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Prognosis and prognostic factors in adult patients with atopic dermatitis: a long-term follow-up questionnaire study

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Summary

Background Atopic dermatitis (AD) is a chronic relapsing skin disease. Several investigations concerning the long-term prognosis of AD among children and teenagers have been performed but there are only few data among adults.

Objectives To investigate the prognosis and prognostic factors in adult patients with AD by a long-term follow-up (25–38 years). The prognostic factors were defined as those factors of importance for the persistence of AD.

Patients and methods A follow-up questionnaire was sent in November/December 1998 to 922 AD patients examined in our outpatient clinic between 1960 and 1973 among 1366 registered patients with AD. The patients were aged 20 years or older when they visited the clinic and 45 years or older when they answered the follow-up questionnaire.

Results The response rate was 90·4%. The age range at the time of follow-up was 45–86 years (mean 55 years). Of the 833 patients who responded, 59% reported AD at some time during the last 12 months, which we defined as persistent AD. The mean value of clearance rate per person-years was 18%. One of the most important factors associated with persistence of AD was a head and neck dermatitis with or without other AD locations at the time of examination according to the old patient records.

Conclusions This study showed that the majority of adults with AD still had AD when they became older. This applies particularly if negative prognostic factors existed.

Key words: adults, atopic dermatitis, prognosis, prognostic factors

Atopic dermatitis (AD) is a chronic relapsing, pruritic and common skin disease. Three phases of AD can be discerned: the infantile phase up to 2 years of age, the childhood phase between 2 and 12 years of age, and the adolescent or adult phase.[1] The most typical locations during the infantile phase are the extensor sides and face, and during the childhood phase, the flexures.[2] In adults, the skin lesions of AD are similar to the childhood phase but the head and neck and hands are more frequently involved.[1] However, the degree and extent vary greatly. The sex distribution of AD according to Scandinavian population-based studies shows a predominance of females to males of 1·4 : 1·0.[3] Several studies have reported an increased prevalence during recent decades.[4] The prevalence in 7-year-old children born before 1960 was 2–3%,[5] compared with 15–20%[4] of those born in the 1980s. AD is dependent on both genetic and environmental factors.[6] The increase of AD has been related to the latter.[7,8] The importance of socioeconomic factors has also been discussed.[9] Many factors may act as triggers and influence the course of AD, such as irritants, aeroallergens, food, microbial organisms, sex hormones, stress factors, sweating and climatic factors.[10,11] AD often starts in early childhood and has a variable prognosis. Several investigations concerning the long-term prognosis of AD among children and teenagers have been performed.[12] A persistence rate after puberty of 40–60% among patients seen in outpatient clinics and university hospitals has been reported.[13] Only a few studies have been performed regarding the long-term

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prognosis among adults.[14,15] The aim of the present study was to define the prognosis and prognostic factors by long-term follow-up of adults with AD.

Patients and methods

Patients

A follow-up questionnaire with 59 questions was mailed in November/December 1998 to AD patients examined between 1960 and 1973 in the outpatient clinic of the Department of Dermatology, Sahlgrenska University Hospital, Gothenburg, Sweden. The study was approved by the Ethics Committee in Gothenburg. To be included in the study, the patients had to be aged ≥ 20 years when they visited the clinic, and consequently ≥ 45 years when the follow-up questionnaire was mailed to them. The diagnostic registers for outpatients, indexed under the diagnosis of prurigo Besnier or eczema atopicum, were used. Of 1366 registered outpatients (894 females and 472 males), we were able to find the current addresses of 922 patients whose old records indicated either of these diagnoses, which we concluded were correct compared with Hanifin and Rajka's diagnostic criteria[16] or the U.K. Working Party's Diagnostic Criteria.[17,18] Their present address was located through the local tax office. All the patient records have been checked by one of the authors (M.H.S.).

The questionnaire

The questionnaire consisted of 59 questions. The majority of the questions had to be answered by 'Yes' or 'No', but some questions had other alternatives. Table 1 shows the factors relevant to this paper, according to the questionnaire.

Statistical analysis

When analysing the data, patients were divided into two categories: those who reported that they had had AD some time during the last 12 months, which we defined as persistent AD, and those who had not, which we defined as healed AD. Those without AD during the past 12 months had not had AD for many years. Fisher's exact test and the χ^2 test were used for statistical analysis. The null hypothesis that no difference existed was rejected at the significance level of 5% ($P < 0{\cdot}05$). A logistic regression analysis was also performed in order to confirm the preliminary findings. PROC CATMOD, SAS version 8·0 (copyright 1999–2001; SAS Institute Inc., Cary, NC, U.S.A.) was used, which results in the same estimations as the special program LOGIST. A clearance rate analysis using person-years as the denominator has been made, i.e. clearance rate per person-year.

Results

Of the 922 patients to whom the questionnaire was mailed, 601 were female and 321 were male. Of these, 833 (90·4%) (545 females, 288 males) responded. The majority of the questions (94–100%, mean 99%) were answered with the exception of one question, which was answered by 78%. The age range at the time when the patient visited the outpatient clinic of the

Table 1. Factors relevant to this paper according to the questionnaire

Gender	Siblings with allergic rhinoconjunctivitis
Age	Allergy to furred animals
Social status	Allergy to pollen
Smoking	Itching or discomfort on lips, mouth or throat due to food allergies
Change of occupation due to eczema	Eczema worsened by food
Age at onset of symptoms of AD	Eczema worsened by infection
Experienced progression of eczema	Eczema caused by skin contact with nickel
Eczema last 12 months, location, severity	Children with AD
Bothered by dry skin	Children with asthma
Bothered by dry hands	Children with allergic rhinoconjunctivitis
Frequently bothered by itching	Hospitalized due to eczema
History of asthma	Skin type
History of allergic rhinoconjunctivitis	Menstruation and eczema
History of parents with AD; if yes, who?	Pregnancy and eczema
History of parents with asthma	Treatments
History of parents with allergic rhinoconjunctivitis	Type of doctor consulted for eczema
Siblings with AD	Doctors consulted in the past year due to eczema
Siblings with asthma	Sick-leave

Department of Dermatology during 1960–1973 was 20–57 years (median 23, mean 25). According to the old patient records, 51% (425/828) had AD located on the head and neck with or without other locations at the time of the visit and 51% (422/829) AD on the hands with or without other locations. Seven percent (59/829) had AD only on the head and neck and 22% (184/829) only on the hands, but with a history of other AD locations consistent with the diagnostic criteria for AD.

The age range at the time of follow-up in November/December 1998 was 45–86 years (median 54, mean 55) and the follow-up time was 25–38 years (Table 2). The age distribution of men and women was equal. The majority of the patients, 72% (593/829), had a job. More than 50% of those employed when responding had administrative jobs, jobs in the medical and nursing fields or in education. However, 15% (127/831) had changed occupation earlier in life due to their AD. Seventeen percent (85/490) of those with persistent AD had changed occupation earlier in life due to their AD, compared with 12% (41/340) in the group whose AD was healed ($P = 0{\cdot}037$). Among those with persistent AD of the hands with or without other AD locations, 22% (62/285) had changed occupation compared with 12% (24/205) among those without AD of the hands ($P = 0{\cdot}004$). The jobs that were most frequently changed were within production and industry (28%, 35/123), service (24%, 29/123) or the medical and nursing fields (24%, 30/123). Comparing women and men, women most often changed occupations from medical, nursing and service jobs, while men most often changed from production and industrial jobs (data not shown). Twenty-two percent of the patients (179/826) were single. Fifty-four percent (451/832) were or had been smokers.

The age at the first appearance of AD according to the information from the patient questionnaires is shown in Table 3. Fifty-nine percent of the patients (490/832) reported that they had had AD some time during the last 12 months, i.e. persistent AD. The remaining patients had not had AD during the last 12 months, i.e. healed AD. There was no significant difference between females and males with respect to persistent AD ($P = 0{\cdot}61$). According to the clearance rate analysis, clearance rate per person-year was minimum 0% and maximum 97% (mean 18%). In patients with persistent AD (490 patients), 46% reported mild AD, 44% moderate AD and 10% severe AD. Fifty-four percent (264/490) reported AD located at the head and neck region with or without other locations. Of these 490 patients, in 58% (285) AD was located on the hands, in 47% (229) on the arms, in 36% (174) on the legs, in 30% (147) on the trunk and in 16% (80) on the feet, all with or without other locations. Nine percent (44) reported that the AD was usually limited to the head and neck and 17% (84) reported AD limited to the hands. The majority of the patients in the study considered that the AD had improved over the years and only 4% considered that their AD had deteriorated.

Table 2. Follow-up time of the patients included in the study

Follow-up time (years)	No. of patients (%)
25–29	441 (53)
30–34	211 (25)
35–38	181 (22)

Table 3. Age in relation to reported onset of atopic dermatitis (AD) in patients with persistent or healed AD

Age at onset of AD (years)	Persistent AD, no. (%)	Healed AD, no. (%)	Total, no. (%)
0–6	379 (62)	230 (38)	609 (74)
7–12	42 (45)	51 (55)	93 (11)
13–18	32 (65)	17 (35)	49 (6)
≥ 19	35 (46)	41 (54)	76 (9)
Total	488	339	827 (100)[a]

$P = 0{\cdot}001$. [a]Missing values 6.

Sixty-six percent of the patients (550/829) reported problems with dry skin and 64% (530/826) with dry hands. Sixty-two percent (514/829) used emollients daily. Dry skin was more common among the 490 patients with persistent AD than among the healed ($P < 0{\cdot}0001$). Forty-four percent (366/822) of the patients were frequently troubled by itching. As expected, itching was more common in the group with persistent AD and among those with dry skin. Among those with persistent AD, 60% (289/483) had frequent itching, compared with 23% (77/338) in the group whose AD was healed ($P < 0{\cdot}0001$). Of those with dry skin, 59% (320/542) reported pruritus, compared with 16% (45/278) of those without dry skin ($P < 0{\cdot}0001$).

The following factors were found to be associated with persistence of AD in the bivariate analysis: (i) head and neck dermatitis with or without other AD locations at the time of examination according to the old patient records; and (ii) factors from the questionnaire: age at onset for AD, asthma, allergic rhinoconjuntivitis (AR), parents with AD, siblings with AD or AR, allergy to

Table 4. Importance of certain factors for persistent atopic dermatitis (AD)

Factors	Number of patients with the factor in persistent AD (%)	Number of patients with the factor in healed AD (%)	*P*-value: bivariate analysis	*P*-value: logistic regression analysis
Head/neck localization[a]	274/487 (56)	151/341 (44)	0·001	0·03
Asthma	122/484 (25)	45/342 (13)	< 0·0001[b]	NS[b]
Previous history of asthma	67/484 (14)	59/342 (17)		
AR	262/480 (55)	114/337 (34)	< 0·0001[b]	NS[b]
Previous history of AR	65/480 (14)	59/337 (18)		
Parent with AD	113/490 (23)	57/342 (17)	0·017	NS[c]
Parent with asthma	79/488 (16)	38/341 (11)	0·117	
Parent with AR	69/488 (14)	30/340 (9)	0·067	
Siblings with AD	128/433 (30)	60/301 (20)	0·006	0·04[c]
Siblings with asthma	72/431 (17)	33/299 (11)	0·098	
Siblings with AR	107/431 (25)	49/298 (16)	0·014	
Allergy to furred animals	274/480 (57)	128/338 (38)	< 0·0001	0·01
Pollen allergy	254/476 (53)	111/336 (33)	< 0·0001	0·01
OAS	230/486 (47)	89/341 (26)	< 0·0001	0·001
Eczema worsened by food	253/475 (53)	131/320 (41)	< 0·0001	NS
Nickel sensitivity	161/486 (33)	71/341 (21)	< 0·0001	0·004

AR, Allergic rhinoconjuntivitis; OAS, oral allergy syndrome. [a]With or without other locations at the time according to the old patient records. [b]Three levels compared. [c]AD, asthma and AR analysed as atopic disease.

furred animals, pollen allergy, oral allergy syndrome (OAS), exacerbation of the AD by certain foods and nickel sensitivity (Tables 3 and 4).

A logistic regression analysis was performed with the factors gender, smoking, AD only in the hands at the time of examination according to the old patient records, skin type and the factors that were significant in the bivariate analysis above. The result showed that the following factors—AD including the head and neck at the time of examination, siblings with atopic disease, furred animal allergy, pollen allergy, OAS and nickel sensitivity—were significantly more common in persistent AD (Table 4).

The following information, not mentioned in Table 4, is still of importance: 69% (561/812) reported that they had or had had asthma and/or AR (AD and asthma in 8%; AD and AR in 33%; and AD, asthma and AR in 28%). In this population, 62% had their asthma onset and 57% had their AR onset before 19 years of age, according to the questionnaire. Although 20% (170/832) of all the patients reported that they had parents with AD, 18% (146/832) reported that they did not know if the parents had AD. Eighty-three patients had a mother with AD, 80 a father with AD and in six patients both parents had AD. There was no significant difference between maternal or paternal heritage of AD and persistent AD ($P = 0{\cdot}95$); 11% (91/829) and 14% (117/828) did not know if the parents had asthma or AR, respectively. Nine percent (64/734) of the patients did not know if their siblings had AD, 7% (51/730) did not know if they had asthma and 8% (60/729) did not know if they had AR. Eighty-three patients did not have siblings. Seven hundred and twenty-two patients (87%) answered that they had children and 48% of them (344/718) had AD, 24% (170/714) had asthma and 42% (302/713) had AR. It was more common to have children with AR ($P = 0{\cdot}012$) but not with AD or asthma among those with persistent AD. There was no significant difference ($P = 0{\cdot}11$) in reported occurrence of nickel sensitivity in persistent AD between those patients with AD on the hands, 36% (101/282), and those without AD on the hands, 29% (59/204). However, there was a difference in the occurrence of nickel sensitivity with regard to gender. Thirty-eight percent (206/543) of the women and 9% (27/285) of the men reported nickel sensitivity ($P < 0{\cdot}0001$). Thirty-four percent (266/791) reported that the AD was exacerbated by infections.

Patients with persistent AD had more often been hospitalized for their AD (49%; 242/490) compared with those who were healed (37%; 124/338) ($P = 0{\cdot}0003$). It was more common to have been treated with ultraviolet (UV) light among those with persistent AD (50%; 246/489) than among those who were healed (27%; 92/342) ($P < 0{\cdot}0001$). This was also seen with private use of UV light, which was reported by 23% (111/487) of those with persistent AD compared with 9% (29/341) of the healed patients ($P < 0{\cdot}0001$). Seventy-three percent (58/80) of those

with sun-sensitive skin (skin types I and II) had persistent AD, compared with 57% (423/739) of those with skin type III/IV ($P = 0{\cdot}008$).

Among the women, 75% (387/514) stated that their AD was unchanged during menstruation, in 22% (115) it became worse and in 2% (12) better. During pregnancy, 54% (241/446) had unchanged AD, 15% (69) became worse and 30% (136) better. Sixty-two of the women had never been pregnant.

In the full study, 28% (234/831) had at some time tried alternative therapy and this was more common in the group who still had AD (34%, 165/489) compared with those who were healed (20%, 69/341) ($P < 0{\cdot}0001$). Twenty-five percent (204/821) had at some time received treatment with systemic corticosteroids for the eczema, while 65% (537/829) used topical steroids periodically. In response to the question concerning which type of doctor was consulted during the previous years for AD, 62% (404/646) answered that they had mainly consulted a dermatologist. However, many (22%, 187/833) did not respond to that question. Thirty-seven percent (183/489) of those with AD during the last year visited a doctor for their AD during that time. Eighty-three percent (152/183) consulted the doctor one or two times during that year, 13% (23/183) three to five times and 4% (8/183) more than five times. In the full study, AD had led to sick-leave at some time in life in 34% (277/823) and 66% (180/272) of these reported a total duration of sick-leave of less than 3 months. Fourteen percent (37/272) reported a total duration of more than 1 year.

Discussion

Those responding to the questionnaire were between 45 and 86 years of age. The material is representative, with 90% patient participation. The majority of the questions were answered. The ratio of women to men was 2 : 1, which corresponded well with figures from the diagnostic patient register used initially. The distribution also corresponded well with figures in the literature.[3,13] Information concerning the diagnosis and extent of AD at the time of consultation was extracted from patient records. Data from the old patient records were not always complete. The diagnosis was made by experienced dermatologists and the data were reviewed by one of the authors. When the patients answered the questionnaire, the follow-up time was between 25 and 38 years. Before the questionnaire was mailed to the 922 patients, it was tested in a pilot group of patients with AD. There is always a risk of recall bias in a retrospective questionnaire study, as well as the disadvantage of not having met personally the patients involved. There might have been a responder bias in relation to those with persistent AD, who may be more likely to volunteer information regarding allergy to animals, nickel, etc.

Earlier follow-up studies concerning AD have focused primarily on children and teenagers. In the present study, we chose to follow-up adults with AD who were ≥ 20 years of age at the dermatological consultation. Patients were divided into two groups: persistent or healed AD, depending on whether or not they had had AD some time during the last 12 months when they answered the questionnaire. Earlier studies have shown a persistence rate of AD after puberty of 40–62%[13,19] or 50–91%, depending on the severity of the AD.[15] In our follow-up study, with considerably older patients than in earlier studies, 59% reported persistence of AD. The mean value for clearance rate per person-year was only 18%. This indicates that many patients with AD still have AD even in old age. We found that those with head and neck dermatitis with or without other AD locations at the time of examination according to the old patient records, had a higher tendency to persistence of AD. In an earlier study of young adults, facial and flexural dermatitis were the most persistent forms of AD.[15] The fact that adults with AD often have a head and neck distribution is well known,[20] but its prognostic value has not previously been shown. There are studies indicating that the normally present yeast, *Malassezia* (formerly *Pityrosporum ovale*), acts as an allergen in some types of AD, primarily head and neck dermatitis in adults.[21,22]

In an earlier study, female gender was a prognostically unfavourable factor for the healing of the AD,[19] whereas in another study gender was not shown to be of importance.[23] We saw no difference in our study between the sexes with regard to persistent AD. Among those with persistent AD, the majority reported residual mild or moderate AD while only 10% reported severe AD. Earlier clinical studies of patients with AD have shown a similar distribution when the patients were examined.[15,24]

Other studies have shown that dry/itchy skin in adulthood was associated with persistent or recurring AD.[19,24] Our study also showed that reported dry/itchy skin was more common among those with persistent AD, which is perhaps not so surprising, considering that the symptoms can be a consequence of AD. Previous reports have shown that chronic AD in

childhood or recurring AD in teenagers has a tendency to persist for several years regardless of occupation.[25] However, only dermatitis of the hands showed a correlation with extensive daily exposure to occupational irritation factors.[25] Regarding change of occupation as a result of AD, we found that it was more common in patients with persistent AD and in those with persistent hand eczema. Thus, AD has a tendency to persist despite change of occupation. However, those with persistent AD had more frequently been hospitalized for their AD, possibly indicating a more severe AD among those patients.

Our study shows, in the bivariate analysis, that an earlier onset of AD increases the risk of persistent AD, which has also been seen in earlier studies.[19,24] We also saw that those with reported onset of AD in their teens (13–18 years of age) had an increased risk of persistent AD. This is probably a result of responder bias; the onset was probably at an earlier age, but could also be a result of hormonal factors.

There is a close connection between AD, asthma and AR; 50–80% of those with AD develop allergic respiratory disease.[11,26] In our material, we found this in 69%. The prevalence of asthma and AR was consistent with earlier studies.[26] This was also true for the combinations of AD, asthma and AR as well as for isolated AD. Those who reported that they had had asthma or AR but primarily those with reported present asthma or AR had, to a greater extent, persistent AD, which is in accordance with earlier studies in younger individuals.[19] However, this is a selected material and there might therefore be a risk of selection bias. Reported worsening of AD due to foodstuffs and OAS was also more common among those with persistent AD in our study. In the logistic regression analysis, reported furred animal allergy, pollen allergy and OAS were significant factors for persistent AD. However, using the logistic regression analysis no statistically significant relations were seen between persistent AD, AR and asthma. Furred animal allergy, pollen allergy and OAS were associated with respiratory and mucous membrane symptoms and the risk of confounding is therefore possible. Furthermore, one cannot be certain that these exposures were present at the examination and it is therefore unclear whether they are true prognostic factors. A family history of atopic disease has previously been shown to be a negative factor in healing of AD.[19] We found in our study that those who had parents with AD had a higher risk of persistent AD. This was also found in those with siblings with AD or AR but not with asthma. However, there were many patients who had no knowledge of parents' or siblings' atopic diseases. In an earlier study of AD, it was found that the patients' parents had AD more frequently than asthma and AR.[26] It thus appears that children develop primarily the same atopic disease as their parents.[27] We also saw a greater reported incidence of AD than respiratory allergies in the patients' children by the patients.

Reported reaction to nickel was also a factor for persistent AD. A higher number of women than men reported nickel sensitivity. Other studies also found a positive history of nickel sensitivity and atopy.[28] Of the patients in our study, 28% reported eczema after skin contact with nickel. This is a considerably higher figure than reported earlier in patch test studies among patients with AD.[29] This high figure in our study group may be explained by both an allergic and a nonallergic (irritative) contact eczema. In persistent AD there was no difference in reported nickel sensitivity between those with AD including the hands and those without hand involvement. Lammintausta and Kalimo found that nickel sensitivity increased the risk of current dermatitis in various locations, including the hands, in patients with a history of mild AD in their teens, but not in patients with moderate or severe AD.[30]

Those with reported sun-sensitive skin (skin types I and II) had a higher prevalence of persistent AD. We do not know the reason for this. Broberg and Augustsson have examined the incidence of melanocytic naevi and AD.[31] In their material, the AD patients had a lower skin type than the control group. UV light is immunomodulating and many patients with AD improve during UV therapy.

When we proceeded with a logistic regression analysis, certain prognostic factors were eliminated because they were no longer statistically significant. Those remaining were head and neck dermatitis with or without other locations at the time of examination according to the old patient record, siblings with atopic disease, furred animal allergy, pollen allergy, OAS and nickel sensitivity.

Earlier studies have shown that some women's AD worsened with menstruation while the majority were completely unaffected.[32] There has been some speculation concerning hormonal and psychological factors. In the majority of the patients, we found no connection between menstruation or pregnancy and AD. However, both improvement and worsening of symptoms were reported. Among those reporting a fluctuation in symptoms, there were more whose AD worsened

compared with those who improved during menstruation and *vice versa* during pregnancy. There was no difference between the groups with persistent and healed AD.

People suffering from a chronic disease often seek alternative therapies when traditional treatment fails.[33] In our study, approximately one-third of the patients with persistent AD had sought alternative therapy, which was a higher figure than among those with healed AD.

Among those with persistent AD, 37% had consulted a physician for AD during the past year. However, the majority had only occasionally consulted a physician, while 4% had consulted a physician several times. Patients in our study had primarily consulted a dermatologist when they needed to consult a physician. The combination of a greater incidence of AD and persistent AD will in the future lead to a greater need for healthcare services.

In summary, this study has shown that the majority of adults with AD still have AD when they become older. Besides the earlier known negative prognostic factors for healing of AD,[22] our study has also shown that head and neck dermatitis with or without other locations is a prognostic factor for persistent AD. Allergy to furred animals, pollen allergy, OAS and nickel sensitivity were also more common among those with persistent AD.

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