

CLINICAL REPORT

Clinical Features of Atopic Dermatitis at Two Years of Age: A Prospective, Population-based Case-control Study

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While atopic dermatitis (AD) usually presents early in life, few prospective studies focus on young children with AD. The objective of this study was to characterize, phenotypically and prospectively, young children with AD. From a community birth cohort of 2,256 children, consecutive children with AD ($n = 221$) were followed to 2 years of age, when they were re-examined and screened for atopic sensitization (skin-prick test to foods; Phadiatop[®]). Ninety-nine controls were also examined. AD debuted during the first year in 88% of cases. At the 2-year examination, when the children had already undergone topical treatment, 157/221 (71%) had ongoing eczema ranging among mild (45%), moderate (53%) and severe (2%). Airway problems indicating asthma had occurred in 9% of cases and 6% of controls (not significant), and allergic rhinoconjunctivitis in 5% and 0%, respectively ($p < 0.05$). The skin-prick test to common food allergens was positive in 27% of cases and Phadiatop was positive in 15%. In 67% both tests were negative. Eczema severity did not differ between sensitized and non-sensitized children. Positive Phadiatop was more common in boys than in girls with ongoing AD (22% vs 3%, $p < 0.01$), and more boys than girls had ongoing AD (82% vs 59%, $p < 0.001$); otherwise, no differences attributable to gender were found. **Key words:** childhood; onset of eczema; atopic sensitization; severity; asthma.

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Atopic dermatitis (AD) is a pruritic, chronically relapsing inflammatory skin disease, which in the majority of cases presents in the first year of life (1, 2). Its aetiology is unknown, but presumed to be multifactorial with interactions between genetic and environmental factors (3). In recent decades the prevalence of AD has increased remarkably (4–7), probably as a result of environmental factors in infancy (5). There is often an abnormal production of immunoglobulin E (IgE) antibodies to common environmental allergens. Other manifestations of atopic disease, such as bronchial asthma, allergic rhinoconjunctivitis and food allergy, are common in AD patients, as is a family history of atopic disease (1, 8). During early infancy, boys seem to be more often affected than girls (3).

Despite the early age of onset in AD, there have been few

prospective studies of its clinical characteristics in young children. Further, most studies are based on hospital material. This prompted the present systematic investigation into signs, symptoms and atopic sensitization in 2-year-old children with AD. They were recruited from a community-based birth cohort of 2,256 children and followed prospectively from the onset of their eczema.

METHODS

Study design

As part of a multidisciplinary epidemiological project (the BAMSE study) with the major aim of investigating the role of indoor environmental factors in the development of atopic disease, a cohort of 2,256 children born in the central and north-western parts of Stockholm between February 1995 and November 1996 was followed. Both urban and suburban areas were included. Access to a community population register ensured that the parents of all infants born in the area during this period could be approached. The children were consecutively recruited to the project at the child-health clinics during their first months (78% at 0–3 months of age). At the same time the parents answered a questionnaire concerning heredity and environmental factors. They were also requested to contact the Karolinska Hospital Department of Dermatology if their child had an itchy rash for 2 weeks or more. All children whose parents contacted the Department were examined within 1–2 weeks. Only cases first seen at the clinic before 25 months of age were included in the study. Children with AD or presumed AD were re-examined at regular intervals to ascertain the diagnosis and to follow the course. In general, examinations were made 3, 6 and 12 months after the first visit. At approximately 2 years (median age 24 months, range 20–29 months), children with AD were systematically re-examined. Controls were also examined at approximately 2 years of age (median 27 months, range 23–32 months). All examinations (structured interview and physical examination) were carried out by the same dermatologist (MB). Information on parental history of atopic respiratory disease was obtained from questionnaire data. All data were stored in a database constructed in Microsoft Access for Windows 95, version 7.0 (Microsoft Corporation, Washington, USA).

Cases

AD was diagnosed according to Hanifin & Rajka (9). Since the original major criteria of Hanifin & Rajka are not defined in detail, the following definitions were made. (a) The child was considered to have pruritus if the parents or the examining dermatologist had observed it rubbing or scratching itself, or if the child had excoriations. Current pruritus and/or a history of pruritus during the past 3 months was required to fulfil the criterion of pruritus. (b) Typical morphology and distribution was defined as erythema with papules and/or scaling, with or without oozing and crusting in at least 2 regions out of 4, namely the head, arms, legs and trunk. (c) Chronicity was defined as dermatitis for at least 3 months aggregate during a period of 6 months, or dermatitis requiring the use of topical corticosteroids at least once a week for 3 months aggregate of 6 months. (d) Atopic history

included a family history of asthma and/or allergic rhinoconjunctivitis and/or AD in parents and/or siblings; or a personal history of airway problems indicating asthma and/or allergic rhinoconjunctivitis. It required a physician's diagnosis or the use of inhaled corticosteroids to be classified as having airway problems indicating asthma. The diagnosis of allergic rhinoconjunctivitis was based on 2 or more separate episodes of blocked/running nose and/or itchy, watery eyes with conjunctival hyperaemia in distinct relation to known allergen exposure. In addition to atopic history according to Hanifin & Rajka (9), parental atopic respiratory history was recorded. This was defined as asthma and/or allergic rhinoconjunctivitis and allergy to furred animals and/or pollen allergy in one or both parents. These diagnoses should have been made by a physician. The diagnosis of asthma also required that the parent had taken some kind of asthma medication.

Scoring of atopic dermatitis

The severity of AD was assessed according to the SCORAD system, which has been thoroughly evaluated (10). The total SCORAD index with a range of 0–103 is based on the individual items extent (0–100) and intensity (0–18) and the subjective symptoms pruritus and sleep loss (0–10 each) according to the following formula: $(\text{extent}/5) + (\text{intensity} \times 3.5) + \text{sum of subjective items}$. Pruritus during the previous 3 days and sleep loss during the previous 3 nights are assessed on 2 separate visual analogue scales by the parents for their young children. The "adjusted" objective items ($\text{extent}/5$ and $\text{intensity} \times 3.5$; range 0–83) were used for dividing the material into mild (< 15), moderate (15–40) and severe (> 40) AD (11).

Skin-prick test and Phadiatop

At the examination of children with AD at 2 years of age, a capillary blood sample was obtained, and serum was kept frozen (-20°C). Serum IgE antibodies to inhalants were analysed in 212 of 221 cases with the Pharmacia CAP System Phadiatop® FEIA (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). The results were expressed as positive or negative, indicating the presence or absence of IgE antibodies to important inhalants (*Dermatophagoide s pteronyssinus*, *Dermatophagoide s farinae*, cat, dog, horse, birch, timothy, mugwort, olive, *Cladosporium herbarum* and *Parietaria judaica*). A skin-prick test for cow's milk, hen's egg white, cod, wheat, soy and peanut was also made with commercially available extracts (ALK, Copenhagen, Denmark); hen's egg white 1/100 w/v, the rest 1/20 w/v; using histamine dihydrochloride 10 mg/ml as a positive and the solvent (ALK) as a negative control. The test was considered positive when the reaction was at least half the diameter of the positive control and not less than 3 mm in diameter (12). Of 221 cases, 215 were skin-prick tested, all by the same nurse (IK).

Controls

The controls, matched for age and gender, were recruited among children in the cohort. They had no history of eczema at 1 year of age according to a questionnaire answered by the parents at that time, and still no history of eczema at 2 years of age according to a telephone interview. (Negative answers to questions: "Has your child at any time had an itchy rash leading to scratching for at least 2 weeks?" and "Has your child had eczema as diagnosed by a physician?") The controls were examined in the same way as the children with AD, except that the skin-prick test and the Phadiatop were not performed. To examine the controls when they were as close to 24 months of age as possible, controls were matched only to the cases born in 1996.

Statistics

The χ^2 test and the Fisher exact test were used for statistical analyses of proportions. Differences in eczema severity scores between groups were tested with the Mann-Whitney test. The Spearman rank-order correlation coefficient was analysed as a measure of association. A p -value < 0.05 was considered significant.

RESULTS

Demography of cases

Of 257 consecutive cases seen before 25 months of age, 238 fulfilled Hanifin & Rajka's AD criteria. Two-hundred and twenty-one were followed up to the age of 2 years, when 157 had ongoing AD and 64 latent AD (AD but no visible eczema at the time of examination at 2 years of age). Most of the children were of Caucasian origin; 95% of subjects with ongoing eczema and 92% of subjects with latent AD. The male/female ratios in the different study groups were: ongoing AD 1.62 (97/60), latent AD 0.52 (22/42) and total AD 1.17 (119/102). Of the 36 children who did not participate in the 2-year follow-up, 19 were excluded since they did not fulfil the diagnostic criteria of AD. The remaining 17 children were lost since they had moved or did not want to participate.

Demography of controls

The parents of 132 children were approached and 99 controls were finally examined. Eleven were excluded in the telephone interview because of a history of eczema and the parents of 14 declined participation. Eight were excluded at the examination, 7 because of ongoing eczema and 1 because of a history of eczema. Of the 99 controls, 98% were of Caucasian origin and the male/female ratio was 1.02 (50/49).

Age at onset of eczema

In 40% of the 221 cases the parents reported onset of eczema before 3 months, 68% before 6 months and 88% before 12 months of age (Fig. 1).

Major clinical features

The point prevalence of the major criteria of Hanifin & Rajka at 2 years of age is presented in Table I. Of the children with ongoing AD 69% had eczema on the legs, 45% on the trunk, 36% on the arms, 28% on the hands and 26% on the head. A history of eczema in the nappy region was reported in 36%. The reported cumulative incidence of airway problems indicating asthma and allergic rhinoconjunctivitis is presented in Table II.

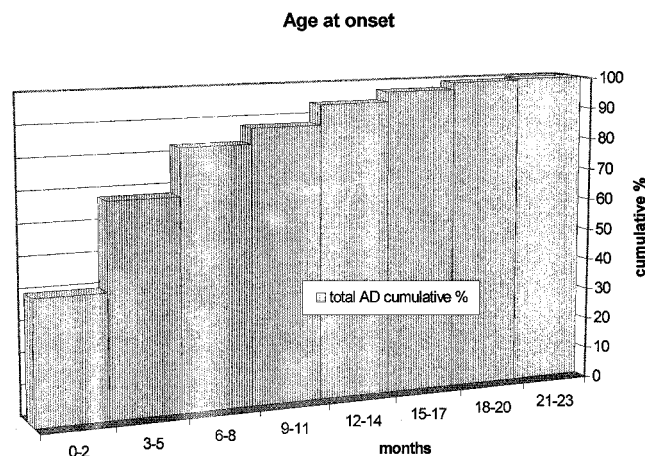


Fig. 1. Age at onset of eczema ($n = 221$). Total subjects with atopic dermatitis (AD) = ongoing AD plus latent AD.

Table I. Point prevalence of Hanifin & Rajka's (9) major criteria for atopic dermatitis (AD) at 2 years of age

	Ongoing AD	Latent AD	Controls
Total no.	157	64	99
Pruritus (%)	76***	45	4
Typical distribution and morphology (%)	68	N/A	N/A
Chronicity (%)	94	95	N/A
Atopic history (%)	78**	84**	57

See Methods for definitions of criteria.

N/A: not applicable.

Significantly more common than in controls ($p < 0.01$); *significantly more common in ongoing AD than in latent AD ($p < 0.001$).

Parental atopic history

Atopic respiratory history in the parents was significantly more common in cases than in controls (40% vs 22%, $p < 0.01$). Atopic respiratory history in one parent occurred in 31% of cases and 19% of controls, whereas atopic respiratory history in both parents was reported in 9% and 3%, respectively.

Atopic sensitization

At least one positive skin-prick test reaction to common food allergens was found in 27% of cases. Hen's egg white induced the majority of the positive reactions (21%), followed by peanut (15%), cow's milk (8%), cod (2%), wheat (2%) and soy (1%). Phadiatop was positive in 15% of the cases (15% of ongoing and 13% of latent AD). The frequencies of positive Phadiatop and/or skin-prick test were 34% in children with ongoing AD and 30% in children with latent AD (not significant), i.e. 67% were negative in both the skin-prick test and the Phadiatop.

Severity of eczema

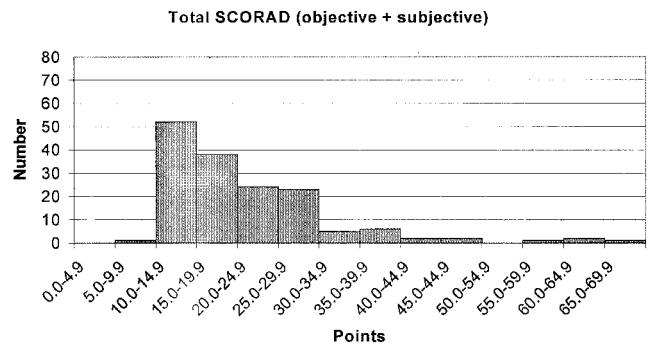
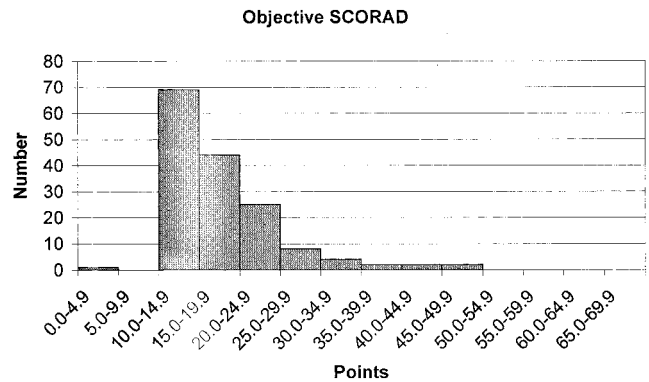
The severity of eczema, according to the SCORAD system, is presented in Figs. 2 and 3. The severity of ongoing AD ranged among mild (45% of cases), moderate (53% of cases) and severe (2% of cases). The individual items of the SCORAD index had the following median values and ranges: extent of body surface 3% (0.5–41.0), intensity 4 (1.0–12.0), pruritus 1.0 (0.0–9.7), sleep loss 0 (0.0–9.3), objective SCORAD 15.9 (3.6–47.9) and total SCORAD 18.0 (5.9–66.8). Pruritus assessed by the parents correlated significantly ($p < 0.001$) with extent, intensity and objective SCORAD. In the same way, sleep loss correlated with pruritus ($p < 0.001$). There was no significant difference in eczema severity (as measured by

Table II. Cumulative incidence of respiratory manifestations by history at 2 years of age

	Ongoing AD	Latent AD	Total AD	Controls
Total number	157	64	221	99
Airway problems indicating asthma (%)	11	3	9	6
ARC (%)	5	6	5*	0
Airway problems indicating asthma and/or ARC (%)	14	8	12	6

AD: atopic dermatitis; ARC: allergic rhinoconjunctivitis.

*Significantly more common than in controls ($p < 0.05$).

Fig. 2. Severity of eczema: total SCORAD ($n = 157$).Fig. 3. Severity of eczema: objective SCORAD ($n = 157$).

objective SCORAD) between sensitized and non-sensitized cases with ongoing eczema.

Gender aspects

Boys significantly more often had ongoing AD than girls ($p < 0.001$). Positive Phadiatop was significantly more common in boys than in girls with ongoing AD (22% vs 3%, $p < 0.01$), whereas no significant difference was found in the latent AD group. No statistically significant differences assignable to gender were found concerning age at onset, pruritus, distribution of eczema, chronicity, atopic history, parental atopic history, respiratory manifestations of atopy, skin-prick test positivity, SCORAD or individual items of the SCORAD.

DISCUSSION

The present study confirmed some results from earlier studies, such as the early age at onset (1–3) and the high point prevalence of hand eczema (13) in childhood AD. Eczema

severity was also in the same range as in other European studies of children (14–16), with most cases being mild or moderate.

Of Hanifin & Rajka's major features, chronicity was the most prevalent in cases with ongoing AD at 2 years of age (94%). The cases were children with known AD, most of them with onset of eczema during their first year of life, who were receiving treatment with topical glucocorticoids and/or emollients. This can explain the fairly low point prevalence of pruritus (76%) and typical distribution and morphology (68%). The cases undergoing treatment must also be kept in mind when considering the severity of eczema. In addition, children with food allergy were managed following clinical routine practice, e.g. if cow's milk was considered a relevant food allergen it was eliminated from the diet. Data on the prevalence of Hanifin & Rajka's minor criteria in the present cases and controls at 2 years of age have been published elsewhere (17).

Some 50–80% of patients with AD develop asthma and/or allergic rhinoconjunctivitis (18). In a prospective study, Diepgen & Fartasch noted that 33% of patients with AD developed allergic asthma and 16% allergic rhinitis during their first 5 years of life (19). In the present material, the cumulative incidence of airway problems indicating asthma did not differ significantly between children with AD and controls, whereas allergic rhinoconjunctivitis was significantly more common in the former than in the latter. The low cumulative incidence is most likely a consequence of the young age of the patients. For the skin-prick test to common food allergens, hen's egg white induced the most frequent positive skin-prick test reaction (21%), followed by peanut (15%). This fairly high prevalence of sensitization to peanut agrees with that in other studies. In a prospective study, Eigenmann et al. found sensitization to peanut in 25% of children with moderate to severe AD (median age 2.8 years, range 0.4–19.4 years) (20).

Bos et al. claim that the presence of allergen-specific IgE should be a mandatory criterion for AD (21). However, in the present study 67% of children with AD had no detectable atopic sensitization, while other studies have shown an inverse relation (9, 19, 22, 23). Once again, this is likely to be explained by the young age of the children studied herein. Moreover, the usefulness of a mandatory criterion that might appear years after the onset of clinical disease manifestations is doubtful.

In a study by Guillet & Guillet, sensitization to food and/or aeroallergens was more common in children with severe AD (100%) than in moderate (33%) and minor AD (0%) (24). In the present study, atopic sensitization did not influence the severity of eczema; nor was there any difference in sensitization between ongoing and latent AD, or in eczema severity between sensitized and non-sensitized children, which is in accordance with the study by Eigenmann et al. (20).

In the total AD group, the boys slightly outnumbered the girls, with a male/female ratio of 1.17, which agrees with earlier observations (1, 3). In the ongoing AD group, however, the male/female ratio was 1.62, with an inverse relation in the latent AD group (male/female ratio 0.52). This may indicate that boys suffer from a more continuous eczema than girls, but in the ongoing AD group there were no differences in SCORAD indices between boys and girls. Further, sensitization to airborne allergens was more common in boys than in girls with ongoing eczema. It may be that children with atopic sensitization have more continuous eczema than non-sensitized

children, which could explain the male/female ratio in the ongoing AD group.

We are not certain how many children with AD in the cohort failed to contact the Department of Dermatology, but 19 controls from the cohort were excluded because of ongoing eczema or a history of what may be eczema. Thus, there is a risk that a proportion of children with AD did not contact the department. Seven controls were excluded because of ongoing eczema at the examination at 2 years of age. Four of them had AD with objective SCORAD scores ranging from 10.6 to 25.7. Three had possible AD, but did not fulfil the criteria of Hanifin & Rajka, with objective SCORAD scores ranging from 7.2 to 18.6, giving in total 4 cases or possible cases with mild severity and 3 with moderate severity. These children may reflect the disease phenotype in potential AD cases not showing up.

In conclusion, in this material of 2-year-old children with AD, 45% had mild, 53% moderate and 2% severe eczema in the ongoing AD group. Twenty-seven per cent had a positive skin-prick test for food allergens and 15% had positive Phadiatop. However, 67% had no atopic sensitization as measured by these tests. The boys were overrepresented both in the ongoing AD group and among cases with positive Phadiatop, otherwise no gender differences were found. Although some children with AD were missed, the mode of recruitment to this study suggests that the cases are representative of AD cases among families contacting any level of the health-care system.

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