

Quantification of IgE antibodies simplifies the classification of allergic diseases in 4-year-old children. A report from the prospective birth cohort study – BAMSE

Wickman M, Ahlstedt S, Lilja G, v Hage Hamsten M. Quantification of IgE antibodies simplifies the classification of allergic diseases in 4-year-old children. A report from the prospective birth cohort study – BAMSE.

Pediatr Allergy Immunol 2003; 14:441–447. ©2003 Blackwell Munksgaard

Allergic diseases are common among small children, but it is still unclear how immunoglobulin E (IgE) antibodies to ambient allergens are distributed in a population-based prospective material of children at 4 years of age. The study is based on 75% ($n = 4089$) of all eligible children from northern Stockholm, born between 1994 and 1996 in pre-defined geographical areas. Data on exposure and outcome were obtained by parental questionnaires when the child was 3 months and 4 years of age. Of the 92% who responded to the 4 years of age questionnaire, serum was obtained in 88% of these children for analysis of IgE antibodies performed with Pharmacia CAP systemTM (Phadiatop[®] and food mix fx5[®]). An antibody level ≥ 0.35 kU_A/l was considered as positive. A positive Phadiatop[®] or fx5[®] was found in 24% of the 4 years old children. A rather poor correlation was found between the two tests ($r = 0.39$). Occurrence of IgE antibodies ≥ 3.5 kU/l for both Phadiatop[®] and fx5[®] in combination could predict any suspected allergic disease [asthma, rhinitis, atopic eczema dermatitis syndrome (AEDS) and allergic reaction to food] to 97.4%. However, the presence of ≥ 3.5 kU_A/l of Phadiatop[®] or fx5[®] used as single tests only, was far less efficient to predict any allergic disease. The two mixes of airborne and food allergens were also associated, not only to the severity of the allergic disease in terms of number of organ involved, but also to the severity of recurrent wheeze, in particular in boys with a positive Phadiatop[®] who exhibited significantly limited peak flows compared to those with a negative test.

Already at the age of 4, one child in four is sensitized to an allergen as assessed by Phadiatop[®] or food mix (fx5[®]). The presence of IgE antibodies seems not only to predict allergic diseases in this age group, but also relates to severity of such diseases, in particular to asthma. Notable, there was a poor correlation between Phadiatop[®] and fx5[®] that needs to be considered when identifying allergic diseases in young children. The study demonstrates that quantification of IgE antibodies in blood may be beneficial, not only to diagnose allergic diseases in young children, but especially to serve as a marker of severity of asthma.

Magnus Wickman^{1,2,4,6}, Staffan Ahlstedt^{2,3,6}, Gunnar Lilja⁴ and Marianne v Hage Hamsten^{5,6}

¹Department of Occupational and Environmental Health, Stockholm County Council, Stockholm, Sweden, ²Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, ³Pharmacia Diagnostics AB, Uppsala, Sweden, ⁴Sachs's Children's Hospital, Institute of Södersjukhuset, Karolinska Institute, Stockholm, Sweden, ⁵Department of Medicine, Unit of Clinical Immunology and Allergy, Karolinska Institutet, Stockholm, Sweden, ⁶Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden

Key words: allergy; antibody; diagnosis; childhood; immunoglobulin E

Magnus Wickman, Department of Occupational and Environmental Health, Norrbacka, Level 3, Karolinska Hospital, SE-171 76 Stockholm, Sweden
Tel.: +468 5177 7912
Fax: +468 5177 7900
E-mail: magnus.wickman@smd.sll.se

Accepted 8 May 2003

Allergic diseases constitute a major cause of morbidity in industrialized countries. Thus, secondary preventive measures, such as early diagnosis, early treatment and patient education have for some period of time been in focus. They are considered as the cornerstones of such strategies (1).

Early sensitization to certain foods followed by sensitization to airborne allergen seems to predict evolving manifest respiratory disease later in childhood (2, 3). Such predictive sensitization has also been shown for children with early signs of allergic disease and development of airway hyper-responsiveness measured by the age of 8 years (4). As it is believed that early treatment and patient education may reduce the risk for deterioration of manifest allergic disease and that the prerequisite for this is early diagnosis, it seems important to scrutinize the possible tools and their optimal use for diagnosis in allergic disease (5).

The aim of this study was to investigate the use of quantification of immunoglobulin E (IgE) antibodies in 4-year-old children participating in a prospective, longitudinal population-based birth cohort study (BAMSE) in relation to classification of allergic disease and severity of such disease (6).

Material and methods

Study subjects

Between 1994 and 1996, 4089 newborn infants were included in a prospective population-based study (BAMSE). Study design, description of study base, enrolment, criteria for inclusion and the procedure of data collections are described in detail elsewhere (7–9).

The ethical committee of Karolinska Institute, Stockholm, Sweden, had approved the study.

Questionnaire

At the median age of 2 months of the children, data on various and allergic heredity was requested. When the children were 1-, 2- and 4-year-old, questionnaires were mailed to all the parents focusing on symptoms often related to IgE mediated allergic diseases including asthma, rhinitis, rhino-conjunctivitis, atopic eczema dermatitis syndrome (AEDS) and reactions to food. According to the responses, the symptoms of the children were classified as asthma, AEDS, rhinitis and suspected allergic food reactions (SARF). The questions utilized in the forms were either taken from the International Study of Asthma and Allergies in Childhood (ISAAC)-question-

naire or from questionnaires previously published by our group (10–12).

The response rate at the follow-up of the questionnaire by 4 years of age was 92%. Only data from the questionnaires at 2 months and 4 years of age will be used in this presentation.

Definitions

Asthma in this study was defined as at least four episodes of wheezing the last 12 months (ISAAC) or one episode with the treatment with inhaled glucocorticosteroids during the last 12 months since this treatment will mask repeated episodes. Severity of wheeze during the 12 last months was graded as; (i) no wheezing, but medication; (ii) wheezing 1–3 times the last 12 months and/or medication of inhaled steroids; (iii) wheezing ≥ 4 times during the last 12 months independent of medication. Furthermore, evaluation of the severity of asthma included the degree of impairment of lung function (peak flow measurements – see below).

Rhinitis was defined according to the ISAAC-questionnaire as runny, itchy or blocked nose during the last 12 months without ongoing cold.

Except for abdominal pain, vomiting and diarrhoea, SARF were defined as specific symptoms exacerbating at least twice in relation to ingestion of food.

Atopic eczema dermatitis syndrome was defined as itchy rash for at least 2 weeks with typical distribution (face/outer limbs/folds of elbows or behind the knees/wrists or fronts of ankles) and dry skin; and/or doctor's diagnosis of eczema. This definition has been proven to have high sensitivity (92%) and specificity (100%) compared with clinical diagnosis by a dermatologist (8).

Measurements of sensitization

At 4 years of age, the children were invited to a clinical examination including a blood and lung function test. Of the 3720 families that answered the questionnaire of their child at the age of 4 year, 2965 parents accepted and showed up for further examination of their child. Blood samples were obtained from 2614 (64%) children. A total of 137 denied blood tests and in another 214 sampling failed. Serum IgE antibodies to inhalant allergens were analysed with Phadiatop[®] (a mixture of cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus* and *Cladosporium* allergens), and to the most common food allergens with fx5[®], (a mixture of milk, egg white, soya bean, peanut, fish and wheat

allergens), Pharmacia CAP SystemTM (Pharmacia Diagnostics AB, Uppsala, Sweden and Phadiatop[®] and fx5[®] are trade marks belonging to company) according to the instructions by the manufacturer. A positive result was defined as ≥ 0.35 kU_A/l. Between children tested for serum IgE antibodies and children not tested, there were no statistically significant differences in the 4 years prevalence of asthma, rhinitis, AEDS or SARF. There was no difference in background factors, such as heredity and various environmental exposures, between those who responded to the 4 years of age questionnaire, examination and blood test compared with those who did not.

Statistical analysis

Spearman rank correlation coefficient was calculated between the results obtained with Phadiatop and fx5.

Logistic curves were fitted for the IgE antibody levels in relation to the likelihood of presence of allergic diseases basically as described elsewhere (13, 14).

The chi-square test was used to test for difference between two proportions, and logit modelling was used to test for trend. Computerized statistical analysis was performed with Statistical Software: release 7.0 (College Station, TX, USA) and SAS System V 8.01.

Results

At 4 years of age 8.7% of the boys and 5.3% of the girls had asthma. A total of 1152 children (31.7%) exhibited at least one manifestation of recurrent wheeze, rhinitis, AEDS or SARF. Three hundred and seventy children (10.2%) were classified as having at least two such manifestations and 85 of the children (2.3%) at least three. Eleven (0.3%) children were reported to have manifestations of both asthma, rhinitis, AEDS and SARF. Little overlap was seen among asthma and AEDS; only 91 individuals (2.5%) suffered from both. Among children with rhinitis 16 children (11.6%) were also suffering from asthma or AEDS.

Of the 2614 children, 414 (15.8%) and 400 (15.3%) were found to be positive for fx5 and Phadiatop, respectively. Six hundred and twenty seven (24%) were positive for any of the mixes of airborne and food allergens, and 187 (7.1%) children were found to be positive for both Phadiatop and fx5. If the allergen specific IgE levels for Phadiatop was 17.5 kU_A/l or more, more than 70% of the children exhibited as positive fx5 (Fig. 1). Even if a trend is obvious,

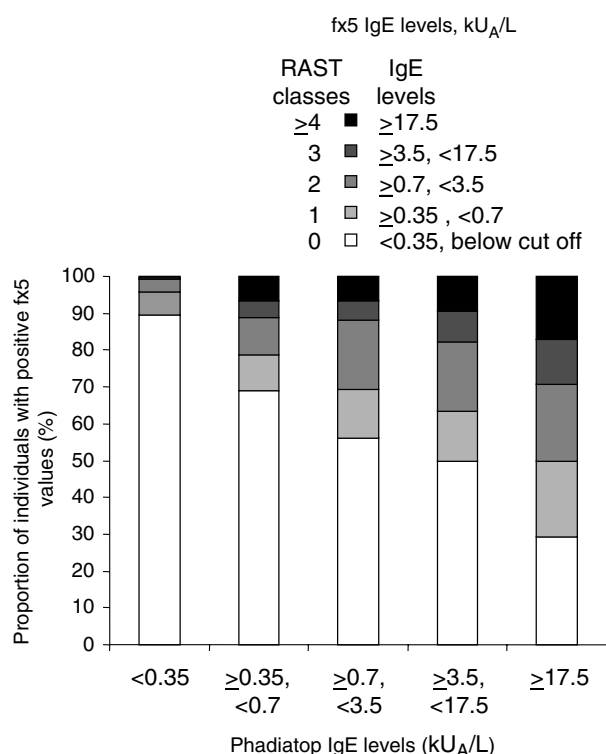


Fig. 1. Association between allergen-specific immunoglobulin E levels measured by Phadiatop and fx5 in 2614 children at age 4.

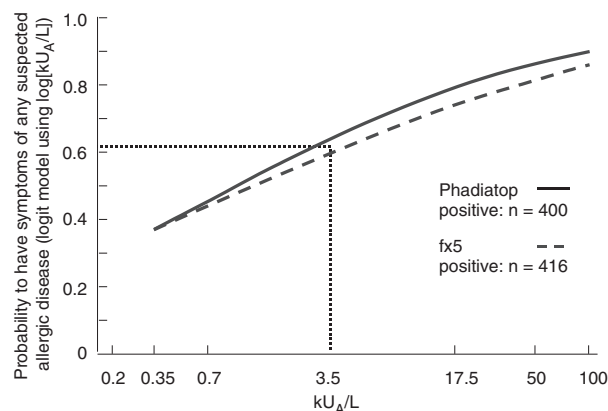


Fig. 2. Likelihood (positive predictive value) of at least one of four suspected allergic diseases at certain immunoglobulin E levels among children at the age of 4.

there was a poor correlation between quantitative levels of Phadiatop and fx5 ($r = 0.39$). Of the boys 18.6% and of the girls 15.0% were positive to either Phadiatop or fx5.

Positive predictive likelihood of allergic disease

The likelihood of getting symptoms in relation to the IgE antibody level has been modelled (Fig. 2)

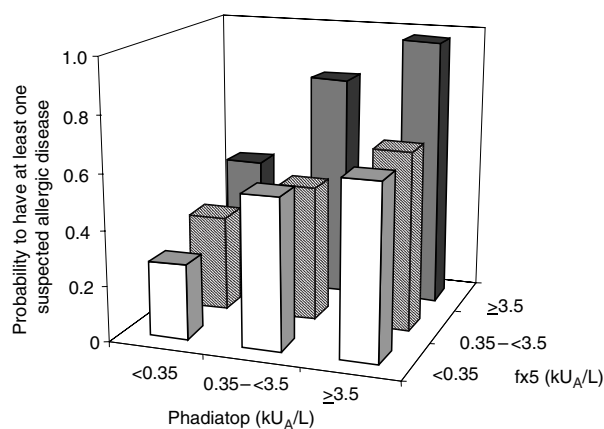


Fig. 3. Probability (positive predictive value) of least one of four suspected allergic diseases at certain immunoglobulin E levels.

and consequently for results of ≥ 3.5 kU_A/l for either Phadiatop or fx5 the positive predictive likelihood (ppl) was > 0.6 . For results ≥ 50 kU_A/l such predictive value was ≥ 0.8 . With the emphasis to get extended information for the use of quantitative IgE, and classification of allergic disease, the combination of being negative or positive to either the mix of airborne allergens or food allergens or both was used (Fig. 3). As the number of children with IgE results ≥ 3.5 kU_A/l for both Phadiatop and fx5 was limited, allocation was made into three groups: (i) < 0.35 kU_A/l, (ii) ≥ 0.35 – < 3.5 kU_A/l and (iii) ≥ 3.5 kU_A/l following grading into radio-allergo-sorbent test (RAST) classes. Of those who were negative for either the mix of airborne allergens or food allergens, still 535 (27.7%) were classified as having recurrent wheeze, rhinitis, AEDS or

SARF (Fig. 3). However, if both Phadiatop and fx5 were highly positive (≥ 3.5 kU_A/l) the ppl was 0.97, as compared with Phadiatop or fx5 used separately and with the same IgE antibody level of 3.5 kU_A/l (ppl 0.71 and 0.81, respectively).

With the use of Phadiatop ≥ 3.5 kU_A/l the likelihood to be classified as having asthma only was 0.25. However, when a high level of ≥ 3.5 kU_A/l for fx5 was combined with a similar level of Phadiatop the ppl value was more than twofold higher (0.51) (Fig. 4). For classification of AEDS and rhinitis an only marginally higher value was found for the combination of the mixes of airborne and food allergens compared with only one of the tests (data not shown). For likelihood to predict classification of SARF there seemed to be an added value to use Phadiatop in combination with fx5 (Fig. 4). Combination of Phadiatop and fx5 values ≥ 3.5 kU_A/l for both tests revealed a predictive value for classification of SARF of almost 0.79. This is to be compared with a predictive value of 0.66 and 0.67, if fx5 at levels of ≥ 3.5 and ≥ 17.5 kU_A/l was used alone.

Levels of IgE antibodies and severity of asthma

From the questionnaire data it was possible to allocate children with asthma into different groups of severity, which was not possible for the other allergic manifestations. Among children with asthma, i.e. ≥ 4 episodes of wheeze during the last 12 months, 25.8% exhibited serum concentrations of allergen specific IgE of ≥ 3.5 kU_A/l measured by the mix of airborne allergens, compared with only 8.7% among those with fewer episodes of wheeze, $p < 0.0001$. For IgE levels between 0.35 and 3.5 kU_A/l to

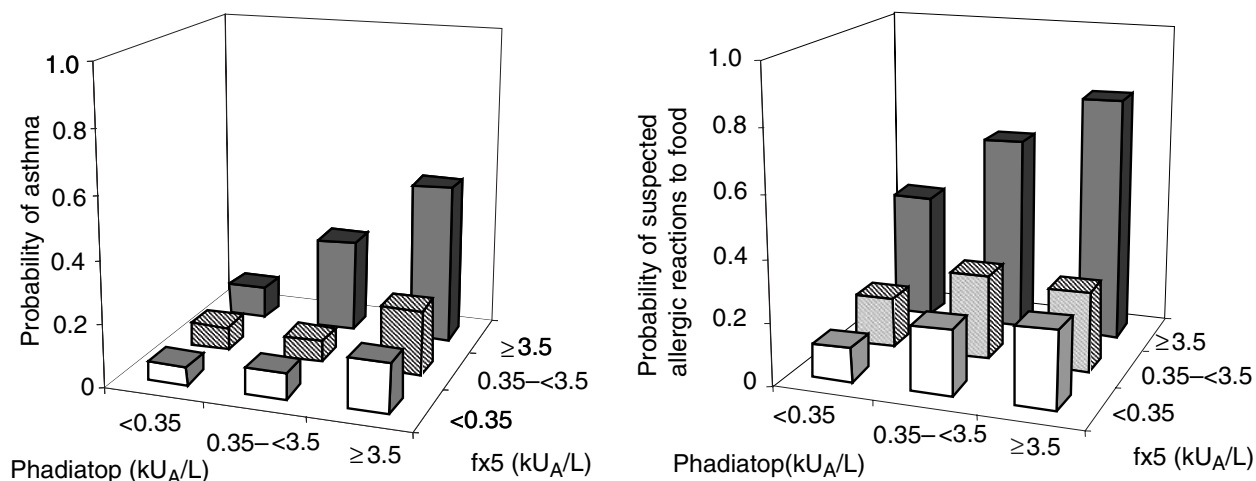


Fig. 4. Probability (positive predictive value) of asthma and suspected allergic reactions to food at certain immunoglobulin E levels.

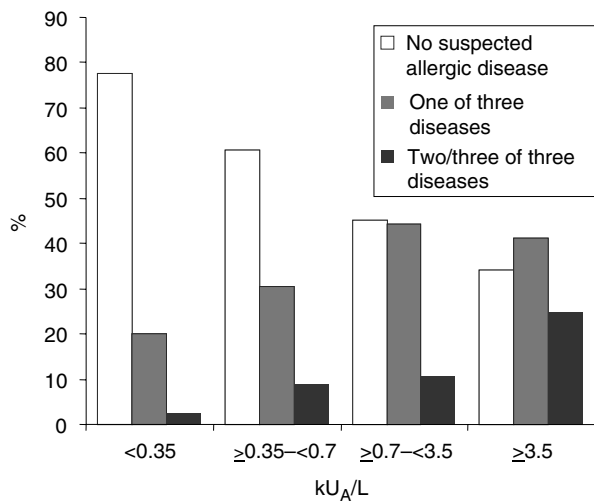


Fig. 5. Proportion of suspected allergic diseases, i.e. asthma, rhinitis and atopic eczema dermatitis syndrome (AEDS), in relation to different levels of Phadiatop. Because of a few number of children with two or all three suspected allergic diseases the upper level was set at > 3.5 kU/L.

airborne allergens (Phadiatop) no such trend was seen (data not shown). For fx5 and concentrations above 3.5 kU_A/l and association with severe asthma the same pattern was seen, children with ≥ 4 episodes of wheeze exhibited positivity in 14.4% compared with 4.8% among children with 0–3 episodes of wheeze during the last 12 months, $p = 0.0004$.

Levels of IgE antibodies and multiple allergic diseases

Among children who were classified with any suspected allergic diseases such as asthma, rhinitis, AEDS or SARF, 28.9% and 24.1% exhibited a positive test to Phadiatop or fx5, respectively. For those with at least 2, 3 or 4 suspected allergic diseases the corresponding figures of positivity were 44% and 65% and 79% for Phadiatop and 36%, and 58% and 79% for fx5, which indicates a positive trend for number of diseases and association between children positive to Phadiatop or fx5. By constructing four classes of severity representing the number of diseases, 1–4, with classification of no disease as the reference value, we performed a test for trend, i.e. a trend of having more manifestations of suspected allergic disease the higher the IgE levels for Phadiatop or fx5. For Phadiatop this resulted in an odds ratio (OR) to have disease of 2.61 (95% CI 2.32–2.93), and for fx5 an OR of 1.93 (95% CI 1.72–2.15).

The proportion of infants with one manifestation of either asthma, rhinitis or AEDS and the proportion with at least 2–3 of such manifestations was found to have a significant

positive trend over the magnitude of allergen specific IgE measured by Phadiatop (Fig. 5). The p -value for trend was $p\text{-trend} = 0.004$ (0 vs. 1 disease) and $p\text{-trend} < 0.001$ (0 vs. 2–3 diseases), respectively.

Discussion

This study was based on a population-based birth cohort of children followed longitudinally. We found that almost one-third of the children at 4 years of age had symptoms related to any suspected allergic disease and every fourth child had allergen specific IgE. However, on an individual basis there was a poor correlation between the presence of IgE antibodies towards food and inhalant allergens. In addition, the diagnostic impact of quantitative compared with qualitative analysis of allergen specific IgE antibodies was higher. Furthermore, the predictive value of the combination of Phadiatop and fx5 was higher than for each test alone for any allergic disease and the combination of the two tests was associated with an increased severity of allergic disease in terms of allergic organs involved. Besides, presence of antibodies to both airborne and food allergen was highly related to severity of recurrent wheeze.

The IgE sensitization pattern, typically associated with atopy, has been demonstrated to be characterized by an early beginning of sensitization, as well as by the persistence of sensitization (2, 3). Several prospective studies from birth and early childhood have observed that the atopic sensitization, i.e. 'the atopic march', starts with IgE antibody synthesis against food allergens followed by IgE antibody production against inhalant allergens and subsequent development of bronchial asthma (2, 3, 15–17). However, most studies performed so far have been dealing with risk groups and there are relatively few population-based studies on the prevalence of IgE sensitization during pre-school ages. In the present study, almost every fourth child had IgE antibodies and one of six had IgE antibodies that were directed towards inhalant allergens (i.e. positive Phadiatop). This is to be compared with data from an other Swedish survey in 1993 studying the same age group and demonstrating that 6% of the individuals had IgE antibodies to inhalant allergens, which indicates an increase in prevalence to inhalant allergens (16). Furthermore, in the multicenter allergy study (MAS) study the corresponding values at 6 years of age was 26% (2). Altogether, these data indicate an increase in prevalence of IgE antibodies to inhalant allergens in younger ages.

Approximately two-thirds of asthmatic subjects have been reported to be sensitized to at least one inhalant allergen depending on age, country etc. However, although 40% of children are sensitized to inhalant allergens by early school age, only 25–30% will have bronchial asthma (18). It is therefore of interest to follow IgE sensitization during early childhood in order to be able to predict and to prevent the development of respiratory diseases. In the present study with children only aged 4 years, the likelihood for recurrent wheeze, defined from the answers in our questionnaire, was found to be 0.25 with the use of Phadiatop ≥ 3.5 kU/l. However, the value increased to 0.51 if Phadiatop was combined with fx5 ≥ 3.5 kU/l.

Our results are consistent with the findings of Illi et al. recently reporting on the correlation between IgE sensitization during early childhood and the development of asthma up to 7 years among 1314 high risk AEDS infants in the MAS90 study (3). The diagnosis of asthma in that study was based on questionnaire and on bronchial histamine challenge. They found that IgE sensitization to inhalant allergens alone before 2 years of age was a poor predictor of the development of bronchial asthma at 7 years of age. However, when sensitization occurred before 2 years of age, the authors found that sensitization to food allergens alone or in combination with inhalant allergen was a strong predictor for the development of asthma before school age. The slight discrepancy of the results between our study and that of Illi et al. might be dependent on at what age the IgE antibody determinations were performed and on our quantitative approach giving more information than the qualitative one used by Illi et al (3). Another and not unlikely explanation might be differences in the definition of bronchial asthma. We have chosen a rather strict definition for bronchial asthma with at least four episodes of wheeze during the last 12 months, or one episode if the child had been treated with inhaled steroids during the last 12 months.

The paediatric patient with more than two organs involved, e.g. AEDS and asthma, AEDS and food allergy, asthma and rhinitis, might reflect an atopic constitution compared to those with only asthma or AEDS in this age group. This speculation was strengthened by our data as that manifestations of hypersensitivity/allergic disease involving more than one organ was more likely to be associated with allergen specific IgE measured by Phadiatop or fx5. This points to the fact that allergic disease should be suspected in children with symptoms of hypersensitivity from several organs. Furthermore, severity of asthma

has been shown to be associated with increased proportions of sensitization to furred pets (19). In this study, the number of episodes of wheeze during the last year was associated with presence and the levels of IgE antibodies, both for airborne and food allergens. To our knowledge these observations have not been shown before and need to be studied and discussed further. However, our data reinforce the importance of sensitization as a predictor not only for recurrent wheeze, but also recurrent episodes including many episodes during the last year and limited air flows. In our study, we were not able to allocate children with difference in severity in AEDS, SARF or rhinitis. Whether or not the same association is prevalent for other manifestations besides recurrent and severe wheeze cannot be shown at this level.

For the diagnosis of IgE-mediated allergy there is an increasing interest in the usefulness of quantitative determination of IgE antibodies. So far most interest and knowledge have accumulated in the diagnostic work regarding food allergy (13, 20). However, publications considering the usefulness of quantitative IgE analysis in inhalant allergy have also appeared (14, 21). In the present study, quantitative analysis of IgE was correlated to the presence of clinical symptoms of various allergic diseases based on the answers in the questionnaire. The definitions of the various allergic diseases were validated as they were based on those used in the ISAAC study and own validation (8). Our study shows that the ppl of various allergic disease by analysis of Phadiatop and fx5 increased with increasing IgE concentrations and especially if the two tests were combined and highly positive (≥ 3.5 kU/l; Fig. 3). Such a correlation has also been observed by others (21–23). As early diagnosis of atopy has been considered important, such diagnosis in pre-school children must include testing of both inhalant and food allergens (2, 3, 24). This needs to be emphasized as we found a rather poor correlation, on individual basis in positive/negative results, between Phadiatop and fx5. Such results have also been observed in previous studies, demonstrating the evolving formation of IgE antibodies with moving specificity from food to inhalant allergen (2, 16, 25).

From our study it can be concluded that quantitative IgE analysis seems promising for the diagnosis of allergic diseases in young children, but also for the severity of the disease. As IgE antibody levels may vary between different age groups, longitudinal studies that provide specific IgE levels at different ages towards various allergens need to be performed.

References

- MELLIS CM, PEAT JK, WOOLCOCK AJ. The costs of asthma. Can it be reduced? *Pharmaco-Economics* 1993; 3: 205–19.
- KULIG M, BERGMANN R, TACKE U, WAHN U, Guggenmoos-Holzmänn and the MAS Study Group, Germany. Long-lasting sensitization to food during the first two years precedes allergic disease. *Pediatr Allergy Immunol* 1998; 9: 61–7.
- ILLI S, von MUTIUS E, LAA S, et al. The pattern of atopic sensitization is associated with the development of asthma in childhood. *J Allergy Clin Immunol* 2001; 108: 709–14.
- XUAN W, MARKS GB, TOELLE BG, et al. Risk factors for onset and remission of atopy, wheeze and airway hyperresponsiveness. *Thorax* 2002; 57: 104–9.
- AGERTOFT L, PEDERSEN S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994; 5: 373–81.
- JOHANSSON SGO, HOURIHANE JOB, BOUSQUET J, et al. A revised nomenclature for allergy. *Allergy* 2001; 56: 813–24.
- LANNERÖ E, KULL I, TOLLIN L, WICKMAN M, NORDVALL SL. Environmental risk factors for allergy and socio-economic status in a birth cohort (BAMSE). *Paediatr Allergy Immunol* 2002; 13: 182–7.
- BÖHME M, LANNERÖ E, WICKMAN M, NORDVALL S, WAHLGREN C. Atopic dermatitis and concomitant disease patterns in children up to two years of age. *Acta Derm Venereol* 2002; 82: 98–103.
- KULL I, WICKMAN M, LILJA G, NORDVALL L, PERSHAGEN G. Breastfeeding reduces the risk of early symptoms of asthma and allergic disease in infants, from a prospective birth cohort study (BAMSE). *Arch Dis Child* 2002; 87: 478–81.
- The international Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Resp J* 1998; 12: 315–35.
- LINDFORS A, van HAGE-HAMSTEN M, RIETZ H, WICKMAN M, NORDVALL SL. Influence of interaction of environmental risk factors and sensitization in young asthmatic children. *JACI* 1999; 104: 755–62.
- KLINTBERG B, BERGLIND N, LILJA G, WICKMAN M, HAMSTEN M. Fewer allergic respiratory disorders among farmer's children in a closed cohort from Sweden. *Eur Respir J* 2001; 17: 1151–7.
- SAMPSON HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001; 107: 891–6.
- AHLSTEDT S. Understanding of the usefulness of specific IgE blood tests in allergy. *Clin Exp Allergy* 2002; 32: 11–6.
- SASAI K, FUOKAWA S, MUTO T, BABA M, YABUTA K, FUKUWATARI Y. Early detection of specific IgE antibody against house dust mite in children at risk of allergic disease. *J Pediatr* 1966; 128: 834–40.
- HATTEVIG G, KJELLMAN B, BJÖRKSTÉN B. Appearance of IgE antibodies to ingested and inhaled allergens during the first 12 years of life in atopic and non-atopic children. *Pediatr Allergy Immunol* 1993; 4: 182–6.
- WAHN U. The immunology of fetuses and infants. What derives the allergic march? *Allergy* 2000; 55: 591–9.
- WOOLCOCK AJ, PEAT JK, TREVILLION LN. Is the increase in asthma prevalence linked to increase in allergen load. *Allergy* 1995; 50: 935–40.
- CRONER S, KJELLMAN N-IM. Natural history of bronchial asthma in childhood – a prospective study from birth to 14 years of age. *Allergy* 1992; 47: 150–7.
- SAMPSON HA, HO DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997; 100: 444–51.
- MATRICARDI PM, NISINI R, BISELLI R, D'AMELIO R. Evaluation of the overall degree of sensitization to airborne allergens by a single serologic test: implications for epidemiologic studies of allergy. *J Allergy Clin Immunol* 1994; 93: 68–79.
- WEVER AMJ, WEVER-HESS J, v SCHAYCK CP, v WEEL C. Evaluation of the Phadiatop® test in an epidemiological study. *Allergy* 1990; 45: 92–7.
- BROCK WILLIAMS P, SIEGEL C, PORTNOY J. Efficacy of a single diagnostic test for sensitisation to common inhalant allergens. *Ann Allergy Asthma Immunol* 2001; 86: 196–202.
- RHODES HL, SPORIK R, THOMAS P, HOLGATE ST, COGSWELL JJ. Early risk factors for adult asthma: a birth cohort study of subjects at risk. *J Allergy Clin Immunol* 2001; 108: 720–5.
- WAHN U, BERGMANN R, KULIG J, BAUER CP. The natural course of sensitisation and atopic disease in infancy and childhood. *Pediatr Allergy Immunol* 1997; 8: 16–20.