

Bronchial and cutaneous responses in atopic dermatitis patients after allergen inhalation challenge

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Summary

Background Atopic dermatitis (AD) is often associated with allergic asthma (AA). Inhalation of allergens influences the activity of AA but the effect on the skin in AD is unclear.

Objectives We evaluated the degree of bronchial hyperresponsiveness to methacholine in eight AD patients with AA (AD⁺) and eight AD patients without AA (AD⁻) and studied bronchial and cutaneous responses after allergen inhalation challenge.

Methods All patients were treated in hospital for their eczema with tar ointment (pix liquida) and orally administered antihistamines (mean hospital stay 37 days). After clearing of the skin lesions allergen inhalation challenge was performed. Cutaneous responses were studied by measuring the 'Costa' score before and 24 h after allergen inhalation challenge.

Results The median value of the provocative concentration of methacholine causing a 20% fall (PC₂₀ Mch) in forced expiratory volume in 1 second (FEV₁) was significantly higher in the AD⁻ group compared to the AD⁺ group with median values of 10.70 and 0.60 mg/mL, respectively. These values did not change significantly in both groups during hospital stay. After challenge all AD⁺ patients showed early and late asthmatic responses whereas only four AD⁻ patients showed early asthmatic responses (mean values of the maximal fall in FEV₁ during the EAR 37%/16% and in PEF during the LAR 27%/4% for AD⁺ and AD⁻ patients, respectively). The 'Costa' score increased in both groups (mean score before 19.1/24.4 and after challenge 26.8/26.9 for AD⁺ and AD⁻ patients, respectively). The increase in the AD⁺ group was significantly higher compared with the AD⁻ group ($P = 0.016$).

Conclusion We conclude that allergen inhalation challenge causes a flare up of the skin lesions in atopic dermatitis patients. This was more prominent in atopic dermatitis patients who already suffered from an IgE-mediated allergic inflammation in the lung.

Keywords: allergen inhalation challenge, asthma, atopic dermatitis, bronchial hyperresponsiveness

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease which is frequently (29–35%) associated with allergic asthma (AA) [1,2]. Both entities are classified as

atopic diseases because of the elevated serum levels of IgE specific for otherwise harmless aeroallergens. Since bronchial hyperresponsiveness (BHR) has been found in AD patients without asthma [3,4] and skin hyperreactivity has been shown in asthmatics [5] an overlap between the pathophysiology of AA and AD seems likely [3].

The activity of AA is largely influenced by inhalation of allergens [6,7]. In contrast to the IgE-dependent respiratory

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atopies, the role of allergens in the pathogenesis of AD is not fully understood. The presence of elevated serum IgE levels to aeroallergens, the binding of IgE to antigen presenting cells in the skin [8] and the presence of allergen specific T cells in lesional AD skin [9,10] suggests that these allergens probably play a role in the pathogenesis of this disease. A recent double-blind placebo-controlled study showed indeed a significant improvement of the skin lesions in AD patients after house dust mite allergen avoidance [11]. It is however, not clear which routes of penetration are involved.

Induction of skin lesions can be observed in AD patients after epicutaneous application of allergens in an atopy patch test (APT). A recent study in a large group of AD patients reported that in 50% of the patients, who have specific IgE for grass pollen or house dust mite, eczematous skin lesions can be induced by epicutaneous testing with these allergens [12]. Only a few studies report a flare up of AD provoked by inhalation of aeroallergens [13,14]. Inhalation of mold extracts could induce eczematous skin reactions in two out of five patients with 'pure' AD [13]. A pruritic dermatitis could be elicited in *Ascaris* sensitized asthmatic dogs after *Ascaris* antigen inhalation provocation, showing similarities with AD [14]. Although many AD patients have high-titre IgE antibodies to house dust mite allergen in their serum [15], only a relatively small percentage (35%) of them develop pulmonary symptoms [1,16].

The course of pulmonary symptoms in relation to the activity of AD varies. They can alternate — 'alternance morbide' — [17] or run parallel with the activity of the eczema [18].

The aim of the present study was to investigate the course of pulmonary function and BHR in AD during clinical treatment of the patients and to study bronchial and cutaneous responses after allergen inhalation challenge.

Materials and methods

Patients

We studied two groups of eight patients (Table 1) who were treated in the department of dermatology/allergology for their eczema with a mean hospital stay of 37 days (range 18–78). One group had atopic dermatitis and allergic asthma (AD⁺), which had been diagnosed on the basis of a history of episodic wheezing and impaired lung function. This was checked in previous family physician and hospital records. The other group of patients only suffered from atopic dermatitis (AD⁻).

The AD⁺ group had relatively mild asthma according to the definition of American Thoracic Society [19], which was adequately controlled with inhaled bronchodilators on an as-needed basis. Control was defined as: no limitations of

Table 1. Characterization of study groups

Patient No.	Age (years)	Sex	IgE kU/L	Specific IgE ^b kU/L
AD⁺				
1	17	F	2070	>100
2	49	M	17696	>100
3	18	F	5269	>100
4	22	M	11920	>100
5	22	F	2091	>100 ^c
6	25	F	8831	>100
7	25	M	29578	>100
8	30	M	28170	>100
Mean	26.0		14808 ^a	
SEM	3.8			
AD⁻				
9	23	F	8268	>100
10	28	M	17198	>100
11	26	F	1324	50 ^d
12	22	M	12214	>100
13	25	F	3835	24 ^c
14	30	F	1232	>100
15	28	F	5199	>100
16	23	M	1848	4
Mean	25.6		4517 ^a	
SEM	1.09			

AD⁺ Atopic dermatitis with allergic asthma.

AD⁻ Atopic dermatitis without allergic asthma.

^a Median values.

^b IgE specific for house dust mite.

^c IgE specific for birch pollen.

^d IgE specific for cat.

daily activities, no sputum, no awakenings at night because of symptoms and on the day of admission all patients had a forced expiratory volume in one second (FEV₁) greater than 60% of predicted normal values before bronchodilator [20]. At enrolment, all AD⁺ patients were required to show increased BHR to methacholine (PC₂₀ Mch ≤8 mg/mL). None of them had received inhaled or oral corticosteroids or cromoglycate 2 months prior to this study.

Both AD groups suffered from severe eczematous skin lesions which involved the sites typical of AD and satisfied the criteria of AD by Hanifin and Rajka [21]. To determine the actual severity and topography of the dermatitis, we used the 'Costa' scoring system [22] (see 'severity score for atopic dermatitis'). This also allowed us to establish variations of disease activity during the study. All patients had raised levels of total serum IgE and specific IgE

antibodies to house dust mite, birch pollen or cat allergen. They also showed positive immediate type skin-prick test reactions to these allergens and were thus considered atopics. Four AD⁺ and four AD⁻ patients had diagnosed IgE-mediated sensitization to food allergens. Clinical relevant food allergens were excluded from these patients' diet.

At the time of the study, all patients were free of infection of the upper and lower airways. The study was approved by the hospital ethical committee and all patients gave written informed consent to participate in the study.

Study design

Patients stayed in an ordinary hospital room in which no flowers or animals were allowed. After admission to the ward the 'Costa' score (see 'severity score for atopic dermatitis') was measured and a spirometric test was performed before and after inhalation of salbutamol. A methacholine inhalation challenge test followed two days later. Morning and evening peak expiratory flow (PEF) readings were recorded on a diary card. Topical treatment with tar ointment (pix liquida) and orally administered antihistamines (hydroxyzine) resulted in gradual clearing of the skin lesions. One week before discharge, when skin lesions were in remission, antihistamines were stopped. Remission was defined as a decrease in 'Costa' score from admission value of at least 20. Once again lung function was measured before and after salbutamol. Three days later a methacholine challenge was performed. The day before discharge a skin-prick titration test (see 'lung function measurements') was performed, followed by an allergen inhalation challenge 2 h later. The allergen challenge, which started at 11.00 h, was followed by PEF measurements at 10, 20, 35, 50, 65, and 80 min and every hour between 2 and 12 h. At each time point three attempts PEF measurements were done. The early asthmatic response (EAR) was defined as a fall in FEV₁ of 20% or more from the post-control value within 10–20 min after allergen exposure. The late asthmatic response (LAR) was defined as a fall in PEF of 20% or more from baseline occurring between 3 and 8 h after allergen challenge. Cutaneous responses were studied by measuring the 'Costa' score before and 24 h after allergen inhalation challenge.

Allergens

Commercial preparations of SQ 503 house dust mite (*Dermatophagoides pteronyssinus*), SQ 555 cat (*Felis catus*) and SQ 197 tree pollen (a mixture of *Alnus glutinosa*, *Betula verrucosa*, *Corylus avellana*) for inhalation challenge and skin-prick tests were obtained from Allergologisk Laboratorium Copenhagen, Denmark.

Severity score for atopic dermatitis

To evaluate the severity of atopic dermatitis we used the simple scoring system described by Costa *et al.* [22]. This method consists of scoring 10 'severity' criteria (erythema, oedema, vesicles, crusts, excoriations, scales, lichenifications, pigmentation/depigmentation, pruritus, loss of sleep) and 10 topographic sites. To evaluate each 'severity' criterion the most severely affected areas were chosen and each was scored from 0 (no lesion) to 7 (extremely severe). The following topographic sites were scored from 0 to 3 according to the extent of the involvement: five symmetrical areas: feet, knees, legs, hands, arms (one value for both) and five non-symmetrical areas: face, scalp, buttock, anterior and posterior aspects of the trunk. In order to check the reproducibility of the scoring system patients were examined independently on the same day by two physicians.

Lung function measurements

Salbutamol inhalation was stopped at least 8 h before all lung function tests. Lung function was measured with a water-filled spirometer. Bronchodilatation was measured as the increase in FEV₁ 10 min after inhalation of 400 µg salbutamol from a pressurized metered dose inhaler through a spacer device (Volumatic^R). PEF measurements were recorded with a mini-Wright peakflow meter. The best of three attempts was registered on a diary card. Airway responsiveness to methacholine was determined with a standard bronchoprovocation technique as described by Cockcroft *et al.* [23]. Briefly, an aerosol of saline followed by doubling concentrations of methacholine (0.3–76.8 mg/mL) were inhaled by tidal breathing for 2 min, and FEV₁ was measured after each inhalation. The test was discontinued if the highest concentration of methacholine was inhaled, or if the 'minimum FEV₁' was reached. This 'minimum FEV₁' was the maximum fall in FEV₁ that could be tolerated by the patients and had to be less than 50% of the predicted value. PC₂₀ methacholine was defined as the concentration of methacholine which causes a 20% fall in FEV₁ from post-saline value [24]. Antihistamines were stopped for at least 48 h prior to methacholine challenge [25]. The bronchial provocation with allergen was performed by 2 min inhalations (tidal breathing) at 10 min intervals [24]. The allergen challenge was preceded by 2 min inhalation of an initial aerosol of buffer (0.03% human serum albumin and 0.5% phenol in phosphate buffered saline) to which none of the patients reacted with a fall in FEV₁ of more than 10% from the initial value.

Increasing concentrations of antigen aerosol were delivered through a nebulizer (Model 646, DeVilbiss, Inc., Somerset, PA, USA). This nebulizer was connected to the central chamber of an in- and expiratory three-way valve

box with an expiratory aerosol filter (Sterivent Filter, DAR, Mirandola, Italy). Antigen was diluted from stock solutions (10 000 biological units/mL). The diluent was the same buffer as the negative control. The weakest allergen solution used for the first inhalation was calculated from the skin-prick titration test and the pre-antigen PC₂₀ for methacholine according to Cockcroft *et al.* [26]. Skin-prick tests were done 2 h before allergen challenge. Inhalations were performed by stepwise doubling of the dose of antigen until the FEV₁ fell at least 20% following allergen exposure. PC₂₀ allergen was defined as the concentration of allergen which causes a 20% fall in FEV₁ from post-control value.

Measurement of total and allergen specific serum IgE

Total IgE concentrations were measured using the paper-radio-immunosorbent test (PRIST, Pharmacia, Uppsala, Sweden) [27] according to the manufacturer's instructions. The results are expressed in kU/L. Specific IgE antibodies to house dust mite, cat and birch pollen allergen were measured by using the CAP method (Pharmacia, Uppsala, Sweden) [27] according to the manufacturer's instructions. The results are expressed in kU/L. No significant difference was found in serum levels of total IgE and specific IgE against the allergen used in the allergen inhalation challenge between AD⁺ and AD⁻ patients.

Statistical analysis

The baseline lung function data and the 'Costa' score are expressed as mean $\pm$ standard error of the mean (SEM). The data for total IgE, PC₂₀ Mch and PC₂₀ allergen are expressed as median values. Statistical analysis was performed using ANOVA test, Students' *t*-test or Kruskal-Wallis test for paired observations when appropriate. *P*-values below 0.05 were considered significant.

Linear regression analysis according to the least squares method was used to assess the correlation between percentage fall in PEF between 3 and 8 h after allergen inhalation challenge and changes in 'Costa' scores.

Results

Lung function measurements and methacholine challenge

Over the period when the skin lesions gradually cleared there was no significant mean increase in baseline FEV₁ in both groups (Table 2). Three AD⁺ patients showed a more than 15% increase in FEV₁. The mean early morning PEF values did not change markedly between admission and discharge (Table 2). On admission all AD⁺ patients and four out of eight AD⁻ patients showed increased BHR (PC₂₀ Mch $\leq$ 8 mg/mL, Table 2). According to Cockcroft *et al.* the

level of increased BHR was arbitrarily divided into mild (1 mg/mL < PC₂₀ Mch $\leq$ 8 mg/mL), moderate (0.125 mg/mL < PC₂₀ Mch $\leq$ 1 mg/mL) and marked (PC₂₀ Mch $\leq$ 0.125 mg/mL) [20]. Six AD⁺ patients had moderate and two had mild BHR. Four AD⁻ patients had moderate BHR and two AD⁻ patients did not respond to the highest concentration of methacholine used (PC₂₀ Mch > 76.8 mg/mL). The median value of the PC₂₀ Mch in the AD⁻ group was significantly (*P* = 0.002) higher than in the AD⁺ group. In the week before discharge, when the skin lesions were in remission, none of the patients showed a significant increase in PC₂₀ Mch. One AD⁺ patient even showed a more than 3-fold decrease in PC₂₀ Mch. All AD⁺ patients showed at least on one occasion a >10% increase in FEV₁ following 400 μ g salbutamol (not shown).

Allergen inhalation challenge

The PC₂₀ allergen is presented in Table 3. The median value of the PC₂₀ allergen was 73 and 1481 BU/mL in AD⁺ and AD⁻ patients, respectively (*P* = 0.002). All AD⁺ patients and four AD⁻ patients developed an early asthmatic response (Table 3). The mean value of the maximal fall in FEV₁ within 20 min after challenge was significantly larger in the AD⁺ group than in the AD⁻ group (*P* = 0.0006) with mean values of $36.4 \pm 2.9\%$ and $15.8 \pm 3.8\%$, respectively. After recovery of the EAR all AD⁺ patients showed a second decrease in PEF of 20% or more between 3 and 8 h after allergen challenge (Table 3), indicating the occurrence of a LAR. None of the AD⁻ patients showed a LAR.

Pulmonary symptoms after allergen inhalation challenge

A prolonged LAR with a severe episode of asthma refractory to bronchodilators was observed in one AD⁺ patient. Therefore an intramuscular injection with corticosteroids was given 24 h after the onset of the EAR. Three AD⁺ patients had an exacerbation of asthma symptoms (shortness of breath, wheezing, difficulty with expectoration) within 2 weeks after allergen challenge. They all had a fall in FEV₁ of more than 20% from baseline values, measured before discharge. One of these patients had signs of pneumonia on the chest x-ray and was treated with oral corticosteroids and antibiotics in combination with bronchodilators. The other two patients were treated with inhaled corticosteroids and bronchodilators. Within 4 weeks of treatment all patients showed significant improvement with normal lung function. During the first 2 weeks after allergen inhalation challenge all three AD⁺ patients showed only mild eczematous skin lesions with 'Costa' scores less than 18.

A tendency to a LAR and complaints of shortness of breath was seen in one AD⁻ patient. On this occasion salbutamol was used for symptomatic relief. Surprisingly

Table 2. Changes in baseline FEV₁, morning PEF rate and PC₂₀

Patient No.	Baseline FEV ₁ (% pred.)†		PEF (L/min)‡		PC ₂₀ Methacholine (mg/mL)	
	Admission	Discharge	Admission	Discharge	Admission	Discharge
AD⁺						
1	77	96	370	410	0.54	0.76
2	65	65	340	250	0.24	0.38
3	113	116	460	480	0.46	0.67
4	92	85	600	560	0.67	0.43
5	92	80	350	410	0.59	1.30
6	103	94	470	400	0.25	0.55
7	80	96	600	630	5.45	0.55
8	57	90	520	600	1.15	0.45
Mean	85	90	464	468	0.60 ^a	0.57 ^a
SEM	6.7	5.2	37	45		
AD⁻						
9	93	88	400	400	5.10	2.88
10	98	101	620	630	2.10	2.40
11	89	94	430	470	>76.80	>76.80
12	94	83	650	650	12.75	4.90
13	107	107	500	500	3.60	3.15
14	98	98	430	420	>76.80	>76.80
15	96	93	380	400	3.50	6.50
16	82	80	670	690	12.50	13.80
Mean	95	93	510	520	10.70 ^{a*}	8.91 ^{a*}
SEM	2.6	3.2	42	42		

On admission and before discharge baseline FEV₁ expressed in percentage of predicted values, morning PEF values and PC₂₀ Methacholine were measured in AD⁺ and AD⁻ patients.

† Mean of 2 respectively 3 study days after admission and before discharge (predicted values according to Quanjer [20]).

‡ Peak flow values are mean of early morning results for 7 days, after admission and before discharge.

^a Median values. PC₂₀ Methacholine >76.80 mg/mL is calculated as 76.80 mg/mL.

* Significant difference between AD⁺ and AD⁻ group ($P < 0.01$).

this patient showed no EAR and did not respond to the highest concentration of methacholine.

Cutaneous responses

Table 4 shows that there was no significant difference in 'Costa' scores between both groups at admission to the hospital and these scores improved significantly in both groups after treatment with tar ointment (pix liquida) and orally administered antihistamines. After clearing of the skin allergen inhalation challenge was performed. Cutaneous responses were studied by measuring the 'Costa' score before and 24 h after allergen challenge. The score significantly increased in all AD patients (mean score before 19.1/24.4

and after challenge 26.8/26.9 for AD⁺ and AD⁻ patients, respectively). The increase in the AD⁺ group was significantly higher compared to the AD⁻ group ($P = 0.016$). Figure 1 shows that the increase in 'Costa' score was significantly correlated to the percentage fall in PEF between 3 and 8 h after allergen challenge ($P < 0.01$).

Discussion

Our data demonstrate that clinical remission of the skin was not accompanied by a significant change in the BHR, baseline FEV₁ or PEF values of AD⁺ and AD⁻ patients. We observed no relation between the courses of AD and BHR in our patients. These results are in agreement with the

Table 3. The effects of allergen inhalation challenge on lung function

Patient No.	Allergen	PC ₂₀ allergen BU/mL	% fall in FEV ₁ from baseline	% fall in PEF from baseline	
			<20 min	<20 min	3–8 h
AD ⁺					
1	<i>D. pteronyssinus</i>	206	32	17	42
2	<i>D. pteronyssinus</i>	11	44	44	26
3	<i>D. pteronyssinus</i>	56	41	45	22
4	<i>D. pteronyssinus</i>	90	22	27	21
5	Tree pollen	21	45	35	24
6	<i>D. pteronyssinus</i>	12	33	27	29
7	<i>D. pteronyssinus</i>	137	32	14	24
8	<i>D. pteronyssinus</i>	250	43	30	30
Mean		73 ^{*a}	37*	30*	27*
SEM			2.8	4.0	2.3
AD [−]					
9	<i>D. pteronyssinus</i>	938	30	5	+5
10	<i>D. pteronyssinus</i>	1463	21	11	3
11	Cat	>1500	7	2	0
12	<i>D. pteronyssinus</i>	1153	29	21	4
13	Tree pollen	>1500	7	16	6
14	<i>D. pteronyssinus</i>	>1500	9	9	16
15	<i>D. pteronyssinus</i>	1343	22	13	8
16	<i>D. pteronyssinus</i>	>1500	3	3	2
Mean		1481 ^a	16	10	4
SEM			3.8	2.3	2.2

In AD⁺ and AD⁻ patients allergen inhalation challenge was performed with house dust mite, tree pollen or cat allergen. After challenge PC₂₀ allergen, percent fall in FEV₁ from baseline within 20 min and percent fall in PEF from baseline within 20 min and between 3 and 8 h were measured.

^aMedian values. PC₂₀ allergen >1500 BU/mL is calculated as 1500 BU/mL.

* Significant difference between AD⁺ and AD⁻ group ($P < 0.01$).

findings of Fabrizi *et al.* who observed no clear relation between the activity of AD and pulmonary symptoms in nine skin test-positive subjects [3]. In his and our study the activity of AD and pulmonary symptoms tended to alternate [3]. In contrast to their study, we investigated our patients in a clinical setting. All patients stayed in 'dust free' hospital rooms, which had low allergen levels compared with the bedrooms in the patients' own houses. In a previous report, Platts-Mills *et al.* showed that avoidance of relevant allergens resulted in reduction in BHR and improvement in PEF values in seven asthmatic patients without AD [28]. This reduction could be found after 5 weeks' hospital stay. In contrast to their report we found no change in BHR. This suggests that the course of BHR and PEF values in pure allergic asthma patients differs from those of allergic

asthma patients with severe AD in an environment with low allergen levels. Improvement of skin symptoms in AD does not parallel the course of BHR.

The results of the present study clearly show that in AD patients the presence of asthmatic episodes, including development of both early and late allergic responses upon challenge, is not correlated with the level of total serum IgE [29]. The allergen specific serum IgE level was >100 kU/L in all AD⁺ patients. All AD⁺ patients showed a LAR on which occasion salbutamol was used for symptomatic relief. Our data support the hypothesis of Dohi *et al.* that a certain level of BHR in AD is a prerequisite for the induction of a LAR [29]. The fact that four AD⁺ patients had an exacerbation of their asthma after allergen inhalation challenge, which had to be treated with corticosteroids, implies that

Table 4. Changes in Costa score

Patient no.	Costa score		
	Admission	Before challenge	24 h After challenge
AD⁺			
1	61	14	22
2	60	16	22 ^a
3	62	28	35 ^a
4	62	23	30
5	61	26	34
6	58	16	21
7	48	10	12
8	58	20	38 ^a
Mean	58.8	19.1	26.8**
SEM	1.6	2.2	3.1
AD⁻			
9	48	22	21
10	69	22	27
11	68	25	28
12	65	41	41
13	64	26	30
14	58	17	23
15	42	20	23
16	70	22	22
Mean	60.5	24.4	26.9*
SEM	3.7	2.6	2.3

Costa scores were measured in all patients on admission, before allergen inhalation challenge and 24 h after challenge.

^a Reactivation of skin-prick test 24 h after allergen inhalation challenge (late phase reaction).

* $P < 0.05$; ** $P < 0.01$ significant difference as compared to before challenge.

these patients are at risk for developing prolonged severe asthma following allergen exposure.

The 'Costa' score increased significantly in all AD patients after allergen inhalation challenge. The significant increase of the 'Costa' score in the AD⁺ group compared to the AD⁻ group, suggests that the presence of allergic asthma aggravates the development of skin lesions after inhalation of allergens. Allergic asthma is characterized by airway inflammation even in patients with mild disease [30]. The LAR is a manifestation of underlying airway inflammation [31] and was found in all AD⁺ patients. The relation between airway inflammation, caused by allergen inhalation, and the development of skin lesions is illustrated by the correlation we found between percentage fall in PEF between 3 and 8 h after allergen inhalation challenge and

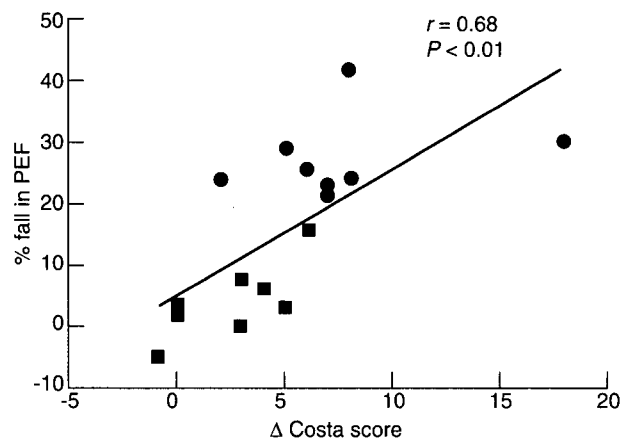


Fig. 1. Correlation between percentage fall PEF and change in 'Costa' score. The change in 'Costa' score 24 h after allergen inhalation challenge is correlated to the percentage fall in PEF between 3 and 8 h after challenge. ●, AD⁺ patients; ■, AD⁻ patients. The values were statistically significant as determined by linear regression analysis according to the least squares method, ($P < 0.01$, $r = 0.68$).

increase in 'Costa' score. Our findings are of practical importance as they indicate that allergens can induce skin lesions in AD via inhalation. The mechanism underlying the linkage between allergen inhalation and flare up of AD is unknown. Possibly, as a consequence of allergen induced inflammation in the airways, diffusible inflammatory mediators, such as cytokines, may transfer the allergic reaction to the skin. Indeed increased levels of GM-CSF and IL-5 have been detected in bronchoalveolar lavage fluid from allergic rhinitis [32,33] and allergic asthmatic patients [34,35] obtained at 48 h after segmental allergen bronchoprovocation (late response) as reviewed elsewhere [36]. Alternatively, a flare up of AD may be caused by allergens that enter the circulation and are transported to the skin. This may occur as free allergens but more likely in complex with IgE and/or processed by dendritic cells which migrate to the skin. The increase of the 'Costa' score in the AD⁺ group as a consequence of psychological stress due to nocturnal dyspnoea cannot be excluded. However, in that case one would expect a parallel between cutaneous and pulmonary symptoms during the clinical course of the atopic diseases of these patients. In addition methacholine induced dyspnoea did not cause any changes in 'Costa' score in both AD⁺ and AD⁻ patients (results not shown). Furthermore, it is not possible to exclude this phenomenon using a placebo control, since a placebo is needed which would induce pulmonary symptoms during 12 h after challenge. In that case however, skin symptoms might still be induced by an increase of soluble mediators entering the circulation and affecting the skin.

In conclusion we found no clear relation between BHR and the activity of AD. Over the period when skin lesions

gradually cleared there was no significant change in mean baseline FEV₁. All AD⁺ patients showed dual asthmatic responses after allergen inhalation challenge. Four of these patients had an exacerbation of their asthma after allergen challenge, which was successfully treated with corticosteroids. Our findings showed that allergens can induce skin lesions in AD via inhalation, and that AD⁺ patients develop skin lesions after allergen inhalation challenge more easily than AD⁻ patients.

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References

- 1 Queille-Roussel C, Raynaud F, Saurat J-H. A prospective computerized study of 500 cases of atopic dermatitis in childhood. *Acta Derm Venereol* (Stockh) 1985; Suppl. 114: 87-92.
- 2 Musgrove K, Morgan JK. Infantile eczema. A long-term follow-up study. *Br J Dermatol* 1976; 95:365-72.
- 3 Fabrizi G, Corbo GM, Ferrante E et al. The relationship between allergy, clinical symptoms and bronchial responsiveness in atopic dermatitis. *Acta Derm Venereol* (Stockh) 1992; Suppl. 176:68-73.
- 4 Corbo GM, Ferrante E, Macciocchi B et al. Bronchial hyperresponsiveness in atopic dermatitis. *Allergy* 1989; 44:595-8.
- 5 Kaliner M. The cholinergic nervous system and immediate hypersensitivity. *J Allergy Clin Immunol* 1976; 58:308-15.
- 6 De Monchy JGR, Kauffman HF, Venge P et al. Broncho-alveolar eosinophilia during allergen-induced late asthmatic reactions. *Am Rev Respir Dis* 1985; 131:373-6.
- 7 Cockcroft DW, Murdock KY. Comparative effects of inhaled salbutamol, sodium cromoglycate, and beclomethasone dipropionate on allergen-induced early asthmatic responses, late asthmatic responses, and increased bronchial responsiveness to histamine. *J Allergy Clin Immunol* 1987; 79:734-40.
- 8 Bruijnzeel-Koomen CAFM, Van Wichen DF, Toonstra J, Berrens L, Bruijnzeel PLB. The presence of IgE molecules on epidermal Langerhans cells from patients with atopic dermatitis. *Arch Derm Res* 1986; 278:199-205.
- 9 Ramb-Lindhauer C, Feldmann A, Rotte M, Neumann C. Characterization of grass pollenreactive T cell lines derived from lesional atopic skin. *Arch Derm Res* 1991; 283:71-6.
- 10 Van der Heijden FL, Wierenga EA, Bos JD, Kapsenberg ML. High frequency of IL-4-producing CD4⁺ allergen-specific T lymphocytes in atopic dermatitis lesional skin. *J Invest Dermatol* 1991; 97:389-94.
- 11 Tan BB, Weald D, Strickland I, Friedmann PS. Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. *Lancet* 1996; 347:15-8.
- 12 Langeveld-Wildschut EG, van Marion AMW, Thepen T, Mudde GC, Bruijnzeel PLB, Bruijnzeel-Koomen CAFM. Evaluation of variables influencing the outcome of the atopy patch test. *J Allergy Clin Immunol* 1995; 96:66-73.
- 13 Rajka G. Delayed dermal and epidermal reactivity in atopic dermatitis. *Acta Derm Venereol* (Stockh) 1967; 47:158-62.
- 14 Butler JM, Peters JE, Hirschman CA, White CR Jr, Margolin LB, Hanifin JM. Pruritic dermatitis in asthmatic basenji-greyhound dogs: a model for human atopic dermatitis. *J Am Acad Dermatol* 1983; 8:33-8.
- 15 Chapman MD, Rowntree S, Mitchell EB, Di Prisco de Fuenmajor MC, Platts-Mills TAE. Quantitative assessments of IgG and IgE antibodies to inhalant allergens in patients with atopic dermatitis. *J Allergy Clin Immunol* 1983; 72:27-33.
- 16 Leung DYM, Geha RS. Immunoregulatory abnormalities in atopic dermatitis. *Clin Rev Allergy* 1986; 4:67-86.
- 17 Brocq L. Conception générale des dermatoses, nouvelle note sur leur classification. *Ann Dermatol Syphiligr* 1927; 8:65.
- 18 Rajka G. Clinical aspects. In: Rajka G, ed. *Essential aspects of atopic dermatitis*. Berlin, Heidelberg: Springer Verlag, 1989, 4-55.
- 19 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987; 136:225-44.
- 20 Quanjer PhH. Standardized lung function testing. Report working party standardization of lung function tests, European community for steel and coal. *Eur Respir J* 1993; 6, Suppl. 16:5-100.
- 21 Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* (Stockh) 1980; Suppl. 92:44-7.
- 22 Costa C, Rilliet A, Nicolet M, Saurat JH. Scoring atopic dermatitis: the simpler the better? *Acta Derm Venereol* (Stockh) 1989; 69:41-5.
- 23 Cockcroft DW, Killian DN, Mellon JJ, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977; 7:235-43.
- 24 Sterk PJ, Fabbri LM, Quanjer PhH et al. Airway responsiveness: standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. *Eur Respir J* 1993; 6, Suppl. 16:53-83.
- 25 Juniper EF, Frith PA, Dunnett C, Cockcroft DW, Hargreave FE. Reproducibility and comparison of responses to inhaled histamine and methacholine. *Thorax* 1978; 33:705-10.
- 26 Cockcroft DW, Murdock KY, Kirby J, Hargreave F. Prediction of airway responsiveness to allergen from skin sensitivity to allergen and airway responsiveness to histamine. *Am Rev Respir Dis* 1987; 135:264-7.
- 27 Bousquet J, Chané P, Chanal I, Michel FB. Comparison between RAST and Pharmacia CAP system: a new automated specific IgE assay. *J Allergy Clin Immunol* 1990; 85:1039-43.
- 28 Platts-Mills TAE, Tovey ER, Mitchell EB, Moszoro H, Nock P, Wilkins SR. Reduction of bronchial hyperreactivity during prolonged allergen avoidance. *Lancet* 1982; ii:675-8.
- 29 Dohi M, Okudaira H, Sugiyama H et al. Bronchial responsiveness to mite allergen in atopic dermatitis without asthma. *Int Arch Allergy Appl Immunol* 1990; 92:138-42.
- 30 Beasley R, Roche WR, Roberts JA, Holgate ST. Cellular

- events in the bronchi in mild asthma and after bronchial provocation. *Am Rev Respir Dis* 1989; 139:806–17.
- 31 Cockcroft DW. Bronchial inhalation tests II. Measurement of allergic (and occupational) bronchial responsiveness. *Ann Allergy* 1987; 59:89–98.
- 32 Ohnishi T, Kita H, Weiler D et al. IL-5 is the predominant eosinophil-active cytokine in the antigen-induced pulmonary late-phase reaction. *Am Rev Respir Dis* 1993; 147:901–7.
- 33 Sedgwick JB, Calhoun WJ, Gleich GJ et al. Immediate and late airway response of allergic rhinitis patients to segmental antigen challenge. *Am Rev Respir Dis* 1991; 144:1274–81.
- 34 Broide DH, Gleich GJ, Cuomo AJ, Coburn DA et al. Evidence of ongoing mast cell and eosinophil degranulation in symptomatic asthma airway. *J Allergy Clin Immunol* 1991; 88:637–48.
- 35 Sur S, Hunt LW, Weiler DA, Ohnishi T, Gleich GJ. In vitro release of eosinophil active cytokines from airway dwelling cells (abstract). *J Allergy Clin Immunol* 1992; 89:215.
- 36 Smith DL, Deshazo RD. Bronchialveolar lavage in asthma. *Am Rev Respir Dis* 1993; 148:523–32.

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