

How to use serum-specific IgE measurements in diagnosing and monitoring food allergy

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Background

Hypersensitivity (adverse reaction) to a food can be broadly divided into allergic hypersensitivity (food allergy) and non-allergic hypersensitivity (food intolerance).¹ Food allergy is defined as an adverse immune response to a food allergen, whereas food intolerance is generally non-immune mediated. Food allergy can be subdivided into two main categories: IgE-mediated and non-IgE-mediated food allergy. The differences between the two are shown in table 1. Food intolerance incorporates several other adverse reactions to foods. These include toxic contaminants in food (eg, histamine in scombroid fish poisoning), pharmacological properties (eg, tyramine in aged cheese or caffeine), host characteristics (eg, lactase deficiency) and food aversion.

Food allergies are common in the paediatric population, with up to 8% of young children affected by IgE-mediated reactions.²⁻⁴ Furthermore, up to a third of parents report their child having a food-related problem within the first 3 years of life, although many prove not to have food allergy.⁵ Health professionals working with children will therefore regularly encounter suspected adverse reactions to food, including food allergy, and therefore need to understand how to evaluate this problem.⁶

Diagnosing food allergy

Medical history is essential and is often the most helpful diagnostic modality. It ultimately aims to identify whether an allergic food reaction has occurred and identify the most likely allergens to direct testing. Box 1 shows vital questions in establishing whether the adverse reaction to food may be IgE mediated.

A diagnosis based on history alone has been found to be accurate in only about

half of the cases. Investigations such as skin prick tests (SPTs) and sIgE levels are therefore required to optimise the diagnostic process. sIgE has the advantage of being widely available to health professionals and being available for a huge variety of allergens. SPTs on the other hand are cheaper, with results being available almost immediately. Training in SPT is required, and food extracts have yet to be standardised. sIgE and SPT have a role in the diagnosis of IgE-mediated food allergy only and do not provide diagnostic information for non-IgE-mediated allergy. The most common IgE-mediated food allergens are shown in box 2. This article will focus only on IgE-mediated food allergy testing using sIgE. For further elaboration on the diagnosis of food allergy in children, we would recommend the recently published National Institute for Health and Clinical Excellence (NICE) guideline.⁷

The physiological basis of specific IgE

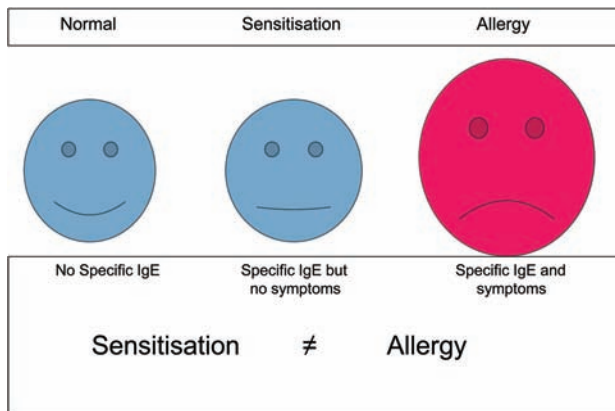
Exposure to environmental antigens occurs by means of inhalation, ingestion, cutaneous or parenteral contact. Once taken up by the antigen-presenting cells, the processed antigen is presented to T helper cells. This results in a complex interaction between T cells, secreted cytokines and chemokines and B-cell lymphocytes. In some cases, B-cell proliferation ensues, and in certain genetically at-risk individuals, sIgE antibodies are produced. Performing an sIgE test will identify circulating sIgE antibodies in the serum and indicates that a patient is 'sensitised' to that allergen. Although patients may be sensitised to an allergen, they may not necessarily have a clinical allergy to it (figure 1).

When a patient is clinically allergic, IgE antibodies will be found bound to high-affinity Fcε receptors on the surface of mast cells so that allergen exposure leads to mast

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Table 1 Differences between IgE- and non-IgE-mediated food allergy^{7 13}

	IgE mediated	Non-IgE mediated
History		
Onset of symptoms	Within 2 h of ingestion	Generally hours or days postingestion
Resolution of symptoms	Usually resolve within 12 h	May continue for many days
Symptoms	Gastrointestinal such as vomiting, pain and diarrhoea Cutaneous such as urticaria, angioedema, pruritus Respiratory such as acute rhinoconjunctivitis, wheezing, coughing, stridor Cardiovascular such as collapse as a result of hypotension	Often non-specific symptoms. These can include diarrhoea, vomiting, colic/pain, blood in the stool, gastroesophageal reflux and food refusal or aversion
Diagnostic tests	Serum-specific IgE ('RAST'), skin prick test, open food challenge	Elimination diet (2–6 weeks) followed by reintroduction
Examples of clinical phenotypes	Acute urticaria and angioedema, anaphylaxis, oral allergy syndrome	Food protein-induced proctocolitis, food protein-induced enterocolitis syndrome, food protein-induced enteropathy, allergic dysmotility

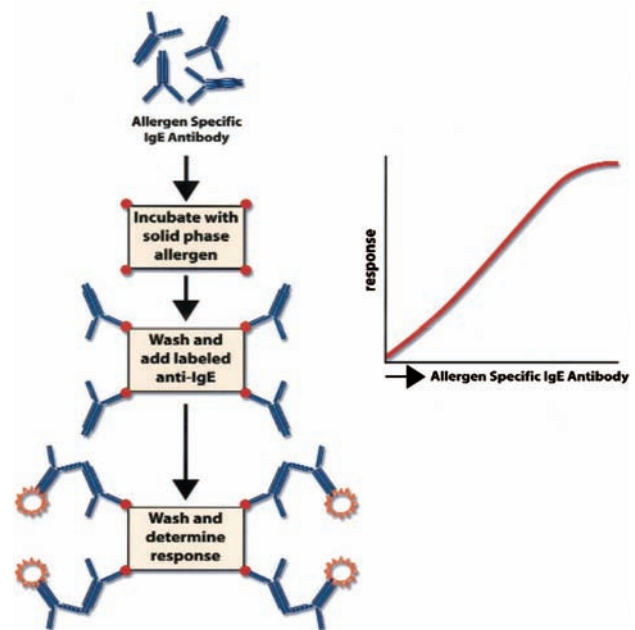
**Figure 1** Clinical allergy versus sensitisation. Modified from a figure described by Dr Louise Michaelis and Dr Helen Cox.

cell activation and the release of preformed mediators (eg, histamine) and newly synthesised mediators (eg, prostaglandins and leukotrienes). This, in turn, leads to the symptoms described in table 1, which are typical of an IgE-mediated allergic reaction.

The sIgE test therefore identifies a state of sensitisation and cannot be used alone for the diagnosis of IgE-mediated allergy because just having serum sIgE does not mean that a child is clinically allergic. When the sIgE results are interpreted in conjunction with a clinical history, it is possible to assess whether or not a patient's presentation represents a clinical allergy.

Technological background

The Phadebas radioallergosorbent test (RAST) was the first assay for the detection of allergen-specific IgE antibodies, which is why the investigation is still commonly called 'RAST'. It involves the incubation of a patient's serum containing allergen-specific antibodies of all isotypes. These specific antibodies will bind to the particular allergen that has been insolubilised onto

**Figure 2** The Phadebas RAST test.¹¹

the solid phase. This is then washed, and radiolabelled anti-human IgE is added. This process quantifies the IgE-specific antibodies to the allergen being investigated (figure 2).

This early allergen-specific IgE antibody assay has now evolved with several technological advances into three different autoanalyser-based allergen-specific IgE antibody assays. These are the ImmunoCap (Phadia, Uppsala, Sweden), the Immulite system (Siemens, Frimley, UK) and the HYTEC-288 system (Hycor/Agilent Technologies, Edinburgh, UK).⁸ All three autoanalysers use non-isotypically labelled anti-human IgE and are calibrated using the same reference data. Although there is improved intermethod agreement

		Likelihood of clinical allergy from specific IgE (KU/L)		
		Low (<0.35)	Intermediate (0.35 to <15)	High (≥15)
Likelihood of clinical allergy from history	High, eg urticaria and wheeze on 2 exposures	Possible allergy	Probable allergy	Allergy
	Intermediate, eg urticaria on a single exposure	Possible allergy	Possible allergy	Probable allergy
	Low, eg non-IgE symptoms	No allergy	Possible allergy	Possible allergy

Figure 3 Schema for paediatricians to use when considering food allergy as a diagnosis.⁹ Children and adolescents in the possible allergy box require an OFC for a definitive diagnosis. Specific IgE values specific for peanuts and tree nuts. Values associated with a high likelihood of clinical allergy are lower for egg, milk and fish (see table 2). Modified from an original design described by Dr Tom Blyth.

among reported IgE antibody results, the specific IgE antibody levels reported by each of these systems are still not directly comparable. Most of the studies referenced in this article have used ImmunoCap.

Interpretation of serum-specific IgE tests

As a general rule, sIgE must be interpreted in the context of the clinical history and not in isolation.⁹ Furthermore, the larger the sIgE, the greater the likelihood that a child has an IgE-mediated allergy. Unfortunately, the severity of the allergy is not related to the sIgE result.

There has been a significant number of studies identifying the values of sIgE that have a positive predictive value (PPV) of 95% for whether a child has an allergy to egg, milk, peanuts, tree nuts or fish using double-blind placebo-controlled food challenges as the gold standard (table 2). These 95% PPVs have proved useful in aiding diagnosis and reducing the number of open food challenges (OFCs) performed. However, a significant proportion of children undergoing this investigation do not have results that are equal or above the 95% PPV. Many children therefore fall into an 'immunological grey zone' where a diagnosis cannot be made with certainty.

Patients with specific IgE results at or above these levels, in the referenced studies, had a 95% chance of clinical allergy. These values will vary with the prevalence of food allergy in the population being tested.

Specific test results can be linked with a specific probability of allergy. However, this probability is heavily influenced by the clinical context, which determines the prevalence of allergy in the specific patient group that is being tested. It is therefore essential that the results of the investigations are interpreted in the context of the clinical history. From the history, it is

possible to estimate the likelihood of a patient having a clinical allergy before the sIgE test is undertaken (pretest probability). Factors that might increase this pretest probability are a short time between contact and symptoms, typical IgE-mediated symptoms and a history of repeated stereotypical reactions with a particular food.

From the estimated pretest probability and the specific likelihood ratio associated with each sIgE test result, the chance of a patient having an IgE-mediated food allergy can be calculated using Fagan's nomogram.¹⁰ This provides greater diagnostic accuracy but is seldom used in clinical practice, probably because it is time consuming and impractical. A simpler approach is to integrate the clinical history and sIgE result using a three-by-three table where each is trifurcated into high, intermediate and low likelihood of clinical allergy (figure 3). This allows the sIgE result to be interpreted in the clinical context as defined by the clinical history. This schema acknowledges that the test results are not always diagnostic and that some patients will need an OFC to confirm a diagnosis.

Clinical questions

Can sIgE tests be used in conjunction with a clinical history to make an accurate diagnosis of IgE-mediated food allergy in a 3-month-old child?

There is often a debate as to the youngest age when sIgE can be used. It is evident that in healthy children, total IgE levels start to increase in the first 6 weeks of life, and it continues to increase progressively up to 10 to 15 years of age.¹¹ There is evidence that specific IgE to milk, egg, fish and peanuts from children (aged 3 months to 14 years) referred for food allergy evaluation can correctly identify greater than 95% of food allergies.¹² This suggests that sIgE can be useful at least from 3 months of age. As at any age, a negative test cannot rule out food allergy in the presence of a suggestive history.

Ruling in IgE-mediated allergy

In children with suspected peanut allergy based on history alone, what is the additional role of sIgE tests in correctly ruling in a diagnosis (see case 1, box 3)?

Clinical history is the cornerstone of making a diagnosis. The history of two adverse reactions to peanuts has an 80% pretest probability of the child, in clinical case 1 (box 3), having a peanut allergy.² A peanut sIgE of 22 kU/l makes the diagnosis of peanut allergy extremely likely (greater than 95% probability) and therefore an OFC would not be required to confirm the diagnosis (figure 3). Similarly, in the presence of a suggestive history, an sIgE result of 10 kU/l would also strongly suggest peanut allergy and make a peanut challenge unnecessary, although the sIgE result is less than the 95% PPV for a positive food challenge. Conversely, an undetectable sIgE (<0.35 kU/l) can also occur in children with IgE-mediated food allergy, albeit rarely. Therefore, in cases where the history is highly

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Table 2 The 95% positive predictive values for serum-specific IgEs for various allergens^{2 12 20 28–30}

	Specific IgE levels (IU/ml) associated with 95% PPV
Egg	≥7
Egg (infants ≤2 years)	≥2
Milk	≥15
Milk (infants ≤2 years)	≥5
Peanuts	≥15
Peanuts (infants ≤2 years)	–
Tree nuts	≥15
Fish	≥20

PPV, positive predictive value.

Box 1 Important information to extract from the history³¹

1. The food responsible for the reaction
2. The quantity of suspected food ingested
3. The length of time between ingestion and development of symptoms (<2 h if IgE-mediated food allergy)
4. Whether similar symptoms occurred when the food was eaten previously
5. Whether other factors (eg, exercise) are necessary
6. When the last reaction to the food occurred

Box 2 Common food allergens in children and adolescents

Peanut
Tree nuts
Cow's milk
Hens' eggs
Soya
Wheat
Fish
Shellfish
Sesame seeds

suggestive, but the sIgE levels are very low, further evaluation is necessary before confirming whether or not the patient has a food allergy.¹³ This will therefore require SPT and perhaps a supervised OFC.

In a child with a history of possible peanut allergy, is there a role for sIgE in correctly making a diagnosis (see case 2, box 4)?

With a careful history and knowledge of the most common food allergens (box 2), the most likely causes for the allergic reaction can be identified and tested using sIgE. Case 2 (box 4) is an example where there is a history of an immediate allergic reaction, although the cause is not clear. A detailed history revealed that peanuts, sesame and egg were present as well as balloons, and

Box 3 Case 1

A 4-year-old boy with eczema that started at 6 months of age presented to a paediatric clinic with a history of a 'nettle rash' all over his body, lip swelling and wheezing within 5 minutes of a bite of a peanut butter sandwich on two occasions. sIgE was tested to peanuts, tree nuts and sesame. The peanut sIgE was 22 kUA/L.

Box 4 Case 2

A 3-year-old child, with an egg allergy that was diagnosed by her local paediatrician at 9 months of age, had a reaction to an unknown food while at her older brother's birthday party. She experienced an itchy blotchy rash on her face and later all over the body. Her mother was concerned that this might have been caused by exposure to peanuts. Her mother was sure she had consumed no egg-containing foods. Given the context of the reactions, sIgE was performed to egg, nuts, sesame and latex. The sIgE to egg was 9 and 4 kUA/L to peanut.

Box 5 Case 3

A 2-year-old child has been referred to the allergy clinic as his mother is concerned he may have a peanut allergy. His elder brother has had an anaphylactic reaction to peanuts in the past and has been diagnosed with peanut and tree nut allergies. As a result of this, peanuts have never been introduced into his diet. His specific IgE to peanuts was <0.35 kUA/L.

Box 6 Case 4

A parent is concerned that their 5-year-old child has food allergy because the child developed symptoms of bloating and abdominal pain, which seem to be related to eating dairy and wheat. The symptoms usually develop several hours after ingestion. The general practitioner (GP) has referred this patient to you requesting allergy tests to evaluate this further.

therefore, the potential allergens were identified and tested. Although sIgE was positive for peanuts, the result was in the intermediate, 'immunological grey zone'. By using the schema in figure 3, it can be suggested that this child has 'possible' peanut allergy. Because there is diagnostic uncertainty, a supervised OFC is required to rule in or rule out a peanut allergy. The gold standard is considered to be a double-blind placebo-controlled food challenge; however, OFCs are regularly performed because the former are impractical, more time consuming and costly. Where available, an SPT to peanut may help to rule in a peanut allergy without a challenge. Incidentally, the investigations also reveal that this child is still likely to be egg allergic because the results are above the 95% PPV (table 2).

Box 7 Case 5

A 3-year-old girl was diagnosed with egg allergy at 2 years of age and had an initial sIgE of 14 kUA/L. Her mother has successfully eliminated all egg from her diet except on one occasion. Ten months previously, she had some cake mixture and developed lip swelling and an urticarial rash. Her specific IgE to egg is now 5 kUA/L.

Box 8 Case 6

A 9-month-old girl is referred to you because of moderate to severe eczema that has not responded to conventional treatment. Her mother is worried that food may be making her eczema worse.

sIgE measurements have limitations in aiding a diagnosis of food allergy when there is uncertainty in the history and the sIgE result falls into the 'immunological grey zone'. However, in the context of a convincing history of an IgE-mediated reaction with a specific allergen, even a low sIgE result would be sufficient to make a diagnosis and a challenge would not be required (figure 3). Knowing the absolute value of sIgE rather than the grading system (grades 0–6) in which sIgE levels are often quoted is of vital importance. The diagnostic investigations would vary significantly depending on this. For instance, in this case, the sIgE result would equate to a grade 3 sIgE to peanut, which would cover sIgE values of 3.5 to 17.5 kU/l. A result of 4 kU/l would result in diagnostic uncertainty as discussed above, whereas an sIgE of 17.5 kU/l for peanut, in conjunction with the history in this case, would support a diagnosis of peanut allergy and an OFC would not be required.

Ruling out IgE-mediated allergy

In a child with possible peanut allergy, is sIgE more effective than just history alone in correctly ruling out a diagnosis (see case 3, box 5)?

This case is a common presentation. Siblings of children with peanut allergy have an increased risk for peanut allergy. The prevalence of peanut allergy has been shown to be 7 to 8.5% compared with a background of 1 to 1.7% in two studies.^{14 15} If case 3 was applied to figure 3, then there would be a low likelihood of peanut allergy based on clinical history. When this history is coupled with the negative sIgE, this child can be seen to be unlikely to have a peanut allergy. In fact, the risk for peanut allergy would be lower than that in the general population and therefore a food challenge is not required in this scenario to exclude a diagnosis of peanut allergy. However, if the sIgE was increased (>0.35 kU/l), and there was no history of previous ingestion, SPT or perhaps a supervised OFC may be required to diagnose whether the individual has a peanut allergy.

Clinical summary

- ▶ Serum-specific immunoglobulin E (sIgE) is a widely available test used to support a diagnosis of IgE-mediated food allergy and a method for monitoring resolution of allergy.
- ▶ The interpretation of sIgE must be taken within the context of the history.
- ▶ A positive sIgE indicates sensitisation to a specific food. This does not necessarily equate with clinical allergy.
- ▶ If there is clinical doubt after the history and sIgE, a supervised open food challenge (OFC) should be performed to make a definitive diagnosis.
- ▶ The result of the sIgE does not correlate with the severity of the clinical reaction. However, the higher the sIgE, the greater the likelihood of clinical allergy.

In general, children with moderate or severe eczema, egg allergy, or siblings with a peanut allergy all have an increased risk for developing peanut allergy. If there is a definite history of a child tolerating peanuts, then an sIgE to peanut would not be required because peanuts are already tolerated in the diet. However, in the absence of ingestion of peanuts or parental anxiety about peanut introduction, sIgE may be helpful.

In a child without a history consistent for an IgE-mediated allergy, is there a role for sIgE testing compared with history alone in confidently ruling out a diagnosis of IgE-mediated food allergy (see case 4, box 6)?

Before embarking on investigation, it is essential for the clinician to take an allergy-focused history.¹⁶ Non-IgE-mediated allergy and alternative diagnoses need to be considered in case 4 (box 6). Performing an sIgE test when an IgE-mediated food allergy is not suspected is rarely helpful because the negative predictive value of an sIgE <0.35 kU/l is not 100%.² Furthermore, an sIgE >0.35 kU/l may result in unnecessary dietary exclusions if it is assumed to indicate clinical allergy. Any positive sIgE would necessitate an OFC to rule out the diagnosis of an IgE-mediated allergy, which was anyway unlikely given the initial clinical history. This case is an example of a clinical history not consistent with an IgE-mediated food allergy and thus sIgE testing is not warranted. A careful evaluation would be required to consider alternative diagnoses, including non-IgE-mediated allergy and coeliac disease.

Monitoring IgE-mediated food allergy

Does sIgE in conjunction with a history provide a more accurate assessment of outgrowing egg allergy compared with history alone (see case 5, box 7)?

Monitoring children with egg allergy, such as in case 5, is important because data suggest that 66% of children will have resolution of their egg allergy

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Quiz

QUESTION 1

Which statement is true?

- A. A serum-specific IgE <0.35 kUA/L to a specific food means that a child does not have an IgE-mediated food allergy
- B. If there is a good history of an IgE-mediated reaction but the sIgE is negative, the child can eat the food in question
- C. Irrespective of the sIgE result, if there is a good clinical history of an IgE-mediated food allergy and there is diagnostic doubt, an OFC should be performed to confirm or disprove clinical allergy
- D. sIgE can be interpreted in isolation of clinical details

QUESTION 2

Which statement is false?

- A. An sIgE can be performed if the food in question has never been ingested
- B. An sIgE should not be performed if there is a history of non-IgE-mediated allergy
- C. An sIgE can be performed to monitor whether a child is 'growing out' of a food allergy and to help decide whether an OFC should be performed
- D. An sIgE can be performed as a reliable screening test for food allergy

QUESTION 3

A 5-year-old girl with egg allergy has a decreasing sIgE over the last 2 years from 14.5 to 5 kUA/L. Which statement is true?

- A. She has a 50% chance of being tolerant to egg
- B. If she had a reaction to egg, the reaction will be less severe
- C. She will be able to tolerate baked egg, but not raw egg
- D. She has outgrown her egg allergy

Answers to the quiz are on page 39

after 5 years of follow-up.¹⁷ The resolution of their allergy tends to occur in stages. Initially, children tolerate cooked egg, followed by lightly cooked egg and finally raw egg.¹⁸ A review of reactions to egg or perhaps tolerance to egg in the preceding year in conjunction with sIgE or SPT or both is helpful in determining whether tolerance is likely to have been achieved.

In case 5 (box 7), the mother was keen to introduce biscuits and cakes that contained well-cooked egg because her daughter had significant dietary restrictions and was starting nursery. In this case, there had been a greater than 50% reduction in her sIgE. Clinical data suggest that, in these situations, children have a 50% probability of having tolerance to egg.¹⁹ It was therefore felt to be reasonable to undertake a cooked or baked egg supervised OFC. She had no reactions and was able to introduce cooked egg into her diet. A raw egg challenge was not performed at this point because, with a recent reaction to raw egg in a cake mix, she was likely to be still be allergic to raw egg.¹⁸

In children with egg, milk or peanut allergy without a history of ingesting cross-reacting allergens, does sIgE correctly rule out associated food allergies?

Allergy testing is valuable not only in supporting the diagnosis but also in considering coexisting allergy. In peanut allergy, up to 60% will be allergic to one or more tree nuts and 25% will be allergic to sesame.²⁰ Similarly, children with egg allergy have a 20% chance of having peanut allergy, whereas 10 to 14% of children with an allergy for cow milk have soya allergy.²¹ As stated earlier, performing sIgE in the absence of a clinical history of exposure may be helpful. The results do however need to be interpreted with caution and may require further evaluation with SPT and OFC.

Infantile eczema

In an infant with moderate to severe eczema, are sIgEs a more accurate way of making a diagnosis of coexisting food allergy compared with history alone (see case 6, box 8)?

Again, in this clinical case, it is essential to take an allergy-focused history. In the context of moderate to severe eczema, where coexisting food allergy is relatively frequent (30–40%),^{22–23} an sIgE equal to or greater than 95% PPV (table 2) makes a diagnosis of food allergy extremely likely. In a more highly selected group of patients with severe atopic eczema, the prevalence of food allergy is up to 60%,²² meaning the same increased sIgE is even more likely to indicate clinical allergy. If the sIgE is only slightly increased, it is unclear whether or not the child is food allergic and therefore an OFC is indicated. However, if the infant is tolerating the food with no history of an IgE-mediated food allergy, then an sIgE should not be performed. If an sIgE has been measured and is increased, the food should not be excluded if it is already tolerated in the diet with no history of an adverse reaction. A negative sIgE is likely to rule out a diagnosis of IgE-mediated food allergy; however, in moderate to severe eczema, non-IgE-mediated allergy may play a significant role and should also be considered.

With the low rate of food allergy in mild eczema, false-positive results are common, meaning that without a specific history suggestive of IgE-mediated food allergy, the tests should not be performed.

Limitations

A minority of children with low levels of food sIgE have clinical allergy.²⁰ If a patient has a history suggestive of an IgE-mediated food allergy but a negative sIgE, a supervised OFC should be performed because this remains the gold standard for diagnosing food allergy. In addition, sIgE can be positive to a food in the absence of clinical allergy. sIgE tests are therefore not effective screening tools and their use must be guided by the clinical context. Where a patient has a weakly positive sIgE result to a food that he or she is not consuming, further evaluation is required with an SPT if available or an OFC is required to rule out

clinical allergy. Finally, sIgE levels can only predict the likelihood of a reaction and not the severity of any reaction.

Future research

sIgE results often fall into the 'immunological grey zone', and therefore, it is essential to consider the history when interpreting the test. However, better tests or models are required to predict clinical allergy without the need of a costly OFC. One group has tried to address this question by developing a model to predict OFC outcome for egg, milk and peanut more effectively than sIgE and history alone.⁹ They examined the predictive ability of six clinical factors: SPT, sIgE, total IgE, symptoms, sex and age.⁹ A model was developed that was able to predict the outcome of the OFC with a 93% accuracy for PN, compared with 61% for sIgE. This approach now needs to be replicated in other population to ensure that it is valid in other clinics.

Another area of interest has been the use of component resolved diagnostics (CRD). For instance, traditional peanut sIgE looks at all peanut allergens, which currently include nine peanut allergens (Ara h 1 to Ara h 9). CRD allows for the identification and quantification of these individual allergens and thus investigate whether they have additional diagnostic value. Many studies have started to evaluate CRD. One study investigated whether CRD could differentiate clinical peanut allergy from peanut sensitisation with tolerance.²⁴ The group identified marked differences in the pattern of component recognition between children with peanut allergy and children tolerant, but sensitised. The peanut component Ara h 2 was the most important predictor of clinical allergy. The CRD approach needs to be replicated in other populations but promises to deliver a further step change in the diagnosis of food allergy.

Conclusions

The above cases have demonstrated that the interpretation of sIgE must be taken in the context of the clinical history and not in isolation. sIgE is an important investigation in the diagnosis and monitoring of resolution of IgE-mediated food allergy. sIgE results are not always diagnostic and sometimes an OFC is required to diagnose or rule out allergy. Finally, after being diagnosed as having food allergy, the patient needs a personalised management plan covering avoidance and managing any subsequent reactions, and both the patient and his or her family need training to successfully implement the plan.²⁵⁻²⁷

Competing interests None.

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