



REVIEW ARTICLE

Egg allergy: An update

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Abstract: Egg allergy is the commonest infant food allergy both in Australia and world-wide. The clinical presentation of egg allergy is varied – egg is involved in both IgE and non-IgE-mediated allergic reactions and has been implicated in conditions such as anaphylaxis, food protein-induced enterocolitis syndrome, atopic dermatitis and eosinophilic oesophagitis. The clinical presentation, pathophysiology and diagnosis as well as the natural history and management of egg allergy will be discussed. Current theories about primary prevention as well as potential future therapies are presented. Finally, practical information about egg allergy and immunisation is provided.

Key words: allergy; anaphylaxis; egg; food.

Introduction

Egg allergy is one of the most common food allergies in infants and young children.¹ Global data indicate that egg allergy affects 0.5–2.5% of young children.¹ A recent population-based study has shown that Australia has the highest reported prevalence of infant egg allergy to date at 8.9%.²

The clinical presentation, pathophysiology and diagnosis as well as the natural history and management of egg allergy will be discussed. Updated information on immunisation and egg allergy as well as future therapy is presented.

Pathogenesis

Egg allergy is defined as an immunologically mediated adverse reaction to egg induced by egg protein which includes IgE-mediated allergy and non-IgE-mediated allergy.

Most allergic food reactions are IgE mediated (type I allergic reactions) and are characterised by the presence of specific IgE antibodies to egg protein allergens.

The five major allergens identified in hens eggs are ovomucoid (Gal d1), ovalbumin (Gal d2), ovomucoid (Gal d3), lysozyme (Gal d4) and albumin (Gal d5). The majority of

allergenic proteins are contained in egg white (Gal d 1–4) rather than in egg yolk (Gal d5). Ovomucoid is resistant to heat and digestive enzyme degeneration so it is the most allergenic protein, whereas ovalbumin is the most abundant protein.^{3–5}

IgE-Mediated Allergies

IgE-mediated allergic reactions are the most common manifestation of egg allergy in children and usually present in the first year of life. The mean age of 10 months typically coincides with introduction of egg into the infant's diet.⁶ Reactions usually occur at first known egg exposure, especially in children with coexisting atopic dermatitis (AD).⁷ Onset of symptoms can occur within minutes of egg consumption and can present up to 2 h after ingestion. Reactions are commonly characterised by urticaria, vomiting and angioedema. Egg can cause anaphylaxis, with respiratory and/or cardiovascular symptoms such as cough, wheeze, chest and throat tightening, hypotension, and collapse and is reported as the trigger in 7–12% of all paediatric anaphylaxis presentations.^{8,9} Fatal cases of anaphylaxis to egg are rare but reported.^{7,10,11} Egg has also been implicated in cases of food-dependent exercise-induced anaphylaxis.¹²

Increasingly, egg allergy is recognised as a spectrum of presentations with some individuals who are clinically allergic to all forms of egg (raw, cooked and baked) and others who are allergic only to raw or partially cooked egg.¹³ The majority of egg allergic children (65–81%) can tolerate egg in a baked product such as a muffin.^{14–16} This is because extensive heating during the baking process reduces allergenicity of the protein and may reduce the access to the allergen by interaction with the food matrix.¹⁷ Children who are allergic to egg have an increased risk of a coexistent peanut sensitisation.¹⁸

Diagnosis of IgE-Mediated Egg Allergy

The diagnosis of egg allergy relies on clinical history. A positive test in the absence of a clinical history has to be interpreted with caution because it may indicate sensitisation rather than a

Key points

- Egg allergy is one of the most common childhood allergies world-wide and can cause anaphylaxis; it is usually outgrown before 10 years of age but may persist in some individuals.
- Egg is involved in IgE and non-IgE mediated allergies.
- Measles mumps rubella vaccination is not contraindicated in egg allergy.

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clinical allergy. Serum-specific IgE (ssIgE) and skin prick testing (SPT) are used to support a positive history in the diagnosis of IgE-mediated egg allergy. SPT size or ssIgE value can be useful in determining the likelihood but not the severity of an IgE-mediated egg allergy. In other words, the larger the wheal size or the higher the ssIgE, the greater the likelihood of a clinical reaction. The risk of anaphylaxis cannot be predicted using either of these parameters. Although many studies have reported 95% positive predictive values (PPV) for both SPT and ssIgE for clinical allergy to egg,^{19,20} the pre-test probability, most importantly prevalence, can significantly influence the PPV threshold. Moreover, many patients have an SPT or ssIgE below the 95% PPV. For all these reasons, clinicians should interpret SPTs and ssIgE in the context of locally generated data and on the pre-test probability of IgE-mediated egg allergy in that particular patient.

Neither the size of the SPT to egg (white or yolk) or the ssIgE to egg is a good predictor of allergy to baked egg. A recent study reported that a ssIgE to ovomucoid at a level of 11 kUA/L indicated a high risk of reaction to both heated egg white (heated at 90° for 60 min, not baked in a matrix) and whole raw egg. A concentration of less than 1 kUA/L indicated a low risk of reacting to heated egg.²¹

Double blind, placebo-controlled food challenges are the gold standard for diagnosis of food allergy; however, for practical reasons, open food challenges are usually performed for young children in Australia. Food challenges are considered when there is no clear recent history of a clinical allergic reaction to egg and/or when there is a small SPT or low ssIgE. Challenges may also be used to assess whether a child has outgrown an allergy. Additionally, they are used to ascertain whether the egg allergic child can tolerate egg in a baked product. Egg challenges serve an important role in management, with a reported significant reduction in anxiety in parents of children who had undergone an egg challenge regardless of whether the challenge outcome was positive or negative.²²

Food challenges can be associated with severe reactions and should only be performed by professionals experienced in the recognition and treatment of food allergic reactions with appropriate resources available to treat anaphylaxis.

Cross Reactivity

Serological and clinical cross reactivity with other bird eggs such as turkey, duck, goose, seagull and quail are common in hens' egg allergy, making these eggs unsafe for the majority of egg-allergic individuals.²³ Rarely, patients also react to chicken meat. Chicken serum albumin (Gal d5) has been found to be responsible for this cross reactivity.²⁴

Management

Traditionally, children with egg allergy have been advised to avoid all forms of egg because of the belief that strict avoidance of food allergens would increase the likelihood and time to attainment of tolerance to egg. Avoidance was also thought to be the safest option for the child. This approach is now under question for several reasons.

In egg allergy, a high percentage of children do tolerate egg in baked products; therefore, a food challenge to extensively

heated egg may be considered by an allergy specialist if a patient is not currently eating egg in this form. If the baked product is tolerated, the child's diet can be liberalised, and the anxiety about a severe reaction to egg in a baked product is reduced. Caution is needed because severe reactions can occur from this type of challenge.¹⁴ Even if tolerance to egg in a muffin is established, it is possible that a patient may have a reaction caused by ingestion of a larger amount of egg or more lightly cooked egg than they ate in the challenge. Strict guidelines about which types of foods containing egg can safely be eaten should be discussed. The notion that strict avoidance speeds up tolerance is unlikely to be true. This is discussed in more detail in the next section.

Although still controversial, ingestion of modified allergic proteins has been suggested as a possible therapy for acceleration and/or induction of tolerance in food allergy. Two recent studies have reported that dietary inclusion of baked egg accelerated the resolution of egg allergy in children;^{15,25} however, both studies lacked a placebo-controlled group and included individuals who were sensitised but did not have clinically proven egg allergy. In support of this possibility, egg-allergic children who are given egg in a baked product do develop immunologic changes that are consistent with changes seen in children who have had resolution of their allergy either naturally or with oral immunotherapy.¹⁴ Randomised double-blind placebo-controlled trials are needed to establish whether baked egg products can be used as a therapy for egg allergy.

All egg allergic individuals should be taught to read food labels and recognise which foods are likely to contain eggs. Ideally, a dietician should be involved in the child's care, especially if there are multiple food allergies.

All children with an IgE-mediated egg allergy should be provided with an allergy plan (Australasian Society of Clinical Immunology and Allergy (ASCIA)) that advises what constitutes a mild, moderate and severe allergic reaction, and provides a clear plan of action in the event of inadvertent exposure. The decision regarding prescription of an adrenaline auto-injector should be discussed with the child's individual allergy specialist or their paediatrician with reference to current ASCIA prescribing guidelines. (http://www.allergy.org.au/images/stories/anaphylaxis/2012/ASCIA_Guidelines_adrenaline_autoinjector_script_2012.pdf).

They should be advised to avoid all egg unless it is established that they can safely ingest egg in a baked form. Re-evaluation is advised approximately yearly.

Future Therapies

Desensitisation for individuals with food allergy has been practiced in since the early 1900s, but safety and efficacy have only recently been established.

A number of promising egg oral immunotherapy trials have been recently undertaken, with the largest recent study reporting oral immunotherapy could desensitise a high proportion of children with egg allergy and induce sustained unresponsiveness in 11 of the 40 children who were treated. However, there is a possibility that these results reflect the natural history of the disease and that treated children could have spontaneously outgrown their allergy given the control group did not undergo exit

challenges.²⁶ Concerns about safety of oral immunotherapy as well as induction of sustained tolerance versus desensitisation persist, and this type of therapy is not yet recommended for routine clinical use.

Sublingual immunotherapy and subcutaneous immunotherapy are also underway but are in the early phases of development as a potential therapy.

Natural History

Regular re-evaluation is required as both IgE and non-IgE mediated egg allergy are usually outgrown. Previously, it was thought that IgE-mediated egg allergy was outgrown by children of early school age. Earlier studies indicated that tolerance was achieved in 50% of egg-allergic children by age 3 years and 66% by age 5 years.²⁷ More recent studies from a tertiary referral centre indicate that egg allergy appears to be more persistent in this highly selected population with a predicted tolerance of 4% by 4 years, 12% by 6 years, 37% by 10 years and 68% by 16 years.^{4,28} The factors that favour development of natural tolerance include: lower specific IgE,²⁹ milder initial reaction,¹⁴ smaller SPT diameter wheals,²⁷ faster rate of decline of specific IgE,¹⁴ absence of atopic disease or coexistent food allergies²⁸ and earlier age of diagnosis.²⁹

Non-IgE-Mediated Egg Allergy

Non-IgE-mediated egg allergy observed in a number of complex atopic disorders include:

AD

Non-IgE-mediated allergy to egg may play a role in a small number of individuals with AD. It is characterised by a clinical flare of the AD typically between 4 and 48 h following ingestion and is postulated to be T cell mediated.³⁰ In a small study, Lever *et al.* reported an improvement in AD following egg elimination, particularly in those subjects with pre-existing IgE sensitisation to egg.³¹ Food elimination (including egg) should only be performed in carefully selected AD patients who have a sufficient degree of AD to justify dietary manipulation. The risk of anaphylaxis on re-exposure following removal of any food from the diet should be appreciated, especially for those children with egg IgE sensitisation but clinical tolerance.

Eosinophilic oesophagitis (EoE)

Egg is an important trigger in EoE,³² an oesophageal inflammatory disorder characterised by the infiltration of eosinophils that is thought to be a consequence of local IgE and local and systemic non-IgE-mediated process.^{32,33} Removal of egg from the diet in patients with EoE has been shown to improve clinical symptoms and to reduce eosinophilic infiltration. Egg may be removed as part of a '6' food elimination diet in some patients with EoE.

Food protein-induced enterocolitis syndrome (FPIES)

Egg can also be the culprit allergen in FPIES^{34,35} where an infant typically presents with profuse vomiting, diarrhoea and intra-

vascular volume depletion 2–4 h following egg ingestion. FPIES has been reported to be induced by baked as well as whole egg.³⁵ The natural history in these cases appears to be for natural resolution by age 2–3 years. Food protein-induced enteropathy to egg from maternal breast milk causing hypogammaglobulinaemia has been reported.³⁶

Both ssIgE and SPTs are useful for diagnosing IgE-mediated egg allergy but play little role in the diagnosis of non-IgE-mediated egg allergy. A good clinical history is paramount, and an oral food challenge is sometimes necessary for confirmation.

Prevention of Egg Allergy

Many infant feeding guidelines have been revised in the last 5 years to alter previous recommendations about delayed introduction of solids, including egg, and avoidance of allergens early in life. This change was based upon a large number of population-based cohorts that have demonstrated either no effect or a positive association between delayed introduction of solids (including egg) and subsequent asthma, eczema and food allergy in infants at high risk of allergic disease at birth.

A recent Cochrane review in 2012 examined the primary prevention of allergic disease by maternal dietary exclusion while pregnant or during lactation and found insufficient evidence to recommend maternal exclusion of allergic foods, including egg.³⁷ Examining egg specifically, a Melbourne population-based cross-sectional study reported that early introduction of egg was associated with a lower rate of egg allergy. This finding suggests that introduction of cooked egg at 4–6 months of age might protect against egg allergy.³⁸

The latter study was not a controlled trial, but randomised double-blind placebo-controlled trials of early egg introduction are underway both in Australia (Beating Egg Allergy Trial) and overseas (Early introduction of allergenic foods to induce tolerance in infants). The Australasian society of Allergy and Clinical Immunology infant feeding guidelines, European Society of Paediatric Gastroenterology, Hepatology and Nutrition, American Academy of Paediatrics and European Academy of Allergy and Clinical Immunology all recommend that if there is no evidence of food allergy, the introduction of complimentary foods (including common allergens such as egg) should not be delayed for the purposes of allergy prevention, even in high-risk infants. http://allergy.org.au/images/stories/aer/infobulletins/2010pdf/ASCI_A Infant_Feeding_Advice_2010.pdf.

Egg Allergy and Immunisation

Individuals with egg allergy are at no greater risk of an adverse reaction to the measles mumps rubella (MMR) vaccine than non-egg-allergic individuals.³⁹

The MMR vaccine is cultured on chicken fibroblast cell cultures, contains no residual egg allergen and has been safely administered to large numbers of egg-allergic individuals.

Many recent studies have been published about egg allergy and influenza vaccines with data suggesting that immunisation is safe in many egg-allergic individuals as long as the amount of residual egg ovalbumin is limited to 1 µg or less per dose.⁴⁰ The administration of the vaccine in a split dose may be recommended

depending on the history, and detailed practice guidelines are published by the ASCIA. (<http://www.allergy.org.au/health-professionals/papers/influenza-vaccination-of-the-egg-allergic-individual>).

The yellow fever vaccine is prepared in egg embryos, and allergic reactions including anaphylaxis to this vaccine have been reported.⁴¹ A specialist allergist should be consulted if this vaccine is needed for an egg-allergic child.

Egg allergy is often cited as a contraindication to the administration of propofol, a common aesthetic agent. This is because propofol contains egg lecithin/phosphatide and soy oil. However, a recent paper investigating the safety of propofol administration in 43 egg-allergic children showed that only one child (who had previously had anaphylaxis to egg) reacted. This suggests propofol is likely to be safe in the majority of egg-allergic children who do not have a history of egg anaphylaxis.⁴²

Summary

Egg allergy is one of the most common allergies in childhood and has a wide spectrum of clinical presentation including anaphylaxis. Individuals may react to egg in all forms or may tolerate it in various cooked forms (e.g. in baked products). Egg allergy may be more persistent than previously thought with treatment still centred on avoidance but with current research pointing to a role for oral immunotherapy in the future.

Multiple Choice Questions

- 1 A 1-year-old boy presents with a generalised allergic reaction to scrambled egg and a large positive skin prick test to egg. Which of the following are true?
 - a. He should not receive his routine MMR.
 - b. He is unlikely to be able to consume egg in any form.
 - c. He has an increased risk of a peanut allergy.
 - d. He is unlikely to outgrow his egg allergy.
- 2 A 2 year old presents with acute vomiting, diarrhoea and lethargy. His mother mentions that he probably ingested egg about 2 h prior to these episodes. His skin prick test is negative. What would you advise?
 - a. He does not have an egg allergy. He should go home and try egg again.
 - b. He most likely have egg-induced FPIES and hence should not try egg again until review.
 - c. He most likely has recurrent gastroenteritis.
 - d. The skin prick test is likely to be incorrect, and he should have sIgE to egg.
- 3 A 6-year-old asthmatic girl with history of anaphylaxis to small amount of fried egg at 1 year of age presents for further advice. She does consume egg in baked products without problems. The school has asked the parents for an adrenaline auto-injector. How would you proceed?
 - a. You would not recommend an adrenaline auto-injector because the event happened a long time ago, and she has probably outgrown her allergy.
 - b. You would prescribe an adrenaline auto-injector and review in 1 year.

- c. You would prescribe an adrenaline auto-injector and advise review by a paediatric immunologist/allergist.
- d. You would prescribe and adrenaline auto-injector and advise parents that she should stop eating egg in any form including baked eggs.

Answers

Question 1

The correct answer is c.

The MMR vaccine is not contraindicated in egg allergy as it is cultured in chicken fibroblast cell cultures, and there is no residual egg allergen. Hence, MMR vaccination should be given to all egg-allergic individuals including those with a history of anaphylaxis to egg.

Although the child in question reacted to scrambled egg and had a large positive SPT, it is still possible that he could tolerate other forms of egg such as egg in baked products. He will, however, need proper assessment and challenge prior to him trying egg in this form. Most children tend to outgrow their egg allergy by the age of 10 years.

Children who have egg allergy are more likely to suffer from peanut allergy.

Question 2

The correct answer is b.

The clinical presentation of FPIES often mimics acute gastroenteritis. The key is the history of food consumption about 2 h prior to acute vomiting and diarrhoea. Often, FPIES is not recognised until recurrent episodes occur and the common denominator of consuming the same food 2 h prior to the event. FPIES is not IgE mediated, and thus, SPTs and sIgE will be negative. The treatment of acute FPIES is fluid resuscitation and in the longer term to avoid the food trigger. The natural history of FPIES to egg is unknown. Individuals with FPIES should be referred to a paediatric immunologist/allergist as they need monitoring and formal in-hospital challenges.

Question 3

The correct answer is c.

All individuals with a history of anaphylaxis should be referred to an immunologist/allergist. An adrenaline auto-injector should be prescribed to all individuals who have had anaphylaxis. We cannot ascertain if individuals have outgrown their allergy without formal investigation and/or food challenge. Asthma further increases her risk of respiratory involvement should inadvertent exposure to egg occur. Baked egg should not be excluded as she has demonstrated tolerance, and this may be lost if the food is discontinued. The inclusion of baked egg in a clearly tolerated form makes the diet less restricted and easier to manage, therefore possibly improving quality of life. There is no evidence that consumption of baked egg by an egg allergic individual slows down their rate of losing the allergy, and in fact, there is a small amount of evidence suggesting that it might speed their rate of acquiring tolerance. More studies are needed in this area.

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