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ORIGINAL ARTICLE

Atopy patch testing with aeroallergens in a large clinical population of dermatitis patients in Germany and Switzerland, 2000-2015: a retrospective multicentre study

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Abstract

Background The diagnostic significance of the atopy patch test for the management of dermatitis possibly triggered by aeroallergens is still controversial. However, sufficiently large studies with routinely tested standardized aeroallergen patch test preparations in dermatitis patients are lacking.

Objective To evaluate the reaction frequency and the reaction profiles of 10 until mid-2015 commercially available, standardized aeroallergen patch test preparations of the 'Stallerpatch' test series (Stallergenes, Antony Cedex, France) in a large multicentre patient cohort.

Methods A retrospective data analysis of patients with suspected aeroallergen-dependent eczematous skin lesions was performed, who were patch tested in 15 Information Network of Departments of Dermatology-associated clinics between 2000 and 2015. Patients were stratified according to their atopic dermatitis (AD) status.

Results The study group included 3676 patients (median age 41 years, 34.8% males, 54.5% AD). The most common aeroallergens causing positive patch test reactions were Dermatophagoides pteronyssinus (19.6%), Dermatophagoides farinae (16.9%), birch (6.2%), timothy grass (6.0%), cat dander (5.4%), mugwort (4.9%) and dog dander (4.6%). Reactions to other pollen allergen preparations, that is 5 grasses (3.2%), cocksfoot (2.1%) and plantain (1.6%), were less common. Positive patch test reactions to aeroallergens were consistently more frequent in patients with AD. These patients showed proportionally less dubious, follicular, irritant and weak positive reactions. Independent of AD status, a patient history of past or present allergic rhinitis was associated with an increased chance of a positive aeroallergen patch test reaction to pollen allergens.

Conclusion The aeroallergen patch test is a useful add-on tool in clinical routine, especially in patients with AD and/or respiratory allergy. A patch test series comprising Dermatophagoides pteronyssinus, Dermatophagoides farinae, birch, timothy grass, cat dander and mugwort seems to be suitable. Controlled studies with specific

provocation and elimination procedures are required to further evaluate the diagnostic significance of the proposed screening series.

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Introduction

Intact protein allergens, which include both a wide variety of aeroallergens and food allergens, can cause, maintain or exacerbate skin diseases such as various types of contact dermatitis or atopic dermatitis (AD).[1–6] The first documented patch tests with aeroallergens in different groups of dermatitis patients were performed by Rostenberg and Sulzberger[7] in 1937. In 1982, Mitchell *et al.*[8] described in more detail that aeroallergen patch test preparations such as Dermatophagoides (D.) pteronyssinus antigen P_1, which normally cause allergic reactions of the immediate type, can also lead to late eczematous skin reactions when applied to the skin of atopic patients for 48 h. They found that a prolonged epicutaneous application of aeroallergens could cause an exacerbation of the existing atopic skin disease. This finding marked the beginning of the development of the 1989 modified patch test called 'atopy patch test' by Ring *et al.*,[9] which was further standardized and validated, and has since been used predominantly, though not exclusively,[10] for diagnosing eczema-worsening by aeroallergens or food allergens in patients with AD.[11–17]

The diagnostic significance of aeroallergen patch testing for the evaluation of triggering factors of eczema in consecutive patients is still controversial.[7,18–21] However, there is probably an underestimation of the prevalence of aeroallergen sensitization that causes, maintains or exacerbates eczematous skin lesions.[2,22] Ultimately, the identification and elimination of responsible aeroallergens, exemplarily with regard to house dust mites (HDMs),[23] have been found to be a crucial prerequisite for disease treatment that can result in marked and sustainable improvement of the skin symptoms.[19,24,25] Thus, there is an ongoing need for research on the routine use of patch testing in larger numbers of patients with suspected aeroallergen-triggered dermatitis.[25–28]

The present retrospective multicentre study aimed to evaluate the reaction frequency and diagnostic significance of 10 formerly commercially available and biologically standardized[29] aeroallergen patch test preparations ('Stallerpatch'; Stallergenes, Antony Cedex, France; Table 1) in 3676 patients undergoing standard patch testing for suspected allergic contact dermatitis and in which an involvement of aeroallergens in the skin lesions was additionally assumed. To the best of our knowledge, studies with a comparably large number of dermatitis patients and standardized aeroallergen patch test preparations are still lacking, even though the atopy patch test methodology has been evaluated in several hundred patients with AD.[30] As a secondary aim, aeroallergen patch test reaction profiles, that is irritant ('IR'), follicular ('f'), doubtful ('?+'), weak ('+') and strong positive reactions ('++' and '+++'), were described and analysed by use of the reaction index (RI)[31] and the positivity ratio (PR).[32] As of now, data on these evaluation parameters of aeroallergen patch test preparations have also been missing, an exception being Brasch *et al.*,[20] who reported a RI of 0.76 for the Dermatophagoides mix 20% in petrolatum (pet.; Chemotechnique Diagnostics, Vellinge, Sweden).

Methods

Study design

For this retrospective multicentre data analysis, we retrieved patch test data of 15 IVDK ('Information Network of

Table 1 Aeroallergens of the patch test series 'Stallerpatch'†

Test allergen	Concentration standardized in biologic unit[29]	Vehicle
Mites		
D. farinae	200 IR/mL	pet.
D. pteronyssinus	200 IR/mL	pet.
Epithelia		
Cat dander	200 IR/mL	pet.
Dog dander	200 IR/mL	pet.
Weed pollen		
Mugwort	200 IR/mL	pet.
Plantain	500 IC/mL	pet.
Tree pollen		
Birch	200 IR/mL	pet.
Grass pollen		
Cocksfoot	200 IR/mL	pet.
Timothy grass	200 IR/mL	pet.
5 grasses	200 IR/mL	pet.

†Stallerpatch, distributed by Stallergenes (Antony Cedex, France) until 31 July 2015.
D., Dermatophagoides; IC, index of concentration; IR, index of reactivity; pet., petrolatum.

Departments of Dermatology')-associated clinics from the IVDK database.[33]

Data collection and management Patients' histories including indications for patch testing, clinical data and patch test results of all patients patch tested in the participating clinics are documented in a standardized way, recorded in local databases and, after pseudonymization, transmitted to the IVDK central office at the University of Göttingen, twice a year.[34,35] Data on skin prick tests, intradermal skin tests and IgE tests are not recorded in the IVDK data documentation system and can therefore not be analysed.

Patient selection

Between 2000 and 2015, a total of 59 174 dermatitis patients (median age 50 years, range 5–85 years; 21 732 males) were consecutively patch tested in the 15 IVDK-associated clinics with the DKG baseline series and relevant supplements. In 3676 patients (median age 41 years, range 6–80 years; 1279 males), patch tests with aeroallergen preparations from the Stallerpatch (Table 1) were simultaneously performed on the macroscopically normal-appearing skin of the back. Indication for aeroallergen patch testing was the suspicion of aeroallergen-dependent skin lesions, independent of the type of dermatitis. This subcohort of patients formed the study group for the present analysis.

Atopy patch testing with aeroallergens

Patch testing and evaluation of reactions were performed according to DKG guidelines.[36,37] For this data analysis, patch test reactions on D3 were taken into account. In a few exceptional cases (<5%), when a reading was performed on D4 instead of D3, this reading was selected. Readings coded as '+', '++' or '+++', that is, positive reactions, according to the ICDRG ('International Contact Dermatitis Research Group') scoring system,[38] with erythema, infiltration, papules and/or (coalescing) vesicles were rated as positive in dichotomized analyses if not otherwise indicated. Aeroallergen patch test preparations were manufactured and marketed by Stallergenes until 31 July 2015. Patch test exposure time was 48 h in 88.6% of patients (n = 3258) and 24 h in 11.4% of patients (n = 418). With only a few exceptions (n = 167 patients, 4.5%), depending on the applicable clinic standard, large (inner diameter 12 mm; n = 2810 patients, 76.4%) and small (inner diameter 8 mm; n = 699 patients, 19.0%) Finn Chambers® on Scanpor® tape (Epitest Ltd Oy, Tuusula, Finland) were used as test chambers. In the exceptional cases, IQ Chambers™(Chemotechnique Diagnostics) were used. As an irritant control, sodium lauryl sulphate (SLS) 0.25% in water was additionally tested in 2717 patients (73.9%).[39] An irritant reaction to SLS generally indicates increased skin irritability of the patch test site at the time of testing,[40] meaning that doubtful or weak positive reactions to allergen patch test preparations are more likely to be irritant and not allergic in nature.

Statistical analysis

For descriptive purposes, we report categorical variables as absolute and relative frequencies and continuous variables as the median and range (minimum, maximum). The statistical significance ($P < 0.05$) of differences in demographic and clinical characteristics of disjunct patient groups was determined by non-overlapping 95% confidence intervals (CIs). Non-overlapping of 95% CIs was also used for assessing significance of differences in crude sensitization frequencies. We stratified for AD. Patients were classified as past or present AD patients based on common diagnostic criteria.[41]

To assess the reaction profiles – and thus diagnostic accuracy – of aeroallergen patch test preparations, we used the RI[31,42] in combination with the PR.[32] Non-overlapping 95% CIs were used for the comparison of RIs and PRs. Patch test preparations with a negative RI and a PR of ≥ 80% have a comparably low diagnostic accuracy as far as identification of true allergic reactions is concerned.[32]

Beyond atopic dermatitis, occurrence of positive patch test reactions to aeroallergens may be influenced by other clinical patient characteristics and by methodological aspects. In order to estimate the impact of these factors on the aeroallergen patch test outcome, we performed logistic regression analyses with positive aeroallergen patch test reactions as target (dependent) variables and 7 dichotomized explanatory (independent) variables. These were 'past or present allergic rhinitis' (AR), 'past or present allergic asthma' (AA), 'dermatitis in air-exposed skin areas (face, neck, forearms, hands)' (AEA), 'polysensitization, meaning sensitization to three or more independent contact allergens of the DKG baseline series' (POLY),[43] 'irritant patch test reaction to SLS' (SLS), 'patch test exposure time of 2 days' (E2D) and 'use of large Finn Chambers®' (LFC). The logistic regression model used was assessed for goodness of fit by the Hosmer–Lemeshow test ($P > 0.05$).[44] Results are presented as odds ratio (OR) estimates with 95% CIs (profile likelihood method).

Data were managed and analysed with the statistical software package SAS® (SAS Institute, Cary, NC, USA), version 9.4.

Ethical approval

The amended study protocol was subjected to review and approved by the ethics committee of the Medical Faculty of the Ruhr University Bochum (registration no. 15–5199; first positive vote dated 25 February 2015; amendment dated 20 July 2016).

Results

Routinely collected patch test data from 12 dermatology clinics in Germany and 3 dermatology clinics in Switzerland were included in the study.

Patients' demographics and clinical characteristics

Demographic and clinical characteristics according to the MOAHLFA index[45] of all patch tested patients are shown in Table 2. Patients of the study group (n = 3676; 6.2%), who were patch tested with aeroallergens, showed a higher proportion of women and were remarkably younger and more likely to have a past or present history of AD and a facial dermatitis than the vast majority of patients (n = 55 498; 93.8%) who had undergone conventional patch tests with contact allergens, but not with aeroallergens. The last two observations will at least in part be due to the indication for atopy patch testing with aeroallergens. When the study group was further stratified by AD status, there was a fairly uniform distribution of the characteristics in both subgroups, except that the patients with AD were remarkably younger.

Aeroallergen patch test results

In the study group, positive patch test reactions to D. pteronyssinus (19.6%, 95% CI: 18.3–21.0%) and D. farinae (16.9%, 95% CI: 15.6–18.3%) were most frequently observed, followed by positive patch test reactions to birch (6.2%, 95% CI: 5.4–7.1%), timothy grass (6.0%, 95% CI: 5.1–6.9%), cat dander (5.4%, 95% CI: 4.7–6.2%), mugwort (4.9%, 95% CI: 4.2–5.7%), dog dander (4.6%, 95% CI: 3.6–5.8%), 5 grasses (3.2%, 95% CI: 2.2–4.5%), cocksfoot (2.1%, 95% CI: 1.3–3.3%) and plantain (1.6%, 95% CI: 1.0–2.4%).

Table 3 shows the distribution of reactions to aeroallergens in the study group stratified by past or present AD. Crude percentages of positive reactions, RIs and PRs are delineated. In both subgroups, positive reactions were most frequently observed to the HDMs. Without exception, the relative reaction frequencies in the patient subgroup with AD were higher, although not significant for plantain, cocksfoot and 5 grasses. These three allergens generally presented the lowest absolute and relative reaction frequencies. Of all aeroallergen patch test preparations, RIs were lower and PRs were higher in the patients without AD, which may indicate that a considerable proportion of the doubtful and weak positive reactions in this subgroup of patients are irritant, and not allergic, reactions. This phenomenon was particularly pronounced in cat dander and pollen of mugwort, plantain, birch, cocksfoot, timothy grass and 5 grasses.

Distribution of the explanatory variables used in the logistic regression analyses in both subgroups is shown in Table 4. Atopic respiratory diseases (AR and/or AA) and irritant patch test reactions to SLS were significantly more common in the patient group with AD. In contrast, involvement of air-exposed skin areas, polysensitization and patch test exposure time of 2 days were quite equally distributed. In the patient group without AD, large Finn Chambers® were used somewhat more frequently. Stratified by AD, ORs as results of multivariate logistic regression analyses are given in Tables S1 and S2, with positive aeroallergen patch test reactions as target variables and the 7 abovementioned items as explanatory variables. In addition, ORs as results of univariate calculations are displayed to show the influence of every single explanatory variable, without adjusting for the others. In the subgroup of patients with AD (Table S1), the use of large Finn Chambers® or patch test exposure for 2 days exhibited the strongest impact of all independent variables in all aeroallergens analysed, with ORs ranging from 3.31 to 9.44 and from 1.76 to 3.62, respectively. Allergic rhinitis significantly increased the chance of a positive aeroallergen patch test reaction to mugwort, birch and timothy grass, with ORs ranging from 1.88 to 2.77. In contrast, allergic asthma did not increase the chance of a positive aeroallergen patch test reaction. Polysensitization to three or more haptens predisposed to positive patch test reactions to cat dander and birch. Increased skin irritability as indicated by a positive (irritant) patch test with SLS increased

Table 2 Demographic and clinical characteristics according to the MOAHLFA index† of patients patch tested with the DKG baseline series and relevant supplements in 15 IVDK-associated clinics between 2000 and 2015, stratified by aeroallergen patch test and stratified by past or present AD; total number of patients = 59 174

Patients	Aeroallergen patch test not performed		Aeroallergen patch test performed		Aeroallergen patch test performed; AD		Aeroallergen patch test performed; no AD	
Total tested	55 498		3676		2005		1671	
Parameters	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)
M	20 453	36.9 (36.5, 37.3)	1279	34.8 (33.3, 36.4)	677	33.8 (31.7, 35.9)	602	36.0 (33.7, 38.4)
O	9062	16.3 (16.0, 16.6)	577	15.7 (14.5, 16.9)	272	13.6 (12.1, 15.1)	305	18.3 (16.4, 20.2)
A	10 315	18.6 (18.3, 18.9)	2005	54.5 (52.9, 56.2)	2005‡		0‡	
H	15 290	27.6 (27.2, 27.9)	999	27.2 (25.7, 28.6)	517	25.8 (23.9, 27.8)	482	28.8 (26.7, 31.1)
L	5351	9.6 (9.4, 9.9)	74	2.0 (1.6, 2.5)	32	1.6 (1.1, 2.2)	42	2.5 (1.8, 3.4)
F	8543	15.4 (15.1, 15.7)	1167	31.7 (30.2, 33.3)	640	31.9 (29.9, 34.0)	527	31.5 (29.3, 33.8)
A	39 436	71.1 (70.7, 71.4)	1927	52.4 (50.8, 54.0)	808	40.3 (38.1, 42.5)	1119	67.0 (64.7, 69.2)

†MOAHLFA index: 'M' male, 'O' occupational dermatitis, 'A' atopic dermatitis (past or present), 'H' hand dermatitis, 'L' leg dermatitis, 'F' face dermatitis, 'A' age ≥ 40 years. ‡By stratification.

AD, atopic dermatitis; CI, confidence interval; DKG, German Contact Dermatitis Research Group; IVDK, Information Network of Departments of Dermatology.

Table 3 Patch test results based on reactions at D3 (or D4 in exceptional cases) in 3676 patients tested with aeroallergens from the patch test series 'Stallerpatch', stratified by past or present AD

Test allergen	*n* tested	*n* negative	?+	f	+	++	+++	IR	% crude positive (95% CI)	RI (95% CI)	PR [%] (95% CI)
Perennial											
D. farinae											
with AD	1443	1079	67	7	221	60	8	1	20.0 (18.0, 22.2)	0.6 (0.5, 0.7)	76.5 (71.1, 81.2)
without AD	1463	1157	68	24	168	33	2	11	13.9 (12.1, 15.8)	0.3 (0.2, 0.4)	82.8 (76.8, 87.7)
D. pteronyssinus											
with AD	1964	1441	66	17	329	93	12	6	22.1 (20.3, 24.0)	0.7 (0.6, 0.7)	75.8 (71.5, 79.8)
without AD	1643	1262	73	25	230	43	1	9	16.7 (14.9, 18.6)	0.4 (0.3, 0.5)	83.9 (79.0, 88.1)
Cat dander											
with AD	1988	1776	42	3	133	26	4	4	8.2 (7.0, 9.5)	0.5 (0.4, 0.7)	81.6 (74.8, 87.2)
without AD	1658	1565	36	15	33	1	1	7	2.1 (1.5, 2.9)	−0.2 (−0.4, −0.1)	94.3 (80.8, 99.3)
Dog dander											
with AD	794	728	8	0	43	14	1	0	7.3 (5.6, 9.3)	0.8 (0.6, 0.9)	74.1 (61.0, 84.7)
without AD	702	683	6	0	11	0	0	2	1.6 (0.8, 2.8)	0.2 (−0.3, 0.6)	100 (71.5, 100)
Seasonal											
Mugwort											
with AD	1743	1568	40	7	108	15	2	3	7.2 (6.0, 8.5)	0.4 (0.3, 0.6)	86.4 (79.1, 91.9)
without AD	1494	1408	39	6	33	1	0	7	2.3 (1.6, 3.2)	−0.2 (−0.4, 0.0)	97.1 (84.7, 99.9)
Plantain											
with AD	673	648	9	0	11	3	1	1	2.2 (1.3, 3.6)	0.2 (−0.2, 0.6)	73.3 (44.9, 92.2)
without AD	591	579	5	0	4	1	0	2	0.8 (0.3, 2.0)	−0.2 (−0.7, 0.4)	80.0 (28.4, 99.5)
Birch											
with AD	1776	1563	50	9	127	21	1	5	8.4 (7.1, 9.8)	0.4 (0.3, 0.5)	85.2 (78.5, 90.5)
without AD	1497	1391	43	6	47	6	0	4	3.5 (2.7, 4.6)	0.0 (−0.2, 0.2)	88.7 (77.0, 95.7)
Cocksfoot											
with AD	449	424	10	0	12	3	0	0	3.3 (1.9, 5.5)	0.2 (−0.2, 0.6)	80.0 (51.9, 95.7)
without AD	441	427	8	0	4	0	0	2	0.9 (0.2, 2.3)	−0.4 (−0.9, 0.0)	100 (39.8, 100)
Timothy grass											
with AD	1449	1271	35	7	109	21	4	2	9.2 (7.8, 10.9)	0.5 (0.4, 0.6)	81.3 (73.7, 87.5)
without AD	1319	1239	38	7	30	1	0	4	2.4 (1.6, 3.3)	−0.2 (−0.4, 0.0)	96.8 (83.3, 99.9)
5 grasses											
with AD	577	538	13	0	23	2	0	1	4.3 (2.8, 6.3)	0.3 (−0.0, 0.6)	92.0 (74.0, 99.0)
without AD	400	386	5	0	6	0	0	3	1.5 (0.6, 3.2)	−0.1 (−0.7, 0.4)	100 (54.1, 100)

AD, atopic dermatitis; CI, confidence interval; D, day; D., Dermatophagoides; f, follicular reaction (considered to be doubtful); IR, irritant reaction; PR, positivity ratio; RI, reaction index; ?+, doubtful reaction.

the chance of a positive aeroallergen patch test reaction to mugwort and cat dander, and, most prominently, to dog dander. Remarkably, dermatitis involvement of air-exposed skin areas did not significantly increase the chance of a positive aeroallergen patch test reaction to any of the aeroallergens listed. In the subgroup of patients without AD (Table S2), fewer significant ORs were found. Patients with allergic rhinitis had a significantly increased chance of a positive aeroallergen patch test reaction to both HDMs, mugwort and birch, while allergic asthma, dermatitis involvement of air-exposed skin areas and polysensitization to three or more haptens had no significant impact. Patients reacting to SLS had an increased chance of reacting to birch in the aeroallergen patch test. Aeroallergen patch test exposure for 2 days and the use of large Finn Chambers®, respectively, increased the chance of a positive test reaction to both HDMs. The latter explanatory variable also increased the chance of a positive test reaction to mugwort.

Discussion

This retrospective multicentre study investigated, for the first time, the reaction frequency to a standardized patch test series with aeroallergens in a sufficiently powered cohort. We took a closer look at the study population and factors most likely influencing the patch test outcome to interpret results. Our findings revealed that the most frequent aeroallergen group causing positive patch test reactions was by far HDM, followed by pollen and pet dander.[11] In line with other studies,[11,12,46,47] we could not observe a significant positive association between eczema in

Table 4 Seven additional factors† possibly associated with the aeroallergen patch test outcome, and used in logistic regression analyses, stratified by past or present AD; total number of patients = 3676

Patients	Aeroallergen patch test performed; AD		Aeroallergen patch test performed; no AD	
Total tested	**2005**		**1671**	
Parameters	***n***	**% (95% CI)**	***n***	**% (95% CI)**
AR	1030	51.4 (49.2, 53.6)	342	20.5 (18.6, 22.5)
AA	385	19.2 (17.5, 21.0)	108	6.5 (5.3, 7.8)
AEA	1206	60.1 (58.0, 62.3)	1054	63.1 (60.7, 65.4)
POLY	221	11.0 (9.7, 12.5)	181	10.8 (9.4, 12.4)
SLS	300 (out of 1449)	20.7 (18.6, 22.9)	202 (out of 1268)	15.9 (14.0, 18.1)
E2D	1782	88.9 (87.4, 90.2)	1476	88.3 (86.7, 89.8)
LFC	1495	74.6 (72.6, 76.5)	1315	78.7 (76.7, 80.6)

†Factors: 'AA' allergic asthma (past or present), 'AEA' air-exposed skin areas (face, neck, forearms, hands) involved, 'AR' allergic rhinitis (past or present), 'E2D' patch test exposure time of 2 days, 'LFC' use of large Finn Chambers®, 'POLY' polysensitization to three or more independent allergens (haptens) of the DKG baseline series, 'SLS' irritant patch test reaction to sodium lauryl sulphate 0.25% aqueous.
AD, atopic dermatitis; CI, confidence interval.

typical air-exposed skin areas and a positive aeroallergen patch test result, but this does not seem to be easily generalizable.[14,48] On the one hand, the contradictory study situation on this point could be explained by a selection bias in larger multicentre studies,[11,12] that is patients with a predominantly air-exposed eczema distribution pattern and patients with eczematous skin lesions which exceeded the air-exposed areas are not separated in the subgroup.[14] On the other hand, it is our experience that some patients also report the worsening or a flare-up of eczematous lesions in non-air-exposed skin areas during the pollen season. Patch tests with 5 grasses, cocksfoot and plantain seem to be dispensable in the future. In broader routine use, the atopy patch test with aeroallergens may be of diagnostic significance, especially in patients with AD and, independently of that, also in patients with AR, which makes the name 'atopy patch test'[9] even more adequate.

The present study showed once again that patch test reactions to aeroallergens can also be observed in patients without AD, although the frequency of these reactions is considerably lower compared to AD patients.[19,21,46,49] So far, however, the problem of atopy patch testing with aeroallergens in patients without AD has been insufficiently investigated and has shown contradictory results. In contrast to our results, Brasch *et al.*[20] reported in a single-centre analysis that positive responses to the Dermatophagoides mix did occur with similar frequency in patients with and without AD, whereas other study groups had not described a single positive patch test response to distinct aeroallergens in patients without AD.[15,16] An increased aeroallergen responsiveness in patients with AD might be mediated by a combination of increased epidermal penetration through the impaired physical barrier and steady-state inflammation found in, for example filaggrin (FLG) and/or hornerin (Hrnr) deficient skin.[50–52] The possible result is an increased access of aeroallergens to Langerhans and inflammatory dendritic epidermal cells with a selective upregulation of the T_h2 immune response.[2,4,53,54]

As patients with AD tend to have more frequent irritant or false-positive reactions to commonly tested haptens,[55–58] it was of special importance to assess the reaction profiles of the distinct aeroallergen patch test preparations. Unexpectedly, considerably more unwanted and weak positive reactions were found in the patient subgroup without AD. However, this is in line with previous study results of Seidenari *et al.*,[19] where non-AD patients showed a lower patch test reaction strength to two Dermatophagoides mixes at different concentrations than AD patients. One explanation could be that patients with epidermal deficiency of, for example, FLG and/or Hrnr exhibit not only more, but also a stronger patch test reaction to aeroallergens.[50,57] Thus, these results speak against the generalizing interpretation of aeroallergen patch test reactions as irritant or unspecific in AD patients,[59] even though there is no morphological way to distinguish a weak irritant reaction from a weak allergic reaction.[60,61]

Largely independent of AD status, our data confirm previous results suggesting a role for patch testing HDM and pollen allergens in patients with respiratory allergy,[19,62] especially when there is a positive history for AR. It is known that patients with AR or AA and negative IgE tests can be detected by an aeroallergen patch test.[22,63] The allergen that is most often positive in this 'intrinsic' form of respiratory disease manifestation is HDM. The underlying pathophysiology is elusive. Hypothetically, as recently suggested for FLG loss-of-function mutations,[64] a pathway that unites the airways and the skin could be responsible for primary respiratory sensitization to aeroallergens being demonstrated by patch testing. It is noteworthy that this sensitization pathway for sesquiterpene lactones, which are detected in the conventional patch test and possibly mediated via inhalation of airborne pollen or mucosal contact of airborne plant trichomes,[65] has already been discussed for some time.[66,67] However, results of no correlation between a positive aeroallergen patch test outcome and a respiratory allergy have also been

reported.[6,16,20,48] Nevertheless, it may be that, if allergy diagnostics is not limited to skin prick tests and IgE tests but enhanced by atopy patch tests with aeroallergens, additional cases of AR are detected.

It is occasionally assumed that there are some unidentified factors that may favour a rather unspecific response to aeroallergens.[20] This aspect was covered in our study by considering SLS reactivity and polysensitization to typical contact allergens. However, polysensitization to haptens, which was evenly distributed between AD and non-AD patients,[68,69] did not prove to be a relevant surrogate marker for a *general* inherent susceptibility to aeroallergen sensitization. With SLS reactivity, the situation was similar. Patients who reacted to the SLS irritation on the skin were not *generally* prone to react to aeroallergens, in line with previous studies.[12–14] In summary, it seems unlikely that the skin reactions to the aeroallergen patch test are mainly unspecific. However, it should be noted that mites and pollen contain major allergens with proteolytic enzyme activity which may cause potentially irritant patch test reactions and may therefore be responsible for an unknown number of false-positive reactions, especially in AD patients with higher positivity rates.[46–48,63,70]

In the logistic regression analyses, the methodological aspects of a larger test chamber or a longer occlusion time turned out to be the strongest association factors for a positive aeroallergen patch test outcome. Varying among studies, for aeroallergens both small[20,62,71–73] and large Finn Chamber® sizes[11,12,19,48] have been used. According to Darsow,[25,30] an intraindividual comparison using D. pteronyssinus, cat dander as well as birch and grass pollen allergens (200 IR/mL; Stallergenes) showed 'better' results with large Finn Chambers®. So far, however, there are no published data and explanations that would justify the use of a particular test chamber size.[60] On the one hand, a larger occluded test area could facilitate aeroallergen penetration and boost true-positive reactions, and[30,74] on the other hand, it could increase the rate of unspecific responses that may be due to the proteolytic enzyme activity of aeroallergen patch test preparations.[19] Our results are also consistent with the findings of Darsow *et al.*,[11] where the 48-h occlusion time led to much more positive results than the 24-h occlusion time. One may speculate whether this reflects the high molecular weight along with a slow skin penetration of the aeroallergens compared to haptens.[75–77]

Limitations

There are limitations concerning the interpretation of our results. In most cases, we do not have reliable information about clinical relevance. However, clinical practice frequently reports positive aeroallergen patch test results of unknown relevance, because the patients' awareness of aeroallergen-specific exacerbation of eczema (e.g. seasonal 'flare-up' or 'summer eruption')[13,78] is often poor, especially in perennial aeroallergens, and there is no gold standard for identifying of such eczema triggers.[11,16,25,28,74,79] Only resolutely realised aeroallergen-specific avoidance strategies[3,5,6,24,80,81] can help evaluating the relevance of positive aeroallergen patch tests on the basis of a clinical improvement.[28]

We did not record any skin prick test data or IgE test data that we could correlate with our aeroallergen patch test results. However, although a positive atopy patch test reaction is frequently observed in patients with corresponding immediate-type sensitizations in skin prick tests or IgE tests,[11,12,16,82,83] positive skin prick tests or allergen-specific IgE levels were found to be non-predictive for the result of the atopy patch test.[28,84] In addition, it was repeatedly reported that a subgroup of patients who did not have a positive skin prick test or elevated specific IgE had a positive atopy patch test.[11,12,16,19,22,63,83] The different compartmentalization of the immune cells in the body is discussed as one possible cause for these test method-dependent results. Furthermore, the atopy patch test seems to provide additional information on eczematous skin inflammation.

Finally, against the background of the ETFAD ('European Task Force on Atopic Dermatitis') recommendations on the implementation of the atopy patch test,[25] one methodological aspect needs to be addressed. Our readings are based on the ICDRG scoring system[38] for conventional patch testing, which largely corresponds to the recommended ETFAD scoring system for atopy patch testing.[25] However, the revised ETFAD scoring system offers one further option ('++++') to describe the different morphology of positive patch test reactions, but this was not relevant for our analyses, as all positive reactions were summarized. Furthermore, clinically meaningful atopy patch test results were also obtained with the ICDRG scoring system.[12,13,15,16,18,49,73,77,85]

Conclusions

This large multicentre cohort study supports the widespread perception that the atopy patch test with aeroallergens is a useful clinically tool for assessing cutaneous delayed-type reactions to protein allergens in patients with allergic skin diseases and respiratory diseases, respectively.[2,22,25,63,74] In the latter patients, the atopy patch test may complement the routine diagnostic workup of a suspected allergy to aeroallergens by means of a skin prick test and/or IgE test.[16] Finally, positive aeroallergen patch tests are not limited to AD patients,[10,19] as the originally proposed name 'atopy patch test' suggests.[9]

Based on our results, reflecting a reaction frequency > 2% in the patient subgroup without AD (Table 3), we propose a reduced aeroallergen patch test series for the clinical routine consisting of D. pteronyssinus, D. farinae, cat dander, mugwort, birch and timothy grass, all 200 IR/mL in pet. However, controlled studies with specific provocation[4] and elimination procedures[23] in patients with positive and negative aeroallergen patch test reactions would remain desirable to demonstrate the

diagnostic significance of such a screening series for the clinical course of the disease.[21,79,81]

Since mid-2015, there has been a large gap in the availability of commercial aeroallergen patch test preparations on the European market, which may lead to impaired disease management of aeroallergen-related allergies, including patient education, specific avoidance strategies and treatment decisions.[3,22,63] Currently, only one Dermatophagoides mix (D. pteronyssinus/D. farinae 50/50; Chemotechnique Diagnostics) patch test preparation is commercially available without marketing authorization in a 30% solution in pet.,[86] of which it has been assumed that its concentration is probably too high.[20,87] In order to generally overcome the restrictions on the availability of approved or marketable commercial patch test preparations in Germany, the Paul-Ehrlich-Institute has sent a first signal to allergen manufacturers and now grants on request a fee reduction to one quarter for scientific advice, new marketing authorizations, official batch release and the processing of variation applications for 'rare test allergens'.[88] In America, patient-specific prescriptions for atopy patch tests can be fulfilled by the SmartPractice Allergen Bank compounding pharmacy (Phoenix, AZ, USA). Prescribing physicians are primarily allergists (Curt Hamann, SmartPractice, personal communication). Finally, due to the public interest also in 'rare test allergens',[88] the availability of commercial aeroallergen patch test preparations should be revived by adequate cost-covering reimbursement to treating physicians,[2,3] as high-quality, effective and safe aeroallergen patch test preparations are considerably more expensive than standardized hapten patch test preparations.[74,82]

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Odds ratios as results of multivariate logistic regression analyses with positive aeroallergen patch test reactions as target variables and seven explanatory factors as independent variables in patients with past or present atopic dermatitis.
Table S2. Odds ratios as results of multivariate logistic regression analyses with positive aeroallergen patch test reactions as target variables and seven explanatory factors as independent variables in patients without atopic dermatitis.