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CLINICAL AND PSYCHOLOGICAL IMPACT OF SARS-COV-2 INFECTION IN BURNING-MOUTH SYNDROME PATIENTS: A COMPARATIVE STUDY

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ABSTRACT

Burning mouth syndrome (BMS) is a chronic disease characterized by the presence of persistent oral mucosa pain, mainly burning sensation without any detectable clinical cause or modified general investigations. Coronavirus infections, in some patients, caused sensations of oral burning, of a neuropathic nature, which mimicked the symptoms of BMS. In addition, the psychiatric manifestations associated with the COVID-19 pandemic have exacerbated the symptoms of patients already diagnosed with burning mouth syndrome. Based on these observations, we conducted a longitudinal study to assess the changes in depressive and anxiety symptoms in BMS patients during the pandemics. We recruited two groups of age and gender-matched BMS patients. The first group included patients with BMS diagnosed with coronavirus infection and the second one without coronavirus infection. The study concluded that in patients with coronavirus infection there was an intensification of anxiety-depressive symptoms more pronounced in the first 6 months after infection (duration being associated with the infection severity and long-COVID symptoms), followed by a recurrence or even decrease in symptoms compared to the initial examination. Oral symptomatology had a similar evolution, the intensity being determined by the severity of the COVID-19 infection episode and by the prolonged use of antivirals. The lack of a larger number of studies and patients with BMS and COVID-19 infection limited the possibility of comparative analyses.

Keywords: burning mouth syndrome, coronavirus infection, oral burning sensation

INTRODUCTION

The COVID-19 pandemic affected well-being and mental health worldwide. An increase in stress levels, anxiety, and depression was reported in the whole population [1].

Psychiatric manifestations have been exacerbated in COVID-19 surviving patients, and are likely to involve, besides psychological trauma and inflammatory mechanisms. Previous research reported an increase in depressive symptoms, anxiety, sleep disorders, obsessive-compulsive disorder, post-traumatic stress disorder, subjective feelings of fatigue, and subjective cognitive dysfunction [2,3]. In the case of patients with previous psychiatric diagnoses and who were infected with SARS-CoV-2, an aggravation of the symptomatology objectified by scales and scores was observed, the changes being similar to the degree of systemic inflammation [4]. A peculiarity was the fact that women presented more pronounced anxiety-depressive symptoms, although they had a significantly lower level of

inflammatory markers [5]. During the pandemic, managing chronic pain was challenging, especially since there are observations that COVID-19 infections also affect the craniofacial complex, with symptoms described by patients as pain, myalgias, and widespread hyperalgesia [6,7]. In particular, there has been an increase in the incidence of acute and chronic neuropathic pain in patients infected with coronavirus [8]. Immunological, inflammatory or direct mechanisms involving viral action were described in neuropathic pain in these patients [9]. In some situations, neuropathic pain in post-COVID patients manifested as painful burning, which persisted for several weeks [10,11].

The oral cavity appears to be an important site for SARS-CoV-2 infection and implicates saliva as a potential route of transmission [12]. A series of oral manifestations were described in COVID patients, such as dysgeusia (taste disorders), oral pain, blisters, ulcerations, desquamative gingivitis, and the exacerbation of autoimmune diseases as well as the herpes simplex and varicella-zoster viruses infections, ulcerations, aphthous stomatitis. It remains open to discussing whether these manifestations are due to coronavirus infection or secondary manifestations resulting from indirect mechanisms (anemia, hemolysis [13]) or other pre-existing pathologies [14,15]. The palatal mucosa and tongue were the most common sites of oral changes in patients infected with coronavirus [16]. In particular, some manifestations commonly described by burning mouth syndrome patients are found more frequently in post-COVID patients: dysgeusia [17], a burning sensation in the mouth [18], and difficulty in swallowing [19]. In rare cases, oral side effects have been reported with COVID-19 vaccines, especially edema of the tongue and lips, acute peripheral facial paralysis (Bell's palsy) [20], oral mucositis, mucosal ulceration, and aggravation of preexisting neuropathic pain [21]. Another controversial aspect is represented by the rare cases of exacerbation of oral mucosal diseases (oral lichen planus, chronic ulcerative stomatitis, pemphigoid mucous membranes) after the administration of anti-COVID vaccines [22].

Burning mouth syndrome (BMS) also named glossodynia is a chronic disease characterized by the presence of persistent oral mucosa pain, mainly a burning sensation without any detectable clinical cause or modified general investigations [23,24]. In this disorder as in general in chronic pain patients, anxiety and depression carry important roles [25]. Data from the literature on patients with glossodynia and coronavirus infection are limited at this time. It is estimated that social stress (even in the absence of coronavirus infection), exacerbation of anxiety and/or depression, sleep disorders, worsening of other chronic health problems of BMS patients, the effects of SARS-CoV-2 infection, etc. may increase symptoms in already diagnosed patients or may trigger chronic burning sensations in the mouth [26]. According to Katz et al study, glossodynia has a higher frequency in COVID-19 patients than in the general population and should be considered a differential diagnosis in oral complications of this infection [27]. The worsening of pre-existing symptoms of BMS after coronavirus infection has been accompanied, in some cases, by an increased risk of suicide [28].

During the COVID-19 pandemic, we expected that BMS disease would have some changes.

The aim of this longitudinal study was to assess the changes in depressive and anxiety symptoms in BMS patients during the pandemics. Moreover, we analyzed the effect of SARS-CoV-2 infection on these psychological features by comparing BMS patients who got infected (COVID+) versus a matched group of uninfected BMS patients (COVID-).

MATERIAL AND METHODS

We recruited participants diagnosed with BMS between January 2020 to February 2021 from the dental and oral medicine practitioners from Bucharest. The study design comprised two groups of age and gender-matched BMS patients. The first one included BMS patients with COVID infection(COVID+) and the second group included BMS patients noninfected with COVID-19(COVID-).

The inclusion criteria were: patients over 18 years, BMS diagnosis established before January 2020, ongoing medical contact for at least 1 year, written consent obtained at the first visit and, informed oral consent during the phone interview.

The exclusion criteria were as follows:

- oral diseases which cause the burning sensation,
-medical diseases and major psychopathological conditions (such as major depressive disorder, schizophrenia, suicidal risk, etc)
- advanced organ failure (cardiac, renal, liver, etc)
- active cancer
-patients with addictions (alcoholism, cannabis users)
- other major oral pathologies (lichen planus, mucositis, oral ulcerations, major dental problems, etc.)
- no written consent to take part in this study.

We used the diagnostic criteria for BMS proposed by the International Headache Society in 2018: recurrent superficial oral pain for at least 2 hours daily over more than 3 months in the absence of visible lesions or any identifiable medical disorder [22,29].

The diagnostic criteria for coronavirus infection were mentioned in the case definitions communicated by the national authorities, which reflected the knowledge of the phenomenon at that time and the WHO recommendations. Patients with glossodynia have been diagnosed and treated in infectious disease departments.

On the first consultation, details of demographic data (eg, age, gender, marital status, body mass index, etc.) and clinical characteristics (onset, duration, location of the pain), other diseases and prescription medication usage diseases were recorded. Also, a complete clinical and radiological examination of the oral cavity (mucosa and teeth) was performed. All the patients had the general investigations within the normal limit (complete blood cell counts, blood glucose levels, serum iron and transferrin levels, serum zinc, magnesium, vitamin B12 and folic acid levels).

The legal restrictions (lockdown), the closure of dental services and medical universities, the psychological impact of COVID-19 panic and patients' fear of coronavirus infection made the direct doctor-patient meeting impractical for a long time. However, to maintain the therapeutic alliance and respect ethics[30], especially in these difficult times, a remote mode of patient-doctor contact was used. Although under ideal conditions phone-based data collection may raise some concerns, during the study this was the only practical method of data collection. Patients offered telephone consent for the use of the data.

The scope of this remote contact was to find out the BMS evolution at 4 different moments 3 months (T3), 6 months (T6), 9 months (T9), and respectively 12 months (T12) from the diagnosis. This scale of BMS symptoms was the following: 1-persistent symptoms, 2-improvement, 3- no symptoms, 4- aggravated symptoms.

The psychological distress was assessed by using practical tools such as questionnaires Hospital Anxiety and Depression Scale (HADS) and Montgomery and Asberg Depression Rating Scale (MADRS). HADS scale is a tool used to screen anxiety disorders and depression and its over 8 value reflects possible or probable anxiety or depression. MADRS scale is a measure of depressive

severity and its over 7 score reflects the presence of depression (7 to 19 – mild depression, 20 to 34 – moderate depression, over 34 – severe depression) [31,32].

Both evaluation scales were applied simultaneously, the first time (T0) at the diagnosis of the BMS and the second at one-year intervals (T12).

The BMS patients used pharmacological treatment: some had Alpha-Lipoic Acid which was previously reported by other studies to have significant improvement [33] and others had antidepressant treatment.

All study procedures were conducted in accordance with the Declaration of Helsinki.

The statistical analysis was performed using SPSS version 20.0. Regarding the socio-demographic and clinical data, categorical variables were tested by means of the chi-square test and continuous variables with the t-test. For the longitudinal analysis (T0 vs T12) the Wilcoxon signed-rank test was applied. The differences between the groups were considered significant when $p < 0.05$.

RESULTS AND DISCUSSIONS

Characteristics

The study sample consisted of 58 BMS patients divided in 2 groups (age and gender-matched) according to the presence of COVID-19 infection (COVID+ and COVID-).The matching of the cases was done in order to increase the efficiency of study. In the whole cohort the age ranged from 33-71 and the mean age was 58.59(± 9.463 years).

The main characteristic regarding socio-demographic data, lifestyle details, and habits of the patients analysed during the study were presented in Table 1.

MADRS scores

Regarding the MADRS total scores (Table 2), in the present study we detected its decrease on the whole cohort. When it was stratified into the two groups according to the association with the COVID-19 infection, it was observed that COVID+ group had no decrease different from COVID- group which had a statistically significant reduction of MADRS (***p=0.004***). The analysis of the patients with depression(score over 7) and without antidepressants found no difference in the whole cohort. In COVID+ group we found an increased score.

HADS scores

In the whole cohort, the HADS score had no change during the pandemic(Table 3). But the stratified analysis found statistically significant increased scores of anxiety in COVID+ group (p=0.007) and decreased scores in COVID- group(p=0.007). The level of anxiety had no change in the COVID+ BMS patients .

At present, to our knowledge, worldwide few studies analyze BMS patients during the pandemic[26,27,28,34]. Results of the psychological impacts are not quite convergent.

A recent study from Spain [26] compared 40 patients before and after the start of the pandemic and detected that the pandemic contributed to worsening anxiety. The authors found significant differences for HADS($p < 0.001$)) and other instruments for psychological profile: Pittsburgh Sleep Quality Index, Pain Catastrophizing Scale and pain visual analog scale.

In Japan, the psychological impact on BMS patients before and after the COVID pandemic showed no significant difference in the scores [34].

The evolution of symptoms is presented in Figure 1.

The data collected from patients, as well as the telephone anamnesis, showed a worsening of anxiety-depressive symptoms in the first 3 months for mild forms of COVID-19(usually home treated) and up to 6 months in moderate and severe forms of COVID-19(which required hospitalization). In addition to the severity of coronavirus infection, some difficult to quantify factors influenced the

psychological reaction. Thus, the state of psychological pressure in society at the onset of the coronavirus pandemic was characterized by anxiety and unpredictability. The psychological reactions were induced by the restrictive travel measures that culminated in lockdowns, reactions to loneliness, fear of abandonment, news of family members or acquaintances' illness, in some cases grieving reactions, problems with work and income, infodemia, etc. This mixture of reasons, against the background of the COVID-19 pandemic, generated a polymorphism of various psychological reactions in BMS patients, whose impact varied depending on individual, family, socio-professional, educational factors, the degree of psychological resilience, etc.

Another trend, which due to the low number of cases in the study did not reach a statistically significant level, is the increase in both persistence and duration (on average 2-4 weeks longer than average) of oral symptoms in patients treated with antivirals (most commonly Remdenesivir). A review study investigating the potential drug interactions between Remdensivir and medication used in dentistry identified 279 possible interactions. Of these, two are major (chloroquine and hydroxychloroquine, 277 moderate (remember - some antibiotics, antifungals, NSAIDs) and alcohol [35]. The observations in our study may be accidental or reflect a degree of antiviral drug interaction rather than the direct effect.

On the other hand, zinc supplements, vitamins D, B tablets and C, widely used empirically as adjuvants in the prevention and therapy of coronavirus infection, were expected to have a protective effect on the oral mucosa and peripheral nerves. This effect could not be monitored in our study, especially due to inconsistent responses and intermittent self-administration.

Similarly, we believe that the improvement in indicators for anxiety and depression up to 6 months after the infectious episode is explained both by the disappearance of viral effects, cessation of anti-COVID medication, and mental relaxation and due to better local care, increased adherence to treatment, better communication with the family, improving sleep quality, awareness of manifestations and in some cases initiating anxiolytic and antidepressant treatment. It is worth mentioning that, within the limits of the telephone dialogue, we also noticed an increased variability of emotional distress and the degree of mnemonic fixation on the details in the spontaneous narration. We believe that in the future, psychological evaluation of BMS patients should also consider the assessment of personality type, the degree of alexithymia and anhedonia during coronavirus infection, screening for memory disorders, eating disorders, psychological resilience, and quality of life.

Although this was not the case in our study, we consider that in situations of prolonged psychological stress, such as COVID-19 pandemia, it is necessary to perform a screening to assess the risk of suicide in patients with persistent glossodynia.

Maintaining the therapeutic alliance, especially in the conditions of a lockdown, represents an approach with a great positive impact on patients with glossodynia, especially since during the pandemic the oral pathology services in Romania were closed. In the case of BMS patients, online consultations (telemedicine) - psychiatry, oral pathology, neurology, etc. -psychological counseling, promotion of online platforms, and mobile self-monitoring applications, can have a disruptive potential by digital phenotyping and maintaining a connection between patients with BMS and medical staff, even in pandemic conditions.

These online communication channels can be used successfully to conduct medical

education sessions, recommendations on compliance with recommendations during the pandemic from experts, the importance of vaccination against vaccination, personalized counseling, and countermeasures against the digital epidemic of fake news, etc. Given the increased frequency of oral manifestations in patients with coronavirus infection, we believe that it is necessary to conduct awareness campaigns for doctors in other specialties (infectious diseases, ENT, neurology, psychiatry, gastroenterology, etc.) who treat patients with moderately-severe forms of covid. In case of persistence of oral burning sensations, it is necessary to make a detailed differential diagnosis, identify the etiology of the pain syndrome and if necessary, include the recommendation of an oral pathology consultation.

Finally, we consider that the small number of studies on patients with BMS and coronavirus infection, it is insufficient for conducting in-depth analyzes and making recommendations based on clinical evidence, so we recommend conducting more research in this area.

This study's limitations are important to consider. First, the relatively small number of participants allowed that in some situations a number of observed trends were not objectified in the form of statistically significant differences. The study included data collected from only one healthcare institution and the findings of this study require confirmation by using data collected from a larger sample size across multiple public and private healthcare institutions. The small number of similar studies in the literature affects the quality and depth of comparative analysis. Another limitation is the indirect interaction, through the telephone, which limited the obtaining of additional data. The change in the case definition of coronavirus-infected patients during the study influenced the way patients were selected.

Table 1. Demographics, life style and habits of the participants

SOCIO-DEMOGRAPHIC DATA			
	COVID+ (N=29)	**COVID- (N=29)**	**Significance**
Age in years (mean±SD)	58.69±9.35	58.48±9.73	p=0.935
Sex (F; M)	24F; 5M	24F; 5M	p=1; χ^2=0
Education in years (mean±SD)	14.45±1.43	14.93±1.75	p=0.255
BMI (mean±SD)	25.90±3.06	27.20±3.39	p=0.131
Weight category (N)	Normal weight= 13 Over-weight= 12 Obesity Gr I= 4	Normal weight= 7 Over-weight= 13 Obesity Gr I= 9	p=0.152; χ^2=3.763

Employment status (N)	Unemployed= 2 Retired= 16 Part-time job= 4 Full-time job= 6 Own business= 1	Unemployed=1 Retired=14 Part-time job=1 Full-time job=9 Own business=4	p=0.323; χ^2=4.667
Marital status (N)	Single= 0 Married= 26 Widow/er= 1 Divorced= 2	Single= 2 Married= 25 Widow/er=1 Divorced= 1	p=0.502; χ^2=2.353
LIFESTYLE and HABITS			
	COVID+ (N=29)	COVID- (N=29)	Significance
Tobacco consumer (N)	Non-smoker= 22 Smoker= 7	Non-smoker= 20 Smoker= 9	p=0.557; χ^2=0.345
Smoker category (N)	Non-smoker= 22 Active smoker= 3 Passive smoker= 1 Smoker>6 months= 1 Smoker>3 years= 2 Iquos smoker= 0	Non-smoker= 20 Active smoker= 4 Passive smoker= 0 Smoker>6 months= 1 Smoker>3 years= 2 Iquos smoker= 2	p=0.663; χ^2=3.5238
Alcohol consumer (N)	No consumer= 16 Sporadic consumer= 13	No consumer= 22 Sporadic consumer= 7	p=0.097; χ^2=2.747
Coffee consumer (N)	No consumer= 7 Sporadic consumer= 15 Chronic consumer (1 coffee/day)= 6 Chronic consumer (2-3 coffee/day)= 1	No consumer= 8 Sporadic consumer= 16 Chronic consumer (1 coffee/day)= 4 Chronic consumer (2-3 coffee/day)= 1	p=0.919; χ^2=0.499

Table 2. Depression analysis MADRS total scores

BMS patients (No)	T0	T12	Significance and comment
All BMS patients involved in the study (N=58)	8.14±3.59	7.12±3.27	**p=0.017** **Decreased of depression**

COVID+ BMS patients (N=29)	8.45±3.64	7.93±3.74	p=0.754 No changes
COVID- BMS patients (N=29)	7.83±3.57	6.76±2.95	**p=0.004** **Decreased of depression**
BMS patients with depression and without antidepressant treatment (N=21)	10.57±2.23	10.33±3.09	p=0.679 No changes
COVID+ BMS with depression and without antidepressant treatment at T0 and at T12 (N=9)	11.22±2.33	13.00±1.50	**p=0.011** **Increase of depression**
COVID- BMS patients without antidepressant treatment at T0 and at T12 (N=12)	10.08±2.11	8.33±2.35	**p=0.048** **Decreased of depression**

Table 3. HADS scores in the participants

BMS patients (No)	**T0**	**T12**	**Significance and comment**
All BMS patients involved in the study (N=58)	7.59±3.31	7.66±3.28	p=0.967 No changes
COVID+ BMS patients (N=29)	7.38±3.06	8.55±3.39	**p=0.007** **Increased anxiety**
COVID- BMS patients (N=29)	7.79±3.59	6.76±2.95	**p=0.007** **Decreased anxiety**
BMS patients with anxiety at T0 (N=27)	10.48±2.24	9.81±2.91	p=0.083 No changes
COVID+ BMS patients with anxiety at T0 (N=12)	10.42±1.56	11.25±2.42	p=0.321 No changes
COVID- BMS patients with anxiety at T0 (N=15)	10.53±2.72	8.67±2.82	**p=0.006** **Decreased anxiety**

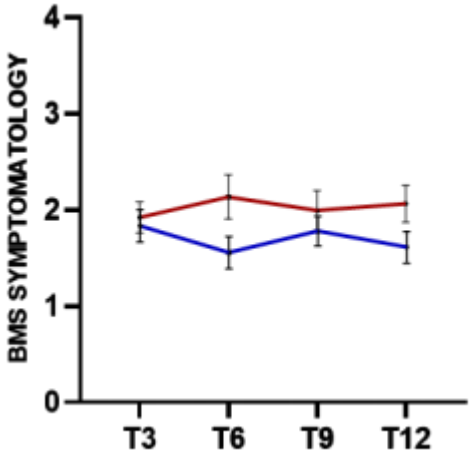

Figure 1. Burning mouth syndrome symptomatology evolution during 1 year follow-up.In red is the COVID + group and blue COVID-.(1-persistent symptoms, 2- improvement, 3- no symptoms, 4- aggravated symptoms.)

CONCLUSIONS

In BMS patients with coronavirus infection, there was an increase of anxiety-depressive symptoms more pronounced in the first 6 months after infection, followed by a recurrence or even decrease in symptoms compared to the initial examination. Oral symptoms had a similar evolution, their intensity was determined by the COVID-19 infection episode severity and by the prolonged use of antivirals.

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