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Pathophysiology of primary burning mouth syndrome

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HIGHLIGHTS

• Most patients with primary burning mouth sdr (BMS) suffer from subclinical neuropathic pain. • Lesions at several levels of neuraxis can give rise to clinically similar BMS symptoms. • Three distinct subclasses of BMS have been neurophysiologically characterized: (i) Peripheral small fibre neuropathy (ii) Subclinical major trigeminal neuropathy (iii) Central pain that maybe related to deficient dopaminergic top-down inhibition. • Accurate diagnosis can only be done with neurophysiologic, psychophysical and neuropathological tests.

ABSTRACT

Primary burning mouth syndrome (BMS) is severe, disabling and chronic intraoral pain condition for which no local or systemic cause can be found and clinical examination is normal. It mostly affects elderly citizens, especially postmenopausal women with prevalence up to 12–18%. In addition to spontaneous burning pain, patients may complain of taste alterations. Recent neurophysiologic, psychophysical, neuropathological, and functional imaging studies have elucidated that several neuropathic mechanisms, mostly subclinical, act at different levels of the neuraxis and contribute to the pathophysiology of primary BMS. Demonstration of loss of small diameter nerve fibres in the tongue epithelium explains thermal hypoesthesia and increase in taste detection thresholds found in quantitative sensory testing. As in neuropathic pain, decreased brain activation to heat stimuli has been demonstrated with fMRI in BMS patients. However, it seems that the clinical diagnosis of primary BMS encompasses at least three distinct, subclinical neuropathic pain states that may overlap in individual patients. The first subgroup (50–65%) is characterized by peripheral small diameter fibre neuropathy of intraoral mucosa. The second subgroup (20–25%) consists of patients with subclinical lingual, mandibular, or trigeminal system pathology that can be dissected with careful neurophysiologic examination but is clinically indistinguishable from the other two subgroups. The third subgroup (20–40%) fits the concept of central pain that may be related to hypofunction of dopaminergic neurons in the basal ganglia. The neurogenic factors acting in these subgroups differ, and will require different treatment strategies. In the future, with proper use of diagnostic tests, BMS patients may benefit from interventions specifically targeted at the underlying pathophysiological mechanisms.

Contents

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1. Introduction

Burning mouth syndrome (BMS) is an intense, chronic intraoral pain state that resembles tooth ache in intensity but differs from it qualitatively (Grushka, 1987; Ship et al., 1995; Zakrzewska, 1995). In previous literature, BMS has also been called stomatodynia, stomatopyrosis, glossodynia, oral dysesthesia, or persistent idiopathic orofacial pain (Woda and Pionchon, 1999). According to current diagnostic criteria (International Headache Society (IHS), 2004), 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 (Woda and Pionchon, 1999; Scala et al., 2003). The pain is continuous and moderate to severe in intensity although it may fluctuate, being often better in the morning and aggravating towards the evening, but it only rarely disturbs sleep. It is most often experienced in the tongue, but may be felt anywhere in the intraoral mucosa. BMS pain is usually bilateral, although it may rarely occur unilaterally, and it does not comply with peripheral nerve distributions. In addition, patients frequently complain of taste alterations (dysgeusia, hypogeusia) or dry mouth (xerostomia) despite normal salivation (Bartoshuk et al., 1999; Granot and Nagler, 2005; Eliav et al., 2007). The diagnosis of primary BMS is purely clinical and based on patients' description of typical subjective symptoms as well as 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 salivation, drugs, nutritional deficiencies, oral habits such as tongue thrusting and bruxism, or lesions related to poorly fitting denture. The secondary BM symptoms disappear with treatment of the underlying cause, whereas no universally efficient treatments are currently available for primary BMS, although some patients may benefit from local clonazepam or neuropathic pain medications (Zakrzewska et al., 2005).

The prevalence of BMS has been reported to range from 3.7% (Bergdahl and Bergdahl, 1999) to 18% (or even up to 40%) in older age groups, especially in postmenopausal women (Grushka et al., 2002). This wide range of prevalence figures of BMS is obviously due to rather loose diagnostic criteria (Merskey and Bogduk, 1994) applied in earlier studies that has resulted in heterogeneous patient populations in many studies performed before the more distinct definitions of primary BMS and secondary BMS were launched (Bergdahl and Bergdahl, 1999; Scala et al., 2003; IHS, 2004). Due to previous diagnostic vagueness, the aetiology and pathophysiology of primary BMS have remained largely unknown until recently and, e.g. psychogenic causes have often been causally linked to the "wastebasket diagnosis" of BMS in earlier reports (Harris, 1974; Eli et al., 1994).

There is now, however, increasing evidence suggesting pathophysiological alterations at different levels of the neuraxis, either alone or simultaneously within the peripheral or central nervous system, in the etiopathogenesis of primary BMS. During the last decade, clinical neurophysiology of the trigeminal system, quantitative sensory testing (QST), structural analysis of epidermal nerve fibre density (ENFD) of the tongue mucosa, and functional brain imaging with positron emission tomography (PET) and fMRI have provided effective and sensitive tools for accurate diagnostic evaluation of clinical patients and scientific studies on pain patients (Cruccu et al., 2004; Jääskeläinen, 2004, 2009; Apkarian et al., 2005; Rolke et al., 2006; Sommer and Lauria, 2007). All these research methods have now been applied in the study of BMS patients, which, together with more rigorous clinical diagnostic definitions separating primary from secondary BMS, has finally resulted in rapid progress in our understanding of the pathophysiological mechanisms underlying primary BMS. This review will summarize the recent neurophysiologic, psychophysical, neuropathological, and brain imaging evidence for neuropathic mechanisms that have been shown to play a key role in the majority of patients with primary BMS (Jääskeläinen et al., 1997, 2001; Forssell et al., 2002; Hagelberg et al., 2003; Lauria et al., 2005; Albuquerque et al., 2006; Eliav et al., 2007; Yilmaz et al., 2007; Puhakka et al., 2010).

2. Evidence for neuropathic aetiology in BMS

2.1. Early evidence indicating neurogenic dysfunction in BMS

Grushka et al. (1987) performed the first systematic psychophysical study on BMS patients utilizing QST methods to investigate tactile and thermal sensory modalities within the orofacial region including tongue mucosa. They could not show any differences between the patients and controls in the detection thresholds of any of the tested sensory modalities. As regards the negative results in thermal QST, the reason may have been in the use of a large thermode that is at present considered unsuitable for the study of the small trigeminal distributions (Jääskeläinen, 2004, 2009; Pigg et al., 2010). They showed, however, that BMS patients had decreased tolerance to heat pain at the tip of the tongue compared to healthy controls (Grushka et al., 1987), which is an unspecific finding that can occur both in musculoskeletal and neuropathic chronic pain (Kehlet et al., 2006). With laser Doppler flowmetry, vasoreactivity of the intraoral mucosa to dry ice stimulation has been shown to be higher in BMS patients than controls (Heckmann et al., 2001), which, as a positive sign, is in line with the sensory phenomenon of decreased pain tolerance.

More convincing evidence for focal involvement of the intraoral small fibre system came from a QST study utilizing argon laser stimulator (Svensson et al., 1993) and showing increased detection thresholds to warming and heat pain (hypoesthesia and hypoalgesia, i.e. negative signs) together with low pain to sensory threshold ratios on the tongue mucosa of BMS patients compared to control subjects. In addition to focal small diameter nerve fibre system pathology in the tongue mucosa, more widespread involvement of the peripheral small diameter nerve fibres has been suggested to occur in about 50% of BMS patients according to an early study with poorly defined diagnostic criteria (Lauritano et al., 1998; in Italian).

2.2. Neurophysiologic evidence

The diagnosis of peripheral neuropathy and neuropathic pain may be difficult or impossible with clinical examination only, especially at later stages of recovery, and clinical neurophysiologic investigation may greatly increase the diagnostic yield in particular when used in combination with QST (Robinson, 2000; Teerijoki-Oksa et al., 2004; England et al., 2005; Kehlet et al., 2006; Løseth et al., 2006; Jääskeläinen, 2009). Within the orofacial region, brainstem reflex recordings (masseter reflex, blink reflex, masseter silent