History, blood tests or skin prick testing? Is it possible to predict the severity of allergic reactions in children with IgE-mediated food allergy?

SCENARIO

A 5-year-old boy with a history of an itchy rash and lip swelling following peanut ingestion several weeks ago comes to see you in your outpatient clinic. His mother would like to know if her son will have a more severe reaction if he is exposed to nuts again. What advice do you give her and which, if any, investigations should be done?

STRUCTURED CLINICAL QUESTION

In a child with a history of an IgE-mediated allergic reaction to food (patient), are (intervention) blood tests, skin prick tests (SPTs) or the medical history helpful in determining the severity of future reactions (outcome)?

Search strategy

A Medline search 1946–2014 was performed, as per [table 1](#). The same search terms were used for the Cochrane library, with nil relevant articles, and also for an Embase search which found one further original research paper.¹ Anaphylaxis was searched separately as (predic* adj3 anaphyl*).mp in Embase, Cochrane and Medline, finding one new review article² and one new original research article.³ Articles were excluded if they did not relate to food allergy or children.

The 16 original research articles included are summarised in [table 2](#).

The findings of the relevant review articles^{2–6} and recommendations from the Royal College of Paediatrics and Child Health care pathway for food allergy⁷ and the National Institute for Health and Care Excellence (NICE) guidelines on food allergy in children and young people⁸ are discussed further in the Commentary section.

COMMENTARY

Immunoglobulin E (IgE)-mediated food allergy is common in children and is on the increase.⁸ There are studies that give a range of positive predictive values (PPVs) for SPT wheal size or specific IgE (sIgE) levels, aiming to help in diagnosis and reduce the need for food challenge in hospitals.^{2,3} The prediction of severity of allergic reactions is less studied and the NICE guidelines recommend further research in this area.^{7,8}

Table 1 Medline 1946–2014

1	exp *Food Hypersensitivity/	11 011
2	allerg*.ti,ab.	132 226
3	1 or 2	134 786
4	(predict* adj3 sever*).ti,ab.	10 216
5	3 and 4	115
	Keep	14

Historically accepted risk factors for severe allergic reactions are asthma, older age and a history of a previous severe reaction. These risk factors were accepted on the basis of older population-based data and case series of fatal anaphylaxis.^{5,8,24}

Table 2 Summary of articles

Citation	Study group	Study type	Outcome	Key result	Comments
Astier <i>et al</i> ⁹	30 peanut allergic patients and 30 controls	Level 4 Prospective case-control study	Diagnostic value of 3 recombinant peanut allergens	Patients monosensitised to rAra h 2 on SPT and sIgE have lower disease severity score (2 vs 3.5, $p<0.02$) than patients polysensitised to rAra h 1, 2 and/or 3	Authors report no correlation between the level of sIgE and severity of allergy but do not show data for this. Patients included were 3–20 years old
Benhamou <i>et al</i> ¹⁰	35 children attending clinic for diagnosis or follow-up of egg allergy	Level 3b Retrospective cohort study. 51 oral food challenges, some open, some DBPCFC	Comparison of response and specific IgE levels	Median sIgE 2.47 kU/L (0.35–14.90) in mild and moderate and 3.7 kU/L (1.18–11.00) in severe reactions; $p=0.006$	Overlapping range between reaction severity groups
Calvani <i>et al</i> ¹¹	163 children with anaphylaxis to food (36 different foods, cow's milk most common) who completed a questionnaire.	Level 2 Multicentre, prospective cohort study, consecutive recruitment	Clinical features in history associated with reaction type during anaphylaxis	History of asthma increased risk of developing wheeze (OR 2.2, CI 1.1 to 4.5). History of chronic GI symptoms increased risk of vomiting (OR 2.1, CI 0.9 to 4.3), hypotension (OR 7.9, 1.9 to 32.0) and bradycardia/arrest (OR 9.2, CI 0.9 to 91.3). Future episodes similar severity in those patients with mild or moderate anaphylaxis	Severity of anaphylactic reaction broken down into five different types. 36 patients (22%) had most severe form
Cianferoni <i>et al</i> ¹²	983 children who underwent OFC to egg, milk and peanut, 110 of whom developed anaphylaxis	Level 3 Retrospective cohort study, OFC	Comparison of severity of reaction to OFC with history, SPT, sIgE with aim of trying to identify children at risk for a severe reaction on OFC	Wheal size, prior non-cutaneous reaction (OR 4.2, $p<0.01$) and older age (OR 1.07, $p<0.03$) associated with anaphylaxis.	Results used to develop a scoring system to predict anaphylaxis on OFC. 1 point for age >5 years, (PPV 70, NPV 60) reaction type (prior GI, respiratory, multiorgan or anaphylaxis) SPT >9 mm, sIgE >5 kU/L. Overall, this score had an 80% specificity but only 44% sensitivity
Clark and Ewan ¹³	1000 patients with a history of a reaction to peanuts or tree nuts	Level 2 Cross-sectional observational study over 7 years	Clinical significance of SPT and sIgE results compared with history of reaction severity	In 162 patients with brazil nut allergy, a history of severe reaction associated with larger SPT diameter, median 14 vs 10 mm in mild-moderate reactions, $p=0.0005$. No association for sIgE or SPT with severity of reaction for any other nuts	
Hourihane <i>et al</i> ¹⁴	622 self-reported peanut allergic patients in UK who completed a questionnaire	Level 4 Case series. Selection bias in further evaluation of minority with skin prick testing and blood tests	Pattern of clinical severity of peanut allergy and symptom progression	Asthma ($p=0.00013$) and abdominal pain ($p<0.0001$) associated with severe reactions Correlation with increased median wheal size and severe reactions ($p=0.04$). No correlation with sIgE	Adults and children included, with severe symptoms more common in adults. Total IgE levels higher in teenagers
Michaud <i>et al</i> ³	98 peanut sensitised children divided into two groups depending on whether highly sensitized—sIgE >100 or sIgE >12	Level 4 Retrospective case-control study	Predictive factors for anaphylaxis	Highly sensitised children sIgE >100 kU/L report more anaphylaxis 41.9% vs 28.8%	Conference abstract
Neumann-Sunshine <i>et al</i> ¹⁵	782 children diagnosed with persistent peanut allergy, either on reaction (486 children) or high sIgE	Level 3b Retrospective case note review	Frequency of inadvertent peanut exposure, secondary outcome reaction severity	685 exposures studied. In 105 patients with initial sIgE >100 kU/L, OR 3.44, (1.82 to 6.5), $p<0.001$ for severe reaction; no association with age, sex and history of asthma and reaction severity	A total of 159 children had two or more reactions. In these children with multiple reactions there was no significant change in severity with time. 7.3%–10.8% postdiagnosis exposure per year
Pourpak <i>et al</i> ¹⁶	24 patients with wheat allergy confirmed on the basis of history or a positive OFC	Level 4 Non-consecutive recruitment, observational study, OFC	Comparison of history and sIgE and SPT results	OR 14.4 for anaphylaxis in patients with sIgE more than 3+ (>3.6 Ucs/mL) CI 1.36 to 152.5	Mean wheat-specific IgE was 73.8 Ucs/mL in patients with history of anaphylaxis and 24.8 Ucs/mL in patients without anaphylaxis, ($p<0.02$). No SD given

Continued

Table 2 Continued

Citation	Study group	Study type	Outcome	Key result	Comments
Sahiner <i>et al</i> ¹⁷	167 patients with history of food allergy, divided into two groups: 79 with anaphylaxis and 88 without and compared with 113 controls	Level 4 Case-control study	Serum basal tryptase levels in the groups	Median basal tryptase higher in anaphylaxis group: 4 ng/mL (2.8–5.8) anaphylaxis vs 3.6 ng/mL (2.3–4.5) (allergy) vs 3.3 ng/mL (2.4–4.4) (control) $p=0.022$	Tryptase >14.5 ng/mL. PPV 90% for severe anaphylaxis, calculated via regression curve analysis, only 4 patients in the study had a basal tryptase >11.4 ng/mL
Sicherer <i>et al</i> ¹⁸	5149 children and adults in the USA who were members of Food Allergy and Anaphylaxis Network and completed a questionnaire	Level 4 Voluntary database. Selection bias present. Self-reporting of allergy not always accurate	Characteristics of patients with peanut and tree nut allergy	Registrants with asthma reported more severe reactions (33% vs 21%; $p<0.0001$). Subsequent reaction(s) more severe than initial reaction and more likely to be treated with adrenaline ($p<0.001$)	Median age of registrant was 5 years, although adults were also included in the database. The first reaction was reported as a positive SPT for peanuts by 287 registrants. This might contribute to future reactions increasing in severity
Sicherer <i>et al</i> ¹⁹	122 children who completed a questionnaire at review in US allergy clinic with history of peanut or tree nut allergy	Level 3b Retrospective cohort study. Unclear if consecutive recruitment	Clinical features following first exposure and then any accidental ingestion of nuts	Majority had the same pattern of symptoms following accidental exposure as at initial exposure	Accidental exposure occurred in 59 patients with following subsequent reactions: skin, 44%; respiratory, 10%; GI, 3%; skin with respiratory, 18%; skin with GI, 8%; GI with respiratory, 2%; all three systems, 15%. One patient reported loss of consciousness
Spergel <i>et al</i> ²⁰	998 food challenges in children with suspected allergy to a range of foods	Level 3b Retrospective review, OFC	Does initial reaction predict future reaction?	Similar reaction to initial reaction on re-exposure during OFC in most, but 12% of patients with initial cutaneous reaction developed anaphylaxis on OFC No significant association of SPT and severe reactions	
Summers <i>et al</i> ²¹	1094 patients with history of allergy to peanuts and tree nuts seen in one UK tertiary referral centre from 1992 to 2004. Clinical history of most severe reaction analysed	Level 2 Consecutive recruitment, cohort study	Clinical features in history, total IgE, specific IgE and serum ACE levels	Severe atopy, such as uncontrolled asthma, or rhinitis was associated with severe reactions. In severe rhinitis the OR was 3.8 (2.1 to 6.9) for pharyngeal oedema. In severe asthma, OR for bronchospasm was 6.8 (4.1 to 11.3). No correlation with SPT and sIgE and reaction severity	Median age 6 years, but 24% participants were adults. Subgroup of 122 patients with sufficient serum stored analysed for serum ACE levels. If low, then there was a 9.6-fold risk of severe pharyngeal oedema, but there was likely selection bias in this group
Van Erp <i>et al</i> ¹	225 children sensitised to peanut on sIgE/SPT having DBPCFC, 48% no previous reaction to peanut	Level 2 Retrospective review DBPCFC used	Are there risk factors in history or SPT/sIgE for positive and severe food challenge outcome?	No correlation for any predictors of positive food challenge for more severe reactions	Note children with history of ITU stay following initial reaction excluded from study
Wainstein <i>et al</i> ²²	89 children referred for peanut challenge. Protocol allowed for challenge to continue despite mild symptoms developing. Only 55 who completed the OFC were included	Level 3 Prospective case-controlled study with consecutive recruitment. OFC ingesting up to 12 g of peanut	Comparison of response and history, sIgE and SPT results	History of atopy and anaphylaxis not associated with anaphylaxis in food challenge. Higher mean wheal size (10.2 mm (6.5–15.5) vs 6.7 mm (3–11.5), $p<0.0001$) and higher sIgE in anaphylaxis group (20.5 kU/L (0.86–>100) vs 0.68 kU/L (<0.37–8.5), $p<0.0001$).	21/27 peanut allergic children completing challenge developed anaphylaxis on OFC (78%). Note 40% of children included had no history of peanut reaction or ingestion and were included as they were skin prick positive to peanut

DBPCFC, double blind placebo-controlled food challenge; GI, gastrointestinal; sIgE, specific immunoglobulin E; ITU, intensive treatment unit; OFC, oral food challenge; NPV, negative predictive value; PPV, positive predictive value; SPT, skin prick testing.

The questionnaire-based population studies^{18–21} included in this study also support asthma as a risk factor for severe reactions. However, three studies looking at children undergoing food challenge^{1 12 22} show no difference in reaction severity for a history of asthma or other atopy. One explanation for conflicting results may lie in the different circumstances of the reactions, particularly the likelihood of the ingested dose of allergen on accidental exposure in the community being higher than in a typical food challenge. One study comparing allergic reactions in the community with double blind placebo-controlled food challenge (DBPCFC) finds only a weak association between reaction severity on DBPCFC and in the community.²⁵ Furthermore, population studies include children with previous anaphylaxis, whereas most food challenge research^{5 22} excludes these children for safety reasons. Another factor to consider is that asthma is a common condition, reported in 50% of children with food allergy by Spergel *et al.*²⁰ So although the questionnaire-based population studies and analysis of fatal reactions show that severe reactions tend to occur in children with asthma, as asthma is so prevalent in children with food allergies, this also means that most food allergic children with asthma will not necessarily develop anaphylaxis. It is also important to note that there is significant variation in the severity of asthma and most research does not differentiate this. Summers *et al.*, however, differentiated this variation and classified atopic children into severe or mild, depending on whether their symptoms were under control. They found that severe asthma gave a significantly increased relative risk (RR) of 6.8 for life-threatening bronchospasm in comparison with patients with milder asthma symptoms who had an RR of 2.7 for a severe reaction.²¹ This underlines the importance of achieving good asthma control in all children, particularly those with a diagnosed food allergy.

In terms of the importance of the history of reaction predicting future severity, Wainstein *et al.*²² show no association between previous reactions and severity of the reaction during food challenge. This is the only study where the food challenge protocol allowed for further challenge doses despite onset of objective symptoms, as most other protocols stop at first onset of objective symptoms. There are limitations to this study such as lack of blinding and a small sample size. However, it is interesting to note that Wainstein *et al.*²² found that 21 of 27 children, or 78% of the children who completed the oral food challenge (OFC), developed anaphylaxis. This suggests that the dose of the allergen consumed is also important in determining the reaction severity. Other much larger studies^{12 15 19 20} show a similar severity of reaction on re-exposure. Calvani *et al.*¹¹ found that the organ system affected in the initial allergy history correlated with the reaction type during acute anaphylaxis. Abdominal symptoms were associated with increased risk of collapse, a finding also noted by Hourihane *et al.*¹⁴ Spergel *et al.*²⁰ found that the overall most common reaction on OFC was cutaneous at 43%, with anaphylaxis counting for 14% of reactions. A total of 218 children had a history of initial cutaneous reaction and 56% of these children also had a further cutaneous reaction on OFC but 12% of children with an initial cutaneous reaction developed anaphylaxis on OFC, showing that a severe reaction is possible following any initial clinical presentation.

Most food challenge studies did not find that older age was significantly associated with reaction severity.^{10 22} Cianferoni *et al.*¹² found that age above 5 years had a PPV over 70 for anaphylaxis. Hourihane *et al.*¹⁴ included adults and children and found more serious reactions in adults.

In 7 of the 11 studies reviewed above which looked at level of sIgE and/or SPT wheal size, a statistically significant correlation with severity of reaction was found. However, there is a wide range of results. For example, in Hourihane *et al.*¹⁴ the range of SPT results in children with severe reactions (4–15 mm) is entirely within the range of those with mild reactions (4–20 mm). Three studies^{8 19 20} found no association and Clark *et al.*¹³ found a significant association with SPT results in severe reactions to brazil nuts only. There is some limited quality data from both Michaud *et al.*³ (level 4) and Neumann-Sunshine *et al.*¹⁵ (level 3b) that highly sensitised children with sIgE >100 kU/L for peanut report more severe reactions. Neumann-Sunshine *et al.* calculated an OR of 3.44 for anaphylaxis based on the reactions of 105 children with sIgE >100 kU/L. This suggests that children who are highly sensitised to peanuts are at higher risk for anaphylaxis. However, first, only a small proportion of children in the study are highly sensitised. Second, some children from this highly sensitised group do not go on to have severe reactions, whereas children with lower levels of sIgE do.¹⁵ Overall, despite associations of higher sIgE levels and higher SPT sizes with more severe reactions, the results are not of clinical significance for predicting future reaction severity in most children.

Component testing for sIgE to individual peanut proteins may be used in the diagnosis of food allergy to try to distinguish sensitisation from allergy with some success, although not necessarily with more accuracy than standard SPT.²⁶ Astier *et al.* hypothesised that there may be a correlation between the components to which an individual is sensitised and the reaction severity. They found that patients monosensitised to rAra h 2 on SPT have a lower disease severity score than patients who are polysensitised to rAra h 2 and rAra h 1 and/or 3 in a case-control study.¹⁰ This is the only paper looking at disease severity score and sensitisation on SPT for peanut components. Other research shows no correlation with level of sIgE for Ara h 2 and disease severity score.²⁷ As the molecular understanding of allergy increases, differentiating between allergen structures may become helpful in determining the severity of a food allergy in the future, although there is currently not enough evidence to support the use of component testing in predicting the severity of allergy.

Median basal tryptase levels were found to be higher in children with anaphylaxis in a case-control study (level 4 evidence) by Sahiner *et al.*¹⁷ However, there was significant overlap in levels between cases and controls and only four children had high tryptase levels, two of whom were non-allergic controls. There is currently not enough evidence that this test will help predict an individual's reaction severity.

In summary, although SPTs and blood tests may be useful in the diagnosis of food allergy, there are currently no tests that will accurately predict which children will go on to develop a severe allergic reaction.

Given the difficulty in predicting future reactions, it is important to educate families about food allergy. Some of the studies reviewed above rely on accidental exposure for their data on reaction severity and report high rates of postdiagnosis exposure, up to 50% over approximately a 5-year period.^{15 19} Avoidance of food allergens is clearly difficult for children and their families. Following accidental exposure, only low numbers of patients (34%) with severe reactions had adrenaline administered.¹⁵ Patient education is therefore the key clinical priority, as highlighted in a recent review on predicting reaction severity in peanut allergy.⁶

Clinical bottom line

- We cannot accurately predict which children with food allergy will have severe reactions in the future.
- The patient described above should have a thorough history taken and skin prick testing and specific immunoglobulin E testing, as per National Institute for Health and Care Excellence guidelines, to confirm the diagnosis.
- Following diagnosis of a food allergy, it is important to educate the family concerning allergy avoidance and management of accidental exposure.

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