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Recent Epidemiological and Genetic Studies in Atopic Dermatitis

T. L. DIEPGEN and M. FARTASCH

Department of Dermatology, Friedrich-Alexander University, Erlangen, Germany

In a prospective computerized study, basic and minor features of atopic dermatitis were studied systematically in established cases of atopic dermatitis (AD; $n = 428$) and compared with subjects randomly collected from the caucasian normal population of young adults (NP; $n = 659$). Complete genetic data (history of AD, allergic rhinitis, allergic asthma) were obtained from the first-degree relatives of all subjects (about 9,000 family members). In young adults, atopy was found in 22.5% (AD 4.7%, allergic rhinitis 17.9%, allergic asthma 4.8%). Of 428 AD patients, 54% had 'pure' AD and 46% suffered from a 'mixed' type with concomitant respiratory allergies (RA). The general risk of developing AD and atopy increases with each first-degree family member already suffering from atopy. Our study further supports the evidence of a genetic influence on symptom specificity. Risk figures for genetic counselling are given. The complex interplay of atopic symptoms and signs in the diagnosis of AD has been analysed by a CART analysis. Compared with non-eczematous controls, the odds ratios (OR) of frequent features in AD are as follows: xerosis (OR 27.9, 95%-CI 23.2–33.8), itch when sweating (OR 25.4, 95%-CI 21.1–30.1), white dermographism (OR 19.3, 95%-CI 16.2–23.2), wool intolerance (OR 15.8, 95%-CI 13.40–18.5), whereas the OR of elevated IgE (> 150 U/ml) was only 5.0 (95%-CI 4.3–5.8). But when comparing the AD patients with concomitant RA separately, the odds ratio is increased to 16.2.

Key words: Atopy; epidemiology; hereditary factors; risk factors; statistics.

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PD Dr. T. L. Diepgen, Dept. of Dermatology, Friedrich-Alexander University, Hartmannstr. 14, DW-8520 Erlangen, Germany.

INTRODUCTION

Atopic dermatitis (AD), as wall as allergic rhinitis and asthma, belongs to the atopies. Since Coca & Cooke introduced the term 'atopy' in 1923, hereditary factors have been shown to play an important role in the disposition of an individual to develop atopic diseases. The present study reports some clinical and genetic data resulting from a prolective computerized case-control study of 428 patients with AD and of a sample of the German general population comprising 659 young adults. The study was conducted between 1988 and 1990.

MATERIAL AND METHODS

Subjects

Patients with atopic dermatitis (AD: $n = 428$; median of age 22 years) were recruited from the in- and out-patients division of our Dermatological Department. All patients revealed clinical or anamnestic data of recurrent flexural itching and lichenified eczema. Additionally a sample of the German normal population of young adults (NP; $n = 659$; median of age 23 years) was taken from urban and rural areas.

A case-control study was performed to analyse the diagnostic value of atopic features. The basis of selection was the presence or the history of chronic / relapsing flexural eczema. Thus the cases included 428 AD patients, whereas the controls consisted of 659 NP subjects. 31 young adults of this group had a history of flexural eczema and have been excluded (NP, $n = 628$). Additionally we differentiated between non-eczematous controls without respiratory allergies (NP-, $n = 510$) and non-eczematous controls with anamnestic or clinical signs of respiratory allergies (NP +; $n = 118$).

Clinical and laboratory examinations

Anamnestic and clinical atopic basic and minor features were investigated in all test subjects as follows (in alphabetical order): ASTH (personal history of allergic asthma), CAP (cradle cap), CHEIL (cheilitis), DENNIE (Dennie-Morgan fold), DERM (white dermographism), EAR (retro-auricular rhagades), ECZ (flexural eczema), FA (family history of atopy, first-degree relatives), FA-AD (family history of atopic dermatitis, first-degree relatives), FA-RA (family history of respiratory allergies, i.e. allergic rhinitis and/or asthma, first-degree relatives), FACIAL (facial pallor/erythema), FOOD (food intolerance), FOOT (fissured dermatitis of the foot), HERT (Hertoghe sign), IGE150 (elevated total serum IgE: IgE > 150 U/ml), ITCH (itch when sweating) KERAT (keratosis pilaris), LIGHT (light phobia), NECK (dirty neck), NIPPL (nipple eczema), PALMS (hyperlinear palms), PERL (pealèche), PHAD (Phaditop® test, a RAST for screening inhalant allergy), PITALB (pityriasis alba), RHIN (personal history of allergic rhinitis), WOOL (wool intolerance), XERO (xerosis). An exact definition is given elswhere (1). Respiratory atopy (RA) was defined as anamnestic or clinical signs of allergic rhinitis and/or asthma.

Family study

The atopic diseases (atopic dermatitis, allergic rhinitis and/or asthma) found in family members were recorded on the basis of questionnaires. It was possible to obtain complete genetic data of all 1,056 AE and NP families comprising over 9,000 family members (1,981 siblings, 1,049 fathers, 1,050 mothers and over 4000 grandparents).

Statistics

Odds ratios and 95%-confidence intervals were calculated, the χ^2-test was used to analyse cross-classified data, the Mann-Whitney U-test to analyse interval and ordinal scaled data (2). A CART analysis (classification and regression trees) was performed for subjects 18–30 years old (3).

RESULTS

Frequencies, course and age at onset of atopic diseases

In all 428 AD patients the ratio of females to males was found to be 2 : 1. 232 patients (54%) had 'pure' AD (AD−) and 196 suffered from a 'mixed' type with concomitant respiratory allergies (AD+): i.e. allergic rhinitis $n = 115$ (27%), allergic asthma $n = 26$ (6%), allergic rhinitis and asthma $n = 55$ (13%). The allergic rhinitis was mostly (81%) seasonal. Seasonal changes in the course of cutaneous manifestations were seen in over two-thirds of our AD patients. In summer an improvement was found in 60% and in winter a deterioration in 65%. In contrast, in 15% of AD patients a deterioration during the summer was observed. 60% of our AD patients

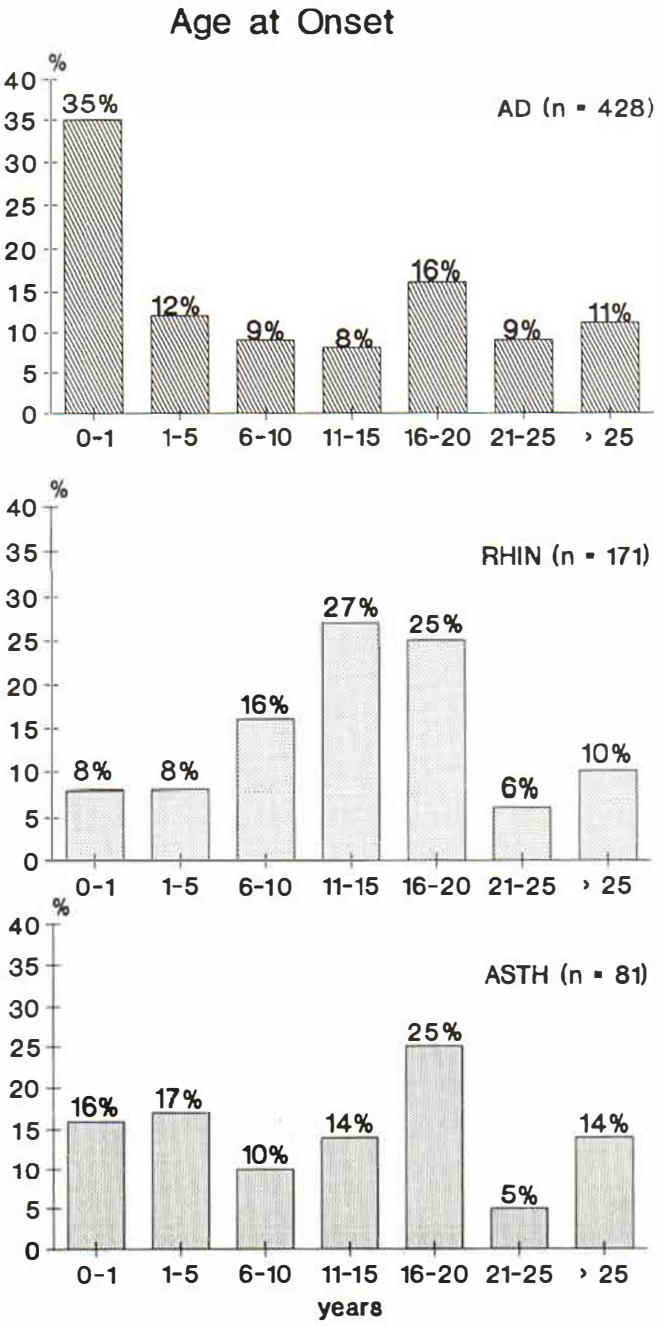

Fig. 1. Age at onset of different atopic diseases (atopic dermatitis: AD $n = 428$; allergic rhinitis: RHIN $n = 171$, allergic asthma: ASTH $n = 81$) in AD patients.

reported that psychic stress was a frequent aggravating factor for AD.

The age at onset of atopic diseases varied widley and showed different distributions (Fig. 1). 47% showed occurrence of AD before the age of 5 years but 20% after the age of 20 years. While respiratory allergies (RA) occurred in the majority of cases at a later age: 16% of our AD patients developed allergic rhinitis and 33% allergic asthma during the first 5 years of life. In AD patients cutaneous manifestations were mostly the earlier symptoms of atopy compared with respiratory atopy. Allergic rhinitis occurred in only 21%, and asthma in only 22% before the onset of cutaneous atopy.

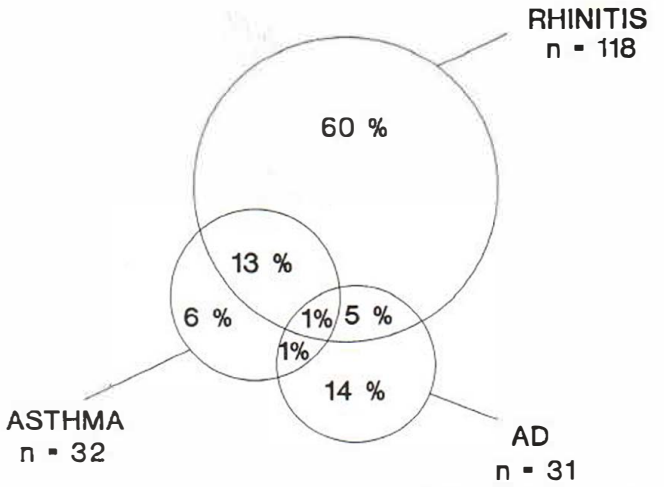

Fig. 2. Rates of pure and concomitant atopic diseases (AD $n = 31$, allergic rhinitis $n = 118$, allergic asthma $n = 32$) in a sample of 659 young adults.

In the sample of young adults (n = 659) a history or clinical picture of atopy were found in 149 subjects (22.6%): 118 subjects with allergic rhinitis (17.9%), 32 with allergic asthma (4.8%) and 31 with flexural eczema (4.7%). In Fig. 2 the percentages of the different manifestations of atopic diseases in our control subjects are shown.

Family history of atopy

The prevalence of atopy in at least one first-degree family member was in AD patients 58% and in NP subjects, 32%. The frequencies of the occurrence of different atopic diseases in the families differ between the families of AD patients, non-eczematous controls with respiratory atopy (NP+) and without RA (NP−) (Table I). When patients suffered from AD, AD was present in 42% of their family members and RA in only 28%. But in families of non-eczematous controls with RA (NP+) other first degree relatives were affected with AD in only 12% and with RA in 43%. In contrast, the families of non-eczematous controls without RA (NP−) presented AD in 10% and RA in 21%. Thus the odds ratio for AD (AD versus NP−) depends on the kind of atopic manifestation found in first-degree relatives. If only RA was found in the family, the odds ratio for AD is 1.5, but if AD was present in the close family, the risk for developing AD increases to 6.7. Comparing the frequencies of a positive family history of atopy be-

Table I. *Frequencies of a positive family history of atopy (FA), family history of AD (FA-AD) and family history of respiratory allergies (FA-RA) in 428 AD patients, 118 non-eczematous controls with RA (NP+) and 510 non-eczematous controls without RA (NP−).*

Family history	AD		NP+		NP−	
	n	%	*n*	%	*n*	%
FA	247	58	63	53	144	28
FA-AD	181	42	14	12	50	10
FA-RA	118	28	51	43	105	21

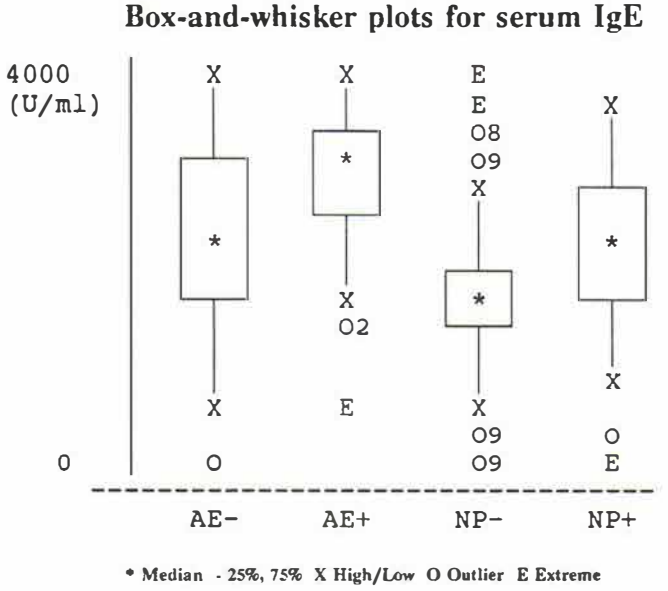

Fig. 3. Distributions ot total serum IgE in patients with pure AD (AD− n = 232), with AD and concomitant RA (AE+ n = 196), non-eczematous controls without RA (NP− n = 510) and noneczematous controls with RA (NP+ n = 118).

tween NP− and NP+ the odds ratio for RA was 2.9 if RA was found in other family members, but the odds ratio was not elevated if only AD was present.

Based on pedigree analysis in the AD-families, the recurrence risks for atopy (AD and/or RA) vis-à-vis AD can be given. If one child already suffers from atopic disorders, but neither parent has atopic manifestations, the risk for the other children in the family of developing AD is 10% and of developing atopy 16%. If one parent is healthy and the other affected, the risk for the other children in the family of developing AD is between 16 and 47% and for atopy, between 19% and 63%, depending on the kind of atopic disease found in the parent. The recurrence risk for atopy was 63% if one parent was suffering from AD and RA, 48% if from pure RA and 19% if from pure AD. If both parents were affected by atopy and one child has AD, the recurrence risk for atopy was 70% for other children, vis-à-vis 45% for AD.

Signs and stigmata of atopic dermatitis

An array of diagnostic criteria for AD is in common use, but there are no laboratory or other objective markers for the disease. The serum total IgE (logarithmic scale) was normally distributed in healthy controls, but bimodally distributed in AD. The mean of logarithmic total IgE of pure AD patients (AD−) was 78 U/ml (95%-CI 59–103 U/ml), of AD patients with respiratory atopy (AD+) 374 U/ml (95%-CI 294–475 U/ml), of non-eczematous controls without RA (NP−) 34 U/ml (95%-CI 30–39 U/ml) and of non-eczematous controls with RA (NP+) 89 U/ml (95%-CI 67–118 U/ml). The differences between all groups are statistically significant (Kruskal-Wallis test: $p < 0.001$). The highest levels of total IgE were found in AD+ and differs significantly from pure AD−. In the 'Box and Whiskers' plots, the distributions of total serum IgE were pointed out in the four different groups and demonstrated a largely overlapping pattern (Fig. 3). Thus the determination of total serum IgE is not of major diagnostic importance for AD.

The frequencies of atopic symptoms and signs varied between 91 and 31% in AD patients, vis-à-vis between 47 and 1% in NP subjects and differed statistically significantly between the two groups (Table II). The odds ratios and 95%-CI are also given and demonstrate that the estimated relative risks (odds ratios) of xerosis, wool intolerance, itch when

Table II. *Frequencies, chi-square test statistics (X^2), odds ratios (OR) and their 95%-confidence intervals (95%-CI) of atopic minor features in AD (n = 427) and non-eczematous controls (NP; n = 628).*

Atopic features	AD (n=428)	NP (n=628)	X^2	OR*	95% CI
XERO (xerosis)	91%	26%	429	27.9	23.2–33.8
WOOL (wool intolerance)	68%	12%	355	15.8	13.4–18.5
DENNNIE (infraorbital fold)	68%	16%	292	11.0	9.4–12.7
PHAD (Phadiatop-test)	67%	28%	141	5.1	4.4– 5.8
ITCH (itch when sweating)	66%	7%	410	25.4	21.1–30.1
CHEIL (cheilitis)	65%	47%	34	2.1	1.9– 2.4
DERMO (white dermographism)	62%	8%	357	19.3	16.2–23.2
PERL (perlèche)	59%	17%	201	7.0	6.1– 8.2
IGE150 (total IgE > 150 U/ml)	53%	18%	131	5.0	4.3– 5.8
PALMS (hyperlinear palms)	50%	8%	242	11.7	9.8–13.9
PITALB (pityriasis alba)	44%	1%	304	60.1	41.6–87.0
HERT (Hertoghe' sign)	42%	2%	282	44.8	32.1–62.6
EAR (ear rhagades)	41%	4%	236	19.2	15.2–24.4
CAP (cradle cap)	40%	6%	184	10.6	8.7–12.9
FACIAL (fucial pallor/erythema)	39%	11%	117	5.3	4.5– 6.3
KERAT (keratosis pilaris)	37%	11%	103	4.9	4.2– 5.8
LIGHT (light phobia)	32%	15%	41	2.6	2.3– 3.1
FOOD (food intolerance)	31%	9%	85	4.7	4.0– 5.7
FOOT ('atopic winter foot')	14%	0%	90	–	–
NIPPL (nipple eczema)	12%	0%	80	–	–
NECK (dirty neck)	10%	0%	66	–	–

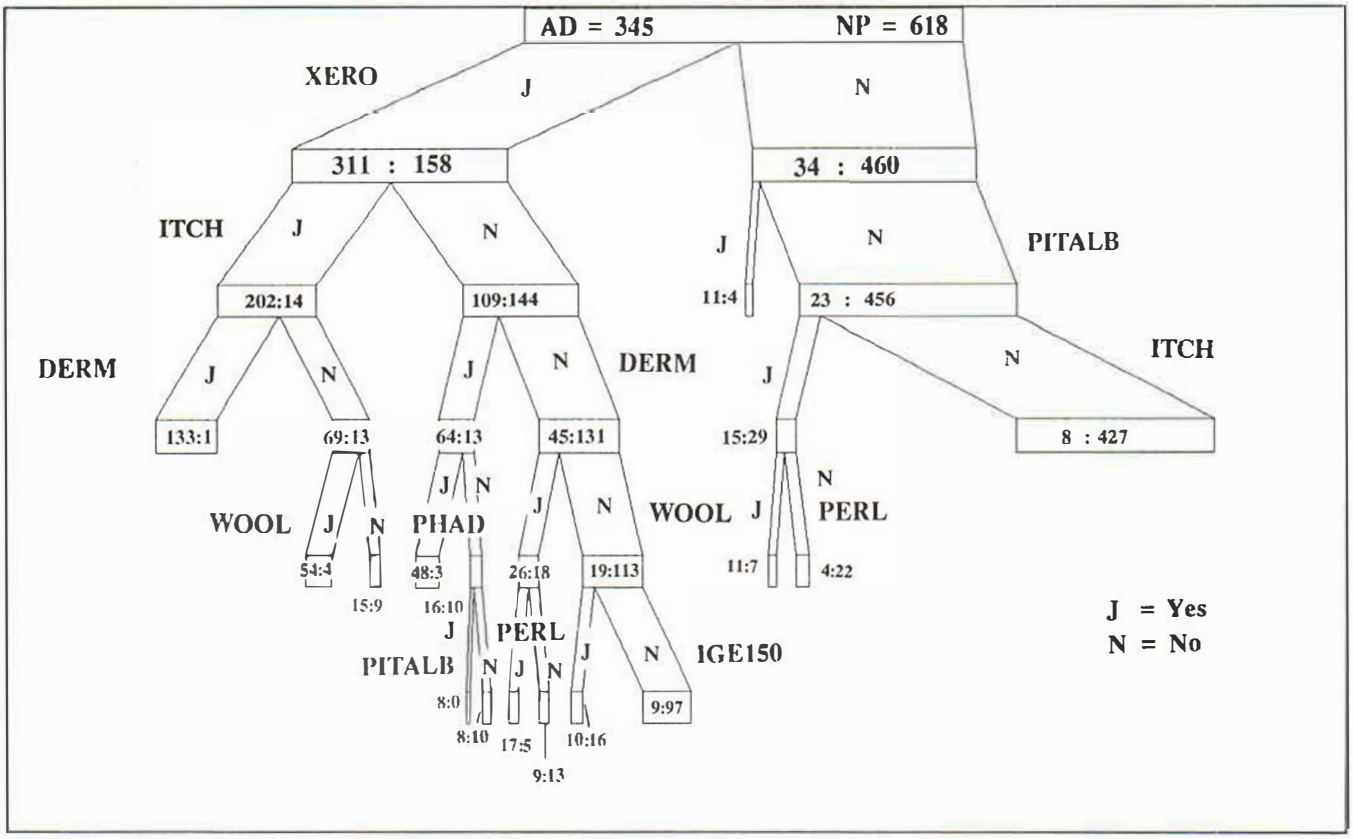

Fig. 4. CART-analysis of 'hard' atopic features in the diagnosis of AD.

sweating (non-eczematous skin), white dermographism, pityriasis alba, Hertoghe' sign and retro-auricular rhagades are very high. Some specific features, like atopic winter feet, dirty neck and nipple eczema did not occur in NP. Sometimes it is hard to judge borderline variants of some atopic stigmata, such as Hertoghe' sign, Dennie-Morgan infraorbital fold, hyperlinear palms, or it is hard to get good data by anamnestic evaluation of food intolerance or cradle cap. Thus we have studied the diagnostic value of the following 'hard' criteria by a multivariate CART analysis (Fig. 4): ASTH, DERMO, FA, IGE150, ITCH, KERAT, EAR, PERL, PHAD, PITALB, RHIN, WOOL, XERO. To separate 345 AD patients and 618 NP at the first step, the most important feature is xerosis (X^2 = 370). If only xerosis is diagnosed the probability for AD is 2 : 1; if xerosis is not given the probability of having no AD is 14 : 1. At the second step, itch when sweating is the most important feature if xerosis is positive and pityriasis alba if xerosis is negative. Then the probability for AD is 15 : 1 for a subject who has XERO and ITCH. Another example: for individuals suffering from XERO, ITCH, or DERMO, the probability of having AD increases to the ratio 133 : 1 according to our epidemiological study. In contrast, the probability for AD is only about 10% (9 : 97) if a subject only shows xerosis, but ITCH, DERMO, WOOL, elevated IgE (IGE150) are not found.

DISCUSSION

Frequencies of AD

Most of the data concerning the rates of atopic diseases are obtained by regional statistics and records of hospitals and not from randomly collected individuals. Much of the available data are difficult to compare because of differences in definitions of the diseases and methods (assessments from questionnaires to clinical examinations). Often it remains unclear which rates are calculated (incidence or prevalence) or whether data in several reports refer to current or past symptoms. In our study the cumultative incidences (lifelong at the time of investigation) in young adults were as follows: 4.7% AD, 4.8% allergic asthma and 17.9% allergic rhinitis. Epidemiological studies on representative populations demonstrate a significant increase in atopic diseases during recent decades (4, 5, 6, 7, 8). In a Danish study of childhood AD (8) the AD prevalence of 6–7-years-old children had increased from 3.8% (1975–76) to 9.1%; in a Danish twin sample (6) the cumulative incidence rate (0–7 years) of AD from 3% for the birth cohort 1960–64 to 10% for the birth cohort 1970–74 and in the nationwide British cohort studies (5) the prevalence of childhood eczema rose from 5.1% for children born in 1946 to 12.2% for those born in 1970. These findings in childhood AD were interpreted as denoting an increase in the incidences of AD. The percentage of in-patients with AD at our Dermatological Department had increased from 3.3 (1970–79) to 6.4% (1980–89) (9). This is in good agreement with Wüthrich & Schnyder

Table III. *Cumulative prevalences of AD in different studies.*

Authors	Year	*N*	Age	Cumulative prevalence	♀:♂
Turner (15)	1974	1,598	6–17 yrs.	5.6%	5.1%:6.0%
Kjellmann (18)	1977	1,325	7 yrs.	8.3%	9.4%:7.2%
Haahtela (11)	1980	922	13–18 yrs.	9.1%	8.6%:6.1%
Larsson (12)	1980	8,298	12–16 yrs.	3.0%	3.8%:2.3%
Svejgaard (13)[a]	1986	665	17–24 yrs.	3.3%	–
Schultz Larsen (6)	1986	563	7 yrs.	3.0%–10.0%	
Own results	1991	659	18–35 yrs.	4.7%	5.3%:4.2%

[a] Danish military recruits.

(10) who reported an increase from 3.5 to 8.6% for in-patients and from 1.5 to 5.1% for out-patients during the same periods, in Zürich.

The prevalence of AD among teenagers was in Finland 9.1% (11) and seems to be lower, according to Swedish estimates: 2.3% for boys and 3.8% for girls (12), and among Danish recruits was 3.3% (13) (Table IV).

In older children and adults, women outnumber men and the reported ratios of AD of females to males include 2 : 1 (14) and 1.2 : 1 (6). In epidemiological studies on the prevalence of atopic disorders the age of the investigated population is very important because the age of onset varies widely and differs between the kind of atopic diseases (Fig. 1). Thus the results obtained from a sample can only be representative for a particular target population.

Genetic aspects

The influence of hereditary factors in atopic disorders has been established by family and twin studies. Monozygotic twins run a risk of about 86% of having AD if the twin partner has the disease, whereas the disease risk of 21% run by dizygotic partners does not differ from the frequency seen in siblings (6). However, the increase in the frequency of AD during less than one generation suggests that time trends in environmental factors play an important role in the manifestation of the disease. In recent years a model of multifactorial inheritance in combination with a threshold is assumed: for the manifestation of an atopic disease the presence of additional realization factors is required (7, 10, 16).

A family history of atopic diseases in first-degree relatives was obtained in 58% of our AD patients and in 32% of NP. Frequencies between 43 and 73% are reported in other studies (17). Most of the former studies did not investigate the frequencies of a positive family history in the general population. The frequency of a positive family history in NP (32%) is supported by previous findings by Kjellman (18), who reported 32.5% in a sample of 7-year-old children.

The inheritability of atopic disorders within families was first proved by Schnyder (14) who coined the term 'intrafamilial organ constance'. This means that the same organ (bronchial system, or skin) is often affected in several family members with atopic diseases. Our findings clearly demonstrate that the risk for a child of developing AD is much higher if there is AD in the family (OR 6.7) than if there is RA in the family (OR 1.5) and that the risk of developing pure RA is 2.9-fold in non-eczematous controls if there is RA in the family, but not elevated if there is pure AD.

Patients with atopic diseases and their relatives are often interested to know the recurrence risk for acquiring atopic diseases. The pedigree analysis of our study of families of 355 AD patients with at least one sibling are comparable to a Swiss study of 74 AD families (14) and another German study of 161 families (19). If both parents are healthy the recurrence risks for atopy/AD are 16.2/9.3% vs. 18.2/6.6% (14) and 15.5/8.8% (19); if one parent is affected the recurrence risks increase to 31.7/21.2% vs. 27.9/7.6% (14) and 34.3/20.6% (19). But these risk figures varied widely, depending on the kind of disease found in the parent in the other studies too. If both parents suffer from an atopic disease, the recurrence risk is only given for atopy in both the other studies, being 66.6% (14) and 50.0% (19) compared with 70% according to our study. According to Kjellman (18) the incidence of atopic disease in children is highest (72.2%) when both parents have an identical type of atopic disease, e.g. respiratory or skin.

Diagnostic criteria for AD

The role of IgE in the etiology of AD is still unclear (20, 21) and it may be a non-specific feature of the disease. It was recently shown that the IgE responsiveness underlying asthma and rhinitis has a dominant inheritance with a linkage between the IgE responses and chromosome 11_q (22). However, the specific IgE response to inhalative allergens is only a facultative attribute of AD. Nearly half of our AD patients showed clinical signs of concomitant respiratory allergies. In a Japanese population, AD patients without RA predisposition comprise about 40% of all AD patients (23). In 20–40% of cases of 'pure' AD neither elevated IgE levels nor a specific IgE sensitization could be found in other studies (10). Wüthrich (24) proposes to distinguish three main subtypes of AD: a 'mixed' type with concomitant respiratory allergies, an 'extrinsic' type of 'pure' AD without RA but with allergen-specific IgE and an 'intrinsic' type without immediate type sensitizations.

Because of the lack of a specific laboratory marker the diagnosis of atopic eczema is entirely dependent on the recognition of the basic and minor clinical features proposed by Hanifin & Rajka (25) which are based on traditional clinical experience. In the present prolective standardized study the occurrence of different atopic features has been compared with those in the general population of young adults because the diagnostic value of atopic symptoms and signs depends on

the frequencies found in the general population. In an earlier study (26) we proposed a score system which is based on statistical evaluation of anamnestic and clinical features without laboratory investigations and could be helpful in the diagnosis of indeterminate eczema or to diagnose a possible atopic skin diathesis in non-affected individuals. On the basis of χ^2 values, every atopic feature obtained three points (XERO, ITCH, DERMO, WOOL), two points (PITALB, DENNIE, HERT, PALMS, EAR) or one point (PERL, CAP, FA, FACIAL, KERAT, FOOD, RHIN, ASTH, METAL, LIGHT). Based on this score system we suggest that a patient with 10 or more points should be considered as having an atopic skin diathesis. There are complex associations between the different atopic signs and we could not find different subgroups with typical patterns of atopic features. The CART analysis allows new insights into the diagnostic value and the complex interplay of atopic stigmata. The knowledge of distribution and frequencies of clinical atopic basic and minor features achieved by further epidemiological studies might give new insights and support in diagnosing the atopic skin diathesis.

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