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ORIGINAL ARTICLE

Burning mouth syndrome: the role of contact hypersensitivity

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BACKGROUND: Burning mouth syndrome is a burning sensation or stinging disorder affecting the oral mucosa in the absence of any clinical signs or mucosal lesions. Some studies have suggested that burning mouth syndrome could be caused by the metals used in dental prostheses, as well as by acrylate monomers, additives and flavouring agents, although others have not found any aetiologic role for hypersensitivity to dental materials.
OBJECTIVE: To evaluate the extent and severity of adverse reactions to dental materials in a group of patients with burning mouth syndrome, and investigate the possible role of contact allergy in its pathogenesis.
MATERIALS AND METHODS: We prospectively studied 124 consecutive patients with burning mouth syndrome (108 males; mean age 57 years, range 41–83), all of whom underwent allergen patch testing between 2004 and 2007.
RESULTS: Sixteen patients (13%) showed positive patch test reactions and were classified as having burning mouth syndrome type 3 or secondary burning mouth syndrome (Lamey's and Scala's classifications).
CONCLUSION: Although we did not find any significant association between the patients and positive patch test reactions, it would be advisable to include hypersensitivity to dental components when evaluating patients experiencing intermittent oral burning without any clinical signs.
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Keywords: burning mouth syndrome; patch test; dental materials; contact allergy

Introduction

Burning mouth syndrome (BMS) is an enigmatic chronic pain condition that affects 1.5–5.5% of middle-aged and elderly women. The International Association for the Study of Pain has identified BMS as a 'distinctive nosological entity' characterised by 'unremitting oral burning or similar pain in the absence of detectable oral mucosa changes' (Merskey and Bugduk, 1994). The pain is usually moderate or severe, may vary during the course of the day and can last for years. Its onset may be spontaneous or associated with drug use, dental treatment or viral infections (van Joost *et al*, 1988; Tourne and Fricton, 1992; Salort-Llorca *et al*, 2008). Recent studies have identified dysfunctions in several of the cranial nerves associated with the sensation of taste as a possible cause, and found that BMS patients show significant alterations in heat pain tolerance, and high sensory and pain thresholds to argon laser stimulation (Lauria *et al*, 2005; Scardina *et al*, 2006; Patton *et al*, 2007; Yilmaz *et al*, 2007).

Lamey and Lamb (1988) classified BMS patients based on daily variations in the pain and identified three clinical subtypes: type 1 characterised by pain-free awakening with symptoms developing during the day; type 2 characterised by constant pain throughout the day; and type 3 characterised by intermittent symptoms. Lamey *et al* (1994) showed that subjects with BMS (especially type 3) have hypersensitive reactions to denture base, dental filling materials and food allergens more frequently than might be expected. Scala *et al* (2003) proposed classifying BMS into two clinical forms: primary or idiopathic BMS, and secondary BMS because of local or systemic pathological conditions susceptible to aetiology-directed therapy.

Burning mouth syndrome is often idiopathic, but various multifactorial local and systemic pathways have been suggested, including contact hypersensitivity to oral allergens, which is mainly associated with intermittent burning or secondary BMS (Brailo *et al*, 2006). The role of allergens in BMS is somewhat controversial: some studies claim a high prevalence of allergy to dentures and dental materials such as acrylates, nickel, mercury, gold and cobalt (Dal Sacco *et al*, 2005), but true allergies to denture materials are rare and patients should not be considered as being affected by them until

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controlled patch testing has been correlated with their clinical symptoms.

Recent studies described contact allergy of the oral mucosa in response to various foods, oral hygiene products and the materials used in dental practice (Virgili *et al*, 1996), any of which may lead to sensitisation. There is no description of any single or specific clinical presentation of contact allergy to dental materials, but patients show various oral mucosa manifestations such as those commonly found after contact with amalgams, palladium, gold, nickel sulphate and resins.

The aim of this study was to evaluate the extent and severity of adverse reactions to dental materials in a group of BMS patients, and investigate the possible role of contact allergy in the pathogenesis of the syndrome.

Material and methods

We prospectively studied 124 consecutive patients with oral burning and no signs of mucosal lesions (108 women and 16 men with a mean age of 57 years, range 41–83) diagnosed as having secondary BMS at the Unit of Oral Pathology and Medicine of Milan University's Dental Hospital (Italy) between January 2004 and July 2007. Any patients with primary BMS (defined according to Scala *et al* as a burning sensation in the mouth, including complaints described as a stinging sensation or pain in association with an oral mucosa that appears clinically normal in the absence of local or systemic diseases or alterations) were excluded.

The associated conditions that could be extrapolated from their histories included depression, cancer phobia, systemic medications (particularly xerostomic drugs), menopause, concurrent diabetes, denture wearing and recent dental treatments.

All of the patients underwent allergen patch testing in accordance with the standard criteria proposed by the Italian Society of Allergological and Environmental Dermatology using a selected 'oral cavity series' of 34 specific haptens, including several dental resins, metal salts and flavours (Lofarma Inc, Milan, Italy). The haptens were tested on the upper part of the back using Finn Chambers on Scanpor tape (Alpharma Inc, Vennesla, Norway), with the readings being made after 72–96 h. The reactions were evaluated using a 5-point scale and criteria similar to those of the North American Contact Dermatitis Group: [–] negative reaction; [+] macular erythema; [++] macular erythema with a weak reaction (non-vesicular erythema, infiltration and possibly papules); [+++] a strong reaction (edematous or vesicular lesions); and [++++] spreading, bullous and ulcerative lesions, or an irritant reaction. Clinical relevance was defined as concordance between patch test positivity and the resolution of symptoms after the removal of the haptens. All of the patients were classified based on the classifications of Lamey (type 1, 2 and 3 BMS) and Scala (primary and secondary BMS).

The study was approved by our local Ethics Committee and all patients gave their written informed consent.

Results

All of the 124 patients had secondary BMS according to Scala *et al*; according to Lamey's classification, 90 (72.6%) had type 3 BMS, 20 (16.1%) type 2 and 14 (11.3%) type 1. Twenty-nine patients (23.4%) wore complete dentures, 31 (25%) partial dentures, and 17 (13.7%) had amalgam fillings. Eight patients (6.4%) reported burning of the mouth after dental treatments: sessions of oral hygiene (3 cases), implant therapy (2 cases), rehabilitation with a fixed prosthesis (3 cases). Eighty-six patients (69.3%) complained of depressive and/or anxiety disorders, and 55 (44.3%) were of menopausal or postmenopausal age.

Sixteen patients (13%), all with type 3 or secondary BMS showed positive patch test reactions (Table 1), which were considered clinically relevant in 14 cases. The reactions were subsequently judged to be certain because the oral burning stable resolved after contact with the positive hapten had been avoided for a period of 1.5–2 years, despite the persistence of other possible precipitating factors. They were considered clinically irrelevant in two cases (No. 6 and No. 13) based on a careful evaluation of the patients' histories and allergen exposure after the removal of the substance.

Table 1 Clinical characteristics and relevance of positive patch test in patients with burning mouth syndrome

Patient No.	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*
Age (years)	69	57	43	75	76	42	74	75	53	57	45	56	43	57	75	43
BMS type[a]	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Positive reaction	IC ++ Mer ++	C ++ P ++	N ++ Mer +	P +	C ++	TC ++	S ++ Mer ++	MM ++	N +++	N ++	P ++	N ++ Mer +	N ++	C ++	P +++	Mer ++
Exposure	DF	D	DF	D	D	D	DF	D	DF	D	D	D F	DI	D	D	DF
Clinically relevant	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Depression	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No
Xerostomia	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Duration of BMS (years)	5	3	3	6	6	4	5	5	4	3	5	3	3	7	10	3

IC, iron chloride; C, cadmium; P, palladium chloride; N, nickel sulphate; TC, tetracaine chloride; S, silver; MM, methyl methacrylate; Mer, mercury; D, denture; DF, dental filling; DI, dental impression; +, macular erythema; ++, macular erythema with a weak reaction (non-vesicular erythema, infiltration and possibly papules); +++, a strong reaction (edematous or vesicular lesions).
[a]All patients were classified as having secondary BMS (Scala *et al*) type 3: intermittent symptoms.

Nine of the patients with clinically relevant reactions were sensitised to metal alloys in dentures; the remaining five had undergone repeated dental restoration treatments and were allergic to the mercury in dental clogging compounds. Nickel sulphate was the most frequent positive allergen (five cases); cadmium was positive in three cases and palladium in four; and iron chloride, methyl methacrylate, silver and iron chloride were positive in one case each. None of these patients complained of xerostomia, but 10 complained of depressive and/or anxiety disorders.

Discussion

Burning mouth syndrome is a diagnostic and therapeutic challenge because of its aetiopathogenetic variability. The latest updates (Scala *et al*) indicate that it is crucial to distinguish primary BMS (apparently related to a neuropathic background and theapeutic resistance) from secondary BMS, which is favoured by local and systemic precipitating factors, and merits careful evaluation because tailored treatment may eliminate or remove the pain. The role of oral allergens in contact hypersensitivity (secondary BMS) is somewhat controversial: some studies suggest that there is a high rate of allergy to denture or dental materials and/or food additives and flavours (Helton and Storrs, 1994; Sardella, 2007), whereas others seem to deny these findings (Skoglund and Egelrud, 1991). However, many of these reports are based on small series of patients studied by means of heterogenous methods.

Sixteen of our 124 patients (13%) patients showed positive allergic reactions, all of whom were affected by intermittent burning, the reactions were confirmed by clinical evidence of stable pain remission after the elimination of contact with the involved allergen in 14 cases. Our findings are in line with those of Lamey *et al* (Lamey *et al*, 1994) who reported 65% of positive patch test reactions in a cohort of 33 patients with intermittent burning (type 3 BMS), 10 of whom were cured after contact with the involved allergens was avoided, which suggests that a positive patch test in patients with intermittent burning is likely to be aetiologically significant. However, the association of contact allergy with this particular type of BMS has not been confirmed in other studies (Torgerson *et al*, 2007).

The number of nickel-positive patients was relatively high, but the relevance of the positive reactions was not always clear and the sensitisation may have been related to other sources. Furthermore, about one-half of these patients also reacted to palladium chloride and one-third to cobalt chloride, which possibly reflects cross-allergy to nickel and not necessarily sensitisation because of dental products. Unlike the reactions to nickel and gold, most of the reactions to mercury seemed to be relevant and the sensitisation seemed to be related to dental sources. The allergen groups with the highest percentage of positive reactions were cadmium sulphate and palladium chloride, which are both generally used as components of metallic dental prostheses.

Although allergens with high rates of positive reactivity tend to receive most attention in the medical literature, we were also interested in identifying compounds with a low percentage of positive reactions and, as previously observed by other authors, we can confirm the low rate of allergies to resin compounds such as acrylates (methyl-methacrylate) (Virgili *et al*, 1996).

We performed patch testing on our patients with chronic oral burning (particularly those with intermittent symptoms) on the basis of previous findings (Lamey *et al*, 1994). The appropriate diagnostic evaluation of such patients requires the use of a specific 'oral cavity series' containing haptens of known significance, such as mint flavourings, as well as a careful assessment of their history and allergen exposure to distinguish the relevant test reactions correctly. Moreover, contact sensitisation to the constituents of plastic dentures must be seriously considered, and the lack of information concerning their ingredients and allergenic potential may not allow a precise diagnosis.

The relevance of each allergen at the 96-h reading was evaluated by the same clinician who obtained the information concerning each patient's history and performed the clinical examination to standardise the interpretation. Determining relevance is possibly the most clinically challenging aspect of interpreting patch tests because although it is theoretically 'pure', purity can never be achieved in practice. The clearance of a reaction after avoiding contact with the positive substance may be the best test of relevance, but the number of contactants encountered in everyday life and their enormous chemical complexity makes avoidance difficult, particularly in the case of oral allergens.

In spite of the limitation of our study, the following conclusions can be made. Allergen skin patch testing is a useful diagnostic means of evaluating patients with BMS but controversy remains as to how to determine the clinical relevance of positive reactions. We did not find any significant association between BMS and positive patch test findings, but we believe it advisable to include hypersensitivity to dental components when evaluating patients with intermittent BMS (type 3 according to Lamey *et al* or secondary according to Scala *et al*).

Author contributions

Marino Roberto and Capaccio Pasquale designed this study and collected the data included in this manuscript. Marino Roberto reviewed the data and wrote the text of this manuscript. Spadari Francesco and Pignataro Lorenzo made the drafting of this work.

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