

Specific immunoglobulin E antibodies to peanut over time in relation to peanut intake, symptoms and age

van Odijk J, Bengtsson U, Borres MP, Hulthén L, Ahlstedt S. Specific immunoglobulin E antibodies to peanut over time in relation to peanut intake, symptoms and age.

Pediatr Allergy Immunol 2004; 15: 442–448. © 2004 Blackwell Munksgaard

The clinical outcome of peanut allergy and some factors associated with development of peanut allergy remain unsolved. It has not been clarified to what extent peanut intake affects immunoglobulin (IgE) antibody formation in peanut sensitized individuals. The aim of the study was to investigate the development of peanut hypersensitivity in children and adolescents with specific IgE antibodies to peanut, using questionnaires and current serum tests and comparing it to information obtained 5–6 yr earlier, to investigate how peanut intake during this period related to subject age, IgE antibody levels and symptoms and to investigate what information this patient group was given at the time of diagnosis regarding avoidance of peanut related food. All patients with detectable peanut-specific IgE antibodies investigated during 1994–1996 deriving from two allergy laboratories in the western region of Sweden were traced and reinvestigated (n=132). A total of 111 subjects (63 with peanut allergy and 48 peanut sensitized) participated in the questionnaire. Eighty-six of them consented to be enrolled in a further interview and renewed testing of specific IgE antibody to peanut 5 yr later. All tests were done using the Pharmacia CAP system[®]. Increased IgE antibody levels during follow-up was related to age; subjects 0–6 yr at initial test occasion were more likely to have higher IgE antibody class than the older individuals (p=0.018). Exposure to peanut during the study, i.e. 5–6 yr since diagnosis, did not seem to affect the result. During the follow-up period, 29 out of 86 (34%) increased their IgE antibody class. At the second test occasion the remaining subjects had similar (28%) or lowered (38%) levels of IgE antibodies. Exposure to peanut during follow-up was more common in subjects with IgE antibody class 1–3 compared to subjects with high value (> 3) at the initial test (p=0.003). Reported symptoms during follow-up were also more common in subjects with initially high IgE antibody value. Individuals with initially high IgE antibodies to peanut had been given more information about peanut allergy and cross-reacting allergens than other individuals. The subjects over 6 yr of age showed a decrease in peanut-specific IgE class over a 5-yr period. Together with the literature, our result suggest that follow-up and renewed testing is recommended, since there may be a change in IgE antibody classes and clinical sensitivity over time. Even in Sweden, with a low consumption of peanuts, the youngest individuals with peanut sensitization experienced a similar course of events that has been reported in other countries.

**J. van Odijk¹, U. Bengtsson²,
M. P. Borres^{3,4}, L. Hulthén¹,
S. Ahlstedt^{4,5,6}**

Departments of ¹Clinical Nutrition, ²Department of Asthma and Allergy Research Group, Respiratory Medicine and Allergy, and ³Pediatrics, Sahlgrenska Academy at Göteborg University, Gothenburg, Sweden, ⁴Pharmacia Diagnostics, Uppsala, Sweden, ⁵Department of Environmental Medicine and ⁶Centre of Allergy Research, Karolinska Institute, Stockholm, Sweden

Keywords: immunoglobulin G; peanut hypersensitivity; food intake and allergic reaction

Prof. Staffan Ahlstedt, Department of Environmental Medicine, Karolinska Institute, S-17177 Stockholm, Sweden

Tel.: + 46 18 163017

Fax: + 46 18 163990

E-mail: staffan.ahlstedt@pharmacia.com

Accepted 9 June 2004

During the last decade there has been an increasing interest in peanut allergy and it is reported to be one of the most fatal food allergies (1). The highest incidence of peanut allergy is among young children and is often reported from countries where peanut consumption is common in all age groups (2–4). Peanut consumption seems to be low in the Nordic countries compared to UK and USA (5). However, peanut sensitization is common despite recommendations to avoid giving peanuts to children during the first years of life and despite a low and steady peanut consumption (6).

The prevalence of tree nut allergy in the general population has not been independently assessed, but studies of adults and children with peanut allergy suggest a high co-prevalence of tree nut allergy (7). Peanut allergy has earlier been regarded as a life-long disease (8), and has shown fewer signs of outgrowth than is found in allergy to milk and egg (9). However, some recent studies have shown that around 20% might outgrow their peanut allergy. This positive prognosis of the disease is associated with sensitization at low age, low specific immunoglobulin E (IgE) antibodies, and initially mild symptoms (10, 11). The first study (10) was based on different diagnosis criteria for peanut allergy and only on subjects with initially low specific IgE antibodies while the other study was based on challenge results in relation to prior reactions. There is still a lack of information concerning how specific IgE antibodies change over time and how antibody formation is connected to peanut intake in relation to age of the subject.

In recent years, quantification of IgE antibodies identifying a certain clinical cut off has been made for some food allergens including peanut allergy (12). These guidelines were put forward based on the recently described 95% predictive decision points in food allergic patients and can be regarded as guidelines for informing paediatric patients. They can also be used to avoid unnecessary food challenges. However, for patients with lower IgE antibodies than these proposed decision points (9), the guidelines are less clear.

Aim

The primary aim of the current study was to investigate development of peanut allergy and peanut intake in children and adolescents with peanut sensitization and peanut allergy, compared with the situation 5 yr earlier. A secondary aim was to investigate what information this

patient group was given regarding their peanut allergy. The study was performed using symptom questionnaires, personal interviews with subjects and their parents, and testing for specific IgE antibodies to peanut.

Material and methods

Study population and design

All individuals 0–18 yr with detectable peanut-specific IgE antibodies to peanut during the years 1994–1996 living in the western area of Sweden (Göteborg and Skövde) were traced through the Laboratory of Allergy at Sahlgrenska University Hospital and the laboratory at Skövde hospital. Altogether 144 persons fulfilled the inclusion criteria. Twenty-one individuals had moved out of the region during this period and could not be contacted for follow-up. A questionnaire (Q1) regarding peanut intake (deliberate or accidental) and adverse reactions before the first serum test, was sent out to the remaining 123 persons, aged 5–23 yr at follow-up (first test occasion). The questionnaire also contained questions about peanut intake and symptoms during this 5-yr study period.

The subjects and their parents were offered re-testing (second test occasion) and a follow up interview. One hundred and eleven subjects completed the questionnaire and 96 of them agreed to participate. A second questionnaire (Q2) was distributed to the follow-up participants. This time the questionnaire focused on questions regarding pre-disposition for atopic allergy, hypersensitivity to animals, pollen and grass and other food allergens such as soy, lentils and tree nuts. Repeated questions were included about peanut intake (as a control question) and also questions regarding what information they had received about peanut allergy from their physician or others at the time of the first test result in 1993–1995. The subject together with an investigator (JvO) reviewed this questionnaire during the interview. Questions about exposure to peanut and soy products were carefully reviewed using pictures and photos of peanut containing products and lists of soy containing products.

Laboratory studies

Blood tests for peanut and soy were performed and analyzed at the same Laboratory of Allergy at Sahlgrenska University Hospital using the same Pharmacia CAP system[®] (Pharmacia, Uppsala Sweden) as in 1995.

All serum tests were analyzed for circulating IgE to peanut (and in current measurements from year 2000 also for soy and hazelnuts). Serum was separated and stored at -20°C . The assay had a lower limit of detection of $0.35 \text{ kU}_\text{A}/\text{L}$ (kilounits antibody per liter), and an upper limit of $100 \text{ kU}_\text{A}/\text{L}$. Since specific kilounit values from 1993 to 1995 were not longer available for analysis, the specific IgE antibodies from the first measurement were grouped as specific IgE antibody classes as stated by the manufacturer's manual, measured in kilounit values ($\text{kU}_\text{A}/\text{L}$). Class 0: <0.35 , class 1: $0.35\text{--}0.7$, class 2: $0.7\text{--}3.5$, class 3: $3.5\text{--}17.5$, class 4: $17.5\text{--}50$, class 5: $50\text{--}100$ and class 6: >100 . Analysis of specific IgE antibodies in relation to peanut intake, reported symptoms and information given, $0.35\text{--}3.5 \text{ kU}_\text{A}/\text{L}$ (class 1–2) has been regarded as low, $3.5\text{--}17.5 \text{ kU}_\text{A}/\text{L}$ (class 3) as moderate and $>17.5 \text{ kU}_\text{A}/\text{L}$ (4–6) as high. Later research has estimated the predictive decision point for predicting peanut allergy to be $15 \text{ kU}_\text{A}/\text{L}$ (12). To be able to compare our tests with the earlier test result from 1993 to 1995, we have chosen the nearest cut off at $17.5 \text{ kU}_\text{A}/\text{L}$.

Classification of symptoms and immunoglobulin E antibody value

Symptoms following peanut intake in the first questionnaire (Q1) were classified according to the following criteria: skin symptoms only (eczema and/or urticaria); respiratory symptoms (angioedema, throat tightness, eye symptoms, asthma, itching in face and throat) and gastrointestinal symptoms (diarrhoea, stomach pain and vomiting). Symptoms involving the skin were characterized as *mild*, *moderate* if including Oral Allergy Syndrome (OAS), facial swelling, oedema or gastrointestinal symptoms and *severe* if including asthma, hypotension or symptoms from three organs or more.

Statistical methods

For comparison of distributions between different groups the Chi-square test was used and in case of less than five subjects in a row, Fisher's exact test. For changes in IgE antibody formation in relation to age, atopy, peanut intake and initial peanut IgE antibody class, Odds Ratio (OR) was estimated and confidence method was used according to Wald. All statistics were performed using SPSS version 10.0 for Windows (SPSS, Chicago, IL, USA; 2002).

The Research Ethics Committee, Göteborg University had approved the study.

Results

Altogether, 111 patients participated in the first questionnaire regarding their exposure to peanuts (Q1). The 111 subjects were used in the analysis for clinical description of initial IgE antibodies in relation to prior reactions and reported reactions during follow up. Ninety-six of them accepted participation in the follow-up study. During the follow-up, three subjects withdrew their consent, two subjects moved out of the area during the study, and five declined to give a blood sample. Therefore, 86 subjects participated in both interview (Q2) and collection of blood samples. The 86 subjects in the results were related to changes of IgE antibodies during the study and reported reactions in relation to IgE antibodies at second test occasion.

There was no difference in the mean age between those who participated and those who did not. However, there was a trend towards more subjects with low and medium high peanut-specific IgE antibody class (1–3) in the group that could not be traced or that did not answer the first questionnaire (not significant).

In the 111 subjects, the distribution of specific IgE antibody class at initial test 1993–1995 was as follows: low/medium (IgE antibody class 1–3): 63%; and high (IgE antibody class 4–6): 37%. Twenty-nine out of the 86 (34%) showed an increase in their IgE antibody class during the follow-up period, and the remaining group had similar (28%) or lowered (38%) IgE antibody class.

Changes in immunoglobulin E antibodies over time

Immunoglobulin E antibody formation was associated with age. Subjects over 6 yr of age that had been assessed to have peanut IgE antibodies in 1993–1995 were more likely to have lowered the IgE antibody class during the 5-yr study period compared to those below 6 yr at first test occasion (OR: $0.12\text{--}0.72$, $p=0.008$). The initial peanut antibody value affected the results slightly although not significantly (OR: $0.90\text{--}1.83$, $p=0.16$). Exposure and/or reaction to peanut during the follow-up period did not seem to affect the change of IgE antibody level (OR: $0.44\text{--}1.63$, $p=0.60$). As shown in Fig. 1, changes seemed related both to age and initial IgE antibody value. Fifty-five percent of young children (26/47) had high IgE antibodies at both test occasions compared to 33% (13/39) of the older individuals. In subjects with low IgE antibodies at both test occasions, the result was

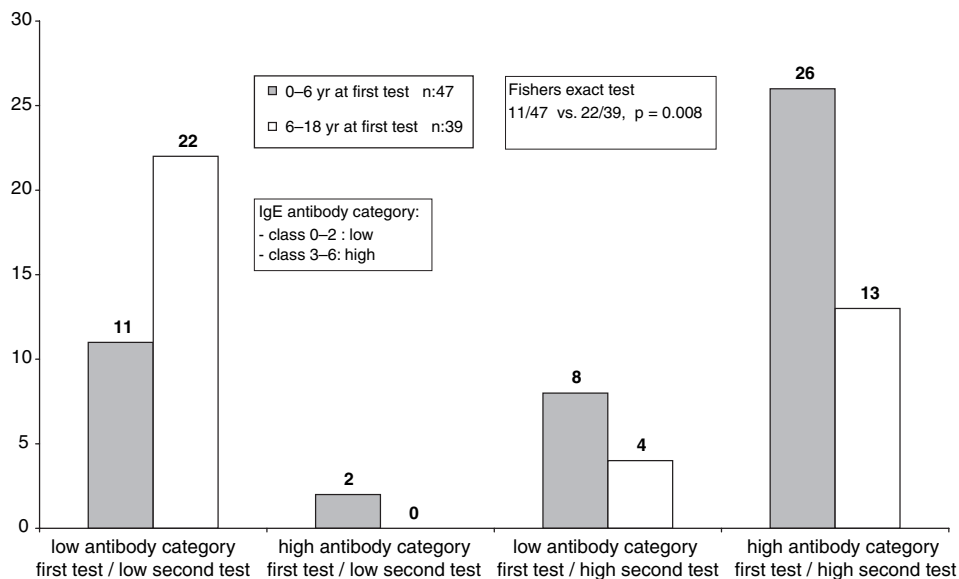


Fig. 1. Changes of IgE antibody category during follow-up study in relation to age.

the opposite. Twenty-three percent of the subjects tested and diagnosed at low age stayed in the same low category, compared to 56% of the subjects tested after 6 yr of age, which means there is a significant difference between the age groups at $p=0.008$. (Fig. 1).

Peanut intake and reaction prior to first test occasion

Fifty-six percent (62/111) had been exposed and had experienced an adverse reaction to peanut before the first test occasion. The remaining subjects had been tested as part of an allergy investigation and were not aware of their hypersensitivity to peanuts. Reactions following intake were less common among subjects with low/moderate antibody level compared to subjects with high antibody level (33/69 vs. 29/42, $p=0.01$).

Subjects with specific IgE antibodies above 17.5 (class 4-6) at first test occasion in 1993-1995 had experienced more severe symptoms before the test than subjects with initially low IgE antibodies ($p=0.01$, results not shown). In the group with initially high IgE antibodies, no one reported mild symptoms. No subjects had reported G-I symptoms alone upon peanut intake.

Serum specific levels at first test occasion in relation to peanut consumption and to adverse reactions during follow-up study

Of the 111 subjects, 86 accepted a second serum test 5 yr later. Based on test results from the initial IgE antibody test, 52% (27/52) of subjects with low and moderate IgE antibody level

(<17.5 kU_A/L) had reported consumption of peanuts, compared to 21% (7/34) with high IgE antibody level ($p=0.003$). Forty-four percent (12/27) of subjects with low/moderate antibodies reported symptoms upon exposure compared to 86% (6/7) with high IgE antibodies ($p=0.05$, Fig. 2).

Subjects classified as peanut allergic due to reported reaction before the first test are marked with red colour in Fig. 2. In the group with initially low IgE antibodies five of 24 had no reaction upon re-exposure and in the group with IgE antibody class 4-6, one of 24 had no reaction. In all, six of 48 had lost their reactivity to peanut during the follow-up (12.5%).

Immunoglobulin E levels at second test occasion in relation to reported reaction during follow-up

During the follow-up, in all 34 subjects reported exposure to peanut, and 18 of them experienced symptoms. Eighty-eight percent (14/16) of subjects reporting no reaction during follow-up had specific IgE antibodies below 3.5 kU_A/L at renewed test (Fig. 3). However, seven of 18 (39%) of reacting subjects had <3.5 kU_A/L at renewed testing, demonstrating that such low IgE antibody levels were not safe and did not always exclude from reactions to peanuts. The subjects reporting reaction had higher mean values of kU_A/l-values for peanut (37.5 vs. 9.0, $p=0.003$) and higher proportion of reported atopic manifestations (=3) compared to non-reacting individuals (9/18 vs. 3/16, $p=0.05$).

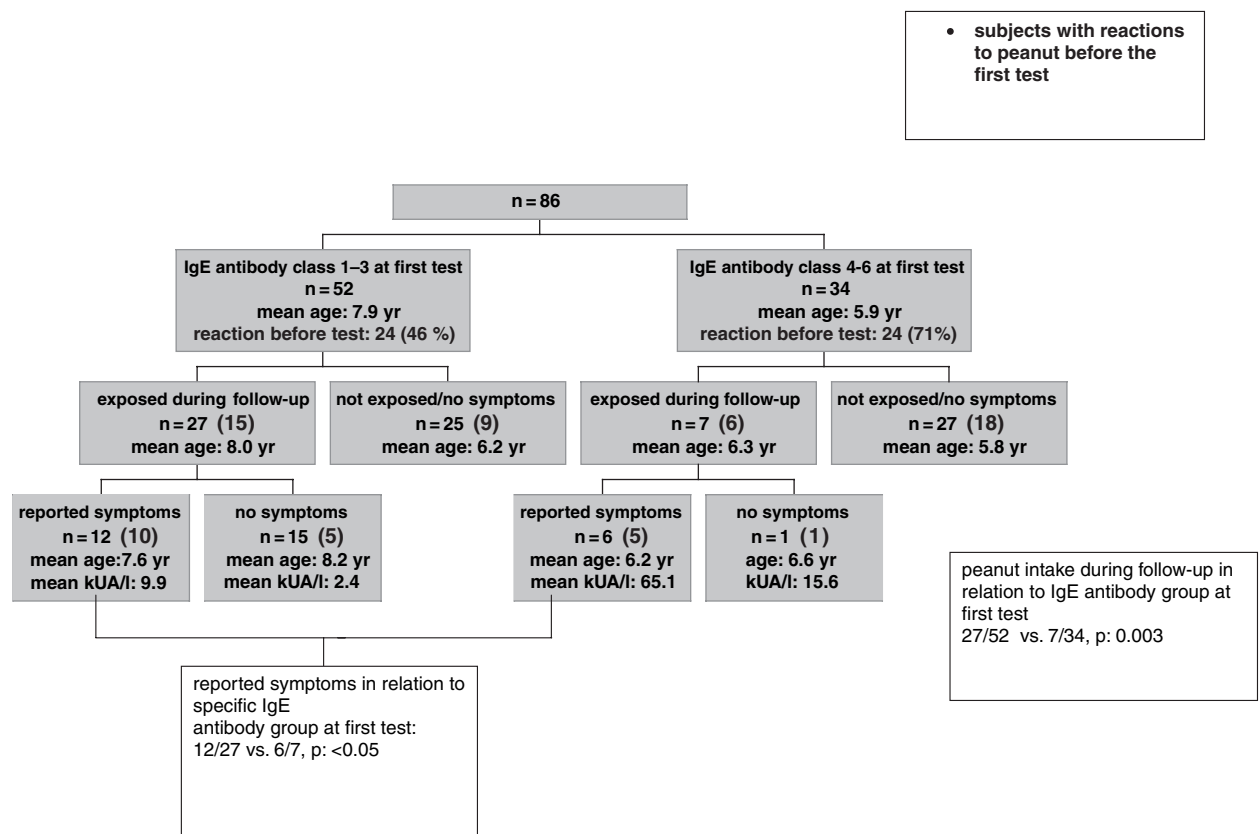


Fig. 2. Peanut intake and reactions during follow-up study in relation to test result of specific peanut antibodies at first test occasion.

Information about cross-reacting food in peanut sensitized subjects

Since exposure to the allergen and to cross-reacting allergens may impact on sensitization and reaction, the subjects were inquired about

what information they had been received regarding avoidance of allergens. Around one-fifth of the subjects or parents did not receive any information about peanut hypersensitivity or eventual risk of cross-reactions (apart from the

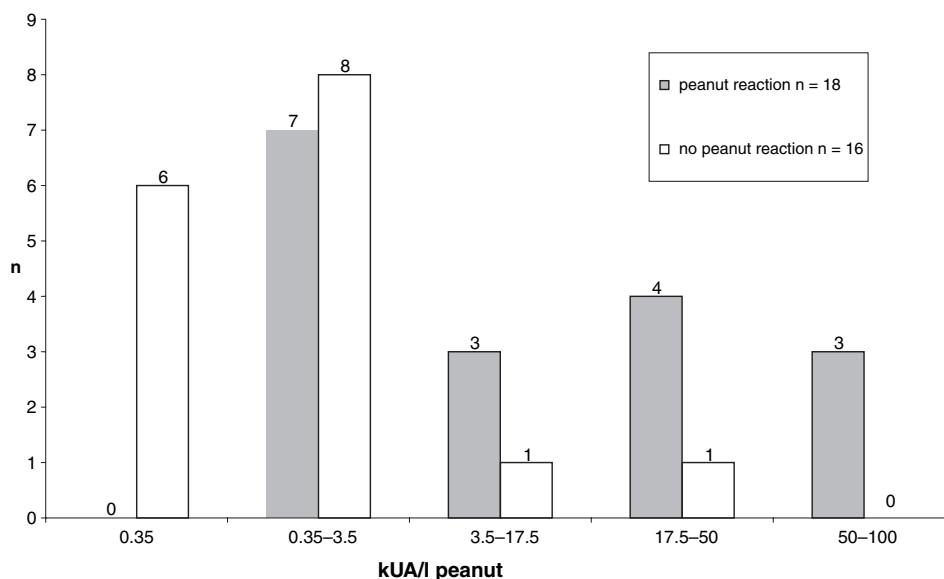


Fig. 3. Grouping of reported peanut reaction in relation to specific IgE antibodies for peanut.

information about the test result). Any information given to the remaining group was related to the IgE antibody class level. A significantly higher proportion of subjects with high IgE antibody class had received information about cross-reactive allergens compared to subjects with low/medium high antibodies (20/23 vs. 13/52, $p=0.002$). The information that were given, that differed from subjects with low IgE antibodies, was generally to avoid soy (21/34 vs. 18/52, $p=0.04$) and peas (14/34 vs. 13/52, $p=0.01$).

Since many patients may be uncertain of contents in different food items, intake of peanut and soy were thoroughly reviewed during the interview. An interesting result was that many more subjects than the 30 who reported avoiding soy, believed that they avoided this food completely. However, during the interview it was revealed that soy products actually were consumed and tolerated. A few subjects were not well informed where soy and peanuts could be found in food. Six subjects out of the 86 in the interview (7%) had given incorrect answers in the first questionnaire (Q1) regarding exposure to peanut. This result implied that a questionnaire should be followed up by personal interviews when collecting data on exposure.

Discussion

This study describes how the level of IgE antibodies to peanut changes over time in many subjects with peanut allergy and peanut sensitization, and that these changes seemed to be more related to initial age than to exposure to peanuts. Twelve percent of the subjects with earlier symptoms to peanuts reported no reaction upon re-exposure. These results emphasize the importance of follow-up testing of specific IgE antibodies to peanut.

The majority of the subjects tried to avoid peanuts and reported accidental exposure only. We have earlier reported a low but steady consumption of peanuts in Sweden (6), but peanut allergy seems to affect patients' behaviour, both physiologically and psychologically to a considerable extent like in many countries with a high consumption of peanuts (4, 13, 14).

During the interviews with patients and parents it was revealed that exclusion of peanuts often included soy products and tree nuts as well to avoid misunderstandings and that patients felt uncertain of the labelling guidelines. This often led to avoidance of all confectionery products including biscuits, chocolates and sometimes ice cream despite varying advice about avoidance from health personnel. The nationwide

recommendation in Sweden is to avoid soy if the patient has severe peanut allergy (<http://www.barnallergisektionen.se>). Based on our findings of exposure and IgE formation, as well as findings of other studies about low prevalence of cross-reaction between soy and peanut, we believe patients with no severe peanut allergy should be tested before recommendations are delivered.

Nearly all testing for IgE mediated allergy in Primary Health Care and hospital care in Sweden includes serum specific tests and/or skin prick tests. Almost all serum specific tests for different allergens performed in western Sweden are analyzed at the laboratories used in this study. We are referring to this group as reflecting the peanut sensitized children and adolescents in this area during the study period. There was no difference in age and initial peanut-specific IgE antibody class between participants and dropouts. However, more subjects with high peanut-specific IgE antibody class participated in our study.

Immunoglobulin E antibody formation and age

When studying changes in IgE antibody formation from the initial and the repeated test, it was apparent that younger individuals had a different antibody formation compared to older subjects. Consumption of peanuts or any other nuts did not interfere with the result. The production of IgE antibodies to food allergens has been reported to be high in small children and is often replaced by IgE antibodies to inhalant allergens as the child grows (15). Whether this pattern also includes peanut is not known, but in our study there seemed to be a similar change towards lower class of antibodies to peanut, as the child grows older.

Symptoms in relation to specific immunoglobulin E

The optimal concentration of food specific IgE antibodies for predicting symptoms from the most common allergens has been developed both in retrospective and prospective studies (12, 16). A value for 95% prediction of positive reaction for peanut has been described at 15 kU_A/L (12, 16). Furthermore, it has been proclaimed that patients with specific IgE antibodies below 5 kU_A/L could be considered for re-challenge (10). These observations/guidelines do not contradict our findings since there are some subjects who report a reaction to peanuts despite specific IgE antibody values below 3.5 kU_A/L. However, all of these subjects had similar or raised IgE antibodies during the follow-up period, suggesting an ongoing sensitization.

When classifying the subjects as peanut allergic due to earlier reaction to peanuts, six of 48 lost their reactivity to peanut. This figure is in line with results from other studies and it has been suggested by others that children and adolescents with low peanut-specific IgE antibodies can tolerate peanuts and some of them might exclude peanuts based on very loose grounds. After termination of this study we performed double blind placebo controlled food challenge on six subjects with current antibody values between 0.5 and 2.9 kU_A/L and no previous reaction to peanut. Seven out of these six had negative challenges. One of the patients reacted with OAS after 50 mg of peanut, and the other patient reacted with respiratory symptoms after ingesting a last dose of 8 g of peanuts (manuscript in preparation). The result implies that it is difficult to predict an eventual reaction but also emphasizes the importance of continuing to challenge with high doses. However, the majority of guidelines have focused on threshold doses of lowest provoking dose for double-blind peanut challenges (17–19).

Conclusion

In our study group where patients with both low and high peanut-specific IgE antibodies have been included, the older subjects over 6 yr at first test showed a decrease in peanut-specific IgE class over a 5-yr period. In accordance with the literature our result suggest that follow-up and renewed testing is recommended, since there may be a change in IgE antibody classes and clinical sensitivity over time. Even in Sweden, with a low consumption of peanuts, the youngest individuals with peanut sensitization experienced a similar course of events that has been reported in other countries.

Acknowledgments

We thank Eva Heuman and Inger Winberg for collection of blood samples in Göteborg, Associate Professor Gunnar Hattevig and Ms Maria Gladh for help with the Skövde study group and Lars Söderström for statistical support.

This work was supported by grants from the Swedish Association against Asthma and Allergy, The Swedish Foundation for Health Care Sciences and Allergy Research and Västra Götalandsregionen.

References

1. EWAN PW. Clinical study of peanut and nut allergy in 62 consecutive patients: new features and associations. *BMJ* 1996; 312: 1074–8.
2. HOURIHANE JO. Peanut allergy—current status and future challenges. *Clin Exp Allergy* 1997; 27: 1240–6.
3. MONERET-VAUTRIN DA, RANCE F, KANNY G, et al. Food allergy to peanuts in France – evaluation of 142 observations. *Clin Exp Allergy* 1998; 28: 1113–9.
4. SICHERER SH, MUNOZ-FURLONG A, SAMPSON HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol* 2003; 112: 1203–1207.
5. FAO/WHO. Food Balance Sheets. Rome: FAO/WHO, 2000.
6. van ODIJK J, AHLSTEDT S, BENGTSOON U, HULTHEN L, BORRES MP. Specific IgE antibodies to peanut in western Sweden – has the occurrence of peanut allergy increased without an increase in consumption? *Allergy* 2001; 56: 573–7.
7. SICHERER SH, BURKS AW, SAMPSON HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics* 1998; 102: e6.
8. BOCK SA, ATKINS FM. The natural history of peanut allergy. *J Allergy Clin Immunol* 1989; 83: 900–4.
9. HOST A, HALKEN S, JACOBSEN HP, CHRISTENSEN AE, HERSKIND AM, PLESNER K. Clinical course of cow's milk protein allergy/intolerance and atopic diseases in childhood. *Pediatr Allergy Immunol* 2002; 13(Suppl. 15): 23–8.
10. SKOLNICK HS, CONOVER-WALKER MK, KOERNER CB, SAMPSON HA, BURKS W, WOOD RA. The natural history of peanut allergy. *J Allergy Clin Immunol* 2001; 107: 367–74.
11. SPERGEL JM, BEAUSOLEIL JL, PAWLOWSKI NA. Resolution of childhood peanut allergy. *Ann Allergy Asthma Immunol* 2000; 85: 473–6.
12. SAMPSON HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001; 107: 891–6.
13. AVERY NJ, KING RM, KNIGHT S, HOURIHANE JO. Assessment of quality of life in children with peanut allergy. *Pediatr Allergy Immunol* 2003; 14: 378–82.
14. PRIMEAU MN, KAGAN R, JOSEPH L, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. *Clin Exp Allergy* 2000; 30: 1135–43.
15. KULIG M, BERGMANN R, TACKE U, WAHN U, GUGGENMOOS-HOLZMANN I. Long-lasting sensitization to food during the first two years precedes allergic airway disease. The MAS Study Group, Germany. *Pediatr Allergy Immunol* 1998; 9: 61–7.
16. 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.
17. TAYLOR SL, HEFLE SL, BINDSLEV-JENSEN C, et al. Factors affecting the determination of threshold doses for allergenic foods: how much is too much? *J Allergy Clin Immunol* 2002; 109: 24–30.
18. WENSING M, PENNINKS AH, HEFLE SL, KOPPELMAN SJ, BRUIJNZEEL-KOOMEN CA, KNULST AC. The distribution of individual threshold doses eliciting allergic reactions in a population with peanut allergy. *J Allergy Clin Immunol* 2002; 110: 915–920.
19. HOURIHANE JB, KILBURN SA, NORDLEE JA, HEFLE SL, TAYLOR SL, WARNER JO. An evaluation of the sensitivity of subjects with peanut allergy to very low doses of peanut protein: a randomized, double-blind, placebo-controlled food challenge study. *J Allergy Clin Immunol* 1997; 100: 596–600.