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Resolution of peanut allergy: case-control study

Jonathan O'B Hourihane, Stephen A Roberts, John O Warner

Abstract

Objectives: To determine whether there are any differences between children who remain mildly or moderately allergic to peanut and children with similar histories but a negative reaction on challenge with peanut.
Design: Case-controls matched for age and sex.
Setting: Children's day wards in two teaching hospitals.
Intervention: Open food challenge with peanut.
Subjects: 15 children with resolved peanut allergy (resolvers) and 15 with persistent allergy (persisters).
Main outcome measure: Reaction on challenge with peanut, serum total and peanut specific IgE concentrations.
Results: The groups had a similar median age at first reaction to peanut (11 months, range 5-38) and similar symptoms. Allergy to other foods was less common in resolvers (2/15) than persisters (9/15) ($P = 0.02$). On skin prick testing with peanut all 13 resolvers tested but only 3/14 persisters had a weal of < 6 mm ($P < 0.0001$). Total and peanut specific IgE concentrations did not differ much between the groups.
Conclusion: Appropriately trained clinicians must be prepared to challenge preschool children with peanut as some will be tolerant despite a history of reactions to peanut and a positive skin prick test with peanut. Preschool children whose apparent peanut allergy is refuted by food challenge show allergy to other foods less often than those in whom peanut allergy persists. The size of weal on skin prick testing to peanut predicts reactivity but not severity on peanut challenge.

Introduction

The diagnosis of peanut allergy has important consequences for patients and their families. They are told that allergic reactions occur after frequent exposure, that reactions are often severe, and that the allergy persists indefinitely.[1]

The dietary habits of the British population have changed, with vegetarianism becoming more popular and the use of peanut butter apparently increasing as a snack food for children. These changes may be linked to a recently observed decrease in the age of onset of peanut allergy.[2 3]

In longitudinal studies allergies to cows' milk and egg usually resolve early in life; 85% of children with cows' milk allergy in the first two years of life are tolerant of milk by 3 years of age[4] and up to 80% of infants with egg allergy are tolerant of egg by 5 years of age.[5 6] There are no similar longitudinal studies of infants with peanut allergy, and the advice that peanut allergy persists is based on a study of older children.[1] The age differences between children with cows' milk or egg allergy and those with peanut allergy may account for the different rates of resolution. Follow up of a population based group of Danish children with cows' milk

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allergy suggests resolution of the allergy is unusual if it has not occurred by 5 years of age.[7]

In our clinical practice we have observed apparent resolution of peanut allergy in several children affected by peanut allergy at a young age. We report the clinical features of these children and of those of age and sex matched controls who have remained allergic to peanut.

Subjects and methods

We studied children who were referred to the regional paediatric acute allergy and anaphylaxis clinic in Southampton (155 children) or to the paediatric allergy clinic in South Manchester (75 children) for evaluation of suspected peanut allergy between April 1995 and December 1996.

Identification of cases and controls

A child was considered to have been allergic to peanuts if the constellation of typical symptoms had been observed after an unequivocal exposure to peanuts in the 3 years before presentation. Children who had undergone peanut challenge were identified by the relevant author in each hospital. Patients were selected for challenges according to the clinical needs of the patient in each case. Some children were challenged because they had had negative results on skin prick testing with peanut despite a convincing history or because their dietary history suggested that an exposure to peanut had been uneventful. Children with life threatening reactions to peanut were not considered for challenge irrespective of the time since the last exposure. Controls and cases with positive results on skin prick testing were challenged either because the last reaction had been a long time before or because of parental request. Parents often wanted to know whether their child was allergic to peanuts before school entry—anecdotally, a time of great anxiety for parents of children allergic to certain foods. The challenges were all open food ones[8] using peanut butter or peanuts according to the age of the subject. Every challenge was performed in hospital.[9]

A child was considered to be no longer allergic to peanuts if two criteria were met: (a), they had a clear history of a reaction to peanut and (b), a formal challenge with peanuts or peanut butter gave negative results. We called these children resolvers.

Matching for age and sex was undertaken to control for effects that would be evident when comparing preschool children with peanut allergy and comparatively few other allergies (either to foods or inhalant allergens) with older children sensitised to a wider range of allergens.[2] For each case one control (persister) was identified from children who had a positive skin prick test and a positive challenge with peanut.

Skin prick testing

Skin prick testing was carried out at the initial hospital visit using a 1:20 (wt/vol) solution (Soluprick, ALK, Uppsala, Sweden). A reaction was considered positive if a weal was >3 mm in diameter in the presence of a reaction to 1% histamine of at least 3 mm in diameter.

Measurement of IgE concentration

The concentration of total IgE was measured in serum using an enzyme linked immunosorbent assay system developed by each hospital. The lower limit of detection was 5 KU/ml in each hospital. The concentration of peanut specific IgE was measured using either a commercially available enzyme linked immunosorbent assay kit (Alstat, Wales) in Southampton or the Pharmacia-CAP system (Pharmacia, Uppsala, Sweden) in Manchester. The lower limit of detection of both assays was 0.35 KU/ml.

Data handling

Data were collected from hospital notes by the responsible clinician using a standard data collection form for both the cases and controls. Details of the age of onset, number of exposures, clinical features of reactions, and length of time since last exposure or reaction were noted. The presence of coexisting asthma, eczema, rhinitis, and food allergies was also determined.

Data were entered blind to patient identity using SPSS software (Windows 6.1, Chicago). Categorical data were compared using Fisher's exact χ^2 test with Yates's correction. Continuous variables were compared using either Student's t test or the Mann-Whitney U test. A P value of <0.05 was considered significant.

Results

Overall, 230 children were referred to the regional paediatric acute allergy and anaphylaxis clinic in Southampton (155 children) or to the paediatric allergy clinic in South Manchester (75 children) for evaluation of suspected peanut allergy. A total of 120 (48%, equal numbers in each unit) were challenged with peanut.[8]

Twenty two cases of resolved peanut allergy were identified but suitable controls with positive results on peanut challenge were available for only 15 (eight in Southampton and seven in Manchester). The remaining seven resolvers were excluded from further analysis. Ten of the 15 resolvers were boys. The median age of the resolvers at the time of challenge was 5 years (range 2-9 years).

Historical features—Table 1 shows the historical features of resolvers and persisters. Allergy to food other than peanuts was less common in resolvers (one child

Table 1 Children whose peanut allergy resolved and children whose allergy persisted. Values are numbers (percentages) of children unless stated otherwise

Variables	Resolvers (n=15)	Persisters (n=15)
Sex ratio (male:female)	10:5	10:5
Median age (years) at challenge (range)	5 (2-9)	5 (2-10)
Asthma, eczema, or rhinitis	8/15 (53)	13/15 (86)
At time of challenge		
Asthma	5/15 (33)	7/15 (46)
Eczema	4/15 (26)	8/15 (53)
Rhinitis	1/15 (7)	3/15 (20)
Allergy to any other food*	2/15 (13)	9/15 (60)
Cows' milk	1/15 (7)	1/15 (7)
Egg†	0	5/15 (33)
Tree nut	1/15 (7)	2/15 (13)
Soy	0	0
Median peanut specific IgE (KU/ml) (range)	0 (0-280)	6.8 (0-30)
Median total IgE (KU/ml) (range)	54 (5-4-500)	375 (49-830)

*P=0.02. †P=0.04.

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was allergic to milk, fish, and tomato and another to hazelnut) than persisters (nine children) ($\chi^2 = 7.03$, $P = 0.02$).

Features of reactions to peanut are shown in table 2. The age at first reaction to peanut was similar in each group (median 11 months, range 5-38). The severity of reactions did not differ between the groups and the number of reactions was similar in each group. The time between last reaction and challenge was longer, but not significantly so, in resolvers (median 40 months, range 15-72) than persisters, as proved by challenge (12 months, range 3-72, $P = 0.10$).

Skin prick testing

The results of skin prick tests were available for 13/15 resolvers and 14/15 persisters (figure). The two resolvers who did not have skin prick tests had raised serum concentrations of peanut specific IgE of 34 and 280 IU/ml. Eight resolvers had a negative skin prick test with peanut. No persister had a negative skin prick test. None of the five resolvers with positive skin prick tests had a weal of >5 mm compared with 17/21 persisters ($\chi^2 = 20.05$, $P < 0.0001$). If a cut off value of a 6 mm weal in response to a skin prick test was chosen, the skin prick test had a positive predictive value of 100% but a negative predictive value of 80% (3/14 children with proved allergy had weals of <6 mm) of reactivity on peanut challenge.

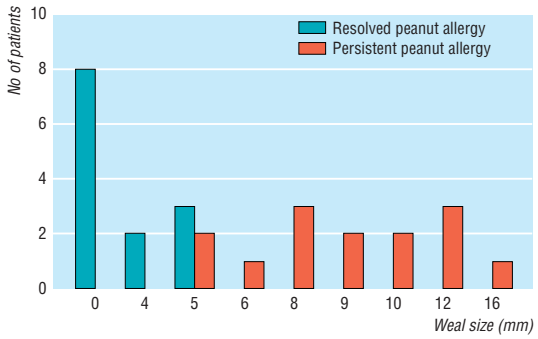
Total and peanut specific IgE concentrations

Total IgE and peanut specific IgE concentrations did not differ between the groups.

Peanut challenge

No subject with a positive challenge (persisters) needed adrenaline treatment for the reaction induced by the challenge test.

Follow up—Telephone follow up of 14 resolvers (one was lost to follow up) up to 2 years after challenge showed that only two had not eaten peanuts since the challenge. Five of the remaining 12 had eaten peanuts but not liked them. Six ate peanuts without problems but one child, who had negative results on skin prick testing, vomited after eating peanuts but did not have symptoms more typical of an allergic response; apparently, this child enjoys eating peanuts despite the vomiting. Two persisters were challenged a second time, which evoked reactions similar to the first challenge.



Results of skin prick testing for peanut in 13 children whose allergy resolved and 14 whose allergy persisted as shown by open challenge with peanut

Table 2 Features of reactions to peanut in children whose peanut allergy resolved and children whose allergy persisted. Values are numbers of children unless stated otherwise

Feature	Resolvers (n=15)	Persisters (n=15)
Median age (months) at first reaction (range)	11 (5-38)	12 (4-120)
Worst feature of severest reaction:		
Rash	3	2
Facial swelling	7	12
Tightness of throat or stridor	3	0
Wheeze	2	1
Collapse or faint	0	0
No of reactions:		
1	6	6
2	7	5
3	2	3
Uncertain	0	1
Median time (months) from last reaction to challenge (range)†	40 (15-72)	12(3-72)
Weal on skin prick testing <6 mm‡	13/13*	3/14

*Both of the resolvers who did not have skin prick tests had raised peanut specific IgE concentrations. †P=0.10. ‡P<0.0001.

Discussion

So far as we know, this case-control study is the first report of resolution of apparent peanut allergy, and it offers some reassurance to patients given a diagnosis early in life and to their families. The mechanism of resolution remains unknown.

Food challenges—Our study confirms the pivotal role of a food challenge in the diagnosis of food allergy. Many units are reluctant to undertake peanut challenges because of the risk of severe reactions. Certainly, all challenges need to be undertaken in appropriately staffed and equipped units,[8 9] and there must be compelling extra reasons to consider challenging people who have had severe reactions. In contrast, a child with positive results on skin prick testing but a doubtful history (such as reacting only to a large dose or having atypical symptoms) or a child with negative results on skin prick testing should always be offered an open challenge. Subjects who report a recent typical reaction need not be challenged. A minimum interval of 1 or 2 years after the most recent reaction is prudent.

Young children with peanut allergy—Our results suggest that preschool children with a history of mild or moderate allergic reactions to peanut who are challenged with peanut have a chance (22/120 challenges, 18%) that the challenge will be negative. The chance of negative results on challenge despite a clear reaction in the past are increased in subjects who do not have allergies to other foods at the time of challenge. Children whose peanut allergy had resolved reported a long time interval since the last reaction and had a negative or minimally positive reaction to peanut on skin prick testing. The benefits to affected children and their families are obvious if the fear of peanut allergy can be dispelled. During follow up of 14 resolvers we found that, to date, further exposures to peanuts had not resulted in allergic reactions, although aversion and continuing avoidance were common.

Limitations of study

The small sample size does not allow us to comment on the usefulness of measurement of serum total or peanut specific IgE concentrations as a predictor of reactivity in our group, but evidence suggests that

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threshold concentrations of allergen specific IgE may predict reactivity on challenge.[10]

Some of the resolvers may never have had peanut allergy. Asymptomatic people may be found to be positive to peanut on skin prick testing during screening for other reasons such as in asthma clinics or population based studies.[11] Children with small reactions on skin prick testing to peanuts, tree nuts, or sesame seeds and negative results on challenge have been reported, but some of the children were identified while having skin prick tests for other reasons.[12] Clinical experience of both persisting and resolving peanut allergy suggests that the first reactions to peanut early in life are due usually to deliberate exposure in the form of a peanut butter snack. The link with peanut is usually made quickly by the parent or doctor. Until recently, referral to centres with expertise in paediatric allergy was not possible, and many children were seen in hospital clinics only several years later.

The resolvers all reported at least one reaction to peanut—that is, none was referred from other clinics because of a positive skin prick test to peanut and no history of exposure or reaction. The number of reactions reported did not distinguish resolvers from persisters. Only a challenge or uneventful definite exposure (to an adequate dose) in the community is evidence of resolution. Negative results from challenges in the community must be supported by negative results from a formal challenge in hospital before dietary restrictions and rescue drugs can be withdrawn.

A British population based study of preschool children (4 years old) found that 13 out of 981 (1.3%) had a positive skin prick test to peanut.[11] Only six (0.6%) of them had had an allergic reaction to peanut; the remaining seven (0.7%) had positive results on skin prick testing but were symptom free. The size of the weal on skin prick testing with peanut was not reported, and we suggest on the basis of our results that a proportion of both the allergic children (reporting reactions) and the symptomless children would be tolerant of peanut if tested by peanut challenge.[11]

Atopic features—Our clinical impression was that the children who were ultimately shown on challenge to have outgrown peanut allergy had fewer other signs of atopy at presentation. The prevalence of asthma, eczema, hay fever, and rhinitis was similar in resolvers and persisters. This may be because of the sample size. The relative scarcity of allergy to tree nuts in resolvers (1/15, 6.6%) and controls (7/30, 23%) compared with that in all children with peanut allergy (approximately 50%) is probably related to age, with preschool children not being exposed to tree nuts as frequently as they are to peanuts.[2 3]

Peanut avoidance—Resolvers tended to report successful avoidance of peanuts for longer than persisters, and we wonder whether people who are allergic to peanuts can really avoid them. Peanut allergy in some preschool children who had no reported symptoms for a long time may have actually resolved over time, with the children not reacting to the unavoidable exposures that are so characteristic of peanut allergy.[1 13]

Key messages

- Peanut allergy rarely resolves in older children and adults
- Skin prick testing with peanut has a high negative predictive value, but some people with positive skin tests do not react to peanut challenge
- Some preschool children with a convincing history of reaction to peanut may become tolerant of peanut. Such children have fewer other manifestations of atopy than children whose peanut allergy persists
- Paediatricians must be prepared to undertake peanut challenges or refer children to units that will undertake such challenges

Conclusion

The commonest food allergies of infancy are to egg or cows' milk. These allergies usually resolve in time.[4–6] Children in whom milk allergy persists often develop other allergies.[7] Severe allergy to peanut is more common in adults than children[13] and rarely resolves in older children or adults.[1] Our work suggests that allergy in a small proportion of young children who become sensitised to peanut early in life resolves in a similar way to allergies to egg or cows' milk in infants and preschool children.

Recent reports suggest that the presence of IgE to linear epitopes of ovomucoid predicts persistence of egg allergy into later childhood, whereas IgE to conformational epitopes is associated with resolution in the usual time scale in infancy and the preschool years.[14] More detailed identification of peanut proteins and their epitopes[15] may allow such a study of peanut allergy, previously regarded as a persistent food allergy. Our report of preschool children in whom clinical peanut allergy apparently has resolved has important implications for both research and clinical paediatric practice.

We thank all the children who underwent the peanut challenges; nurses Nikki Barker, Melanie Seabrook, Dorothy Denton, and Sandra Croft, who supervised the challenges; and Mrs Lesley Ann Gudgeon and Ms Linda Butler for their secretarial help.

Contributors: JH supervised the challenges in Southampton, initiated and co-ordinated data collations, and drafted the first paper; he will act as guarantor for the paper. SAR supervised the challenges in Manchester, contributed to the design and execution of the study, and helped write the paper. JOW was the consultant responsible for the Southampton children; he also provided input into the design and interpretation of the data, and reviewed and contributed to drafts of the paper.

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Science commentary: Why do some children grow out of peanut allergy?

Editorial
Berger and Smith

One hypothesis which may explain why some children grow out of their peanut allergy lies in the physical structure of the peanut proteins. If the protein is visualised as a string of amino acid beads scrunched up into a 3-dimensional ball there are two ways an antibody can bind to that structure. Firstly, an antibody can bind to a specific antigen by attaching itself to sequential amino acid beads in the protein. These sections of the protein are known as linear epitopes. Alternatively, an antibody binds to a section which is effectively folded up so that it not only binds to a number of amino acid beads in one part of the protein string but also to beads in other sections of the string. These antigenic binding sites are known as conformational epitopes.

Research in other food allergies suggests that children who develop tolerance to peanuts may have peanut specific IgE which binds much more to conformational peanut epitopes (which are generally more labile and easily destroyed by heat) and that children who remain reactive to peanuts have IgE which binds mostly to linear epitopes (which are very stable). As the gut matures with age more linear epitopes than conformational epitopes pass through the gut wall. So if the hypothesis is found to be true this could explain why some people continue to react to peanuts and others seemingly outgrow their allergy.

Such differences in IgE binding have already been observed in children with egg or cows' milk allergy. An interesting question is why up to 50% of children with egg or cows' milk allergy outgrow the allergy while only about 10% seem to develop tolerance to peanuts.

Abi Berger, *science editor, BMJ*

Effectiveness of antibiotic prophylaxis in critically ill adult patients: systematic review of randomised controlled trials

Roberto D'Amico, Silvia Pifferi, Cinzia Leonetti, Valter Torri, Angelo Tinazzi, Alessandro Liberati on behalf of the study investigators

Abstract

Objective: To determine whether antibiotic prophylaxis reduces respiratory tract infections and overall mortality in unselected critically ill adult patients.

Design: Meta-analysis of randomised controlled trials from 1984 and 1996 that compared different forms of antibiotic prophylaxis used to reduce respiratory tract infections and mortality with aggregate data and, in a subset of trials, data from individual patients.

Subjects: Unselected critically ill adult patients; 5727 patients for aggregate data meta-analysis, 4343 for confirmatory meta-analysis with data from individual patients.

Main outcome measures: Respiratory tract infections and total mortality.

Results: Two categories of eligible trials were defined: topical plus systemic antibiotics versus no treatment and topical preparation with or without a systemic antibiotic versus a systemic agent or placebo. Estimates from aggregate data meta-analysis of 16 trials (3361 patients) that tested combined treatment indicated a strong significant reduction in infection (odds ratio 0.35; 95% confidence interval 0.29 to 0.41) and total mortality (0.80; 0.69 to 0.93). With this treatment five and 23 patients would need to be treated to prevent one infection and one death, respectively. Similar analysis of 17 trials (2366 patients) that tested only topical antibiotics indicated a clear reduction in infection (0.56; 0.46 to 0.68) without a significant effect on total mortality (1.01; 0.84 to 1.22). Analysis of data from individual patients yielded similar results. No significant differences in treatment effect by major subgroups of patients emerged from the analyses.

Conclusions: This meta-analysis of 15 years of clinical research suggests that antibiotic prophylaxis with a combination of topical and systemic drugs can reduce respiratory tract infections and overall mortality in critically ill patients. This effect is significant and worth while, and it should be considered when practice guidelines are defined.

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