Burning Mouth Syndrome: Patch Test Results from a Large Case Series

Carrie B. Lynde, Miriam Grushka, and Scott R.A. Walsh

Background: **Burning mouth syndrome (BMS) is a burning or sore mouth in the absence of changes in the oral mucosa. It is often difficult to diagnose and treat. Numerous theories of the etiology have been suggested, including contact allergy.**

Objective: **To determine the clinical utility of patch testing in patients with BMS.**

Methods: **We retrospectively reviewed the charts of patients diagnosed with BMS who had patch testing performed between January 1, 2008, and July 31, 2012.**

Results: **Of 142 consecutive patients with BMS, 132 consented to patch testing; 89 (67%) had allergic patch test reactions. Of the patients with positive results, 66 (74%) had results that were deemed to have possible relevance. The most common allergens detected were nickel sulfate 2.5%, dodecyl gallate 0.3%, octyl gallate 0.3%, fragrance mix 8%, benzoyl peroxide 1%, and cinnamic alcohol 1%.**

Conclusions: **Our findings suggest that contact allergy may be an etiologic factor in some patients with BMS. Patch testing is a useful investigation for BMS patients.**

BURNING MOUTH SYNDROME (BMS) is a chronic condition characterized by a burning or sore mouth with the absence of changes in the oral mucosa and no underlyng causative systemic disease.[1] The prevalence is about 0.71 to 1.5%,[2,3] and there is a female predominance. Typically, the onset is perimenopausal, and patients are more than 50 years old.[2,4]

Patients with BMS are often difficult to diagnose and treat. Numerous theories of the etiology have been suggested; the current evidence appears to support the presence of peripheral and/or central neuropathic changes.[5] However, the source of these changes, as well as the role of local tissue changes,[6] including the presence of a contact reaction, continues to be an area of inquiry including contact allergy. Most of the literature on BMS and contact allergy consists of case reports or small case series.[7] There is no agreement in the literature on the utility of patch testing patients with BMS. Some researchers have recommended limited patch testing for select patients,[8] whereas others have not recommended routine patch testing for BMS.[9–11] More recent research has supported the role of contact allergy.[7] The allergens identified have included metals, prosthodontic materials, flavorings, and food additives.[7]

We retrospectively reviewed patch test reactions in patients with BMS to determine if a delayed-type hypersensitivity reaction may be a component in the pathogenesis of this condition.

Methods

We retrospectively reviewed the charts of patients diagnosed with BMS who had patch testing performed between January 1, 2008, and July 31, 2012, in a general dermatology clinic at the Division of Dermatology, Sunnybrook Health Sciences Centre, Toronto. This study was approved by the Sunnybrook Health Sciences Research Ethics Board.

BMS was established clinically by both a dentist specializing in this area (M.G.) and the staff dermatologist (S.R.A.W.). Patients with oral changes or concomitant oral disease, such as oral lichen planus, were excluded. Where

From the Faculty of Medicine, University of Toronto, Toronto, ON; Division of Dermatology, University of Toronto, Sunnybrook Health Science Centre, Toronto, ON; and Department of Surgery, William Osler Health Centre, Etobicoke Campus, Etobicoke, ON.

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Address reprint requests to: Carrie B. Lynde, MD, M1 700- Division of Dermatology, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, ON M4N 3M5; e-mail: carrie.lynde@utoronto.ca.

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appropriate, patients had bloodwork or appropriate testing (salivary gland biopsy, Schirmer testing) to rule out underlying systemic diseases, such as Sjögren syndrome. Patients with sicca syndrome associated with an autoimmune connective tissue disease were excluded.

All patients were patch-tested to the North American Standard tray (Table 1), our dental tray (Table 2), and our cheilitis tray (Table 3). Where appropriate, patients were patch-tested to additional trays (such as additional metals) or the patients' own products. Using standard methods,[12] antigens were placed on the back and occluded using Finn Chambers (Epitest Ltd, Tuusula, Finland) and secured with Scanpor tape (Alpharma Inc., Vennesla, Norway). Allergens were removed at 48 hours after ensuring that there had been appropriate skin contact. Readings were performed 48 and 96 hours after the initial application of the antigens. The North American Contact Dermatitis Group scoring system was used. Reactions $\geq$ 1+ were considered positive.[12] Irritant reactions were identified by either a pustular reaction, edge effect, or prominence of the 48-hour reaction over the 96-hour reaction.

Results

Of 142 consecutive patients with BMS, 132 consented to patch testing (Table 4). Eighty-six percent (113) were women, and the mean age was 59.5 years (median 58.5 years, range 29–88 years). The mean duration of disease prior to presentation to our patch test clinic was 2.6 years (median 1.2 years, range 0.33–27 years). Ten patients were not patch-tested because they either elected not to have patch testing or withdrew consent on their subsequent appointment(s).

Eighty-nine (67%) patients with BMS had positive allergic patch test reactions. Of the patients with positive results, 66 (74%) had results that were considered possibly relevant and 14 (16%) had results of questionable current relevance. The results of patch testing are summarized in Table 5. The most common allergens were nickel sulfate (30%), dodecyl gallate (28%), octyl gallate (18%), fragrance mix (13%), benzoyl peroxide (13%), and cinnamic alcohol (11%). Of the patients with allergic patch test results who returned for follow-up in the dermatology clinic (those who had comorbid unrelated skin disease), 93% (13 of 14) had partial or complete resolution following allergen avoidance. Some of the behavioral changes implemented by these patients included changing toothpaste, avoidance of gallates in food products (eg, salad dressing) and lipstick, avoidance of flavoring, cinnamon; two patients also improved on a

Table 1. North American Screening Series

Benzocaine 5%
2-Mercaptobenzothiazole 1%
Colophony 20%
4-Phenylenediamine 1%
Imidazolidinyl urea 2%
Cinnamic aldehyde 1%
Amerchol L 101 50%
Carba mix 3%
Neomycin sulfate 20%
Thiuram mix 1%
Formaldehyde 1%
Ethylenediamine dihydrochloride 1%
Epoxy resin 1%
Quaternium 15 2%
4-tert-Butylphenoformaldehyde resin 1%
Mercapto mix 1%
N,*N*-Phenyl-4-phenylenediamine 0.1%
Potassium dichromate 0.25%
Balsam of Peru 25%
Nickel sulfate 2.5%
2,5-Diazolidylurea 1%
DMDM hydantoin 1%
Bacitracin 20%
Mixed dialkyl thioureas 1%
Methychloro-2-methyl-4-isothiazolin-3-one (Kathon CG) 0.01%
Paraben mix 12%
Methyldibromoglutaronitrile 0.5%
Fragrance mix 8%
Glutaraldehyde 0.5%
2-Bromo-2-nitropropane-1,3-diol 0.5%
Sesquiterpene lactone mix 0.1%
Fragrance mix II 14%
Propylene glycol 30%
20-Hydroxy-4-methoxybenzophenone 3%
4-Chloro-3,5-xylenol 1%
Ethyleneurea-melamine formaldehyde mix 5%
Iodopropynyl butyl carbamate 0.2%
Disperse blue 106/124 mix 1%
Ethyl acrylate 0.1%
Glyceryl monothioglycolate 1%
Toluenesulfonamide formaldehyde resin 10%
Methyl methacrylate 2%
Cobalt II chloride hexahydrate 1%
Tixocortol-21-pivalate 0.1%
Budesonide 0.01%
Compositae mix 5%
Hydrocortisone-17-butyrate 1%
Dimethylol dihydroxyethylene urea 4.5%
Cocamidopropylbetaine 1%
Triamcinolone acetonide 1%

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Table 2. Cheilitis Series

Anethole 5%
Carvone 5%
Cinnamic alcohol 1%
Peppermint oil 2%
Menthol 2%
Oil of cinnamon 0.5%
Butyl hydroxyanisole 2%
Butyl hydroxytoluene 2%
Dipentene 1%
Sorbic acid 2%
Propyl gallate 1%
Octyl gallate 0.3%
Dodecyl gallate 0.3%
Diallyl disulfide 1%
Propolis 10%
Benzoyl peroxide 1%
Sorbitan sesquioleate 20%
Cetyl/steryl alcohol 20%
Benzalkonium chloride 0.1%
Triclosan 2%
Shellac 20%
Cinnamic aldehyde 1%
Oxybenzone 10%
Toluenesulfonamide formaldehyde resin 10%

nickel-free diet, and one patient improved on a balsam of Peru–free diet.

The most common allergens identified fall within into two large categories: foods/flavors and metals found in dental materials or restorations. Table 6 identifies the sources relevant to BMS of the top allergens in our study.

Table 3. Dental Series

Bisphenol A 1%
Hydroquinone 1%
Ammonium hexachloroplatinate 0.1%
Ammoniated mercury 1%
Gold sodium thiosulfate 0.5%
Palladium chloride 1%
Titanium 10%
Titanium IV oxalate 1%
Titanium IV oxide 10%
Bis-GMA 2%
Ethyleneglycol dimethacrylate 2%
2-Hydroxyethyl methacrylate
2-Hydroxypropyl methacrylate 2%
Triethyleneglycol dimethacrylate 2%
Eugenol 1%
Benzoyl peroxide 1%
Peppermint oil 2%
Menthol 2%
Ethyl methacrylate 2%
Methyl methacrylate 2%

Table 4. Characteristics of BMS Patients Who Were Patch-Tested

Characteristic	n
Number of patients	132
Age, yr	
Mean	59.5
Median (range)	58.5 (29–88)
Female sex (%)	113 (86)
Duration of disease before presentation, yr	
Mean	2.6
Median (range)	1.2 (0.33–27)
Positive patch test (%)	89 (67)
Relevant patch test results (%)	66 (74)
Improvement with allergen avoidance (%)	13 (93)

BMS = burning mouth syndrome.

Discussion

The role of allergy in the pathogenesis of BMS has been supported by previous research yet remains controversial. We found a strong link between BMS and contact allergy, with two-thirds of our patients having a positive patch test reaction. Of the positive reactions, three-quarters had a potentially relevant positive reaction. Ours is the largest case series of patch testing in BMS in the literature to date.

A recent retrospective chart review of 75 BMS patients found that 37% had allergic patch test reactions.[7] The most frequent allergens cited in this previous study were nickel (29%), balsam of Peru (29%), gold (29%), palladium (25%), and dodecyl gallate (18%).[7] These results compare well to ours. We had a higher rate of allergic positive reactions, demonstrating the importance of patch testing in these patients. Nickel, the gallates, fragrance mix, benzoyl peroxide, and cinnamic aldehyde were more common in our BMS patients than in patch test patients in general patch test clinics, suggesting a possible etiologic factor in BMS. For example, the patch test results of the North American Contact Dermatitis Group in 2005–2006 found 19% positive patch test results to nickel, 11.5% to fragrance, and 4.4% to cinnamic alcohol.[13] Results on the gallates are less widely published, but one center reported 7% prevalence to dodecyl gallate and 3% to octyl gallate.[14]

It is important to identify and educate the patient as to the source of the allergen identified. We encouraged patients to read ingredients and to avoid identified allergens. Sources of top allergens identified by our study that are relevant to BMS are listed in Table 6. The dental metals (nickel, cobalt,

Table 5. Most Common Allergens Identified

Allergen	n *(%)*
Nickel sulfate 2.5%	28 (31)
Dodecyl gallate 0.3%	25 (28)
Octyl gallate 0.3%	16 (18)
Fragrance mix 8%	13 (13)
Benzoyl peroxide 1%	13 (13)
Cinnamic alcohol 1%	10 (11)
Balsam of Peru 25%	9 (10)
Cobalt II chloride hexahydrate 1%	9 (10)
Gold sodium thiosulfate 0.5%	8 (9)
Palladium chloride 1%	6 (7)
Neomycin sulfate 20%	6 (7)
Ammoniated mercury 1%	4 (4)
Chrome	4 (4)
Methyl methacrylate 2%	4 (4)
4 Dimethymethacrylate	3 (3)
Propolis 10%	3 (3)
Peppermint oil 2%	3 (3)
Lanolin	3 (3)
Formaldehyde 1%	3 (3)
Quaternium 15 2%	3 (3)
Fragrance mix II	2 (2)
Kathon CG 0.01%	2 (2)
Ethelyenediamine	2 (2)
Propylene glycol 30%	2 (2)
Carba mix 3%	2 (2)
Benzocaine 5%	2 (2)
5 Triehtylglycol	2 (2)
Potassium dichromate 0.25%	2 (2)
Eugenol 1%	2 (2)
Colophony 20%	2 (2)
Arm & Hammer Sensitive Whitening	2 (2)
Sensodyne Brilliant Whitening	2 (2)
Hydroquinone 1%	2 (2)
Diburcaine hydrochloride	1 (1)
Ethylcyanoacrylate	1 (1)
Menthol 2%	1 (1)
Shellac 20%	1 (1)
Carvone 5%	1 (1)
Chromate	1 (1)
Methacrylic monomer	1 (1)
Cocoaminopropyl betaine 1%	1 (1)
N,*N*-Phenyl-4-phenylenediamine 0.1%	1 (1)
Benzalkonium chloride 0.1%	1 (1)
Cetyl/stearyl alcohol 20%	1 (1)
Titanium 10%	1 (1)
Epoxy resin 1%	1 (1)
Iodopropylbutyl carbamate	1 (1)
Compositae mix 5%	1 (1)
Oak moss absolute	1 (1)
Bacitracin 20%	1 (1)
Dipentene 1%	1 (1)
Methyldetromeglutaronitrile	1 (1)

and gold) can be found in dental materials and restorations. The source of metal in our patients was predominantly found in dental restorations and fillings. This was elicited on the patient history and from the patient's dentist. Specific tests such as the dimethylglyoxime test for nickel were not conducted in our patients. Gallates, cinnamic alcohol, fragrance mix, and balsam of Peru can be found in many common foods and flavors, especially toothpaste and chewing gum. Patients were not challenged after confirmation of food allergy; rather, avoidance was emphasized. Benzoyl peroxide can be found in dental acrylates, dentistry bleaching, and toothpaste bleaching.

Patients may benefit from allergen avoidance.[7,15] Lamey and colleagues found that more than half of patients with positive patch test reactions benefited from allergen avoidance in a study of 33 patients with BMS.[15] Similarly, Steele and colleagues demonstrated that approximately half of patients with a positive patch test result improved with avoidance of the allergen.[7] Allergen avoidance may take the form of removing dental materials or restorations, discontinuing a certain brand of toothpaste, or dietary modifications (eg, nickel-free diet; gallate-free diet, or balsam of Peru–free diet). It should be noted that in cases where patients may be required to remove or revise extensive dental restorations, there should be consideration for the risks associated with dental surgery, and discussion with the dental provider should be undertaken to weigh the potential benefit with the risk.

We recognize that a retrospective review of patient medical records is not optimal; however, we benefited from the concurrence of a dentist, specializing in oral medicine, and a dermatologist on the diagnosis of BMS and the consistency of only one dermatologist reading the patch test results. The Division of Dermatology, Sunnybrook Health Sciences Centre, as a tertiary care center, may have a referral bias. Further limitations include the lack of follow-up for many of the patients and the fact that relevant sources of allergens were not always available.

Conclusion

Prospective studies are needed to further clarify the underlying causes of BMS. We recommend patch testing

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Table 6. Sources of Top Allergens Identified Relevant for BMS

Allergen	*Relevant Sources for BMS*
Dental metals	
Nickel sulfate	Dental materials and restoration
	Dietary sources such as shrimp, chocolate milk
Cobalt II chloride hexahydrate	Dental materials and restoration
Goldsodium thiosulfate	Dental materials and restoration
Foods and flavors	
Gallates	Preservative present in fatty products to prevent rancidity, such as oils, fats, margarines, peanut butter, salad dressing
	Also found in chewing gum, lipsticks, lip balm
Cinnamic alcohol	Cinnamon, cola drinks, chewing gum, toothpaste, cough mixtures, throat lozenges
Fragrance mix	Cinnamic alcohol is a component
	Flavoring agents in mouthwashes and toothpastes
Balsam of Peru	Spices, cinnamon, cinnamon-related compounds, vanilla, essential oil or orange, tomatoes, citrus fruits, flavor for toothpaste, chewing gum, cough lozenges and cough medicine
Other	
Benzoyl peroxide	Dental acrylates, dentistry bleaching, toothpaste bleaching

BMS = burning mouth syndrome.

patients with BMS using the standard, dental, and cheilitis series as part of a routine evaluation.

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