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Is Burning Mouth Syndrome Based on a Physiological Mechanism which Resembles that of Neuropathic Pain?

Comparación entre el mecanismo fisiológico del síndrome de la boca ardiente y el dolor neuropático

ABSTRACT: Burning mouth syndrome (BMS) is a chronic intraoral pain state that has been described as burning pain, tingling or numbness in the oral mucosa, in the absence of any organic disease. Most often affecting the tongue, anterior palate, and/or lips. The diagnosis of primary BMS is purely clinical and based on patients' description of typical subjective symptoms as well on the exclusion of any systemic or local factors that may give rise to secondary burning pain sensations within the oral mucosa. Relevant studies links BMS to a peripheral neuropathy and BMS patients have revealed distinct abnormalities within the trigeminofacial large and small fiber systems and the trigeminal brainstem complex. Therefore, treatment approach should involve a multidisciplinary character similar to the treatment for neuropathic pain including factors that might also play a role on the BMS etiology and pathophysiology.

KEYWORDS: Burning mouth syndrome; Neuropathic pain; Pathophysiology.

RESUMEN: El síndrome de la boca ardiente (SBA) es un estado crónico de dolor intraoral descrito por pacientes como dolor o sensación quemante, de cosquilleo o adormecimiento de la mucosa oral, con ausencia de lesiones visibles en la boca. Puede afectar la lengua, el paladar anterior y o los labios. Su diagnóstico es basado en la típica descripción subjetiva del paciente, excluyendo cualquier otro factor sistémico o local que podría provocar cualquier otra sensación quemante dentro de la mucosa oral. Estudios relevantes han mostrado que SBA primario parece tener una patofisiología de origen de tipo neuropático donde pacientes con SBA pueden presentar distintas anormalidades en el complejo trigeminal a nivel de las fibras sensoriales delgadas y gruesas. Por tanto, el tratamiento y manejo de estos pacientes debe ser de la misma manera multidisciplinaria como en el caso con el dolor neuropático, sin olvidar incluir el manejo de todos los factores que podrían intervenir en la etiología del SBA.

PALABRAS CLAVE: Síndrome de la boca ardiente; Dolor neuropático; Patofisiología.

Burning mouth syndrome (BMS) is an intense, chronic intraoral pain state (1,2) that has been described as burning pain, tingling or numbness in the oral mucosa, in the absence of any organic disease (3). Most often affecting the tongue, anterior palate, and/or lips (4).

BMS pain is often bilateral, although it may rarely occur unilaterally, and it does not comply with peripheral nerve distribution (3). Patients frequently complain of taste alterations (dysgeusia, hypogeusia) or xerostomia despite normal salivation (5,6).

According to diagnostic criteria of International Headache Society (7) primary BMS is classified under the heading "central causes of facial pain" and is characterized by spontaneous burning pain arising from a visibly intact oral mucosa, normal findings in clinical examination, and no identifiable medical or local dental cause (8,9).

BMS can be divided into primary (essential or idiopathic) and secondary forms. The diagnosis of primary BMS is purely clinical and based on patients' description of typical subjective symptoms as well on the exclusion of any systemic or local factors that may give rise to secondary burning pain sensations within the oral mucosa. These factors include, e.g., endocrinopathies, oral candidiasis, decreased of salivation, drugs, oral habits like tongue thrusting and bruxism, or lesions related to poorly fitting denture. The secondary BMS symptoms, mentioned above, disappear with treatment of the underlying cause. Importantly, no universally efficient treatments are currently available for BMS, although some patients may benefit from local clonazepam or neuropathic pain medications (10).

Burning pain of the oral mucosa is the cardinal feature of BMS (9,11). Recent studies using several relevant, objective neurophysiologic or psychophysical methods, such as blink reflex (BR) and thermal quantitative sensory testing (tQST) as well as neuropathological, neurobiological, and functional brain imaging techniques, have provided convincing evidence for neuropathic involvement in the pathophysiology of primary BMS(12,13). Abnormalities have been found along the whole neuraxis from the peripheral trigeminal system to the central nervous system and top-down inhibitory control systems (3).

Three distinct subclasses of BMS have been neurophysiologically characterized (3):

- The first subgroup (50%-65%) is characterized by peripheral small fiber neuropathy of intraoral mucosa.
- The second subgroup (20%-25%) consists of patients with subclinical lingual, mandibular, or trigeminal neuropathy.
- The third subgroup fits the concept of central pain that may be related to deficient dopaminergic top-down inhibition in the basal ganglia (20%-40%).

Evidence in the literature links BMS to a peripheral neuropathy. Superficial biopsies of the anterolateral tongue from BMS patients showed a significantly lower density of epithelial and subpapillary nerve fibers than controls (14). Morphologic changes were consistent with axonal degeneration. This supports a trigeminal small-fiber sensory neuropathy or axonopathy.

Borelli *et al.* (15) found increased levels of nerve growth factor, a neuropeptide vital to nociceptive function in adults, in the saliva of BMS subjects. Other histopathologic studies of patients with BMS have shown an increased density of TRPV1 ion channels and P2X receptors on scattered nerve fibers, a finding previously linked to hypersensitivity and neuropathic pain symptoms in various models of human pain conditions (3).

Regarding peripheral neuropathic mechanisms, blink reflex recordings with stimulation of the distal branches of the third trigeminal division in primary

BMS patients have revealed distinct abnormalities within the trigeminofacial large and small fiber systems and the trigeminal brainstem complex (12,13,16). In a large study with 52 primary BMS patients, the results of the BR studies indicated sub-clinical brainstem pathology or peripheral trigeminal neuropathy, mostly lingual or mandibular nerve lesions, in 20% of the patients (14).

On the other hand, neuropathic pain has been revised to "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" (17). Neuropathic pain is characterized by shooting or burning pain, allodynia, hyperalgesia, and other altered sensory functions. It occurs when there is injury to the trigeminal nerve as well as during dentoalveolar or orthognathic surgical procedures. In patients with neuropathic pain, distinct changes include structural changes in the brain with areas of degeneration, cortical reorganization, maladaptive neuroplasticity, and disruption of central neural networks (6).

Although BMS pathophysiology may involve hormonal and psychosocial factors, it is considered a neuropathic pain state. Studies indicate, as mentioned before, that BMS may be a common clinical phenotype for variable dysfunctions affecting the central and peripheral nervous system. Some other indications that may confirm this, are a decreased tolerance to heat pain and increased detection thresholds to warming and heat pain (18,19) Qst profiles in some patients indicate loss of small fibers (13,20). Immunocytochemistry has also shown upregulation of nerve growth factor, purinergic, sodium, and vanilloid receptors like in other neuropathic pain states (21,22) Moreover, patients who had experienced BMS for a prolonged period of time had an increased electric taste/ tingling detectors threshold ratio, suggesting progressive neural damage (23).

We can conclude that overall, BMS patients display brain activations patterns similar to those of patients with neuropathic pain conditions. Therefore, treatment approach should involve a multidisciplinary character similar to the treatment for neuropathic pain including the management of possible underlying factors that might also play a role in this pathology.

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