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CASE REPORT

Add-on administration of ultramicronized palmitoylethanolamide in the treatment of new-onset burning mouth syndrome

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Aim: The purpose of this study was to treat burning mouth syndrome (BMS) with a combination of painful gabapentin and ultramicronized palmitoylethanolamide (umPEA), in an attempt to improve the severe symptomatology of BMS.

Methods: We examined the case of a 60-year-old male, suffering from late-onset burning mouth syndrome. He found that gabapentin had a poor control of symptoms, thus we added umPEA, after administering a Visual Analog Scale (VAS), showing a score of 8–9. The patient also underwent laboratory examinations, neuroimaging exams such as brain CT/MRI and others, which all showed normal results.

Results: The result of combined therapy was satisfactory. After 3 months, the frequency and intensity of the pain had improved considerably, as demonstrated clinically and by VAS, with a score of 5.

Conclusion: BMS is an oral pain-burning syndrome scarcely responsive to therapy. The most widely used medications are GABA-like substances, antidepressants, topiramate. In this case, we used PEA, which proved effective in the treatment of BMS, as well as in neuropathies and migraines.

Keywords: burning mouth syndrome, ultramicronized palmitoylethanolamide, gabapentin

Introduction

Burning mouth syndrome (BMS) is a disorder characterized by chronic pain and burning in the tongue and oral cavity, in the absence of apparent causes. It is a rare syndrome, estimated to occur in about 1%–5%, while the age of onset is around 30 years and postmenopausal women are more frequently affected than men. Etiological factors are considered local (orodentaI diseases, bacterial–fungal infections, salivary gland disorders), systemic (folate deficiency and B hypovitaminosis, diabetes, thyroid disease, Sjogren syndrome), psychiatric (depression, anxiety, obsessive–compulsive disorder), whereas there are also primary forms which do not have a cause. Current knowledge includes BMS into peripheral neuropathies.[1] The International Headache Society identifies it as "an intraoral burning sensation for which no medical or dental cause can be found."[2] Treatment is necessary for the chronicity and intensity of pain and burning, but the results are not always satisfactory. Few drug trials have yet been conducted. Gabapentin and pregabalin are used showing inconstant effectiveness in BMS treatment. These are GABA-analog anticonvulsants, also efficient in the treatment of peripheral neuropathies. Oral treatment with clonazepam has been beneficial in BMS. The efficacy of antidepressants is controversial.

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Ultramicronized palmitoylethanolamide (umPEA) has already been used in BMS.[3] It is an endogenous molecule widely present in animal and plant tissues. It has a structure similar to endocannabinoids, which are produced by the body to repair the damage caused by various pathological situations, thanks to their antioxidant, immunosuppressive, anti-inflammatory and painkiller activity. It has proved effective in neuropathic disorders and in migraine as demonstrated by the studies of Chirchiglia et al in 2016, 2017, and 2018.[4–7]

We describe the case of a 60-year-old patient who had suffered for 1 year with severe BMS. We tried umPEA together with gabapentin, obtaining a dramatic improvement of the symptomatology.

Case report

A 60-year-old male, suffering from BMS for 1 year, manifested pain at the tip of the tongue, extending to the whole tongue and inside the oral cavity. The pain was associated with burning, not dependent on meals, the intensity was severe, and the episodes had an initial frequency of 2–3 per month, lasting about 2–3 hours a day. Alterations of taste were absent.

Laboratory tests showed normal results, since none of the parameters were altered, both infective and systemic. The examinations of the teeth and the mouth were normal. Examinations of salivary glands showed normal results. Brain CT, MRI, and angio-MRI were unremarkable. The Hamilton Depression Rating Scale (HDRS) did not show signs of depression, manifesting a score of 6 (normality range 0–7). For about a year, the patient took topiramate at a dose of 100 mg daily and paroxetine at a dose of 10 mg daily. They were ineffective and so he was treated with gabapentin. This was administered at an oral dose of 400 mg three times a day, but the result was not satisfactory as pain-burning still occurred 2–3 times a month, almost steadily, decreasing the intensity and duration of each episode slightly. We thus administered, in addition to the gabapentin, umPEA at a dose of 600 mg, twice daily orally, and we monitored the efficacy using the Visual Analog scale (VAS), which showed an initial score of 8–9. After 1 month, symptoms improved slightly, reducing the frequency of episodes from 3 to 2, and the VAS score was 7. Two months later, the pain-burning improved further with the reduction of episodes to one and a VAS score of 6. After 3 months, there was one episode of a half-hour duration and a VAS of 5. No adverse effects were reported.

Discussion

BMS is defined as a chronic pain condition characterized by a burning sensation in clinically healthy oral mucosa. International Classification of Headache Disorders-3 (ICHD-3) has included BMS between the painful lesions of the cranial nerves and other facial pain 13.11.[2] Diagnostic criteria: pain has both of the following characteristics: burning quality, felt superficially in the oral mucosa. Oral mucosa is of normal appearance as well as clinical examination.

Incidence and prevalence

BMS incidence diagnosed in 2013 in the Department of Oral Medicine of Bucharest University was 16.23%.[8] Prevalence varied according to the studies of Rodriguez-de-Rivera-Campillo and López-López[9] from 0, 7–14% to 8–15%. Sardella et al[10] found a prevalence of BMS between 0.5 and 5%. Gurvits,[11] in over 1,000 patients randomly selected from the Swedish public dental service found 3.7% of subjects with BMS. The average prevalence of reported cases is calculated as between 0.7 and 5% of the population. Therefore, the percentages regarding the prevalence of BMS are extremely variable.

Etiology

About the etiology, BMS can be classified into two forms: primary (essential/idiopathic), peripheral type, cause of neuropathy, or central type, and secondary determined by local, systemic or psychiatric factors. In favor of neuropathic theory, some studies show possible peripheral neuropathic changes: a lower density and axonal degeneration of nerve terminations in biopsies of the anterior 2/3 of the tongue was observed in BMS patients compared to the controls, suggesting a possible neuropathy of small nerve fibers.[12]

Regarding psychiatric factors, in subjects with BMS there is a high prevalence of psychiatric disorders. Analysis of the literature shows that in >50% of cases, BMS is associated with personality disorders and mainly with depression. A study carried out according to the diagnostic criteria of DSM-IV showed a psychiatric disorder in 71.6% of the patients examined, compared to the control group.[13] Regarding correlation with age and sex, BMS can affect any age between 27 and 87 years old, with an average age of 61 years, and women are 2.5–7 times more frequently affected than men. In addition, up to 90% of female patients with BMS are around menopause age, with typical onset of symptoms from 3 years before to 12 years after the menopause. BMS association with gender, age and menopause has long been suspected because of hormonal changes that occur and which could have a pathogenic role.[14]

However, women are more affected by the disease than men. Studies conducted by Demarosi in 2013 range from 0.7 to 14%, 8 to 15% or 0.5 to 5%.[15]

BMS distribution predominantly in women during menopause is the result of hormonal changes. Local factors have a direct effect on the oral mucosa irritation. They are mainly represented by bacterial or fungal infections. According to an interesting study, the onset of erosive or ulcerative mouth lesions may precede or follow by months or years the onset of vulvovaginal lesions. It would be evidence of an inflammatory-infectious process in BMS.[16] BMS local factors involve qualitative and quantitative changes in saliva. In a study by Sharma and Kaur,[17] 34% of 150 patients evaluated reported xerostomia or variations in salivary protein and electrolyte concentration.[17] The composition of saliva may play a role in the etiopathogenesis of BMS, and some authors thought that it important to analyze and dose with low molecular weight salivary proteins. Other studies have shown a significant increase in the level of sodium, lysozyme, amylase and immunoglobulins in BMS saliva as compared to a control group.[17]

Vitamin deficiencies (B1, B2, B6, B12, C and folic acid) and iron deficiency anemia are considered systemic factors. Recently, BMS has been associated with lower serum zinc levels.[18]

The exact mechanism through which these nutritional deficiencies can lead to the onset of burning oral mucosa is unknown. In clinical situations characterized by sideropenic BMS, a compound containing an iron enzyme is considered responsible for cytochrome oxidase deficiency. It is postulated that quantitative enzyme involvement becomes responsible for the induction of functional changes in the epithelium, and the presence of folic acid and B12 vitamin deficit that alter the morphology of the oral mucosa.[18]

Some hormonal changes such as hypoestrogenemia, diabetes mellitus, hypothyroidism and thyroid- type immunological diseases affecting the endocrine glands were also described as possible causal factors of BMS.[19,20]

Palmitoylethanolamide (PEA) is an endogenous N-acylethanolamide, which plays an important role in resolving neuro-inflammatory and algic processes. Preclinical studies have shown that PEA acts on the mechanisms of neuroinflammation giving an effective neuroprotective effect. At the beginning of the 1990s, the research group of the Nobel Prize laureate Rita Levi Montalcini discovered the mechanism ALIA (Autacoid Local Injury Antagonism), identifying in PEA the substance able to act on peripheral and central neuroinflammation through the synchronic modulation of non-neuronal cells such as astrocytes, microglia, and mast cells.

PEA may be in micronized form when the particle size is between 6 and 10 microns, or ultramicronized, if the particle size is between 0.2 and 5 micron. The ultramicronized form makes the substance more effective and safer. Ultramicronized PEA (umPEA) has been shown to effectively reduce central and peripheral neuroinflammatory disorders such as migraine, neuropathies, and radiculopathies.[4–7] The case offers two considerations: the late onset of BMS and the efficacy of PEA on pain-burning. It is a promising result that demonstrates the efficacy of this substance.

Conclusion

Burning mouth syndrome (BMS) previously named stomatodynia is an intraoral burning without clinically evident causal lesions. It is a rare syndrome that doesn't always respond to drugs. In our case, we treated BMS with a combination of gabapentin and umPEA successfully.

Ethics statement

Written informed consent was provided by the patient. No institutional approval was required to publish the case details.

Disclosure

The authors report no conflicts of interest in this work.

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