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Phenotypical differences of child- and adult-onset atopic dermatitis

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Abstract

Background—Little is known about adult-onset atopic dermatitis (AD).

Objectives—To determine the associations and clinical characteristics of adult-onset AD.

Methods—A prospective study of 356 adults with AD (age ≥ 18 years) was performed using standardized questionnaires and examination. AD severity was assessed using Patient Oriented Eczema Measure (POEM), Eczema Area and Severity Index (EASI), Scoring AD (ScorAD), body surface area (BSA), numeric rating scale (NRS)-itch and sleeplessness. Latent class analysis (LCA) was used to determine dominant clinical phenotypes. Multivariate logistic regression was used to determine the relationship between adult-onset AD and distinct phenotypes.

Results—149 (41.9%) reported onset of AD during adulthood, with 87 (24.4%) after age 50 years. Adult- vs. childhood-onset AD was associated with birthplace outside the US (chi-square, $P=0.0008$), but not sex, race/ethnicity, current smoking or alcohol consumption ($P=0.11$); and decreased personal history of asthma, hay fever and food allergy and family history of asthma and food allergy ($P=0.0001$ for all). There was no significant difference of EASI, SCORAD, BSA, NRS-itch, NRS-sleep or POEM between adult vs. childhood-onset AD (Mann-Whitney U test, $P=0.10$). LCA identified 3 classes: 1. high probability of flexural dermatitis and xerosis with

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intermediate to high probabilities of head, neck and hand dermatitis; 2. high probability of flexural dermatitis and xerosis, but low probabilities of head, neck, and hand dermatitis; 3 lower probability of flexural dermatitis, but highest probabilities of virtually all other signs and symptoms. Adult-onset AD was significantly associated with class 1 (multivariate logistic regression; aOR [95% CI]: 5.54 [1.59–19.28]) and 3 (14.03 [2.33–85.50]).

Conclusions—Self-reported adult-onset is common and has distinct phenotypes with lesional predilection for the hands and/or head/neck.

Keywords

atopic dermatitis; eczema; adult onset; asthma; hay fever; atopic history; severity

Introduction

Atopic dermatitis (AD) is an inflammatory skin disorder that commonly affects both children and adults. Most clinical and epidemiological research has focused on childhood AD, but few have studied AD in adults¹. Recent studies suggest that AD may be more common in adults than previously recognized, with 1-year US prevalence ranging from 3–10%^{2,3}. The higher than expected prevalence of AD may be attributed to high rates of persistent childhood disease and/or adult-onset disease. One longitudinal study found that 80% of children have persistence of AD symptoms into adulthood, with only 50% achieving a period of disease clearance by age 20 years⁴. However, a recent meta-analysis of 44 studies suggested that 50% and 80% of children with AD achieved a period of observed clear skin by 3 and 8 years of follow-up, respectively⁵. Thus, persistence of childhood AD is likely not the only factor contributing to adult AD. Over the past decade, several studies have reported substantial proportions of adults with AD having disease onset in adulthood (>18 years of age), i.e. adult-onset AD^{6–12}. We hypothesized that adults with AD have high rates of adult-onset of disease.

Previous studies found that foreign born American children had significantly lower rates of AD than those born in the US; however, odds of AD increased with US residence for >10 years¹³. Similarly, foreign born American adults had significantly lower rates of asthma than those born in the US; the odds of asthma also increased with US residence for >10 years¹⁴. These results suggest that foreign-born Americans may have later onset of AD and atopic disease. We hypothesized that adults born outside the US have higher rates of adult-onset AD.

Still, little is known about the phenotypical differences between childhood and adult-onset AD. Recent studies showed an important role of barrier disruption in childhood AD and the atopic march in the development of atopic disease¹⁵. We hypothesized that adults with adult-onset AD has lower rates of atopic disease than those with long-standing AD and associated barrier disruption since childhood. Moreover, we hypothesized that adult-onset AD may present with different clinical characteristics than childhood disease. The present study sought to determine the proportion of adult AD with adult-onset, risk factors and phenotypical differences of adult-onset AD.

Methods

Study design

We performed a prospective dermatology practice-based study to determine the predictors of adult onset AD. Self-administered questionnaires were completed by adult (> 18 years) patients of the eczema clinic prior to their encounter. Surveys included questions about socio-demographics, birthplace and age of moving to the US for those born outside the US. Patients were then evaluated with a medical history and skin examination by a dermatologist (JS). Surveys were administered between January, 2014 and June, 2016. The study was approved by the institutional review boards of Northwestern University and informed consent was waived.

Assessment of AD

AD was assessed using the Hanifin and Rajka major and minor criteria¹⁶. Specific elements presented in this analysis, include the major criteria - pruritus, distribution of eczematous lesions, personal or family history of AD, asthma or hay fever, and minor criteria - xerosis, ichthyosis, palmar hyperlinearity, keratosis pilaris, age of AD onset, nipple dermatitis, cheilitis, Dennie-Morgan infraorbital folds, facial pallor/erythema, conjunctivitis and eyelid dermatitis, pityriasis alba, dermatitis of the anterior neck folds, history of cutaneous infections, clinical course worsened by environmental or emotional factors, pruritus when sweating. AD severity was assessed using the numeric rating scale (NRS) for itch and sleeplessness, body surface area (BSA) of involved skin, Scoring AD (SCORAD) and Eczema Area and Severity Index (EASI).

Data Processing and Statistical Methods

All data analyses and statistical processes were performed using SAS version 9.4 (SAS Institute). Chi-square and Fisher's exact tests were used to compare age of AD onset (<18 vs. ≥ 18 years) with birthplace in the US (binary), continent of birth (North America, Canada, South America, Europe, Asia, Africa), whether AD preceded migration, personal history of asthma, hay fever, food and medication allergy (binary), family history of AD, asthma, hay fever, food or medication allergy (binary), distribution of eczematous lesions and other signs and symptoms of AD (all binary). Median (interquartile range [IQR]) were determined for the number of combined signs and symptoms, EASI, SCORAD, BSA, NRS-itch and NRS-pruritus. Mann-Whitney U tests were used to compare these outcomes between adult- vs. child-onset groups. A 2-sided P-value < 0.01 was taken to indicate statistical significance for all hypothesis tests.

Latent class analysis (LCA) was used to examine phenotypical patterns of binary variables of 19 signs and symptoms of AD. LCA uses observed categorical or binary data to identify patterns, termed latent classes. Subjects with similar response patterns are categorized into specific classes. Conditional probabilities were estimated using maximum likelihood to characterize the latent classes by indicating the chance that a member would give a certain response (yes or no) for the specific item. Conditional probability plots are presented, where probabilities closer to 0 or 1 indicate lower or higher chances, respectively. LCA regression models examine the differential effects of individual variables across unobserved classes.

The ideal number of latent classes and best fitting models were selected by minimizing the Bayesian Information Criterion (BIC), Consistent Akaike information criterion (CAIC) statistics and interpretability. Multivariate logistic regression was then performed to determine the association between adult-onset AD and membership in the latent classes. Gender, race/ethnicity, BSA and EASI were included as covariates to address potential confounding. Adjusted odds ratios (aOR) and 95% confidence intervals (CI) were estimated.

Sample size calculation

A priori sample size calculations were performed based on two co-primary analyses: the association between adult onset AD and 1. foreign birthplace and 2. personal history of asthma or hay fever. For the association with foreign birthplace, the referent and test groups were predicted to be 13% and 26% based on the proportion of foreign born adults in the US population¹⁷ and an expected doubling of the proportion in adult-onset AD. For the association with personal history of asthma, the referent and test groups were predicted to be 50% and 25% based on previously observed prevalences in adults with AD¹⁸ and an expected halving of that proportion in adult onset AD. A total of 308 and 123 adults were needed based on the Chi-square test, assuming 90% power with the use of 2-sided tests and an alpha level of 0.01 for each outcome¹⁹.

Results

Patient characteristics

Overall, 356 adults (ages 18–93 years) were included in the study, including 230 women (64.6%) and 228 whites (64.0%). The mean $\pm$ std. dev. age at enrollment was 42.8 ± 16.7 years and age of self-reported AD onset was 30.5 ± 31.7 years. Two hundred and seven (58.1%) reported onset of AD during childhood and adolescence, with 88 (24.7%) before age 5 years and 87 (24.4%) after age 50 years (Figure 1).

Among patients with adult-onset AD, skin biopsies were performed in 66 (44.3%); 65 showed a pattern of spongiotic dermatitis with eosinophils and none were consistent with cutaneous T cell lymphoma. Patch testing was performed in 82 (55.0%); 56 were negative and 11 showed at least one *irrelevant* positive reaction. Fifteen showed at least one relevant positive reaction. However, strict avoidance of the observed allergens only resulted in partial mitigation of their underlying skin disease, with all patients having ongoing chronic AD. Skin prick testing results were available for 38 and 14 patients with childhood- and adult-onset AD, with high rates of at least one positive allergen (single positive to aeroallergen: 7 [18.4%] and 2 [14.3%]; multiple positives to aeroallergens: 28 [73.7%] and 11 [78.6%]; multiple positives to food allergens: 2 [5.3%] and 0 [0.0%]; negative: 1 [2.6%] and 1 [7.1%], respectively). Total serum immunoglobulin E levels were available for 11 and 6 patients with childhood- and adult-onset AD; 8 (72.7%) and 3 (50.0%) had levels ≥ 100 IU/ml with median (IQR) levels of 3,000 (1,240, 24,055) and 87.2 (30.0, 236.8) IU/ml, respectively. Forty nine patients were excluded from the study because they did not meet the Hanifin and Rajka criteria for AD (63.3%), were found to have an alternative diagnosis on skin biopsy (6.1%) or were found to allergic contact dermatitis that resolved with allergen avoidance (30.6%).

Patients with adult-onset AD were significantly more likely to be born outside the US compared to those with childhood onset AD (22.5% vs. 11.5%; chi square, $P=0.008$) (Table 1). Among foreign-born adults with childhood onset AD, 2 (14.3%) developed AD after migration to the US. Whereas, among adults with adult-onset AD, 27 (75.0%) developed AD after migration ($P=0.0003$). However, adult-onset AD was not associated with sex, race/ethnicity, current smoking or alcohol consumption ($P=0.11$).

History of atopic disease

Adult-onset AD compared with childhood-onset AD was associated with a significantly decreased personal history of asthma (17.8% vs. 51.7%; $P<0.0001$), hay fever (37.7% vs. 58.7%; $P=0.0001$) and food allergy (15.4% vs. 43.9%; $P<0.0001$), but not medication allergy (30.5% vs. 32.5%; $P=0.70$) (Table 2). Moreover, adult-onset compared with childhood-onset AD was associated with a significantly decreased family history of AD (35.5% vs. 60.6%; $P<0.0001$), asthma (20.0% vs. 43.9%; $P<0.0001$), and food allergy (10.4% vs. 25.0%; $P=0.0009$), but not hay fever (23.9% vs. 36.2%; $P=0.017$) or medication allergy (9.0% vs. 14.8%; $P=0.12$).

Signs and symptoms of AD

Adult-onset compared with childhood-onset AD was associated with significantly higher rates of nummular eczema lesions, but lower rates of 11 of 18 signs and symptoms of AD, including dermatitis affecting anterior neck fold; scalp; face; eyelids and conjunctivitis; Dennie-Morgan folds; hands or feet; or nipples; cheilitis; pityriasis alba; keratosis pilaris or palmar hyperlinearity or ichthyosis; clinical course worsened by emotional or environmental factors, or pruritus when sweating and tendency toward cutaneous infections (Table 3). However, there were no significant differences of dermatitis affecting the flexural areas, xerosis, white dermatographism, follicular eczema, anterior subcapsular cataracts and keratoconus. Further, patients with adult vs childhood-onset AD had a significantly lower number of combined AD signs and symptoms (median [IQR]: 6 [2, 8] vs. 10 [6, 13], $P<0.0001$) (Figure 2A).

AD severity

There were no significant differences of disease severity between adult-onset and childhood-onset AD as judged by EASI (median [IQR]: 8.3 [2.8, 24.1] vs. 10.0 [2.8, 14.8]; Mann-Whitney U test, $P=0.44$) (Figure 2B), SCORAD (39.5 [23.0, 52.6] vs. 39.7 [27.4, 55.4]; $P=0.56$) (Figure 2C), and BSA (16.8 [6.0, 54.9] vs. 27.0 [9.4, 58.9]; $P=0.10$) (Figure 2D). However, there were no differences of NRS-itch (7 [4, 10] vs. 7 [5, 9]; $P=0.60$) (Figure 2E), NRS-sleep (4 [2, 5] vs. 4 [1, 6]; $P=0.51$) (Figure 2F) or patient-reported AD activity (POEM: 10 [5, 17] vs. 12 [6, 18]; $P=0.43$) (Figure 2G).

Latent class analysis of the adult-onset AD phenotype

LCA was used to identify phenotypical patterns associated with adult-onset AD. The best-fit model had three classes based on minimal BIC, CAIC and interpretability. Conditional probabilities of having different physical signs and symptoms in each class are plotted in Figure 3. Class 1 had high probabilities of flexural dermatitis and xerosis with intermediate

to high probabilities of head, neck and hand dermatitis. Class 2 had high probability of flexural dermatitis and xerosis, but low probabilities of head, neck, and hand dermatitis. Class 3 had a lower probability of flexural dermatitis, but highest probabilities of virtually all other signs and symptoms. Adult-onset AD was significantly associated with Class 1 (multivariate logistic regression; aOR [95% CI]: 5.54 [1.59–19.28]) and 3 (14.03 [2.33–84.50]). That is, adult-onset AD was more likely to present with a phenotype consisting of lower probability of flexural dermatitis (class 3) and/or higher probability of hand and/or head and neck dermatitis (classes 1 and 3).

Discussion

The present study demonstrated that adult-onset AD is associated with a distinct phenotype compared with child-onset AD, including less frequent personal and/or family history of atopic disease, fewer signs and symptoms of AD, with a higher probability of lesions affecting the head/neck and hands and lower probability of flexural lesions. These findings are consistent with previous studies showing more nummular eczema lesions, less flexural involvement and lesional predilection for the hands and face in adult-onset AD ^{7, 20}. However, we found significantly lower rates of scalp and posterior auricular lesions and no differences for rates of follicular eczema. This is contrast with a previous study that found higher rates of both scalp and posterior auricular involvement and follicular eczema ⁷. Despite the observed phenotypical differences, we found no significant differences of AD severity, patient-reported intensity of itch or sleeplessness, disease activity (POEM) or pruritus when sweating. Thus, adult-onset and childhood-onset AD appear to have similar severity, symptomatology and quality of life impairment, despite the observed phenotypical differences. It is important for clinicians to account for the different phenotypes of adult-onset AD when evaluating and managing adult patients with dermatitis.

There are several practical points from this study for the management of adult AD. First and foremost, clinicians must recognize that the presentation of adult AD is more heterogeneous and may have different phenotypes. It is of course important to rule out other entities in the differential diagnosis, e.g. allergic contact dermatitis and cutaneous T cell lymphoma. However, the clinician can comfortably make the diagnosis of AD if the clinical presentation is consistent with AD and the appropriate workup for other etiologies is negative. Second, the lesional predilection for the head/neck and hands may require site-specific targeted treatment with either low-potency topical corticosteroids or non-steroidal topical agents for the head/neck area, and super-potent topical corticosteroids for the hands. Third, the similar rates of xerosis between childhood and adult-onset AD suggests that moisturizers and other barrier repair therapies are warranted in both patient subsets. Fourth, given the low rates of history and manifestations of atopic disease, skin-prick and RAST testing may not be warranted in the routine workup of most patients with adult-onset AD. Whereas, these may be useful in a subset of adults with childhood-onset AD, and those with comorbid asthma and rhino-conjunctivitis. On the other hand, it may be that uncontrolled AD in adulthood may predispose to eventual higher rates of adult-onset atopic disease. This is analogous to the “atopic march” observed in a subset of childhood AD ²¹. Thus, improved long-term control of the skin disease may offer an opportunity to mitigate or prevent adult-onset atopic disease. Finally, it is unknown if the distinct phenotypes observed in this study are

associated with different prognosis or treatment response. A recent meta-analysis found that children with already persistent, later onset and/or more severe AD had increased persistence²². Adult-onset AD may similarly be associated with increased persistence and thus warrant long-term treatment regimens. Yet, it is unknown whether specific clinical interventions may prevent childhood AD from becoming adult AD. Future long-term studies are needed to elucidate these points.

The results of this study confirm our hypothesis adults with AD have high rates of adult-onset of disease. Adult-onset AD may be more common than commonly recognized and may affect almost half of adult cases. A US population-based telephone survey of 60,000 households similarly found that 54% of respondents with self-reported AD reported their disease onset in adulthood⁶. Studies from Turkey, Singapore, Australia, Italy, Nigeria and China also reported substantial proportions (range of 9% to 88.0%) of AD patients had onset after 18 years of age⁷⁻¹². Of course, some of these patients may have in fact had childhood disease but were unaware of or have forgotten it. Regardless of whether such cases are adult onset *per se* or adult recurrence, there appears to be a larger subset of patients with activation of their skin disease in adulthood than previously recognized.

The present study confirms our hypothesis that that foreign-born patients were more likely to have adult-onset AD compared with those born in the US. We previously demonstrated that foreign-born American children had significantly lower rates of AD and atopic disease than those born in the US²³. However, the odds of AD significantly increased in foreign-born children after residing in the US for 10 or more years²³. Together, it appears that foreign-born Americans are at risk for later-onset AD, particularly in adulthood.

We found no significant sex-associations with adult-onset AD or with the associated phenotypes involving the hands and/or head/neck. In contrast, the US prevalence of adult AD was associated with female sex³ and one study showing a male preponderance of adult-onset AD⁷. The complex relationship between sex, skin care practices, occupational exposures and the pathogenesis of AD require further study. We observed high rates of cigarette smoking and alcohol consumption in this cohort overall, consistent with previous reports of increased smoking in children and adults and alcohol consumption in adults with AD^{24, 25}. However, there were no associations between adult-onset AD *per se* and current smoking status or alcohol consumption. This is in contrast with a case-control study of 225 Taiwanese adults that found that early and/or current exposure to cigarette smoking was associated with adult-onset disease²⁶. However, that study compared adult-onset AD to non-AD controls and those findings may have been attributable to AD, in general, and not adult-onset AD, in particular.

The mechanisms of adult-onset AD remain unclear. Perhaps the biggest question is whether such cases are truly adult-onset vs. adult-recurrence of AD. It is possible that adults presenting with new-onset disease including the full spectrum of AD signs and symptoms and comorbid allergic disease are actually adult recurrent disease. Whereas, adults presenting with prominent head/neck and hand/foot involvement and lower rates of allergic disease may truly be adult-onset AD. Alternatively, it is possible that even adult-recurrent disease is more likely to present with prominent head/neck and hand/foot involvement.

Either way, it is mysterious that patients should have decades or a lifetime of clear skin and subsequently develop full-blown AD. Presumably, any genetic predisposition toward AD would have been programmed from birth. A study of 241 patients with AD found that the 4 most common FLG loss-of-function mutations were only associated with early childhood-onset AD (2 or 2–8 years), but not late-childhood (8–17 years) or adult-onset disease (18 years)²⁷. This suggests that there are different genetic and/or environmental determinants of adult-onset AD, which warrant further study. Future studies are warranted that compare the genetics and transcriptome of childhood vs. adult-onset AD.

This study has several strengths, including being prospective, standardized assessment of AD signs, as well as pruritus, sleeplessness, disease activity and severity using multiple validated instruments. In addition, alternative diagnoses in the differential diagnosis were ruled out using skin biopsy and/or patch testing when indicated. LCA was used to identify the dominant phenotypes of adult AD, and was able to detect 3 unobservable subgroups of patients, including those with lesional predilection for the hands/feet and/or head/neck. However, the study has limitations. In particular, the study was performed in an academic dermatologic setting and may not be generalizable to milder cases of AD or the entire US population.

In conclusion, adults with AD have high rates of self-reported adult-onset, lower prevalence of personal or family history of atopic disease, and distinct phenotypes with less flexural lesions and more involvement of the hands and/or head/neck, and nummular lesions. Future longitudinal studies are underway to determine whether these phenotypes are associated with different prognosis or treatment response.

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Abbreviations used

AD	atopic dermatitis
EASI	Eczema Area and Severity Index
SCORAD	Scoring Atopic Dermatitis
POEM	Patient Oriented Eczema Measure
NRS	Numeric Rating Scale
LCA	latent class analysis
aOR	adjusted odds ratio
95% CI	95% confidence interval

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What is already known about this topic?

The risk factors and clinical characteristics of adult-onset atopic dermatitis are poorly understood.

What does this article add to our knowledge?

Adults with AD have high rates of self-reported adult-onset, lower prevalence of personal or family history of atopic disease, and distinct phenotypes with less flexural lesions and more involvement of the hands and/or head/neck.

How does this study impact current management guidelines?

Clinicians caring for patients with AD should recognize the phenotypes associated with adult-onset AD. Further studies are needed to determine whether these phenotypes are associated with different treatment outcomes.

Figure 1.
Distribution of age of AD=onset among adults with AD.

Figure 2. Associations between adult- vs. childhood-onset AD with signs, symptoms and severity of disease

Box-whisker plots and overlaid jitter plots of (A) frequency of AD signs and symptoms, (B) EASI, (C) SCORAD, (D) BSA, (E) NRS-itch, (F) NRS-sleepiness, and (G) POEM.

Figure 3.

Latent class analysis (LCA) was performed to determine the dominant patterns of signs and symptoms in adults with AD. LCA identified 3 classes: 1. high probability of xerosis and intermediate probabilities of flexural or hand dermatitis; 2. high probability of xerosis, flexural, head, neck and hand dermatitis; 3. highest probabilities of all signs and symptoms.

Table 1

Association of gender and birthplace outside the US with adult onset atopic dermatitis.

Variable	Age of AD onset ^{\$}		
	Childhood (<18) (n=207)	Adulthood (≥18) (n=149)	
	Freq (%)	Freq (%)	p [#]
Sex			
Male	70 (33.8%)	56 (37.6%)	0.46
Female	137 (66.2%)	93 (62.4%)	
Race/ethnicity			
White, non-Hispanic	127 (61.4%)	101 (67.8%)	0.72 *
Black	30 (14.5%)	15 (10.1%)	
Hispanic	13 (6.3%)	9 (6.0%)	
Asian	34 (16.4%)	22 (14.8%)	
Multiracial/Other	3 (1.4%)	2 (1.3%)	
Current cigarette smoker			
No	169 (88.0%)	126 (91.3%)	0.62
Yes	23 (12.0%)	12 (8.7%)	
Current alcohol consumption			
No	67 (35.3%)	37 (27.0%)	0.11
Yes	123 (64.7%)	100 (73.0%)	
Birthplace in US			
Yes	170 (88.5%)	107 (77.5%)	0.008
No	22 (11.5%)	31 (22.5%)	
Continent of birth (outside US)			
North America	3 (13.6%)	0 (0.0%)	0.057 *
South America	1 (4.6%)	7 (22.6%)	
Europe	7 (31.8%)	8 (25.8%)	
Asia	10 (45.5%)	16 (51.6%)	
Africa	1 (4.6%)	0 (0.0%)	
Timing of migration			
AD preceded migration	20 (90.9%)	9 (29.0%)	<0.0001 *
AD developed after migration	2 (9.1%)	22 (71.0%)	

[#] Chi-square test was used for all tests unless where indicated.^{*} Fisher-exact test^{\$} Column percentages are presented. Some frequencies may not sum to the total number of childhood and adult-onset cases due to missing values.

Table 2

Differences of atopic history, signs and symptoms of atopic dermatitis between child and adult-onset of disease.

Sign	Missing values	Age of AD onset [§]		
		Childhood (<18) (n=207)	Adulthood (≥ 18) (n=149)	
		Freq (%)	Freq (%)	P-value [#]
Personal history				
Asthma	8	104 (51.7%)	26 (17.8%)	<0.0001
Hay fever	9	118 (58.7%)	55 (37.7%)	0.0001
Food allergy	14	87 (43.9%)	22 (15.4%)	<0.0001
Medication allergy	18	64 (32.5%)	43 (30.5%)	0.70
Family history				
Atopic dermatitis	17	120 (60.6%)	50 (35.5%)	<0.0001
Asthma	20	86 (43.9%)	28 (20.0%)	<0.0001
Hay fever	21	71 (36.2%)	33 (23.9%)	0.017
Food allergy	33	47 (25.0%)	14 (10.4%)	0.0009
Medication allergy	33	28 (14.8%)	12 (9.0%)	0.12
Physical signs				
Flexural dermatitis	22	149 (76.4%)	92 (66.2%)	0.04
Anterior neck fold dermatitis	18	122 (61.0%)	52 (37.7%)	<0.0001
Facial dermatitis	18	118 (59.0%)	42 (30.4%)	<0.0001
Conjunctivitis or eyelid dermatitis	18	111 (55.5%)	36 (26.1%)	<0.0001
Dennie-Morgan fold	18	75 (37.5%)	16 (11.6%)	<0.0001
Cheilitis	18	79 (39.5%)	17 (12.3%)	<0.0001
Hand or foot dermatitis	22	134 (68.7%)	63 (45.3%)	<0.0001
Nipple dermatitis	22	29 (14.9%)	7 (5.0%)	0.004
Xerosis	16	162 (81.0%)	113 (80.7%)	0.95
Pityriasis alba	26	23 (12.0%)	3 (2.2%)	0.0007*
Palmar hyperlinearity/ichthyosis/keratosis pilaris	22	121 (62.1%)	45 (32.4%)	<0.0001
Scalp	18	96 (48.0%)	35 (25.4%)	<0.0001
Posterior auricular	18	83 (41.5%)	23 (16.7%)	<0.0001
Nummular lesions	29	12 (6.4%)	21 (15.0%)	0.0097
White dermatographism	24	8 (4.1%)	6 (4.3%)	0.94
Follicular eczema	21	11 (5.6%)	7 (5.0%)	0.82
Anterior subcapsular cataracts	17	6 (3.0%)	8 (5.8%)	0.21
Keratoconus	17	3 (1.5%)	1 (0.7%)	0.65*
Symptoms				
Clinical course worsened by environmental or emotional factors	17	182 (91.9%)	116 (82.3%)	0.008

Sign	Missing values	Age of AD onset ^{\$}		
		Childhood (<18) (n=207)	Adulthood (≥18) (n=149)	
		Freq (%)	Freq (%)	P-value [#]
Pruritus when sweating	20	138 (70.1%)	90 (64.7%)	0.31
Tendency toward cutaneous infections	0	64 (30.9%)	28 (18.85)	0.0099

[#] Chi-square test was used for all tests unless where indicated.

^{*} Fisher exact test

^{\$} Column percentages are presented. Some frequencies may not sum to the total number of childhood and adult-onset cases due to missing values.