

IgE-mediated allergy in adults with severe atopic eczema

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Summary

A study was carried out of 45 adults with atopic eczema sequentially admitted to the Dermatology wards in the Royal Infirmary, Edinburgh. The clinical course of the eczema, the associated atopic conditions and the possible role of inhalant and food allergens were assessed. Most subjects had developed eczema in early childhood, but nine of the 45 developed it for the first time after the age of 15 yr. Eleven subjects outgrew their eczema around puberty only to experience recrudescence in their late teens. In 18 subjects the eczema was flexural until the late teens, when it became widespread. In this group of severely affected subjects, 25 had a history of asthma, 29 had either seasonal or perennial rhinitis, and 10 had current symptoms of food allergy. All but one had elevated total serum IgE concentrations (range 63–50 000 kU/l). Using dilutions of the subjects' serum in the radio-allergosorbent test, an estimate of the specific IgE to 10 allergens (three inhalants, seven foods) was obtained, where 1 RAST unit is roughly equivalent to 1 IU total IgE. Most of the IgE was produced in response to the inhalant allergens tested (grass pollen, house dust mite and cat epithelium), 32 of the subjects having a RAST score of 3 or 4 to each of the three inhalant allergens, with the remaining 13 having a RAST score of 3 or 4 to at least one. The highest levels were to house dust mite, exceeding 1000 RAST units in 13 subjects. Thirteen subjects had a RAST score of 4 to at least one food allergen, with levels up to 1000 RAST units. Although this usually correlated with a history of allergy to the food (except in the case of wheat), some subjects with a positive RAST to a specific food could eat the food without problem. Overall these findings indicate that almost all subjects with severe atopic eczema have inhalant allergy, and produce high concentrations of IgE to inhalant allergens: roughly 25% of such subjects also have IgE-mediated food allergy, and they have high IgE concentrations to certain food allergens. The role of inhalant and food allergy in adult atopic eczema remains questionable, but should be considered in the overall management of the subject.

Clinical and Experimental Allergy, Vol. 19, pp. 321–325. Submitted 25 July 1988; revised 30 November 1988; accepted 5 December 1988.

Introduction

Atopic eczema is relatively common in adult life and can be very disabling, disrupting both the working and family life of the subject. Surprisingly, it has received little attention in the literature as most studies have involved children with atopic eczema. Adults with severe atopic eczema present a complicated picture, few having eczema alone: most have respiratory allergy in the form of asthma and allergic rhinitis, and some have IgE-mediated food

allergy. It is important therefore, to take into consideration the inter-relationship between the different facets of the atopic diathesis when treating the subject.

We have studied 45 adults with severe atopic eczema to assess the course of the disease in adults and the possible roles played by inhaled and ingested allergens.

Subjects and methods

Subjects included in the study were adults admitted sequentially to the Dermatology wards in the Royal Infirmary, Edinburgh, for treatment of eczema. The

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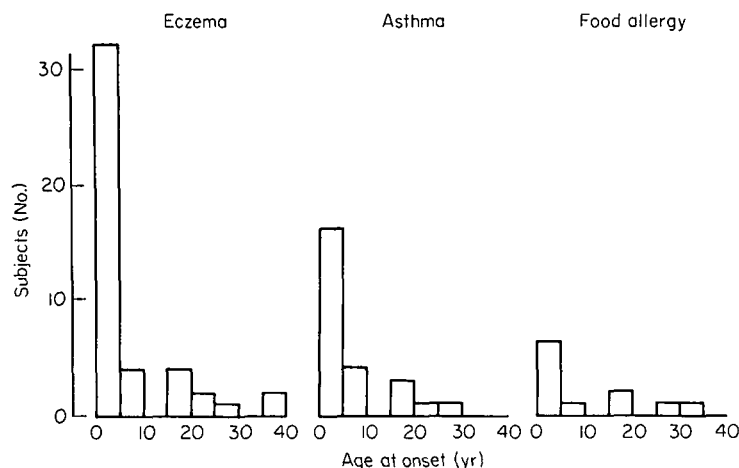


Fig. 1. Age at onset of eczema, asthma and food allergy in 45 subjects with eczema.

diagnosis was made clinically: subjects had to fulfil five out of seven of the following diagnostic criteria [1] for atopic eczema: (1) onset in early childhood, (2) flexural distribution of the eczema at some time during the disease, (3) presence of lichenification at some time during the disease, (4) history of asthma or allergic rhinitis, (5) family history of atopic eczema, asthma or hay fever, (6) positive radio-allergosorbent tests to common allergens (e.g. grass pollen, house dust mite, and animal fur), and (7) serum IgE concentrations > 180 kU/l.

Details of their atopic disease including eczema, asthma, allergic rhinitis and food allergy were recorded in a questionnaire. Drug allergies were also noted. All clinical data were stored on a 512K ACE Sirius micro-computer.

Venous blood was withdrawn from all subjects and assays for total IgE were performed using a double-antibody radioimmunoassay (Pharmacia IgE RIA, Uppsala, Sweden). Radio-allergosorbent tests (RAST, Pharmacia, Uppsala, Sweden) were used to assay specific IgE antibodies for three inhalants (grass pollen, house dust mite (*Dermatophagoides pteronyssinus*), and cat epithelium), seven foods (hens' eggs, cows' milk, codfish, wheat, peanut, brazil nut and crab), and two drugs (penicillin V and G). Dilutions of the subject's serum were made in order to establish a quantitative estimate of the specific IgE in units (RAST Units) roughly equivalent to International Units (IU) total IgE [1], RAST score 1 = 0.35–0.7 RAST units, RAST score 2 = 0.7–3.5 RAST units, RAST score 3 = 3.5–17.5 RAST units and RAST score 4 = > 17.5 RAST units.

Skin-prick tests were also performed, using Bencard allergens (Bencard, Middlesex, U.K.) to mixed grass pollens, house dust mite (*D. pteronyssinus*), cat epithelium, hens' eggs, cows' milk, codfish, wheat, mixed nuts and crab.

Results

Forty-five subjects (29 male, 16 female) admitted sequentially to the ward fulfilled the diagnostic criteria for atopic eczema and were included in the study. Ages ranged from 17 to 61 yr (median age 26).

The first symptoms of eczema occurred at ages which ranged from 1 month to 37 yr. In 30 subjects initial symptoms had started in the first 5 years of life, 27 of these during infancy. Six subjects developed eczema between the age of 5 yr and 10 yr but none had their first symptoms between the ages of 10 yr and 15 yr, (Fig. 1). Nine developed eczema for the first time after the age of 15 yr, two at the age of 16, and one each at 17, 18, 21, 23, 27, 36 and 37 yr. Amongst the younger subjects some had had widespread eczema from the inception of the disease. However, 11 had outgrown their disease at a median age of 13 yr (age range 5–19), only to experience recrudescence at a median age of 19 yr (age range 14–27). A change of pattern was seen in some subjects, in 18 the eczema had been confined to the flexures before developing into widespread involvement, and in two cases, into an extensor ('reverse pattern') distribution: these changes in pattern occurred at a median age of 19 yr (age range 7–57).

Eighteen of the 45 subjects were also asthmatic and a further seven were asthmatic in childhood, having outgrown the condition at a median age of 13 yr (age range 9–22). Twenty subjects developed asthma during the first decade but five had the onset of symptoms after 15 yr (but in a similar manner to eczema, no one developed the condition for the first time between the ages of 10 yr and 15 yr) (Fig. 1). The asthma was never severe and in most cases was controlled by the use of inhaled salbutamol. In three cases, additional beclomethasone dipropionate was given by aerosol. Twenty-nine subjects had symptoms of

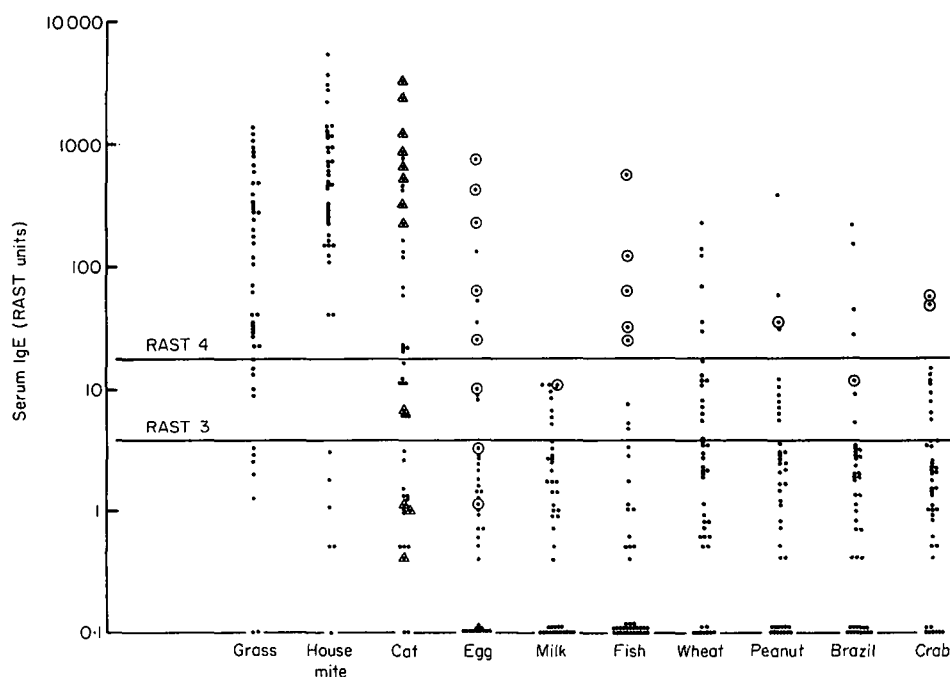


Fig. 2. Specific IgE concentrations (RAST units) in 45 subjects with eczema, to grass pollen, house dust mite, cat epithelium, hens' egg, cows' milk, codfish, wheat, peanut, brazil nut and crab. Cat owners are denoted by (Δ), and those with a history of allergy to a food are denoted ($\circ$).

rhinitis, which occurred during the grass pollen season in 14, and was perennial in the remainder. The age of onset of these symptoms ranged between 2 yr and 24 yr (median age 7).

Eleven of our 45 subjects gave a history of allergy to one or more foods, in seven before the age of 10 yr, and in four after the age of 15 yr. One of these had outgrown his symptoms by the age of 18 yr. The foods implicated were hens' eggs (eight subjects), fish (five), shellfish (two), nuts (one), and cows' milk (one). Symptoms precipitated by ingestion of these foods were immediate, resulting in angioedema and urticaria. Three subjects additionally reported a delayed exacerbation of their eczema. Penicillin allergy was reported by six subjects who had developed a widespread rash after ingestion of the drug. In all cases, this had occurred more than 5 yr previously.

Skin-prick tests

The number of subjects who had weals > 5 mm diameter to inhalant and food allergens were as follows: grass pollen, 25; house dust mite, 34; cat epithelium, 27; hens' egg, eight (all egg-allergic from the history); cows' milk, 0; wheat, 0; codfish five (all fish-allergic from the history); mixed nuts, 0; and crab, two (both shellfish-allergic from the history). In eight of the 10 subjects with a recent history of food allergy there was a positive skin-prick test (> 5 mm diameter) to the food implicated. There was a

significant correlation ($P < 0.05$; Spearman rank correlation) between skin-prick test diameters and the RAST scores for grass pollen, house dust mite, cat epithelium, hens' egg, codfish and crab, with no correlation for cows' milk, wheat and nuts, where skin tests were negative.

IgE Assays

Total IgE. Ranged from 63–50 000 kU/l with a mean value of 12 269 kU/l. Only one subject had total IgE within the normal range, i.e. < 180 kU/l.

Specific IgE to inhalant allergens. Thirty-two subjects produced a RAST score of 3 or 4 to each of the three inhalant allergens tested (Fig. 2) with the remaining 13 subjects having a raised IgE level (RAST 3 or 4) to at least one inhalant allergen. The highest levels of IgE were to house dust mite (in 13 subjects > 1000 kU/l).

There was no significant relationship between the presence or absence of seasonal and perennial rhinitis and the levels of specific IgE to grass pollen and house dust mite respectively (Mann-Whitney *U*-test).

Twelve subjects owned cats; eight of them had specific IgE levels to cat > 100 RAST units (Δ) in Fig. 2). However, the other four cat owners had much lower levels—one had a RAST score of 3 to cat epithelium, two had a RAST score of 2 and one had a RAST score of 1.

Specific IgE to food allergens. Thirteen subjects had a RAST score of 4 (i.e. > 17.5 RAST units) to at least one

food with a further 12 having a RAST score of 3 (3.5–17.5 RAST units) to at least one food. Except for wheat, a RAST score of 4 was usually associated with either definite clinical symptoms of allergy to the food or a positive dislike of the food. However, three subjects with a RAST score of 4 to egg tolerated its ingestion, and of five subjects with a RAST score of 4 to brazil nut, peanut or both, only one had definite symptoms; two subjects disliked nuts and avoided them, although they denied symptoms of allergy, and two further subjects ate nuts without problem.

A RAST score of 3 was found in three subjects with clinical symptoms of allergy to egg, milk and nuts respectively, but the majority of subjects with a RAST score of 3 to food, tolerated ingestion of those foods. Also, two subjects with egg allergy had a RAST score of 2; both had a skin-prick test weal > 5 mm diameter.

Specific IgE to penicillin allergens. None of the six subjects with a clinical history of penicillin allergy had circulating IgE antibodies to either penicillin V or penicillin G.

Discussion

This study involved 45 subjects with severe atopic eczema who were admitted to a Dermatology ward: they would therefore be expected to have IgE-mediated allergy with asthma, allergic rhinitis, and food allergy, and to have high total serum IgE concentrations. Our observations would therefore not necessarily reflect the findings in the whole spectrum of atopic eczema in adults, 20% of whom have normal serum IgE concentrations [2]. In addition, our group contained a preponderance of males, whereas atopic eczema affects the sexes equally: this probably reflects the fact that males are admitted to hospital more readily, so that they can return to work quickly, than females who may not be working and who can attend more easily for out-patient dressings.

The clinical course of atopic eczema and its associated conditions varied considerably in this group of subjects. Most subjects had their initial symptoms in the first 5 years of life. However, no fewer than nine of the 45 had late onset eczema after the age of 15 yr, an entity which is not generally appreciated. None of our subjects developed either eczema, asthma or food allergy for the first time between the ages of 10 and 15 yr, and 11 subjects outgrew their eczema at the age of about 13 yr, only to redevelop it at the age of 19 yr. Thus, it appears that in some, the eczema remains in abeyance during the first few years of the second decade, at a time when puberty is approaching. The reason for redevelopment of the eczema in the late teens is unclear: in some it might be occupational and associated with starting work, (e.g. as a motor mechanic

or hairdresser and being exposed to additional skin irritants). Alternatively, redevelopment of eczema could follow viral infections such as infectious mononucleosis [3], which is common in the late teens and is known to be capable of producing immunomodulating effects. Further studies of this phenomenon of outgrowing and subsequently redeveloping eczema are needed, as an understanding of the mechanisms involved would be extremely helpful. It might be expected that immunomodulation plays an important role in this, and it is interesting to note that subjects with AIDS can redevelop atopic manifestations when their immunodeficiency state becomes apparent, while their symptoms improve on treatment with interferon- γ [4].

The role of inhalant allergens in atopic eczema is controversial. There is some evidence to suggest that house dust mite in the environment exacerbates eczema if scratched into the skin [5,6] and it has been shown that subjects with eczema have raised lymphoproliferative responses to the mite, confirming that they also mount delayed hypersensitivity responses to mite antigens [7]. Our observation that subjects with atopic eczema produce very high concentrations of IgE to house dust mite may therefore represent more than a chance association. Other inhalants such as cat epithelium may also have an exacerbating role when scratched into the skin, particularly in those with high IgE concentrations to feline antigens. When eczema and asthma coexist in subjects who are sensitive to inhaled allergens they do not usually undergo exacerbations at the same time. On the contrary, it is traditionally recognized that when the eczema is in a good phase, the asthma may be severe and vice versa, and this is in keeping with our experience. None of the subjects with asthma in our study had symptoms severe enough to warrant oral steroid therapy, and only three required inhaled beclomethasone; the reason for this is unclear: but it is possible that house dust mite antigens scratched into the skin could play a part in suppressing the asthmatic response to inhaled mite, though this remains to be proven.

The role of food allergy in atopic eczema is also controversial. Ten of our subjects had current symptoms of food allergy, together with strongly positive skin-prick tests or RASTs. In general, skin-prick test positivity (weal > 5 mm diameter) correlated with a clinical history of food allergy, but RAST gave positive results in a number of individuals who had no history of reactions provoked by food. This nevertheless included subjects who avoided the appropriate food because they had always disliked it. However, some subjects were eating foods such as egg, nuts and wheat without problems, despite a RAST score of 3 or 4 for that allergen. In the case of egg, denaturation of the egg albumin by cooking may have modified the

response, since subjects with egg allergy can often eat cooked egg but develop angioedema on eating raw egg albumin in foods such as meringues. A false positive to nuts or peanuts is harder to explain, and two of the subjects affirmed that they could eat nuts and peanuts without allergic symptoms, despite a RAST score of 4 to peanut or brazil nut. Sixteen subjects had a RAST score of 3 or 4 to wheat, though none had experienced symptoms following ingestion of wheat-containing foods: in all these cases, skin tests to wheat allergens were negative. It seems likely that the false positive RAST results occur because of cross-reactivity between grass pollen and wheat allergens [8], a factor which may have interfered with the specificity of RASTs, but not of skin tests. All but one of the subjects with a high RAST score to wheat also had RAST score of 4 to grass pollen.

We do not believe that food allergy is the cause of atopic eczema, but three of our subjects recognized that certain foods caused delayed exacerbation of the eczema, a feature which we have found previously [9]. Enquiry about possible food intolerance is therefore an important part of the history, but it should be emphasized to subjects that food allergy is unlikely to be the sole cause of their problems. Our results also demonstrate the importance of correlating clinical history and skin tests with RAST results. Even strongly positive RAST results may be unreliable, especially for antigens derived from wheat, which are especially prone to cause cross-reactions. The relative parts played by inhalant and food allergens probably differ in childhood and adult atopic eczema. The vast majority of our subjects had high IgE levels to the inhalant allergens, whereas less than one-third had significant levels to food allergens. In babies it has been shown that the presence of IgE antibodies to foods are much more common than to the inhalant allergens, which begin to appear later in childhood [10]. However, food allergy present in infancy is often outgrown.

In the past we have been interested by the number of subjects with atopic eczema who have a history of a rash following penicillin administration, and have also found that a number of eczema subjects have IgE antibodies to penicillin antigens (unpublished data). None of the six subjects in the study had measurable IgE penicillin antibodies, but it is well recognized that specific IgE antibodies to penicillin may only circulate for periods as short as a few months [11].

IgE-mediated allergy is common in subjects with severe atopic eczema. It seems likely that in some subjects, allergy to inhalants such as house dust mite and cat

epithelium, and certain foods, acts as an important complicating factor for the eczema. There is a need to clarify the role of both immediate and delayed hypersensitivity to inhalants and foods in eczema. There is also a need to investigate the mechanisms involved in the development and outgrowing of eczema; this may lead to new modalities in the treatment of this disease.

Acknowledgment

We are grateful to Professor M. H. Lessof for his advice on the manuscript.

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