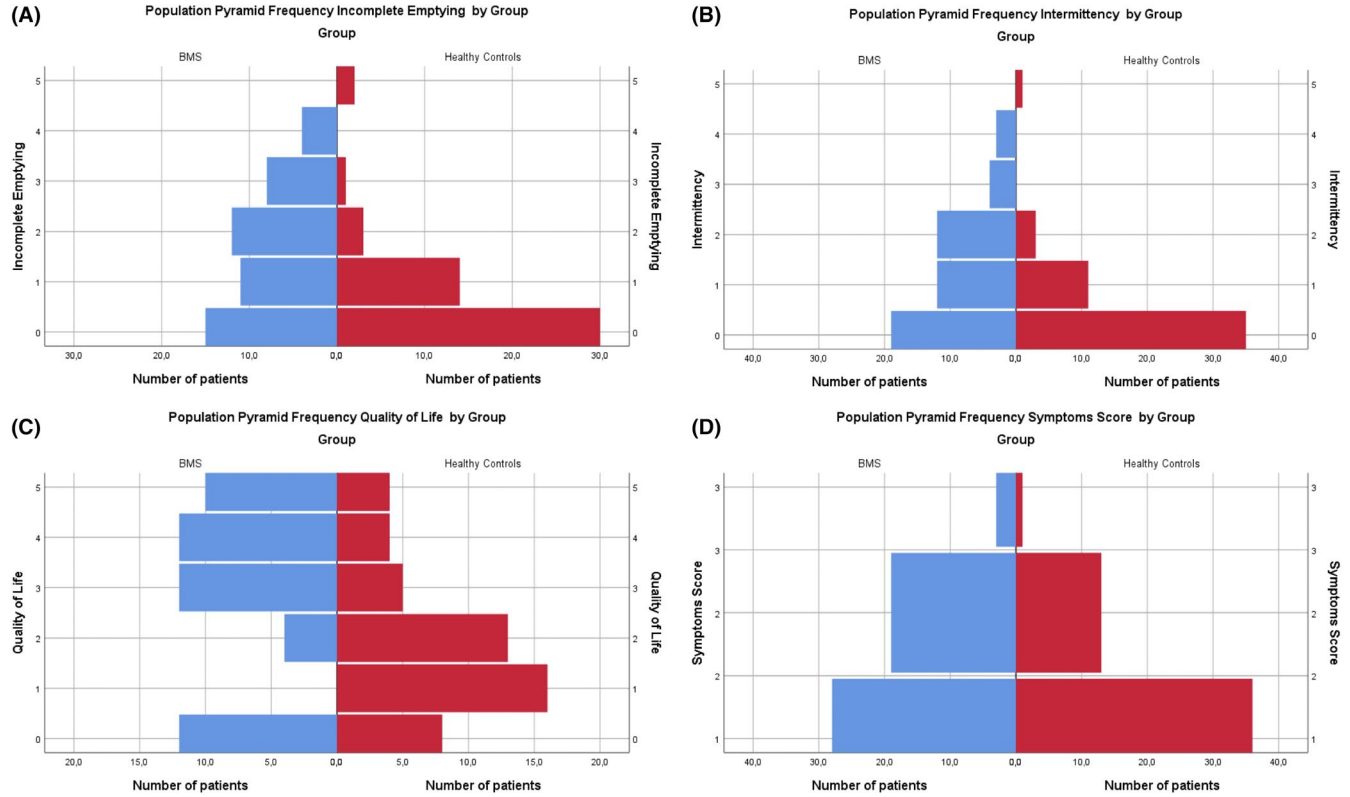

FIGURE 1 Population pyramid frequency for IPSS statistically significant differences: A, Incomplete emptying ($P < .001$), B, Intermittency ($P < .001$), C, Quality of Life ($P < .005$), and D, Symptom score ($P = .05$)

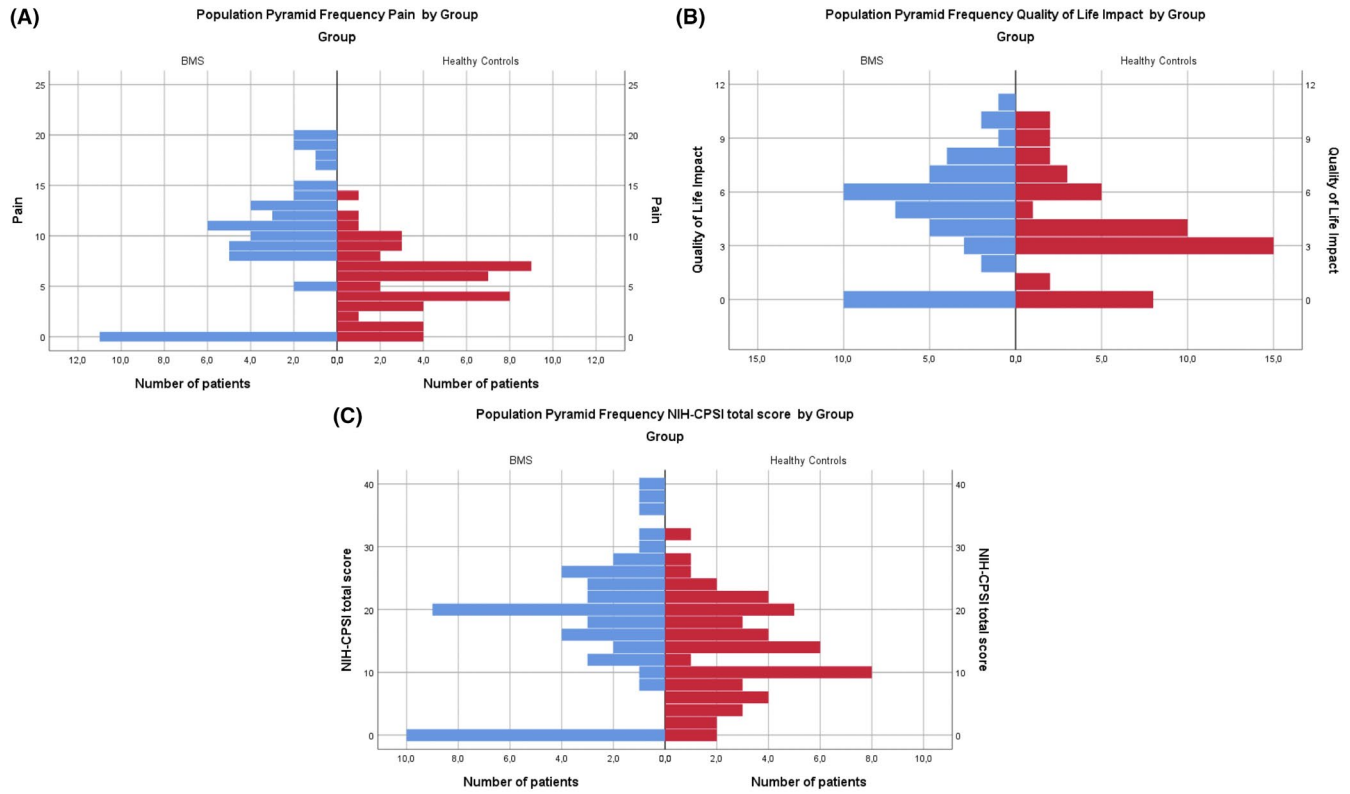

FIGURE 2 Population pyramid frequency for NHI-CPSI statistically significant differences: A, Pain subscale ($P < .001$), B, Quality of Life subscale ($P = .05$), and C, NIH-CPSI total score ($P = .002$)

could develop or report an UCPSS-like syndrome. Moreover, different examples of orofacial dynias coexisting with urological symptoms are already reported in literature,[28-30] while, as far as we know, no other study, besides Mignogna et al., reports the association between UCPSS and BMS.

We reported a significant prevalence of functional urinary symptoms and urological pain in BMS patients with an overall worsened QoL compared to healthy controls. In particular, the analysis of the IPSS questionnaire to both groups showed 24% of BMS patient that reported an incomplete emptying sensation at least half of times when urinating versus 6% in the control group. Similarly, 14% of BMS patients reported the needing of urinate in multiple times to fully void the bladder half of times compared with 2% in the control group. Moreover, 24% of BMS patients complained the needing to urinate frequently (<2 hours) at least half of times versus 14% of healthy controls but this result did not reach enough statistical significance ($P = .96$). Nevertheless, it is possible that this consideration could be confirmed by an increased number of patients enrolled. Overall, 44% of BMS patients complained moderate-to-severe urinary symptoms with a mostly dissatisfied QoL compared to, respectively, 28% and 16% of healthy patients. Similarly, the analysis of NIH-CPSI/GUPI questionnaires reported 54% and 60% of BMS patients with a sensibly higher score, respectively, in pain domain (with a score >10) and QoL domain (with a score >5) vs 12% and 30% of healthy patients. It is of particular importance the consideration that NIH-CPSI/GUPI questionnaires are commonly used in daily clinical practice to assess symptoms and QoL in men with chronic abacterial prostatitis and women with interstitial cystitis. For this reason, the questionnaires focus more on pain and discomfort rather than on urinary symptoms, for which we used the IPSS which allow to evaluate LUTS presence and severity. The results were consistent also when the analysis was made stratifying males and females in both groups, confirming the increased rate of urinary symptoms and urogenital pain in BMS patients. Chronic pain syndromes have a multifactorial etiology and share common pathogenetic mechanisms as well as having a unique pathway for each pathology.[31] Brain structure and function play an important role in pathogenesis of chronic pain.[32] Neuroimaging data in UCPPS patients showed alterations in medial areas of the motor and sensory cortex, the right posterior insula, and the periaqueductal gray area of the brainstem.[33,34] Findings of altered gray matter structure, white matter structure, and resting-state function are presented also in fMRI of BMS patients that show alterations in the insula (insula/frontal operculum), in the anterior cingulate gyrus, and in primary somatosensory area.[35] Therefore, BMS and UCPPS share structural and functional brain changes and have a common centralized pain phenotype that could explain the association between these two somatic syndromes. In addition to alterations of the central nervous system, in both conditions there is a painful small fibers peripheral neuropathy. Among the risk factors for small fiber neuropathy, the neurotoxic effects of alcohol and smoking cigarettes are widely described[36,37]; however, previous studies on the role of lifestyle in the pathogenesis of BMS and UCPPS are controversial with conflicting results.[38-40] As shown in Table 2, in our study the prevalence of risk factors (cigarette smoking and alcohol) is similar in the study group and in the control group; therefore, their role has not been explored. The study has, however, different limitations: first, the relatively small sample size of the groups; second, the prevalence of females which, however, is consistent with published data[41,42]; and third, the self-report nature of questionnaires. To the best our knowledge, our findings highlight for the first time the possibility of an association between UCPPS and BMS; however, further studies with a larger sample also with more male patients are needed to confirm our data and to explore the role of "potential" risk factors. The intriguing correlation between oral/urological and neuropsychiatric aspects would be useful to understand in order to outline a specific subset of patients with a specific phenotype of the disease.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Felice Crocetto: Conceptualization; Investigation; Writing-original draft. **Noemi Coppola:** Conceptualization; Investigation; Writing-original draft. **Biagio Barone:** Data curation; Formal analysis; Software. **Stefania Leuci:** Methodology; Resources; Visualization. **Ciro Imbimbo:** Validation; Visualization; Writing-review & editing. **Michele Davide Mignogna:** Supervision; Validation; Writing-review & editing.

ETHICS APPROVAL

The study protocol was approved by the local Ethics Committee No. 125/19.

PEER REVIEW

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