

Original article

Prevalence and risk factors for allergic contact dermatitis to topical treatment in atopic dermatitis: a study in 641 children

Background: There is little information regarding the risk of sensitization associated with topical atopic dermatitis (AD) treatment.

Objectives: To assess the frequency of sensitization to topical treatment of AD in children and to determine risk factors associated with skin sensitization.

Methods: Six hundred and forty-one children with AD were systematically patch tested with seven agents of common topical treatment: chlorhexidine, hexamidine, budesonide, tixocortol pivalate, bufexamac, sodium fusidate and with the current emollient used by the child. The following variables were recorded: age, sex, age at onset of AD, associated asthma, severity of AD, and history of previous exposure to topical agents used in the treatment of AD. Skin prick tests to inhalant and food allergens were used to explore the IgE-mediated sensitization.

Results: Forty-one positive patch tests were found in 40 patients (6.2%). Allergens were emollients (47.5%), chlorhexidine (42.5%), hexamidine (7.5%), tixocortol pivalate and bufexamac (2.5% each). Risk factors associated with sensitization to AD treatment were AD severity [OR: 3.3; 95% confidence interval (CI): 1.5–7.1 for moderate to severe AD], AD onset before the age of 6 months (OR: 2.7; 95% CI: 1.2–6.1), and IgE-mediated sensitization (OR: 2.5; 95% CI: 1.1–5.9).

Conclusions: Topical treatment of AD is associated with cutaneous sensitization. Antiseptics and emollients represent the most frequent sensitizers and may be included in the standard series in AD children when contact dermatitis is suspected. Risk factors associated with sensitization to AD topical treatments are AD severity, early AD onset and IgE-mediated sensitization.

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Atopic dermatitis (AD) is a common inflammatory skin disease with a prevalence of 6–9% in the French paediatric population (1). Treatment of AD is primarily based on basic skin care and long-term topical treatments with emollients and topical corticosteroids (2, 3). Epidermal barrier dysfunction is an extremely important component of AD pathophysiology. Both genetic and acquired impairments are implicated in skin barrier dysfunction in AD. The permanent skin barrier defect in AD is associated with a greater permeability to foreign antigens (4). This may be associated with a greater risk of sensitization to topical agents including topical treatment in patients with AD. It has been shown that long-term exposure to allergens may be a risk factor of allergic contact dermatitis (ACD) in AD (5). In order to minimize the risk of irritation and sensitization, attention should focus on everything that comes into contact with the skin, especially the topical formulations used to treat AD (6). Studies investigating the frequency of positive patch tests to common antigens in children with AD have shown a

prevalence of about 40% (7). Epidemiological studies did not find a higher risk of contact sensitization in AD patients as compared to the general population (8–10). In a prospective study including 137 children with AD (7), positive patch tests were observed in about 43% of children. The most frequent allergens from the European standard series were metals, especially nickel (19.3%), fragrance (4.4%), balsam of Peru (2.6%), lanolin (4.4%), neomycin (2.6%). Emollients tested positively in 2.6% of patients. This study showed that emollients, an essential part of AD treatment, were the sixth most frequent contact sensitizer in children with AD.

Few data are available on the prevalence of allergic contact dermatitis to topical treatment in children with AD (7, 8, 11–14).

The aim of our study was to assess the frequency of cutaneous sensitization to topical AD treatments, in a group of 641 children with atopic dermatitis and to determine the risk factors associated with skin sensitization to topical AD treatment.

Patients and methods

Patients

From January 1997 to January 2007, 641 consecutive children under the age of 16 with atopic dermatitis were referred by their general practitioner or medical specialist for multidisciplinary clinical and allergological evaluation by a dermatologist and a paediatrician both with expertise in Allergy at the University Dermatology Clinic in Toulouse, France. Parental agreement was obtained for all children.

Data collection

Clinical data were collected on a standardized electronic case report form elaborated by the medical team. The following parameters were systematically recorded: age, sex, clinical diagnosis of AD following the criteria of the United Kingdom Working Party (15), age at onset of AD, presence of asthma, clinical examination and severity evaluation using the scoring of atopic dermatitis (SCORAD) index (3). AD severity was defined as mild: SCORAD < 25, moderate: SCORAD from 25 to 50, severe: SCORAD > 50 as used in a precedent study (7). History of previous exposure to topical agents used in the treatment of AD was assessed including exposure to bufexamac, chlorhexidine, hexamidine, sodium fusidate, topical steroids and emollients.

Patch testing

Oral treatments with antihistamines and systemic steroids were stopped respectively 3 and 7 days before patch testing. The use of topical steroids and topical immunomodulators was prohibited on tested areas within 7 days before patch testing.

Patch testing was performed on normal looking skin of the back with Haye's Chamber Test® (Chemotechnique Diagnostics, Vellinge, Sweden). All patients were systematically tested for seven components of common topical agents used in AD (all were provided by Chemotechnique Diagnostics except bufexamac, hexamidine and emollients). These were bufexamac (5% petrolatum) Trolab® provided by Stallergenes (France), chlorhexidine digluconate (0.5% aqueous), hexamidine (Hexomedine lotion®: hexamidine diisetonate 1% in hydroxyethylcellulose, acetic acid, alcohol and water), sodium fusidate (2% petrolatum) and the emollient used by the patient at the time of the tests. In addition, tixocortol pivalate (0.1% petrolatum) and budesonide (0.01% petrolatum) which are the recommended screening agents for the detection of corticosteroid contact allergy were tested (16). Bufexamac was tested although it was not frequently used in France for AD. This was done to be able to compare the incidence of positive reactions to bufexamac to the one reported in previous studies in Japan and Germany. The inclusion of bufexamac provided some kind of internal control and allowed to correlate the incidence of positive reactions to the exposure in the population.

Patch tests were removed at 48 h and readings were performed at 48 and 72 h based on ICDRG criteria (17). Only the readings taken at 72 h were evaluated for this study. Readings classified as +, ++ or +++ were defined as positive for an allergic reaction in contrast to all other readings (negative, doubtful or irritative) which were defined as negative. Parents were asked to examine the corticosteroids patch test sites every day after the 72 h reading and for 1 week. When an allergic reaction was suspected, a visit to the dermatologist involved in the study was performed.

In case of positive patch test for topical treatment, previous exposure was systematically assessed and recommendations for allergen avoidance were given to the parents.

Skin prick test

Prick tests to inhalant and food allergens regarding the child's environment were performed to substantiate the IgE-mediated sensitization defined as at least one positive prick test to any allergen (18).

Statistical analysis

Continuous variables are presented as mean [standard deviation (SD)] or median [inter quartile range (IQR)] according to their distribution (normal or skewed). Differences between groups (sensitization to topical AD therapy versus no sensitization) were compared using *t*-test or Wilcoxon's rank sum test and the chi-square test as appropriate. Logistic regression was used to take into account possible confounding factors. The first model included all the variables which were associated to sensitization in a bivariate analysis with a conservative *P*-value of 0.2. A stepwise analysis in descending sequence was performed to obtain the best reduced model. First order interactions were tested at the end of the modelling process. Adequacy of fit of the model was checked using Hosmer and Lemeshow test. Tests were two-sided and *p* values lower than 0.05 were considered significant. Data analysis was performed using STATA 9.0 software (Stata Corporation, College Station, TX, USA).

Results

Demographic characteristics of the 641 children included in the study

The median age was 3.4 years (IQR 1.3–6.9), and 48% of the population was male. Median age at onset of AD was 0.3 years (IQR 0.1–1.0), and the duration of AD before patch testing was 2.43 years (IQR 0.89–5.56). The median SCORAD was 22 (IQR 14–32) with 43% of children having a SCORAD of 25 or more indicating moderate to severe AD. Twenty-four percent of children suffered from asthma and 57% had an IgE-mediated sensitization as defined by at least one positive prick test to any allergen (18).

Table 1. Prevalence of positive patch tests to topical treatments of AD

	Positive patch tests (<i>n</i> = 41)*	% of the positive patch tests	% of tested population
Chlorhexidine	17	42.5	2.7
Hexamidine	3	7.5	0.5
Tixocortol pivalate	1	2.5	0.2
Budesonide	0	0	0
Sodium fusidate	0	0	0
Bufexamac	1	2.5	0.2
Current emollient	19	47.5	3
Total	41		

*One patient tested positive to both chlorhexidine and his current emollient.

Prevalence of positive patch tests to topical AD treatment

Results of the patch tests are displayed in Table 1. Six hundred and forty-one children were patch tested with the six active components of their topical AD treatment and with their current emollient. Among the 641 patients tested, 601 (94% of tested population) were negative for the seven patch tests studied and 40 children (6%) were positive to one of the seven studied components. One child was positive to two components (chlorhexidine and his current emollient). Chlorhexidine tested positive in 2.7% and hexamidine in 0.5% of tested children. No simultaneous sensitization for both antiseptics was found. Only one (0.2%) child was positive for tixocortol pivalate and none for budesonide. Three per cent were positive for their current emollient. In children testing positive for their emollient the single ingredients responsible for the reaction were investigated. Single ingredients contained in emollients testing positive were requested from the manufacturer and tested separately in the child when provided. Nine positive single ingredients have been identified in the nine patients for whom the single ingredients were provided. The responsible ingredients were avena extract (5% petrolatum): 1+ in five patients (four Avena Rhealba® and one Avena sativa), palmitoyl hydrolyzed wheat protein (50% aqueous): 1+ in one patient, calendula officinalis (10% petrolatum and 10% aqueous): 2+ in one patient, fragrance (as is): 1+ in one patient, and lanolin alcohol and paraffinum liquidum (brand name: Amerchol L101®) (50% petrolatum): 1+ in one patient. There was one positive (0.2%) test for bufexamac. No child tested positive to sodium fusidate. Regarding history of exposure, previous use of chlorhexidine was found in 5/17 positive patients and 1/17 used chlorhexidine at the time of patch testing. Regarding hexamidine, 2/3 reported previous use of hexamidine with no continuing exposure. The patient positive to tixocortol pivalate reported a history of previous use. No previous usage was found for bufexamac in the patient testing positive.

Risk factors associated with sensitization against topical treatment of AD

Children with sensitization to AD topical treatment were significantly younger than children without sensitization (mean age 2.8 vs 4.8 years, $P < 0.001$). Severity of AD was significantly associated with an increased risk of sensitization: the median SCORAD for AD severity was 29 (19–40) for children with a positive patch test to topical AD treatment vs 21 (14–32) for patients with no positive patch test ($P = 0.006$). As linearity assumptions were not observed for these two quantitative variables they were further transformed in qualitative ones. Results of the bivariate analyses are shown in Table 2. The risk of sensitization to topical AD treatment was higher in children who had onset of AD before 6 months of age

Table 2. Risk factors associated with cutaneous sensitization to topical treatment

	No sensitization	Sensitization	OR	95% CI	P
	n (%)	n (%)			
Sex (female)	315 (52.4)	19 (47.5)	0.8	0.4–1.6	0.547
Age (years)					
Above 5	223 (37.1)	6 (15.0)	1		
1–5	262 (43.6)	21 (52.5)	3.0	1.2–7.6	0.016
Under 1	116 (19.3)	13 (32.5)	4.2	1.5–14	0.003
Age of AD onset					
Under 6 months	315 (53.1)	30 (75.0)	2.6	1.3–5.5	0.007
AD duration					
Under 1 year	157 (26.5)	18 (45.0)	2.3	1.2–4.4	0.011
SCORAD					
Above 25	237 (40.9)	28 (71.8)	3.7	1.8–7.6	<0.001
Asthma	136 (23.6)	9 (23.7)	1.0	0.5–2.2	0.996
IgE-mediated sensitization	304 (55.3)	30 (81.1)	3.5	1.5–8.1	0.002
Previous exposure to					
Chlorhexidine	218 (37.3)	15 (37.5)	1.0	0.5–2.0	0.976
Hexamidine	170 (29.1)	8 (20.0)	0.6	0.3–1.4	0.220
Bufexamac	214 (36.6)	7 (17.5)	0.4	0.2–0.8	0.015
Sodium fusidate	341 (58.3)	24 (60.0)	1.1	0.6–2.1	0.832

(OR 2.6; 95% CI: 1.3–5.5). A total of 75% of sensitized children had AD beginning before 6 months of age as compared to 53.1% of children in the non positive group. Sex and history of asthma were not associated with sensitization to topical AD treatment.

The results of the logistic multivariate analysis are shown in Table 3. AD onset before 6 months of age was independently associated with an increased risk of sensitization [adjusted odds ratio (ORa) 2.7; 95% CI: 1.2–6.1; $P = 0.011$]. A SCORAD of 25 or more indicating moderate to severe AD was associated with a 3-fold increase in the risk of sensitization (ORa 3.3; 95% CI: 1.5–7.1; $P = 0.02$) and an IgE-mediated sensitization with a 2.5-fold increase (ORa 2.5; 95% CI: 1.1–5.9). A

Table 3. Multivariate logistic analysis of risk factors associated with sensitization to topical treatment

	Initial model			Final model		
	ORa*	95% CI†	P	ORa	95% CI	P
Age (years)						
Above 5	1					
1–5	1.8	0.8–4.9	0.263			
Under 1	1.0	0.2–5.0	0.953			
Age at onset of AD						
Under 6 months	2.5	1.0–5.9	0.043	2.7	1.2–6.1	0.018
SCORAD						
Above 25	3.2	1.5–6.8	0.003	3.3	1.5–7.1	0.002
AD evolution duration						
Under 1 year	1.9	0.5–6.5	0.307			
IgE-mediated sensitization	2.5	1.0–5.9	0.043	2.5	1.1–5.9	0.038
Previous exposure to bufexamac	0.4	0.2–1.0	0.043	0.4	0.2–0.9	0.033

*Adjusted odds ratio.

†Confidence interval.

statistically significant protective effect of previous exposure to bufexamac was shown (ORa 0.4; 95% CI: 0.2–0.9; $P = 0.038$).

Discussion

This study shows that the prevalence of contact allergy to AD topical treatment is not negligible in children with AD. Antiseptics and emollients appear to be the most frequent providers of contact allergy to topical treatment. Chlorhexidine seems to be the most frequent allergen. Analysis of risk factors for contact sensitization shows that early onset of AD before 6 months, IgE-mediated sensitization and moderate to severe disease as assessed by SCORAD > 25 are risk factors for cutaneous sensitization to topical treatment in AD patients.

This single-centre study investigating the prevalence of cutaneous sensitization to topical AD treatment in 641 children with AD represents to our knowledge the largest series in the children AD population. It provides important information regarding the risk of allergic contact dermatitis to topical treatments in patients with AD. A limitation of the study is that only a limited number of emollients and topical corticosteroids were tested. Among steroids we included only group A and group B topical corticosteroids screening agents which account for 70% of cutaneous sensitizations to topical corticosteroids (16). In addition the topical calcineurin inhibitor tacrolimus was not included in the panel of potential allergens due to limited exposure in the population tested and to its introduction on the French market only in 2003. Finally, the absence of a control group of children without atopic dermatitis may be a limitation of the study. However, inclusion of a control group of healthy children would have been difficult to envisage due to ethical and practical issues.

The role of antiseptics which are responsible for about 50% of cases of contact sensitization deserves further attention. Although chlorhexidine was found to be the most frequent allergen with 17 patients testing positive, clinical relevance as determined by history of previous use of chlorhexidine was confirmed in only 8 of the 17 cases. Previous contact with chlorhexidine may have been underestimated by the patient given the large exposure to chlorhexidine in the population. Chlorhexidine is largely used in maternal wards for umbilical cord disinfection, in cosmetics or as an antiseptic to disinfect the skin following minor skin injury (19). These potential contacts may remain unknown to the parents despite constituting an opportunity for sensitization to the allergen. Roul et al. (8) tested hexamidine in 269 children between 3 and 15 years of age (67% of them had AD) and found only one positive patch test (0.4%) for hexamidine. In the report by the French Dermato-Allergy Vigilance network (Revidal) summarizing the spontaneous

reports of allergic contact dermatitis to topical products, Barbaud et al. (19) reported 75 cases of allergic contact dermatitis to antiseptics including 16 to chlorhexidine and 20 to hexamidine which appeared to be the most frequent allergens among antiseptics. Regarding these results, it is impossible to completely rule out an irritant reaction to chlorhexidine in some patients. This issue of distinction between allergic and irritant dermatitis after patch testing is faced with all patch testing studies. However, allergic contact dermatitis to chlorhexidine does exist (20) and we believe that the findings of our study are important for the clinician. In clinical practice, relevance of patch testing needs to be assessed on a case by case basis. The clinical relevance of the patch test reaction observed can always be questioned: in patients with atopic dermatitis, it is often difficult to distinguish between the natural course of the disease and the effect of an allergic contact sensitization. However in our cohort of patients, 43% of patients had uncontrolled AD as shown by a SCORAD > 25. Moreover, chlorhexidine and fragrance and protein extracts contained in emollients are well known sensitizers. In addition in patients retested to the individual component of the emollients, the positive patch testing could be reproduced suggesting the reaction observed had clinical relevance. Given the very limited data about the utility of antiseptics in AD, caution should be exercised regarding their use due to the potential risk of cutaneous sensitization (21).

We found only one patient testing positively to bufexamac. In the study by Tada et al. (11) about ACD to topical products in 74 patients with AD suffering of severe facial lesions (including children), three patients (4%) had a positive patch test to bufexamac. Heine et al. (22) studied frequency of contact allergy in German children and found 5% of patients having a positive patch test to bufexamac (4.6% in children and 1.9% in adolescents). These apparent differences in rate of sensitization to bufexamac are probably explained by the difference in exposure to bufexamac in the French, German and Japanese population. In contrast to Germany and Japan, bufexamac is very rarely used in AD patients in France. The use of bufexamac to treat AD appears to be more prevalent in certain countries such as Germany and Japan (23, 24). The potential protective role of bufexamac found in our study remains unexplained but due to the low incidence of bufexamac sensitization, caution should be exercised regarding the clinical relevance of this protective effect observed. Severity of AD may be a confounding factor as bufexamac is primarily used in patients with mild disease.

Despite recommendations for regular use of emollients, only 19 (3%) of 641 atopic children displayed positive patch test to their current emollient. The frequency of positive patch test to emollients in children with AD in this study is close to the one found in our previous study (2.6%) (7). Cosmetics, including emollients were

previously shown to be the second most frequent contact allergen (2.5%) in children (25). Conti et al. (26) found that 44% of children with positive patch tests to a preservative were atopic. In nine patients, we were able to individually test the components of the emollients testing positive. Protein extracts and fragrance were demonstrated to be the causative agents in these cases. Hydrolysed vegetal proteins have been first reported as contact allergens in emollients by Pazzaglia et al. (27). Subsequently wheat (28) and oat (6,29) proteins used in emollients were shown to be contact allergens in atopic and non atopic patients. In the study by Rancé et al. in atopic children (29), 2.6% of patients displayed positive patch tests to the oat extract present in their emollient. In our study, two patients had a positive reaction to the fragrance included in the emollient. In both cases, positive patch tests to fragrance mix of the European Standard Series were also observed. One potential criticism of our study is that a positive reaction to emollients might be caused by irritation as suggested by Beattie et al. (14). This is unlikely to have occurred in our study. Indeed, contact sensitization to a single ingredient of the emollient was confirmed in 9 out of 9 patients for whom the ingredients of the emollient were individually tested. Identification of the culprit ingredient is a strong argument in favour of the clinical relevance of positive patch tests to emollients in our cohort. Such identification is important for the future counselling of patients. Specific ingredients such as vegetal protein extracts and fragrances contained in emollients appear to be the most common sensitizers. As a result, it may be advisable to use emollients devoided of proteins and fragrances.

Of note, positive patch tests to topical corticosteroids or topical antibiotics were found to be very rare. One possible limitation of the study is the inclusion of only two topical corticosteroids in the series. As shown by Davis et al. (30), the use of two topical corticosteroids in the series may allow detecting only two-thirds of allergic skin reactions.

The multivariate analysis of risk factors for positive patch tests against components of AD topical treatments provides important information regarding variables that may be associated with an increased risk of cutaneous sensitization. Severity of AD and early onset disease were both independently associated with an increased risk of cutaneous sensitization. Early onset AD was already shown to be a predictor of AD severity (2). The presence of an IgE-mediated sensitization as assessed by positive skin prick tests against inhalant and food allergens seemed to have a promoting effect regarding cutaneous sensitization to topical treatment.

Conclusion

Topical treatment of AD may be associated with documented cutaneous sensitization in some patients. Contact sensitization to topical treatment must be suspected when AD is not controlled with conventional topical treatment. Caution should be exercised with antiseptics and emollients which appear to be the most frequent contact sensitizers. The regular use of antiseptics in AD is questionable as the therapeutic value of these agents has not been established. Individual risk factors for developing cutaneous sensitization are moderate to severe disease, early onset AD and IgE-mediated sensitization. Antiseptics and emollients used by patients may be included in the standard patch test series in AD children in whom contact dermatitis is suspected.

Conflicts of interest

Françoise Giordano-Labadie, Fabienne Rancé and Carle Paul have received research grants and honoraria from Pierre Fabre laboratories.

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