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The Diagnosis and Management of Egg Allergy

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Egg allergy is a common food hypersensitivity in children. Atopic dermatitis represents the main clinical manifestation in infancy. On first exposure, many of these infants present with urticaria, angioedema, or anaphylaxis. The role of egg allergy in gastrointestinal conditions is less well understood. The "gold standard" for the diagnosis of egg allergy is the double-blind, placebo-controlled food challenge. Diagnostic cut-off levels have been defined for food-specific serum immunoglobulin E antibody level and skin prick test wheal diameter that predict an adverse challenge outcome. This has significantly reduced the need for formal food challenges. Atopy patch testing, in conjunction with immunoglobulin E-based tests, may further improve the accuracy of predicting a positive challenge. The treatment of egg allergy consists of dietary elimination, or a maternal elimination diet in breast-fed infants. Approximately two thirds of infants with egg allergy will become tolerant by 7 years of age.

Introduction

Allergy to egg is one of the most common food hypersensitivities in childhood. The estimated prevalence of egg allergy varies between 1.6% and 3.2%, depending on ascertainment method or definition [1,2,3]. Hen's eggs are a common food source in many cultures, and egg protein is found in a wide range of cooked or manufactured foods. This may increase the risk for inadvertent allergen exposure. Egg-derived proteins are also present in vaccines [4–7]. Recent advances in our understanding of diagnostic in vitro and in vivo tests for egg allergy have simplified the diagnostic process [8]. In this review, we focus on the clinical presentation, diagnosis, treatment, natural history, and prevention of egg allergy.

Egg Allergens

Allergens in egg can elicit either immediate-type, immunoglobulin E (IgE) mediated reactions, or cell-mediated, delayed-type reactions [9]. Egg white represents the albumin fraction of the egg and contains more allergenic proteins than the yolk. During the past decade, five major allergens in egg have been characterized (Gal d 1 to 5; Table 1) [10,11]. The proteins in egg white include the allergens ovomucoid (Gal d 1) [11–13], ovalbumin (Gal d 2) [14–16], ovotransferrin (Gal d 3), lysozyme (Gal d 4), and ovomucin. Ovalbumin is the most abundant egg-white protein (65%–68%) [17]. Previously, ovalbumin was considered the main egg allergen. Later studies suggested that the glycoprotein ovomucoid was the immunodominant allergen in egg white [14]. Ovotransferrin (also called conalbumin) is a non-heme, iron-binding, acute-phase protein in chicken plasma and egg white [18]. The main allergen in egg yolk, chicken serum albumin (also called alpha-livetin, Gal d 5), is thought to be involved in the pathogenesis of bird-egg syndrome [19,20]. The role of other egg-yolk allergens, such as apovitellenin I and IV, is not well understood. Egg lecithins, which are commonly used as emulsifiers in manufactured foods, may have residual allergenic properties [21]. However, it is not clear whether egg-derived lecithins are present in manufactured foods in sufficient quantities to elicit adverse effects.

Epitopes

The antigenicity of egg allergens depends greatly on their resistance to heat and digestive enzymes, as well as the presence of IgE-specific epitopes on the proteins or peptides. Heating of ovalbumin to 95°C has no significant effect on IgE binding in humans, suggesting that ovalbumin-specific IgE predominantly binds to linear epitopes [22]. Raw ovalbumin at an acid pH < 2 is relatively resistant to peptic digestion, whereas heat-coagulated egg is more easily digested [23]. By contrast, the same authors found that ovomucoid was easily digested at a pH range of 1.5 to 2.5, but proteolysis was inhibited when the pH was higher than 3.0 [23].

Several epitopes on ovalbumin and ovomucoid have been characterized [10–16]. Five distinct IgE-binding epitopes have been found on ovalbumin [15]. The clini-

Table 1. Major egg allergens

Protein	Abbreviation	Mass, kDA	Amino acids, n	Comments
Egg white				
Ovomucoid	Gal d 1	28	186	Serine protease inhibitor [17]
Ovalbumin	Gal d 2	45	385	Serpin family
Ovotransferrin	Gal d 3	78	686	Iron transport, acute phase protein
Lysozyme	Gal d 4	14	129	1,4- β -N-acetyl-mucramidase C
Egg yolk				
Chicken serum albumin	Gal d 5	70	592	Transport protein; colloid pressure

cal pattern of egg allergy was initially thought to relate to specific T-cell clones with different cytokine profiles and antigen recognition by T-cell receptors [24]. However, a subsequent study by the same group failed to align the immunologic phenotypes of defined T-cell clones with patients' clinical manifestations of egg allergy [25].

Egg Antigens in Amniotic Fluid and Breast Milk

Food-allergic manifestations may occur in exclusively breast-fed infants due to the transfer of intact food proteins into amniotic fluid and breast milk [26,27•]. This early contact of the fetal immune system with food and environmental antigens may modulate early immune responses and, if genetically susceptible, predispose to allergic sensitization [27•,28]. Several intact food proteins have been demonstrated in human milk, including β -lactoglobulin, ovalbumin, ovomucoid, and peanut [26,27•,29•,30–32]. After a defined egg challenge, ovalbumin was detected in the breast milk of 76% women [29•]. There was a direct dose-response correlation between the ingested amount of egg and levels in human milk. Maternal ovalbumin-specific serum IgG levels are markers of maternal egg consumption and correlate well with cord-blood levels [33•]. This finding suggests that transplacental transfer of ovalbumin-specific IgG antibodies may influence the risk for atopic sensitization of the infant. A recent study measured cord-blood and breast-milk concentrations of ovalbumin following a maternal egg-avoidance diet [27•]. At 3 months postpartum, in 35% of lactating women, ovalbumin was present in higher concentrations in breast milk than in blood. Strict dietary elimination of egg did not reliably prevent passage of ovalbumin into breast milk. Although diets in this study were closely monitored, persistence of breast-milk ovalbumin despite dietary elimination most likely reflects inadvertent maternal egg intake or prolonged excretion [26].

Threshold Doses

Contamination of manufactured foods with egg and other food proteins may potentially cause significant

food-allergy reactions. To aide industries in developing safe food standards, efforts have been made to define the minimum food-allergen dose that may elicit clinical food-allergic reactions. A French study assessed 125 individuals with positive food challenges to egg [34]. In that study, the lowest observed adverse effect level (LOAEL) of egg protein was less than 2 mg. A consensus conference has recently developed a double-blind, placebo-controlled, low-dose challenge protocol, starting with an allergen dose of 10 μ g, with doses increasing at 30-minute intervals [35•]. This protocol allows exact and standardized determination of LOAEL and cumulative allergen doses for egg and other foods. It is not known if a similar threshold dose for ovalbumin can be defined in breast milk.

Clinical Presentation of Egg Allergy

Immediate allergic reactions to egg

Infants and young children may develop acute-onset reactions after ingesting egg-containing foods. Many of the reactions occur after first exposure to egg, particularly in infants with atopic dermatitis (AD) [36]. Reactions span the full spectrum of allergic reactions, from vomiting, urticaria, and angioedema, to anaphylaxis. Egg anaphylaxis accounts for less than 10% of all anaphylactic reactions in children and only rarely occurs in adults [37]. Egg allergy may occur in association with other food allergies, most commonly allergy to cow's milk and peanut. Table 2 summarizes the prevalence of food allergic manifestations in a cohort of 207 consecutive infants with egg allergy (mean age 12.2 ± 4.6 months, range 2–24 months, 65% male), treated in the Allergy Department the Royal Children's Hospital, Melbourne (Hill et al., Unpublished data). In Australia, it is recommended that the introduction of egg be delayed until 12 months of age, which may account for the mean age at diagnosis of our cohort.

Atopic dermatitis

AD is the most common clinical manifestation of egg allergy in infancy. AD in infancy is associated with the increased production of ovalbumin-induced interleukin (IL)-5 production [38]. More than 80% of

Table 2. Initial clinical manifestations of egg allergy in 207 infants (mean age 12 months)

Immediate-type reactions (IgE-mediated), n (%)	
Urticaria /rash	67 (32.4)
Facial angioedema	24 (11.6)
Anaphylaxis	18 (8.7)
Cough/stridor	7
Wheeze	11
Vomiting	7 (3.4)
Irritability/distress	10 (4.8)
Rhinorrhea/sneezing	3 (1.4)
Atopic dermatitis	170 (82.1)
Never ingested egg (SPT $\geq$ 5 mm)	104 (50.2)
Other food allergies	
Cow's milk	84 (40.6)
Peanut	11 (5.3)

IgE—immunoglobulin E; SPT—skin prick test.

infants with egg allergy suffer from AD (Table 2). Food allergy-induced AD may occur in breast-fed infants who have never directly ingested egg [36,39]. In an Australian study of 620 infants who were at risk for atopy and studied to 12 months of age, the risk for IgE-mediated egg allergy increased in parallel with the severity of AD [40•]. Testing for food allergies has, therefore, become an integral part in the management of AD in infants and young children. AD developing in older children or adults is usually associated with other etiologic factors, including staphylococcal skin infection or exposure to house dust mite [41].

Asthma and sensitization to inhalant antigens

Egg allergy is a risk factor for the development of asthma [42•,43]. High IgG₁ serum antibody levels to ovalbumin at 1 year of age were predictive of asthma (sensitivity 64%, specificity 74%) and may be useful markers for identifying infants with an increased risk for asthma [44•]. Sensitization to food allergens in early childhood is usually transient and often associated with early sensitization to inhalant allergens and asthma [45].

Allergy to egg may develop in response to inhaled liquid and aerosolized egg proteins used in the baking and confectionary industry. A recent case series described four bakery workers who had developed occupational asthma due to allergic sensitization to egg white proteins [46]. Adults with the bird-egg syndrome present with respiratory and gastrointestinal reactions to both egg proteins and bird feathers or dander [47]. Chicken serum albumin (Gal d 5) has been found to be the main cross-reacting egg allergen in this condition [19,20,48].

Gastrointestinal manifestations

Gastrointestinal manifestations account for a minority of egg-allergic manifestations. Egg proteins may be involved in a variety of gastrointestinal disorders, including allergic proctocolitis and eosinophilic esophagitis [49,50]. In a study of 95 infants with food protein-induced proctocolitis, 19% responded to dietary elimination of egg [49]. Similarly, in 26 patients with eosinophilic esophagitis, 36% had evidence of sensitization to egg on SPT, and 24% had a positive patch test to egg [50]. These findings highlight that egg might have a role in the pathogenesis of specific gastrointestinal disorders. It is unclear whether sensitization to egg proteins is just a marker of these disorders, or whether egg proteins are directly involved in the pathophysiology.

Vaccines

Several vaccines have been associated with adverse effects in children with egg allergy, including influenza and yellow fever vaccine [5,6]. Hypersensitivity to the measles-mumps-rubella (MMR) vaccine was initially thought to be due to egg allergy [51], but has more recently been shown to be associated with gelatin allergy [52]. A prospective study demonstrated that MMR vaccine can be safely administered in egg-allergic children [53].

Influenza vaccine is cultured in allantoic cavities of embryonated hen's eggs and may contain small amounts of intact ovalbumin and other egg proteins [6]. Egg allergy is, therefore, still considered a relative contraindication to immunization against influenza, particularly in individuals with a history of egg anaphylaxis. Protocols for the safe administration of influenza vaccine have been devised [7]. Exacerbation of asthma after administration of influenza vaccine appears to be unrelated to hypersensitivity to egg proteins [54].

Diagnosis

The diagnosis of egg allergy is suggested by a previous adverse reaction to egg-containing foods, usually before the age of 2 years. Confirmation of the diagnosis by double-blind, placebo-controlled food challenge (DBPCFC) remains the definitive test [55], but it is not considered practical in the primary care setting. Measurement of egg-specific serum IgE antibody levels, skin prick testing, and atopy patch testing are the other main diagnostic tests available.

Food challenge

Although DBPCFC is the definitive test for food allergy, open food challenges (OFC) are considered sufficient as long as the clinical reaction can be objectively observed. DBPCFC is required in clinical research or for confirmation of subjective or delayed food-allergy reactions. Food challenges have become an integral part in assessing infants with AD [56]. Food challenges are resource-consuming and associated with a risk for anaphylaxis [57•]. The recent definition of

Table 3. Diagnostic cut-offs for CAP-FEIA and skin prick test predicting a positive food challenge in patients with egg allergy

Study	Year	PPV, %	CAP-FEIA, kU _A /L	Age group
Sampson and Ho [62]	1997	95	6.0	Children/adolescents
Boyano Martínez et al. [67]	2001	94	> 0.35	Infants ≤ 2 y
Perry et al. [64•]	2004	50	2.0	Children/adolescents
Celik-Bilgili et al. [66•]	2005	90	6.3	Children ≥ 1 y
		95	12.6	
		99	59.2	
		90	4.2	Infants < 1 year old
		95	10.9	
		99	88.6	
SPT wheal diameter, mm				
Sporik et al. [69]	2000	100	≥ 7.0 mm	Children > 2 y
		100	≥ 5.0 mm	Infants ≤ 2 y
Verstege et al. [70•]	2005	95	> 13.0 mm	Children < 15 y
		99	> 17.8 mm	

PPV—positive predictive value; SPT—skin prick test.

PPV—positive predictive value; SPT—skin prick test.

predictive cut-off values for SPT and CAP-FEIA has significantly reduced the need for formal food challenges [58].

Efforts have been made to standardize challenge protocols [59•]. Many centers commence a food challenge with a labial challenge of a drop of raw egg for 2 minutes, observing for localized angioedema, labial swelling, urticaria, or systemic reactions [60]. The use of uncooked egg has been abandoned in some centers owing to the risk for contamination with *Salmonella enteritidis* or related strains [61]. Increasing doses of egg are administered every 15 to 30 minutes, as tolerated. If no adverse reaction occurs on the first day of the challenge, ingestion of the food is continued for a total of 2 to 7 days to allow detection of delayed cutaneous or gastrointestinal reactions.

Food-specific immunoglobulin E antibody levels

Measurement of egg-specific serum IgE antibodies is a convenient way of testing for egg allergy. However, presence of IgE antibodies by itself is not sufficient to distinguish between true egg allergy and asymptomatic sensitization. Studies by Sampson and Ho [62] demonstrated that a serum IgE level to egg > 6 kU_A/L (CAP-FEIA, Pfizer-Pharmacia) predicted a positive challenge with > 95% accuracy (Table 3). This finding has subsequently been confirmed in a prospective study [63]. In children with a convincing history of an adverse reaction to egg, in conjunction with a CAP-FEIA to egg > 6 kU_A/L, formal challenges are no longer routinely performed. This has reduced the need for formal food challenges by up to 50% [58] (Table 3).

In clinical practice, challenges are often considered when patients have at least a 50% chance of being tolerant

to a particular food item. Perry et al. [64•] defined cut-off values at which a patient has a 50% chance of passing a food challenge. In that retrospective review, the authors found that at least 50% of patients with an egg-specific CAP-FEIA below 2 kU_A/L passed their food challenge [64•]. Østerballe et al. [65] found the 95%-predictive egg IgE at 1.5 kU_A/L (CAP-FEIA), but demonstrated no relationship between egg-specific IgE concentrations and minimal threshold dose on food challenge.

In a recent German study, the 95%-predictive CAP-FEIA IgE concentration for a positive egg challenge was 12.6 kU_A/L [66•]. In that study, the predictive cut-off levels in infants younger than 12 months were generally lower than in older children [66•]. An earlier Spanish study in infants younger than 2 years of age with egg allergy defined the 94%-predictive CAP-FEIA cut-off at > 0.36 kU_A/L [67], which was significantly lower compared with the German study [66•]. The range of cut-off values in the studies discussed may be due to differences in the clinical characteristics of cohorts or in challenge procedures. Table 3 summarizes the currently available diagnostic decision points for CAP-FEIA and SPT.

Skin prick test

SPT is based on the cutaneous release of mast cell mediators after introduction of food antigens into the superficial layers of the skin with a lancet [68]. The size of the wheal diameter depends on several factors, including the level of mast cell mediator release and the antigen dose (allergen extracts vs raw egg). Wheal diameter cut-off levels have been defined that predict a positive food challenge (Table 3). A wheal diameter of ≥ 7 mm has been

shown to be 100% predictive of a positive egg challenge [69]. In infants and children younger than 2 years of age, the predictive cut-off for a positive challenge was lower (≥ 5 mm) [69]. In our practice, food challenges are not required for a diagnosis of egg allergy if the SPT wheal diameter exceeds the age-specific predictive cut-off. Verstege et al. [70•] have recently published their predictive wheal cut-off diameters. The higher cut-off values compared to the data by Sporik et al. [69] may be due to the use of raw egg rather than extract for SPT [71].

Atopy patch test

In recent years, the atopy patch test (APT) has become recognized as a diagnostic tool for food allergy in children [72,73]. The APT is based on cutaneous cell-mediated responses after epicutaneous application of allergens for 48 hours. APT appears particularly useful in determining the role of food allergens in infants and children with non-IgE (cell-mediated) or mixed (IgE and cell-mediated) food-allergic manifestations, including atopic dermatitis [72,74,75]. The test may also have a role in diagnosing underlying food allergies in patients with gastrointestinal cow's milk allergy (CMA) [76•] or eosinophilic esophagitis [50]. The methodology involves application of fresh egg onto the skin for 48 hours, occluded by a 12-mm aluminium chamber (Finn chamber) [73,77]. The APT has a low sensitivity but high specificity. Østerballe et al. [78] found that the APT alone was insufficient to predict egg allergy. However, if used in conjunction with SPT (high sensitivity, low specificity), the diagnostic accuracy increases significantly. Roehr et al. [79] showed that for a combined positive APT and SPT to egg, the positive predictive value was 94%. Use of the APT in conjunction with SPT or other IgE-based tests, therefore, has the potential to reduce the need for formal food challenges.

Treatment

Oligo-allergenic elimination diet

Dietary avoidance of egg-containing food is the main principle of treating egg-allergic individuals [80]. If patients are predominantly sensitized to heat-labile egg epitopes, small amounts of well-cooked egg may be tolerated [20]. The need for dietary elimination should be reassessed on a regular basis. Elimination diets in young children may be associated with adverse nutritional outcomes, and growth parameters should be closely monitored [81].

Maternal elimination diet

Elimination of egg from the maternal diet is now considered a standard treatment in breast-fed infants with food allergies [26,27•,49,82,83], including atopic dermatitis [82], colic [83], and food protein-induced proctocolitis [49]. Although there appears to be a direct dose-effect relationship between concentrations of ovalbumin in breast milk in relation to the maternally ingested amount [29•],

a strict elimination diet may not completely eliminate egg proteins from breast milk [27•]. Broad-based maternal elimination diets need to be balanced with regard to protein, energy, and micronutrient content, and require careful monitoring by an experienced dietitian [80].

Treatment of anaphylaxis

Intramuscular epinephrine is the treatment of choice for acute anaphylaxis [84]. In the ambulatory setting, epinephrine is easily administered by an autoinjector (EpiPen, Dey L.P., Napa, CA) [84–89]. An epinephrine autoinjector is required if a patient is at significant risk for anaphylaxis, regardless of etiology [85]. Concerns have been raised whether the EpiPen always ensures adequate intramuscular administration, as in obese adults the thickness of the fat layer at the lateral thigh may exceed the needle length [90]. In children, the EpiPen Jr. or EpiPen is usually administered by parents or caregivers, and adequate training in the use of the device is essential [86]. The need for an epinephrine autoinjector should be reviewed on a regular basis.

Prognosis and Natural History

Epidemiologic studies of egg allergy found a much lower prevalence of egg allergy in adults and adolescents, compared to young children [2•,3•], suggesting that egg allergy resolves spontaneously in most cases. Prospectively collected data on the natural history of egg allergy are limited [91]. A retrospective study found that of 25 young children with challenge-proven egg allergy, 11 (44%) developed tolerance within 2.5 years [92]. Children with cutaneous and gastrointestinal reactions appeared to have a better prognosis than those initially presenting with angioedema or respiratory symptoms [92].

Specific oral tolerance induction (SOTI) protocols have recently been trialed in an attempt to hasten the development of tolerance in food-allergic children. The SOTI protocol aimed for a controlled, stepwise increase toward a target dose of 4.5 g egg protein per day over 37 to 52 weeks [93]. Although patients gradually tolerated increasing doses of egg, food-allergic symptoms recurred on formal challenge after a period of dietary elimination. These findings suggest that SOTI induces tachyphylaxis rather than long-term immune tolerance [93].

The prognosis of egg allergy in infants younger than 2 years is generally good: it is estimated that approximately 50% will be tolerant within 3 years, and 66% within 5 years of the initial presentation [94]. Monitoring for the development of tolerance relies on repeated skin and IgE testing, as well as food challenges [95]. In a recent study, food-specific IgE levels (CAP-FEIA) correlated well with the development of tolerance and were found useful in the monitoring of egg-allergic patients [94,96•]. Although the egg-specific IgE level at first presentation did not predict transience or persistence of egg

allergy [97], the rate of the decline in antibody levels may provide some prognostic information [96*].

Conclusions

Maternal dietary elimination during pregnancy and lactation have been assessed as possible strategies in primary food allergy prevention [65]. There was no evidence for a protective effect of a maternal elimination diet during pregnancy [98]. Elimination diets are associated with a lower birth weight, highlighting the risk for adverse nutritional outcomes for the infant [65]. Maternal egg avoidance during lactation may reduce the risk of AD in the young infant [65]. In addition, the Study on the Prevention of Allergy in Children in Europe (SPACE) provided preliminary evidence that, compared with controls, the rate of sensitization to cow's milk and egg is significantly reduced in infants avoiding these foods [99]. It is currently recommended to delay the introduction of egg until 12 to 24 months of age, particularly in infants with a positive family history of atopy [98,100].

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