Allergic reactions in oral and perioral diseases—what do allergy skin test results show?

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Objective. The aim of this study was to examine potential allergic reactions to different materials in oral and perioral diseases.

Study Design. The study included 230 consenting subjects in total—180 patients with oral and perioral diseases (30 patients each in the following groups: angioedema, oral lichenoid reactions [OLRs], burning mouth syndrome [BMS], gingivostomatitis, cheilitis, and perioral dermatitis) and 50 healthy controls. Comprehensive diagnostic workups were performed prior to patch testing with standard series allergens and with specific dental materials and skin prick testing (SPT) for food, preservatives and additives, and inhalants.

Results. Positive allergy test results were more common in patients with oral diseases than in controls, with significantly greater frequency of contact allergies in the cheilitis group ($P = .048$). The most common allergens in the majority patients were cobalt chloride (13.3% in BMS vs 10% in controls) and nickel sulfate (10% in gingivostomatitis and 6.7% in cheilitis vs 3.3% in controls), and preservatives (23.3% in angioedema and BMS).

Conclusions. Allergy skin tests are reliable and justified for diagnosing allergies in cases of persistent or recurrent oral diseases. This is the only way to confirm allergies and is the basis for consequent allergen avoidance for the benefit of the patient. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;127:40−48)

When treating patients who suffer from persistent oral and perioral diseases, one often encounters the issue of potential allergies, especially those connected to dental materials and dental procedures.[1-4] Although this topic has been researched extensively, the results are still ambiguous. The role of allergies in oral diseases has not been completely clarified, but there is significant evidence that various substances can cause both immediate-type (type I) and, more commonly, delayed-type (type IV) reactions.[1,2,5] In terms of clinical presentation, they can manifest as oral lichenoid reactions (OLRs), cheilitis, stomatitis, gingivitis, perioral dermatitis, burning mouth sensations, and swelling of the lips and face.[5-10] Other possible symptoms include paresthetic and burning sensations in the oral cavity, which could point to oral allergy syndrome (OAS), or pollen-food allergy syndrome, a hypersensitivity reaction (type I) to plant-based foods, manifesting most commonly with pruritus of the lips, tongue, and mouth.[11,12]

In previous studies, where tests for immediate-type allergies (type I) were not included, results were contradictory (Table I)[4,6-8,10,13,14] Because the frequency of allergic reactions in oral conditions has not been sufficiently established and the data are contradictory, it remains unclear how justified the use of allergy skin tests is and which allergens are most commonly involved in oral allergic reactions. This is of particular interest in persistent/recurrent oral conditions of unknown etiology in relation to dental alloys and materials for dental appliances and restorations as well as for preparations for the oral cavity. The aim of our study was to examine potential allergens and allergic reactions in frequent oral and perioral diseases by conducting allergy skin tests.

SUBJECTS AND METHODS

This prospective research was conducted from September 2011 to January 2016 at the Department of Dermatovenereology, University Hospital Center Sestre milosrdnice, and the Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Croatia. The study was approved by the Ethics Committee of the University Hospital Center Sestre milosrdnice (No. EP-7999/11-18). After the participants provided their informed consent, they were incorporated into the study. The study was conducted according to the guidelines of the Helsinki Declaration.

Statement of Clinical Relevance

In cases of persistent or recurrent oral and perioral diseases, allergy skin tests are reliable and justified for diagnosing allergies because it is the only way to confirm allergies to ensure a good outcome for the patient.

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Table I. Prominent studies results regarding allergy in oral and perioral diseases

Ref. No.	Year	Author/country	Respondents	Methods	Results	Common allergens
[7]	2006	Khamaysi et al./ Israel	121 patients (cheilitis and perioral dermatitis; burning mouth; oral lichen planus; orofacial granulomatosis; glossodynia; recurrent aphthae; hand dermatitis)	Patch test with the dental screening and bakery series	Positive with regard to diagnosis: cheilitis and perioral dermatitis (41.9%); burning mouth (42.1%); oral lichen planus (35.3%); orofacial granulomatosis (46.2%); glossodynia (12.5%); recurrent aphthae (16.7%); hand eczema (38.9%)	Gold sodium thiosulfate (14.0%) Nickel sulfate (13.2%) Mercury (9.9%) Palladium chloride (7.4%) Cobalt chloride (5.0%) 2-Hydroxyethyl methacrylate (5.8%)
[10]	2007	Torgerson et al./USA	331 patients (BMS, lichenoid tissue reaction, cheilitis, stomatitis, gingivitis, orofacial granulomatosis, perioral dermatitis, recurrent aphthous stomatitis)	Patch test with an 85-item oral antigen screening series to flavorings, preservatives, dental acrylates, medications, and metals	Positive patch test (after 96 hours) in 44.7% patients with oral diseases (27.2% patients had 2 or more positive reactions) Positive with regard to diagnosis: BMS (42.1%); lichenoid tissue reaction (55.9%); cheilitis (25.9%); stomatitis (55.6%); gingivitis (64.0%); orofacial granulomatosis (30.8%); perioral dermatitis (80%); recurrent aphthous stomatitis (33.3%)	Potassium dicyanoaurate (19.6%) Nickel sulfate hexahydrate (12.5%) Gold sodium thiosulfate (11.6%) Fragrance mix (9.8%) Palladium chloride (9.7%) Balsam of Peru (7.2%) Beryllium sulfate tetrahydrate (5.4%) Cobalt chloride (5.2%) 2-Hydroxyethyl methacrylate (5.2%) Gold chloride (4.3%)
[13]	2009	Raap et al./ Germany	206 patients who underwent patch testing because of suspected contact allergy to dental metals	Patch test with the European baseline series	Patch test was positive in 13.6% patients Positive with regard to diagnosis: oral lichen planus (18.4%); stomatitis (20%); periodontitis (22.2%); cheilitis (16.7%); recurrent aphthosis (5.6%); glossodynia (33.3%); burning mouth/ tongue (21.4%)	Gold sodium thiosulfate (4.9%) palladium chloride (4.9%) Nickel sulfate (4.9%) Amalgam (2%) Ammoniated mercury (2%) Cobalt chloride (2%) Amalgam-mixed metals (0.5%) Ammonium tetrachloroplatinate (0.5%)
[6]	2014	Ahlgren et al./Sweden	83 patients with biopsy-verified OLL	Patch test with a recently developed lichen series, consisting of 66 relevant substances from the dental series and the cheilitis series of the Department of Occupational and Environmental Dermatology in Malmö	Total of 129 contact allergies were found 20.2 % of the allergic reactions in 23 patients were seen on day 7 only 25.2 % increase in positive test reactions with an additional reading on day 7 (statistically significant)	Mercury, nickel, gold, and cobalt (the highest frequency of late positive allergic reactions)
[4]	2014	Rai et al./India	20 patients who had undergone dental procedures with symptoms of oral lichen planus, oral stomatitis, burning mouth, and recurrent aphthosis; including dental personnel with history of hand dermatitis	Patch test with Chemotechnique dental series	6 patients with stomatitis, lichenoid lesions, and oral ulcers showed positive patch tests to a variety of dental materials; 7 dental personnel with hand dermatitis showed multiple allergies to various dental materials; 7 patients with ulcers had negative patch tests	Nickel sulfate and potassium chromate

(*continued on next page*)

Table ? I. Continued

Ref. No.	Year	Author/country	Respondents	Methods	Results	Common allergens
[8]	2015	Kim et al./Korea	44 patients (oral lichen planus, cheilitis, BMS, and others)	Patch test with Chemotechnique dental screening series	70.5% positive reactions to one or more allergens Positive with regard to diagnosis: oral lichen planus (75%), cheilitis (75%); BMS (25%), and others (75%)	Gold sodium thiosulfate (25.0%) Nickel sulfate (25.0%) Potassium dichromate (22.7%) Cobalt (15.9%) Palladium (6.8%) Mercury (4.5%) Copper (4.5%) Methylhydroquinone (4.5%)
[14]	2016	Yoshimura et al./Brazil	54 patients using dental prostheses (total or partial)	Patch test with Brazilian standard series and complementary dental series	63% patients were positive to at least one substance 35.2% had oral complaints (oral burning, labial itching or gingival erythema)	Thimerosal (14.49%) Nickel sulfate (14.49%) Benzoyl peroxide (24.63%) Vanillin (alcoholic extract) (8.69%) Cobalt chloride (5.79%) Perfume (mix) (4.34%) Eugenol (4.34%)

BMS, burning mouth syndrome; *OLL*, oral lichenoid lesions.

Subjects

The study included 230 consenting subjects in total—180 patients with oral and perioral diseases and 50 healthy controls (HCs). We had 6 patient groups according to clinical presentation: angioedema, OLRs, burning mouth syndrome (BMS), gingivostomatitis, cheilitis, and perioral dermatitis. Each disease category comprised 30 patients. The angioedema group comprised patients with recurrent or persistent marked swelling of the lips, tongue, and perioral skin, not affecting the throat or other parts of the body. Hereditary angioedema was excluded. The OLRs group included patients with solitary, unilateral lesions in direct contact of affected mucosa with offending agents or amalgam restorations.[15] A diagnosis of OLR was confirmed on the basis of clinical presentation and histopathologic findings. Patients who fulfilled clinical criteria for idiopathic BMS and complained of oral mucosal burning without visible oral diseases or oral lesions were included in the BMS group; the majority had intermittent symptoms of burning with unknown and unidentified local and systemic causes (as confirmed by diagnostic workup before allergy tests).[16] The cheilitis category included patients with various clinical cheilitis forms (angular cheilitis, cheilitis simplex, exfoliative cheilitis, contact cheilitis, and granulomatous cheilitis). Diagnoses were established on the basis of clinical criteria.[17-19] The category of gingivostomatitis comprised patients with affected gingiva and adjacent oral mucosa, including those with plasma cell gingivitis, exfoliative gingivitis, and ulcerative stomatitis, as well as those with aphthous stomatitis.[17] Diagnostic criteria for ulcerative stomatitis were those established by Chorzelski et al.[20] The diagnosis of perioral dermatitis was based on a clinical picture of clusters of tiny 1- to 2-mm erythematous papules or papulopustules on perioral skin around the mouth not involving vermilion and accompanied by burning and itching sensations.[17]

Prior to allergy skin tests, all patients underwent a comprehensive diagnostic workup, which included detailed patient history, comprehensive clinical examination of the patient's oral cavity and skin, total blood count test, microbiological examination of oral swabs for gram-positive cocci and *Candida* species, and biopsy and direct and indirect immunofluorescence studies to exclude other diseases. The workup also checked blood glucose levels, autoimmune markers, C1 esterase inhibitor (C1-INH) levels, and total/specific immunoglobulin E. Mucosal biopsy was mandatory in patients with a clinical diagnosis of granulomatous cheilitis, plasma cell gingivitis, desquamative gingivitis, and ulcerative stomatitis to confirm the clinical diagnosis.

When choosing diseases of interest for this study, we considered that the above-mentioned diseases are very common in the general population among all age groups and may also be associated with allergy-causing substances (allergens) and allergic reactions. The complete inclusion criteria were age (18 years and older); clinically significant oral and perioral disease diagnosed by an experienced dermatologist and oral medicine specialist; signed informed consent and subject willingness to undergo all recommended diagnostic and allergy tests; and absence of known or verified local or systemic factors of the underlying disease. Exclusion criteria were specific nonallergic subtypes of oral and perioral diseases with known etiology; positive microbiologic test results for fungal and bacterial infection (swabs taken from labial and oral mucosa and perioral skin); positive direct and/or indirect immunofluorescence test results for an autoimmune disease; a history of hereditary angioedema or decreased C1-INH levels; verified drug-induced angioedema and herpetic gingivostomatitis/cheilitis; and use of particular drugs (corticosteroids, antihypertensives, antihistamines, tricyclic antidepressants, asthma medications, proton pump inhibitors, and nonsteroidal anti-inflammatory drugs).

Allergy skin tests were performed, and allergic reactions were interpreted by a dermatovenerologist. Patch tests were performed with relevant contact allergens (standard series allergens in Croatia and specific dental materials, based on medical history), and skin prick tests (SPTs) were performed with preservatives and additives, foods, and inhalants. Subjects who tested positive were given instructions on how to avoid allergens and were referred to their primary physician or dentist for further monitoring and care.

Patch testing

Patch testing was performed on all subjects, and the European Society of Contact Dermatitis guidelines were followed.[21] Allergens were applied to the patients' upper backs (Patch Test Strips Curatest, Lohman & Rauscher International, Rangsdorf, Germany), and the results were read after 48 and 72 hours. Reactions were recorded as weak (+), strong (++), and very strong (+++). Standard allergen kits were used, supplied by the Institute of Immunology, Zagreb, Croatia: potassium dichromate (0.5% pet.), cobalt chloride (1% pet.), nickel sulfate (5% pet.), fragrance mix (8% pet.), epoxy resin (1% pet.), p-phenylenediamine (0.5% pet.), N-Isopropyl-N-phenyl-4-phenylenediamine (0.1% pet.), mercapto mix (2% pet.), thiuram mix (1% pet), carba mix (3% pet.), paraben mix (15% pet.), balsam of Peru (25% pet.), neomycin sulfate (20% pet.), colophony (20% pet.), formaldehyde (1% water), thimerosal (0.1% pet.), quaternium-15 (1% pet.), lanolin (30% pet.), ammoniated mercury (10% pet.), phenylmercuric acetate (0.01% water), ichthammol (10% pet.), and sulfur precipitated (10% pet.).

Also, each subject was asked about potential dental allergens. When an allergy to another dental material not included in the standard allergy kit was suspected, in coordination with the supervision of dentists, patch tests to additional dental substances created in our laboratory were conducted: the gold−silver casting alloy Auropal (2% pet.), methyl methacrylate (2% pet.), 2-hydroxyethyl methacrylate (2-HEMA) (2% pet.), the cobalt-chrome alloy Wironit (2% pet.), Ivocron polymer (2% pet.), hexachlorophene (1% pet.), and resorcinol (2% pet.). Other substances were not tested.

Prick tests

SPTs were conducted by the application of allergen drops (supplied by the Institute of Immunology, Zagreb, Croatia) to the forearm (with 1% histamine as positive controls and saline solutions as negative controls). Results were read after 15 minutes, a wheal diameter of at least 3 mm being considered a positive result.[22] SPTs were performed for inhalants (house dust, mites, feathers, pollens [grass, trees, weeds], animal hair, fungi, mold, bacteria, herbal fibers, wool fabrics, silk, synthetics and flours), for food (eggs, milk, meat [groups 1 and 2], vegetables [groups 1 and 2], fruits [groups 1, 2, and 3], fungi, coffee, tea, cocoa, freshwater fish and sea fish, and flour), and for preservatives and additives (acetylsalicylic acid, sodium benzoate, tartazine, potassium metabisulfite, sodium glutamate, glutaraldehyde, and citric acid).

Statistical analysis

Our statistical analysis considered (1) prevalence of allergic reactions detected by each type of test (contact, inhalants, nutritive, additives) as a dichotomous variable (0 = absent; 1 = present) and (2) severity as the number of allergens detected in each test type (scalar value). The presence of allergens was analyzed also as a group by all tests together (0 = no detected allergens; 1 = at least one allergen detected by one of the tests).

To compare differences between patient groups, the χ^2 test was used, and to compare each patient group with controls, Fisher's exact test was used. Effect size was assessed by the φ coefficient. Kruskal-Wallis and Mann-Whitney tests with Bonferroni correction were used to compare age groups and number of allergens between groups. Bivariate and multiple logistic regression models determined which tests could be used as disease predictors. Age was grouped by decade and included in the model as a continuous predictor, and gender was a dichotomous variable (0 = female; 1 = male). Presence of at least 1 allergen was used as a dichotomous variable (0 = absent; 1 = present). Odds

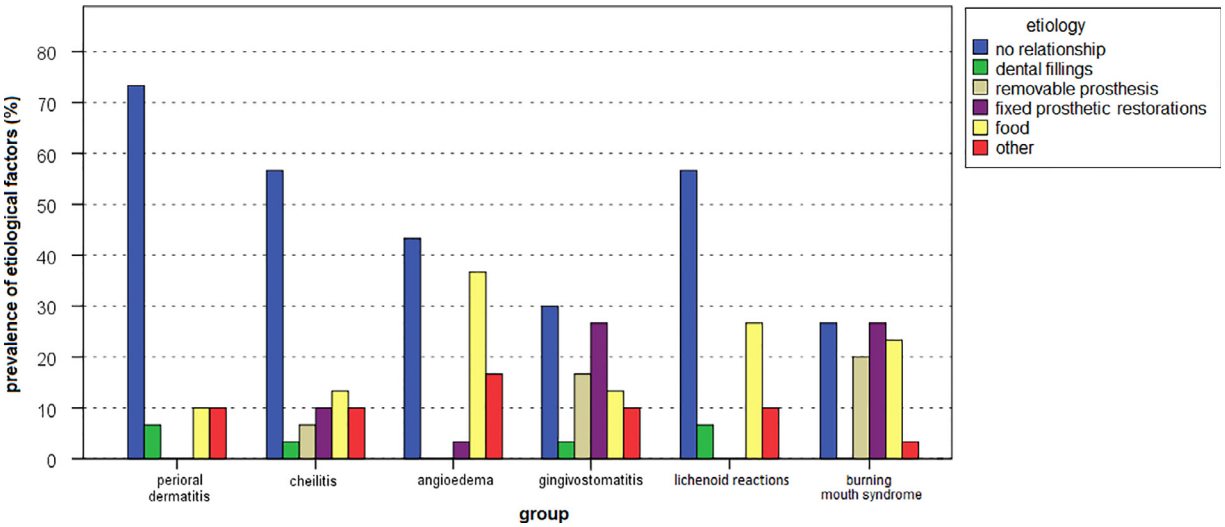

Fig. 1. Self-reported etiologic factors in patient groups.

ratios (ORs) with 95% confidence intervals (95% CI) served as a measure of association between presence of each allergen group and disease manifestation in comparison to controls (0 = diseased; 1 = healthy). Multiple linear regression analysis assessed whether diagnosis of a particular disease is able to predict total number of allergens. We used the commercial statistical software SPSS version 22.0 (SPSS Inc., Chicago, IL), and statistical significance was set at $P < .05$.

RESULTS

Demographics and medical history

Of the 230 subjects included in the study, 78.3% were females and 21.7% were males. Women were predominant in every group, but the differences between groups in gender distribution were not significant.

The patients' ages ranged from 18 to 90 years (median 50), patients with BMS being the oldest (median 60 years) and those with perioral dermatitis the youngest (median 30 years).

All disease groups, except the gingivostomatitis group (93.3%), comprised fewer females compared with the HC group (84%), but the differences were not significant. Those with angioedema, gingivostomatitis, and BMS were significantly older (median age range 50−60 years) compared with controls (median 40 years; $P < .05$).

Gender differences were not significant between the tested groups (χ^2 test), and neither were there any differences between any of the disease groups and the HCs (individual Fisher's exact tests). According to patients' medical histories, self-reported causes of oral diseases were, in order of prevalence, as follows: unknown etiological factors, foods, and prosthetic appliances (Figure 1).

Prevalence of allergens in individual oral diseases

Allergic reactions were most commonly found in cheilitis (60%) and BMS (56.7%) and least frequently in gingivostomatitis (43.3%) and in HCs (34%). The presence of an allergen was a significant predictor only for BMS and the risk of BMS was 6 times higher in persons with 1 or greater detected allergen than in those without any established allergen (95% CI 1.7−20.8; $P = .005$).

The number of allergens ranged from 1 to 11; the highest number of allergens was found in angioedema and OLRs and the least in gingivostomatitis (up to 4). The mean number was between 0 and 1 and did not differ significantly between types of diseases and controls. Diagnosis of a particular disease failed to predict total number of allergens in multiple linear regression.

Patch test results

Delayed-type allergic reactions determined by patch testing were mostly established in cheilitis (26.7%) and BMS (20%) (Table II). Such reactions were least common in angioedema (6.7%) and in HCs (8%).

The most common allergens in the majority of groups were cobalt chloride, especially prominent in BMS (13.3% vs HCs 10%) and nickel sulfate (gingivostomatitis 10% and cheilitis 6.7% vs HCs 3.3%)

Positive reactions to cobalt were commonly observed in cheilitis, gingivostomatitis, perioral dermatitis, BMS, OLR, and angioedema. Also, nickel sulfate was frequently positive in cheilitis, gingivostomatitis, and angioedema.

The largest number of contact allergens was found in patients with cheilitis.

Table II. Numbers and percentages of subjects with positive tests and most common allergens

Disease	Numbers and percentages of subjects with positive tests	Most common allergens	Subjects with positive reactions (%)
Cheilitis	8/30	Cobalt chloride	10
	26.7%	Nickel sulfate	6.7
		Mercury precipitate	6.7
Gingivostomatitis	5/30	Nickel sulfate	10
	16.7%	Cobalt chloride	6.7
		Mercury precipitate	3.3
Perioral dermatitis	5/30	Fragrance mix	6.7
	16.7%	Cobalt chloride	6.7
		Nickel sulfate	3.3
Burning mouth syndrome	6/30	Cobalt chloride	13.3
	20%	P-phenylenediamine	3.3
		colophony	3.3
Oral lichenoid reactions	3/30	Cobalt chloride	6.7
	10%	Gold	3.3
		Thimerosal	3.3
Angioedema	2/30	Cobalt chloride	3.3
	6.7%	Nickel sulfate	3.3
Controls	4/30	Cobalt chloride	10
	8%	Nickel sulfate	3.3

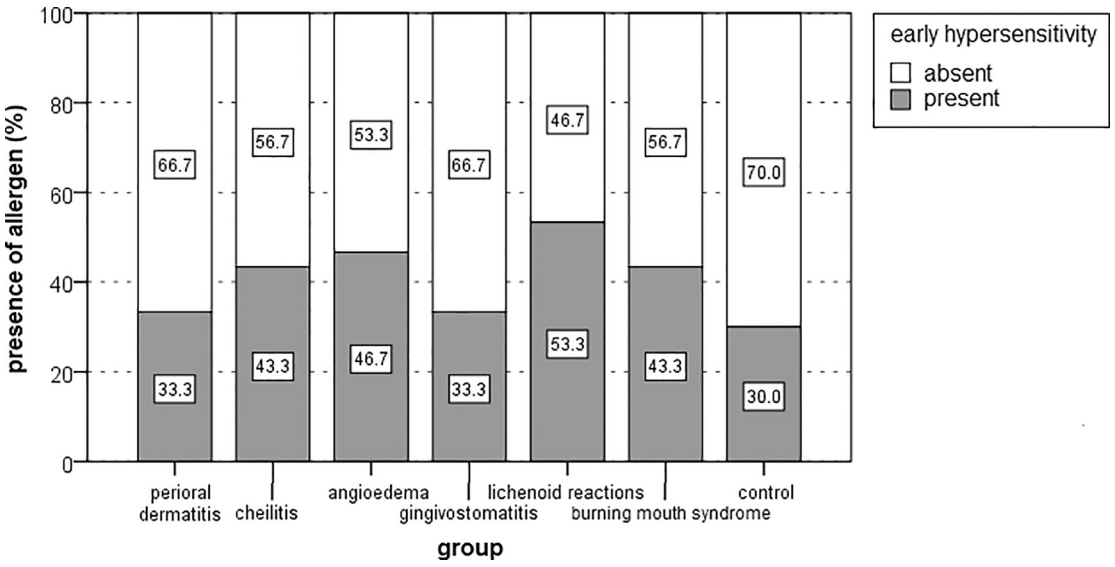

Fig. 2. Distribution of subject groups to positive prick test results (early hypersensitivity to inhalants and nutritive allergens, preservatives, and additives).

SPT results

Immediate-type allergic reactions occurred most often in OLRs (53.3%) and least often in gingivostomatitis, perioral dermatitis and controls (≤33.3%) but with no significant differences between groups (Figure 2). Allergies to inhalants were most common in OLRs (46.7%); nutritive allergies were most common in BMS (16.7%); and allergies to preservatives and additives were mostly found in BMS and angioedema (both 23.3%). Grass pollen was the most common inhalant in most of the diseases; in OLRs, it was dust and tree pollen. In subjects with OLRs, inhalants were statistically more frequent, with a low effect size of 5.5% ($P = .049$). The most common additive allergen was glutaraldehyde, followed by citric acid. The most common nutritive allergen was fruit; in BMS, it was mushrooms, fruits, and vegetables. In SPTs, the highest number of allergens was in angioedema and BMS. Positive SPT results in patients did not significantly differ from those in HCs.

Disease associations

Disease prediction from allergy tests was successful only for BMS. Persons with a positive SPT were 3.5

times more likely to have BMS (95% CI 1.0−11.8; $P = .045$). Increased age also increased the probability of BMS. The probability of BMS was 8.9 times higher in subjects allergic to foods (95% CI 1.3−63.4; $P = .029$); 7.7 times higher with a contact allergen (95% CI 1.2−50.4; $P = .033$) and 5.8 times higher with an additive allergen (95% CI 1.1−31.0; $P = .038$). The risk of angioedema was 3 times higher in subjects with at least any one allergen detected (95% CI 1.1−8.9; $P = .032$).

DISCUSSION

Various dental materials and oral preparations, such as alloys, prosthetic material, antiseptics, toothpastes, lip cosmetics, acids, and so on, may cause both allergic and nonallergic (irritative) contact reactions.[5] Among the materials used in dentistry, alloys are the most frequent allergens, followed by rubber, polymers, and acrylates, whereas reactions to local anesthetics are quite uncommon[1,9,23] Both noble dental alloys (comprising more than 40% gold, palladium, and/or platinum) and semiprecious and nonprecious alloys are of base metals, which contain a large percentage of nickel, cobalt, chromium or beryllium, and stainless steel or titanium.[8,9]

Patch test results in other studies of oral and perioral diseases show various frequencies of allergens, revealing particular allergens found in dental metals (e.g., nickel and gold).[13,24] According to Khamaysi et al.,[7] contact allergic reactions were most frequently found in cheilitis (41.9%), perioral dermatitis (41.9%), and OLRs (35.3%), the most commonest allergens being gold sodium thiosulfate, nickel sulfate, mercury, palladium, chloride, cobalt chloride, and 2-hydroxyethyl methacrylate. Torgerson et al.[10] discovered positive contact allergies in 44.7% of patients with oral diseases, and possible multiple positive reactions caused by cross-reactions which we also observed. Analyzing patch test results for patients with metals in their oral cavities, Raap et al. found 13.6% positive reactions, particularly to gold sodium thiosulfate and palladium chloride.[13] According to Kim et al.,[8] positive patch tests for dental materials were found in 70.5% of patients, mostly in oral lichen planus (75%), cheilitis (75%), and BMS (25%); the most common allergens were gold sodium thiosulfate and nickel sulfate, potassium dichromate, cobalt, palladium, mercury, copper, and methylhydroquinone.

Cheilitis can be a consequence of contact with various substances, such as medications, toothpaste ingredients (e.g., sodium lauryl sulfate), cleaning agents for braces (potassium-persulfate), dental floss (colophony), nail polish, cosmetics (e.g., lipstick, lip gloss), musical wind instruments (nickel, wood), etc.[25] A study of cheilitis patients who had undergone patch testing confirmed irritant contact dermatitis in 36%, allergic contact dermatitis (25%), atopic eczema (19%), and unknown causes of disease (9%).[25] Torgerson et al. observed a similar frequency (25.9%).[10] Kim et al. observed a higher frequency (75%), particularly to metals used in dentistry.[8] In our study, allergies to mercury were uncommon (cheilitis 6.7%, gingivostomatitis 3.3%), similar to results from Khamaysi et al. (4.1% of patients).[7]

Perioral dermatitis is occasionally associated with allergic reactions, as supported by our study, too. Although Torgerson et al. reported positive patch tests for perioral dermatitis in 80% of patients,[10] and Khamaysi et al. showed them in 41.9%,[7] positive test results were less frequent (16.7%) in our study, with fragrances, cobalt chloride, and nickel sulfate being the most common contact allergens. Although some studies have suggested a connection between perioral dermatitis and dental alloys as causative or aggravating factors, some others have reported no adverse reactions in patients allergic to nickel upon application of dental crowns or bridges.[26,27]

OLRs are often associated with contact allergies and positive patch test results.[28-31] Torgerson et al. observed positive patch test results in 55.9% of patients with OLRs.[10] Using patch tests on patients with OLRs, Laine et al. found allergies to metals in 67.7%, particularly mercury, gold, and cobalt.[29] Studies[28,29] often mention allergic reactions to mercury, but we observed no positive reactions and neither did Kim et al. (who explained it as being caused by reduced use of amalgams).[8] When patch tests yield negative results, irritative contact reactions to mercury are possible; thus, removal of an adjacent amalgam can initiate improvement.[5,28] Because these patients often complain of oral sensitivities and unpleasant oral burning sensations, the immediate-type hypersensitivity test is also useful.[5,32]

Gingivostomatitis may also be associated with contact allergies after exposure to dental materials (e.g., metals or plastics in braces).[5] Torgerson et al. observed statistically more frequent contact allergies in 55.6% of tested patients with stomatitis and in 64% of those with gingivitis.[10] In our patients with gingivostomatitis, positive patch test results were less frequent (16.7%), mostly to nickel sulfate, cobalt chloride, and mercury precipitate. Cobalt chloride was the most commonly recorded contact allergen in the majority of our disease groups, whereas in the gingivostomatitis group, it was nickel sulfate. In dentistry, nickel is used for fabrication of space maintainers, brackets, fillings, and crowns.[9,33,34] Allergic reactions to nickel from alloys may manifest as burning sensation, gingival hyperplasia and severely inflamed hyperplastic gingival tissue, numbness on the sides of the tongue,

alveolar bone loss, and edema of the gums, palate, and throat.[9,33] Also, allergies to nickel sulfate are frequently associated with chromium and cobalt reactivity. Thus, according to the patient's medical history, a possible allergy to nickel sulfate should be explored by a dermatologist who would conduct a patch test.[9]

BMS is a disease of unknown etiology; however, various substances, such as foodstuffs, additives, metals, and plastics, have been cited as potential causes.[5] It is, therefore, necessary to rule out all possible etiologic factors, including allergies. Torgerson et al. reported positive patch test results in 42.1% of subjects with BMS,[10] whereas in our study, they were less frequent (20%); the most frequent contact allergens were cobalt chloride, p-phenylenediamine, and colophony. Also indicated were allergies to nutritive allergens (16.7%).[10] As indicated by our results, the risk of this disease is higher in patients with atopia, although with no statistical significance. In certain cases, BMS may manifest similarly to OAS, which appears in those with atopia manifesting an allergy to food as a result of cross-reactions with inhalants (and commonly is determined with SPTs). However, positive allergy test results do not necessarily indicate a connection to oral symptoms because BMS has multifactorial etiology and other causes must be excluded. Skin test results are influenced by many variables, including a patient's skin response, the specific technique used, and tester consistency. Also, potential interference from particular medications should be taken into account before testing. Steele et al. showed that patch testing can identify patients with BMS who are allergic to dental metals or dietary additives and may benefit from the removal or avoidance of these.[35] According to Lynde et al., contact allergies may be an etiologic factor in some patients with BMS, making patch testing useful in this disease.[36]

Angioedema can be induced by various factors and allergens (predominantly immediate-type, but also delayed type), such as drugs, foodstuffs, preservatives, and cosmetics. Such reactions can occur as a result of a latex allergy, dental products, food ingredients, and so on.[1,25] We found additive allergens in 23.3% of patients with angioedema, and we then advised them to avoid additives so that we could monitor their condition after elimination. Our results indicate the risk of angioedema is 3 times higher in subjects with confirmed allergens, and this risk increases with age.

The importance and usefulness of patch testing is in revealing allergies, along with long-term patient monitoring during avoidance of the offending allergen for a mandatory period to establish clinical relevance. Clinical relevance is defined by specific morphologic symptoms in the oral cavity, together with a positive patch test reaction to dental materials containing the suspected contact allergen.[4] Previous research has shown that positive patch test results predominantly correlate with clinical oral symptoms.[4] However, according to other study results, only some patients (those with lichen planus and stomatitis) had a clinically relevant contact allergy and positive patch test reactions to dental metals containing the suspected allergen.[13]

Our research presents the results of allergy tests in common oral and perioral diseases. Given the varying results of individual studies on the usefulness of allergy tests in oral and perioral diseases with nonspecific sensations, in cases of persistent or recurrent diseases, carrying out allergy tests is justified. Therefore, in cases of nonspecific oral problems, it is important to examine patients' medical histories and, in consultation with their dentists, carry out allergy tests on the specific dental substances/allergens that have been or will be used in treatments.[37] The choice of allergens to be tested is also important; it varies by studies, countries, and number of allergens.[14]

One should also keep in mind that patch tests have a few limitations and pitfalls with regard to oral diseases.[3] These are caused by different allergen concentrations in the oral mucosa and in the standard patch preparations and by the differences in the pH of the skin and oral mucosa, which may result in either false-positive/false-negative reactions or nonspecific irritative reactions. Also, sometimes positive allergy test results just reflect sensitivity of the general population. When carrying out patch tests and recording reactions, a standard reading may be insufficient, so subsequent tests should be read after 7 and 10 days or more, such as in patients allergic to mercury.[6] One should always keep in mind that the same substances to which a patient tested negative might still induce an irritative (nonallergic) reaction.

As this study did not include patient follow-up, future long-term studies would enhance the understanding the relevance of allergy in these diseases. The most important measures include giving patients advice on how to avoid allergens and monitoring their conditions and clinical pictures. Likewise, allergy tests can be conducted before complex and expensive procedures are performed, both for the patient's benefit and for the doctor's satisfaction.

CONCLUSIONS

To our knowledge, this is the first research involving patients with different oral and perioral diseases in which patch and prick tests were performed in the same patients and the results compared with healthy subjects as controls. However, our study did not include monitoring for final outcomes, so long-term studies in future are necessary to supplement our current findings. It remains to be seen whether future analyses of the effects of elimination of certain substances

will prove efficient. at the end of DISCUSSION, and "Allergy skin tests are reliable and justified for diagnosing allergies in cases of persistent or recurrent oral diseases. This is the only way to confirm allergies and is the basis for consequent allergen avoidance for the benefit of the patient."

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