

Food allergy and atopic dermatitis in infancy: an epidemiologic study

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Atopic dermatitis is common in infancy. The role of food allergy in atopic dermatitis of infancy is unclear. We examined the relationship between atopic dermatitis and immunoglobulin E (IgE)-mediated food allergy in infancy. A birth cohort of 620 infants with a family history of eczema, asthma, hayfever or immediate food allergy in a parent or sibling; 487 children had complete data including skin prick tests (SPTs) to evaluate IgE-mediated food allergy to cow milk, egg and peanut. Participants were grouped as no atopic dermatitis (Gp 0) or in quartiles of increasing severity of atopic dermatitis (Gps 1–4) quantified by days of topical steroid use as reported monthly. Adverse reactions to foods were recorded. The cumulative prevalence of atopic dermatitis was 28.9% to 12 months (10.3% of the cohort of moderate severity). As atopic dermatitis severity increased so did the prevalence of IgE-mediated food allergy (Gp 0, 40/346 vs. Gp 1, 6/36 vs. Gp 2, 8/35 vs. Gp 3, 12/35 vs. Gp 4, 24/35; $\chi^2 = 76$; $p < 10^{-6}$), and the frequency of reported adverse food allergy reactions (Gp 0, 43/346 vs. Gp 1, 4/36 vs. Gp 2, 8/35, vs. Gp 3, 5/35, vs. Gp 4, 13/35; $\chi^2 = 17$; $p = 0.002$). The relative risk of an infant with atopic dermatitis having IgE-mediated food allergy is 5.9 for the most severely affected group. Atopic dermatitis is common in infancy. There is a strong association between IgE-mediated food allergy and atopic dermatitis in this age group.

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Atopic dermatitis is a chronic relapsing pruritic inflammatory disease of the skin frequently associated with allergen sensitization, raised serum immunoglobulin E (IgE) levels, and a family history of allergic diseases. In Australia, the cost of management and the impact of atopic dermatitis on families is greater than for juvenile diabetes mellitus (1).

Clinically, IgE-mediated food allergic skin reactions commonly elicit urticaria, angioedematous and maculopapular eruptions but the relationship of these to atopic dermatitis is controversial. However, Sampson has noted that children with food allergy who have atopic dermatitis may develop urticaria on double-blind placebo-controlled food challenges (DBPCFC) when in diet-induced remission but when their disease is active the same DBPCFC can elicit eczematous (non-urticarial) eruptions (2).

As well, controlled studies (3, 4) have demonstrated a low food allergen diet is associated with a significant reduction in prevalence of atopic dermatitis of infancy. Despite these data, several published reports by expert panels suggest that food allergy is of minor importance in the pathogenesis of childhood atopic dermatitis (5–7).

Both IgE-mediated food allergy, and atopic dermatitis, have their greatest prevalence in the first 12 months of life (3, 8) but the relationship between IgE-mediated food allergy and atopic dermatitis in this age group has not been studied in detail. We have previously reported a threefold increase of the risk of atopic dermatitis in infants with high levels of IgE sensitization to foods (9), but the relationship of atopic dermatitis to IgE-mediated food allergy was not clear.

In this part of a continuing study, we examined the prevalence of, and the role of IgE-mediated

food allergy in atopic dermatitis in a community-based birth cohort of atopy 'at-risk' infants studied to the age of 12 months. The role of IgE-mediated food allergy in atopic dermatitis was tested by examining the strength of association between IgE-mediated food allergy and atopic dermatitis of increasing severity across the cohort.

Materials and methods

Subjects from the Melbourne Atopy Cohort Study which commenced in 1990 were studied until 12 months of age. A cohort of 620 subjects were recruited at birth on the basis of one or both parents or any sibling(s) having either atopic dermatitis, asthma, hayfever or severe reactions to foods, i.e., this was not a random population but an 'atopy-at-risk' one. Detailed demographic, family medical history, and environmental data were obtained during pregnancy. Questionnaires, administered by a trained allergy research nurse, were completed by telephone interview at 4-weekly intervals. They included questions on infant feeding, the introduction of solids, the development of atopic dermatitis and other infant illnesses, contact with health care professionals and medications used. Skin prick tests (SPT) to common food and inhalant allergens were performed on the infants at 6 and 12 months of age.

Mothers were encouraged to breast-feed and to delay the introduction of solids until after the age of 6 months when low allergen solids were introduced into the diet (excluding egg, peanut and fish). After 12 months appropriate diet for age was encouraged.

The 487 infants (238 female) who had completed all questionnaires to 12 months and had SPTs performed at both 6 and 12 months of age. There was no significant difference in the prevalence of atopic dermatitis in those infants who were not allergen skin tested (22%) and excluded from further analyses, and those who were (29%) ($\chi^2 = 1.83$, $p = 0.18$).

Definition of atopic dermatitis

The definition of atopic dermatitis was based on the criteria of Williams (10) modified for infant use (11). That is, they had a positive family history of atopy, a relapsing skin eruption with a characteristic distribution which was treated with topical steroids by a family practitioner. In addition, the timing of its appearance, and frequent personal history of atopy (positive SPT and food allergy) were typical of atopic dermatitis.

Because this was an epidemiologic study and day-to-day patient management was not under our control, we did not, in the initial phases of the study always have a physician diagnosis of 'atopic dermatitis'. However, the research nurse who examined the children at 6 and 12 months at the time of SPT was, in many instances, able to confirm the presence of a rash consistent with eczema.

At the end of each 4-wk period the research nurse documented the number of days during that period on which topical steroid preparations had been applied. To quantify eczema severity over the 12-month study period, an operational definition was devised using the relationship between the number of days of steroid use and the presence of a physician diagnosis of eczema via an Receiver Operating Characteristic (ROC) curve.

The ROC curve analysed of the sensitivity and ($1 - \text{specificity}$) of the days of topical steroid use in the first 12 months against the proportion of parents recalling their physician designating the rash as eczema, i.e., physician-diagnosed eczema (DDE+). The part of the curve nearest the point $y = 1$ for sensitivity and $x = 0$ for ($1 - \text{specificity}$) was represented by 8 days of steroid use. In the subsequent analysis (see Results) this definition was robust and not sensitive to minor changes (from 6 to 10) in the number of days of steroid treatment. Therefore, for the purposes of this study, 8 days of topical steroid use was chosen as the discriminator between infants who did and did not have atopic dermatitis. The presence of atopic dermatitis defined by the ROC curve analysis, and the physician diagnosis of atopic dermatitis as reported by parents to the allergy research nurse, were strongly associated ($\chi^2 = 98$; $p < 10^{-6}$) (Figure 1).

A total of 141 infants had atopic dermatitis, i.e. greater than 8 days of topical steroid use; 57 parents could recall 'the DDE+' and another 84 infants had used topical steroids to treat skin rash for 8 days or more but these parents could not recall their physician using the term 'eczema' during the first 12 months of this study (DDE-). However, in subsequent follow up after the 12-month period of this study, 62 of these 84 infants were diagnosed as having 'eczema' by their family practitioner. The remaining 22 of these 84 infants had mild eczema and were in groups 1 or 2 (see below).

The severity of atopic dermatitis was quantified by dividing those subjects with atopic dermatitis into quartiles according to nurse-recorded topical steroid use:

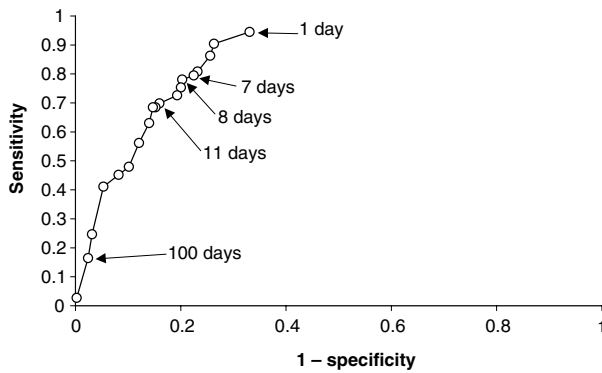


Fig. 1. The receiver operating characteristic curve for the relationship between physician-diagnosed eczema (DDE+) and days of topical steroid preparation use in the first 12 months of life. Eight days of topical steroid use was the point chosen to best discriminate between infants with, and infants without eczema.

Gp 0 (no atopic dermatitis): <8 days of topical steroid treatment in the first 12 months (n = 346).

Gp 1: 8–14 days of topical steroid treatment in the first 12 months (n = 36).

Gp 2: 15–28 days of topical steroid treatment in the first 12 months (n = 35).

Gp 3: 29–73 days of topical steroid treatment in the first 12 months (n = 35).

Gp 4: 74–232 days of topical steroid treatment in the first 12 months of life (n = 35).

The above methods were used to quantify eczema severity over the 12-month study period.

In addition, at the time of clinical assessment and SPT at 6 and 12 months, the allergy research nurse examined for the presence of an eczematous rash.

Skin prick tests

Skin prick tests were performed according to a standard technique (12) to cow milk, egg, and peanut allergen extracts (Bayer, Spokane, WA, USA). The mean diameter of the weal, after subtraction of the diameter of the saline control, was compared with that induced by 1% histamine acid phosphate and graded from 0 to 3 (12) where 3 mm weal was +3. In our other studies, +4 approximated a 6 mm weal diameter or greater (13). For the purposes of this study a negative SPT was no greater than the saline control.

Definition of IgE-mediated food allergy

Infants were diagnosed as having IgE-mediated food allergy if the mean weal diameter to any of the three food extracts, at either 6 or 12 months, was greater than or equal to twice the histamine

reference standard, i.e., 4+ Histamine Equivalent Units (9). We have previously reported all patients under 2 yr with these SPT weal diameters, 4+, have had a positive open food challenge to cow milk, egg or peanut (13). We have termed these, the positive challenge predictive SPT weal diameters.

Reported adverse reactions to food

Details of adverse reactions to foods were documented at 4-wk intervals by parental interview with an allergy research nurse. 'Adverse reactions' were defined as parent-reported, and occurred within 2 h of ingestion of a food on at least one occasion during the study period. We have described good agreement between parent-reported food reactions occurring within 2 h of ingestion, and immediate positive food challenges in infants and young children (14).

Statistical methods

Chi-square contingency tables were analysed using the chi-square or Fisher's exact test of the EPISTAT computer program. Regression and ANOVA utilized the Minitab suite of programs.

Results

Prevalence of atopic dermatitis in Infants

Of the cohort of 487, 141 had atopic dermatitis (57 DDE+, 84 DDE-), i.e., had treatment with topical steroids for 8 days or more to the age of 12 months. Thus, the cumulative prevalence of atopic dermatitis for the cohort was 28.9%. A sensitivity analysis of the cut-off point was performed using 6, 8, and 10 days of treatment. The cumulative prevalence of atopic dermatitis at 6 and 10 days was 31.8% and 27.3% respectively. Thus, the definition of atopic dermatitis was robust and not sensitive to minor changes in the number of days of steroid treatment.

Clinical features of atopic dermatitis in infants

The clinical features of infants with atopic dermatitis who were DDE+ and DDE- were compared; the age of onset of atopic dermatitis (commenced at 3 months and peaked at 6 months) and the proportion being treated with topical steroids each month was similar. In addition, there was no statistical difference in the incidence of a positive SPT to any food allergen (40/57 vs. 59/84). The distribution of the rash was similar; on the face (54/57 vs. 72/84),

trunk (47/57 vs. 61/84), arms (38/57 vs. 43/84), legs (38/57 vs. 47/84) as was the total days of steroid-treated rash [64 (95% CI: 49–79) vs. 42 (95% CI: 32–51)], and physician-visits [5.7 (95% CI: 5.1–6.2) vs. 5.5 (95% CI: 4.9–6.0)] for the 12-month study period. The number of infants treated for a rash on the scalp alone (0/57 vs. 0/84), or for a 'diaper contact dermatitis' rash alone (0/57 vs. 5/84) with topical steroids was not significantly different between the two groups.

When atopic dermatitis patients were grouped by severity from, group 0 (no atopic dermatitis) to most severe, group 4, according to the topical steroid use over the 12 months, there was no difference between the groups (chi-square analysis) in possible confounding factors: the timing of the introduction of solids, the duration of breast-feeding, social factors, environmental allergen exposure, i.e., presence of pets and carpeting, parental smoking, and the presence of gas heating or cooking facilities in the home.

Association between atopic dermatitis and IgE-mediated food allergy

There were 90 subjects with IgE-mediated food allergy by SPT of whom 82% were allergic to egg, 35% to peanut and 17% to cow milk. Of these 90 subjects, 50 were categorized as having atopic dermatitis.

Table 1 is a summary of the clinical and immunologic features of the group of subjects and the strength of their association with IgE-mediated food allergy, according to increasing atopic dermatitis severity.

The IgE-mediated food allergy was strongly associated with the presence of atopic dermatitis. Fifty of the 141 infants with atopic dermatitis were IgE food allergic compared with 40 of the 346 infants without atopic dermatitis ($\chi^2 = 36.4$; $p < 10^{-6}$). As well the proportion of children

with IgE-mediated food allergy increased from those without atopic dermatitis (group 0), through to those with the most severe atopic dermatitis (group 4); (Gp 0, 40/346, vs. Gp 1, 6/36, vs. Gp 2, 8/35, vs. Gp 3, 12/35, vs. Gp 4, 24/35; $\chi^2 = 76$; $p < 10^{-6}$). Conversely, the proportion of children with no evidence of IgE-sensitization, i.e., SPT 0 to all food antigens tested, decreased as the severity of atopic dermatitis increased (Gp 0, 239/346 vs. Gp 1, 25/36 vs. Gp 2, 19/35 vs. Gp 3, 14/35 vs. Gp 4, 8/35; $\chi^2 = 39$; $p < 10^{-6}$).

In general, there was an increase in the proportion of infants with parent-reported adverse reactions to specific food(s) as the severity of atopic dermatitis increased from Gp 0 to Gp 4 (19/346 vs. 2/36 vs. 1/35 vs. 3/35 vs. 9/35; $\chi^2 = 20$; $p = 0.0004$). Those subjects with IgE-mediated food allergy (by SPT) were more likely to have reported reactions to ingested foods than those without IgE-mediated food allergy; relative risk 3.2 (95% CI: 1.5–6.7). Although parents were asked to avoid contact with cow milk, egg and peanuts, in three cases an immediate hypersensitivity reaction occurred to cow milk, in four cases to egg, but none to peanut. Adverse reactions to wheat (five cases), potato (four cases), banana (five cases), rice (four cases), chicken (four cases), and a variety of other foods including fruits and vegetables (18 cases) were also noted.

For the cohort the relative risk of atopic dermatitis because of IgE-mediated food allergy for all the children with atopic dermatitis (i.e., Gps 1–4), compared to those without atopic dermatitis (Gp 0) was 3.1 (2.1–4.4). In a further analysis to take account of the effect of the increasing severity of atopic dermatitis the most severe atopic dermatitis group, group 4, were compared to those with no atopic dermatitis, group 0; the relative risk of atopic dermatitis because of IgE-mediated food allergy for group 4 was 5.9 (3.9–9.0).

Table 1. Comparison of features of eczema groups

Gp	Days of treatment*	Sites affected†	IgE food allergy (%)‡	Reported food reaction (%)§	Relative risk food allergy¶
0	0.8	2.6	40/346 (12)	19/346 (5.5)	1
1	10.7	3.2	6/36 (17)	2/36 (5.5)	1.4
2	20.9	3.9	8/35 (23)	1/35 (3)	1.9
3	42.9	4.2	12/35 (34)	3/35 (8.5)	3.1
4	129.8	4.7	24/35 (69)	9/35 (26)	5.7

*Mean days of topical steroid treatment to age 12 months.

†Mean number of sites affected (maximum affected equals 6).

‡Percentage of group with immunoglobulin E (IgE)-mediated food allergy by skin prick test (SPT).

§Nurse-documented parent-reported infants with adverse food reactions.

¶Relative risk of IgE-mediated food allergy for each group compared with Gp 0.

Discussion

Our results show that the probability of IgE-mediated food allergy being associated with atopic dermatitis by chance was < 1 in 1 million. As the severity of atopic dermatitis increased so did the frequency of IgE-mediated food allergy and reported adverse food reactions. For the most severely affected, group 4, 69% had IgE food allergy and the relative risk of atopic dermatitis because of IgE-mediated food allergy compared with the unaffected (group 0) infants was 5.9. However, this risk is likely to be higher

in a general population. Although causation cannot be proven by this study, epidemiologically, the strength of association between IgE-mediated food allergy and atopic dermatitis, together with recent human studies of diet responsiveness (15–18), and animal models of IgE-mediated food allergy-induced atopic dermatitis (19), is not inconsistent with a causal relationship (20). Possible confounding factors (including age of introduction of solids and duration of breast-feeding) were explored and found not to be significantly different between the atopic dermatitis severity groups.

The cumulative prevalence of atopic dermatitis for our cohort was 28.9% using the 8-day ROC-derived model. Cohort studies from the Isle of Wight (8) and Melbourne (21) suggest that 58.5% and 79% respectively of newborn infants have a first-degree relative with a history of atopy. If we assume that these proportions are similar in our cohort and use the mean of these studies (69%), then 20% of infants in our general community, will have atopic dermatitis and a family history of atopy. However, 25% of infants with atopic dermatitis do not have such a family history (9, 22). Thus, the incidence of infantile atopic dermatitis in the Melbourne population calculated using our cohort as the baseline, and adjusting for them being a selected population is estimated to be 27%. The UK birth cohort study reported the presence of atopic dermatitis of more than 6 wk duration in the first 12 months of life was 10% (22), similar to another UK study (23). Fifty of our infants had atopic dermatitis of this severity, a cohort prevalence of 10.3%, adjusting to a community cumulative prevalence of 9.4%.

As this was an epidemiologic study we developed surrogates for atopic dermatitis severity and IgE-mediated food allergy. We did not have access to medical records, or the opportunity of clinical examination of the infants, outside the designated review appointments by the allergy research nurse. Nor did we have the opportunity of performing *in vitro* laboratory studies.

The surrogate marker for atopic dermatitis severity was 'days of topical steroid use'. This was recorded at the monthly research-nurse interview, as an operational measure of atopic dermatitis severity to take account of the fluctuating severity of the disease. The subjects defined by the ROC curve, had the features of atopic dermatitis in terms of, a family history of atopy, a frequent personal history of atopy, i.e., positive SPT/food allergic reactions, the characteristic distribution of the rash and an absence of rash restricted to the scalp alone (thereby excluding seborrhea capitis) or a diaper-area rash alone

(excluding a nappy rash). The validity of the ROC method, in identifying 'atopic dermatitis' and 'non-atopic dermatitis' is supported first by the physician diagnosis of atopic dermatitis in 74% of those infants with 'atopic dermatitis' (by the ROC method), and secondly, by the observations of the research nurse at the 6 and 12 month assessments who examined the infants for atopic dermatitis. The clinical features of our infants was similar to those of the UK Working Party's diagnostic criteria for atopic dermatitis in childhood (10) and modified for infant use (11).

The second surrogate developed was for IgE-mediated food allergy. We have previously reported SPT levels to cow milk extracts above which all children develop an adverse reaction on cow milk challenge (24). Those findings were extended in a study which demonstrated the validity of the method for egg and peanut allergy as well as for milk (13). Similar data using serum food-specific IgE concentrations to predict symptomatic food allergy for cow milk, egg and peanut have been published in retrospective (25) and prospective studies (26) in children. However, in children < 2 yr of age we have demonstrated the positive challenge predictive SPT weal diameter is superior to measurement of serum food-specific IgE concentrations in identifying these food allergies (27), as have others (28). In infancy, this phenomenon is attributed to the high affinity for circulating IgE to tissue Fc ϵ receptors on mast cells and basophils (27).

We have significantly underestimated the incidence of food allergy in our cohort thus weakening the strength of association between IgE-mediated food allergy and infantile atopic dermatitis. The factors contributing to this weakening include: we defined food allergy by the positive challenge predictive SPT weal diameter for allergy to cow milk, egg and peanut (13) but these levels will only identify 23% of cow milk allergic, 52% of egg allergic and 87% of peanut allergic young children (13); secondly, we studied only three foods, those responsible for 80% of food allergy in young children (29). It was noted that many of the parents reported adverse reactions to foods other than milk, egg and peanut which had been specifically avoided during the first 12 months of life. The spectrum of foods reportedly causing these adverse reactions in our study was similar to those reported by others in this age group (29). Finally, there is evidence that up to 10% of infants with food-induced atopic dermatitis have no evidence of an IgE-mediated mechanism (30).

A third of young children with atopic dermatitis, attending Johns Hopkins Hospital Derma-

tology Clinic, had IgE-mediated food allergy and their atopic dermatitis exacerbated by DBPCFC (31). Our study in younger children show that more than two-thirds of infants with significant atopic dermatitis have IgE-mediated food allergy. Our results also show that the strength of association between IgE-mediated food allergy and atopic dermatitis increases with the increasing severity of the atopic dermatitis. These two factors, first, the age of the child – our study was on infants, and secondly, the severity of atopic dermatitis – our findings show the frequency with which IgE-mediated food allergy is associated with atopic dermatitis is dependant on the atopic dermatitis severity, may account for the different perception of the frequency and role of IgE-mediated food allergy in atopic dermatitis of childhood (5–7).

We have shown atopic dermatitis in infancy is common and there is a strong association between IgE-mediated food allergy and atopic dermatitis in this age group. Clinical studies, have demonstrated relapse and remission of eczema in children following DBPCFC (2) and the benefit of a low-allergen diet in reducing the prevalence of eczema in infancy (3, 4). An experimental model of IgE-mediated food allergy-induced eczema has been described (15, 16). Following food challenge of IgE-sensitized eczema patients an increase in mast cell-derived histamine elicits pruritic, erythematous, maculopapular and/or urticarial eruptions (17). An IgE-dependent late-phase infiltration of eosinophils, neutrophils and later, Th₂ mononuclear cells follows, probably associated with the activation of CLA⁺ T lymphocytes (18). Compared with acute eczema, chronic eczema is characterized by increased number of cells expressing mRNA of IL-12, IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF) and interferon- γ (16). In addition, a mouse model of low-dose milk- and peanut-induced eczematous eruptions characterized by infiltrates of CD₄⁺ T cells, eosinophils and mast cells and increased expression of IL-5 and IL-13 mRNA which responded to topical steroids has recently been described (19). All these features resemble human eczema.

Despite these observations and our own findings, the immunopathologic basis by which food allergy induces eczema remains complex (16–19) and may not be restricted to an IgE-mediated mechanism (30).

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