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SPECIAL REPORT

Factors That Predict Remission of Infant Atopic Dermatitis: A Systematic Review

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The individual prognosis of infants with atopic dermatitis (AD) is important for parents, healthcare professionals, and society. The aim of this study was to investigate predictors for remission of infant AD until school age. A systematic review was carried out of clinical and epidemiological studies investigating the effect of filaggrin gene (*FLG*) loss-of-function mutations, sex, exposure to pets, topical anti-inflammatory treatment, disease severity, and atopic sensitization during infancy on complete remission of infant-onset AD until 6–7 years of age. Systematic electronic searches until September 2013, data abstraction, and study quality assessment (Newcastle-Ottawa Scale) were performed. From 3,316 abstracts identified, 2 studies of good study quality were included. Parental allergies and sex did not significantly affect remission. For non-remission of AD, the included articles reported an association with any atopic sensitization at 2 years old (adjusted odds ratio [aOR] 2.76; 95% confidence interval (CI) 1.29–5.91), frequent scratching with early AD (aOR 5.86; 95% CI 3.04–11.29), objective severity score at 2 years old (aOR 1.10; 95% CI 1.07–1.14), and exposure to pets (cat OR 2.33; 95% CI 0.85–6.38). It is largely unknown which factors predict remission of infant AD. This is a highly relevant research gap that hinders patient information on the prognosis of infant-onset AD. *Key words: atopic dermatitis; children; remission; longitudinal study; systematic review; epidemiology.*

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Atopic dermatitis (AD) is the most frequent inflammatory childhood disease, affecting approximately 20% of infants in the western world (1, 2). AD constitutes a considerable burden because of its high impact on the wellbeing of affected children and their families (3, 4). Approximately half of children with infant-onset AD are clear until school age (i.e. they show stable and complete remission) (5, 6).

In routine care, parents of infants with AD are interested in the individual prognosis of AD and the likelihood of complete remission. Knowledge regarding factors associated with remission of AD is also important for identifying risk groups and to develop targeted, individualized models of care for infants with AD, particularly if risk factors for persistent AD are modifiable.

Common loss-of-function mutations within the filaggrin gene (*FLG*) have been identified as a risk factor for incident AD (7). There is some evidence for an effect modification between *FLG* mutations and exposure to cats on incident AD (8). However, the combined effects of these exposures and of gene-environment interactions on the persistence of AD are unknown. With regard to exposure to pets, contradictory recommendations have been made concerning the benefits of keeping pets for children with AD (9, 10). Two systematic reviews on keeping pets and the risk of incident and prevalent AD concluded that ownership of furry pets is protective in terms of the risk of AD (11, 13), but methodological uncertainties were revealed. In longitudinal studies, only one study adjusted for avoidance behaviour. In this study, the positive effect of pet ownership on incident AD disappeared after adjustment for avoidance behaviour (14). Severe AD in childhood is more likely to persist into adulthood (5, 15, 16). Improved clinical management of AD might modify the course of the condition (17, 18). To the best of our knowledge, previous reviews have not examined the effectiveness of treatment for remission of AD, but rather reported the prevention of new flare-ups (19).

Previous systematic reviews of epidemiological studies have focused on risk factors for incident AD. The evidence concerning predictors for remission of infant-onset AD has not yet been systematically summarized. Therefore, we conducted a systematic review of all accessible randomized controlled trials (RCTs) and observational studies addressing the association between loss-of-function mutations within *FLG*, exposure to pets during early childhood, topical anti-inflammatory treatments of AD, severity of AD or atopic sensitization during infancy and preschool age, and remission of AD at 6–7 years old.

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MATERIALS AND METHODS

Search strategy

A systematic literature search was performed according to a pre-specified protocol in MEDLINE and the Cochrane register of RCTs (CENTRAL). RCTs and observational studies (cohort studies and case-control studies) were independently identified by 2 reviewers. The Cochrane high sensitivity search strategy for RCTs was used. Observational studies were identified according to recommendations in the Cochrane Handbook (20). In addition, we performed a manual search in reference lists of included papers and conference reports (European Academy of Dermatology and Venereology, International Symposium on Atopic Dermatitis, International Dermato Epidemiology Association Congress, and International Investigative Dermatology Congress). The search included articles published until 5 September 2013 (search strategy; see Appendix S1[1]).

Inclusion criteria

Articles were included that evaluated the effects of loss-of-function mutations within *FLG*, sex, exposure to pets (cats and dogs) during early childhood, topical anti-inflammatory treatments of AD, severity of AD, and atopic sensitization (skin-prick test or IgE) in children with infant-onset AD with the likelihood of remission of AD until 6–7 years old. Infant-onset AD was defined as physician-diagnosed AD or AD in accordance with UK working party diagnostic criteria between the ages of 0 and 2 years (21).

Primary outcome and secondary outcomes

Remission was defined as the absence of signs and symptoms of AD as assessed by a physician (clinical assessment), or by the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire in at least 2 subsequent follow-up visits covering a period of at least 12 months until 6–7 years old (22).

Secondary outcomes were as follows: (*i*) complete remission of infant-onset AD in older children until 10, 11–14, 15–17 years old, and adulthood (> 18 years); and (*ii*) partial remission in children until 6–7, 10, 11–14, 15–17 years old, and adulthood (> 18 years), and the proportion of participants developing asthma, rhinitis, or allergic sensitization.

Primary and secondary exposures

Primary exposures of interest were as follows: (*i*) *FLG* loss-of-function mutations, (*ii*) sex, (*iii*) exposure to pets during infancy, (*iv*) topical anti-inflammatory treatment of AD in infancy, (*v*) severity of AD in infancy, and (*vi*) atopic sensitization during infancy. These exposures were systematically covered by the electronic search strategy in this study.

Secondary exposures were a family history of allergic disease, number of siblings, socioeconomic status (indicated by education, occupation, and income), breastfeeding, home environment (house location, rural/urban), and day-care attendance in infancy. These exposures were not systematically covered by the electronic search strategy in this study.

Evaluation of eligibility of studies

The identified articles were independently reviewed for eligibility by all authors in pairs of 2 reviewers for each article. All of the reviewers discussed the final decisions.

Data abstraction and assessment of methodological quality of included studies

Primary selected studies were further examined using a list of features for collecting information on study design and a sheet for data abstraction. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included epidemiological studies (23). Data abstraction and quality assessment were also performed independently by 2 researchers.

Statistical analysis

The primary measure of association used was the odds ratio (OR). It was planned to perform a random-effect meta-analysis of qualitatively homogeneous studies.

If ORs were not reported, we aimed to calculate crude ORs with corresponding 95% confidence intervals (CIs) from the data presented in the papers included if possible by using the method suggested by Bland & Altman (24). The 95% CI was estimated by first calculating the standard error for the log OR. Secondly, we assessed 1.96 standard errors on either side of the estimate, which gives a 95% CI for the log OR. Finally, we calculated the antilog of these limits. Analysis was performed using Stata IC 11.0 Statistics Data Analysis.

RESULTS

A total of 3,316 abstracts were identified, with 1,637 reporting RCTs and 1,679 observational studies. Among 18 articles, 17 reported cohort studies and 1 reported a RCT, and these were primarily identified for full-text review (Fig. S1[1]). Finally, only 2 cohort studies met the inclusion criteria (5, 25). A total of 16 articles were excluded because of a lack of outcome data for remission ($n = 11$) or outcome data on age groups other than 6–7 years ($n = 5$). Of the 2 included studies, 1 was performed in Sweden, and the other study was performed in Germany (5, 25). The quality of the studies according to the NOS was good (NOS scores: 8 and 9; Table SI[1]).

The number of participants was 1,314 and 2,916 (Table I) (5, 25). The definition of complete remission in the cohort study by Illi et al. (5) was no AD after the age of 2 years (reported by a family physician, parental report of symptoms of AD, and visible AD at the time of follow-up). In the cohort study by Ballardini et al. (25), remission at the age of 4 or 8 years was defined as not having a specific allergy-related disease (in this case, AD) that had been present at the previous follow-up and that will be present at one or more future follow-ups. The follow-up in the studies was 7 (5) years and 12 (25) years.

The Swedish study (25) reported that remission between 2 and 4 years old was 30%, and remission between 4 and 8 years old was 49%. In the German study (5), 43% of those with AD in infancy were in remission at 6–7 years old (Table SII[1]). Illi et al. (5) investigated the effect of severity of infant AD and reported that "72.2% of the children with persistent AD reported frequent scratching with early AD, whereas this was the case in only 35.6%

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Table I. *Characteristics of birth cohorts included in the systematic review: settings, populations, and variables*

Authors	Year of enrolment	Mean follow-up, years	Cohort, type and size	Definition of infant eczema	Main predictors	Outcome[a]	Age at enrolment
Illi et al. (5)	1990	7	Birth cohort with normal risk and high risk infants *n* = 1,314 *n* = 1,123 (85.5%); included in any analysis *n* = 858 (76.4%); had complete data on the course of AD	At least one of the following: (*i*) reported diagnosis by the family physician, (*ii*) parental reporting of symptoms of AD, and (*iii*) visible AD at the time of follow-up Early manifestation of AD: onset of disease in the first 2 years of life	Predictors were not clearly reported Sensitization Severity of AD before 2 years old Maternal breast-feeding and feeding practices up to 2 years old Parental smoking habits assessed at 1 month old Keeping pets (exposure to cats or dogs), assessed at 3 months old Early wheeze	Remission at 7 years old Complete remission (CR) after 2 years old (comparator): no AD after the age of 2 years	Birth
Ballardini et al. (25)	1994–1996	12	Population birth cohort; invited (*n* = 4,089) and participated (*n* = 2,916)	Eczema: dry skin, itchy rashes with age-specific location for 2 weeks or longer and/or doctor's diagnosis of eczema in the past 12 months	Parental allergy	Remission at 4 and 8 years old: not having a specific allergy-related disease (in this case, AD) that had been present at the previous follow-up and that will be present at one or more future follow-ups	2 months

[a]Including how absence of signs of eczema for a period of at least 12-months has been assessed.
AD: atopic dermatitis.

of the children with an intermittent pattern and in only 14.5% of the children with complete remission after age 2 years (adjusted OR [aOR] 5.86; 95% CI 3.04–11.29)." Ballardini et al. (25) reported that parental allergy and sex did not affect remission of AD, but did not show specific results. Neither of these 2 studies investigated the effect of *FLG* loss-of-function mutations, topical anti-inflammatory treatments of AD, or atopic sensitization in infancy on the likelihood of remission of infant-onset AD until 6–7 years old (Table SII[1]).

Secondary exposures and outcomes

Illi et al. (5) reported that none of the predefined secondary exposures, such as older siblings, breast-feeding, parental smoking, maternal smoking during pregnancy, and parental level of education, were associated with the prognosis of AD (Table SII[1]). In addition, the additional factors of age at introduction of solid foods, level of mite allergen exposure, number of infectious diseases, and age at onset of AD were not significantly associated with the prognosis of early AD. However, specific results were not reported (5).

Ballardini et al. (25) reported that sex was not significantly associated with remission of AD. However, the specific results and the level of association were not reported.

Ballardini et al. (25) and Illi et al. (5) investigated which factors were associated with non-remission of AD and found that the following factors affected non-remission: a strong atopic family history (2 or more atopic family members (OR not reported, $p < 0.001$) (5, 25); any atopic sensitization at 2 years old (aOR 2.76; 95% CI 1.29–5.91); any food sensitization (aOR 2.87; 95% CI 1.27–6.48), sensitization to wheat (aOR 7.43; 95% CI 2.21–25.02), sensitization to soy beans (aOR 4.46; 95% CI 1.34–14.87), severity score at 2 years old (an objective severity score on a scale of 0–83 points was used on the basis of the extent and intensity of erythema, oedema, oozing, excoriation, lichenification, and dryness; aOR 1.10; 95% CI 1.07–1.14); frequent scratching with early AD (aOR 5.86; 95% CI 3.04–11.29); exposure to pets during early childhood (cats: OR 2.33; 95% CI 0.85–6.38; dogs: not significant, data not reported); and early wheeze (aOR 1.80; 95% CI 1.01–3.23) (Table SII[1]) (5). Illi et al. (5) studied the effect of corticosteroid treatment (assessed by parental questionnaire) on the persistence of AD, and found in crude analysis that corticosteroid treatment increased the odds of persistence (OR 2.20; 95% CI 1.10–3.71). When adjusting the model for severity of early AD, corticosteroid treatment was no longer significantly associated with persistence. Within the group of children with severe early AD, no association between corticosteroid treatment and persistence was found (crude OR 1.14; 95% CI 0.45–2.85).

Secondary analysis

The data obtained by Illi et al. (5) were used to assess the relationship of frequent scratching with early AD, more than 2 atopic family members, parental AD, parental hay fever, parental asthma, increased cord blood IgE levels, increased total IgE levels (≥30 kU/l), any sensitization, any food sensitization, any inhalant sensitization, early wheeze, and remission of eczema. Based on calculations using the data from Illi et al. (5), the factors that most decreased the odds of remission were frequent scratching, which decreased the odds of remission by nearly 90%, and sensitization (any, food and inhalant), which produced a 70% lower odds of remission. More than 2 atopic family members and early wheeze decreased the odds of remission by 61% and 57%, respectively (Table SIII[1]). Parental AD, hay fever or asthma, and increased levels of serum IgE did significantly affect the course of disease in these analyses.

DISCUSSION

Main findings

Approximately half of the children with AD in infancy are in complete remission at the age of 6–7 years (5, 25). In the Swedish cohort, the proportion in total remission was 41.5% at all observation time-points, and this cohort was followed until the age of 12 years (25). It is of great interest to parents to provide them with individualized prognosis and information on information related to exposure of infants with AD predicting clearance until school age. Also, knowledge of the disease characteristics of infant AD that predict remission are highly relevant for targeted preventive and therapeutic measures. Despite this high relevance of prognostic factors of prevalent infant AD, we could identify only 2 studies that investigated this issue. In the 2 studies included in this review, remission of AD was not predicted by cats or dogs in the child's home, parental allergy, or sex. However, the effect of *FLG* mutations on remission of infant-onset AD has not yet been studied systematically, and there is a lack of data regarding the other predefined factors and remission of infant AD until 6–7 years of age.

In secondary data analyses, having fewer than 2 atopic family members was a predictor for remission. No association with remission was found with parental allergy or onset in the first or second year of life. Even among the predefined secondary exposures of older siblings, breast-feeding, parental smoking, maternal smoking during pregnancy, and parental level of education, no factor affecting AD remission could be identified. The factors associated with non-remission of AD until 6–7 years old were a strong atopic family history, sensitization, severe AD, and early wheeze (5, 25).

Secondary analysis suggested that factors that most decreased the likelihood of remission of AD were frequent scratching, strong heredity, atopy, and early wheeze. The lack of studies made it impossible to pool data.

Strengths and limitations

A major advantage of this study was the comprehensive search including RCTs and prospective studies using a predefined protocol. The study quality of the 2 included studies was assessed as good. An advantage of both included studies was the prospective design, which makes the results less vulnerable to recall bias and allows the temporal relationship to be assessed. Diagnoses by questionnaire, which was used in both studies, is advantageous because AD can be sporadic, and AD cases might be missed by a physical examination at specific time-points. However, information bias regarding AD diagnosis cannot be excluded because, to the best of our knowledge, the questionnaires used have not been validated for preschool children. The large sample sizes of both studies minimized chance as the source of the findings for the predefined main analysis. However, because only 2 studies met the inclusion criteria, more evidence is required. The population-based design used by Ballardini et al. (25) enabled the results to be less prone to selection and ascertainment bias. Even half of the cohort used by Illi et al. consisted of an unselected population sample (5). Because participation was voluntary, there was a risk for some selection bias. In the study by Ballardini et al. (25), families with children who have allergic symptoms might have been more likely to participate. However, in that study (25), loss to follow-up was more common among children with allergy-related diseases. Both studies had a limited loss to follow-up. In the study by Illi et al. (5), 76.4% of children had complete data, and in that by Ballardini et al. (25), 71% had complete data on the course of AD. Even though the adequacy of follow-up was assessed as intermediate (<80%) according to the NOS criteria, we believe that this is acceptable, taking the length of the follow-up into account (5). However, some associations could not be analysed with adequate power, such as the cat/non-remission relationship indicated by a large CI (aOR 2.33; 95% CI 0.85–6.38).

Currently, there is no consensus concerning the definition of remission of AD, and the 2 studies defined remission differently. Illi et al. (5) defined remission as no sign of AD after the age of 2 years. Ballardini et al. (25) defined remission as not having a specific allergy-related disease that had been present at the previous follow-up and that will be present at one or more future follow-ups. In both studies, remission was not the main outcome, and not all results on assessed relationships regarding remission were reported. Secondary analysis that used the data from Illi et al. (5) must be interpreted with caution. No raw data were accessible, the variab-

les analysed were selected based on availability in the results section, and no adjustments could be performed. Therefore, this secondary analysis can only be regarded as hypothesis generating.

Comparison with other studies

In studies on persistence of AD, atopy, *FLG* mutations, and heredity predicted non-remission of AD. Because our review investigated the effect of various factors on remission of AD, these studies were not included (16, 27, 28).

Our review supports findings reported by Peters et al. (29) who prospectively followed German participants of ISAAC. They found that breast-feeding, parental smoking, kindergarten attendance, sex, birth order, and the number of infectious diseases were not associated with an increase in the odds of AD persistence. Because no results on remission were reported in the article by Peters et al. (29) and the study population consisted of adults, this article was not included in our review. In accordance with findings reported by Gustafsson et al. (15) and Ricci et al. (16), we found that eczematous children with high severity scores had increased odds of no remission of AD. Eller et al. (1) were unable to show an association between time of onset and relapse of AD. The articles by Eller et al. (1), Gustafsson et al. (15) and Ricci et al. (16) did not report results on remission of AD, and therefore, were not included in our review. However, reassuringly, the results of our study are in line with articles reporting on non-remission of AD (1, 15, 16, 29). The fact that there have been only a few studies that investigated factors associated with remission is surprising in light of the many cohort and birth cohort studies that have been conducted to investigate the causes and course of AD and allergies in children. This appears to be another example where important questions are not brought to the agenda of researchers (26). However, secondary analysis suggested that even remission of AD is related to multiple factors with a large effect of heredity, factors associated with atopy (sensitization, other allergic disease), and skin barrier function (scratching).

Implications, generalizability and future studies

Understanding the predictors of remission of AD has a large effect on management of patients because allergic diseases can lead to high impairment and costs. The factors of parental allergy, sex, and keeping pets could be excluded as potential predictors in our review. Identifying risk groups is important in healthcare planning. Based on our data, there is no evidence to recommend that families with children with AD should change their home environment.

Despite the good study quality, there were only 2 studies that were able to be included in our review, and none had remission as the main outcome. Caution is therefore required before generalizing these results to other childhood populations.

Future studies should examine whether interventions such as effective treatment (vs. non-treatment) have an effect on later remission of AD. Further evidence is required to determine the effect of other factors on remission, especially for modifiable factors, using interventional studies and observational studies, and to unravel the underlying mechanisms of the factors associated with remission.

In conclusion, keeping pets in the home in early childhood, parental allergy, and sex did not predict remission of infant-onset AD until the age of 6–7 years. There is a lack of evidence regarding factors associated with remission of childhood AD. Further studies, focussing on remission of AD, are required to identify risk groups and disease-modifying therapies.

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