þÿFactors associated with severity of atopic derma cross-sectional study

Salava, A.

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ORIGINAL ARTICLE

Factors associated with severity of atopic dermatitis – a Finnish cross-sectional study

A. Salava, V. Salo, J. Leppänen, A. Lauerma, A. Remitz

Skin and Allergy Hospital, Helsinki University Hospital, Helsinki, Finland

*Correspondence: A. Salava. E-mail: alexander.salava@hus.fi

Abstract

Background Severity-associated factors in atopic dermatitis (AD) have focussed on early onset, concomitant atopic diseases, markers of Th2-shifted inflammation and filaggrin mutations.

Objectives To investigate factors associated with severe AD in Finnish patients.

Methods We conducted a single-centre, cross-sectional observational study with 502 AD patients aged 4.79 to 79.90 years (mean 32.08 years). Disease severity was assessed with the Rajka–Langeland severity score and EASI and associated clinical signs were evaluated. Data regarding onset, relatives, atopic and other comorbidities was gathered retrospectively. We investigated total serum IgE-levels, a panel of filaggrin null mutations and functional variants of genes associated with skin barrier defects.

Results Factors more frequent in severe AD included early onset ($P = 0.004$, 95%CI 0.000–0.024), male sex ($P = 0.002$, 95%CI 0.000–0.11), history of smoking ($P = 0.012$, 95%CI 0.000–0.024), concomitant asthma ($P = 0.001$, 95%CI 0.000–0.011), palmar hyperlinearity ($P = 0.013$, 95%CI 0.014–0.059), hand dermatitis ($P = 0.020$, 95%CI 0.000–0.029) and history of contact allergy ($P = 0.042$, 95%CI 0.037–0.096). Body mass indices ($P < 0.000$, 95%CI 0.000–0.011) and total serum IgE-levels ($P < 0.000$, 95%CI 0.000–0.011) were higher in severe AD. No differences were observed for allergic rhinitis, allergic conjunctivitis, food allergy, peanut allergy, prick positivity, keratosis pilaris, history of herpes simplex infections, filaggrin null mutations and other gene variants.

Conclusions Severity determinants in Finnish patients seem to be early-onset, male sex, smoking, overweight, concomitant asthma, palmar hyperlinearity, hand dermatitis and high IgE-levels. A sub-typing of patients in relation to confirmed severity determinants may be useful for course prediction, prognosis and targeted AD management.

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Conflicts of interest

All authors declare no conflicts of interest.

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Introduction

Atopic dermatitis (AD) is the most frequent chronic skin disease in Finland and causes a significant burden.[1,2] Typically, the disease begins in early childhood, but in recent years, an increase in adult-onset has been reported.[3] The multifactorial pathogenesis is based on environmental interactions, defects in skin barrier and immune dysregulation, resulting in both cutaneous and systemic inflammation.[4,5] The clinical picture is diverse, often age-dependent and has a wide spectrum of severity.[6]

As a chronic relapsing skin disease, AD tends to exacerbate spontaneously or by patient-related factors.[7] In most cases, disease activity decreases during childhood.[8] However, in subgroups of patients, AD follows a severe or chronic relapsing course during child- and adulthood.[9] There have also been reports of increasing numbers of severe adult-onset AD.[10] Factors that have been associated with severity are early onset, profound Th2-immune shift, high serum IgE-levels and eosinophil counts, concomitant asthma and known history of severe AD in first-degree relatives.[11,12] There have also been studies on predictive biomarkers, filaggrin mutations (FLG) and polygenic prediction regarding severity, but results have been inconsistent.[13–17]

In a recent study, we observed that persistence of AD into adulthood and adult-onset have increased and prevalence numbers in Finland are among the highest worldwide, but severity-associated factors have not been characterized.[18] Our aim was to

investigate which clinical signs and patient characteristics associate with severe AD in Finnish patients.

Material and methods

We performed a single-centre, investigator-driven, cross-sectional observational study at Helsinki University Hospital, Finland. Five hundred and two patients of the hospital with dermatologist-confirmed AD were randomly selected to participate. The study size was based on statistical power calculations (statistical power 80%, alfa 0.05; anticipated means and incidences were compared with our former Finnish population-based study and data of the Finnish National Institute for Health and Welfare)[18] and recruitment and data collection were carried out during 2011–2015. In Finland, mild and moderate AD patients are mostly managed in primary care, and moderate-to-severe cases are sent to specialist care institutions.[19] Eligibility criterium was AD, and there were no specific exclusion criteria. None of the study patients were currently on systemic immunosuppressive therapies or phototherapy since patients were sent to the university clinic for first consultation. During a comprehensive clinical examination disease severity, retrospective data regarding patient history and clinical signs were evaluated. The study was designed as a cross-sectional setting with a single clinical examination at the time point of contact with the tertiary care consultation. Data on disease onset, history of smoking (more than 5 years), hereditary factors in first-degree relatives, contact allergies (confirmed by patch tests), history of herpes simplex (HSV) infections, prick positivity (confirmed positivity to any of the aeroallergens birch, timothy, mug wort, cat, dog, horse, house dust mite and *Cladosporium herbarum*), peanut allergy, food allergies (confirmed by allergy tests) and atopic comorbidities was patient-reported and not verified by health records. Clinical information included disease severity (Rajka–Langeland severity score, RLS[20] and eczema area and severity Index, EASI[21]), age, sex, height and weight (body mass index, BMI) and associated clinical signs: the presence of hand dermatitis, palmar hyperlinearity, white dermographism and keratosis pilaris. Because the cross-sectional setting with a single time point of clinical patient evaluation, we decided to classify severity by the RLS which takes the disease course during the previous year into account.[22] Clinical examinations were carried out by experienced dermatologists.

In addition, total serum IgE-levels and FLG null-mutation status were investigated. Serum IgE-levels were analysed with a sensitive enzyme-linked immunoassay. The highest total serum IgE-levels of the past 10 years were obtained from patient records, if available. The collection of DNA samples (whole blood) regarding FLG mutation status was conducted at the clinical visit, but all samples were analysed together. We investigated four most frequent FLG null mutations in the European population (R501X, 2282del4, R2447X, S3247X), two FLG null mutations enriched in Finland (S1020X, V603M), and the 12-repeat allele (rs12730241). In addition, 59 functional variants of 10 barrier genes associated with skin barrier defects were investigated (e.g. claudin-1, filaggrin-2). The genetic testing methods have been described in detail in a former study.[23] All laboratory tests were performed in the Laboratory of Helsinki University Hospital (HUSLAB®) and were based on accredited methods. The study protocol was approved by the local ethics committee of the University Hospital Helsinki, Finland.

To analyse factors associated with AD severity, patients were classified into three groups: mild AD (RLS 3.00–4.00), moderate AD (RLS 5.00–7.00) and severe AD (RLS 8.00–9.00). Comparisons were conducted between patients with severe and mild AD.

Statistical analyses were performed with IBM SPSS® Statistics version 27.0. Dependency between nominal variables was calculated with the Pearson's Chi-squared test. In addition, strength of association was measured with Cramér's V coefficient (from 0, no relationship to 1, perfect association). Based on the wide spectrum of heterogeneous factors investigated (e.g. nominal retrospective data, numeric laboratory, and clinical data) and the small cross-sectional sample size with uneven distribution between study groups, there were no adjusted analyses carried out (e.g. regression analysis).[24] Dependency between quantitative data was assessed with the Mann–Whitney *U* test. A *P*-value of <0.05 was considered significant, and 95% confidence intervals (CI) were designated.

Results

AD severity

There were 146 patients with mild, 231 patients with moderate and 125 with severe AD. The median RLS in the mild AD group was 3.50 (IQR 3.00–4.00) and 8.00 (IQR 8.00–9.00) in the severe AD group. Patients with severe AD had significantly higher EASI scores at the clinical visit ($P < 0.001$, CI 0.000–0.011; Table 1). The median EASI in severe AD patients was 19.50 (IQR 12.97–28.72) and in mild AD 0.60 (IQR 0.00–1.80; Fig. 1b).

Age and sex

Patients with severe AD were older than patients with mild AD ($P = 0.020$, CI 0.007–0.45). The median age in severe AD was 36.02 years (IQR 24.10–47.04) and in mild AD, 28.25 years (IQR 21.62–40.17; Table 1). There were more males observed with severe AD ($P = 0.002$, CI 0.000–0.11; Fig. 1a).

Smoking and BMI

History of smoking was more frequent in patients with severe AD ($P = 0.012$, CI 0.000–0.024). 54.4% of patients with severe AD had a history of smoking, compared to 38.6% with mild AD (Table 1). The median BMI in severe AD patients was 25.21 (IQR 22.27–28.08) and in mild AD, 22.75 (IQR 20.51–24.93) and thus higher in patients with severe AD ($P < 0.000$, CI 0.000–0.011; Fig. 1b).

Table 1 Demographic and patient history data; the table includes absolute numbers of patients with existing valid data, and where applicable the %-percentage, descriptive statistics (median, interquartile range, mean, range) and statistical comparison of patients with mild and severe atopic dermatitis

	All patients	Mild AD	Moderate AD	Severe AD	Comparison mild *vs.* severe AD
Patients, *n*, M:F, *n* (%)	502, 188 (37.5): 314 (62.5)	146, 47 (32.2): 99 (67.8)	231, 77 (33.3): 154 (66.7)	125, 64 (51.2): 61 (48.8)	***P* = 0.002** (0.000–0.11)†, CV 0.193
AD severity‡, RLS, median, IQR (mean, range)	6.00, 4.00–7.62 (5.80, 3.00–9.00)	3.50, 3.00–4.00 (3.50, 3.00–4.00)	6.00, 5.00–7.00 (5.87, 4.5–7.5)	8.00, 8.00–9.00 (8.37, 8.00–9.00)	***P* < 0.000** (CI 0.000–0.011)§
EASI, median, IQR (mean, range)	4.05, 0.90–11.77 (8.23, 0.00–57.60)	0.60, 0.00–1.80 (0.99, 0.00–5.80)	4.50, 1.80–8.00 (5.51, 0.00–30.40)	19.50, 12.97–28.72 (21.98, 0.20–57.4)	***P* < 0.000** (CI 0.000–0.011)§
Age, years median, IQR (mean, range)	28.38, 21.00–40.04 (32.08, 4.79–79.90)	28.25, 21.62–40.17 (32.11, 6.93–79.90)	26.69, 19.49–36.72 (29.92, 4.79–73.18)	32.48, 24.10–47.04 (36.02, 6.57–76.34)	***P* = 0.020** (CI 0.007–0.45)§
History of smoking yes (%), no (%)	206 (43.6), 267 (56.4)	54 (38.6), 86 (61.4)	90 (41.1), 129 (58.9)	62 (54.4), 52 (45.6)	***P* = 0.012** (CI 0.000–0.024)†, CV 0.158
BMI, median, IQR (mean, range)	22.81, 20.88–25.96 (23.67, 13.13–42.27)	22.75, 20.51–24.93 (22.75, 14.49–35.14)	22.34, 20.44–25.88 (23.32, 13.13–42.27)	25.21, 22.27–28.08 (25.42, 16.65–37.87)	***P* < 0.000** (CI 0.000–0.011)§
AD onset <2 years, *n* (%)	335 (73.8)	91 (69.5)	152 (70.7)	92 (85.2)	***P* = 0.004** (CI 0.000–0.011)†, CV 0.185
AD onset >2 years, *n* (%)	119 (26.2)	40 (30.5)	63 (29.3)	16 (14.8)	
AD in FDR, yes (%), no (%)	340 (73.3), 124 (26.7)	89 (65.4), 47 (34.6)	169 (77.9), 48 (20.8)	82 (73.9), 29 (26.1)	*P* = 0.153 (CI 0.132–0.223)†, CV 0.091
Dry skin in FDR, yes (%), no (%)	259 (71.2), 105 (20.9)	76 (69.7), 33 (30.3)	123 (73.2), 45 (26.8)	60 (69.0), 27 (31.0)	*P* = 0.909 (CI 0.989–1.000)†, CV 0.008
Ichthyosis vulgaris in FDR, yes (%), no (%)	7 (3.4), 197 (96.6)	2 (3.4), 57 (96.6)	2 (2.2), 89 (97.8)	3 (5.6), 51 (94.4)	*P* = 0.576 (CI 0.678–0.783)†, CV 0.053
Positive prick¶, yes (%), no (%)	273 (62.8), 162 (37.2)	82 (62.1), 50 (37.9)	126 (62.7), 75 (37.3)	65 (63.7), 37 (36.3)	*P* = 0.801 (CI 0.843–0.920)†, CV 0.016
Positive peanut prick, yes (%), no (%)	130 (29.8), 306 (70.2)	36 (27.1), 97 (72.9)	62 (30.8), 139 (69.2)	32 (31.4), 70 (68.6)	*P* = 0.471 (CI 0.539–0.656)†, CV 0.047
Peanut allergy, yes (%), no (%)	150 (35.9), 268 (64.1)	38 (31.1), 84 (68.9)	71 (36.2), 125 (63.8)	41 (41.0), 59 (59.0)	*P* = 0.127 (CI 0.135–0.227)†, CV 0.102
Allergic rhinitis, yes (%), no (%)	380 (76.3), 118 (23.7)	102 (70.8), 42 (29.2)	180 (78.3), 50 (21.7)	98 (79.0), 26 (21.0)	*P* = 0.124 (CI 0.158–0.255)†, CV 0.094
Allergic conjunctivitis, yes (%), no (%)	345 (69.0), 155 (31.0)	98 (67.6), 32.2 (32.4)	157 (68.0), 74 (32.0)	90 (72.6), 34 (27.4)	*P* = 0.373 (CI 0.391–0.509)†, CV 0.054
Food allergies, yes (%), no (%)	321 (65.1), 172 (34.9)	87 (61.3), 55 (38.7)	149 (65.6), 78 (34.4)	85 (68.5), 39 (31.5)	*P* = 0.215 (CI 0.223–0.330)†, CV 0.076
Asthma, yes (%), no (%)	197 (39.4), 303 (60.6)	48 (33.1), 97 (66.9)	84 (36.4), 147 (63.6)	65 (52.4), 59 (47.6)	***P* = 0.001** (CI 0.000–0.011)†, CV 0.195

Statistically significant *P*-values are bolded ($P < 0.05$).
† Pearson's Chi-squared test.
‡ Based on the Rajka and Langeland severity score.
§ Mann–Whitney *U* test.
¶ Prick test included aeroallergens birch, timothy, mug wort, cat, dog, horse, house dust mite and *Cladosporium herbarum*.
AD, Atopic dermatitis; BMI, Body mass index; CI, 95% confidence interval; CV, Cramér's V value; EASI, eczema area and severity index; FDR, first-degree relatives; IQR, interquartile range; RLS, Rajka–Langeland score.

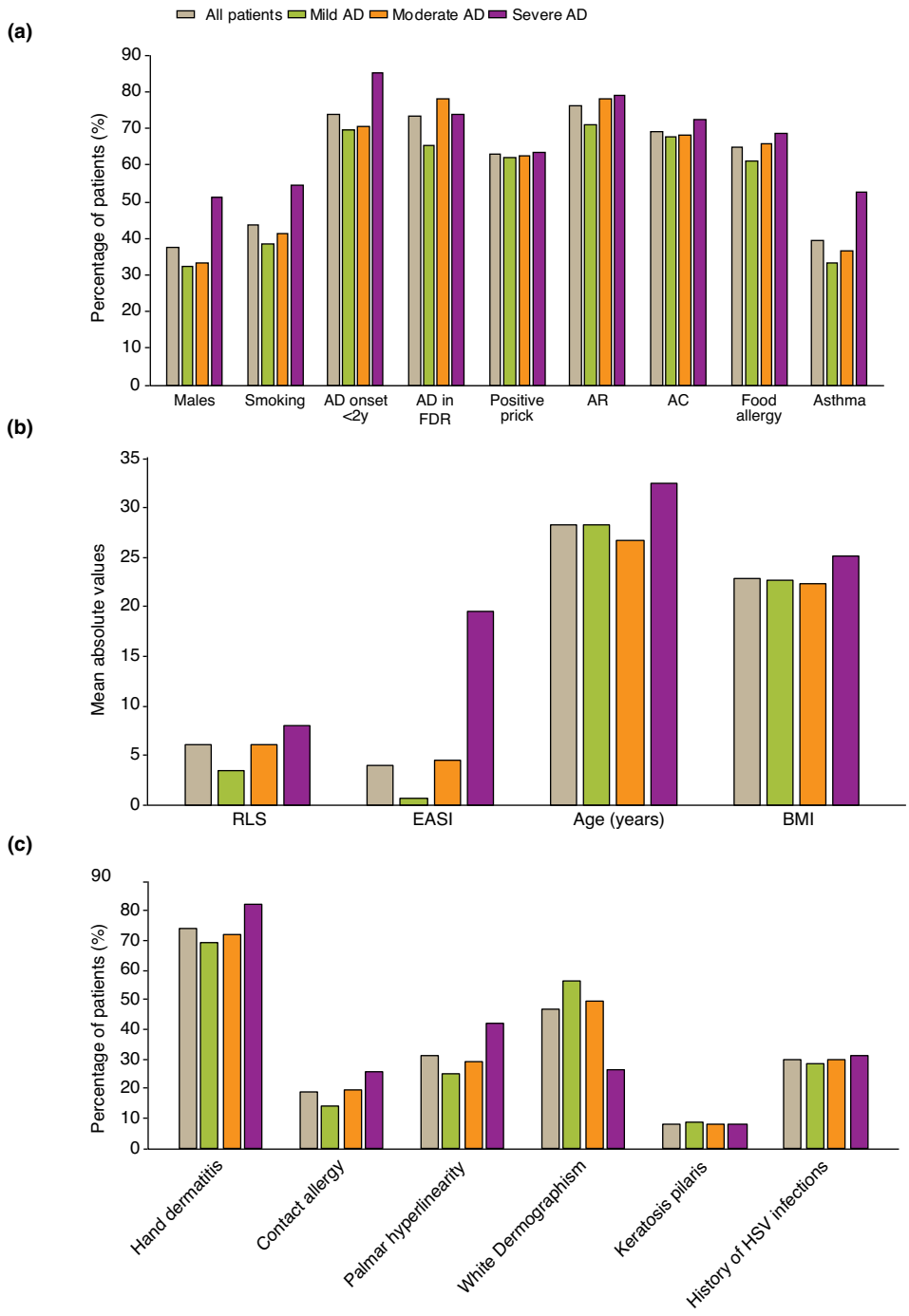

Figure 1 Clinical signs and patient history data; (a) Proportion (%) of patients regarding sex (males), smoking (history of smoking >5 years), disease onset >2 years, atopic dermatitis in first-degree relatives (FDR), prick positivity to aeroallergens, allergic rhinitis (AR), allergic conjunctivitis (AC), food allergy and asthma; (b) Mean absolute values of disease severity (Rajka and Langeland severity score, RLS), EASI, age and body mass index (BMI); (c) Proportion (%) of patients with different associated clinical signs, HSV: Herpes simplex virus.

AD onset and first-degree relatives

Disease onset <2 years of age was more frequent in patients with severe AD ($P = 0.004$, CI 0.000–0.011). There were no significant differences regarding positive family history (first-degree relatives) of atopic dermatitis ($P = 0.153$), dry skin ($P = 0.909$) or ichthyosis vulgaris ($P = 0.576$; Table 1).

Asthma and atopic comorbidities

Severe AD patients had more asthma than mild AD patients ($P = 0.001$, CI 0.000–0.011). A total of 52.4% of patients with severe AD had asthma, compared to 33.1% of patients with mild AD (Table 1). No differences were observed regarding allergic rhinitis ($P = 0.124$), allergic conjunctivitis ($P = 0.373$), food allergy ($P = 0.215$), peanut allergy ($P = 0.127$), positive prick tests to aeroallergens ($P = 0.801$) and positive prick test to peanut ($P = 0.471$; Fig. 1a).

Associated clinical signs

Hand dermatitis ($P = 0.020$, CI 0.000–0.029, Cramér's V (CV) 0.147) and palmar hyperlinearity ($P = 0.013$, CI 0.014–0.059, CV 0.178) were more frequent in patients with severe AD. There were 92 patients (82.1%) with hand dermatitis in the severe AD group and 95 patients (69.3%) in the mild AD group (Table 2). Palmar hyperlinearity was diagnosed in 38 patients (41.8%) of the severe AD group and in 26 patients (25.0%) of the mild AD group. In addition, there were more severe AD patients with contact allergies ($P = 0.042$, CI 0.037–0.096, CV 0.150; Fig. 1c). In mild AD, there were more patients with white dermographism than in severe AD patients ($P < 0.0001$, CI 0.000–0.011).

Palmar hyperlinearity ($P < 0.0001$, CI 0.000–0.006, CV 0.330) and keratosis pilaris ($P = 0.010$, CI 0.013–0.042, CV 0.138) was associated with positive FLG null-mutation status in all patients. There were, however, no significant differences between mild, moderate or severe AD regarding palmar hyperlinearity ($P = 0.093$, CI 0.014–0.158, CV 0.318) and keratosis pilaris ($P = 0.787$, CI 0.891–1.00, CV 0.103).

Total serum IgE-levels

Serum IgE-levels were higher in patients with severe AD ($P < 0.0001$, CI 0.000–0.011) (Table 3). The median total serum IgE-level in severe AD was 2178.00 kU/L (IQR 271.25–9888.00) compared to 396.00 kU/L (IQR 108.00–1343.00) in mild AD (Fig. 2a). In addition, maximum IgE-levels of the last 10 years were higher in severe AD (median 3609.00 kU/L, IQR 299.00–12454.50) than in mild AD (median 965.00 kU/L, IQR 254.50–5758.50; $P < 0.0001$, CI 0.000–0.011; Fig. 2b). There were also more severe AD patients with IgE-levels over 10 000 kU/L in the past 10 years ($P < 0.0001$, CI 0.000–0.011).

FLG mutation status

Carriers of FLG null-mutations R501X, 2282del4 and R2447X were detected in the patient cohort, but no significant differences observed regarding AD severity (Table 3). We identified some cases of combined FLG mutation heterozygosity with no link to severity. In both groups, mild and severe AD, there were 17 patients with detected FLG null mutations, 11.6% and 13.6%, respectively (Fig. 2c). Other investigated FLG null mutations (S1020X and S3247X) and gene variants involved in skin barrier function and those enriched in the Finnish population had low allele frequencies and were not associated with AD or disease severity. The results have been reported in detail formerly.[23]

Discussion

The study aim was to identify severity-associated factors in Finnish AD patients. Evaluation of severity showed similar data for

Table 2 Associated clinical signs; the table includes absolute numbers of patients with existing valid data, where applicable, the %-percentage and statistical comparison of patients with mild and severe atopic dermatitis

	All	Mild AD	Moderate AD	Severe AD	Comparison mild vs. severe AD
Hand dermatitis, yes (%), no (%)	340 (73.8), 121 (26.2)	95 (69.3), 42 (30.7)	153 (72.2), 59 (27.8)	92 (82.1), 20 (17.9)	***P* = 0.020** (CI 0.000-0.029)*, CV 0.147
Contact allergies, yes (%), no (%)	65 (19.1), 276 (80.9)	15 (13.8), 94 (86.2)	31 (19.6), 127 (80.4)	19 (25.7), 55 (74.3)	***P* = 0.042** (CI 0.037-0.096)*, CV 0.150
Palmar hyperlinearity, yes (%), no (%)	111 (31.0), 247 (69.0)	26 (25.0), 78 (75.0)	47 (28.8), 116 (71.2)	38 (41.8), 53 (58.2)	***P* = 0.013** (CI 0.014-0.059)*, CV 0.178
White dermographism, yes (%), no (%)	176 (46.6), 202 (53.4)	67 (56.3), 52 (43.7)	87 (49.4), 89 (50.6)	22 (26.5), 61 (73.5)	***P* < 0.000** (CI 0.000-0.011)*,†, CV 0.295
Keratosis pilaris, yes (%), no (%)	28 (8.1), 319 (91.9)	9 (8.7), 95 (91.3)	12 (7.7), 144 (92.3)	7 (8.0), 80 (92.0)	*P* = 0.880 (0.989-1.000)*, CV 0.011
History of HSV infections, yes (%), no (%)	138 (29.7), 326 (70.3)	40 (28.6), 100 (71.4)	63 (29.7), 149 (70.3)	35 (31.3), 77 (68.8)	*P* = 0.644 (CI 0.686-0.790)*, CV 0.029

Statistically significant *P*-values are bolded ($P < 0.05$).
CI, 95% Confidence Interval; CV, Cramér's V value; HSV, Herpes simplex virus.
*Pearson's Chi Square test.
†Number of patients with white dermographism was significantly higher in the group of mild AD.

Table 3 Serum total IgE-levels and filaggrin mutation status; the table includes absolute numbers of patients with existing valid data, and where applicable the %-percentage, descriptive statistics (median, interquartile range, mean, and range) and statistical comparison of patients with mild and severe atopic dermatitis

	All patients	Mild AD	Moderate AD	Severe AD	Comparison mild vs. severe AD
Total serum IgE level evaluated, patients	496	143	229	124	
Total serum IgE level at clinical visit (kU/L) median, IQR (mean, range)	570.50, 158.50–2993.00 (4019.97, 2.0–189 500)	396.00, 108.00–1343.00 (1374.45, 2.0–22 683)	513.00, 137.50–2033.50 (2321.24, 2.0–43 774)	2178.00, 271.25–9888.00 (10208.01, 11.00–189 500)	***P* < 0.000** (CI 0.000–0.011)†
Highest total serum IgE level (kU/L) in past 10 year) median, IQR (mean, range)	965.00, 254.50–5758.50 (7096.32, 2.0–270 440)	638.00, 189.00–4109.00 (4099.92, 2.0–47 942)	(761.00, 208.00–3822.00 (4340.71, 2.0–148 280)	3609.00, 499.00–14454.50 (15664.53, 11.00–270 440)	***P* < 0.000** (CI 0.000–0.011)†
Total serum IgE-level over 10 000 kU/L in the past 10 year, yes (%), no (%)	85 (17.0), 416 (83.0)	20 (13.8), 125 (86.2)	24 (10.4), 207 (89.6)	41 (32.8), 84 (67.2)	***P* < 0.000** (CI 0.000–0.011)†
FLG mutation status evaluated, patients	502	129	231	125	
FLG null mutations (any), yes (%), no (%)	58 (11.6), 444 (88.4)	17 (11.6), 129 (88.4)	24 (10.4), 207 (89.6)	17 (13.6), 108 (86.4)	*P* = 0.629 (CI 0.690–0.794)‡
R501X	9 (1.8%)	1 (0.7)	4 (1.7)	4 (3.2)	*P* = 0.126 (CI 0.138–0.231)‡
2282del4	37 (7.4%)	10 (6.8)	16 (6.9)	11 (8.8)	*P* = 0.550 (CI 0.690–0.745)‡
R2447X	15 (3.0%)	6 (4.1)	5 (2.2)	3 (2.4)	*P* = 0.435 (CI 0.446–0.565)‡
2282del4 & R501X (combined heterozygosity)	1 (0.2%)	0 (0.0)	1 (0.4)	0 (0.0)	***P* = 1.0001**‡
R2447X & 2282del4 (combined heterozygosity)	1 (0.2%)	0 (0.0)	0 (0.0)	1 (0.8)	*P* = 0.280 (CI 0.494–0.554)‡

Statistically significant *P*-values are bolded ($P < 0.05$).
†Mann–Whitney *U* test.
‡Pearson's Chi-squared test.
AD, atopic dermatitis; CI, 95% confidence interval; FLG, Filaggrin; IQR, Interquartile range.

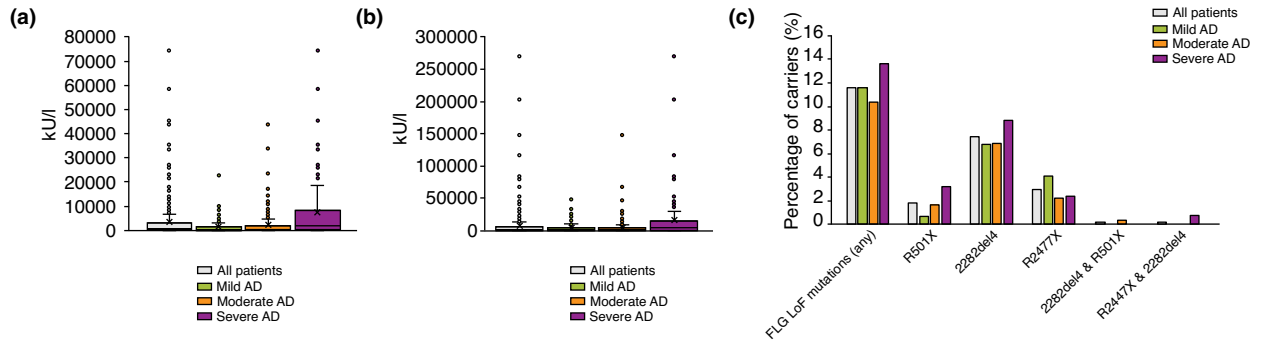

Figure 2 Total serum IgE-levels and filaggrin null-mutation status; (a) Comparison of serum total IgE-levels (kU/L) at the clinical visit; 2 highest outliers are not shown in the graph (patients with severe AD, 189 500 and 157 240 kU/L); lower and upper hinge of the box: 1st and 3rd quartile; whiskers: 1.5 * IQR; line: median, cross: mean; dots: outliners; (b) Highest total serum IgE-levels (kU/L) of the preceding 10 years; whiskers: 1.5 * IQR; line: median, cross: mean; dots: outliners; (c) Proportion (%) of patients with carrier status regarding indicated filaggrin null mutations and combined heterozygosity.

both clinical scores (RLS and EASI) and distribution was consistent in all severity groups.[22] The relatively high number of patients provided a representative picture regarding clinical and patient history features of Finnish AD patients in a tertiary healthcare centre.

The median age was higher in severe AD, which may be based on the continuous need for follow-up at a specialist centre in case of severe disease. We observed a considerably higher proportion of men with severe AD, which has been described in former studies.[25] For example, Holm *et al.* observed in a similar Danish cross-sectional study a higher proportion of men with severe AD.[26] Although severe AD is shown to be more frequent in men, the impact on quality of life seems to be higher in women.[27] Important observations were also the higher smoking frequencies and BMIs in severe AD. Both factors have been linked to disease severity and we could show their relevance also in Finnish patients.[28] Ascott *et al.* reported in recent population-based study from the United Kingdom a link between obesity and atopic dermatitis, but there was no proportional association with disease severity.[29] Based on our findings, it is important to counsel AD patients about possible links and the promotion of smoking cessation and treatment of obesity should be seen as an integral part of patient management.

Most of our patients with severe AD (85.2%) had disease onset before the age of 2 years, and there was a significant difference to patients with mild disease (69.5%). Thus, early onset seems to be associated with disease severity also in Finnish patients. Similar observations have been made by Thorsteinsdottir *et al.* in Danish patients, where besides early onset, FLG mutations and elevated IgE-levels were associated with severity.[30] Gerner *et al.*[31] observed in another Danish nationwide study that very early onset (before 6 months of age) predicted a more severe disease. But different from our findings, allergic rhinitis and female sex were associated with AD severity. In our study, there was a high number of patients with AD in first-degree relatives, but we did not observe differences regarding disease severity. Other hereditary factors, for example dry skin and ichthyosis, have been discussed as predisposing factors of severe AD but we did not make this observation.[32]

A total of 55% of our patients with severe AD had asthma, compared to 33% with mild disease. Studies have proposed Th2-shifted systemic inflammation as a factor for development of multiple atopic comorbidities in severe AD.[33,34] There have been reports that link the pronounced immunologic Th2-shift of asthma directly with epidermal skin barrier effects, causing susceptibility to more severe AD, skin infections and microbiome changes.[35] However, despite intensive research, it has remained unclear whether severe AD triggers transcutaneous IgE-mediated sensibilization and concomitant atopic diseases, or whether this frequently observed association is based on indirect or yet undetermined factors.[36]

Ha *et al.*[37] showed in a Korean paediatric cross-sectional study that AD severity correlated with the extent of allergic sensitization and eosinophilia. In our patients, we did not measure blood eosinophil counts and could not specify IgE-mediated sensitization because data were based on patient history. However, an important observation was the high percentage of atopic comorbidities, such as allergic rhinitis (severe AD 79.0%, mild AD 70.8%), allergic conjunctivitis (severe AD 72.6%, mild AD 67.6%) or food allergy (severe AD 68.5%, mild AD 61.3%), prick positivity to aeroallergens (severe AD 63.7%, mild AD 62.1%) and peanut allergy (severe AD 41.0%, mild AD 31.1%). This could be explained by the generally high prevalence of atopic disorders in Finland, but we did not identify an association with

disease severity.[38] Prevalence of atopic diseases varies between populations, for example, Sanclemente *et al.* reported in a comparable cross-sectional study from Colombia a substantially lower prevalence in AD patients (chronic rhinitis 68.9%, allergic conjunctivitis 29.7%, asthma 28.8%).[39]

There were more severe AD patients with hand dermatitis (82.1%), palmar hyperlinearity (41.8%) and contact allergies (25.7%), which seem to be linked to a more severe disease in Finnish patients. Palmar hyperlinearity has been linked to FLG mutations and possible markers of AD severity.[40] Hand dermatitis and contact allergy has been linked to epidermal barrier dysfunction and FLG mutations but not with AD severity.[41] We observed an association of FLG null-mutations both with palmar hyperlinearity and keratosis pilaris, but there were no differences regarding AD severity. White dermographism was more frequent in patients with mild AD, which has not been reported previously.

AD has been associated with cutaneous infections but their correlation with disease severity has remained uncertain.[42] Severe AD has been reported to predispose to HSV infections, possibly due to direct effects of the Th2-shift, aberrations in native immunity or epidermal barrier dysfunction.[43] Wan *et al.*[44] could show in population-based study from the United Kingdom that AD is associated in a dose-dependent manner with herpesvirus infections with increasing severity. We could not confirm this in our patients, which may be due to the generally low reported number of HSV infections.

We did not observe associations between FLG null mutations and AD severity. Although FLG mutations have been studied as predisposing factors, the link with disease severity in different populations has remained unclear.[15] Luukkonen *et al.*[23] could show in a Finnish observational study, that FLG null mutations constitute risk factors for AD but questioned their practicability as biomarkers for severity prediction. Based on our observations, it seems that the investigated FLG null-mutations are not associated with severe AD in Finnish patients. In addition, the investigated gene variants involved in skin barrier function were not associated with AD or disease severity. However, a more comprehensive analysis of FLG mutations may lead to identification of a causal link between AD severity and FLG mutation status also in Finnish patients. There might also be other polygenic factors that play a more significant role regarding the prediction of severe AD.[45]

Total serum IgE-levels have been used to evaluate AD severity and we could also observe an association of high total serum IgE-levels and severe AD.[46] However, it remains uncertain, whether elevated total serum IgE-levels are directly linked to atopic comorbidities, such as asthma, or constitute independent significance in assessing disease severity. It has also remained unclear if elevated IgE-levels play a direct role in the pathogenesis of AD or represent an epiphenomenon of Th2-shifted inflammation indirectly attributed to AD severity.[47,48]

Limitations

Due to the relatively high number of patients of a single-centre and cross-sectional study design, there were recognized limitations. For example, the study population consisted of patients visiting a university clinic which probably lead to a selection of severe AD cases and impact on associated factors such as obesity and smoking. Possible selection of more severe AD cases will thus reduce generalization of the results on a population level or in primary care. On the contrary, our specific aim was to investigate characteristics of AD patients and severity-associated factors in a tertiary health centre. We did not subdivide disease onset to cover more specific age groups in small children. Possibly, a very early onset could have yielded more significant results. For example, Wan *et al.* showed in a cohort study from the United States that early-, mid- and late-onset paediatric AD appear to be clinically distinct subtypes of the disease.[47] In addition, there are risks of information and recall bias because patient-related data were partly based on patient history (e.g. contact allergies and prick sensitivity) and information about AD severity of first-degree relatives was not classified. The diagnosis of asthma and other atopic comorbidities was patient-reported and not verified from records and there was no asthma grading. The diagnosis of HSV infections was not confirmed by microbiological tests and severity could not be addressed. There was a limited panel of FLG mutations and other relevant mutations or single nucleotide polymorphisms in the FLG gene could have been overseen. Lastly, total serum IgE-levels represented a time point and temporal variation was not assessed and eosinophil counts were not measured.

Conclusions

To our knowledge, we present the first Finnish data on associated factors of AD severity. Possible determinants of disease severity were disease onset <2 years of age, male sex, smoking and high BMI, concomitant asthma, palmar hyperlinearity, hand dermatitis, history of contact allergy and elevated total IgE-levels. Because AD is the most frequent chronic skin disease in Finland, the identification of severity-associated factors are important for designing optimal treatment and management protocols.[48,49] However, features that may predict a more severe disease course vary considerably between populations and need further research.[50]

In conclusion, there seem to be valuable factors which relate to severe AD.[51] A sub-typing of patients in relation to confirmed severity determinants may be useful for course prediction, prognosis and targeted management.[52-54]

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Data availability statement

The data that support the findings of this study are available from the corresponding author, (A.S.), upon reasonable request.

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