



THE RELATIONSHIP BETWEEN BURNING MOUTH SYNDROME AND ALLERGENS FROM THE DENTAL MATERIALS: A CASE-CONTROL STUDY

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Patients with burning mouth syndrome (BMS) present a difficult diagnostic challenge. This study is trying to determine if BMS is associated with a higher incidence of allergy to dental materials and to assess the utility of patch testing in the management of BMS patients. The present study is a case-control study which began in October 2013 and ended in June 2015. A number of 32 patients diagnosed with BMS were included in the case group, each patient presenting at least one dental filling. The control group consisted of 19 patients with no symptoms of BMS. All the subjects were assessed for contact allergy (type IV hypersensitivity) to dental materials with the aid of epicutaneous patch tests. The results achieved showed that 13 patients (40.62%) tested positive for at least one hapten in the case group. Only 3 patients (15.78%) tested positive in control group. Most of the positive reactions in study group were recorded to the following haptens: Sodium tetrachloropalladate(II) hydrate (76.92% of the patients with positive reactions), followed by Potassium dichromate (23.07% of the patients with positive reactions) and Gold(I)sodium thiosulfate dehydrate (23.07% of the patients with positive reactions). Positive reactions in control group were recorded to the following haptens: Gold(I)sodium thiosulfate dehydrate, Nickel(II)sulfate hexahydrate and Mercury. The high percentage of positive reactions (40.62%) in the case group versus the small number of control cases that had positive reactions (15.78%) suggests that these local allergens play an important role in the etiology of BMS. Removing of these possible etiological agents may be used as a therapeutic method.

Key words: burning mouth syndrome (BMS), dental materials, allergy.

INTRODUCTION

Burning mouth syndrome (BMS) is clinically characterized by burning pain in the mouth in the absence of evident lesions and is often associated with dysgeusia and xerostomia, despite normal salivation. Classically, symptoms are better in the morning, worsen during the day and typically subside at night^{1,2}. BMS can be classified by etiology into primary and secondary. Based on diurnal fluctuation of symptoms it can be divided into: type 1 BMS (*symptom-free upon awakening with worsening symptoms throughout the day and variable symptoms at night*), type 2 BMS (*continuous symptoms in the day but none at night*)

and type 3 BMS (*intermittent symptoms interspersed with symptom-free days*)^{3,4}.

Scala *et al.* proposed the following fundamental criteria for the diagnosis of BMS: (1) daily and deep bilateral burning sensation of the oral mucosa; (2) burning sensation for at least 4 to 6 months; (3) constant intensity or increasing intensity during the day; (4) no worsening but possible improvement on eating or drinking; and (5) no interference with sleep⁵.

Epidemiology: Women (more frequently postmenopause) are 2.5 to 7 times more commonly affected than men^{2,6,7}. Prevalence varies widely in the literature: Tammiala-Salonen *et al* reported a rate of 15% of BMS in Finnish adult population⁸. In Swedish patients, 3.7% of subjects were diagnosed

with BMS while Lipton *et al* reported a prevalence of 0.7%^{9,10}.

The exact **etiology of BMS** remains imprecise and is likely multifactorial.

Allergic reactions (type IV) have been demonstrated to play an important role. Among the local factors, dental materials such as zinc, cobalt, mercury, gold, and palladium have been identified as causal agents for BMS¹¹. Often, dental materials allergy is associated with type 3 BMS¹². Although the majority of authors confirm the role of dental materials allergy in the etiology of BMS, there are some that deny it¹³⁻¹⁶. Sodium lauryl sulfate (a detergent in toothpaste known to cause dry mouth) and dietary antigens (sorbic acid, cinnamon, nicotinic acid, propylene glycol, and benzoic acid) may also be involved in the development of BMS¹⁷⁻¹⁹.

Neuropsychiatric and endocrine factors also play an important role in BMS²⁰⁻²³. Various studies have shown significant differences in thermal and nociception thresholds of patient with BMS compared to control subjects^{24,25}.

Finally, **autoimmune connective tissue disorders** such as Sjogren's syndrome and systemic lupus erythematosus are also associated with BMS²⁶.

Management of BMS: the first step is to determine if it's primary or secondary. When a causing factor is suspected (food, dental materials, oral hygiene products), it must be removed^{27,28}. Management of primary BMS, however, remains unsuccessful. It can be regarded as a chronic neuropathy and treated with benzodiazepines, antidepressants, topical capsaicin, alpha-lipoic acid. Hormone replacement therapy, anticonvulsants, biofeedback technique and psychosocial therapies can also be used^{2,19,29}.

MATERIALS AND METHODS

The objectives of the study were:

- 1) To determine if BMS is associated with a higher incidence of allergy to dental materials;
- 2) To assess the utility of patch testing in the management of BMS patients;
- 3) To determine which of the dental allergens caused the majority of the positive reactions in the tested patients.

Inclusion criteria: patients with clinical manifestations of BMS were included in the study group. Patients with no signs and symptoms of

BMS or other pathology of the oral mucosa were included in the control group.

Exclusion criteria: patients who presented visible lesions of the oral mucosa were excluded from the study.

Study design: This case-control study began in October 2013 and ended in June 2015. A number of 32 patients diagnosed with BMS were included in the study group, each patient presenting at least one dental filling. The control group consisted of 19 patients with no symptoms of BMS. On the other hand, 14 patients were excluded from the study due to the presence of visible lesions on the oral mucosa. All the subjects underwent epicutaneous patch testing with a dental series to assess them for dental materials allergy. The aim was to compare the incidence of dental materials allergy in study group with the one in control group and to determine which of the haptens determined positive reactions in each group.

All the patients who underwent the testing procedure were in the first place instructed about how the testing would go, what they could do and what they couldn't do while they had the tests applied on the skin, were presented the possible adverse events and serious adverse events, and after that they gave their written consent for the testing procedure. The study was approved by the Ethic Committee of Colentina Clinical Hospital, Bucharest.

All the patients (in number of 19) from the study group were selected from the Oral Pathology Department, "Carol Davila" University of Medicine and Pharmacy, Bucharest. A number of 10 of the 32 study group patients were men (31.25%) (maximum age 74 years old, minimum age 25 years old and average age 54.3 years old), and 22 were women (68.75 %) (maximum age 85 years old, minimum age 40 years old and average age 61.4 years old).

The control group patients consisted of 4 males (21.05%) (maximum age 31 years old, minimum age 25 years old, average age 28.33 years old) and 15 females (78.95%) (maximum age 75 years old, minimum age 23 years old, average age 30.5 years old) and they all were dental clinics personnel.

All the patients were tested for allergic skin reactions with **standardised and authorised by ICDRG (International Contact Dermatitis Research Group) patch tests. The DS (Dental Screening) – 1000** (Chemotechnique Diagnostics, Sweden) series of tests, that consists of dental materials haptens was used.

All 31 haptens (Table 1) that the DS 1000 kit contained were applied on Chemotechnique Diagnostics IQ Ultra Chambers that were attached onto the back of the patients.

Table 1

Allergens (under the form of patches) contained in the DS-1000 Patch Test Kit³⁹

1. Methyl methacrylate	6. N,N-dimethyl-4-toluidine
2. Triethylene glycol dimethacrylate	7. Benzophenone-3
3. Urethane dimethacrylate	8. 1,4-Butanediol dimethacrylate
4. Ethylene glycol dimethacrylate	9. Bisphenol A dimethacrylate
5. Bisphenol A glycerolate dimethacrylate	10. Potassium dichromate
11. Mercury	16. Eugenol
12. Cobalt (II) chloride hexahydrate	17. Colophonium
13. 2-Hydroxyethyl methacrylate	18. N-Ethyl-p-toluenesulfonamide
14. Gold (I) sodium thiosulfate dihydrate	19. Formaldehyde
15. Nickel (II) sulfate hexahydrate	20. 4-Tolyldiethanolamine
21. Copper (II) sulfate pentahydrate	26. Dimethylaminoethyl methacrylate
22. Methylhydroquinone	27. 1,6-Hexanediol diacrylate
23. Palladium (II) chloride	28. Drometrizole
24. Aluminiumchloride hexahydrate	29. Tetrahydrofurfuryl methacrylate
25. Camphoroquinone	30. Tin (Cositor)
31. Sodium tetrachloropalladate (II) hydrate	

The tests remained applied for 48 hours on the back of the patients and after 48 hours they were removed. The skin was cleaned with alcohol and

was marked with skin marker to facilitate the reading. There were two readings: the first reading was performed when the tests were removed from the back of the patients and the second reading took place after 72 hours from the moment that the tests were applied to the patient's back. The reading was facilitated by the visual scale included in the testing kit.

After the interpretation of the tests, patients with BMS were referred to the Oral Pathology Department for stomatological treatment in case they were allergic to one of the tested haptens and if that hapten was contained in their dental fillings.

RESULTS

In the study group: Positive reactions were recorded in 13 (40.62%) of the 32 subjects. 3 patients (23.07%) with positive reactions were men and the remaining 19 (76.93%) were women.

Most of the positive reactions were recorded to the following haptens: **Sodium tetrachloropalladate(II) hydrate** (76.92% of the patients with positive reactions), followed by **Potassium dichromate** (23.07% of the patients with positive reactions) and **Gold(I)sodium thiosulfate dehydrate** (23.07% of the patients with positive reactions).

Positive reactions to **Cobalt(II)chloride hexahydrate and Palladium(II)chloride** were recorded in two cases each and the rest of the haptens were positive in one case each.

Sodium tetrachloropalladate(II) hydrate positive reactions were recorded in 3 male patients and 7 female patients.

Multiple positive reactions were recorded in 8 patients (61.53%). One patient presented positive reaction to 5 haptens, 1 patient presented positive reactions to 4 haptens and 6 patients presented positive reactions to 2 haptens. Most common association of positive reactions were the following: 3 patients (23.07% of positive cases) presented allergy to Potassium dichromate and Sodium tetrachloropalladate(II) hydrate; 2 patients (15.38% of positive cases) presented allergy to Palladium(II)chloride and Sodium tetrachloropalladate(II) hydrate; 2 patients (15.38% of positive cases) presented allergy to Cobalt(II)chloride and Gold(I)sodium thiosulfate dehydrate.

The most intense reactions were ++ type (erytoma, edema, papules and vesicles). A number of 4 patients had this type of reaction, and they

presented hypersensitivity to the following haptens: Ethylene glycol dimethacrylate, Potassium dichromate, 2-Hydroxyethyl methacrylate, Gold(I)-sodium thiosulfate dehydrate, Nickel(II)sulfate hexahydrate, Copper(II)sulfate pentahydrate, Palladium(II)chloride and Sodium tetrachloropalladate(II) hydrate.

Two patients had doubtful reactions to the following haptens: Urethane dimethacrylate and Gold(I)sodium thiosulfate dehydrate.

Only one patient had a positive reaction that lasted more than 10 days and it was to Gold(I)sodium thiosulfate dehydrate.

No adverse or serious adverse events were recorded in study group.

In the control group there were only 3 patients (15.78%) who presented positive reactions. Each patient was positive to only one hapten. All the positive patients were females and had positive reactions to the following: Gold(I)sodium thiosulfate dehydrate, Nickel(II)-sulfate hexahydrate and Mercury.

No adverse or serious adverse events were recorded in control group.

DISCUSSION

The results of our study show that BMS is associated with a high incidence of hypersensitivity to dental materials (40.62%) compared to the control group (15.78%).

Similar results were reported by other studies. In a study published in 2014 by Lynde *et al.*³⁰, 89 (67%) out of 132 patients diagnosed with BMS presented positive reactions to the tested allergens. 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%³⁰.

A study performed by Steele *et al.* at Mayo Clinic, Rochester, Minnesota, between January 2000 and April 2006 on 75 de patients with BMS who had patch testing showed that 28 of these patients (37.3%) had allergic patch test reactions. The most common allergens were nickel sulfate hexahydrate 2.5%, balsam of Peru, and gold sodium thiosulfate 0.5%¹¹.

There are also studies that deny the connection between type IV hypersensitivity to dental materials and BMS. Marino and Capaccio³¹ evaluated 124 consecutive patients with burning mouth syndrome, all of whom underwent allergen patch testing

between 2004 and 2007. Sixteen patients (13%) showed positive patch test reactions and were classified as having burning mouth syndrome type 3 or secondary burning mouth syndrome. So the authors concluded that although they 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.

Another strong argument that BMS is caused by dental materials allergy is that the majority of positive reactions in study group were to compounds that are not common, such as Palladium, Chromium and Cobalt. Positive reactions to these haptens are rarely quoted in similar studies. Other authors confirm positive reactions to haptens such as Nickel, Mercury, Gold and Thiomerosal^{11,30,31}. The fact that the majority of positive reactions in the tested patients with BMS were to Palladium, Chromium and Cobalt can only confirm the strong association between their disease and allergy. The source for these compounds can only be in the patients' dental fillings, while the small percent of allergies in the control group was to common compounds such as Nickel and Gold.

One may wonder why and how dental fillings are causing the sensitization of the oral mucosa of the patient. A lot of complicated reactions take place inside the mouth. Saliva can have a corrosive effect on dental fillings and cause metal ions to detach from the filling. A galvanic current is generated by these ions that cause the release of more and more ions, even from the safest and longest lasting fillings. All these metal ions that are released from the dental filling can cause a sensitization of the oral mucosa³². So there's a need for stronger, stable and more biocompatible materials for dental restorations. For now Titanium, Zirconium and hybrid ceramics are the best choices, but even these two can cause BMS and other diseases³³.

BMS can also be caused by a large number of allergens such as medication, cosmetical products, condiments, foods and beverages, food additives³⁴. All these possible causes of BMS can explain why there are also patients with BMS that tested negative for DS-1000 haptens.

A strong collaboration between dermatologists and dentists is needed for a good management of the BMS patient that has dental materials allergies. Even though the allergic cause of BMS is

discovered, patients can be unpersuadable to replace their dental filling. In these cases a very important desiderate is the good follow-up of the patient in order to prevent further harming of the oral mucosa by the allergic reaction³⁵⁻³⁷.

Even if the patient agrees to change his dental filling, some aspects are worth mentioning. In principle, all restorations with allergy-positive elements need to be removed. After the removal, sometimes a transient aggravation of the allergic symptoms is observed because a large quantity of allergy-positive material dust is released. Since the reliability of the patch-test results have not been proven to be perfect, allergy-negative metal elements could still potentially cause allergy symptoms. So there's a need for patient follow-up for at least one month³⁸.

CONCLUSIONS

In our study BMS was clearly associated with a higher incidence of dental material allergy. The highest numbers of allergic reactions were caused by Palladium, Chromium, Cobalt and Gold. *Patch testing* is the only reliable method for diagnosis of dental materials allergy. This investigation can be used before a dental restoration and also after a dental restoration if allergy is suspected. When a patient is allergic to compounds found in his restoration and he has BMS symptoms, the restoration can be replaced with an allergen free one.

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