

IgE responses to environmental antigens in atopic children

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Summary

The levels of IgE antibodies to inhaled and dietary antigens and total serum IgG, IgA, IgM and IgE were studied in two highly selected populations of children who had either severe asthma and no history of eczema, or severe asthma and generalized eczema. These populations were age-matched with a healthy control population. The results showed that the eczematous children had significantly higher levels of IgE antibodies to common environmental antigens than the non-eczematous patients with severe asthma. Both patient groups had significantly higher IgE antigen specific antibody levels than the control population to these antigens. Minor differences in total IgG, IgA and IgM levels were noted between the groups. The variations in total IgE levels between the groups showed the same pattern as for specific IgE antibodies.

Introduction

The high incidence of elevated total and allergen specific IgE antibody levels and the good correlation between these parameters and bronchial reactivity to inhaled antigens, suggests the importance of both IgE hypersensitivity and inhaled antigens in childhood asthma (Aas, 1970; Aas & Johannsen, 1971). Models of human asthma in dogs and monkeys add support to these concepts (Patterson *et al.*, 1967). Passive transfer of bronchial reactivity to inhaled nematode and ragweed antigens from sensitized to non-sensitized animals by IgE containing serum has been demonstrated (Kessler *et al.*, 1974).

High levels of total and allergen specific IgE antibodies to ingested antigens (Church *et al.*, 1976; Hoffman *et al.*, 1975) and IgE complexes containing food antigens have been demonstrated in atopic eczema (Brostoff *et al.*, 1979). These findings, together with the benefit of dietary manipulation in the prevention (Matthew *et al.*,

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1977), and treatment of childhood eczema (Atherton *et al.*, 1978) suggest both IgE hypersensitivity and ingested antigens contribute to this condition.

Based on these observations we proposed two hypotheses. Firstly, that children with asthma would demonstrate high levels of IgE antibodies to inhaled antigens whereas children with eczema would show high IgE levels to dietary antigens. The second hypothesis was that these IgE responses would be independent of each other and separate according to whether severe asthma or severe eczema was the major clinical disease. To test these hypotheses we attempted to define three age-matched homogeneous populations of children; one with severe eczema, another with severe asthma, and a third with severe eczema and asthma. However, only two of these populations could be identified. They had either severe eczema with severe asthma or severe asthma alone without any history of eczema. In this study the IgE immune response to exogenous antigens and serum immunoglobulin levels in these two groups were compared with a control population.

Patients

There were three groups of children.

Group EA

Nineteen children had severe eczema and severe asthma at the time of blood collection. The eczema was generalized, extended beyond the classic flexural sites and was poorly controlled with regular topical steroid applications. All of the patients required daily inhalations of nebulized solutions of bronchodilators for treatment of their asthma. In eight patients, sodium cromoglycate was added to this nebulized solution. The remaining eleven patients used inhalational beclomethasone dipropionate as well as bronchodilator inhalations daily. Two patients required long term daily prednisolone treatment for control of their asthma and two others required several courses of prednisolone over a 12-month treatment period. These four patients were on long term theophylline treatment as well as their inhalational bronchodilators and beclomethasone dipropionate medication.

Four children gave a history of severe angio-oedema after ingesting egg, three after peanut and one each after milk, and fish. These children had not ingested these substances for at least 12 months before this study. Two children gave a history of acute asthma on exposure to dog dander.

Group A

Nineteen children had chronic asthma of comparable clinical severity to those in EA at the time of sampling, but they had no history of eczema. They all required regular daily inhalational treatment with nebulized bronchodilator solutions for their asthma. Sodium cromoglycate was administered in this solution to six of the group. In thirteen patients inhalational beclomethasone dipropionate was also required for control of asthma. Five patients required repeated courses of oral prednisolone over a 12-month treatment period for control of asthma, in addition to maintenance therapy. None of these children had a history of angio-oedema with food or acute asthma precipitated by inhalant allergens.

Group C

Twenty children made up the control population. They were from a Community

Health Survey of randomly selected children and were included in this study regardless of whether they suffered from any atopic diseases or whether there was any family history of atopy.

The ages of the children in this study ranged from 2 to 11 years and were matched between groups. There were twenty-three girls and thirty-four boys.

All the asthmatic children were under the long term care of one paediatrician. They all had chronic asthma, i.e. a long history of wheezing and evidence of chronic airways obstruction when clinically asymptomatic. The physiological disturbance in lung function of older children with asthma of such severity has been previously described by us (Hill *et al.*, 1972).

Children with severe eczema and mild asthma, or severe asthma with mild eczema or a history of eczema, were specifically excluded from this investigation to ensure the populations studied were as uniform as possible.

Methods

Serum from children was collected and stored at -20°C until analyzed. The following studies were performed:

- (1) Total serum IgG, A and M were determined by nephelometry. To allow comparison between groups the level in i.u./ml. was corrected for age by conversion to a percentile (Shelton *et al.*, 1972).
- (2) Total serum IgE was measured in i.u./ml (PRIST, Pharmacia).
- (3) Specific IgE antibodies in serum to the following antigens were measured (RAST, Pharmacia): whole egg, cow's milk, wheat, cod fish, peanut, *D. pteromyssinus*, *L. perenne*, cat, dog, cladosporium, alternaria.

These antibody levels were measured in the authors' laboratory by the same technician using the same batches of allergen discs and labelled anti-IgE donated by Pharmacia. For each antigen a single batch of discs and radiolabelled anti-IgE were used so that a comparison could be made between groups of the levels of antigen specific IgE bound as reflected by radioactive counts. Due to apparent plateauing of the counts to *D. pteronissinus* at high levels, suggesting antigen saturation by antibody, serum was retested to this allergen in a dilution of 1 in 10 and the counts compared. The standard scale of scoring (RAST, Pharmacia) was not used in this analysis.

Statistics:

Comparison of results between groups was made using the non-parametric Mann-Whitney *U*-test.

Results

Total immunoglobulin levels

The levels of immunoglobulin percentiles and total IgE levels in i.u./ml for each child are shown in Fig. 1. The Mann-Whitney *U*-values indicated that there was no significant difference in the median percentiles of immunoglobulins IgG, IgA or IgM between groups EA and A, but the IgE was significantly higher in EA than A ($P < 0.002$). Similar analysis between EA and C revealed that IgE was higher in EA than C ($P < 0.002$), and IgG was higher in EA than C ($P < 0.02$), but there were no differences between IgA and IgM percentile values for these two groups. However,

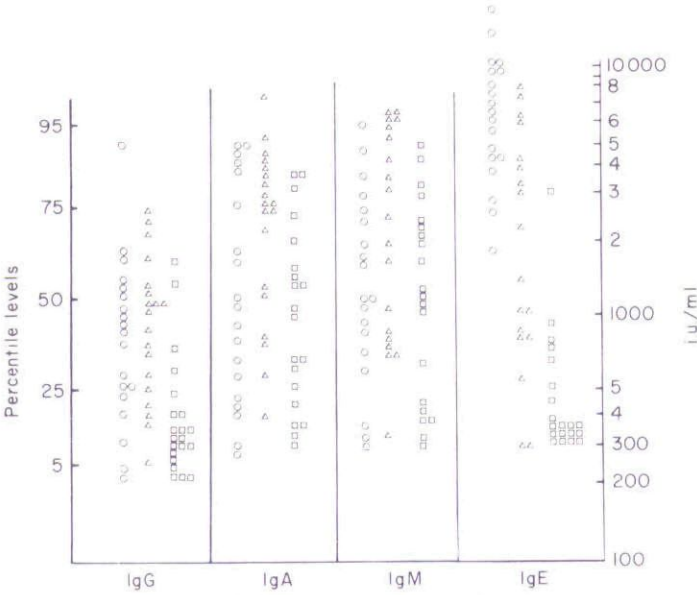


Fig. 1. Percentile levels of IgG, IgA and IgM and absolute levels of IgE as i.u./ml for each child. The symbols indicate these levels for each patient in each group. Thus: O, eczema-asthma; Δ, asthma; □, control.

comparing this data between groups A and C, all four immunoglobulin classes were significantly higher in A compared with C. The total IgE and percentile IgG levels were both greater in A than C ($P < 0.002$); IgA and IgM were also higher in A than C ($P < 0.02$).

Specific IgE antibody levels

The radioactive counts of anti-IgE uptake against each of the antigens for each child in this study is shown in Figs 2 and 3.

The Mann-Whitney *U*-test showed that the levels of IgE antibodies to each food antigen was significantly higher in EA than A, and the children in A had higher levels than those in C. For all the food antigens, this difference was highly significant ($P < 0.002$) except for IgE milk antibody levels between A and C where the level of difference was slightly less significant ($P < 0.02$).

Similar results were seen when comparing the levels of IgE antibodies to inhalant antigens between groups (Fig. 3). The level of IgE antibodies to each inhaled antigen was higher in EA than A, and higher in A than C. These differences were significant at $P < 0.002$ except for cat and *D. pteronyssinus* between EA and A ($P < 0.02$).

Variation in specific IgE antibody levels

The level of IgE antibodies to individual food antigens was greater in EA than A or C, but different levels of IgE antibodies to different antigens was demonstrated for children within each group. These findings are shown diagrammatically in Fig. 4 where IgE antibody levels to three common dietary antigens are plotted for six of the children with severe eczema and asthma. Some children (JD) showed high levels of specific IgE antibody levels to these three antigens, but others showed high levels of antibodies to only two of these antigens (AC, SI) or to one antigen alone (BC, PF, OS). These results

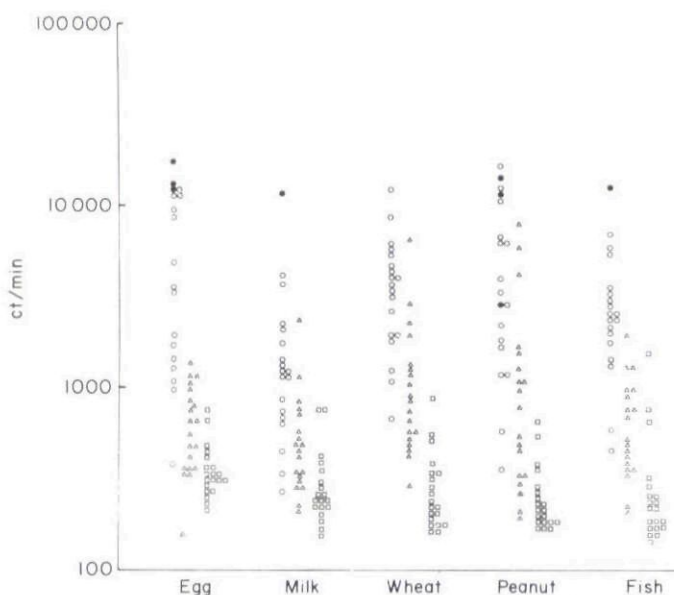


Fig. 2. IgE antibody levels, measured as isotope uptake, to five common dietary antigens. The symbols indicate these levels for each patient in each group. Thus: ○, eczema-asthma; △, asthma; □, control. Closed symbols (●) indicate acute angioedema on ingestion.

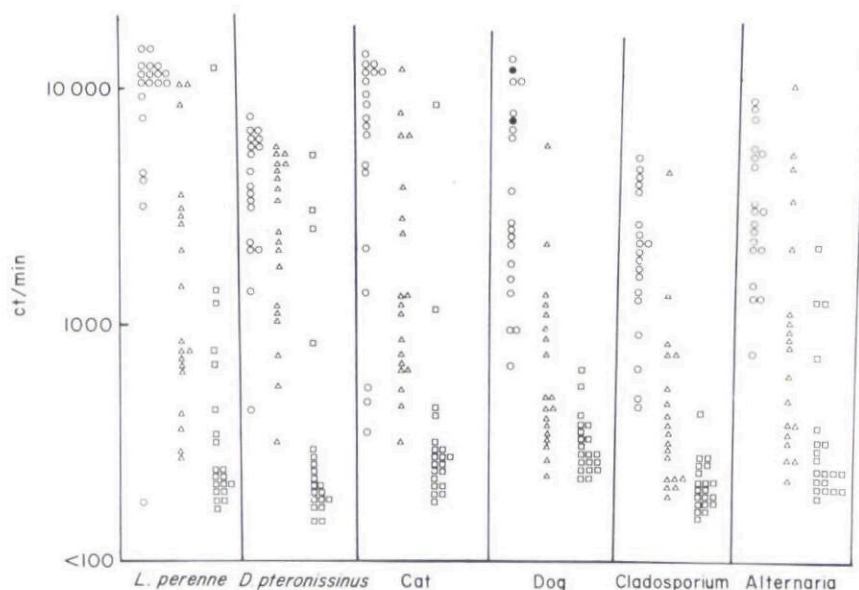


Fig. 3. IgE antibody levels measured as isotope uptake to six common inhalant antigens. The symbols indicate these levels for each patient in each group. Thus: ○, eczema-asthma; △, asthma; □, control. Closed symbols (●) indicate acute rhinitis and wheezing on exposure.

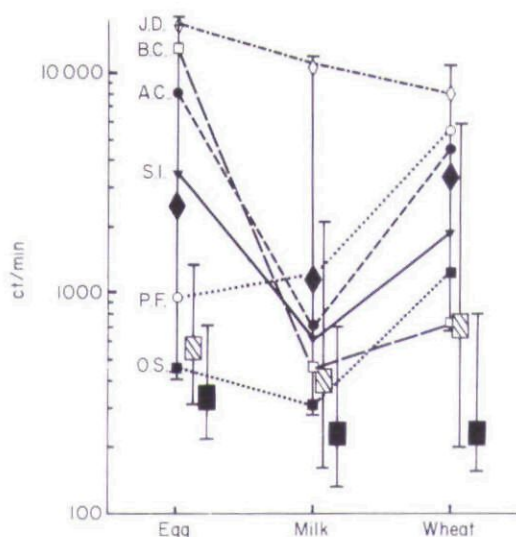


Fig. 4. IgE antibody levels to egg, milk and wheat in children with eczema/asthma demonstrating different degrees of hypersensitivity to these allergens. The vertical lines indicate the range of specific IgE antibody levels to these allergens for each group. The block figures indicate median antibody levels for each group (♦, eczema-asthma; ■, asthma; ■, control). The horizontal lines connect individual patients' RAST count for each food.

indicate that these children do not have high IgE antibody levels to all antigens they encounter. In addition the findings suggest non specific uptake of IgE by the antigens studied is minimal.

Discussion

Several studies have reported the high incidence of IgE antibodies to both ingested and inhaled antigens in children with eczema and asthma (Church *et al.*, 1976; Hoffman *et al.*, 1975), but populations in these studies were not as carefully defined as in this investigation, and did not include age-matched controls. Our patients were selected to emphasize the different skin and respiratory aspects of the atopic disorder and patients with, or with a history of, minor forms of either eczema or asthma were specifically excluded. Using these strict criteria for selection we were unable to identify an age matched population of eczematous children without asthma. In particular, many patients with severe eczema who were screened for this study, denied any history of asthma. However, on careful clinical evaluation, they did give a history of wheezing and were therefore excluded. Others have reported similar difficulties in identifying a population of children with severe eczema without asthma (Buckley *et al.*, 1976).

A comparison of the frequency of wheezing episodes, clinical findings during periods of remission, and use of anti-asthma medication suggests the asthmatic populations were uniform with regard to severity of respiratory disease. However, patients with eczema and asthma had higher total IgE levels than those with asthma alone. This suggests that non-IgE immune factors may be important in determining the clinical severity of asthma in childhood. In this regard, an unexpected finding was the elevation in IgG, IgA and IgM levels in the non-eczematous asthmatic children. The explanation for these findings is not clear. Possibly the factors responsible for these

elevated immunoglobulin levels contribute to the clinical severity of asthma in this non-eczematous group.

In our original hypothesis we proposed that children with atopic eczema demonstrate a hyper-IgE responsiveness to ingested antigens independent of that to inhaled antigens. Because we were unable to identify an age-matched population of eczematous children without wheezing, this hypothesis could not be tested. However, our results suggest that children with severe asthma synthesise IgE antibodies to both ingested and inhaled antigens to a greater degree than a control population. This capacity to synthesise IgE antibodies to both inhaled and ingested antigens is greatest in children with both severe eczema and severe asthma. These results suggest that atopic individuals synthesise IgE antibodies to a broad spectrum of environmental antigens regardless of the major clinical manifestations of their disease. Despite this broad spectrum of hyper-responsiveness to different antigens, specificity of the IgE response to individual antigens could be demonstrated.

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