Critical Commentary 1

Steroid Dysregulation and Stomatodynia (Burning Mouth Syndrome)

Joanna M. Zakrzewska, MD, FFPMRCA
Consultant, Oral Medicine
Facial Pain Lead
Eastman Dental Hospital–UCLH
256 Gray's Inn Road
London WC1X 8LD
United Kingdom
Fax: 44 (0) 20 7915 1105
Email: jzakrzewska@nhs.net

Burning mouth syndrome (BMS) or stomatodynia remains an enigma, but considerable progress has been made in defining it more accurately and there are an increasing number of studies being reported that enable a new hypothesis such as the one proposed by Woda et al.[1] Pain is extremely complex, as it is an aggregate of several phenotypes associated with central and peripheral nerve changes, autonomic balance, neuroendocrine function, psychological responses, and inflammatory changes, and it is also shaped by environmental factors.[2] Genetic factors may affect both hormonal changes and psychological factors, but local changes in innervation of highly specialized taste buds may also play a role and are not subject to hormonal influence. This Commentary will focus on these aspects.

We still know very little about why some individuals develop particular orofacial pain conditions such as BMS and not others, why some pain conditions are more common in women, or why there are individual and sex differences in pain perception. Although some of these differences may be accounted for by cognitive and sociocultural gender differences, there is increasing evidence for significant primary biological differences in pain perception and processing between the sexes, and women report greater sensitivity to experimental pain than men.[3,4] BMS does show a more marked sex difference than other facial pain conditions and so may be a suitable condition on which to test these hypotheses.

With recent advances in genotypying, the list of genes associated with persistent pain is rapidly increasing. It is postulated that identified genes may be implicated in more than one condition, as many pain states share similar comorbidities.[2] The genes involved may have a variety of functions varying from transporters, metabolic genes and transciption regulators, receptors, cytokines, and ion channel modifiers.[2] In some diseases, the inheritance of specific gene polymorphisms has been found to account for pain conditions and there is now good evidence from clinical and animal studies that gene polymorphisms play such a role in orofacial pain conditions.[2] Susceptibility to chronic pain could be genetically predetermined through lowered pain thresholds or altered pain sensitivity but only become manifest after exposure to an appropriate noxious insult,[5] the type of pain condition being determined by the nature of the insult. Alternatively, poor adaptive responses in the central nervous system could result in a persistent sensitized pain state in some and recovery in others following a noxious insult.[6] As Woda et al[1] have hypothesized, it is possible that gonadal steroids play a role in BMS and there could be specific candidate estrogen receptor (ER) gene polymorphisms or genes whose expression is altered by estrogen which predisposes individuals to BMS.

Fillingim and Ness[7] in their review have shown that *(1)* sex steroids affect both peripheral and central pathways involved in nociceptive processing, *(2)* the effects of sex hormones account partly, but not completely, for differences in pain sensitivity between males and females, and *(3)* hormonal effects on pain responses are complex, dynamic, and bidirectional. Thus, genetic factors can contribute to pain differences between the sexes. Indeed, it has recently been shown that inheritance of a specific polymorphism of the melanocortin-1 receptor gene mediates female-specific mechanisms

of analgesia in both mice and humans.[8] This study showed that redheaded women required less pentazocine to reach analgesia than redheaded men.

More recently, Guimarães et al[9] in a small study have shown that BMS patients have interleukin-1 beta and serotonin transporter gene polymorphisms. These polymorphisms have been associated with pain sensibility not only following exposure to environmental and drug challenges but also in the normal state and have been found in neuropathic pain sufferers. Interleukin-1 beta has also been associated with depression and so this may be the reason why depression is found in some patients with BMS.

Patients with BMS have been especially well studied from the psychological perspective in the past due to a previous lack of any physiological explanation for the pain.[10] Now it is being increasingly recognized that variations in genetic characteristics could explain variations in pain perception and psychological factors. Variation in the gene encoding catechol-O-methyltransferase (COMT) can substantially influence pain sensitivity, and several haplotypes have been identified.[11] Slade et al[12] tried to determine whether variations of the gene encoding COMT as well as psychological factors increased the risk of temporomandibular disorders (TMD) in a 3-year prospective study of TMD patients. Depression, stress, and mood were found to be significant risk factors for TMD development but different haplotypes of COMT did not seem to play a role, suggesting that there may be more confounding factors but also highlighting the need for larger cohorts when looking prospectively at disease entities. Thus, other gene polymorphisms will need to be investigated in common pain conditions such as TMD before studies are carried out in rarer conditions such as BMS.

Psychological factors in themselves can result in stress and anxiety, which in turn lead to metabolic and endocrine changes. But equally, environmental factors such as significant life events will result in stress. Either way this can then lead to changes in cortisol levels, which Amenabar et al in a small case study found to be altered in comparison to healthy controls, which is in line with findings in other chronic pain conditions.[13] However, a recent study of 87 cases of BMS compared with matched controls showed no statistically significant differences in adverse life events but did report that in the menopausal or postmenopausal BMS patients, follicle-stimulating hormone levels were higher and estradiol levels were lower (although the study did not measure cortisol levels).[14]

Woda et al[1] point out that BMS is often associated with taste disturbance and suggest that this may be due to degeneration of fine gustatory primary fibers and changes in inhibitory control. Is there a potential link with gender that makes women more predisposed to BMS? Bartushuk et al[15] showed that people who rate 6-n-propylthiouracil (PROP) as intensely bitter are likely to belong to a group called supertasters who also perceive stronger tastes from a variety of bitter and sweet substances, and perceive more burn from oral irritants (alcohol and capsaicin). They showed that this was related to the density of taste receptors on the anterior tongue (fungiform papillae, taste buds) and that women were more likely to be supertasters. Thus, there is significant correlation with perceived bitterness of PROP and supertaster status. Further studies have suggested that those with higher density of taste buds are more prone to developing BMS.[16,17] This could be because of the increased innervations to the large number of papillae, and the potential for the greatest loss of inhibition if there is damage to this innervation. Taste sensation of the anterior two-thirds of the tongue is supplied by the chorda tympani nerve, a branch of the facial nerve, and at the tip of the tongue innervation may come from both sides. The lingual nerve, a branch of the mandibular division of the trigeminal nerve, supplies mechanical and thermal sensations. Eliav et al[18] found taste hypofunction on at least one side of the tongue in more BMS patients than in controls, thus suggesting chorda tympani dysfunction. They hypothesized that dysfunction of the chorda tympani then leads to lingual nerve hyperfuntion and this imbalance leads to BMS. This increased prolonged abnormal input could then lead to central sensitization and spread of the symptoms beyond the initial site. This model could explain the lack of effect of hormone replacement therapy once neural symptoms are established.[19]

Thus, as with all pain conditions it is important to identify patients early and, based on the hypothesis put forward by Woda et al,[1] there would be justification in relooking at hormonal therapies in BMS patients with well-designed randomized controlled trials.

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