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6. Contact allergic reactions in patients with atopic eczema

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Medicament allergy is a not uncommon problem both with antibiotics and topical corticosteroids. Patients with atopic eczema have a significant degree of reactivity to these agents similar to non-atopics.

INTRODUCTION

Are atopic dermatitis (AD) patients more prone to contact dermatitis? On theoretical grounds one might expect them not to be, but the situation is complex. The skin barrier might not be as good as in non-atopics, and atopic patients may use topical agents and creams for prolonged periods.

DINITROCHLOROBENZENE

The controversy concerning the sensitizing potential of a common agent to which there is contact sensitivity, dinitrochlorobenzene, has been reassessed by Rees et al. (1). Dose-response relationships for contact sensitization and elicitation at three different concentrations of dinitrochlorobenzene were determined for 22 patients with minimal atopic eczema compared to 27 non-atopic healthy control subjects. Atopic patients were significantly less responsive, with smaller reactions at all challenge doses and exhibited flatter challenge dose-response curves than did healthy controls. This is in keeping with the classic cytokine route of sensitization, which indicates that atopics should be less prone to sensitization under experimental conditions.

HAIRDRESSING ALLERGENS

All hairdressers are exposed repeatedly to potentially sensitizing agents in the workplace. The sensitizing potential of hairdressing allergens was determined by patch testing in non-atopic hairdressers and in atopic hairdressers and is shown in Table I (2). No significant differences in the frequency of positive patch tests were found between eczematous atopics, mucous membrane atopics and non-atopics. A positive patch test was seen to the nine common allergens in 60% of eczematous atopics, in 53% of mucous membrane atopics (asthmatics/hay fever sufferers) and in 58% of controls. No differences were seen for individual allergens.

COMMON ALLERGENS

AD patients do become sensitized to contact allergens. Chromate, thiuram mix, nickel sulphate, perfume mix,

Table I. *Sensitizing potential of hairdressing allergens*

		Eczematous atopics (n=45)	Mucous membrane atopics (n=32)	Non-atopics (n=66)
Hairdressing allergens	Strength	No. (%) allergic	No. (%) allergic	No. (%) allergic
No. of patients with positive test to allergens 1–9		27 (60)	17 (53)	38 (58)
1 Glyceryl monothioglycolate	0.5/1.0%	23 (51)	12 (38)	27 (41)
2 Ammonium thioglycolate	0.5%	4 (9)	2 (6)	5 (8)
3 p-Phenylenediamine	1%	11 (24)	11 (34)	22 (33)
4 p-Toluenediamine sulphate	1%	2 (4)	4 (13)	14 (21)
5 o-Nitro-p-phenyl-diamine	1%	0 (–)	2 (6)	4 (6)
6 Ammonium persulphate	2.5%	7 (16)	4 (13)	10 (15)
7 Pyrogallol	1%	1 (2)	0 (–)	1 (2)
8 Resorcinol	2%	0 (–)	0 (–)	0 (–)
9 Hydroquinone	1%	0 (–)	0 (–)	0 (–)
10 Nickel sulphate	5%	12 (27)	15 (47)	23 (35)
11 Mercaptobenzoate	2%	–	–	–
12 Thiuram mix	1%	1	2	2
13 Fragrance mix	8%	2	1	2
14 Formaldehyde	1%	1	1	3
15 Kathon CG	100 ppm a.i	2	2	2
Quaternium 15	1%	1	3	1

Taken from Sutthipisal et al. (2).

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Table II. *Allergy to common allergens**

	Atopic eczema now	Atopic eczema in past	Mucous membrane atopic	Non-atopic	No information
Total no. of patients	191	120	156	510	12
No. of patients (%) allergic to one or more allergens	72 (38)	63 (53)	84 (54)	257 (50)	
No. of patients (%) allergic to:					
Chromate	2 (11.1)	4 (3.3)	88 (5.1)	25 (4.9)	
Thiuram mix	5 (2.6)	3 (2.5)	8 (5.1)	32 (6.3)	
Nickel sulphate	35 (18.3)	28 (23.3)	36 (23.1)	93 (18.2)	
Perfume mix	14 (7.3)	9 (7.5)	15 (7.5)	41 (8.0)	
Neomycin	4 (2.1)	7 (5.8)	5 (5.8)	22 (4.3)	
Wood alcohols	5 (2.6)	3 (2.5)	1 (2.5)	7 (1.4)	

*In 989 patients patch-tested to 6 common allergens.
Taken from Cronin & McFadden (3).

neomycin and wool alcohols are common allergens in atopic eczema patients. However, a significant difference between the frequency of a positive patch test between non-atopics and atopics was observed only for those atopics who had eczema currently. No difference was observed for patients who had a history of atopic eczema but no current lesions (Table II) (3).

TOPICAL ANTIMICROBIALS

Goh (4) compared the sensitizing potential of topical antimicrobials using a modified Buehler technique in guinea pigs. Medicaments were generally only modest sensitizers. Of commonly used topical antimicrobials, neomycin was a modest sensitizer, whilst fusidic acid was only a weak sensitizer.

The sensitizing potential of some topical antimicrobials was determined recently (5). The proportion of patients with atopic eczema and patients who had never had atopic eczema who were sensitized to various antibiotics and antiseptics is shown in Table III. Patients with venous leg ulcers and stasis eczema were excluded.

After controlling for the confounding effect of sex and in particular age, there was no evidence that patients with atopic eczema had a generally higher risk compared with normal individuals. However, determination of odds ratios showed that neomycin hypersensitivity was more common in atopics (OR 1.24; 95% CI 1.02–1.50), in patients over 40 years of age (OR 2.40; 95% CI 2.01–2.89) and borderline more common in women as a whole (OR 1.17; 95% CI 0.99–1.39). Chloramphenicol hypersensitivity was also more common in women aged over 40 years (OR 2.75; 95% CI 1.29–6.83). All other tests for the influence of atopy, age over 40 years and for females showed no difference. The authors concluded that while the risk of sensitization should always be considered when applying topical antimicrobials, available data do not support a very restrictive use of these agents in the management of AD.

At St John's, we patch-tested all 1119 patients attending the contact dermatitis clinic over a 1-year period with fusidic acid, clioquinol and neomycin (6). The overall frequency of a positive patch test was neomycin (3.6%), clioquinol (0.7%) and fusidic acid (0.3%). The primary site of dermatitis in the patients studied and in a total of 48 additional

Table III. *Frequency of sensitization to antimicrobials in patients with atopic dermatitis and in non-atopic individuals*

Substance (all tested in petrolatum)	Concentration (%)	Atopic patients		Non-atopic individuals	
		Total tested	% positive (95% CI)	Total tested	% positive (95% CI)
Neomycin sulphate	20	7619	2.1 (1.75–2.46)	26056	1.73 (1.57–1.88)
Gentamicin sulphate	20	1635	2.11 (1.42–2.80)	5697	2.60 (2.14–3.05)
Erythromycin	1	579	0.14 (0.0–0.40)	1802	0.25 (0.03–0.47)
Fusidic acid	2	48	0 (0.0–6.05)	207	1.76 (0.23–3.30)
Oxytetracycline	3	714	0 (0.0–0.42)	2650	0.20 (0.0–0.44)
Chloramphenicol	5	733	1.04 (0.24–1.84)	2797	1.21 (0.79–1.63)
Framycetin sulphate	10	403	2.33 (0.78–3.87)	1797	2.78 (1.98–3.57)
Bacitracin	20	721	0.66 (0.05–1.26)	2687	1.59 (1.07–2.10)
Polymyxin sulohate	3	1196	0.19 (0.0–0.47)	4025	0.32 (0.16–0.47)
Nitrofurazone	1	5	0 (0.0–45.07)	154	2.49 (0.01–4.98)

Taken from Jappe et al. (5).

Table IV. *Comparative frequency of patch test reactions to topical antibiotics*

Lesion site	Patch test population (n=1119)	Neomycin positive (n=40)	Clioquinol positive (n=8)	Fusidic acid positive (n=3)	Fusidic acid positive (total from 1980 to 2000) (n=48)
Widespread	242	12	0	3	3
Face/neck	290	15	1	0	7
Hands only	248	4	2	0	4
Legs/feet	81	3	2	0	26
Anogenital	0	0	0	0	2
Trunk	0	0	0	0	2
Ear canal	0	0	0	0	1

Taken from Morris et al. (6).

Table V. *Characteristics of the patch test positive subjects*

Characteristic	Patch test population (n=1119)	Neomycin positive (n=40)	Clioquinol positive (n=8)	Fusidic acid positive (n=3)	Fusidic acid positive (total from 1980 to 2000) (n=48)
Mean age (years)	41.5	46	48.5	41.5	57.6
Female	699 (62.5%)	29 (72.5%)	1 (12.5%)	3 (100%)	27 (56.2%)
Rash >5 years	430 (38.4%)	17 (42.5%)	2 (25%)	2 (66.7%)	15 (31.2%)

Taken from Morris et al. (6).

patients seen at St John's between 1980 and 2000, who had a positive patch test to fusidic acid, are shown in Table IV. Characteristics of the subjects who had a positive patch test are shown in Table V. Neomycin sensitivity was five times more common than clioquinol sensitivity and about 12 times more common than fusidic acid sensitivity. When considering all the patients seen at our clinic over 20 years, who were found to be sensitive to fusidic acid, the majority had lesions on the legs and/or feet. A large number of these patients were seen in the early 1980s and had applied a topical tulle (gauze) impregnated with a lanolin-containing fusidic acid ointment. This preparation is no longer available in the UK and the number of eczema patients we now see who are allergic to fusidic acid is very small.

Fig. 1 shows the frequency of a positive patch test to fusidic acid in our clinic over the period 1982–1999 and the amount of topical fusidic acid used in the UK. Despite a marked increase in the amount used, which has trebled since the 1980s, there has been no increase in the frequency with which we have detected a positive patch test to fusidic acid at our clinic. Overall, the frequency of fusidic acid allergy in our eczema population is low.

The overall frequency of a positive patch test was:
- neomycin 3.6%
- clioquinol 0.7%
- fusidic acid 0.3%

CORTICOSTEROID SENSITIVITY

This is a not uncommon observation and often found in patients with chronic eczema who have used significant amounts of cortisone creams on large parts of the body. It may present with either poor response to topical treatment or a worsening and spreading of the eczema. The usual screening agent for corticosteroid sensitivity is tixocortal pivalate, but budesonide is also applied. At St Johns, where a patient has been identified with steroid sensitivity, an extensive panel is then applied to assess which individual steroids they are allergic to.

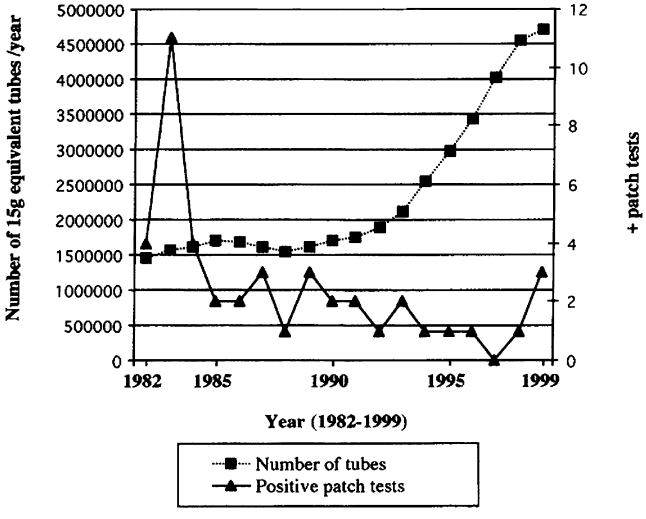

Fig. 1. Frequency of positive patch tests to fusidic acid in relation to consumption from 1982 to 1999.

There are two significant points about patch testing with steroids. Firstly, the reactions often only come up on the last reading and some would advocate a 7-day reading as the reaction is often delayed. Secondly, there is still debate about the right concentrations to use, as the allergic patch test reaction may theoretically be suppressed by the anti-inflammatory action of the cortisone. Atopic eczema patients, both children and adults, have been found to have significant reactions to corticosteroid.

OTHER ALLERGENS

Latex allergy is more common in atopics. Protein contact dermatitis, usually to foods in caterers, with a negative patch test and a positive prick test, is more common in atopics and is usually seen in caterers. The relative frequency of patch test positivity in patients with intrinsic or extrinsic disease has not been fully assessed.

CONCLUSION

Overall, medicament allergy does not seem to be much higher in atopic patients and may simply reflect more common or intensive use rather than any increased predisposition to contact eczema per se.

DISCUSSION

Thestrup-Pedersen; Do you have any data on steroid sensitivity?

McFadden; There are data on patch testing in children showing a sensitivity rate of 1%.

Taieb; Could this be related to use of nasally administered steroids such as tixocortol or budesonide?

McFadden; I doubt it, fluticasone is of a similar structure to hydrocortisone and may penetrate the skin better. Patch testing of steroids is difficult as it suppresses its own response.

Taieb; Hydrocortisone is not widely used in France and the positive patch tests are more frequently related to a mucosal route of sensitization.

Andersen; When patch testing corticosteroids the result depends on the concentration tested, lower concentrations often give higher sensitization rates. Late readings are needed to ensure detection of a positive response.

Thestrup-Pedersen; It is also confusing that you can have a group of people with an armed immune system in whom you do not get a positive response.

Andersen; My overall impression is that the incidence of contact allergy in atopics is the same as in non-atopics.

Diepgen; Most of the data indicate that around 40% of atopics are sensitized.

McFadden; The importance of the second reading cannot be stressed too highly in assessing contact allergy in atopics. One of the most interesting things is that whilst the medicaments we use are sensitizers, they are not strong sensitizers even though we apply them to already inflamed skin.

Thestrup-Pedersen; Are any of these sensitization rates of clinical relevance?

Agner; 60% or more of our positive tests have clinical relevance.

McFadden; Those studies which have addressed the question have found a high relevance, but more studies are needed. The relevance also depends upon the allergen. Nickel allergy is common, but when you get a positive patch test it has clinical importance.

Leung; Some allergens elicit a Th1 response, others a Th2 response and some a mixed response. On top of that there is the effect of proteins, allergens versus haptens. What influence could this have?

Thestrup-Pedersen; It will be interesting to see the pattern in the intrinsic as opposed to the extrinsic types.

Leung; You are more likely to make an IgE response to protein than a hapten.

McFadden; Lots of our data come from allergy clinic patients, and are thus influenced by that fact. The study with hairdressers could be more relevant in this respect. One way we look at the atopic data is that whilst they have a poor skin barrier, maybe their 'sensitization process' is less responsive. Excluding atopics can be advantageous when investigating sensitization rates.

Diepgen; I agree; it would be interesting to look at the extrinsic and intrinsic types. Is nickel allergy more common in atopics or not?

McFadden; Assessing patch tests to metals in atopics is very difficult and should only be done by experienced personnel, as there is commonly an irritant effect. Beware of false positives.

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