REPORT

Contact allergy in oral disease

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Background: The role of contact allergy in oral cavity disease processes is unknown.

Objective: We sought to determine the prevalence of contact allergy to flavorings, preservatives, dental acrylates, medications, and metals in patients with oral disease.

Methods: Patients were tested with an 85-item oral antigen screening series. Data were analyzed retrospectively.

Results: We evaluated 331 patients with burning mouth syndrome, lichenoid tissue reaction, cheilitis, stomatitis, gingivitis, orofacial granulomatosis, perioral dermatitis, and recurrent aphthous stomatitis. Positive patch test results were identified in 148 of the 331 patients; 90 patients had two or more positive reactions. Allergens with the highest positive reaction rates were potassium dicyanoaurate, nickel sulfate, and gold sodium thiosulfate. Of the 341 positive patch test reactions, 221 were clinically relevant.

Limitations: No follow-up data were available in this retrospective analysis.

Conclusion: The positive and relevant allergic reactions to metals, fragrances, and preservatives indicated that contact allergy may affect oral disease. (J Am Acad Dermatol 10.1016/j.jaad.2007.04.017.)

Oral disease is prevalent in the general population, and its symptoms can disrupt a person's daily activities. The spectrum of signs and symptoms of oral disease is broad. Patients with no clinically evident lesions may experience burning or paresthesias, whereas other patients may have pain attributable to lichenoid tissue changes or frank oral ulceration. Because clinical findings do not always account for presenting symptoms, treatment of these patients can present both diagnostic and therapeutic challenges.

The use of patch testing to evaluate patients with oral diseases and symptoms has been controversial. Numerous studies have addressed the effects of metal allergies in patients with dental restorations or orthodontic devices.[1-11] However, few studies have used larger oral allergen screening series that, in addition to metals, included flavorings, preservatives, and dental acrylates.[12-16] We report the results of patch tests to the 85 allergens in our oral screening series.

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METHODS

Patient selection

In this retrospective study, 620 patients who underwent patch testing to allergens in an oral antigen screening series were identified from a clinical database. Allergen patch testing was performed between May 1, 2000, and April 30, 2004, at Mayo Clinic (Rochester, Minn, and Scottsdale, Ariz). Medical histories of the patients were reviewed, and records of 331 eligible patients with a presenting symptom of oral disease or oral symptoms were retained for the study. Patient demographics were also obtained from the database. Patients who denied research authorization were excluded from the analysis. This study was approved by our institutional review board.

Allergen patch tests

Allergens analyzed in this study were those in our oral screening series. For each patient, the specific

allergens tested were determined by the treating physician's judgment of relevant contactants. Patch testing was conducted using Finn Chambers on Scanpor tape (Alpharma Inc, Vennesla, Norway). Allergens were purchased from Chemotechnique Diagnostics (Vellinge, Sweden) or compounded in our pharmacy. Allergens were applied to the skin of the back, torso, extremities, or a combination of the above and left in place for 48 hours. Readings were obtained at 48 and 96 hours.

Patch test reactions were evaluated using criteria similar to the North American Contact Dermatitis Group criteria[17]: negative reaction, macular erythema, weak reaction (nonvesicular erythema, infiltration, and possibly papules), strong reaction (edematous or vesicular lesions), extreme reaction (spreading, bullous, and ulcerative lesions), or irritant reaction. For this study, weak, strong, or extreme reactions were considered positive results. For each patient, the treating physician judged each positive patch test result to be relevant or irrelevant on the basis of the patient's history and clinical examination findings. The grades of relevance, which included definite and questionable relevance, were recorded in the patient's medical record when the 96-hour reading was performed.

Statistical analysis

Patient data were entered into a clinical database (Sybase Incorporated, Dublin, Calif). All statistical analyses were performed using a software package (Statistical Analysis System, SAS Institute, Cary, NC).

RESULTS

In all, 85 allergens were studied to determine the prevalence of contact allergy to flavorings, preservatives, dental acrylates, medications, and metals in patients with oral disease. Patch testing was performed on 331 patients with oral symptoms or evidence of disease during oral examination. The demographics of this population are presented in Table I.

Table II shows the number of patients tested with each of the allergens and the percentage of positive and relevant reactions. After 96 hours, 148 of 331 patients (45%) had at least one positive reaction, and 90 patients (27%) had two or more positive reactions. The 10 allergens with the greatest percentage of positive reactions were 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%), and gold chloride (4.3%). Of the 341 positive reactions to allergens, 221 (65%) were considered relevant.

Table I. Patient demographics (N = 331)

Characteristic	Patients	
	No.	%
Patient sex		
Female	268	81
Male	63	19
Race		
White	220	96
Black	5	2
Hispanic	3	1
Asian	2	1
Not disclosed	101	...
Age, y		
Mean	58	
Range	12-90	
25th percentile	47	
75th percentile	70	

The patients were categorized into 8 disease groups: burning mouth syndrome (145 of 331, 43.8%), lichenoid tissue reaction (59 of 331, 17.8%), cheilitis (54 of 331, 16.3%), stomatitis (27 of 331, 8.2%), gingivitis (25 of 331, 7.6%), orofacial granulomatosis (13 of 331, 3.9%), perioral dermatitis (5 of 331, 1.5%), and recurrent aphthous stomatitis (3 of 331, 0.9%). The number of positive reactions and relevant reactions in each disease group are reported in Table III. Patients with burning mouth syndrome formed the largest disease group and thereby accounted for the largest number of positive reactions. Patients with gingivitis had the highest percentage of positive reactions, and patients with recurrent aphthous stomatitis had the lowest percentage of positive reactions. None of the 13 patients with orofacial granulomatosis had relevant reactions.

The most common allergens for each of the 8 disease groups are presented in Table IV. Metals and flavorings predominated the list. Each of the 5 most common allergens for patients with gingivitis was a metal, whereas for patients with cheilitis, only one of the 5 most common allergens was a metal.

DISCUSSION

We evaluated 331 patients with oral disease using an oral screening series with 85 allergens. Our report emphasizes positive patch test results categorized by individual allergens and specific diseases.

Our study is unusual because it investigated a large series of allergens and included all patients with oral disease who underwent patch testing (evaluation was not limited to patients with positive patch test reactions). In this work, 45% of patients had at

Table II. Positive and relevant reactions to oral allergens (N = 331)

Allergen	No. of patients tested	Reactions, % Positive	Relevant
Potassium dicyanoaurate 0.1% Aq*	184	19.6	55.6
Nickel sulfate hexahydrate 2.5%	320	12.5	52.5
Gold sodium thiosulfate 0.5%	293	11.6	50.0
Fragrance mix 8%	264	9.8	84.6
Palladium chloride 2%	196	9.7	68.4
Balsam of Peru 25%	264	7.2	78.9
Beryllium sulfate tetrahydrate 1% Aq	186	5.4	20.0
Cobalt chloride 1%	307	5.2	56.3
2-Hydroxyethyl methacrylate 2%	77	5.2	75.0
Gold chloride 0.5% Alc*	186	4.3	62.5
Dodecyl gallate 0.25%	288	4.2	41.7
Mercury 0.5%†	190	4.2	87.5
Copper sulfate 2%	79	3.8	33.3
Potassium dichromate 0.5%	150	3.3	60.0
Benzoic acid 5%	285	3.2	100
Cobalt sulfate 1%	195	3.1	100
Mercury ammonium chloride 1%†	184	2.7	100
Octyl gallate 0.25%	278	2.2	83.3
Amalgam 5%†	198	2.0	75.0
Mercuric chloride 0.1%	198	2.0	100
Ethyleneglycol dimethacrylate 2%	300	2.0	66.7
Benzoyl peroxide 1%	289	1.7	20.0
Spearmint oil 2%	297	1.7	80.8
Silver nitrate 1% Aq	182	1.6	66.7
Ammonium persulfate 2.5%	284	1.4	25.0
Isoeugenol 2%	291	1.4	100
Vanillin 10%	296	1.4	75.0
Natural fragrance mix 2%	167	1.2	100
Caine mix III	87	1.1	100
Methyl methacrylate 2%	287	1.0	66.7
Clove oil 2%	296	1.0	100
Menthol 2%	298	1.0	66.7
Colophony 20%	266	0.8	100
Tixocortol pivalate 1%	269	0.7	0
Ethyl acrylate 0.1%	270	0.7	100
Dipentene (limonene) 1%	288	0.7	50.0
Propyl gallate 1%	290	0.7	100
Eugenol 2%	297	0.7	100
Peppermint oil 2%	297	0.7	100
Orange oil 2%	298	0.7	50.0
Zinc chloride 2% Aq	180	0.6	0
Chromium chloride 5%	182	0.5	100
Resorcinol 1%	242	0.4	100
Sorbitan sesquioleate 20%	286	0.3	0
Anethole 5%	290	0.3	100
Benzyl alcohol 1%	290	0.3	0
Amyl cinnamic aldehyde 2%	298	0.3	100
Triethyleneglycol dimethacrylate 2%	303	0.3	100
1,4-Butanediol dimethacrylate 2%	51	0.0	0
1,6-Hexanediol diacrylate 0.1%	55	0.0	0
2-Hydroxypropyl methacrylate 2%	31	0.0	0
Aluminum powder 100%	182	0.0	0
Ammonium tetra-chloroplatinate 0.25% Aq	183	0.0	0
Bisphenol-A-glycidylmethacrylate 2%	302	0.0	0
Bisphenol-A-dimethacrylate 2%	51	0.0	0
Budesonide 0.1%	264	0.0	0
Cadmium chloride 1% Aq	182	0.0	0
Citric acid 1% Aq	289	0.0	0
Ethyl cyanoacrylate 10%	38	0.0	0
Eucalyptus oil 2%	298	0.0	0
Ferric chloride 1% Aq	184	0.0	0
Fluocinonide 1%	24	0.0	0
Glutamic acid 1%	289	0.0	0
Hydrocortisone 17-butyrate 1% Alc	142	0.0	0
Lemon oil 2%	295	0.0	0
Lidocaine 5%	71	0.0	0
Maganese chloride 2% Aq	183	0.0	0
Methyl salicylate 2%	297	0.0	0
Molybdenum chloride 1%	187	0.0	0
N,N-Dimethylaminoethyl methacrylate 0.2%	49	0.0	0
Propionic acid 3%	289	0.0	0
Rhodium 1%	34	0.0	0
Sodium benzoate 5%	288	0.0	0
Sorbic acid 2%	291	0.0	0
Tartrazine yellow 0.1%	291	0.0	0
Tetraethyleneglycol dimethacrylate 2%	26	0.0	0
Tetrahydrofurfuryl methacrylate 2%	55	0.0	0
Theobroma 5%	291	0.0	0
Tin 50%	198	0.0	0
Titanium alloy disk	151	0.0	0
Triamcinolone acetonide 1%	269	0.0	0
Triclosan 2%	257	0.0	0
Urethane dimethacrylate 2%	49	0.0	0
Zinc 2.5%	184	0.0	0
n-Butyl methacrylate 2%	56	0.0	0

Table II. Cont'd

Alc, Alcohol; *Aq*, aqueous.
*Gold.
†Mercury.

Table III. Positive and relevant reactions in patients with oral disease (N = 331)

	Patients		Patients with at least one positive reaction		Patients with at least one relevant reaction	
Diagnosis	No.	%	No.	%	No.	%*
Burning mouth syndrome	145	43.8	61	42.1	35	57.4
Lichenoid tissue reaction	59	17.8	33	55.9	20	60.6
Cheilitis	54	16.3	14	25.9	11	78.6
Stomatitis	27	8.2	15	55.6	13	86.7
Gingivitis	25	7.6	16	64.0	12	75.0
Orofacial granulomatosis	13	3.9	4	30.8	0	0
Perioral dermatitis	5	1.5	4	80.0	2	50.0
Recurrent aphthous stomatitis	3	0.9	1	33.3	1	100

*Percentages were calculated by using the number of patients with at least one positive reaction as the denominator.

least one positive reaction. Other studies investigating reactions to oral allergens in patients with oral or perioral symptoms showed 64%[15] and 70%[16] of patients had positive patch test reactions. Given the differences in patient selection criteria, allergens, test protocols, and data analysis, it is impossible to compare all of our findings with other studies; however, some comparisons warrant consideration.

The majority of our patients were women between 50 and 60 years old. This was consistent with similar oral allergy and disease studies that showed study subjects were predominantly middle-aged women.[12,14-16] When compared with other age and sex demographic groups, it is not clear whether middle-aged women have more oral disease, present to physicians more frequently, or are more likely to undergo patch testing as part of their evaluation. Of our 220 patients who disclosed their race, 96% were white (not of Hispanic origin). Although this generally reflects our patient population, it may also be indicative of disease prevalence, physician access, or type of clinical evaluation.

Many studies have addressed the effects of metal allergies in dental restorations or orthodontic devices.[1-3,18-21] These studies underscore the importance of metal sensitivity, particularly in patients with oral lichenoid lesions. In our group, 7 of the 10 allergens with the highest percentage of positive reactions were metals. These results further support previous studies[2-5,10,11] that showed positive patch test results to metals were seen in patients with lichenoid tissue reactions and lichen planus. Furthermore, metals had the highest percentage of positive reactions for patients with burning mouth syndrome, stomatitis, gingivitis, or perioral dermatitis (Table IV). Thus, the effects of metal allergy may extend beyond the lichenoid processes.

The other allergen groups with the highest percentage of positive reactions were flavorings and preservatives. Fragrance mix (positive reactions, 9.8%) was the most allergenic flavoring. Fragrance mix is used as a flavoring in food products, skin care products, and dentifrices. Fragrance mix contains 8 components, including eugenol and cinnamic aldehyde. We tested eugenol as a single allergen (positive reactions, 0.7%), but cinnamic aldehyde was not included in our series. Other studies showed eugenol-induced positive reactions in 0%, 0.6%, and 2% of patients.[12,13,15] Cinnamic aldehyde was rarely tested, and no positive reactions were identified.[15] Balsam of Peru, found in dentifrice, mouthwash, lipstick, and food,[22] was the second most reactive flavoring (positive reactions, 7.2%). This allergen was not tested in other large-scale studies. Dodecyl gallate was the preservative with the highest percentage of positive reactions (4.2%). It is used to extend the shelf life of oil-based foods such as salad dressings, peanut butter, soups, and pastries. One study testing dodecyl gallate measured a positive reaction rate of 2%.[15] The second most reactive preservative was benzoic acid (positive reactions, 3.2%). Kanerva et al[13] similarly measured a 4.3% positive reaction rate to benzoic acid. The high rate of positive reactions to flavorings and preservatives suggests that a comprehensive oral antigen screening series should include allergens other than metals.

Although allergens with high rates of positive reactivity tend to get the most attention in the medical literature, we were also interested in identifying compounds that did not produce positive reactions. Each class of allergens (flavorings, preservatives, dental acrylates, medications, and metals) included substances that did not provoke a positive reaction (Table II). The corticosteroids had a low percentage of positive reactions. Tixocortol pivalate was the only corticosteroid allergen that induced a positive reaction, and the rate was very low (2 of 269, 0.7%). Corticosteroids were included in our testing of medications to guide treatment. Although positive reactions to corticosteroids were rare, patients who are treatment resistant because of a medication allergy may benefit most from expanded patch testing that includes corticosteroid allergens.

Despite the low positive reaction rates with acrylates (31%), we noted that 5 of the 16 acrylates did have at least one positive reaction. 2-Hydroxyethyl methacrylate provoked the most positive reactions (5.2%), and it had the seventh highest overall

Table IV. Most common allergens for specific oral diseases

Disease	Allergen	Patients with positive reactions, %
Burning mouth syndrome		
	Potassium dicyanoaurate	16.4
	Nickel sulfate hexahydrate	12.3
	Gold sodium thiosulfate	10.9
	Palladium chloride	9.3
	Fragrance mix	8.3
Lichenoid tissue reaction		
	Potassium dicyanoaurate	28.0
	Fragrance mix	17.1
	Gold sodium thiosulfate	15.1
	Nickel sulfate hexahydrate	13.8
	Balsam of Peru	11.9
Cheilitis		
	Fragrance mix	13.0
	Gold sodium thiosulfate	6.8
	Dodecyl gallate	6.1
	Caine mix III	5.6
	Benzoic acid	4.0
Stomatitis		
	Mercury	14.3
	Balsam of Peru	12.5
	Gold sodium thiosulfate	11.5
	Nickel sulfate hexahydrate	11.5
	Dodecyl gallate	9.5
Gingivitis		
	Potassium dicyanoaurate	34.8
	Nickel sulfate hexahydrate	33.3
	Palladium chloride	29.2
	Beryllium sulfate tetrahydrate	20.8
	Gold sodium thiosulfate	17.4
Orofacial granulomatosis		
	Nickel sulfate hexahydrate	15.4
	Benzoyl peroxide	7.7
	Dodecyl gallate	7.7
	Gold sodium thiosulfate	7.7
Perioral dermatitis		
	Cobalt chloride	60.0
	Gold sodium thiosulfate	25.0
	Balsam of Peru	20.0
	Nickel sulfate hexahydrate	20.0
Recurrent aphthous stomatitis		
	Vanillin	33.3

positive reaction rate in our series. This was consistent with the results of Kanerva et al[13] that showed a 2.8% positive reaction rate to 2-hydroxyethyl methacrylate. However, their study participants included patients with occupational dermatoses, such as hand dermatitis, in addition to patients with oral disease.

Even for a large patch testing center, conducting an 85-item oral antigen screening series is daunting. Thus, it is important to identify and recommend allergens for a smaller but still effective oral screening examination. A series that includes the 20 allergens with the highest percentage of positive reactions in this study would include the 10 most common allergens for burning mouth syndrome, stomatitis, and perioral dermatitis. Most allergens for lichenoid tissue reaction would be included, except for spearmint oil, which was the 10th most common allergen for the disease but ranked 23rd most common overall. Gingivitis allergens would be included, except for ethyl acrylate and natural fragrance mix. Interestingly, the patient who reacted to ethyl acrylate also reacted to 2-hydroxyethyl methacrylate, which was among the 20 most common allergens

and could be considered a representative contactant for acrylates. Natural fragrance mix was the ninth most common allergen for gingivitis but only the 28th most common overall. Therefore, an oral allergen series that included the 20 most common allergens in this study would test patients with the majority of the 10 most common allergens for each of the disease groups, with the exception of cheilitis, orofacial granulomatosis, and recurrent aphthous stomatitis. The two flavorings, spearmint oil (lichenoid tissue reaction) and natural fragrance mix (gingivitis), are allergens that would be omitted, but these could be added (total of 22 allergens in the series).

Few of the allergens associated with cheilitis are included in this smaller oral allergen series because it had the fewest positive reactions to metals. The trend is clear enough that patients with cheilitis should be tested with a different allergen series that includes more flavorings and preservatives.

The results for orofacial granulomatosis and recurrent aphthous stomatitis raise the question of the usefulness of patch testing in evaluation of these diseases. Although positive reactions occurred for patients with orofacial granulomatosis, none were classified as relevant. Vanillin, the 27th most common allergen overall, was the only positive patch test result for patients with recurrent aphthous stomatitis. This may indicate that patch testing is unnecessary in the evaluation of such patients. However, only 13 patients with orofacial granulomatosis and 3 patients with recurrent aphthous stomatitis were included in our study, and further examination is needed.

Of the 341 positive patch test reactions in our study, 221 (65%) were deemed relevant by the treating clinician. Of the 18 allergens with 100% relevance, only 4 were metals. Flavorings and preservatives had the highest relevance, comprising 11 of the 18 most relevant allergens. Two of the 18 were acrylates, and one of the 18 was a drug. These data emphasize the importance of including other allergens (in addition to metals) for a comprehensive oral antigen screening series.

Our study contains weaknesses inherent to a retrospective database analysis. A limitation of this study is that no follow-up data are available. The relevance status of each allergen, determined at the 96-hour reading, was based on the opinion of the treating physician, who considered each patient's history and clinical examination findings. Our results were likely influenced by physician bias about the effects of contact allergy in a specific disease process. Those who favor the role of contact allergy as an aggravating or causative factor were more likely to classify a reaction as relevant, whereas others were more likely to classify reactions as irrelevant.

The determination of relevance is possibly the most clinically challenging aspect of patch test interpretation. Theoretically, relevance is a "pure" concept, but in practice, such purity can never be achieved. Clearance of a reaction after avoiding a contactant may be the best test for relevance. However, the number of contactants encountered in daily life and the tremendous chemical complexity of these contactants makes avoidance challenging. This is particularly true for oral allergens.

Determination of relevance at the 96-hour reading relies heavily on patient history and does not include a prescribed period of allergen avoidance. However, to consider this a definite weakness of the study, one assumes that additional follow-up data improves the accuracy of the determination of relevance. This is not always true. For example, if a patient inadvertently ate something containing a suspected allergen during a period of avoidance and did not improve clinically, a follow-up relevance determination would erroneously classify the positive patch test result as irrelevant. In addition, avoidance of one allergen may inadvertently introduce another allergen that perpetuates the clinical reaction. Conversely, there are situations where a period of prescribed avoidance and follow-up might provide a more accurate determination of relevance. This is particularly true for allergens with a high percentage of positive reactions in patients with various diseases. Thus, the controversy about relevance determination in patch testing continues.

CONCLUSION

Allergen patch test results in patients with a broad spectrum of oral diseases are frequently positive for metals, flavorings, and preservatives. Although allergic contact dermatitis to metals is common in patients with oral lichenoid lesions, our results indicate that metal allergies are seen in patients with other oral diseases. In addition, the high frequency of positive reactions to flavorings and preservatives emphasizes the need to use a comprehensive allergen series when evaluating patients with oral disease.

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