COMMON ALLERGIES AND ALLERGENS IN ORAL AND PERIORAL DISEASES

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SUMMARY – Allergic reactions sometimes participate in the development of perioral and oral diseases, indicating the need for appropriate allergen assessment. This review discusses current knowledge on the potential allergic reactions to different dental materials in patients with oral and perioral diseases. Aside from allergies to various dental materials, similar non-allergic, non-immune contact reactions (irritant or toxic) can occur. Among dental materials, the most frequent allergens are alloys, followed by rubber materials, polymers and acrylates. Allergic reactions to dental alloys that contain nickel, cobalt and amalgam are especially frequent since dentists use them for prosthetic and other restorations. There is a broad spectrum of clinical presentations of oral and perioral diseases possibly related to allergies, such as lichenoid reactions, cheilitis, perioral dermatitis, burning sensations, etc. Despite some limitations, patch test is crucial in the diagnosis and recognition of causative allergens because it reveals contact allergies, and is still superior in differentiating allergic and irritant contact reactions. It is important to examine patient medical histories (e.g., occurrence of symptoms after dental therapy or food consumption), and in consultation with their dentist, carry out allergy tests to specific dental allergens which are used or planned to be used in subsequent treatment.

Key words: Allergy; Burning mouth syndrome; Cheilitis; Gingivostomatitis; Oral disease; Oral lichenoid reactions; Patch test

Introduction

Oral and perioral diseases are relatively frequent in the general population, and their symptoms can significantly affect the patient’s quality of life. In cases of perioral and oral diseases, possible relations to various dental materials and procedures should always be taken into consideration when treating a patient1-3. Although there are many scientific papers on this issue, their results are ambiguous. Various substances can cause both immediate (type I) and delayed (type IV) allergic reactions, of which type IV allergic reactions are more common1,4,5.

On the other hand, some substances can provoke non-allergic, irritant or toxic reactions in which the immune mechanism is not involved4. Furthermore, patients often complain of unspecified sensations in peri-oral and oral soft tissues, which also makes it more difficult to evaluate the influence of allergies in peri-oral and oral diseases. Although there are no precise data on the incidence of side effects (unwanted reactions) from dental procedures and use of dental materials, it can be assumed that they are not very common.

Oral and Perioral Diseases Related to Allergic Reactions and Common Causative Allergens

There is a broad spectrum of clinical signs and symptoms of oral and perioral diseases that can be related to allergies, such as lichenoid reactions, cheilitis,
stomatitis, gingivitis, perioral dermatitis, burning sensations, swelling of the lips and face, etc.\textsuperscript{1,7-12}.

Early allergic reactions (type I) with manifestations in oral and perioral regions mostly manifest with angioedema but sometimes may include oral paresthetic and burning sensations, pointing to oral allergy syndrome (OAS), a form of type I allergic reaction. Oral allergy syndrome usually occurs in patients who suffer from allergic rhinitis, mostly after taking fresh food (such as vegetables, fruits and various nuts), due to the cross-reaction between food and inhalants\textsuperscript{13}.

On the other hand, various dental materials used in dental procedures may cause both allergic contact (delayed, type IV) and non-allergic contact reactions (irritant, toxic contact reactions). They appear when these materials have allergic or irritant effects on coming in contact with skin or oral mucosa. Unlike allergic reactions, in irritant contact reactions there is no allergic pathomechanism, no previous sensitizations to an allergen and no lesion spread\textsuperscript{14}. The most common contact allergens that can cause allergic reactions in the oral cavity and perioral region are antiseptics, dental alloys, impression materials, local anesthetics, dental cement, latex gloves, acrylate, adhesives, mouth rinse liquids, various dental hygiene preparations, and others\textsuperscript{7}.

Among dental materials, the most frequent allergens are dental alloys, followed by rubber materials, polymers and acrylates. (Notably, allergic reactions to local anesthetics are very uncommon). Metal salts in dental alloys, for example, have weak interactions with skin proteins and form complexes that make strong allergens that initiate hypersensitivity reactions\textsuperscript{14}. Allergic reactions to dental alloys that contain nickel, cobalt and dental amalgam are especially frequent since dentists use them for prosthetic and dental restorations\textsuperscript{3,4,15}. Positive allergy skin patch tests to gold are usually associated with the amount of gold used in dental procedures, although definite correlation between contact allergic reactions to gold and oral lesions has not been proven\textsuperscript{1}. While gold is not common allergen, it is especially important to take into consideration the percentage of other gold alloy ingredients such as silver, copper, and smaller amounts of platinum, palladium and zinc. Silver-palladium alloys (also contain zinc and copper, and occasionally palladium and silver), as well as many other metals such as cobalt, chromium, molybdenum, beryllium, gallium, rhodium, iridium and some others are also used in dental procedures. In their systematic review, Levi et al. point out that each type of metal exposure has a different rate of allergic reaction, which they explain by the extent of corrosion of the alloy, population exposure, and the biologic environment of each patient\textsuperscript{16}.

One of the most commonly mentioned allergens is rubber, which can be found in latex gloves (worn by dentists and their assistants) and rubber dams (used to isolate the operative site from the rest of the mouth)\textsuperscript{17-19}. Cases of adverse patient reactions to latex gloves worn by dental health care workers have been reported by Agrawal et al. Their study results showed that 16% of dental professionals reported allergy to latex gloves, with the prevalence significantly higher in those who had allergy to pollen grains, foodstuffs and rubber dam, asthma and eczema in their medical history\textsuperscript{17}. Other allergic reactions may be caused by substances which contain acrylates (most commonly methyl methacrylate, triethylene glycol dimethacrylate and polymethyl methacrylate) used for the fabrication of dentures, as well as for complex restoration procedures and as binding materials\textsuperscript{20}. Reactions to traces of benzoyl peroxide in dentures, hydroquinone and plasticizer dibutyl phthalate inhibitors, pigments, dyes, nylon fibers, titanium and zinc oxides are also possible.

The process of evaluating lesions and symptoms affecting the oral and perioral region is quite challenging due to their numerous possible manifestations. Some patients have burning symptoms and paresthesias without clinically evident oral lesions, whereas some patients have clear clinical signs such as lichenoid tissue changes or oral ulcerations\textsuperscript{12}. In the diagnosis and recognition of causative allergens, patch test is crucial because it reveals and confirms contact allergies, including patients with orofacial changes (particularly
prior to dental treatment) and dental workers with chronic dermatitis of the hands and face (Fig. 1). Patch test is still superior in differentiating contact allergic and contact irritant reactions; however, its usefulness has not yet been fully established because studies have yielded variable results\textsuperscript{14,21}.

There are numerous studies that have confirmed metal allergies in patients with dental alloys in their orthodontic devices and considering that it is important to emphasize which allergens are most common to cause diseases such as burning mouth syndrome (BMS), gingivostomatitis, cheilitis and oral lichen planus (OLP)\textsuperscript{22-25}. According to Budimir et al., some particular allergens increase the risk of certain oral diseases and symptoms\textsuperscript{22}. This risk is several times higher in atopic patients and those with existing allergies even in the absence of statistically significant differences in the occurrence of allergic reactions between...
| Oral and perioral disease | Author (year) | Number of patients | Causative agent |
|--------------------------|--------------|--------------------|-----------------|
| Cheilitis                | Budimir et al., 2018 | 230 subjects (78.3% females, 21.7% males) | Cobalt chloride (10%), nickel sulfate (6.7%), mercury precipitate (6.7%) |
|                         | Khamaysi et al., 2006 | 121 dental personnel with clinical presentation of oral and perioral disease were patch tested | Nickel sulfate (25.8%), gold sodium thiosulfate (22.6%), mercury (16.1%), palladium chloride (12.9%) |
|                         | Torgerson et al., 2007 | 331 patients with BMS, LTR, cheilitis, stomatitis, gingivitis, orofacial granulomatosis, perioral dermatitis and recurrent aphthous stomatitis | Fragrance mix (13%), gold sodium thiosulfate (6.8%), dodecyl gallate (6.1%) |
|                         | Raap et al., 2009 | 206 patients who underwent patch testing because of suspected contact allergy to dental materials | Amalgam (100%) |
|                         | Kim et al., 2015 | 44 patients with oral disease from 2004 to 2011 (oral lichen planus, BMS, cheilitis) | Cobalt chloride hexahydrate (33.3%), nickel sulfate (16.6%), potassium dichromate (16.6%), mercury (16.6%) |
| (Gingivo)stomatitis      | Budimir et al., 2018 | 230 subjects (78.3% females, 21.7% males) | Nickel sulfate (10%), cobalt chloride (6.7%), mercury precipitate (3.3%) |
|                         | Torgerson et al., 2007 | 331 patients with BMS, LTR, cheilitis, stomatitis, gingivitis, orofacial granulomatosis, perioral dermatitis and recurrent aphthous stomatitis | Mercury (14.3%), balsam of Peru (12.5%), gold sodium thiosulfate (37.5%) |
|                         | Raap et al., 2009 | 206 patients who underwent patch testing because of suspected contact allergy to dental materials | Nickel sulfate (50%), palladium chloride (37.5%), gold sodium thiosulfate (37.5%) |
|                         | Rai et al., 2014 | 20 patients who undergone dental procedures (13 patients with symptoms of oral lichen planus, oral stomatitis, burning mouth symptoms and recurrent aphthosis and 7 dental personnel) | Potassium chromate, nickel, palladium |
| Perioral dermatitis      | Budimir et al., 2018 | 230 subjects (78.3% females, 21.7% males) | Fragrance mix (6.7%), cobalt chloride (6.7%), nickel sulfate (3.3%) |
|                         | Khamaysi et al., 2006 | 121 dental personnel with clinical presentation of oral and perioral disease were patch tested | Nickel sulfate (25.8%), gold sodium thiosulfate (22.6%), mercury (16.1%), palladium chloride (12.9%) |
|                         | Torgerson et al., 2007 | 331 patients with BMS, LTR, cheilitis, stomatitis, gingivitis, orofacial granulomatosis, perioral dermatitis and recurrent aphthous stomatitis | Cobalt chloride (60%), gold sodium thiosulfate (25%), balsam of Peru (20%) |
| Oral and perioral disease                  | Author (year)          | Number of patients                                                                 | Causative agent                                                                 |
|-------------------------------------------|------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Burning mouth syndrome                    | Budimir et al., 2018   | 230 subjects (78.3% females, 21.7% males)                                        | Cobalt chloride (13.3%), P-phenylenediamine colophony (3.3%)                     |
|                                           | Khamaysi et al., 2006  | 121 dental personnel with clinical presentation of oral and perioral disease were patch tested | Nickel sulfate (15.9%), mercury (15.8%), palladium chloride (10.5%), gold sodium sulfate (10.5%) |
|                                           | Torgerson et al., 2007 | 331 patients with BMS, LTR, cheilitis, stomatitis, gingivitis, orofacial granulomatosis, perioral dermatitis and recurrent aphthous stomatitis | Potassium dicyanoaurate (16.4%), nickel sulfate hexahydrate (12.3%), gold sodium thiosulfate (10.9%) |
|                                           | Raap et al., 2009      | 206 patients who underwent patch testing because of suspected contact allergy to dental materials | Gold sodium thiosulfate (66.6%), nickel sulfate (66.6%), palladium chloride (33.3%), cobalt chloride (33.3%) |
|                                           | Rai et al., 2014       | 20 patients who underwent dental procedures (13 patients with symptoms of oral lichen planus, oral stomatitis, burning mouth symptoms and recurrent aphthosis and 7 dental personnel) | Methylhydroquinone                                                             |
|                                           | Kim et al., 2015       | 44 patients with oral disease from 2004 to 2011 (oral lichen planus, BMS, cheilitis) | Cobalt chloride hexahydrate (25%)                                               |
| Oral lichen planus (lichenoid tissue reaction) | Budimir et al., 2018   | 230 subjects (78.3% females, 21.7% males)                                        | Cobalt chloride (6.7%), gold (3.3%), thimerosal (3.3%)                          |
|                                           | Khamaysi et al., 2006  | 121 dental personnel with clinical presentation of oral and perioral disease were patch tested | Gold sodium thiosulfate (11.8%), nickel sulfate (5.8%), mercury (5.8%)            |
|                                           | Torgerson et al., 2007 | 331 patients with BMS, LTR, cheilitis, stomatitis, gingivitis, orofacial granulomatosis, perioral dermatitis and recurrent aphthous stomatitis | Potassium dicyanoaurate (28%), fragrance mix (17.1%), gold sodium thiosulfate (15.1%) |
|                                           | Raap et al., 2009      | 206 patients who underwent patch testing because of suspected contact allergy to dental materials | Palladium chloride (44.4%), nickel sulfate (22.2%), gold sodium thiosulfate (22.2%) |
|                                           | Rai et al., 2014       | 20 patients who underwent dental procedures (13 patients with symptoms of oral lichen planus, oral stomatitis, burning mouth symptoms and recurrent aphthosis and 7 dental personnel) | Nickel, potassium chromate, copper sulfate, amalgam                             |
|                                           | Kim et al., 2015       | 44 patients with oral disease from 2004 to 2011 (oral lichen planus, BMS, cheilitis) | Gold sodium thiosulfate (33.3%), nickel sulfate (33.3%), potassium dichromate (33.3%), cobalt chloride hexahydrate (8.3%) |

BMS = burning mouth syndrome; LTR = lichenoid tissue reaction
subjects with certain oral diseases and healthy controls. This was shown to be true for BMS and its association to nutritive allergens and food additives, for oral lichen planus and inhalants, and for cheilitis and contact allergens such as cobalt-chloride and nickel-sulfate found in dental alloys. These findings contribute to the knowledge of the etiology of these diseases and the justification of using skin tests in these particular oral diseases.

According to Torgerson et al., positive contact allergens were established in 44.7% of patients that underwent patch testing, as well as possible multiple positive reactions due to cross-reactions, which has also been noted in other studies. The frequency of positive patch tests to dental materials was higher in some other studies, even reaching 70.5%. Many studies show various frequencies of positive patch tests for allergens in certain oral and perioral diseases. Particularly common allergens established with patch testing are metals found in dental materials. According to Khamaysi et al., the most common contact allergens established with patch testing in their study were gold sodium thiosulfate (14.0%), nickel sulfate (13.2%), mercury (9.9%), palladium chloride (7.4%), cobalt chloride (5.0%) and 2-hydroxyethyl methacrylate (5.8%). In a study by Kim Tae-Wook et al., the most common contact allergic reactions in oral and perioral diseases were established in oral lichen planus (75%), cheilitis (75%), BMS (25%), and other oral diseases (75%). In the study by Khamaysi et al., these were cheilitis (41.9%), perioral dermatitis (41.9%) and lichenoid reactions (35.3%). In addition to patch tests, immediate hypersensitivity tests such as prick tests and serum tests for determination of specific IgE can also be used sometimes.

Review of Oral and Perioral Diseases and Causative Allergens

Cheilitis (inflammation of the lips) includes many clinical types and is possibly related to many allergens (Table 1). Cheilitis can present alone or be associated with stomatitis or perioral eczema. According to the latest classification of cheilitis, proposed by Lugović-Mhić et al., it can be divided into three groups, as follows: mainly reversible (simplex, angular/infective, contact/eczematous, exfoliative, drug related); mainly irreversible (actinic, granulomatous, glandular, plasma cell); and cheilitis connected to dermatoses and systemic diseases (lupus, lichen planus, pemphigus/pemphigoid group, angiodema, salivation disorder, etc.). Contact/eczematous cheilitis is the result of an irritative or allergic contact effect with various substances, such as medications, toothpaste ingredients (e.g., sodium lauryl sulfate), cleaning agents for dentures (potassium-persulfate), dental floss (colophony), nail polish, cosmetics (e.g., lipstick, lip gloss), food and flavors, musical wind instruments (nickel, wood), etc. (Fig. 3). Allergies and allergens can sometimes be difficult to establish in some patients. A study conducted in cheilitis patients established irritant contact dermatitis in 36% of patients having undergone patch testing, allergic contact dermatitis in 25%, atopic eczema in 19%, and unknown causes in 9%. According to a recent study by Budimir et al., patients with cheilitis showed a statistically significantly higher frequency of positive patch tests (26.7%) compared to healthy controls, and the common allergens were cobalt-chloride (10%), nickel-sulfate (6.7%) and mercury precipitate (6.7%). Torgerson et al. observed a similar frequency of positive patch tests in their patients (25.9%), whereas Kim et al. report an even higher frequency (75%), particularly when metals used in dental medicine were involved.

Angiodema can be induced by various factors and allergens, such as drugs, foodstuffs, preservatives, cosmetics, etc. (Fig. 4). It predominantly appears as a hypersensitivity reaction type I, or sometimes type IV, and such reactions can occur after contact with latex, dental products, etc. during dental treatment (when dentist’s glove comes in contact with the lip, or in contact with cinnamaldehyde, menthol or eugenol in toothpaste), etc. In dental practice, also possible are allergic reactions to formaldehyde (used for disinfection in root canals), immediate-type allergies to local anesthetics or delayed-type allergies from longer operative procedures (e.g., additives from the glove rubber or rubber dam). These reactions should be examined for both immediate and delayed hypersensitivity reactions, usually by skin allergy tests, which are conducted during remission of angiodema and when the patient is not under anti-allergic therapy. Also, food ingredients, e.g., benzoates, antioxidants or spices, can be the possible causes of angiodema. According to the results of the study by Budimir et al., additive allergens were confirmed in 23.3% of angiodema.
patients, and physicians were advised to monitor patient conditions after allergen elimination\(^2\). In addition, facial edema sometimes occurs due to metals in the oral cavity (e.g., crowns with palladium), and removal of such metals has proved beneficial. In a recent study by Budimir \textit{et al.}, patch test was positive in 6.7% of angioedema patients, and the most frequent contact allergens were cobalt-chloride (3.3%) and nickel-sulfate (3.3%)\(^2\). In the study by Khamaysi \textit{et al.}, the number of patients positive to gold and nickel was high (13.2%), but one half of the patients positive to nickel were also positive to palladium chloride and cobalt chloride, which most probably indicated cross reaction with nickel\(^9\). According to Budimir \textit{et al.}, recent results on allergic reactions in the oral and perioral regions show that the risk of angioedema is 3-fold higher in subjects with established allergies and in men. Furthermore, the risk increases with age. It was also established that patients with angioedema exhibited reactions to more allergens than other patients\(^2\).

**Perioral dermatitis** is sometimes, although rarely, associated with allergic reactions and is possibly connected to many allergens (Table 1)\(^2\). The disease is benign and it is usually contact dermatitis caused by substances in toothpaste, gum, lipstick, or medications\(^28\). While some studies suggest that metals (e.g., nickel and chrome) in dental appliances can be the cause or aggravating factor for this disease, others did not record adverse reactions in patients allergic to nickel following application of dental crowns or bridges\(^29,30\). Torgerson \textit{et al.} report positive patch tests in 80% of patients with perioral dermatitis, but positive patch tests were less frequent in the study by Budimir \textit{et al.} (16.7%)\(^12,22\). Fragrances, cobalt-chloride and nickel-sulfate were the most common contact allergens in both these studies\(^12\). It is possible that perioral lesions are similar to allergic contact dermatitis and irritant contact dermatitis. Allergic contact dermatitis is a manifestation of type IV hypersensitivity reaction to agents that come in contact with the skin, and patients may present with inflammatory papules, vesicles, weeping or crusting, while distribution of lesions is dependent upon the specific sites of contact with the initiating agent. Unlike perioral dermatitis, intense pruritus is usually present, scaling is often prominent, and lesions fail to improve with antibiotic therapy. On the other hand, in irritant contact dermatitis, clinical findings vary based upon the nature of the external trigger and site of involvement, and usually include papules, vesicles, scales, erythema or edema, and a burning rather than itching sensation, unlike allergic contact dermatitis but similar to perioral dermatitis. In irritant contact dermatitis, patient history is of value for identifying this diagnosis (as an example, irritant dermatitis related to chronic lip-licking behavior can resemble perioral dermatitis).

**Oral lichenoid reactions** (OLR) are often associated with contact allergies and positive patch tests (Table 1). In patients with oral lichenoid lesions, determination of metal sensitivity is quite important\(^12,31-33\). There are many studies that confirm the effect of metal allergies in oral lichenoid lesions, especially in dental restorations and orthodontic devices. Laine \textit{et al.} established allergies to metals in 67.7% of OLR patients using the patch test, particularly to mercury (66.1%), gold (9.3%), cobalt (3.3%), and others (tin, silver, palladium and chrome)\(^31\). Studies often point out allergic reactions to mercury, although their percentages vary\(^13,34\). Irritant contact reactions to mercury are possible in cases when patch test is negative; thus, removal of an adjacent amalgam can initiate improvement due to the fact that amalgam releases mercury\(^7,32,33\). Dunsche \textit{et al.} report that 27.7% of 134 patients with oral lichenoid lesions showed positive patch test results to inorganic mercury or amalgam. Amalgam removal led to improvement in 97.1% of patients\(^31\). However, two studies (performed by Budimir \textit{et al.} and Kim \textit{et al.}) observed no positive reactions to mercury, which may be connected to the use of amalgam as restorative material, as shown previously by Choi \textit{et al.}\(^10,22,35\). Scalf \textit{et al.} report that 49% of 51 patients with lichenoid lesions in different regions and tissues (oral, genital, cutaneous) had positive patch test with at least one mercurial allergen\(^36\). In the same study, positive patch test reactions were detected to chromate, gold and thimerosal exposure, and interestingly, 100% of patients declared improvement after metal replacement. Torgerson \textit{et al.} established positive patch tests in 55.9% of OLR patients, whereas Budimir \textit{et al.} found positive patch test (10%) less frequently, and the commonest contact allergens were cobalt-chloride (6.7%), gold sodium thiosulfate (3.3%) and thimerosal (3.3%)\(^12,22\). In OLR, a connection with other metals (particularly gold, chrome and cobalt) is also sometimes observed\(^12\). Gold can cause various oral difficulties (including OLR, facial dermatitis and oral burning symptoms); in such
cases, removal of gold can result in improvement\textsuperscript{37}. This leads to a conclusion that contact allergy to different metals is more common among people having lichenoid tissue changes. Taking all the above into consideration, performing patch tests before dental procedures or implanting orthodontic materials is quite important. In addition, for instance, after consumption of sour or spicy food or drinks, people with OLR can react to other substances in various ways, ranging from pricking sensation to severe pain. Because these patients often complain of oral sensitivity and an unpleasant burning sensation in the mouth, the immediate hypersensitivity test is also useful\textsuperscript{7,38}. By using prick tests in different oral diseases, recently we established that allergic reactions were most common in lichen (53.3%), and also more frequently occurred in atopic patients, thus appropriate diagnostics should be carried out to establish possible OAS\textsuperscript{22}.

**Gingivostomatitis** is a disease of oral cavity that can also be associated with contact allergies after exposure to dental materials (e.g., metals or plastics in dentures), as it has been shown that stomatitis is associated with partial dentures and some dental metals (e.g., palladium, gold or manganese) (Table 1)\textsuperscript{7,39,40}. Gingivostomatitis was nickel-sulfate, cobalt-chloride and manganum precipitate, although with no statistical significance in comparison to healthy controls\textsuperscript{22}. However, it is possible that an established allergy may not be related to oral symptoms, so positive allergy tests should be taken with caution and additional diagnostic workup should be considered.

**Importance of Examination for Allergy and Patch Test Usefulness**

Given the different results of individual studies on the usefulness of performing allergy tests in diagnosing oral and perioral diseases with non-specific sensations, it is justified in the cases of unknown etiology to carry out allergy tests in order to establish possible allergies (mostly using patch tests and prick tests). Skin patch testing is a simpler procedure and preferred to mucosal testing. Other reasons for choosing skin test before mucosal are the higher specificity and sensitivity of the skin patch test and the requirement of a significantly higher concentration of allergens for mucosal testing, which often results in many adverse reactions\textsuperscript{42}. Taking into account the fact that burning symptoms in the oral cavity can be caused by allergic cross-reactions between food and inhalants (OAS), it is also justified to examine the possible immediate al-
ergic hypersensitivity, usually by prick testing\textsuperscript{13}. The choice of the allergens to be tested is also important; it varies by studies, countries and number of allergens. Allergy unit prepares testing samples according to patient history and in consultation with dentists.

One should also keep in mind that patch tests have a few limitations and pitfalls when it comes to the significance for oral diseases\textsuperscript{2}. This is due to different allergen concentrations and standard preparations for patch testing, as well as due to different pH of the skin and oral mucosa, which may result in false-positive/negative reactions or non-specific irritant reactions\textsuperscript{3}. When carrying out patch test and establishing reactions, it is important to consider that standard reading may be insufficient and subsequent test (in 10 days or more) should be read in case of false-positive results (e.g., up to one-third of patients allergic to mercury)\textsuperscript{1}. When establishing reactions, other potential factors should be considered, as well as the possibility that oral difficulties are in no way connected with the suspected dental materials or that the same substances can cause different reactions in one patient (either allergic or irritant). In such cases, it is possible that, regardless of a negative patch test, such a substance induces an irritant (non-allergic) reaction. Here it is crucial to emphasize that occasionally, some patients may have negative results to patch tests in either on standard reading and positive results on delayed reading after 10 days (this often refers to allergy to mercury)\textsuperscript{14}.

Clinical relevance of positive results to haptns in patch test is also difficult to evaluate because of the high number of products and their contents that are in contact with patient oral cavity and mucosa every day, which makes it difficult to prove one particular hapten blameworthy by avoiding method\textsuperscript{2}. However, patch tests with dental screening series are worth considering for oral diseases, especially for oral lichen planus\textsuperscript{10}. In a study by Holmstrup, the author suggests indications for patch testing, including OLRs and mucositis resistant to treatment, objective and evident relation between allergen and lesions, and absence of symmetry in lesions, in order to prevent adverse effects and sensitization in these patients\textsuperscript{43}. There are some other diagnostic tools that could be helpful in the future for determination of allergies in the oral and perioral area, such as persistent manifestations. Some studies suggest that histology would be useful in case of revealing whether the specific T cells for certain allergen are present at the lesion site, or that the flow cytometry technique could demonstrate increase in the concentration of T cells in blood after exposure to allergen, which would improve both diagnostic and treatment aspects of oral and perioral manifestations/diseases\textsuperscript{15,44}. There also are some other new methods for detecting type IV hypersensitivity to metals, which are promising but not yet widely available, such as memory lymphocyte immunostimulation assay or MELISA\textsuperscript{44}.

Conclusion

In conclusion, we would like to point out that in the cases of non-specific oral difficulties, it is important to examine patient medical histories (e.g., occurrence of symptoms after dental therapy or food consumption) and in consultation with their dentist, carry out allergy tests to the specific dental allergens that are used or planned to be used in subsequent treatment. One should always keep in mind that the same substances can cause undesirable (either allergic or irritant) and different reactions in patients. Therefore, it is important to follow up patients and determine whether elimination of certain substances will contribute to the elimination of ailments.

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Sazetak

UČESTALE ALERGIJE I ALERGENI U ETIOLOGIJI ORALNE I PERIORALNE SLUZNICE I KOŽE

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Alergijske reakcije ponekad sudjeluju u razvoju perioralnih i oralnih bolesti, što ukazuje na potrebu određivanja potencijalnih alergena. Ovaj pregledni članak govori o trenutnim saznanjima o potencijalnim alergijskim reakcijama na različite dentalne materijale u bolesnika s oralnim i perioralnim bolestima. Uz alergije na razne dentalne materijale mogu se pojaviti slične nealergijske, neimmunske kontaktne reakcije (nadražujuće ili toksične). Među zubnim materijalima zubne legure najčešći su alergeni, a slijede gumeni materijali, polimeri i akrilati. Alergijske reakcije na zubne legure koje sadrže nikal, kobalt i amalgam osobito su česte, jer ih stomatolozi koriste za protetičke i druge restauracije. Postoji širok spektar oralnih i perioralnih bolesti koje su vjerojatno povezane s alergijama, poput lihenoidnih reakcija, heilitisa, perioralnog dermatitisa, osjećaja pečenja itd. Unatoč određenim ograničenjima epikutani test je presudan u dijagnozi i prepoznavanju uzročnih alergena, jer otkriva kontakte alergije i još je superiorniji u razlikovanju alergijskih i irritativnih kontaktnih reakcija. Važno je uzeti detaljnu anamenu bolesnika (npr. pojavu simptoma nakon stomatološke terapije ili konzumiranja hrane) i uz savjetovanje sa stomatologom provesti alergološko testiranje na specifične stomatološke alergene koji se koriste ili se planiraju koristiti u sljedećem liječenju.

Ključne riječi: Alergija; Sindrom pečenja usta; Heilitis; Gingivostomatitis; Bolesti usne šupljine; Oralne lihenoidne reakcije; Epikutani test