14 Natural History of Atopic Eczema

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Most studies examining the natural history of atopic eczema to date have been retrospective case series, i.e., they have identified previous cases from hospital notes or registers and requested up-to-date information on subsequent clearance or recurrences [1]. Cases in retrospective studies are likely to have been assembled using different age groups, rendering it difficult to make summary statements about prognosis according to age of onset unless very large samples (i.e., > 1,000) are employed. By definition, referral to the hospital is related to disease severity, limiting the generalizability of the study. Case definition is unlikely to be uniform unless a special study was designed at the outset. Studies that look at entire populations of atopic eczema cases in the community are needed to overcome these biases. Another challenge facing studies of the natural history of atopic eczema is defining terms such as "remission" or real and apparent clearance rates. Another major problem in atopic eczema research studies in relation to cohort studies is defining a truly incident case. There seems to be no way around this problem until better gold standards are available for defining incident cases [1].

14.1 Studies on the Long-Term Prognosis of Atopic Eczema After Childhood

Most studies based on hospital-ascertained cases have probably overestimated the proportion of cases of atopic eczema with early onset because early onset may be a predictor of disease severity [2]. The usefulness of such studies, therefore, may be limited by possible selection and response bias. Some of past writings have tended to be overly optimistic about the prognosis of atopic eczema after childhood [3, 4]. In his private practice, Vickers found a persistence rate for children of only 8 % – 13 %; however, it is unclear whether or not any distinction was made between seborrheic and atopic eczema [3]. Despite the above limitations, studies of well-defined cases give a persistence rate of around 40 % – 60 % for most cases with onset during childhood [2, 5 – 15] (Table 14.1).

Our follow-up studies were conducted in a cohort of 121 patients who had suffered from atopic eczema in infancy. They were examined when they were at the mean age of 15 years (n = 121) and 23.5 years (n = 106), respectively [12, 15]. Ten different courses (I–X) of atopic eczema after infancy could be differentiated [16] (Fig. 14.1). Of these, only 11 % disappeared after childhood (courses I and II). The persistence rate was 63 % (courses VI–X), and in 32 % there was a continuous chronic course (X). During puberty, 25 % cleared up (courses III–V), but in another 20 % atopic eczema reappeared (courses VII–IX).

14.2 Studies Reporting Data on the Long-Term Prognosis of Atopic Eczema Based on Community Samples

To our knowledge, there are at present only two studies based on community samples. In a cross-sectional questionnaire study of Swedish 14-year-olds with past "eczema" (n = 694), Äberg and Engstrom [17] found a clearance rate of 34 %. The age of inception cohort and the length of follow-up in years were, however, unclear. Within the framework of a national birth cohort study in the UK, Williams [18] did a study using a questionnaire and examining a sample size of 571 with an age of inception of the cohort of 7 years. The follow-up was 9 years, with some additional data at age 23 years. Loss to follow-

Table 14.1. Persistence rate of atopic eczema after childhood in various studies (modified after [1])

Author, year	Sample size	Source of sample	Age of inception cohort	How disease was defined at follow-up	Length of follow-up in years (losses at follow-up)	Persistence rate
Edgren 1943 [5]	311	Hospital inpatients and outpatients	Onset before 2 years	Examination at home (nurse) and questionnaire	17–38 years (unclear)	57 %
Osborne & Murray 1953 [6]	98	Hospital clinic	Under 2 years	Examination	3–5 years (not stated)	80 %
Oehme 1960 [7]	269	Hospital clinic	Under 2 years	Questionnaire and examination	5–37 years (examination 66 cases)	34.2 % (51.8 %: examination)
Roth and Kierland 1964 [8]	221	Hospital inpatients and outpatients	Children and young adults	Questionnaire	20 years (55 %)	81 % (severe cases) 60 % (mild cases)
Stifler 1966 [9]	40	Hospital	Onset before 1 year	Questionnaire	22–25 years (20 %)	35 % (severe cases)
Musgrove and Morgan 1976 [10]	99	Hospital	Aged under 5 years	Examination	15–17 years (32 %)	58 %
Van Hecke and Leys 1981 [11]	50	Hospital inpatients and outpatients	Aged less than 5 years	Not stated	20 years (not stated)	62 %
Wüthrich and Schudel 1983 [12]	227	Hospital inpatients and outpatients	Onset before 2 years	Questionnaire and examination	15 years (55 %; examination 121 cases)	58 % (questionnaire) 62 % (examination)
Rystedt 1986 [2]	955	Hospital inpatients (549) and outpatients (406)	0–14 years	Questionnaire and examination	22–44 years (less than 3 %)	62 % (inpatients) 40 % (outpatients)
Businco et al. 1989 [13]	68	Hospital clinics	4 months to 10.5 years	Examination by pediatrician	5 years (18 %)	43 %
Linna et al. 1992 [14]	40	Hospital inpatients	Under 2 years	Examination	11–13 years (unclear)	72 % (severe cases) 35 % (less severe cases)
Kissling and Wüthrich 1993 [15]	106	Hospital inpatients and outpatients	Under 2 years	Questionnaire and examination	20 years (12 %)	61 %

up was less than 10 %. The clearance rate after 4 years was 53 % and 65 % after 9 years.

14.3 The Atopic March: Atopic Eczema and the Development of Asthma and Hay Fever

Studies of well-defined cases suggest that most cases (70 %) become manifest within the first 5 years of life [1]. According to the medical literature, 30 %–60 % of children with atopic eczema will develop respiratory diseases such as asthma bronchiale, hay fever, or perennial allergic rhinitis at later age, the so-called atopic march [2, 14, 15, 17, 19–21] (Table 14.2). These high rates of concurrent or subsequent asthma are likely to reflect the fact that most studies have "ascertained" their eczema cases from hospital clinics, the implication being that severe atopic eczema is a predictor for increased subsequent or current asthma [18]. This is

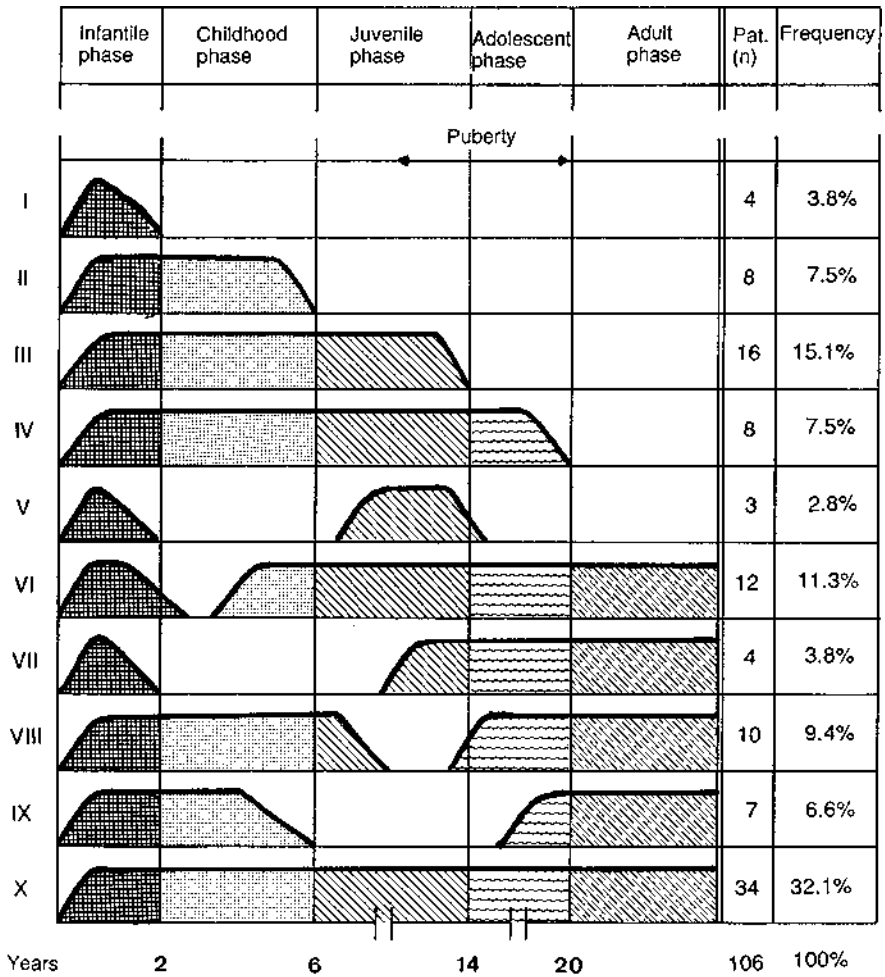

Fig. 14.1. The phases and possible courses of atopic eczema after infancy. (Frequency of the ten different courses [I–X] according to Kissling and Wüthrich [15]).

clearly shown by Rystedt's study [2], where 39 % of former hospital inpatients with atopic eczema developed asthma compared with 22 % of former outpatients.

The time course of the three main atopic diseases is also interesting in that it may inform us about possible environmental exposures and possible time windows for subsequent allergic disease prevention [1]. Äberg and Engstrom's study [17] of 1,335 14-year-old children in the community with a past history of asthma, allergic rhinitis, or atopic eczema suggested that eczema was the first disease to become manifest, followed closely by asthma (41 % within a 2-year interval). Our follow-up studies of 121 and 106 children with atopic eczema in infancy showed that at the ages of 15 and 23 years, 55 % and 60 % of the patients, respectively, also suffered from atopic respiratory diseases [12, 15, 16]. The mean age at which the associated respiratory disease became manifest was 6.3 years for asthma, 8.1 years for perennial rhinitis, and 9.7 years for hay fever. The course of atopic eczema worsened when the asthma improved or vice versa in 15 of 34 cases, with a parallel course in five cases and an independent course in 14 children. The alternate course was predominant ($p < 0.05$), whereas in patients with hay fever, the independent course prevailed (23/34 cases, $p < 0.001$).

We were also interested in the clinical effects of hyposensitization (allergen-specific immunotherapy) with pollen or house dust mite vaccines on respiratory allergies in these patients with concomitant atopic eczema. Only in two of 34 cases did the atopic eczema

Table 14.2. Frequency of subsequent atopic respiratory diseases in various studies (modified after [1])

Author, year	Sample size	Source and ages of inception cohort	Follow-up rate and duration	Asthma bronchiale	Hay fever
Luoma et al. 1983 [19]	543	Maternity unit: from atopic families (n = 395) and nonatopic families (n = 148)	5 years	29 %	35 %
Rystedt 1986 [2]	955	Atopic eczema patients: 549 former inpatients and 406 former outpatients	24 – 44 years	39 % among inpatients 22 % among outpatients	66 % among inpatients 53 % among outpatients
Äberg and Engstrom 1990 [17]	694	14-year-old children in the community	Birth to 14 years	16 % had a history of concurrent or past asthma	28 % had a history of concurrent or past allergic rhinitis
Lammintausta et al. 1991 [20]	801	Hospital clinic, 12 – 16 years	81 % Duration unclear, 10 – 18 years?	10 % – 19 % (lower in less severe cases)	59 % – 69 %
Linna et al. 1992 [14]	40	Children who had been previously hospitalized because of atopic eczema	10 years	53 %	78 %
Kissling and Wüthrich 1993 [15]	121	Hospital clinic, in- and outpatients	Up to 20 years	25.5 % (disappearance in 12 % who had asthma at 15 years [12])	41 % hay fever (disappearance in 6 % who had hay fever at 15 years [12]); 24.5 % perennial rhinitis
Kayahara et al. 1994 [21]	48	Hospital clinic	Up to 6 years	48 %	Unclear

worsen during treatment; the respiratory allergies had improved in 70 % of cases after 3 years of vaccination. Atopic eczema did not change during the course of immunotherapy in 80 % of cases.

14.4 The Atopic March: Early Sensitization to Foods and Aeroallergens Is the Main Risk Factor for the Development of Asthma

Currently, very little is known – other than genetic predisposition based on family history of organ manifestation of atopic diseases [22] – about the factors that may increase the risk of a child with atopic eczema developing asthma or hay fever, but the few studies done suggest that IgE sensitization may be the preceding event.

A prospective 3-year follow-up study by Guillet and Guillet [23] in France looked at the natural history of sensitization in 29 children who had a severe form of atopic eczema at 4 months of age. In all cases, causal allergen sensitization against food was found, and this food allergy was still clinically significant at 3 years of age in 83 % of cases. During this 3-year period, 79 % of the children also developed respiratory disorders, and in 93 % sensitization to aeroallergens (which had been negative at age 4 months) was found.

The ETAC (Early Treatment of the Atopic Child) study was designed to find out if an early intervention in children with atopic eczema by cetirizine, an antihistamine with some in vitro and in vivo activity on inhibiting eosinophil migration, can reduce the risk of developing subsequent asthma [24]. An earlier randomized double-blind placebo-controlled trial of ketotifen in 91 infants with only atopic eczema who were followed up for 52 weeks suggested that children in the active group developed less asthma and less severe eczema [25].

The ETAC multicenter double-blind, randomized, placebo-controlled trial with cetirizine, sponsored by the manufacturers of the antihistamine, set about comparing the incidence of symptoms of asthma in 817 atopic eczema infants aged 1 – 2 years with a history of atopic diseases in parents or siblings, who took daily cetirizine or placebo for 18 months. Although there were

no differences in the cumulative prevalence of asthma between active and placebo treatment in the intention-to-treat population ($p = 0.7$), those infants with sensitivity to grass pollen, house dust mite, or both who were treated with cetirizine were significantly less likely to have asthma compared with those treated with placebo for 18 months ($p = 0.005$ and 0.002, respectively) [24, 26]. In the 18 months of posttreatment follow-up, this favorable effect was sustained for the grass pollen-sensitized infants over the full 36 months ($p = 0.008$). In the house dust mite-sensitized group, there was a gradual narrowing of the difference between active and placebo treatment in terms of cumulative prevalence of asthma at the end of 36 months but no evidence of a rebound immediately after the treatment stopped ($p = 0.04$). In the placebo population, there was a significantly higher risk of developing asthma in those sensitized at baseline to egg (relative risk 1.4; 95% CI 1.1–1.7), house dust mite (relative risk 1.6; 95% CI 1.3–1.9), grass pollen (relative risk, 1.7; 95% CI 1.4–217), or cat (relative risk 1.5; 95% CI 1.2–1.9). Earlier and persistent sensitization conferred a higher risk than transient or later sensitization. Caution has to be exercised in interpreting such post hoc subgroup analyses, but the magnitude of the benefit (relative risk for developing asthma when treated with cetirizine 0.6, 95% CI 0.4–0.9) for those infants sensitized to house dust mite or grass pollen was impressive, and certainly warrants further testing in future trials to substantiate this finding [1, 26].

Another study of the ETAC-study-group [27] investigated the natural course of sensitization to egg and to cow's milk and its relationship with the severity of atopic eczema. At inclusion, children sensitized to both egg and to cow's milk had the most severe eczema. These sensitizations were more common in atopic children with severe atopic eczema at all time points (3, 12, and 18 months after inclusion). The degree of sensitization expressed in RAST classes was significantly related to the severity of atopic eczema. Furthermore, children sensitized to egg or to cow's milk at inclusion had a higher risk for persistence of eczema (84% and 67%, respectively, vs 57% in those not sensitized) [27].

14.5 Children with the Non-IgE-Associated Variety of Atopic Eczema (Intrinsic Atopic Eczema) Rarely Get Asthma

In the ETAC study, 34% of the children with clinical atopic eczema were not atopic in terms of IgE not being greater than 30 kU/l and negative skin prick tests to the tested allergens. They belonged to the so-called intrinsic type of atopic eczema or nonallergic (non-IgE-associated) atopic eczema [28, 29]. Two recent studies suggested that children with this nonatopic variety of atopic eczema at age 2 rarely get asthma [30, 31].

Novembre et al. [30] evaluated 77 children who had atopic eczema at the age of 2 years, 9 years later, at the age of 11; 64% belonged to the early atopic group (EA), i.e., they were already sensitized at the age of 2 years, 21% developed atopy later at 11 (late-onset atopic, LOA), and 15% remained an "intrinsic" type ("non-IgE-associated") (IAE). The persistence of atopic eczema at the follow-up was with 67% higher in the IAE than in the EA (43%) or LOA (44%) group ($p < 0.0002$). The prevalence of bronchial asthma at the follow-up was with 60% higher in the EA group compared with 25% in the LOA group. None of the nonatopic children developed asthma by age 11 (Table 14.3).

In our study [31], we performed clinical and allergological investigations (skin prick tests [SPT], total and

	At age 2 years	Follow-up, 9 years later
Atopic eczema ($n = 77$) [30]	77/77 (100%)	36/77 (46%)
Asthma bronchiale	17/77 (22%)	33/77 (43%)
– Extrinsic type ($n = 55$)	17/55 (31%)	33/55 (60%)
– Intrinsic type ($n = 12$)	0/12 (0%)	0/12 (0%)
	At age 2–4 years	**Follow-up, 9 years later**
Atopic eczema ($n = 22$) [31]	22/22 (100%)	15/22 (68%)
Asthma bronchiale	2/22 (9%)	10/22 (45%)
– Extrinsic type ($n = 15$)	2/15 (13%)	9/15 (60%)
– Intrinsic type ($n = 7$)	0/7 (0%)	1/7 (14%)
Hay fever ($n = 77$)	0/0 (0%)	9/22 (41%)

Table 14.3. Subsequent asthma in children who had atopic eczema at age 2 years, according to the classification into an extrinsic (IgE-associated) and an intrinsic (non-IgE-associated) subtype of atopic eczema [30, 31]

specific IgE determinations [RAST CAP] against an inhalant [Sx1] and a food mix [Fx5] in a group of 22 children with atopic eczema seen at the age of 2–4 years. Eight years later, the same children, then aged 10–12 years, were re-evaluated. In the follow-up, we investigated the persistence of atopic eczema after early childhood and the development of respiratory allergic diseases. In particular, we were interested in knowing how many patients with the first diagnosis of intrinsic atopic eczema were still SPT- and IgE-negative. The clinical and allergological data of this study are also shown in Table 14.3. At re-evaluation 8 years later, 68% of the children still suffered from atopic eczema, 45% from asthma, and 41% from seasonal rhinoconjunctivitis. The percentage of sensitization against common inhalant allergens (Sx1) increased from 50% to 80% and against food (Fx5) the percentage decreased from 41% to 27%. Four of the seven children with intrinsic atopic eczema were still without any detectable sensitization, but three had evolved to an extrinsic type of atopic eczema. One of them developed asthma; however, the risk of developing asthma is much higher in the extrinsic type (9/15; 60%) than in the intrinsic type at age 2 years (1/7; 14%).

14.6 Conclusions

Recent studies clearly confirm that the prevalence of atopic eczema in childhood is high, at around 10%–15%, in Europe. In addition, the persistence rate after puberty (around 40%–60%) in the present studies of well-defined cases is considerably higher than reported in most textbooks, and the risk of developing respiratory symptoms in later years is also around 40%–60%. Recommendations for future studies of the natural history of atopic eczema and the atopic march are summarized – according to Williams and Wüthrich [1] – in Table 14.4. Moreover, it is important to classify the disease into an extrinsic, IgE-associated, and an intrinsic, non-IgE-associated, atopic eczema for each age group (infancy, childhood, teenage years, and adult phase) [28–31] (Fig. 14.1). For the long-term prognosis, therefore, it is important to know that the risk of the development of an atopic respiratory disease is much lower in the intrinsic type (now called nonatopic eczema [32]).

Table 14.4. Recommendations for future studies of the natural history of atopic eczema (modified after [1])

- Is the disease definition clear and valid?
- Is the sample representative of all persons with the condition?
- Has the inception cohort been assembled at a uniform and early point of the disease?
- Was the follow-up sufficiently long and complete?
- Was a range of clinically relevant and objective outcome measures examined?
- Were outcome measures recorded in a blind fashion?
- Were prognostic subgroups (e.g., IgE-associated or non-IgE-associated) identified a priori?

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