

Long-term follow-up of atopic dermatitis: Retrospective analysis of related risk factors and association with concomitant allergic diseases

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Background: The association of atopic dermatitis (AD) with other allergic diseases has been extensively studied; however, there is a lack of reports focusing on long-term studies of the clinical and allergometric evaluations observed during the course of AD in respect to its evolution and association with allergic responses in affected patients.

Objective: The aim of this study was to evaluate, with defined criteria of clinical diagnosis, severity assessment, and objective allergometric test at the time of inclusion, the natural course of AD, the factors influencing its healing or persistence, and the appearance of other allergic diseases with particular focus on asthma and the presence of specific immunoglobulin E at first observation.

Methods: This study included only children, aged between 6 and 36 months, whose first clinical examination was made between 1981 and 1989. A total of 252 children satisfied these criteria. A semistructured interview was performed by the physician using a preformed questionnaire, which was completed for 205 children (104 boys and 101 girls).

Results: AD had completely disappeared in 124 cases (60.5%). Other allergic manifestations that appeared included asthma in 70 cases (34.1%) and rhinoconjunctivitis (RC) in 118 cases (57.6%). Generally the average age of patients recovering from AD was higher in severe AD (6.0 ± 3.5 years) than in its moderate or mild forms (5.8 ± 4.5 and 5.5 ± 3.9 years, respectively). This phenomenon was particularly evident in children with hen's egg sensitization, who show a longer persistence of the condition (Student $t = 2.462$ and $P < .02$). The initial severity score of AD was found to be associated with a high frequency of asthma appearance (Pearson $\chi^2 = 14.225$ and $P < .001$). Hen's egg sensitization was significantly related to the appearance of asthma (Fisher's exact test $P < .007$) and RC (Fisher's exact test $P < .05$). A retrospective analysis of related risks factors and their association with concomitant allergic diseases in our case studies shows that the egg sensitization, severity of AD, and onset of RC were positively related to the occurrence of asthma. In addition, our analysis shows that, although the appearance of RC was proportional to the incidence of atopy and asthma, it was inversely related to the persistence of AD (corrected odds ratio confidence intervals < 1).

Limitations: The study includes children referred to the hospital. However, it is the practice of local national health pediatricians to send all patients with suspected AD, whatever the severity grade, to hospital specialists to perform allergometric assessment.

Conclusion: The use of defined criteria of clinical diagnosis for the determination of the condition's severity, along with the performance of objective allergometric tests at the time of inclusion, shows that the course of AD is significantly related to egg sensitivity. In addition, the average healing time is higher in egg-sensitive patients affected by the most severe form of AD than in mild or moderate cases. (J Am Acad Dermatol 2006;55:765-71.)

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Atopic dermatitis (AD) is the most frequent chronic skin disease of childhood, with onset especially in the first years of life. As recently reviewed,¹ many epidemiologic studies have reported an increased prevalence of AD during the past 3 decades in industrialized countries. The association of AD with other allergic diseases has been widely observed; early onset of AD has been associated with an increased risk of asthma,² and many authors have indicated AD as the first manifestation of the so-called atopic march.

On the other hand, the factors that may influence the evolution of the disease are not completely understood. The long-term evolution of AD has been reported in many articles,³⁻⁶ but it remains difficult to assess the relative importance of risk factors, because of differences in diagnostic evaluation (the criteria of Hanifin and Rajka⁷ were first established in 1980). Furthermore, determining the relationship between the course of AD and the coexistence of specific allergies is complicated by the lack of standardization in allergometric tests performed on different populations.

The aim of our work was to evaluate with defined criteria of clinical diagnosis, severity assessment, and objective allergometric tests at the time of inclusion the clinical course of AD in relation to some risk factors, and to analyze the association of AD with the appearance of other allergic diseases with a particular relation to the presence of specific immunoglobulin (Ig)E at first observation.

METHODS

Study population and semistructured interviews

From the beginning of 1980 in our departments of pediatrics and dermatology, a clinical protocol was applied to children with defined diagnosis of AD. The protocol included, at the first examination, the compilation of detailed history, determination of the severity of the disease through a clinical score, and performance of allergometric assessment.

This study included only children affected by AD with the following criteria: (1) first clinical examination made between 1980 and 1989; and (2) age between 6 and 36 months at the first observation. It is interesting to note that although our center may be considered a tertiary one, it is the practice of local national health pediatricians to send all patients with suggested AD, even with mild severity, to a specialist to perform allergometric assessment, with the result that the severity grading of this population has a wide variability.

Diagnosis of AD was made by the same physicians, on the basis of the criteria of Hanifin and

Abbreviations used:

AD: atopic dermatitis
Ig: immunoglobulin
OR: odds ratio
RC: rhinoconjunctivitis

Rajka⁷; parents or siblings were regarded as atopic if they reported diagnosis of AD, allergic rhinoconjunctivitis (RC), asthma, or food allergy urticaria.

All children were followed up by our clinics until remission or stabilization of AD. In the majority of cases the appearance of new symptoms were recorded; however, a diagnosis of allergic diseases (eg, RC, asthma) made by another physician or specialist was also considered valid.

In 2002 an interview was carried out, after informed consent, with the parents and, above all, the mother, using a preformed questionnaire. The questionnaire consisted of 34 items regarding, briefly, the clinical evolution of AD after discharge from our clinical control, the possible appearance of other allergic diseases, the current clinical conditions, and drugs used.

Clinical assessment

At first observation the evaluation of the severity of AD was obtained by completing a rating scale for 10 clinical features (erythema, edema, vesiculation, crusting, excoriation, scaling, lichenification, pigmentation, pruritus, loss of sleep) as reported in one of our previous works.⁸ For each feature the score was defined as absent (0 points), slight (1 point), moderate (2 points), marked (3 points), and severe (4 points). For each child a total eczema score was derived by adding all the points together. A total severity score was calculated as the sum of grading. The 3 categories were as follows: a total score of up to 14 was considered mild AD; 15 to 27, moderate AD; and 28 to 40, severe AD.

When the standardized Scoring of Atopic Dermatitis (SCORAD) index was published,⁹ we adopted this new tool to assess the severity of AD. We compared the two clinical scores with the aid of the clinical case report form. Even though some small differences in the final score of each patient were observed, the values obtained were generally similar and the attribution of a patient to the group with mild, moderate, or severe AD was the same.

Allergometric assessment

Allergometric assessment was performed at baseline using skin prick test and determination of total

and specific IgE; in this study we used the value of specific IgE to avoid personal differences in skin prick test evaluation.

The determination of total serum IgE level was performed by PRIST (Pharmacia, Uppsala, Sweden); the value assumed as normal or increased was obtained by comparison with normal children of the same age group.¹⁰

The determination of specific IgE was performed by radioallergosorbent test (Pharmacia, Sweden) and was measured in all patients for the following allergens: cow's milk, egg white, soybean, wheat, peanut, nut, codfish, tomato, grass pollen (Bermuda grass, Timothy grass), house dust mite (*Dermatophagoides pteronyssinus*, *D farinae*), cat dander, horse dander, dog dander, and *Alternaria*. The scale observed at that time was 1+, 2+, 3+, and 4+ in accordance with the manufacturer's instructions. We assumed that the presence of sensitization to a specific allergen was defined by a value of 1+ or more for inhalant allergens, and 2+ or more for food allergens.

Statistical analysis

Statistical analysis was performed using software (SPSS 12 for Windows, SPSS Inc, Chicago, Ill). The evolution of AD was related to the following factors: sex, severity of the disease at first observation, family or personal history of first-degree atopy, sensitization to food and inhalant allergens, IgE level, persistence and duration of AD, and appearance and age at onset of asthma and RC.

The presence or absence of the above-mentioned factors in patients with different severity scores of AD was evaluated by contingency table, whereas Fisher's exact test was used to test AD evolution for all the other mentioned variables that were dichotomous.

Time of duration of AD or onset age of RC or asthma were compared by Fisher's analysis of variance in the different severity classes of AD (with Scheffé post hoc test if necessary), and by unpaired Student *t* test for all the dichotomic variables. The χ^2 for trend was also performed to evaluate the influence of age of AD, RC, and asthma onset on AD evolution. The risk of incomplete recovery of AD, RC, or asthma onset was evaluated by corrected odds ratio (OR) in models of logistic regression backward stepwise (likelihood) method. First type error was accepted at *P* less than .05.

RESULTS

A total of 252 children fulfilled the two above-mentioned criteria of inclusion (age of onset and time of observation). The interview questionnaire was completed for 205 children (104 boys and 101

girls) (81.3%); 46 children had changed addresses and were not available, and one child had died. The mean follow-up of these patients was 16.9 ± 2.9 years (range 13-22 years).

Baseline data

At the first observation 130 children were aged between 6 and 12 months, 50 between 13 and 24 months, and 25 between 25 and 36 months. In all cases the diagnosis of AD was made at the time of our first observation on the basis of the criteria of Hanifin and Rajka.⁷

The severity of AD on the basis of our clinical score, and when successively we applied the standardized Scoring of Atopic Dermatitis index, was mild in 67 of the 205 children (32.7%), moderate in 99 children (48.3%), and severe in 39 children (19.0%).

First-degree familial atopy was present in 110 patients (53.7%), involving the father in 41 cases (37.3%), mother in 39 cases (35.5%), both parents in 17 cases (15.5%), and brothers or sisters in 13 cases (11.7%).

Total IgE serum level was increased in 92 cases (44.8%). Sensitization to food allergens was observed in 76 cases (37.1%): to egg white in 52 cases (25.4%), cow's milk 34 (16.5%), nut 24 (11.7%), wheat 18 (8.8%), peanut 18 (8.8%), and to a lesser extent to other foods. Sensitization to inhalant allergens was observed in 53 cases (25.9%): to grass pollen in 34 cases (16.6%), house dust mite 18 (8.8%), cat dander 21 (10.2%), dog dander 6 (2.9%), horse dander 7 (3.4%), and *Alternaria* 2 (1%).

Outcome and evolution of AD

At the time of performing the interview AD had completely disappeared in 124 cases (60.5%). The other allergic manifestations that had appeared (alone or associated) included: asthma in 70 cases (34.1%) and RC in 118 cases (57.6%). The curve of AD recovery and the curve of appearance of RC and asthma are shown in Fig 1.

The mean age of recovery is slightly higher in severe AD (6.0 ± 3.5 years) than in the moderate (5.8 ± 4.5 years) or mild (5.5 ± 3.9 years) forms, but no statistically significant difference was found. The same trend can be seen in children with hen's egg sensitization (Fig 2): a longer period is required in severe AD (9.36 ± 3.07 years) than in moderate (5.92 ± 4.3 years) or mild (4.83 ± 2.9 years) forms (Fisher's *F* = 3.511 and *P* < .05). Moreover, AD heals later in sensitized patients. Regarding the various risk factors, patients with egg sensitization present longer dermatitis persistence (mean 11.1 ± 6.9 years) versus nonegg-sensitized patients (8.3 ± 6.9 years) (Student *t* = 2.502 and *P* < .02).

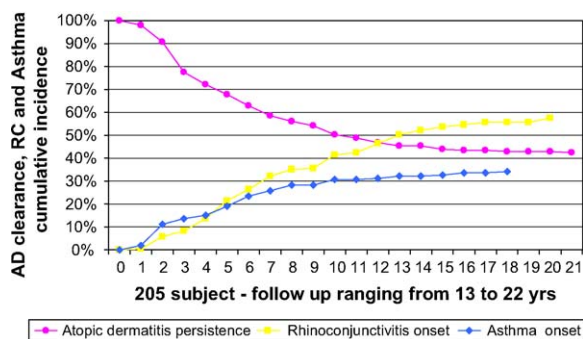


Fig 1. Retrospective analysis of evolution of atopic dermatitis (AD) in 205 children with age of onset within 3 years and curve of appearance of rhinoconjunctivitis (RC) and asthma.

The different variables related to the evolution of AD are reported in Table I: in particular initial severity score is significantly ($P < .001$) related to the appearance of asthma; hen's egg sensitization is related to RC and asthma onset ($P < .01$).

RC and asthma are significantly related to one another: about half (53 of 118, 44.9%) of children with rhinitis also show asthma, and 75.7% (53 of 70) of those with asthma also show RC.

A logistic regression backward stepwise (likelihood ratio) method was performed for evaluation of AD persistence, RC, and asthma onset. The most suited models are expressed in Table II.

No acceptable and statistically meaningful model was obtained with AD persistence as dependent variable, and sex, severity score, familial or personal atopy, IgE level, and AD onset age as independent variables.

For RC onset, the sex, AD severity, familial or personal atopy, IgE level, age of AD onset, years of AD persistence, AD resolution age, and asthma onset were put in the model as independent variables. An elevated AD persistence seems to be moderately protecting to RC onset, whereas atopy nearly doubles the risk of RC onset and asthma presence triples the probability of RC presence.

For asthma onset, the RC onset replaced asthma onset, whereas the other variables remained unchanged. AD severity can predict asthma onset, because the change from mild to moderate nearly doubles the risk of asthma onset, whereas the transition from moderate to severe quadruples the risk. Hen's egg sensitization doubles the risk, whereas RC presence triples the probability of also having asthma. Hen's egg sensitization is less predictive (2.225) of the appearance of asthma than AD severity score (2.588 and 4.770, respectively) and less predictive than RC onset (3.448).

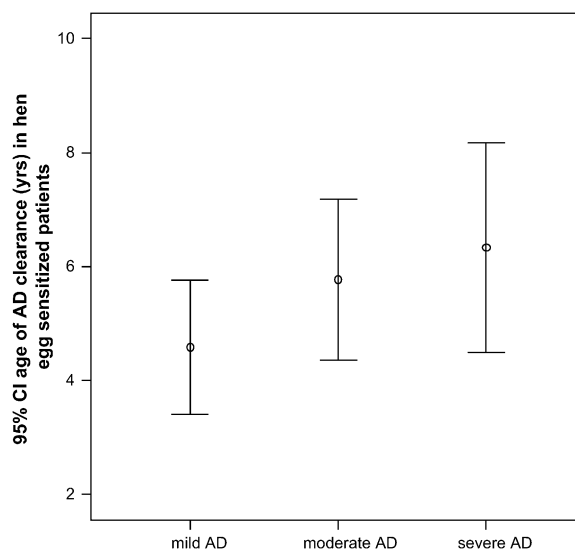


Fig 2. Age of atopic dermatitis (AD) healing in children with hen's egg sensitization related to clinical severity score at first observation (Fisher's $F = 3.511$ and $P < .05$). CI, Confidence interval.

DISCUSSION

In 1980, Hanifin and Rajka⁷ defined the criteria available for the diagnosis of AD. After their publication our team decided to apply a simple protocol to all children with diagnosed AD: at the time of their first examination a dermatologic investigation was carried out to define the diagnosis and the disease severity, and an allergometric assessment.

Our patients' data from the first observation show that the percentage of children with familial atopy (53.7%) is lower than expected. However, we evaluated only restricted criteria in the anamnesis of allergic disease for parents and siblings and similar data have been observed in a recent study¹¹ in a prospective observational birth cohort with a follow-up of 7 years.

The evaluation of AD severity was performed using our own scoring system already reported in a previous publication,⁸ because at that time no standard system was generally accepted.

At the time, the evolution of AD was also controversial on account of the use of different diagnostic parameters. Therefore, in our opinion, the criteria of Hanifin and Rajka⁷ was useful because for the first time a standardization of the clinical parameters was available, even though successive adjustment has subsequently been necessary. Vickers³ reported a percentage of persistence much lower than ours (8%-13%), but in the majority of cases the percentage of persistence of AD observed in our patients was lower (39.5%) than those observed in other studies: Roth and Kierland⁴ in 1964 observed a persistence

Table I. Persistence of atopic dermatitis and appearance of rhinoconjunctivitis and/or asthma related to different evaluated variables

Variables	Category	N	AD persistence	RC appearance	Asthma appearance
Initial severity score	Mild	67	23 34.3% (24.1-46.3)	34 50.7% (39.0-62.4)	22 32.8% (22.8-44.8)*
	Moderate	99	43 43.4% (34.1-52.3)	60 60.6% (50.7-69.7)	25 25.3% (17.8-34.7)*
	Severe	39	15 38.5% (24.9-54.2)	24 61.5% (45.8-75.1)	23 59.0% (43.3-73.0)*
Parental atopy	Absent	95	43 40.0% (30.7-50.1)	64 56.8% (46.8-66.4)	39 32.6% (24.0-42.6)
	Present	110	38 39.1% (31.0-48.5)	54 48.9% (58.2-67.0)	31 35.5% (27.1-44.8)
Cow's milk sensitization	Absent	171	64 37.4% (30.5-44.9)	94 55.0% (47.5-62.6)	57 33.3% (26.7-40.7)
	Present	34	17 50.0% (34.0-66.0)	24 70.6% (53.7-83.1)	13 38.2% (23.9-55.1)
Hen's egg sensitization	Absent	153	56 36.6% (29.3-44.5)	83 53.6% (45.7-61.3) [†]	48 28.8% (22.2-36.4) [§]
	Present	52	25 48.1 (35.1-61.4)	36 69.9% (55.7-80.1) [†]	22 50.0% (36.8-63.2) [§]
Inhalant sensitization	Absent	157	55 36.3% (29.2-44.1)	83 54.8% (47.0-62.4)	48 31.8% (25.1-39.5)
	Present	48	26 50.0% (36.3-63.7)	35 66.7% (52.5-78.3)	22 41.7% (29.0-44.8)
IgE	Normal	92	33 35.9% (26.8-46.1)	46 50.0% (40.0%-60.0%)	31 33.7% (24.9-43.9)
	Increased	113	48 42.5% (33.7-51.7)	72 63.7% (54.5-72.0)	39 34.5% (26.4-43.7)
Atopic sensitization	Absent	71	22 31.0% (21.4-42.5)	31 43.7% (32.7-55.3)	19 26.8% (17.9-38.1)
	Present	134	59 44.0% (35.9-52.5)	87 64.9% (56.5-72.5)	51 38.1% (30.3-46.5)
Appearance of RC	Absent	87	27 31.0% (22.3-41.4) [‡]		17 19.5% (12.6-29.1) [‡]
	Present	118	54 45.8 (37.0-54.8) [‡]		65 44.9% (36.2-53.9) [‡]
Appearance of asthma	Absent	135	50 37.0% (29.4-45.5)	65 48.2% (39.9-56.2) [¶]	
	Present	70	31 44.3% (33.2-56.0)	53 75.7% (64.4-84.2) [¶]	

95% Confidence intervals are included for each item.

AD, Atopic dermatitis; IgE, immunoglobulin; RC, rhinoconjunctivitis.

*Pearson $\chi^2 = 14,225$; $P < .001$.

[†]Fisher's exact test; $P < .001$.

[‡]Fisher's exact test; $P < .0001$.

[§]Fisher's exact test; $P < .007$.

^{||}Fisher's exact test; $P < .005$.

[¶]Fisher's exact test; $P < .05$.

rate varying between 60% and 71%; Musgrove and Morgan⁵ in 1976 observed a persistence of 58%, and Kissling and Wüthrich⁶ in 1993 observed a persistence of 63%. A percentage of persistence similar to ours was observed by Businco et al¹² in 1989 (43%), but with a follow-up of only 5 years.

The percentage of complete remission of AD in adolescence is about 60% in our study, but if we also

evaluate the absence of other allergologic diseases, only 42 children (20.5%) are free of symptoms. Moreover, the onset of new atopic clinical manifestations occurs in the majority of our cases before the pubertal age (Fig 1).

The results of our study show that the age of healing from AD in patients with hen's egg sensitization is significantly lower ($P < .05$) in patients with

Table II. Evolution of atopic dermatitis in 205 children: Retrospective analysis of related risk factors and association with concomitant allergic diseases

Dependent variables	Covariate	OR	OR LCL _{95%}	OR UCL _{95%}	P
RC onset*	AD persistence	0.951	0.911	0.994	.025
	Atopic sensitization	1.968	1.057	3.664	.033
	Asthma onset	3.229	1.668	6.252	.001
Asthma onset*	Mild AD	1			
	Moderate AD	2.588	1.084	6.175	.032
	Severe AD	4.770	2.063	11.032	.0001
	RC onset	3.448	1.741	6.827	.0001
	Hen's egg sensitization	2.225	1.102	4.494	.026

Logistic regressions applied to characterize risk factors or protective factors from the asthma or RC onset.

AD, Atopic dermatitis; LCL, lower confidence limit; OR, odds ratio; RC, rhinoconjunctivitis; UCL, upper confidence limit.

*In the models the constant has been included.

mild form than moderate or severe, the most important difference being between severe to mild to moderate AD (Scheffé post hoc test $P < .05$) (Fig 2).

Many data indicate that AD is strongly related to asthma and rhinitis, as reported in the International Study of Asthma and Allergies in Childhood¹³ where a strong correlation between prevalence of AD and prevalence of rhinitis and asthma was observed.

The risk factor of evolving from AD to other allergic manifestations has only been partially investigated: in a study by Ohshima et al¹⁴ a greater risk for developing asthma was associated with the persistence of AD. Our study, too, shows that the severity of AD is significantly related to the appearance of asthma (Table D).

The presence of an associated sensitization allergic phenotype, as observed in previous articles, is an important risk factor for evolution into respiratory allergy. Several longitudinal studies have been performed to provide evidence for this evolution: the presence of elevated total IgE serum levels has been correlated to the risk of developing asthma.¹⁵ In a study performed by Rhodes et al¹⁶ on 100 infants from atopic families during a 22-year period it was observed that AD was reduced from 20% to 5% of the patients at the end of the study (ie, a reduction of 75%), but the major risk factor for asthma was early sensitization to foods (OR 12.3) or aeroallergens (OR 4.6). Another longitudinal study¹⁷ examined 92 children with AD for 8 years: AD improved in more than 80% of children, and asthma appeared in 43% of patients and rhinitis in 45%. The severity of AD was seen to be a risk factor for subsequent development of asthma: 70% of the patients with severe AD developed asthma compared with 30% of the patients with mild AD. The severity of AD was also correlated with the risk of developing allergic rhinitis.¹⁸

We considered asthma the most serious complication of AD. For the sake of thoroughness we also

tested logistic regressions, with RC or AD persistence as dependent variable.

In particular, the age of AD onset does not seem to have any influence on the linear trend of AD clearance, the χ^2 for trend being 2.963 (not significant), showing an OR of 2.58 for 1-/2-year onset and an OR of 1.35 for 2-/3-year onset. A completely casual phenomenon is very likely.

More interesting results were found in regressions where the asthma and RC appearance were the dependent variables.

From Table II it is possible to see that the presence of personal atopic sensitization nearly doubles risk of possible RC onset, whereas asthma presence triples the probability.

AD severity is predictable for asthma onset, because passing from mild to moderate AD doubles the risk of asthma onset, whereas it is quadrupled when passing from moderate to severe. Hen's egg sensitization doubles the risk, whereas RC presence triples the probability of also having asthma.

The evidence that egg sensitization at the age of 1 year is predictive for later sensitization to inhalant allergen¹⁹ has been confirmed in a recent article,¹⁴ where patients already sensitized to egg white acquired specific IgE to mite sensitization in the follow-up period.

In the Early Treatment of Atopic Child (ETAC) study, only children with mite or grass sensitization (and not with hen's egg and/or milk allergy) who were at risk of developing asthma showed the benefits of a prevention program.²⁰

In our study early sensitization to egg appears to constitute a target for evolution into inhalant allergic diseases. The observation of a relationship between egg sensitization with the subsequent appearance of allergic diseases (asthma and RC) indicates that this group of children is particularly at risk and could be included in a preventive intervention program.

In conclusion, by using defined criteria of clinical diagnosis, severity assessment, and objective allergometric test at the time of inclusion, our study shows that the possibility to predict the healing of AD is significantly related to the presence of the mild form without egg sensitization, and is inversely related to the initial severity of AD; moreover, the mean age of recovery is higher in severe AD than in mild AD.

In addition to the presence of RC (inhalant allergic diseases are strongly related together), the appearance of asthma tends to be linked to hen's egg sensitization rather than other clinical characteristics.

In a recent study, Illi et al¹¹ postulate that "rather than early AD being a risk factor for subsequent asthma in a progressive atopic march, it seems more likely that a certain phenotype exists as a coexpression of asthma and AD. . . ." Our data seem to support such a hypothesis, namely that allergen sensitization (particularly hen's egg) is predictive of the appearance of allergic respiratory diseases.

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