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The role of allergy in oral mucosal diseases

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Summary

We retrospectively assessed the prevalence of positive results to cutaneous patch testing, and the relevance of exclusion of identified allergens in the disease process, in 1252 patients with oral mucosal diseases presenting to the Department of Oral Medicine in Glasgow Dental Hospital and School and referred to the Contact Dermatitis Investigation Unit in Glasgow Royal Infirmary. The prevalence of patch-test positivity in each disease cohort was compared with that in 100 control volunteers. Patients with oral mucosal diseases were significantly more likely to have demonstrable hypersensitivity to food additives, especially benzoic acid, and perfumes and flavourings, especially cinnamaldehyde, than controls, and avoidance therapy caused improvement in the majority. Patch testing and the resultant avoidance therapy are useful adjuncts in the management of oral mucosal diseases.

Introduction

Oral mucosal diseases are extremely prevalent: recurrent aphthous stomatitis (recurrent oral ulceration) affects 20% of the population,[1] and oral lichen planus, up to 4%.[2] These conditions cause significant morbidity and may present a severe management problem.

The mouth is subjected to a wide spectrum of antigenic agents, including foodstuffs and drugs, cosmetics, metals in eating utensils, dental materials including toothpastes and filling materials, and micro-organisms. Allergic reactions to such antigens may manifest in a number of diverse ways, including angioedema and ulceration or lichenoid reactions. Allergy or hypersensitivity, however, has not been widely investigated as a cause of oral mucosal disease, although identification of exogenous antigens of aetiological significance may provide important therapeutic options in the management of common and otherwise intransigent oral mucosal diseases.

Patch testing and contact urticaria testing is a recognized and accepted method of identifying allergens responsible for Type I and Type IV allergic reactions of the skin,[3,4] and may be an important adjunct in the management of oral mucosal diseases.

Since 1980, patients from Glasgow Dental Hospital and School have been referred to the Contact Dermatitis Investigation Unit in Glasgow Royal Infirmary to investigate the role that allergy played in their oral mucosal diseases. This was assessed by patch testing and contact urticarial testing. Patients were subsequently instructed on avoidance therapy, and the effect on their disease monitored. In 1996, the patient database was analysed and the results in individual patient disease cohorts compared with a control population without oral mucosal disease. A retrospective postal questionnaire of compliance with, and response to, avoidance therapy was then used to assess the

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relevance and benefits of patch testing on oral mucosal disease in some patients.

Methods

Patients

A total of 1252 patients were referred from the Oral Medicine Department of Glasgow Dental Hospital and School to the Contact Dermatitis Investigation Unit between 1980 and 1996 for patch testing. Forty-four patients were patch tested on two occasions. Patients suffered from a range of oral mucosal diseases, including recurrent aphthous stomatitis (RAS), orofacial granulomatosis (OFG), oral lichen planus (OLP), angioedema (AE) and erythema multiforme (EM). These were diagnosed on the following criteria: patients with RAS suffered recurrent self-healing oral ulcers affecting exclusively the non-keratinising oral mucosa on at least two occasions per year; patients with OFG had pathognomonic clinical features such as chronic lip swelling, buccal cobblestoning, angular cheilitis and ulceration associated with a histological appearance consistent with the diagnosis; patients with OLP had an intra-oral lichenoid appearance associated with a histological appearance consistent with a lichenoid reaction; patients with AE had recurrent acute orofacial swelling, and those with EM had typical recurrent or intransigent stomatitis with or without cheilitis and skin lesions, and a histological appearance consistent with the diagnosis of erythema multiforme.

The mean age of the total group was 39 years (range 2–94); 34% were male ($n=420$), and 66% were female ($n=832$). The age and sex distributions for those with specific diseases are shown in Table 1.

Controls

Ethical Committee approval was obtained to allow patch testing of control subjects. Controls were derived from staff working at Glasgow Dental Hospital and School, students studying at Glasgow Dental Hospital and School and friends and family of the above. All were patch tested at Glasgow Dental Hospital from July to December 1996. A short series of questions was asked of all volunteers, and informed consent was obtained prior to the tests commencing. Questions sought information on age, sex, geographical area, occupation, medical history, etc. Individuals were excluded if they had been patch tested on a previous occasion or gave a history of RAS, OFG, LP, AE or EM. The 100 controls were derived from 114 consecutive volunteers after 14 were excluded on the above criteria. The age and sex distribution of the control population is also shown in Table 1.

The control group was demographically similar to the total patient group, although individual disease cohorts varied in their age and sex distribution. The control group of 100 patients was compared to individual disease cohorts rather than to the total group, and therefore provided the context within which to interpret prevalence of allergy. Relevance rather than prevalence of allergy was the outcome assessed as important, although a geographically-relevant set of control prevalence data was considered essential.

Patch testing (contact urticaria and delayed hypersensitivity testing)

Testing was performed by standard methodology using Finn Chambers and Scanpor tape.[3] Patches for contact urticaria testing were applied to the inner aspect of the forearms, removed after 20 min and read immediately. A positive response was urticaria at the test site. Patients were asked to observe the test sites at hourly intervals for the next 6 h and to record what they found. Reagents for delayed hypersensitivity patch testing were applied to the upper back, removed after 2 days and read 1 h after removal (on day two) and at day four. Reactions were scored as recommended by the Swedish Multi Centre Grading System 5 for the patients by a consultant dermatologist (AF), and the volunteers by a trained researcher (SR), after suitable inter-operator calibration. All patients were

Table 1 Age and sex distribution of patients with oral mucosal disease and controls

Disease	Mean age (years)	Range (years)	Male (*n*)	Female (*n*)
RAS	31	3–83	94	183
OFG	24	3–72	151	113
OLP	52	2–79	63	198
AE	48	13–73	22	23
EM	32	12–65	19	23
Total group	39	2–94	420	832
Controls	33	19–60	29	71

tested to allergens that were suspected to be contributing to their disease. A total of 48 different allergens were placed on the backs of volunteers. All patients and volunteers were tested with the modified Standard European Series[3] and food additives, perfumes and flavourings and chocolate. Most patients were also tested for other allergens in addition, for example, dental materials and so patients had between 48–111 patches placed on their upper back (average 73 per patient). All allergens were made up in paraffin molle flavum (PMF) except for formaldehyde and one chocolate essence preparation, which were both carried in an aqueous solution. Plain PMF was included in all subjects as a control. Food additives used as test allergens for both the volunteers and the patients were benzoic acid, salicylic acid, tartrazine, glutamic acid, butylated hydroxytoluene, butylated hydroxyanisole, propylene glycol, sorbic acid and sodium metabisulphite. Perfumes and flavourings tested were cinnamyl alcohol, cinnamaldehyde, eugenol, amylcinnamaldehyde, hyroxycitraonellal, geraniol, isoeugenol, oak moss absolute, benzyl alcohol, and musk ambrette. Sorbitan sesquiolate being added as an emulsifier to the fragrance mix in the Standard European Series, was included in the testing. All were tested in the delayed hypersensitivity test, and all but sorbitan sesquiolate were tested in the contact urticaria test. The number of positive results was expressed as percentages of the number of patients tested to each allergen. Since not all patients in each disease group were tested to all the allergens in the series, when analysing the total number of positive reactions in a series, the percentage was calculated from the maximum number of those having the tests so as not to artificially inflate the percentage of positive reactions.

Avoidance of relevant allergens

Patients who had a positive skin reaction identified to a food-related allergen were given detailed avoidance advice specifically targeted at the particular allergen. This was given both verbally, usually by a senior dietician, and in the form of written instructions. In 1996, some patients were contacted to ascertain whether they had understood the dietary advice, how successful they had been in maintaining their dietary changes or restrictions, and whether their symptoms had changed in any way since receiving the advice. This was assessed on a scoring system of 1 to 10, both before and after the initiation of avoidance therapy. Patient records were also accessed to determine the improvement in clinical appearance of any of the lesions.

Four hundred and seventy-six patients who had one of the five disease categories under consideration, and who also had a positive reaction to a food substance on patch testing, were sent a letter enclosing a questionnaire and a reply paid envelope.

Statistical analysis

The total patient group and each of the five disease groups were compared in turn to the control group using a test of equality of two binominal proportions. A p value for the test of equality of the proportions for the difference between the two proportions was calculated. Significance for p values was taken to be at the 5% level.

Results

Of the 1252 patients referred for patch testing, 277 had RAS, 264 had OFG, 261 had OLP, 45 had AE and 42 had EM. The remainder were referred with miscellaneous oral conditions such as burning mouth syndrome, facial eczema, gingivitis, and putative allergy to local anaesthetic agents or dental materials.

Of the 1252 patients tested, 879 (70%) reacted to one or more substances, compared to 60% of controls (Table 2). The number of patients in each disease category who were allergic to groups of allergens and to specific allergens is also shown in Table 2. These data are expressed both as the total numbers showing positive reactions to either contact urticaria or delayed hypersensitivity testing in each group, and as a percentage of the total tested. Controls, who were mostly health-care workers, showed a much higher delayed hypersensitivity response to thiomersal, which was presumed to be due to its presence as a preservative in hepatitis B vaccines[6] (24/1252 patients, 1.9% vs. 21/100 controls, 21%) and hence thiomersal data was removed from the further analysis.

Patients with RAS and OFG were significantly more likely to have reactions to food additives, especially benzoic acid, and to chocolate, although the numbers allergic to chocolate were too small to be statistically reliable. All patient groups were significantly more likely to have allergy to perfumes and flavourings, especially cinnamaldehyde, though the delayed hypersensitivity results to perfumes and flavourings were unreliable again due to the small numbers involved. Patients with AE showed no particular pattern of allergy, and those with OLP were more likely to react to mercury and other metal salts, indicating reactions to amalgam fillings (data not shown). Patients with RAS and OFG were significantly more likely to show contact urticaria

reactions to food additives and perfumes and flavourings than other disease cohorts or controls.

To assess the response to avoidance therapy, 476 patients were contacted by letter. Of those contacted, 261 (55%) questionnaires were returned. Of those, 44 were returned 'not at this address', one patient could not remember the clinic attendances, and one patient had died. Two hundred and fifteen patients, therefore, completed the forms. Of these, 185 (86%) completed the form correctly. Three patients filled out only one side of the questionnaire, and a further 28 incorrectly completed the linear analogue scales. Most of these, however, ($n=18$) indicated their answer in writing and were assigned a score on that basis. The assessable numbers in each disease group are shown in Table 3.

Compliance with avoidance therapy, self-assessed on a scale of 1 to 10, indicated that most patients considered that they had shown good compliance (mean score 7.9 ± 2.7 SD: median 9). Most patients recorded scores of severe symptoms, self-assessed using a score of 1–10, pre-patch testing (mean score 8.7 ± 2.0 SD: median 10), and a reduction in perceived symptoms after avoidance therapy (mean score 4.5 ± 3.1 SD: median 4). The compliance rate and individual scores for each disease category are shown in Table 3. Among those who showed good compliance, patients with RAS showed an overall improvement of 4.5, those with OFG an improvement of 4.9, and those with OLP an improvement of 4.4. The numbers of returned questionnaires from those with AE and EM were very small, and indicated no improvement apart from one EM patient with an improvement score of 7. Those patients who indicated that they had achieved moderate or poor compliance achieved less symptomatic improvement (data not shown).

Table 2 The prevalence of patch test and contact urticaria positivity among patients with oral mucosal disease and controls

Allergen	All patients	RAS	OLP	OFG	AE	EM	CTS
Food additives CU	381 (35.2)	111 (40.7)*	48 (21.6)	116 (49.8)*	10 (29.4)	5 (11.9)	22
Food additives DH	165 (15.3)	43 (16.0)	39 (17.6)	23 (9.7)	14 (38.9)*	5 (12.2)	13
Food additives total	488 (41.4)*	136 (49.8)*	79 (35.6)	129 (54.0)*	20 (58.0)*	8 (19.0)	33
Benzoic acid CU	366 (34.0)*	106 (39.6)*	46 (20.7)	110 (46.0)*	10 (27.8)	17 (41.5)*	21
Benzoic acid DH	124 (11.5)	31 (11.6)	29 (13.1)	17 (7.1)	9 (25.0)*	6 (14.6)	7
Benzoic acid total	446 (41.5)*	126 (47.0)*	66 (29.7)	122 (51.0)*	15 (41.7)	20 (48.8)*	28
Perfumes and flavourings CU	331 (28.5)*	92 (33.5)*	47 (20.1)*	99 (39.1)*	9 (21.4)*	10 (23.8)*	6
Perfumes and flavourings DH**	148 (12.7)*	30 (10.9)*	30 (12.8)*	17 (6.7)	8 (19.0)*	7 (16.7)*	4
Perfumes and flavourings total	429 (37.0)*	112 (40.7)*	69 (29.5)*	108 (42.7)*	15 (35.7)*	15 (35.7)*	9
Cinnamaldehyde CU	300 (25.8)*	86 (31.3)*	38 (16.2)*	90 (35.6)*	8 (19.0)*	9 (21.4)*	6
Cinnamaldehyde DH**	44 (3.8)	7 (2.5)	7 (3.0)	9 (3.6)	4 (9.5)	1 (2.4)	2
Cinnamaldehyde total	327 (28.2)*	89 (32.4)*	43 (18.4)*	97 (38.3)*	12 (28.6)*	10 (23.8)*	7
Chocolate CU**	9 (0.8)	4 (1.5)	1 (0.5)	4 (1.6)	0 (0)	0 (0)	0
Chocolate DH**	42 (3.9)	7 (2.6)	6 (2.7)	17 (7.0)	1 (2.9)	2 (4.9)	1
Chocolate** total	49 (4.5)	10 (3.7)	7 (3.2)	20 (8.2)	1 (2.9)	2 (4.9)	1
Modified Standard European Series***	446 (35.6)	98 (35.4)	102 (39.1)	63 (23.9)*	15 (33.3)	10 (23.8)	35
Total positive***	879 (70.2)*	219 (79.1)*	162 (62.1)	192 (72.7)*	35 (77.8)*	30 (71.4)	60
Total number of patients	1252	277	264	261	45	42	100

Figures in brackets represent %; CU, contact urticaria; DH, delayed hypersensitivity; CTS, controls, *$p<0.05$. **p value not reliable due to small numbers. ***Excludes thiomersal.

Table 3 Response to avoidance therapy among patients with oral mucosal disease who showed good compliance

Diagnosis	*n*	Good compliance*	Mean pre-test score	Mean post-avoidance score
RAS	85	66%	9.4	4.9
OFG	61	85%	8.8	3.9
OLP	52	73%	8.6	4.2
AE	4	50%	7.5	7.5
EM	6	50%	9.7	7.3

*Score of 7–10.

Discussion

Oral mucosal disease is prevalent, and may present significant management challenges for both medical and dental practitioners. Patch testing and contact urticarial testing are recognized methods of investigating known allergic diseases. They have not, however, been widely applied to the investigation of oral mucosal disease.

These results demonstrate that of 1252 patients with oral mucosal disease, 70% were patch-test positive, compared to 60% of controls. These data excluded thiomersal because of the very high prevalence among control volunteers. Thiomersal is an organic mercurial preservative used in skin disinfectants, contact lens solutions, cosmetics, mouthwashes and vaccines. Of the 24 patients who reacted to thiomersal, five were health-care workers, and of the 21 controls who reacted, all were health-care workers who had received hepatitis B vaccine containing thiomersal as a preservative.[6]

A number of other significant differences were found between patients and controls. Those with RAS and OFG were significantly more likely to react to food additives, especially benzoic acid, and all patient groups were more likely to react to perfumes and flavourings, especially cinnamaldehyde. The biological significance of these findings is emphasized by the positive response to avoidance therapy, although this was not observed among those with AE and EM. Although only less than half the response questionnaires were returned, this does not negate the beneficial response to avoidance therapy: even if all non-responders to the questionnaire had achieved no therapeutic benefit, a useful proportion of those with RAS, OFG and OLP still benefited from avoidance therapy (RAS 28%; OFG 38%; OLP 31%). There was also subjective clinical benefit which encouraged continued investigation of these patient groups over several years.

The patient groups were not, however, subjected to blind avoidance therapy or to formal rechallenge, although a clear-cut cause and effect relationship could be demonstrated clinically in many patients. The contribution of spontaneous remission also cannot be determined from these data. Other studies have used blind avoidance therapy and other methods of assessing food reactivity, but only in isolated disease groups.[7]

This study is the largest reported series covering a wide range of mucosal diseases, and compares the findings with a control group.

The association between allergy and mucosal disease may influence disease expression or severity in a number of ways: in AE, Type I hypersensitivity is involved, whilst in EM, Type III hypersensitivity is more likely. In RAS and OFG, Type I reactions may have direct effects on the aetiology or may cause immune modulation of an underlying Type IV reaction. The role of Type I reactions is implied by the higher prevalence of contact urticarial reactions compared to delayed hypersensitivity reactions seen in these disease cohorts. Recent evidence suggests that OLP results from Type IV cell-mediated damage.[8] Regardless of the mechanisms involved, patch testing is clearly of therapeutic benefit in selected patients with oral mucosal disease and should be available as an adjunct in the investigation of oral mucosal diseases which present a management problem.

Patch testing must be accompanied, however, by high-quality verbal and written advice, since the commonest allergens implicated, food additives and perfumes and flavourings, are ubiquitous in modern convenience foods and drinks. Patients require expert advice, particularly by experienced dieticians and skilled liaison medical and nursing staff, if avoidance therapy is to be successful.

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