

The association of atopic dermatitis in infancy with immunoglobulin E food sensitization

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Objective: To prospectively investigate the association of high levels of immunoglobulin E (IgE) sensitization to foods and the presence of atopic dermatitis (judged by reported topical steroid use during the first 16 months of life) in a birth cohort of 620 Australian children "at risk" of allergic disease because of family history.

Results: A total of 559 of the children in the cohort were fully evaluated, and the cumulative prevalence of atopic dermatitis was 24%. More children in the cohort who had atopic dermatitis had strongly positive skin test results ($\geq 4+$, histamine equivalent units, ≥ 6 -mm wheal), consistent with IgE food sensitization to either cow's milk, egg, or peanut at 6 months (22% vs 5%, $\chi^2 = 35$; $P < 10^{-6}$) and at 12 months (36% vs 11%, $\chi^2 = 41$; $P < 10^{-6}$) than those without atopic dermatitis. The calculated attributable risk percent for IgE food sensitization as a cause of atopic dermatitis was 65% and 64% at these times. In a separate group of infants with severe atopic dermatitis, the equivalent rates of IgE food sensitization at 6 months was 83% and at 12 months, 65%.

Conclusion: IgE food sensitization is a major risk factor for the presence of atopic dermatitis in infancy. (J Pediatr 2000;137:475-9)

Atopic dermatitis is associated with increased serum immunoglobulin E levels, allergen sensitization, and a family history of allergic diseases.^{1,2} The role of hypersensitivity to dietary antigens in the induction and maintenance of this common chronic relapsing inflammatory response is controversial. An

expert panel of American pediatric dermatologists recently concluded that "food allergy affects only a minority of atopic dermatitis patients."³ Hanifin⁴ estimated that only 10% of children with atopic dermatitis have food allergy contributing to their disease. Sampson⁵ reported that 74% of children

with atopic dermatitis deteriorated while receiving formal food challenge⁵; this result has been attributed to patient selection bias.⁶

IgE-mediated food hypersensitivity has its greatest incidence in infancy and early childhood.⁷ Previous studies have shown a strong association between high levels of IgE sensitization to common foods, IgE-mediated food hypersensitivity, and atopic dermatitis in children.⁸ However, these studies were conducted on a referred population and thus were subject to selection bias.

These reports question whether IgE food sensitization is an epi-phenomenon of atopic dermatitis, that is, a marker of atopy, or whether IgE food sensitization has a causal role in the pathogenesis of atopic dermatitis. We tested the hypothesis that there is an association between IgE sensitization to common foods and atopic dermatitis in infants and young children. To seek evidence of a dose effect of IgE food sensitization on atopic dermatitis, we examined the strength of this association in target populations of children with atopic dermatitis of increasing severity.

Ig MACS	Immunoglobulin Melbourne Atopy Cohort Study
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METHODS

The frequency of IgE food sensitization was compared among 3 groups of infants at 6 and 12 months of age.

Subject Groups

Group 1 included subjects with a family history of atopy without atopic der-

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Table I. The incidence of IgE food sensitization in infants without and with atopic dermatitis of varying severity*

6 months of age					
	Group 1	Group 2	Group 2A	Group 2B	Group 3
Patients	402 (F:190)	125 (F:63)	25 (F:14)	25 (F:16)	41 (F:21)
Cow's milk	4 (1) [†]	4 (3)	0 (0)	1 (4)	21 (51)
Egg	16 (4)	23 (18)	0 (0)	13 (52)	29 (70)
Peanut	4 (1)	6 (5)	0 (0)	2 (8)	15 (37)
Any food	20 (5)	28 (22)	0 (0)	13 (52)	34 (83)
12 months of age					
	Group 1	Group 2	Group 2A	Group 2B	Group 3
Patients	394 (F:188)	121 (F:61)	25 (F:14)	25 (F:16)	29 (F:7)
Cow's milk	8 (2)	5 (4)	0 (0)	4 (16)	9 (31)
Egg	34 (9)	40 (33)	2 (8)	18 (72)	15 (52)
Peanut	15 (4)	14 (12)	1 (4)	6 (24)	11 (38)
Any food	44 (11)	44 (36)	2 (8)	19 (76)	19 (65)

F, Female.
 *Group 1 had no atopic dermatitis; group 2 had mild atopic dermatitis; group 2A and group 2B were subgroups of group 2, with 2B having more severe atopic dermatitis than 2A; patients in group 3 had severe atopic dermatitis.
 †Percent in brackets.

matitis; group 2 included subjects with a family history of atopy with atopic dermatitis (generally mild), and group 3 included patients with severe atopic dermatitis. Subjects in group 1 and group 2 were from the Melbourne Atopy Cohort Study. Patients in group 3 were referred to the Children's Allergy Centre with severe atopic dermatitis unresponsive to standard dermatologic care.

Group 1 and Group 2

Subjects were from MACS, which commenced in 1990. A cohort of 620 subjects was recruited after birth on the basis of one or both parents or any sibling(s) having either atopic dermatitis, asthma, hay fever, or severe adverse reactions to food. Detailed demographic, family medical history, and environmental data were obtained during pregnancy. Questionnaires administered by telephone interview at 4 weekly intervals included questions on infant feeding, the introduction of foods, the development of atopic dermatitis, contact with health care professionals, and medications used. Overall, 559 subjects completed all

questionnaires (from 6 to 16 months) and had skin prick tests performed at 6 months of age, 12 months of age, or both. No difference was found in the prevalence of atopic dermatitis in those infants who were not allergen skin tested (23.5%) and excluded from further analyses and those who were (23.8%).

Patients with atopic dermatitis were defined, for the purpose of the MACS study, as those treated with a steroid-containing skin preparation for greater than a total of 10 days between 6 and 16 months of age as reported on the questionnaire. Ten days of steroid use was the optimal point that identified clinically significant atopic dermatitis based on a receiver operating characteristic curve analysis of the specificity and sensitivity of days of steroid use as a predictor of a doctor's diagnosis of eczema, as reported by a parent (details of receiver operating characteristic curve available from authors).

Patients in group 2 had mild atopic dermatitis requiring a median of 45 days of topical steroid treatment over the 308-day period covered by the survey questionnaires. Two subgroups of

group 2 were group 2A, the 25 subjects with the least severe atopic dermatitis (median 14 days of topical steroid treatment), and group 2B, the 25 subjects with the most severe atopic dermatitis from group 2 (median 145 days of topical steroid treatment).

Group 3

Group 3 was a consecutive group of patients referred between 1992 and 1995 to the Children's Allergy Centre with severe atopic dermatitis that had not responded to conventional treatment with steroid-containing and moisturizing skin preparations and avoidance of skin irritants. Their records were examined retrospectively.

Atopic dermatitis was defined according to the criteria of Hanifan and Rajka as modified by a U.K. working party.⁹

Patients in group 3 were clustered around 6 and 12 months of age to allow comparisons with groups 1 and 2: at 6 months (range 3 to 9 months), 41 subjects (female, 21); and at 12 months (range 10 to 18 months), 29 subjects (female, 7). Skin pricks tests were done on only one occasion.

Skin Prick Tests

Skin prick tests were performed according to a standard technique⁹ to cow's milk, egg, and peanut allergen extracts (Bayer). The mean diameter of the wheal, after subtraction of the diameter of the saline solution control, was compared with that induced by 1% histamine acid phosphate.¹⁰

Definition of IgE Food Sensitization

IgE food sensitization was diagnosed in infants if the mean wheal diameter to the food extract was greater than or equal to twice the histamine reference standard, that is, $\geq 4+$ histamine equivalent units,¹⁰ usually ≥ 6 -mm wheal. In previous studies we showed that this level of sensitization is likely to be associated with adverse clinical reactions on food challenge.^{11,12}

Statistical Methods

Contingency tables were analyzed by the χ^2 method or the Fisher exact test, and analysis of variance (Minitab Statistical Package) was used for continuous data sets.

Attributable risk, a measure of the proportion of atopic dermatitis attributable to IgE food sensitization, was calculated by expressing the risk difference as a percentage of the absolute risk of atopic dermatitis in subjects with IgE food sensitization.¹³

RESULTS

The cumulative prevalence of atopic dermatitis for the children in the MACS study was 23.8% over the duration of the study. There was no difference between the children without atopic dermatitis (group 1) and those with atopic dermatitis (group 2) in feeding regimens, social factors, environmental allergen exposure, history of atopy in first-degree relatives, parental smoking, and the presence of gas heating or cooking facilities in the home (details available from authors).

Table II. The probability of atopic dermatitis in infants with IgE food sensitization

	At 6 months	
	With atopic dermatitis (group 2)	Without atopic dermatitis (group 1)
IgE food sensitive positive	28	20
IgE food sensitive negative	97	382
Relative risk	(28/48)/(97/479)	= 2.88
Risk difference	28/48-97/479	= 0.38
Attributable risk % =	(28/48-97/479)/(28/48) $\times$ 100	= 65.28
	At 12 months	
	With atopic dermatitis (group 2)	Without atopic dermatitis (group 1)
IgE food sensitive positive	44	44
IgE food sensitive negative	77	350
Relative risk	(44/88)/(77/427)	= 2.77
Risk difference	44/88-77/427	= 0.32
Attributable risk % =	(44/88-77/427)/(44/88) $\times$ 100	= 63.9

More of the children in group 2 than those in group 1 had IgE sensitization (to at least one of the foods tested) at 6 months (28 of 125 vs 20 of 402, $\chi^2 = 35.0$, $P < 10^{-6}$) and at 12 months (44 of 121 vs 44 of 394, $\chi^2 = 41.0$; $P < 10^{-6}$) (Table I). In addition, more of the children in group 2B had IgE food sensitization than those in group 2A at 6 months (13 of 25 vs 0 of 25, Fisher exact test; $P = 1.5 \times 10^{-5}$) and at 12 months (19 of 25 vs 1 of 25; Fisher exact test; $P < 10^{-6}$). The proportion of children with IgE food sensitization in group 3 was greater than those in group 2 at 6 months of age (83% vs 22%, $\chi^2 = 46$; $P = 10^{-6}$) and at 12 months of age (65% vs 36%, $\chi^2 = 7.0$; $P = 8 \times 10^{-3}$).

More children in each group and at each assessment were sensitized to egg than to peanut or cow's milk (Table I).

More children in group 2 reported adverse reactions to specific food(s) within 2 hours of ingestion compared with those in group 1 (28.6% vs 12.4%, $\chi^2 = 18$; $P = 5 \times 10^{-6}$), and more of those in group 2B reportedly reacted

than those in group 2A (48% vs 16%, Fisher exact test; $P = .02$). Those with IgE food sensitization were more likely to report these reactions than those without food sensitization; relative risk 16.4 (95% CI 8.3 to 32.6).

In patients in group 3, 76% had a family history of atopy in a first-degree relative. There was no difference in the proportion of patients with IgE food sensitization in those infants with a family history in a first-degree relative(s) compared with those without such a history (40 of 53 vs 11 of 16; $P = .89$).

The attributable risk percent of atopic dermatitis caused by IgE food sensitization was calculated for the children in the cohort, group 1 and group 2, to be 65.3% at 6 months and 63.9%, respectively, at 12 months (Table II).

DISCUSSION

This association between IgE food sensitization and atopic dermatitis satisfies an epidemiologic definition of causation: "a factor (IgE food sensi-

zation) is a cause of an event (atopic dermatitis in infants and young children) if its operation increases the frequency of the event."¹⁸ A strength of association of this magnitude, taken together with evidence from studies showing an improvement in atopic dermatitis with food avoidance in children sensitized to IgE and exacerbations with relevant food exposure,^{5,11,19-23} further supports such a causal relationship. Based on these results, most infantile eczema will be associated with IgE sensitization to common foods and is consistent with a growing body of evidence that links high levels of serum IgE food sensitization to adverse reactions on challenge in children with atopic dermatitis.²⁴

The contribution of IgE food sensitization to the burden of atopic dermatitis was calculated as the attributable risk percent.¹³ This calculation estimated that in our "at risk" cohort, IgE food sensitization was responsible for 64% to 65% of atopic dermatitis. This result contrasts with the widely held view that IgE food sensitization is not important in atopic dermatitis.^{3,4,6}

Atopic dermatitis is not the only clinical outcome of food allergen exposure in children sensitized to IgE food. Adverse food reactions may manifest in other organs and as other skin lesions.^{5,19,20,25} Thus at 12 months of age, 11% of the infants in the group 1 cohort had IgE food sensitization but no atopic dermatitis. In addition, the patients in group 1 who reportedly reacted to food were 16 times more likely to show IgE food sensitization than those who did not report such reactions.

What is the relevance of our findings to atopic dermatitis in a nonselected population of infants? A large consecutive birth cohort study from the United Kingdom reported 74% of infants with atopic dermatitis have a family history of atopic disease in a first-degree relative,²⁶ that is, they are similar in genetic background to the infants in group 1 and group 2. Thus the findings from the infants in group 1 and group

2 have wide application. What of the remaining 26% of infants with atopic dermatitis who have no family history of atopy? We found no difference in the infants with severe atopic dermatitis (group 3) in the incidence of IgE food sensitization between infants with or without a family history of atopy. This finding suggests that IgE food sensitization has an important role in the pathogenesis of atopic dermatitis in infancy irrespective of family history. These findings are supported by a report by Kjellman and Hattevig,²⁷ who showed that the presence of IgE antibodies to foods was associated with the development of eczema in the first years of life, but not thereafter.

We conclude that IgE food sensitization is strongly associated with atopic dermatitis in infancy and early childhood. The clinical implications of these findings require further clarification.

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50 Years Ago in The Journal of Pediatrics

PATHOLOGIC LESIONS IN CYSTIC FIBROSIS OF THE PANCREAS

Bostick WL, Rinehart JF. J Pediatr 1950;37:469-77

Although cystic fibrosis (CF) was recognized as a distinct entity in the late 1930s, the disorder continued to be discussed as a subtype of celiac disease at the time of this report. The authors conducted a review of all pediatric autopsies performed at the University of California Hospital over a 26-year period and studied tissue samples from children who had signs and symptoms of celiac syndrome. About one fourth of these 80 children had CF of the pancreas revealed on pathologic examination. Their ages ranged from 8 weeks to 12 years at the time of death, and all had evidence of bronchopneumonia or bronchiectasis on pathologic examination of the lungs. The liver and intestines showed abnormalities in many cases.

The authors' predictions of etiology of CF accurately foretold scientific advances that came to fruition almost 4 decades later. They postulated that CF is caused by "two basic factors underlying this disease; one being essentially a congenital defect, and the other having an inflammatory background." Further studies led to clear delineation of CF as an autosomal recessive disorder, and in 1989 the gene for CF and the predicted sequence of the CF transmembrane conductance regulator protein (CFTR) were described. As knowledge of the function of normal and abnormal CFTR has advanced, so has our understanding of the early, overwhelming, and progressive inflammatory response in the CF lung. Many factors involved in severity and progression of the disease have been identified; CF genotype, other genes regulating inflammation, and psychosocial and environmental factors all appear to play a role in pathogenesis.

In summarizing their findings, the authors note that "therapeutic efforts have been consistently disappointing," specifically with respect to continued pathologic progression of the disease in cases that were recognized and treated early in their course. Fifty years later, largely because of the efforts of the Cystic Fibrosis Foundation in coordinating patient care and research, we have made substantial progress in CF therapy. However, although median life expectancy for individuals with CF in the United States is now over 30 years, current therapy does not prevent progression of and premature death from pulmonary disease in the vast majority of those affected. Clinical trials of therapies that may reverse the underlying cellular abnormalities in CF are currently underway. With ongoing efforts to understand and reverse these abnormalities, further improvements in quality and length of life are within reach.

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