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CLINICAL REPORT

Course of Skin Symptoms and Quality of Life in Children Referred for Patch Testing – A Long-term Follow-up Study

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Children are patch-tested in the same manner as adults, but little has been done to establish whether positive or negative findings influence the course of skin symptoms. To uncover the course of skin symptoms and the impact of persistent eczema on life quality in paediatric patients referred for patch testing, a retrospective questionnaire was sent to children and adolescents referred for patch testing during a 9-year period. Persistent eczema at follow-up was strongly associated to atopic dermatitis, but was not explained by gender, age, contact allergy or time span from patch testing to follow-up. Among patients without atopic dermatitis, 23.5% reported to suffer from chronic eczema. Persistent eczema increased the risk of severe impairment of life quality. Our findings indicate a significant risk of childhood eczema becoming chronic and affecting life quality considerably. Patch testing did not affect the course of eczema, highlighting the difficulties of avoidance behaviour. ***Key words: patch testing; children; adolescents; allergic contact dermatitis; contact allergy; atopic dermatitis.***

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Allergic contact dermatitis (CD) is a common dermatological disorder and often results in ongoing disease and disability (1, 2). Even young children may become sensitised and suffer from allergic CD (3). Early identification and subsequent avoidance of the contact allergen by the patient should reduce the duration and disability of the disease and its progression. However, studies on the outcome of patch testing in children with suspected allergic CD are limited (4) and little has been done to establish whether positive or negative findings influence the course of skin symptoms (5).

It is well known that many skin diseases have a significant impact on quality of life (QoL) (6). This has been demonstrated in children with atopic dermatitis (7) as well as in adult patients with allergic CD (1), but little attention has been paid to children and adolescents suffering from the latter.

The aim of this study was to uncover the course of skin symptoms in paediatric patients referred for patch testing, and to evaluate the impact of skin symptoms on QoL.

METHODS

Patient selection

From 1 January 2003 to 31 December 2011 a total of 2,594 patients aged 1–17 years were patch-tested in 12 dermatological clinics throughout Denmark (The Danish Group for Contact Dermatitis), which is estimated to cover about 1/5 of patients patch-tested in Denmark. All patients either suffered from recalcitrant eczema or had a suspected diagnosis of allergic CD. Characteristics according to the MOAHLFA index (Male, Occupational dermatitis, Atopic dermatitis, Hand dermatitis, Leg dermatitis, Face dermatitis) were registered by the dermatologist prior to patch testing. The diagnosis of atopic dermatitis was established according to the Hanifin and Rajka criteria (8).

Patch testing

The children were tested with either the European Baseline Series (allergens retrieved from either Chemotechnique Diagnostics, Malmö, Sweden, or from Almirall Hermal, Reinbek, Germany) or with TRUE test (SmartPractice Denmark, Hilleroed, Denmark) supplemented with the allergens from the European Baseline Series that are not included in the TRUE test. Patch tests were removed on day 2. Readings were performed according to The International Contact Dermatitis Research Group Guideline on minimum day 2 or day 4, and often also day 2 and day 7. Reactions designated either "1+", "2+", or "3+" were regarded as positive.

Follow-up

Of the 2,594 patients in the database, 2,591 were registered in the Danish Civil Registration System, and 2,567 had a valid address in Denmark. Since 307 did not wish to be contacted for research purposes, the questionnaire-based follow-up was conducted on the remaining 2,260 patients in the spring of 2013.

Questionnaire

The questionnaire designed for this follow-up study aimed to describe the skin status of the cohort and to uncover persisting skin symptoms. Since some of the patients were younger children, we made it optional for them to either answer the questionnaire themselves or with help from their parents. To investigate how well the outcome of the patch test was remembered by the patients and/or their parents, they were asked if they had contact allergy to metals, fragrances, preservatives, plants or rubber. To study the current skin status of the patients, they were asked "how often do you/your child have eczema?" with the response options "never",

"all the time/every day", "every week", "1–3 times every month", "4–6 times every year", and "1–3 times every year". To investigate the QoL of those with persisting skin symptoms, the Children's Dermatology Life Quality Index (CLDQI) questionnaire (9) was used for patients aged 16 or younger. For patients aged 17 and above, the Dermatology Life Quality Index (DLQI) (10) questionnaire was used. The CDLQI and DLQI each consists of 10 questions that focus on the effects of skin disease on activities of daily life during the preceding week. Since this was a follow-up study, the temporal parameter was expanded to the preceding year.

Definitions

To classify the severity of skin symptoms at follow-up and identify the patients that were severely affected, we defined the variables "persistent eczema" as eczema all the time/every day or at least once every week, "frequent eczema" as eczema 1–3 times each month, and "rarely eczema" as episodes of eczema less than 6 times each year.

The CDLQI/DLQI is calculated by summing the score for each question, which results in a maximum score of 30 and a minimum score of 0. The scoring and interpretation was done according to the authors' instructions (9, 11). "Severely affected life quality" was defined as a CDLQI score ≥ 13 or DLQI score ≥ 11 ("very large" or "extremely large" effect on patient's life).

Statistics

Characteristics of participants were compared using the χ_2 test. A binary logistic regression analysis was performed with "persistent eczema" as the dependent variable, and atopic dermatitis, contact allergy, gender, age at patch testing (1–5 years, 6–12 years, and 13–17 years) and follow-up time (2–4 years, 5–7 years, 8–10 years) as independent, explanatory variables. Since atopic dermatitis was a major confounder, the logistic regression model was repeated, including only the patients without atopic dermatitis. The χ_2-test was used to compare groups and assess explanatory parameters of "severely affected life quality". All results were expressed as odds ratios with 95% confidence intervals and employing a 5% significance level.

The data analysis was done using statistical software (Statistical Product and Service Solution package for Windows, Release 19, SPSS® Inc., Chicago, IL, USA).

RESULTS

In total, 1,039 questionnaires were returned after one reminder, giving a response rate of 46%. The demographic characteristics of the cohort and differences between the responders and non-responders are summarised in Table I. Respondents were more likely to be female, younger than 20 years at follow-up, patch-tested less than 5 years ago, and having a diagnosis of atopic dermatitis at the time of patch testing.

The respondents were 3–17 years (mean 12.8 years) at the time of patch testing. Time to follow-up was between 2 and 10 years (mean 5.2 years), and the current age of the respondents was 4–28 years (mean 17.7 years). More than two thirds of the respondents were girls (68.1% vs. 32.9%), 48.6% ($n=505$) had a diagnosis of atopic dermatitis (AD) when patch-tested, and 25% ($n=260$) had at least one positive patch test reaction. Among respondents, there were no sex difference in the likelihood of having at least one positive patch test reaction, and the share that suffered from AD was the same in the 2 groups.

Table I. *Demographic characteristics of responders versus non-responders*

	All patients 2,260 (100) *n* (%)	Responders 1,039 (46) *n* (%)	Non-responders 1,221 (54) *n* (%)	OR (95% CI)
Age, years				
<10	124 (5.5)	84 (8.1)	40 (3.3)	2.60 (1.77–3.82)***
11–15	394 (17.4)	205 (19.7)	189 (15.5)	1.34 (1.08–1.67)**
16–20	990 (43.8)	479 (46.1)	511 (41.9)	1.19 (1.01–1.40)*
>21	752 (33.3)	271 (26.1)	481 (39.4)	0.54 (0.45–0.65)*
Gender				
Male	776 (34.3)	331 (31.9)	445 (36.4)	0.82 (0.68–0.97)*
Female	1,484 (65.7)	708 (68.1)	776 (63.6)	
Atopic dermatitis				
Yes	1,011 (44.7)	505 (48.6)	506 (41.4)	1.34 (1.13–1.58)**
No	1,249 (55.3)	534 (51.4)	715 (58.6)	
Contact allergy				
Yes	556 (25.0)	260 (25.0)	306 (25.1)	1.00 (0.83–1.21)
No	1,694 (75.0)	779 (75.0)	915 (74.9)	
Follow-up, years				
2–4	937 (41.5)	493 (47.4)	444 (36.4)	1.58 (1.34–1.87)***
5–7	691 (30.6)	302 (29.1)	389 (31.9)	0.88 (0.73–1.05)
8–10	632 (28.0)	244 (23.5)	388 (31.8)	0.66 (0.55–0.80)***

*$p<0.05$, **$p<0.005$, ***$p<0.001$.
Odds ratio (OR) found by χ_2 testing across subgroups.
CI: confidence interval.

Skin symptoms at follow-up

Of all respondents, 90.8% ($n=943$) answered the question regarding their current skin status. In this group, 51.5% ($n=486$) had a diagnosis of AD and 80.3% ($n=757$) reported that they still suffer from eczema at least once every year. Persistent eczema at follow-up was reported by 31.1% ($n=293$) and was not surprisingly associated with having AD at the time of patch testing (OR 2.10, CI 1.59–2.78, $p<0.01$), but not with having contact allergy (OR 0.91, CI 0.66–1.25, $p=0.55$) or having 2 or more allergies (OR 0.65, CI 0.40–1.04, $p=0.07$). No difference between genders or across age groups was observed, and the risk of having persistent eczema at follow-up was the same regardless of the time from patch testing to follow-up (Table II). The same applied when the analyses were stratified by AD (Table SI[1]). Among respondents without AD, 70.4% ($n=342$) reported to suffer from eczema at least once every year and 23.5% ($n=114$) suffered from persistent eczema.

Metals, fragrance and rubber chemicals were the most frequent sensitisers, but no specific group of allergens was associated with having continuous eczema at follow-up.

Of the 260 patients who were sensitized to at least one allergen, 66.5% ($n=173$) answered the question regar-

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1911

Table II. *Logistic regression analysis with the outcome "persistent eczema" and different explanatory variables*

Explanatory variables	Persistent eczema[a] % (n/n_{total})	Crude OR[b] (95% CI)	Adjusted OR[b] (95% CI)
Gender			
Male	30.9 (94/304)	1 (ref)	1 (ref)
Female	31.1 (199/639)	1.01 (0.75–1.33)	1.01 (0.74–1.36)
Age, years			
<10	34.6 (27/78)	1 (ref)	1 (ref)
11–15	27.6 (51/185)	0.72 (0.41–1.27)	0.86 (0.48–1.53)
16–20	31.5 (138/438)	0.87 (0.52–1.44)	1.02 (0.60–1.72)
>21	31.8 (77/242)	0.88 (0.51–1.51)	1.22 (0.64–2.32)
Atopic dermatitis			
No	23.5 (114/486)	1 (ref)	1 (ref)
Yes	39.2 (179/457)	2.10 (1.59–2.78)	2.05 (1.54–2.72)*
Contact allergy[c]			
No	31.6 (220/696)	1 (ref)	1 (ref)
Yes	29.6 (73/247)	0.91 (0.66–1.25)	0.98 (0.71–1.35)
Follow-up, years			
2–4	33.8 (152/450)	1 (ref)	1 (ref)
5–7	28.2 (78/277)	0.77 (0.55–1.07)	0.74 (0.52–1.06)
8–10	29.2 (63/216)	0.81 (0.57–1.15)	0.72 (0.45–1.13)

*$p<0.05$.
[a]$n=293$. [b]Adjusted for all explanatory variables. [c]Positive patch test reaction to at least one allergen.
OR: odds ratio; CI: confidence interval.

ding the outcome of the patch test and 55.5% ($n=96$) of these were able to correctly identify the group of allergens to which the specific allergen belonged. The ability to correctly recall the allergen group decreased with time. There was no association between having persistent eczema at follow-up and being unable to identify the correct group of allergens (OR 0.91, CI 0.46–1.81, $p=0.79$).

Life quality

Among those who suffered from eczema at least once a year, 76.1% ($n=576$) answered the CDLQI or DLQI depending on age. The mean CDLQI score was 6.38 (range 0–23) vs. mean DLQI score of 6.81 (range 0–29). The CDLQI/DLQI score was correlated to the severity of the eczema and patients with AD were more affected than patients without this diagnosis in both groups (Fig. S1[1]).

Persistent eczema was a strong and significant risk factor for having severely impaired life quality in both patients ≤16 years and in patients ≥17 years. However, the majority of patients had CDLQI/DLQI scores corresponding to a small or moderate impact on life quality.

In the group of respondents ≤16 years, young children were more likely to have severely affected life quality at follow-up (Table III). This was associated to AD whereas no gender difference was observed. The association to AD did not reach statistical significance at a 5% level, which is likely due to small sample sizes. Because of the strong link between having AD and persistent eczema at follow-up, analyses were stratified by AD. Persistent eczema was still the strongest predictor of severely affected life quality. The pattern was similar in patients ≥17 years. In this age group, the role of AD was less pronounced. As in the youngest age group, the risk of having severely affected life quality increased with the severity of eczema, and this pattern persisted when stratified by AD. There was no age difference within this group but we did observe a significant gender difference, with the life quality of females being more affected than that of males (Table IV).

Table III. *Predictors of having severely affected life quality. Patients ≤16 years*

	All patients		Without atopic dermatitis	
Explanatory variables	CDLQI severely affected ($n=124$) % (n/n_{total})	Crude OR[a] (95% CI)	CDLQI severely affected ($n=54$) % (n/n_{total})	Crude OR[a] (95% CI)
Gender				
Male	15.8 (9/57)	1 (ref)	12.0 (3/25)	1 (ref)
Female	16.4 (11/67)	1.05 (0.40–2.74)	6.9 (2/29)	0.54 (0.08–3.55)
Age, years				
≤10	24.4 (12/49)	1 (ref)	12.5 (2/16)	1 (ref)
11–16	10.76 (8/75)	0.37 (0.14–0.98)*	7.9 (3/38)	0.6 (0.09–3.99)
Atopic dermatitis				
No	9.3 (5/54)	1 (ref)		
Yes	21.4 (15/70)	2.67 (0.91–7.90)**		
Contact allergy[b]				
No	16.0 (15/94)	1 (ref)	9.8 (4/41)	1 (ref)
Yes	16.7 (5/30)	1.05 (0.35–3.19)	7.7 (1/13)	0.77 (0.08–7.58)
Persistent eczema				
No	7.1 (6/84)	1 (ref)	4.8 (2/42)	1 (ref)
Yes	35.0 (14/40)	7.00 (2.44–20.09)*	25.0 (3/12)	6.67 (0.97–45.92)*

[a]Odds ratios (OR) calculated by χ^2 testing across subgroups.
[b]At least one positive patch test reaction.
*$p<0.05$, **$p=0.07$.

DISCUSSION

To our knowledge, this is the first long-term follow-up study exploring the course of skin symptoms in children referred for patch testing.

A significant share of the respondents still suffered from flare-ups of eczema at follow-up and many suffered from persistent eczema. AD was the single most important risk factor for having persistent eczema at follow-up, but even among the children and adolescents without diagnosed AD the share of patients who suffered from persistent eczema was substantial. At baseline, all patients were suspected of having allergic CD either as a complicating factor or as the main cause of disease. However, a positive patch test result was not found to affect the prognosis of eczema. There are several possible explanations for this. First of all, the accuracy of patch testing is multifactorial and depends on the competence of the tester (12). A satisfactory result requires careful consideration of exposures and selection of appropriate allergens for the patch testing. Further, the benefits of patch testing

Table IV. *Predictors of having severely affected life quality. Patients ≥ 17 years*

	All patients		Without atopic dermatitis	
Explanatory variables	DLQI severely affected ($n=452$) % (n/n_{total})	Crude OR[a] (95% CI)	DLQI severely affected ($n=198$) % (n/n_{total})	Crude OR[a] (95% CI)
Gender				
Male	9.5 (11/116)	1 (ref)	6.0 (3/50)	1 (ref)
Female	25.3 (85/336)	3.23 (1.66–6.31)**	22.3 (33/148)	4.50 (1.32–15.38)*
Age, years				
17–21	21.9 (69/315)	1 (ref)	19.1 (26/136)	1 (ref)
≥22	19.7 (27/137)	0.88 (0.53–1.44)	16.1 (10/62)	0.81 (0.36–1.81)
Atopic dermatitis				
No	18.2 (36/198)	1 (ref)		
Yes	23.6 (60/254)	1.39 (0.88–2.21)		
Contact allergy[b]				
No	21.3 (72/338)	1 (ref)	18.4 (4/41)	1 (ref)
Yes	21.1 (24/114)	0.99 (0.59–1.66)	17.7 (11/62)	0.96 (0.44–2.10)
Persistent eczema				
No	11.8 (32/271)	1 (ref)	7.2 (9/125)	1 (ref)
Yes	35.4 (64/181)	4.09 (2.53–6.59)**	37.0 (27/73)	7.57 (3.31–17.32)**

[a]Odds ratios (OR) calculated by χ^2 testing across subgroups.
[b]At least one positive patch test reaction.
*$p<0.05$, **$p<0.001$.

depends on the information given regarding avoidance of allergens (13, 14), and most importantly the patient's ability to recall the results of the patch testing (12) and subsequently avoid the contact allergen.

Avoidance of allergens can be a major challenge, as demonstrated by Lewis et al. (15). Among 43 patients with allergic CD, only half were able to avoid the allergens concerned. Accordingly, our results suggest that the patients who were diagnosed with allergic CD may have had difficulties in adopting suitable avoidance behaviour.

Another aspect of avoidance behaviour is the patient's ability to recall the results of the patch test. Jamil et al. (12) showed that patients' ability to recall the diagnosed allergen decreased over time and at 10-year follow-up only 17% percent were able to recall the correct allergen. In our study only 55.5% were able to correctly identify the group of allergens. We hypothesised that being unable to remember the outcome of the patch test was correlated to having persistent skin symptoms at follow-up. However, we were not able to show that this was the case. It could be argued that our question regarding the outcome of the patch test was too vague, i.e. asking the respondents to name the allergen to which they had a positive reaction would have been more accurate. It is also possible that the challenge of avoidance behaviour biased the result, i.e. those who correctly recalled the outcome, were unable to avoid the specific allergen. In any event, our results indicate that there is a need of reminding patients of any positive results, and this is likely to be even more pronounced if the patch testing is carried out at an early age, where information is primarily given to the parents.

We cannot reject the possibility that AD in some cases were misclassified, which would help explain the large share with persistent skin symptoms. However, it is well known that CD often results in ongoing disease (2), and it could also be that a share of the children and adolescents with skin symptoms not explained by AD or contact allergy, represent a group suffering from irritant CD, indicating that this is a significant problem among children. Other differential diagnoses are nummular eczema, seborroheic dermatitis, and solar dermatitis.

Finally, it is possible that some of the patients developed new contact allergies in the time from primary patch testing to follow up. Mortz et al. (16) recently showed that the incidence rate of contact allergy increased from adolescence to adulthood.

As expected, life quality and disease severity were correlated. Life quality was severely affected in a significant share of patients with persistent eczema. However, in an even larger proportion of patients, persistent eczema only had a small to moderate effect on life quality. This finding may help to explain why so many suffered from persistent eczema, i.e. the impact on life quality is not perceived as significant enough to offset the efforts of implementing avoidance strategies in daily life.

Children aged 3–10 years were more likely to have severely affected life quality than children aged 11–16, which was explained by the interaction effect of AD and persistent eczema. Because of the small size of the subgroups among respondents of the CDLQI, we were unable to make strong conclusions for children ≤16. Statistical analyses with adjustment for gender, age, AD, and any interaction effects between explanatory variables would have been ideal. Unfortunately our sample size did not allow this.

Several studies have explored the impact of different skin disorders on life quality in children and adolescents and most concern AD. Like Gånemo et al. (17) we were unable to show any gender difference in children ≤16 year. We demonstrated a convincing gender difference in our population of patients ≥17 years with ongoing eczema regardless of the natural history. Similar to our results, Ballardini et al. (18) found pre-adolescent girls with mild eczema to have greater impairment of self-perceived health compared to boys. Our finding may well reflect that adolescent girls and young women are more concerned about appearance than males of the same age.

Despite the relatively low response rate of 46%, we did achieve a large sample size of 1039 subjects. The low response rate may to some extent be explained by the large span in follow-up time, i.e. patients may be less likely to respond to questionnaires regarding events that happened several years ago.

There was an overrepresentation of female respondents. The unequal gender distribution was, however, to some degree expected, as two thirds of the patients in our original data set was female and accordingly, several studies have shown that there is a female predominance among patients referred for patch testing (12). In addition, it has previously been demonstrated that young men are more likely to be non-responders than responders (19), and that women are more likely to return a mailed questionnaire (1). Stratified data analyses should eliminate any confounding. Another possible limitation is the fact that patients who suffer from eczema may be more likely to participate in questionnaire surveys concerning skin disease and further, retrospective questionnaire studies imply the inevitable limitation of recall bias. As regards to the assessment of continuous eczema, this was based on the patient's information, and one could argue that a clinical assessment would have been more accurate.

Our findings indicate a significant risk of childhood eczema becoming chronic and affecting life quality considerably. As expected persistent eczema was strongly associated to AD, but was not explained by gender, age, contact allergy or time span from patch testing to follow-up. Persistent eczema at follow-up increased the risk of severe impairment of life quality and this was especially pronounced in females ≥ 17 years. Patch testing did not affect the course of eczema, indicating that it can be extremely difficult to avoid the responsible allergens and further, patients may forget the patch test outcome. Children with skin symptoms should be carefully treated and guided, in order to minimise the disease burden and avoid chronicity and future socioeconomic consequences. We recommend providing each patient with a personal allergy information card.

The subject of this study is largely unexplored and there is a need of further elucidation of the area. Future studies should include clinical follow-up. It would also be of interest to repeat the patch test in order to determine if any new allergies have evolved.

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