Definitive diagnosis of nut allergy

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Abstract
***Objective*—To compare findings of tests for nut allergy in children.**
***Design*—Retrospective survey of a clinical practice protocol.**
***Setting*—Children's hospital paediatric outpatient clinic.**
***Subjects*—96 children referred by general practitioners and accident and emergency doctors over 27 months (1994–96).**
***Main outcome measures*—Allergic manifestations (generalised urticarial rash, facial swelling, bronchospasm, anaphylactic shock, vomiting on three occasions) related to specific nut IgE concentrations and following touch, skin prick, or oral ingestion of nuts.**
***Results*—16 children from a sample of 51 who were tested for nut allergy had no reaction to an oral challenge. Positive IgE against peanuts was found in nine of these 16 children.**
***Conclusions*—Skin prick testing and IgE measured by radioallergosorbent testing are inadequate tests for nut allergy. The definitive diagnostic test for nut allergy in the hospital setting is direct oral challenge.**
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Keywords: allergy; nuts; skin prick testing

The incidence of nut allergy, and peanut allergy in particular, appears to be increasing.[1–3] Media publicity has probably contributed to increased parental concern. Children with an apparent allergic reaction after the intake of food which could, or is known to, contain tree nuts or peanuts (monkey nuts, ground nuts) often present to general practitioners and accident and emergency units. In many cases the specific trigger is not known, although it is clear if nuts alone have been ingested. In uncertain circumstances some doctors may assume nuts to be the causal agent and plan further management on that basis. Comprehensive long term management plans then need to address all the implications of a specific diagnosis because peanut and tree nut allergy are considered to be lifelong.[4 5] Considerations include reading and labelling of foodstuffs, treatment of anaphylaxis, and involvement of all parties concerned in a child's care, potential for other family members to be affected, and the emotional needs of the family and child of having a lifelong condition. Such far reaching implications impose a need for the diagnosis to be as specific as possible.

Despite the availability of skin testing procedures and IgE concentration measurement, no general consensus exists as to what constitutes a definitive practical test of allergy, although direct challenge is considered to come closest.[6] We developed a protocol for testing children with nut allergy to provide the basis for a study comparing commonly employed tests.

Patients and methods

A total of 96 children aged 18 months to 15 years were studied over a period of 27 months. They had been referred from general practitioners or accident and emergency department doctors after presenting with a clinical history suggesting an acute allergic reaction. This included one or more episodes of vomiting, non-specific rash, urticaria, angio-oedema, stridor, bronchospasm, or collapse, and followed ingestion of foodstuffs likely, but not always known with certainty, to contain nuts. We included children who had presented more than once in a similar way but in whom there was doubt about a single allergenic cause.

Children with a clear history of an acute allergic reaction immediately after ingestion of a food in which a nut was the only possible allergen were excluded from further study using skin and oral challenge tests. However, they had blood taken for subsequent measurement of IgE concentration against the implicated nut and some other nuts. The respective risks of anaphylaxis at home or in hospital, possible benefits of a more specific diagnosis, and information about the testing procedure were discussed with parents of the remaining children and, where appropriate, with the children themselves. If they agreed to proceed, they were admitted to the day procedure unit (DPU). In some cases, blood IgE concentrations against certain nuts were obtained before admission, mainly to facilitate choice of test materials. IgE concentrations were measured by radioallergosorbent testing and were grouped as: strongly positive, > 17.5 Ku/l; positive, > 0.7 and < 17.5 Ku/l; weakly positive, > 0.35 and < 0.7 Ku/l; negative: < 0.35 Ku/l. The positive group concentrations are subsequently described together as positive (weakly positive–positive–strongly positive).

On admission to the DPU, emergency drug doses were calculated and made available for use in the event of a severe anaphylactic reaction. Full resuscitation facilities and skilled staff were available. We used the following test procedure with 30 minute intervals between consecutive steps:

- Rubbing the cut nut surface over the child's skin. The nut was cut once to reveal the inside surface, and this was then rubbed firmly along the forearm three times, producing a red line
- Intradermal injection of 20% nut solution. A drop of the solution was placed on the fore-

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arm, and through this solution a 25 G needle was inserted intradermally
- Application of increasing concentrations of nut solution to the child's lip at 10 minute intervals. These solutions were prepared by the pharmacy department. A total of 2 g of purified nut was diluted with 10 ml of sterile water to give a 20% nut solution. This 20% solution was diluted by adding a further 10 ml of sterile water and taking 10 ml of the resulting solution, thus giving a 10% solution. This step was repeated a total of nine times to give 10 solutions ranging in concentration from 20% to 0.02%
- Drinking increasing concentrations of nut solutions at 10 minute intervals. Children were encouraged to drink as much as possible, but at least 5 ml of each solution had to be consumed before proceeding to the next step
- Eating food containing implicated nut (chosen by child or parent). Care was taken to exclude any other type of nut or known allergenic substance.

We considered nut allergy confirmed if a child developed a generalised urticarial rash, facial swelling, bronchospasm, or anaphylactic shock at any stage; or vomiting immediately after ingestion on three occasions. A generalised urticarial rash was defined as a rash that was present over more than two parts of the body, and at a different area from where skin testing had taken place. An urticarial rash present—for example, over the trunk and arms, was described as being a positive reaction. The challenge test was considered to be negative if there was no generalised reaction or if skin signs were limited to mild localised erythema and/or localised induration or lumpiness. An isolated single area of localised urticaria or induration present only at the site of skin testing was termed a negative reaction.

Table 1 Comparison of IgE grouping and skin prick tests after challenge with nuts in children perceived to be allergic to nuts

	Type of reaction to nut challenge	
	Negative reaction (n = 27)	*Positive reaction (n = 35)*
Single suspected exposure to nuts	25	18
⩾ 2 suspected exposures to nut	2	17
Number of children with positive IgE against nuts (%)	20 (74) Weakly positive 10 Positive 8 Strongly positive 2	33 (94) Weakly positive 3 Positive 23 Strongly positive 7
Number of children with negative IgE against nuts (%)	7 (26)	2 (6)
Number of children having localised red/hard skin reaction (%)	7 (26)	19 (55)

Table 2 IgE status and type of reaction in children with positive challenge to nuts

Positive reaction to skin touch or skin prick	*Uncertain reaction to skin touch or skin prick and positive reaction to oral challenge*
IgE status against nuts	
14 (42.4%)	19 (57.6%)
Weakly positive n = 0	Weakly positive n = 3
Positive n = 13	Positive n = 10
Stronly positive n = 1	Strongly positive n = 6
Type of reaction	
Generalised urticaria n = 19	Urticaria or facial swelling n = 16
Skin touch n = 8	Mild bronchospasm n = 2
Skin prick n = 3	
Lip touch n = 8	

Key messages

- Definitive diagnosis of nut allergy is important because of anxiety, lifestyle, and resource implications
- A history of apparent allergic reaction to nuts is usually inadequate for diagnosis
- IgE titres and skin tests are limited by false positive and false negative results
- Oral challenge is the practical definitive test of nut allergy
- When allergy to one type of nut is confirmed, allergy to other nuts should be considered

Results

Peanut allergy was suspected in 72 (75.0%) of 96 children, and 24 (25.0%) were suspected to be allergic to tree nuts. Fourteen children (14.6%) had a definite history and therefore required no further diagnostic action. Seven parents (7.3%) chose not to proceed with further tests. Tables 1 and 2 show the number of previous exposures to nut, IgE status, and challenge reactions.

Some children who were thought to be allergic to one type of nut were subsequently readmitted for challenge testing to other types of nut(s) because serum IgE testing had been found to be positive (weakly positive–positive–strongly positive) to one or more types of nut. Fourteen of these children had a positive challenge: six had generalised urticaria after skin touch, and four developed symptoms after lip touch. Four children went on to have an oral challenge, which resulted in facial swelling and urticaria. After the tests, two children developed bronchospasm, which was immediately and successfully treated with salbutamol. Sixteen children with positive (eight positive, eight weakly positive) IgE antibody status against other types of nut had no reaction on challenge.

Twenty of 27 children with suspected nut allergy who had negative nut challenges subsequently included nuts in their diet for more than 11 months without allergic manifestations.

Discussion

The results of this study using an open challenge approach show that a history of apparent allergic reaction to nuts is inadequate in determining future management. Also, IgE antibody tests are no more successful and provide uncertain evidence of allergic tendency. More than half of the children thought to have previously reacted to peanuts and with positive (weakly positive–positive–strongly positive) IgE antibody titres had negative challenge tests. However, none of these had strongly positive IgE antibody titres. Negative IgE antibody titres may provide false assurance as shown by 5.7% of the children having positive reactions when challenged. In addition, more than half of the children considered on history to be allergic to tree nuts and with positive (weakly

positive–positive–strongly positive) IgE tree nut titres were negative on challenge testing.

Skin tests of the type used in this study (rubbing a cut nut surface along the skin and intradermal injection of 20% solution) have been shown to be an unreliable indicator of significant allergy unless distant or generalised signs of allergy are manifest. Local redness or induration, or both, were relatively common findings in children subsequently found to have no reaction on oral challenge.

In allergy testing, patients and doctors have to be convinced about the reliability of results. It is reassuring that no child found to be negative on challenge tests had a subsequent allergic reaction to contact with or ingestion of the specific nut tested.

If allergy to one type of nut is evident, allergy to other types should be considered. Allergy to tree nuts on direct challenge was noted in 17.6% of children thought to be allergic to peanuts on history and subsequently challenged, while 47% of suspected peanut allergic children also had positive (weakly positive–positive–strongly positive) IgE titres to tree nuts. Similarly, 21% of children considered to be allergic to tree nuts showed allergy to peanuts on challenge testing. Testing against individual nuts, or even groups of nuts, to define specific nut allergy is time consuming and labourious, and some families prefer total avoidance of all nuts (peanuts and tree nuts). Others choose to pursue a plan to specify as exact a diagnosis as possible.

All challenge tests are potentially dangerous, but risk can be minimised by testing in an environment with full resuscitation facilities and skilled staff. Clarification and increased certainty of diagnosis through challenge testing provides the basis for a comprehensive management plan. Such a plan involves relatively intensive education programmes for teachers and parents/children, detailed avoidance measures and dietetic advice, and provision of adrenaline (epinephrine) syringes. All of these have resource implications, emphasising the need for accurate diagnosis. Definitive diagnosis also allays misplaced parental fears and provides the focus for professional and parent commitment in specific and appropriate nut allergy management.

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