

Elevated IgE and Atopy among Asthmatic and Non-Asthmatic Children in Northern Jordan

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Abstract

Objectives: The aim of this study is to explore the rates of elevated total IgE levels and sensitization among asthmatic and non-asthmatic children visiting the clinic in one of the main Children Hospital in northern Jordan.

Methods: A total of 177 children aged between 1 month and 16 years were classified into 3 groups: Outpatients without any symptoms of atopic diseases (n=82), Asthmatics (n=50) and a control group (n=45). Serum IgE levels were measured in addition to IgE antibodies against panels of inhalant and food allergens for samples with total IgE above 200 IU/ml.

Results: The highest mean value for total IgE (737.9 IU/ml) was in the asthmatic children above the age of 10 years. The rates of high total IgE (above 200 IU/ml) was 44% in asthmatic, 23.2% in outpatient and 13.3% in control children. Twenty one out of the 22 (95.5%) samples of asthmatic children showed reactivity to at least one tested allergen. In this group, sensitization to domestic house dust mites (*Dermatophyoides pteronyssinus*) was the most prevalent (70%). For the other groups, 55.5% of subjects were sensitized to mixed grass pollen. Regarding food allergens, the highest percentage of children was sensitized to carrot followed by wheat flour. IgE antibodies specific to food allergens predominate in younger ages whereas IgE to both aero and food allergen groups was noticed in older ages.

Conclusion: High levels of IgE were recorded among Jordanian children visiting a pediatric clinic with the highest sensitization among asthmatics being to house dust mites.

Keywords: IgE levels, asthmatic, Jordan

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Introduction

The prevalence of allergic diseases is still increasing worldwide despite the accumulating knowledge about the steps of allergic reactions. In the UK as an example, the prevalence of atopic diseases such as asthma was 32.2% whereas occupational dermatitis reached as high as 49%.^{1,2} Such diseases are thought to have onset in the early childhood.³ Allergen specific skin reactivity and blood antibodies at birth have been demonstrated to an array of common allergens indicating that sensitization to allergens may occur in utero.^{4,5} Therefore, the analysis of specific IgE in combination with other information could be a valuable tool to predict the progression of atopic diseases and provide early information for intervention. Follow up studies showed that elevated cord blood IgE could be used as a marker for later atopic disease development.⁶ Furthermore, IgE to food allergens such as egg white and cow's milk was found to be elevated before the appearance of symptoms.⁷ Further studies showed the disparity in the chronological appearance of food and inhalant specific antibodies. Specific IgE antibodies against food dominated in young children whereas those against inhalants became important as for 18 months to 2 years of age.³ Children with early and long lasting sensitization to food allergens had a greater risk of developing allergic rhinitis and asthma or even developing allergy to inhalants later in life.^{7,8}

In Jordan, there is a shortage of information about the situation of atopic diseases, the prevalence of sensitization to food and/ or inhalant allergens in various children groups. Therefore, the aim of this study was to analyze the rates of high IgE levels due to aero and food allergens afflicting 1 month to 16 year old children visiting the Pediatric clinic of major Children Hospital in northern Jordan. Moreover, the correlation between sensitization to both allergen groups and asthma will be addressed.

Materials and Methods

Patients (study groups): One hundred and 77 children (99 boys and 78 girls, Table 2) with ages ranging between 1 month and 16 years were enrolled in this study between February and May 2003. All children were visiting the pediatric clinic at Princess Rahmah Hospital in northern Jordan as patients or healthy companions. Patients were examined by the same physician. Some of the children had medical records with known history and others came to the clinic for the first time. In addition to information gained from medical records, the guardian (mainly the mother) answered a standard questionnaire about the clinical manifestations of their children. Accordingly, children were classified into 3 groups. The first group was that of outpatients who came for the first time or had several visits with complains of regular problems such as common cold and respiratory infections, gastroenteritis or other diseases without allergic symptoms (outpatients; 48 M and 34 F, total 82 children). The second group was the asthma patients who were suffering from wheezy chest and visiting the emergency unit regularly for nebulization with typical symptoms of asthma (asthmatics; 30 M and 20 F, total 50 patients). The third group was that of healthy children who accompanied their parents with ages comparable to children in the former groups. Those children were chosen so that they did not suffer from any diseases at the time of visit and blood collection (Controls; 21 M and 24 F, total 45 cases). The companion of each child was informed about the study and all gave consent to be involved in the study. All ethical issues pertaining to this study were met.

Blood Collection and IgE Analysis

Peripheral blood samples were collected in plain vacutainer tubes by specialized nurses in the children clinic. Serum was separated and stored at -50°C until use.

Serum samples were tested for total IgE using either the ultrasensitive Elecsys 2010 system (Roche, Mannheim, Germany) or sandwich ELISA using Greiner microtiter plates (Greiner, Germany) following standard protocols. Goat anti-human IgE was used as primary antibody whereas HRP-conjugated anti-human IgE was used as secondary antibody (both from Serotec, UK). IgE concentration standard curve was plotted using both IgE calibration sets (Roche, Mannheim, Germany). The results were expressed in standard IU/ml (1 IU=2.4 ng of IgE). The sensitivity of the assay was 0.1 IU/ml. Lower results were scored as <0.1 IU/ml.

Serum allergen specific IgE was determined using RIDA^R Allergy Screen Immunoblot kit containing panels I, II and III (r-biopharm, Darmstadt, Germany). Only sera containing high total IgE values (≥ 200 IU/ml) were tested for allergen specific IgE. Three panels of allergens were used: food, respiratory and mixed allergens. Immunoblot scoring of band intensity was determined using the blot scanner (RIDA-X screen, r-biopharm, Darmstadt, Germany). The results were expressed in Standard Units (SU/ml) and values above 0.5 SU/ml were considered as significant.

Statistical Analysis

Statistical analysis was performed using the SPSS-11.5 Version software. Differences among groups and age groups were analysed using Tamhane's multiple comparison test (ANOVA) since equality in variances was not assumed. For the analysis of sex effect on total IgE, the parametric test was used whereas for high IgE groups the non-parametric (Mann-Whitney) test was done as it was not possible to assume normality. Sex distribution among groups was tested using the non-parametric Chi Square test. Results were considered significant at $P < 0.05$.

Results

Asthma Patients Had High Total IgE in their

Blood: The total IgE mean values were significantly higher in asthma (482.8 IU/ml) than in outpatients (269.6 IU/ml) and control groups (89.3 IU/ml) (Table 1). Significant differences in mean IgE values in asthma patients ($P=0.001$) were found when tested against the control group. The highest mean IgE value was in asthma patients (737.9 IU/ml) in the age group of 10-16 years. In this age group, a significant difference was only found between asthmatics and controls ($P=0.043$). The percent of high total IgE (above 200 IU/ml) was the highest among asthmatics (44%) compared to outpatients (23.2%) and controls (13.3%) (Table 2). On the other hand, total IgE values below 0.1 IU/ml were recorded mainly among children below the age of one year (3 out of 4 cases).

With respect of gender, no statistically significant differences were found in the percentages of total IgE between boys and girls in all study groups ($P=0.57$) as well as among those children having high total IgE values ($P=0.33$, Table 2). Furthermore, IgE values for children aged 10-16 years were significantly higher than those of children below the age of 1 year ($P=0.015$) whereas no significant difference was found among age groups of children with IgE values above 200 IU/ml ($P=0.317$).

Sensitization to Inhalant Allergens is Highly Frequent in Asthmatic Children:

The presence of IgE antibodies specific to inhalant and food allergens was variable among asthmatic and non-asthmatic groups being significantly less common among younger allergic subjects. Out of the 47 cases with high total IgE values, 30 (63.8%) were sensitized to a minimum of one out of 40 food or aero-allergens tested. Of these, 21 were asthmatic children (Table 3) and 9 were from the other groups (Table 4).

In particular, 20 out of the 21 (95.2%) asthma patients had inhalant specific IgE antibodies. Of these, 8 cases showed concurrent food and inhalant specific IgE antibodies whereas 1 case was reactive to food but not to any aero-allergens (Table 3 and Fig. 1A). Thus, the rate of sensitization to food allergens among asthma patients with high total IgE antibodies was 40.9% (9 out of 22). In contrast, the rate of sensitization to inhalant allergens among outpatients with high IgE was 7 out of 19 (37.0%) and 3 out of 19 (15.8%) to food allergens (Fig. 1B). None of the control group children with high IgE (6 cases) showed any sensitization either to food or aeroallergens (Fig. 1C).

Analysis of the frequency of allergy related to the age of the subjects showed higher frequency among older children. Twenty one out of 27 (77.7%) children with allergen specific IgE were above the age of 5 years with the greatest percentages at 10-16 years of age. Young children below the age of 5 years had higher food specific IgE (4 out of 6 cases) (Fig. 2).

Asymptomatic Atopy in Outpatients and Control Children: Sensitization to a minimum of one allergen was found in 9 of the outpatients and none of the control group children who showed high total IgE values (Fig. 1). In this way, asymptomatic atopy among outpatients and control children can be calculated at 11.0% (9/82) and 0% (0/45), respectively. The overall rate for both groups is 7.1% (9/127).

House Dust Mite is the Most Common Allergen in Asthma Patients: Study children with asthma presented high frequency of IgE to the indoor inhalant house dust mites *Dermatophygoide* *pteronyssinus* at 70.0% and *D. farinae* at 65.0% (Table 3). Alder and rye pollen were the second most common inhalant allergens with a 25.0% sensitization rate for each. Regarding allergy to food, IgE antibodies to hazelnut, peanut, carrot and wheat flour were detected in 4 out of 9 (44.4%) children with food specific IgE. In contrast, sensitization to mixed grass pollen was the most common among individuals of the other groups (55.5%) followed by both species of the domestic house dust mites (33.3% for each, Table 4).

Table 1: Means of total IgE (IU/ml) and ranges for children included in all study groups.

| Groups | Age Groups | | | | Total | P-value† |
|------------------------|---------------------|---------------------|------------------------|----------------------|---------------------|----------|
| | ≤1Y | >1-5 Y | ≥6-9 Y | ≥10-16 Y | | |
| Asthma patients | 60.3 (6.9-139.7) | 375.5 (8.5-1147) | 271.7 (18.3-1562.8) | 737.9 (21.2-2500) | 482.8 (6.9-2500) | 0.001 |
| Outpatients | 67.2 (0.1-377) | 376.0 (2.5-2500) | 331.0 (3.1-1950) | 201.0 (1.1-1236) | 269.6 (0.1-2500) | 0.067 |
| Controls | 14.4 (0.1-46.0) | 85.8 (0.1-487) | 102.4 (22.5-322) | 129.2 (15.2-477) | 89.3 (0.1-487) | |
| Total | 69.3 (0.1-479) | 254.6 (0.1-2500) | 304.5 (3.1-2023) | 460.7 (1.1-2500) | 305.3 (0.1-2500) | 0.002 |

† P value was calculated for each group in comparison with the control group using Tamhane`s multiple comparison test (ANOVA).

Table 2: The sex distribution of all children included in the study and those with high IgE (above 200 IU/ml).

| Total | No. Examined | | | | No. and % with IgE levels \geq 200 IU/ml | | | | | | |
|-----------------|--------------|-----------|------------|-------------------|--|-------------|-----------|-------------|-----------|------------|--------------------|
| | M | | F | | M | | F | | Both | | P-value \ddagger |
| Group | M | F | Both | P-value \dagger | No. | % | No. | % | No. | % | |
| Asthma patients | 30 | 20 | 50 | 0.61 | 11 | 47.8 | 11 | 45.8 | 22 | 46.8 | 0.65 |
| Outpatients | 48 | 34 | 82 | 0.96 | 11 | 47.8 | 8 | 33.3 | 19 | 40.4 | 0.7 |
| Controls | 21 | 24 | 45 | 0.12 | 1 | 4.4 | 5 | 20.9 | 6 | 12.8 | |
| Total | 99 | 78 | 177 | 0.57 | 23 | 49.0 | 24 | 51.0 | 47 | 100 | 0.33 |

\dagger P-values were calculated for sex effect on IgE values using parametric t-test.

\ddagger P-values were calculated for sex effect on high IgE values using the non-parametric (Mann-Whitney) test.

Table 3: The distribution of specific IgE antibodies to food and inhalant allergens among high IgE asthma patients N=21 (20 inhalant cases, 8 both food and inhalant and 1 food alone).

| Inhalant allergens | No. Positive cases (%) | Food Allergens | No. Positive cases (%) |
|---------------------------------------|------------------------|----------------|------------------------|
| <i>Dermatophygoidea pteronyssinus</i> | 14 (70.0) | Hazelnut | 4 (44.4) |
| <i>D. farinae</i> | 13 (65.0) | Peanut | 4 (44.4) |
| Alder | 5 (25.0) | Walnuts | 2 (22.2) |
| Birch | 3 (15.0) | Almond | 2 (22.2) |
| Hazel | 3 (15.0) | Milk | 3 (33.3) |
| Oak | 2 (10.0) | Egg white | 2 (22.2) |
| Grass pollen | 3 (15.0) | Egg yolk | 1 (11.1) |
| Rye (pollen) | 5 (25.0) | Casein | 1 (11.1) |
| Wormwood | 3 (15.0) | Potato | 2 (22.2) |
| Ribwort (Plantain) | 3 (15.0) | Celery | 2 (22.2) |
| Cat | 3 (15.0) | Carrot | 4 (44.4) |
| Horse | 3 (15.0) | Tomato | 2 (22.2) |
| Dog | 2 (10.0) | Cod | 0 |
| Guinea pig | 0 | Crab | 1 (11.1) |
| Hamster | 2 (10.0) | Orange | 2 (22.2) |
| Rabbit | 1 (5.0) | Apple | 2 (22.2) |
| <i>Penicillium notatum</i> | 0 | Wheat flour | 4 (44.4) |
| <i>Cladosporium herbarum</i> | 2 (10.0) | Rye meal | 2 (22.2) |
| <i>Aspergillus fumigatus</i> | 0 | Sesame | 2 (22.2) |
| <i>Alternaria alternata</i> | 4 (20.0) | Soya | 1 (11.1) |

Table 4: The distribution of specific IgE antibodies to food and inhalant allergens (mixed panel) among all high total IgE cases (> 200IU/ml) other than asthma patients. N=9 cases (7 inhalant, 1 both food and inhalant and 2 food alone).

| <i>Allergens in mixed panel</i> | <i>No positive cases (%)</i> |
|--------------------------------------|------------------------------|
| <i>Dermatophyoides pteronyssinus</i> | 3 (33.3) |
| <i>D. farinae</i> | 3 (33.3) |
| alder | 1 (11.1) |
| birch | 1 (11.1) |
| hazel | 1 (11.1) |
| mixed grasses | 5 (55) |
| Rye (pollen) | 3 (33.3) |
| mugwort | 1 (11.1) |
| Ribwort (Plantain) | 1 (11) |
| cat | 1 (11.1) |
| horse | 1 (11.1) |
| dog | 1 (11.1) |
| <i>Alternaria alternata</i> | 1 (11.1) |
| egg white | 2 (22.2) |
| milk | 2 (22.2) |
| peanuts | 1 (11.1) |
| hazelnuts | 0 |
| carrot | 2 (22.2) |
| wheat flour | 2 (22.2) |
| Soya beans | 0 |

Fig. 1: The reactivity frequency to allergens in children with high IgE (above 200 IU) among Asthma patients A (N=22), outpatients B (N=19) and control group C (N=6) in relation to the total IgE values. Squares represent aeroallergens whereas triangles represent food allergens. * Represents the number of allergens that same patient is sensitized to. Some subjects were sensitized to both aero and food allergens concurrently.

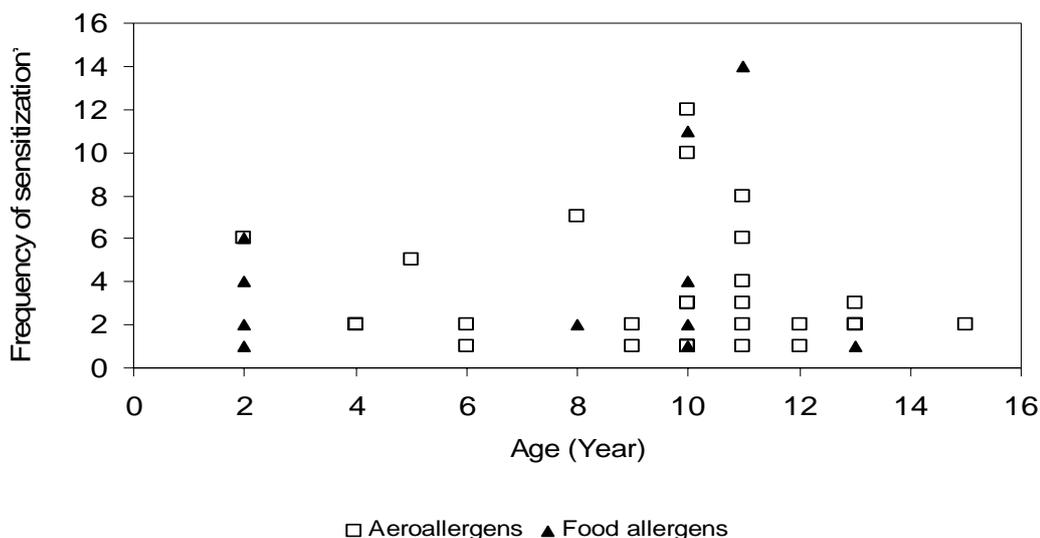


Fig. 2: The reactivity frequency to aero and food allergens in children with high IgE (above 200 IU) of all study groups in relation to their ages. Squares represent aeroallergens whereas triangles represent food allergens. * Represents the number of allergens that same patient is sensitized to. Some subjects were sensitized to both aero and food allergens concurrently.

Discussion

The present study provides a baseline data on the rates of high IgE antibody and sensitization of asthmatic and non-asthmatic children from northern Jordan. Evidently, asthmatic children showed a gradual increase in total IgE antibody values with age which was markedly high in 10-16 year old children (Table 1). This is consistent with earlier studies dealt with asthmatic patients in other countries.⁹⁻¹¹ In this way, serum IgE levels can be used as a marker to determine subclinical atopy and to predict susceptibility to developing asthma in the future.^{9, 11, 12} Asymptomatic atopy among outpatient and control children from northern Jordan range between 0-11% with an overall rate of 7.1%. This is significantly higher than that reported in Denmark at 2%¹³ but much lower than the 30% that was recorded in Turkey (6 out of 20 controls).¹⁴

The continued persistence of these antibodies may result in the development of atopic diseases mainly asthma.

The present study showed an association between asthma and sensitization to allergens of the house dust mites (sensitization rate of 65-70%, Table 3). Similar results were reported for asthmatic Brazilian children with a sensitization rate of 59.3-69.5%.¹¹ The association between sensitization to indoor allergens of house dust mites and the development of asthma is still inconclusive. While several investigators considered the house dust mites as major determinants of sensitization during childhood creating a risk for development of asthma.^{10, 15, 16} Lau et al.¹⁷ found an association between the concentration of household house dust mites and mites specific IgE.

However, these authors could not establish an association between mites high specific IgE and asthma development. Despite these conflicting results, the worldwide increase of asthma and its association with house dust mites specific IgE indicates the importance of this allergen in the development of asthma. Indeed, the Third International Workshop on indoor allergens and asthma in 1995 concluded that exposure to house dust mites during infancy is the main risk factor for the development of childhood asthma.¹⁶

Sensitization to food allergens was found in all age groups but was particularly high in children below 5 years of age (Fig. 2). Previous studies showed that sensitization to specific allergens vary with age.¹⁸ Specific IgE antibodies to egg white and cow's milk were found in infants starting from the age of 3 months and peaked at the age of 8 months.⁷ In northern Jordan, sensitization to allergens from carrot followed by wheat flour was the most prevalent in Jordanian children regardless of age. It should be stressed that sensitization to food allergens may differ according to environment and/ or dietary differences.^{4, 19} Therefore, the exposure of pregnant women or neonates to certain allergens may correlate with lower sensitization prevalence to children after birth.²⁰

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