Phenotypic differences of atopic dermatitis stratified by age

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Background: Atopic dermatitis (AD) is common across all ages. Understanding heterogeneous age-related phenotypes may improve AD management.

Objective: To determine age-related clinical phenotypes of AD.

Methods: A prospective, dermatology practice-based study was performed (n = 380). AD severity was evaluated using questionnaires and full-body examination. Phenotypes were determined using latent class analysis.

Results: There were 23 (6.1%) pediatric patients (<18 years), 176 (46.3%) young adults (18-39 years), and 181 (47.6%) older adults (≥ 40 years). Both young and older adults experienced less AD on ankles (adjusted odds ratio [95% confidence interval]: 0.41 [0.19-0.90], 0.43 [0.20-0.94]), moderate-severe AD on flexures (0.47 [0.26-0.87], 0.30 [0.16-0.56]), pityriasis alba (0.24 [0.11-0.52], 0.07 [0.03-0.18]), oozing lesions (0.44 [0.25-0.79], 0.35 [0.20-0.63]), moderate-severe excoriations (0.49 [0.28-0.85], 0.44 [0.26-0.76]), and severe itch (adjusted β [95% confidence interval], −1.46 [−2.63 to −0.29], −1.79 [−2.94 to −0.65]) compared with pediatric patients. Young adults experienced more AD around the eyes (2.92 [1.21-7.02]). Older adults experienced more AD on elbows (0.34 [0.19-0.64]), nipples (0.40 [0.16-0.99]), knees (0.27 [0.14-0.53]), keratosis pilaris (0.38 [0.15-0.98]), and lichenification (0.47 [0.22-0.98]). Four classes were identified for distribution of AD and associated signs.

Conclusion: Distinct phenotypes exist by age with younger patients experiencing more AD signs and symptoms. Clinicians should consider them when managing AD. (JAAD Int 2023;11:j-j).

Key words: Atopic dermatitis; eczema; patient-reported outcomes; physical activity; severity.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disorder affecting ∼20% of children, 10% adults, and 1-3% of geriatric patients. Recent studies suggest the clinical characteristics of AD differ across age groups. In a systemic review and meta-analysis, patients from pediatric studies were found to have AD involvement of the eyelid, auricular area, and wrist, whereas patients from adult studies were found to have hand and foot involvement as well as chronic signs of AD.

The heterogeneity of AD has led to the identification of various clinical phenotypes and a movement toward personalized medicine in dermatology. Previous studies have found differences in the clinical characteristics of AD depending on age of AD onset, ethnic background, and AD severity. However, none have prospectively compared the...
clinical characteristics and associated signs by age group. Improved understanding of the clinical phenotypes of AD may help guide choice of treatment and improve health outcomes. In this study, we sought to identify the phenotypic differences between pediatric, young adult, and older adult patients with AD.

METHODS

Study design

The study was approved by the institutional review board at Northwestern University. A prospective dermatology practice-based study was performed between 2013 and 2019 that included patients with a diagnosis of AD as defined by the Hanifin-Rajka diagnostic criteria. Participants were recruited from an eczema clinic at an academic medical center. Exclusion criteria included those with an alternative diagnosis (determined by epicutaneous patch testing and skin biopsy), lack of definitive diagnosis (determined by the Hanifin-Rajka criteria), or the inability to complete questionnaires. Patients were categorized into 1 of 3 age groups: "Pediatric" (0-17 years), "Young adult" (18-39 years), and "Older adult" (≥ 40 years). Participation was formally assessed where virtually all (>99%) patients who were invited agreed to participate.

Outcome measures

Data were collected using self-administered electronic questionnaires before the appointment. Questionnaires included age of AD onset, sociodemographics, Visual Analog Scale itch and sleep for Scoring AD (1 question each, range 0-10), and Numeric Rating Scale for skin pain and itch (range 0-10). AD severity was assessed using Eczema Area Severity Index (0 = clear, 0.1-5.9 = mild, 6.0-22.9 = moderate, 23.0-72 = severe). A full body skin exam was performed by a dermatologist (J.S.). The distribution of AD involvement (scalp, face, neck, chest, upper, and lower extremities), AD signs (lichenification, skin oozing, swelling, excoriation, and redness), and associated signs (xerosis, keratosis pilaris, ichthyosis, palmar hyperlinearity, nummular, and follicular eczema). Repeated-measure, linear regression models were constructed to analyze the relationship between age and AD symptoms. The dependent variables were Numeric Rating Scale average-itch or skin pain. Multivariable models were adjusted for race and sex. Adjusted odds ratios, beta, and 95% confidence intervals (CIs) were estimated. A P value of <.05 was considered statistically significant.

Latent class analysis was used to examine the phenotypic patterns of 8 signs and 8 sites of AD lesions. The conditional probabilities were estimated using maximum likelihood to characterize the latent classes. Conditional probabilities indicate the chance that a patient would have that feature, with probabilities closer to 0 indicating lower chances, and probabilities closer to 1 indicating higher chances. The number of latent classes was selected using Akaike’s Bayesian Information Criterion.

RESULTS

Baseline characteristics

Overall, 380 patients were recruited in the study, including 234 (61.6%) females, 176 (46.3%) adults between 18 and 39, and 181 (47.6%) adults 40 years or older (Table I). The mean ± standard deviation age of AD onset was 18.4 ± 28.9. At baseline, patients commonly reported history of asthma (41.9%), history of hay fever (48.9%), and other food allergies (35.4%); most had mild (47.0%) or moderate (33.8%), followed by severe (11.6%) or clear/almost clear (7.5%) AD determined by EASI score.

Distribution of AD lesions

The most common sites of AD were hands (75.0%), fingers (67.9%), and flexures (63.3%) in pediatric patients (0-17 years); flexures (57.5%), anterior neck (56.8%), and elbows (54.3%) in young
adults (18-39 years); anterior neck (59.7%), hands (57.9%), and around the eyes (48.5%) in older adults (≥ 40 years) (Fig 1).

Compared with pediatric patients, young adults were less likely to report AD lesions on the ankles (adjusted odds ratio [95%CI]: 0.41 [0.19-0.90]), but more likely to develop AD around the eyes (2.92 [1.21-7.02]). Older adults were less likely to report AD on the nipples (0.40 [0.16-0.99]), elbows (0.34 [0.19-0.64]), flexures (0.48 [0.28-0.83]), knees (0.27 [0.14-0.53]), and ankles (0.43 [0.20-0.94]). In addition, in comparison to pediatric patients, young adults were less likely to have moderate-severe AD lesions on the flexures (0.47 [0.26-0.87]). Older adults were less likely to have moderate-severe AD on flexures (0.30 [0.16-0.56]), as well as the postauricular area (0.47 [0.20-0.98]), (Table II, Supplementary Tables 1-3, available via Mendeley at https://data.mendeley.com/datasets/5z56x8fvkg).

AD signs

The most common signs of AD among pediatric, young, and older adults were redness (94.1%, 94.3%, 90.0%), lichenification (92.6%, 84.8%, 78.5%), and excoriations (85.2%, 80.6%, 77.9%) respectively. Compared with pediatric patients, young adults were less likely to have pityriasis alba (0.24 [0.11-0.52]) and oozing lesions (0.44 [0.25-0.79]) on physical exam, but no differences in cheilitis, follicular eczema, ichthyosis, keratosis pilaris, nummular eczema, palmar hyperlinearity, lichenification, redness, excoriations, swelling, or xerosis. Older adults were also less likely to have pityriasis alba (0.07 [0.03-0.18]) and skin oozing (0.35 [0.20-0.63]) as well as lichenification (0.47 [0.22-0.98]), and keratosis pilaris (0.38 [0.15-0.98]).

Younger adults were less likely to have moderate-severe excoriations (0.49 [0.28-0.85]), whereas older adults were less likely to have moderate-severe pityriasis alba (0.05 [0.00-0.54]), lichenification (0.50 [0.28-0.86]), skin oozing (0.27 [0.27-0.88]), and excoriations (0.44 [0.26-0.76]). (Table II, Supplementary Tables 1-3, available via Mendeley at https://data.mendeley.com/datasets/5z56x8fvkg).

AD symptoms

Severe itch was most commonly reported in children (47.1%), followed by young adults (43.4%), and older adults (38.6%). Compared with pediatric patients, both younger adults (aβ [95%CI]: 1.46 [2.63 to 0.29]) and older adults (1.79 [2.94 to 0.65]) had less severe itch (Table II, Supplementary Table 3, available via Mendeley at https://data.mendeley.com/datasets/5z56x8fvkg).

Skin pain was most common in younger adults (41.7%) followed by older adults (38.1%), and least common in children (28.6%). Severe levels of pain were most common in older adults (18.0%), whereas moderate levels were most common in young adults and children (15.2%, 14.3%). Severity of skin pain was similar between children and young adults (0.51 [-0.57 to 1.60]) or older adults (0.25 [-0.85 to 1.20]) (Table II, Supplementary Table 3, available via Mendeley at https://data.mendeley.com/datasets/5z56x8fvkg).

Latent class analysis

Latent class analysis was used to identify the phenotypic patterns of AD lesional distribution and associated signs (n = 380). The best-fit model was determined by minimal Akaike’s Bayesian Information Criterian and interpretability. Conditional probabilities of the various sites and symptoms in each class are plotted in Fig 2.
Distribution of AD lesions

Four classes were identified for distribution of AD lesions. Class 1 had low probabilities of AD involvement at all sites examined. Class 2 had low probabilities of scalp, face, and foot involvement, and intermediate probability of all other AD sites. Class 3 had low probabilities of hand and foot involvement, high probability of facial erythema, and intermediate probability of all other AD signs. Class 4 had intermediate probability of postauricular and foot involvement, and high probability of all other AD sites examined. Pediatric patients were most commonly in class 4 (33.3%), followed by classes 1 and 2 (26.7%), and least commonly in class 3 (13.3%). In young adults, classes 4 and 1 were most common (32.4%, 29.4%), followed by class 2 (27.9%), and least commonly class 3 (10.3%). In older adults, class 1 was most common (40.3%), followed by class 4 (23.6%), and least commonly classes 2 and 3 (18.1%).

AD signs

Four latent classes were identified for the signs and symptoms of AD. Class 1 had zero-low probability of all AD signs; class 2 had low probability of all AD signs; class 3 had high probability of oozing lesions, and low probability of all other signs; and class 4 had high probability of xerosis, intermediate probability of ichthyosis and palmar hyperlinearity, and low probability of all other AD signs. The most common class across all age groups was class 1, affecting 85.6% of older adults, 81.8% of younger adults, and 82.6% of pediatric patients. In pediatric patients, class 3 was the second most common (8.7%), followed by classes 2 and 4 (4.4%). In young adults, class 4 and 1 were most common (32.4%, 29.4%), followed by class 2 (27.9%), and least commonly class 3 (10.3%).

Table II. Summary of associations of AD lesional distribution, morphology, and symptoms with age

| Distribution of AD lesions | Age, y | Effect | Morphology of lesions and associated signs of AD | Age | Effect | AD symptoms | Age, y | Effect |
|---------------------------|--------|--------|-----------------------------------------------|-----|--------|-------------|-------|--------|
| Scalp                     | 18-39  | ↓      | Follicular eczema                              | 18-39| ↓      | Skin pain   | 18-39| ↑      |
|                           | 40+    | ↓↓     |                                               | 40+ | ↓↓     |             | 40+  | –      |
| Around the eyes           | 18-39  | ↑      | Ichthyosis                                     | 18-39| –      | Itch        | 18-39| ↓      |
|                           | 40+    | –      |                                               | 40+ | –      |             | 40+  | ↓      |
| Postauricular             | 18-39  | ↓↓     | Keratosis Pilaris                              | 18-39| –      |             |       |        |
|                           | 40+    | ↓↓     |                                               | 40+ | ↓↓     |             |       |        |
| Face                      | 18-39  | ↓      | Nummular eczema                                | 18-39| ↑      |             |       |        |
|                           | 40+    | ↓      |                                               | 40+ | ↑      |             |       |        |
| Neck                      | 18-39  | ↓      | Palmar hyperlinearity                          | 18-39| ↓      |             |       |        |
|                           | 40+    | –      |                                               | 40+ | –      |             |       |        |
| Nipples                   | 18-39  | ↓↓     | Pityriasis Alba                                | 18-39| ↓↓     |             |       |        |
|                           | 40+    | ↓↓     |                                               | 40+ | ↓↓     |             |       |        |
| Elbows                    | 18-39  | ↓↓     | Lichenification                                | 18-39| ↓↓     |             |       |        |
|                           | 40+    | ↓↓     |                                               | 40+ | ↓↓     |             |       |        |
| Flexural sites            | 18-39  | ↓↓     | Ooze                                          | 18-39| ↓↓     |             |       |        |
|                           | 40+    | ↓↓     |                                               | 40+ | ↓↓     |             |       |        |
| Wrists                    | 18-39  | ↓      | Redness                                       | 18-39| ↓      |             |       |        |
|                           | 40+    | ↓      |                                               | 40+ | ↓      |             |       |        |
| Hands                     | 18-39  | ↓↓     | Excoriation                                    | 18-39| ↓↓     |             |       |        |
|                           | 40+    | ↓↓     |                                               | 40+ | ↓↓     |             |       |        |
| Fingers                   | 18-39  | ↓↓     | Swelling                                       | 18-39| ↓↓     |             |       |        |
|                           | 40+    | ↓↓     |                                               | 40+ | ↓↓     |             |       |        |
| Genitalia                 | 18-39  | –      | Xerosis                                        | 18-39| ↓      |             |       |        |
|                           | 40+    | –      |                                               | 40+ | –      |             |       |        |
| Knees                     | 18-39  | ↓↓     | Cheilitis                                      | 18-39| ↓      |             |       |        |
|                           | 40+    | ↓↓     |                                               | 40+ | ↓↓     |             |       |        |
| Ankles                    | 18-39  | ↓      |                                               |       |        |             |       |        |
|                           | 40+    | ↓      |                                               |       |        |             |       |        |
| Feet                      | 18-39  | ↓      |                                               |       |        |             |       |        |
|                           | 40+    | ↓      |                                               |       |        |             |       |        |

AD, Atopic dermatitis.

†† indicates an adjusted odds ratio of ≥4.000 or adjusted beta coefficient of ≥2.000; † indicates an adjusted odds ratio of 2.000 to 3.999 or adjusted beta coefficient of 0.5000 to 1.999.

— indicates an adjusted odds ratio of 1.000 to 1.999 or adjusted beta coefficient of -0.4999 to 0.4999.

↓ indicates an adjusted odds ratio of 0.751 to 0.999 or adjusted beta coefficient of -0.5000 to -1.999; ↓↓ indicates an adjusted odds ratio of ≤0.75 or adjusted beta coefficient of ≤ -2.000.
adults, 9.7% were in class 2, 5.7% class 4, and 2.8% were in class 3. In older adults, 8.3% were in class 4, 4.4% in class 2, and 1.67% in class 3.

**Discussion**

This study demonstrated that the phenotypic presentation of AD varies across age groups. Consistent with previous studies, pediatric and adult patients had similar likelihood of xerosis, head and neck involvement, cheilitis, and nummular eczema.\(^3\,15\) Additionally, we found similar likelihood of AD involving the fingers, wrist, hands, genitalia, feet as well as the associated signs: follicular eczema, ichthyosis, excoriations, swelling, and redness. However, we found increased likelihood of AD lesions around the eye in young adults as well as
decreased likelihood of moderate-severe lichenification in older adults. This is in contrast to a previous study that found increased prevalence of eye involvement in pediatric patients and increased lichenification in adult patients with AD. These results may be because of differences in the prevalence of respiratory atopy and environmental exposures.

In older adults, AD was previously shown to present similarly as adolescents and young adults with respect to presence of AD lesions on elbow and knee folds, face and neck, and presence of Dennie-Morgan lines, and nummular eczema lesions. We found that older adults aged ≥40 years, but not young adults, were less likely to develop AD on the nipples and flexures. They also were less likely to have the associated signs keratosis pilaris and lichenification, as well as less severe signs than younger patients. Our results suggest that clinical manifestation of AD varies with age in previously unrecognized ways; clinicians should account for these differences when evaluating patients of different age groups.

Itch is the most common and burdensome symptom of AD. Consistent with previous studies, we found that itch is ubiquitous across all age groups. However, pediatric patients were more likely to experience severe itch compared to younger and older adults. More severe itch was likely related to more extensive AD lesions compared to adult patients. Interestingly, despite increased itch in pediatric patients, we found no difference in the severity of skin pain across all age groups. Moreover, pediatric patients reported skin pain less often than adult patients. This may be because of age-related differences in pain perception. For example, one study found that children tend to perceive severe itch and pain as the same sensation, whereas adults perceive these symptoms separately.

Previous studies found differences of AD presentation by age of AD onset, AD severity, ethnicity, and progression throughout childhood. Our study identified an additional subtype of AD, with distinct differences across age. Consistent with the Hanifin-Rajka major criteria, all age groups experienced significant pruritus, however, both young and older adults were less likely than pediatric patients to experience several minor criteria. This wide variation in presentation may make the diagnosis of AD difficult. In pediatric patients, acute contact dermatitis, scabies, molluscum dermatitis, tinea corporis, psoriasis, and actinic prurigo may mimic AD and should be ruled out. In adult patients, psoriasis, cutaneous T-cell lymphoma, drug eruptions, contact dermatitis, scabies, tinea corporis, dermatomyositis, and polymorphous light eruption should be considered as part of the differential diagnosis. The broad differential diagnosis is particularly important in adult patients without flexural eczema or with hand or facial dermatitis.

Despite the growing evidence of unique AD phenotypes, treatment is currently based on AD severity. Although recent treatments such as dupilumab have been a turning point for many patients, there are still a subset of patients who are partial or complete nonresponders. Although it is unclear why some patients do not respond, it may be due in part to their subtype of AD. Though, 1 open-label Italian observational study of 221 patients treated with dupilumab found that it was effective across multiple AD phenotypes, including nummular eczema, prurigo, and erythroderma. Further studies are needed to identify whether more phenotypes of AD exist, how these phenotypes relate to biomarkers of disease, and what treatment regimen is best suited for each of the subtypes.

This study has several strengths, including the large sample size, standardized assessment of AD signs, and prospective design. Previously validated patient-reported measures were used for AD severity. Latent class analysis was used to identify the dominant phenotypes of AD across age groups, with 4 subgroups identified for both AD sites and signs. The limitations of this study include recruitment of patients from a single academic center that may limit generalizability, lack of data on treatment effects on the various phenotypes, and lower proportion of pediatric patients in the cohort. Future even larger multicenter studies are warranted.

In conclusion, the clinical presentation of AD differs between children, young adults, and older adults. In particular, pediatric patients are more likely to experience AD in classical sites such as the knees and have more associated and severe signs of disease. Older adults tend to present with less flexural eczema and the fewest associated signs, potentially making the diagnosis difficult in this population. Clinicians should recognize the various clinical phenotypes of AD and consider a personalized approach for the management of AD. Further research is needed to understand how these distinct phenotypes respond to current treatment options.

Conflicts of interest
None disclosed.

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