

Review

Cracking the egg: An insight into egg hypersensitivity

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ABSTRACT

Hypersensitivity to the chicken egg is a widespread disorder mainly affecting 1–2% of children worldwide. It is the second most common food allergy in children, next to cow's milk allergy. Egg allergy is mainly caused by hypersensitivity to four allergens found in the egg white; ovomucoid, ovalbumin, ovotransferrin and lysozyme. However, some research suggests the involvement of allergens exclusively found in the egg yolk such as chicken serum albumin and YGP42, which may play a crucial role in the overall reaction. In egg allergic individuals, these allergens cause conditions such as itching, atopic dermatitis, bronchial asthma, vomiting, rhinitis, conjunctivitis, laryngeal oedema and chronic urticaria, and anaphylaxis. Currently there is no permanent cure for egg allergy. Upon positive diagnosis for egg allergy, strict dietary avoidance of eggs and products containing traces of eggs is the most effecting way of avoiding future hypersensitivity reactions. However, it is difficult to fully avoid eggs since they are found in a range of processed food products. An understanding of the mechanisms of allergic reactions, egg allergens and their prevalence, egg allergy diagnosis and current treatment strategies are important for future studies. This review addresses these topics and discusses both egg white and egg yolk allergy as a whole.

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1. Allergy

Allergy is a symptomatic and an abnormal overreaction by the immune system to innocuous environmental substances, such as grass pollen and eggs, known as allergens. Allergens are a type of antigen, which trigger a complex immune response upon contact with the immune system. Allergy is classified as a *type 1* hypersensitivity reaction because of the immediate and inflammatory immune response that is characterised by the excessive production of the antibody Immunoglobulin E (IgE). An allergic response involves two reaction phases based on the contact of the allergen with the immune system; primary and secondary response. The primary response (upon initial contact with allergen), stimulates the generation of IgE by T-lymphocytes. The secondary

response (upon secondary contact with the same allergen) results in the degranulation of mast cells (mastocytes) and basophils (basophil granulocytes). The mediators (e.g. histamine) released by the degranulation process elicit clinical allergic symptoms such as bronchoconstriction, sneezing, rashes, itching or life threatening conditions such as anaphylaxis, just to name a few (Janeway and Traverse, 1994; Kay, 2001).

2. Allergic response

2.1. Allergic sensitisation

Upon contact with the immune system, an allergen is engulfed and processed by antigen presenting cells (APCs) and presented to naïve T-helper cells (Th0). This causes Th0 cells to differentiate into T-helper type 2 (Th2) cells in the presence of cytokines including Interleukin-4 (IL-4). Th2 cells then further secrete IL-4, IL-5 and IL-13, which induce B-cell differentiation into plasma cells secreting IgE. The IgE antibodies subsequently bind to the high affinity FcεRI receptors on mast cells and basophils, thus sensitizing the immune system to the allergen (Kay, 2001) (Fig. 1).

Abbreviations: OIT, oral immunotherapy; SIT, specific immunotherapy; SPT, skin prick test.

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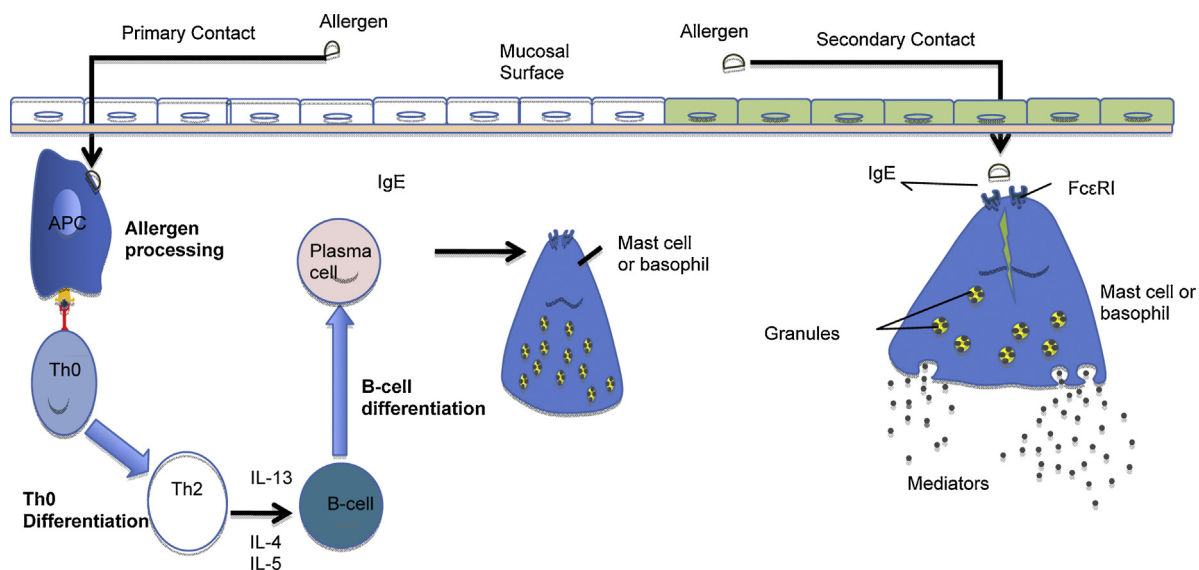


Fig. 1. Illustration of the allergic reaction. This figure outlines the steps of an allergic reaction. Once the initially encountered allergen is processed and presented by APCs to the Th0 cells, the Th0 cells differentiate into Th2 cells in allergic individuals. These Th2 cells then further secrete IL-4, IL-5 and IL-13, triggering B-cell differentiation into plasma cells. Subsequently, these plasma cells proliferate and produce excessive amounts of allergen specific IgE, which bind to the FcεRI receptors on mast cells and basophils, thus sensitizing the immune system to the allergen. Upon secondary encounter of the immune system with the same allergen, the allergen binds to multiple IgE held on mast cells and basophils. Cross linking of the FcεRI receptors, as a result of interaction between a single allergen and multiple IgE molecules, triggers the release of mediators including histamine, causing an allergic inflammation.

2.2. Allergic reaction

Upon secondary exposure to the same allergen (unprocessed by APCs), the allergen binds to the membrane bound IgE molecules on mast cells and basophils. Cross-linking of FcεRI occurs when multiple IgE molecules interact with the same intact allergen, triggering degranulation of mast cells and basophils, consequently releasing granule-derived vasoactive chemicals such as histamine, serine protease tryptase, lipid mediators such as leukotrienes, prostaglandins and platelet activating factor, chemokines and cytokines IL-4, IL-5 and IL-13 (Fig. 1). These mediators cause allergic symptoms such as airway smooth muscle constriction (bronchoconstriction), mucus hypersecretion, mucus cell metaplasia, redness, rashes, sneezing and anaphylaxis (Kay, 2001).

3. Food allergy

Food allergy is one of the major allergies in today's society. In a double-blind placebo controlled food challenge study conducted by Allan Bock et al. (1988), 80% of the subject children were found to develop hypersensitivity symptoms to food allergens. In the developed world, 10% of children are affected by food allergies, while emerging or developing nations has a prevalence of 7% (Prescott et al., 2013). Occurrence of food allergy, like other atopic diseases, is rising and remains a problem throughout the world. It is a major cause of anaphylaxis, especially by nuts, and treated worldwide in emergency departments and hospitals, incurring a massive financial burden on the governments and the public (Bock et al., 2001; Hugh, 2004). Food hypersensitivities include abnormal overreactions caused by intolerance to food (non-allergic) and allergic responses caused by an antigen in the food. Intolerance to food is due to some physiological abnormality, such as the lack of lactase which causes intolerance to lactose, whereas the allergic food reactions are mediated by IgE or non-IgE immune responses (Hugh, 2004). Food allergies arise through the interaction between the intestinal immune system and food allergens present in the food that we consume on a daily basis. Allergenic foods include, but not limited to, eggs, peanuts, fish and milk. Antigens (allergens)

present in these foods are responsible for IgE mediated hypersensitivity reactions. For example, people allergic to milk react to the milk whey protein allergen β-lactoglobulin (Jabed et al., 2012) and patients allergic to egg may be due to the egg white protein ovomucoid (Ando et al., 2008). Most of these allergens are glycoproteins that can withstand heat, acids and proteases (Hugh, 2004), this explains why most allergenic foods remain allergenic even after cooking or processing.

4. Egg allergy

Hypersensitivity to the chicken (*Gallus gallus*) egg is a widespread disorder mainly affecting children, with a recent meta-analysis suggesting a prevalence of 0.5–2.5% of children (Rona et al., 2007). It is the second most common food allergy next to cow's milk allergy and it is the most common allergy among children with atopic dermatitis (Caubet and Wang, 2011; Langeland, 1985; Sampson, 1983). According to an Australian study conducted by the Murdoch Children's Research Institute (MCRI), 8.9% of infants are allergic to eggs (Osborne et al., 2011). However, egg allergy is not limited to children, with cases that have been reported of adult onsets (Unsel et al., 2013). Children allergic to egg generally grow out of the condition by school age (Boyano-Martínez et al., 2002; Venter et al., 2008). Hypersensitivity to allergens present in the eggs causes conditions such as itching, atopic dermatitis, bronchial asthma, vomiting, angio-oedema, rhinitis, conjunctivitis, laryngeal oedema, chronic urticaria and allergic eosinophilic gastroenteritis (Eigenmann, 2000; Fremont et al., 1997; Jaffe et al., 1994; Quirce et al., 2001). Egg allergic patients produce IgE specific to sequential (linear) and conformational epitopes of egg allergens. However some sequential epitopes recognised by persistent egg allergic patients are not recognised by patients with transient egg allergy (Järvinen et al., 2007). This suggests a difference in severity of allergic reaction between persistent and transient egg allergic patients. Anaphylaxis may also occur in some individuals, however this depends on the processing of the egg. This may be due the reduction in IgE reactivity in heated egg, possibly due to the disruption of conformational IgE binding epitopes in the egg

allergens. It has also been found that eggs heated on its own are more IgE reactive when compared to eggs heated in the presence of another substance such as wheat (Bloom et al., 2014; Watanabe et al., 2014). This suggests that an egg allergic patient may show less reactivity to food items such as cakes or muffins than to fried or baked egg. The prevalence of egg allergy and the aforementioned conditions highlight the importance of egg allergy research. An understanding of the different egg allergens, egg allergy diagnosis methods and treatment methods are imperative for future research.

5. Allergy to egg white

Egg allergy is mainly caused by 4 of the many different proteins that make up the egg white (Leduc et al., 1999; Rupa and Mine, 2003). However, these may not be the only allergenic egg white proteins, particularly in the wake of new discovery of a large number of other proteins in the egg white (Mann and Mann, 2011). These allergens are namely ovomucoid, ovalbumin, ovotransferrin and lysozyme, with ovomucoid being the most allergenic of the four and ovalbumin being the most abundant (Fig. 2). A few studies have identified egg yolk allergens, such as chicken serum albumin and YGB 42 (Fig. 2). The four aforementioned egg white allergens are produced by tubular gland cells which comprise the majority of the magnum portion of the chicken oviduct (Kohler et al., 1968; Palmiter et al., 1970). Induction of expression of these allergens are highly dependent on estrogens and this has been demonstrated in studies involving chicks in which upon administration of estrogens the tubular gland cells started producing the allergenic proteins (Kohler et al., 1969; Oka and Schimke, 1969; Palmiter and Wrenn, 1971). Egg allergy can be caused by consumption of raw or cooked eggs, however a study conducted by Lemon-Mulé et al. (2008) indicates that majority of the egg allergy patients are tolerant to heated eggs, although the allergenicity of proteins are not exclusively dependent on their resistance to heat and enzymes (Astwood et al., 1996). The same study shows that continued exposure to the heated egg is associated with immunological changes similar to the changes observed in developing tolerance to raw eggs. These immunological changes include increasing IgG4 levels and a reduction in wheal sizes in egg white specific skin prick testing (SPT). IgA and IgA2 may also be of importance in developing tolerance to egg white (Konstantinou et al., 2014). However, more studies involving a larger number of subject individuals are necessary to confirm the effects of heating on egg white allergens, resulting IgE reactivity and other immunological changes in patients. Given that the structure of the proteins may play a crucial role in IgE binding and eliciting an allergic response, an understanding of the structure and function of each of the four allergens is essential for future studies.

6. Allergens in the egg white

6.1. Ovomucoid (Gal d 1)

Ovomucoid is the most allergenic and the dominant allergen found in the chicken egg white. Constituting 11% of the total egg white, ovomucoid is a trypsin inhibitory glycoprotein with a molecular weight of 28 kDa (Kato et al., 1987; Mine and Zhang, 2002a). It is comprised of 186 amino acids arranged in three tandem domains, each approximately 60 amino acids in length, containing nine intra-domain disulfide bonds and five carbohydrate side chains. The trypsin inhibitory activity is limited to the second domain, in which a putative reactive site is present for trypsin inhibition (Abdou et al., 2013; Kato et al., 1987). The arrangement of the three domains is also similar to the pancreatic trypsin inhibitor. Previous studies have indicated that allergenicity

or IgE binding capacity of ovomucoid is not considerably affected by heat and proteinase activity (Järvinen et al., 2007; Konishi et al., 1985). This suggests that the structure of the IgE binding epitopes of ovomucoid is mainly linear, however there are some conformational epitopes present in all domains (Mine and Zhang, 2002a). This suggests that cooking of eggs may have little or no effect on the allergenicity of ovomucoid. In addition, the third domain of ovomucoid shows more IgE binding activity when compared to the other two domains (Zhang and Mine, 1998). It can be suggested that the third domain would be an ideal target for studies focusing on the production of hypoallergenic variants of ovomucoid that may be used for treatment strategies such as immunotherapy.

6.2. Ovalbumin (Gal d 2)

Ovalbumin is the most abundant (58%) protein in the egg white and it is considered to be the second most important allergen in egg hypersensitivity. Ovalbumin is a water soluble glycoprotein made up of 385 amino acids and has a molecular weight of 45 kDa (Nisbet et al., 1981). Mine and Zhang (2002b) reported that carboxymethylation, urea treatment or heat denaturing at 95 °C of ovalbumin does not significantly affect its IgE binding capacity. This suggests that anti-ovalbumin IgE primarily recognises linear epitopes than conformational epitopes. Similar to ovomucoid, this indicates that cooking may not significantly affect the allergenicity of ovalbumin, however digestive enzymes may affect the allergenicity. The major function of ovalbumin in the chicken egg is currently unknown, however it is a member of the serpin family of proteins although it is incapable of inhibiting protease activity. This lack of protein inhibitory activity is explained by the absence of an important serpin conformational change in the reactive centre loop of ovalbumin (Huntington and Stein, 2001). Ovalbumin is also known to exhibit biological functions including antibacterial and immunomodulating activities (Kovacs-Nolan et al., 2005). The antibacterial properties are however not exerted by intact ovalbumin, instead, proteolytic digestion of the protein has shown to produce peptide fragments capable of acting against organisms such as, but not limited to, *Bacillus subtilis* and *Candida albicans* (Pellegrini et al., 2004). It is also believed that ovalbumin may act as a source of amino acids for embryonic development (Abdou et al., 2013).

6.3. Ovotransferrin (Gal d 3)

Transferrins are a group of iron-binding proteins found in vertebrates that has structural and functional similarities among each member. The molecular mass of these monomeric glycoproteins is about 76.6 kDa, and a molecule of transferrin can bind to two Fe³⁺ with high affinity. Ovotransferrin is one of the members of transferrins expressed in the chicken oviduct. Expression of ovotransferrin in the oviduct is under steroid control and it differs from serum hen transferrin only by an attached carbohydrate (Kurokawa et al., 1995; Williams et al., 1982). *In vitro*, ovotransferrin exhibits antimicrobial and immunomodulating activities (Kovacs-Nolan et al., 2005). Ovotransferrin is capable of penetrating the outer membrane of *Escherichia coli*, allowing selective penetration of ions which causes decadence of electrical potential of the cell, which in turn halts the ability of the bacteria to reproduce (bacteriostasis) (Aguilera et al., 2003). Some research has been conducted to study the changes in allergenicity and conformational structure of ovotransferrin when heated. A study conducted by Tong et al. (2012) showed that the allergenicity of ovotransferrin correlated with the structural changes caused by heating. Unfolding of the structure caused an increase in allergenicity and cleavage and rearrangement of disulfide bonds lead to a decrease in allergenicity (Tong et al., 2012). This suggests that ovotransferrin is one of the

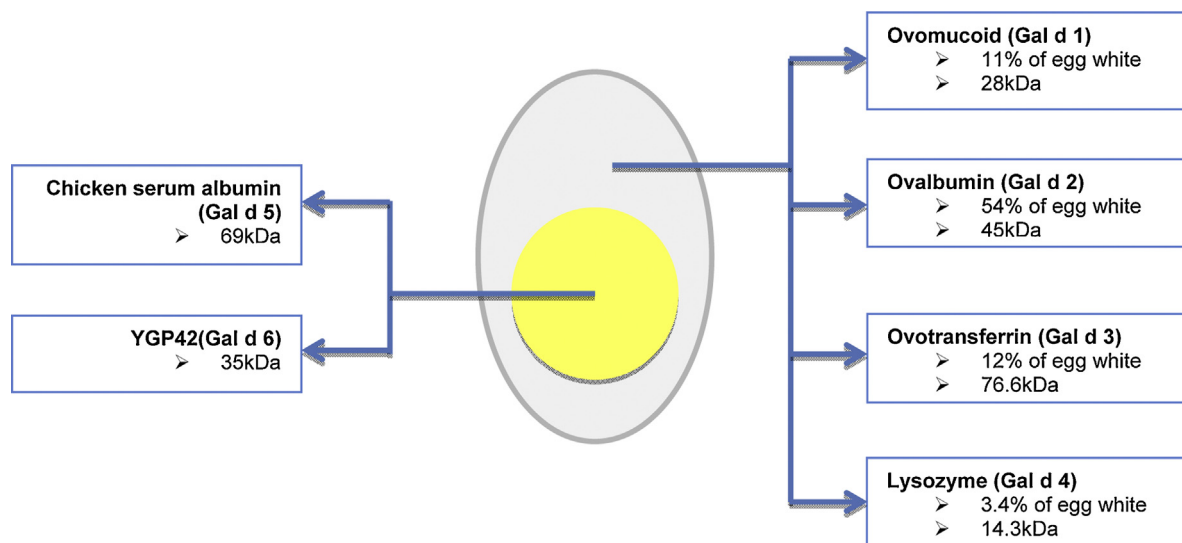


Fig. 2. A depiction of chicken egg allergens and their properties. This figure shows basic properties of allergens found in the chicken egg white and egg yolk.

allergens responsible for hypersensitivities caused by consumption of cooked eggs as well as raw eggs. Therefore, it is wise to suggest that research should be focused on ovotransferrin as much as on ovomucoid and ovalbumin.

6.4. Lysozyme (Gal d 4)

Lysozyme, 14.3 kDa in size, is an enzyme that exhibits antimicrobial activity in the chicken egg, thus providing protection from potential microbial hazards. It is known to exert lytic activity on cell walls of microbes, therefore it is widely used in pharmaceutical products (Perez-Calderon et al., 2007). It is also used in various food products such as cheese (Fremont et al., 1997; Weber et al., 2009), which therefore poses a risk to egg allergic patients. Structurally, lysozyme contains conformational and sequential epitopes and it has *in vitro* biological functions such as antibacterial, antiviral, immunomodulating and antitumor activities (Kovacs-Nolan et al., 2005; Weber et al., 2009). Although lysozyme is less allergenic than ovomucoid and ovalbumin (Caubet and Wang, 2011), the high occurrence in many food and pharmaceutical products makes it an important target in egg allergy research.

7. Allergy to egg yolk

Chicken's egg yolk is also responsible for causing IgE mediated allergy, although with much lower prevalence than egg white hypersensitivity. Unlike allergy to egg white, which is commonly seen in young children with atopic dermatitis, allergy to egg yolk mostly affects during the adulthood. However, underlying immunological reactions to egg yolk allergens are mainly IgE-mediated, and usually produce symptoms such as urticaria, vomiting, abdominal pain and diarrhoea, as in allergy to egg white (de Maat-Bleeker et al., 1985; Mandallaz et al., 1988; Szepefalusi et al., 1994).

8. Allergens in the egg yolk

8.1. Chicken serum albumin (Gal d 5 or α -livetin)

Chicken serum albumin is the first allergen identified from the hen's egg yolk. It is a water soluble globular glycoprotein with a molecular weight of 69 kDa. The main function of this protein is to transport metals in the blood stream (Predki et al., 1992). Serum

albumin had been confirmed as an inhalant allergen as well as food allergen through bronchial provocation and oral challenge tests, respectively. The main route of sensitisation for serum albumin is through the respiratory tract as seen in bird-egg syndrome. However, the vice versa of bird to egg allergy is also true, where initial sensitisation to egg yolk proteins pave the way to respiratory allergic symptoms in egg-bird syndrome. Serum albumin is a partially heat resistant allergen, thus some patients are able to tolerate extensively heated egg yolk, but not raw egg yolk (Quirce et al., 2001).

8.2. YGP42 (Gal d 6)

Yolk glycoprotein 42 (YGP42) is the second allergen identified from the hen's egg yolk. It is a glycoprotein with a molecular weight of 35 kDa. According to the homology search conducted by BLAST, YGP42 is a fragment of the vitellogenin-1 (VTG-1) precursor. YGP42 contains three glycosylation signals at positions: 1662, 1698 and 1703. The periodate oxidation treatment of YGP42 did not abolish the IgE binding capacity indicating that sugar residues are not related to allergenicity. Furthermore, heat treatment and reduction did not affect allergenicity of YGP42 at all, while simulated gastric acid digestion completely eliminated its IgE reactivity. YGP42 was also investigated for any implication in bird-egg syndrome. However, inhibition immunoblotting experiments did not demonstrate any degree of inhibition of allergens from chicken meat and feather extracts. Therefore, YGP42 is not considered to be involved in bird-egg syndrome (Amo et al., 2010).

8.3. Other IgE binding proteins in the egg yolk

Apart from the recently discovered egg yolk allergens Gal d 5 and Gal d 6, few other proteins from the hen's egg yolk proteome have exhibited a possible allergenic potential (Anet et al., 1985; Walsh et al., 1988). Three abundant egg yolk proteins from the egg yolk known as apovitellenin I, VI and phosvitin have demonstrated substantial IgE binding capacity in egg allergic patients' sera. Furthermore, all the proteins were found to be effectively inhibit binding of egg yolk specific IgE. However, the clinical relevance of these proteins to egg yolk allergy have not been established to date, and therefore their status as allergens is uncertain (Walsh et al., 1988).

9. The bird-egg syndrome

Bird-egg syndrome is an IgE-mediated hypersensitivity disorder where a human develops an allergy to egg yolk, specifically to serum albumin, following sensitisation to inhalant avian antigens derived from sources such as bird's blood serum, feathers, droppings and dander (Mandallaz et al., 1988) (Fig. 3). This is different to allergen cross reactivity in which a patient allergic to a certain allergen is reactive to homologous or non-homologous allergens from the same or other species (Bublin et al., 2013; Rhijn et al., 2013). Majority of patients with bird-egg syndrome claim to have regular exposure to pet birds or poultry where sensitisation to airborne avian allergens take place, which then proceed to egg yolk allergy. Patients suffering from bird-egg syndrome suffer from both respiratory and gastrointestinal allergic symptoms such as asthma, rhinoconjunctivitis, edema, diarrhoea and vomiting. However, unlike allergy to egg white, which is predominantly seen in children with atopic dermatitis, bird-egg syndrome mainly affects adults with an obvious gender predisposition where majority of patients tend to be females. In addition, allergens produced by birds at workplace may also increase IgG levels in excess and can lead to allergic alveolitis. Currently, these IgG levels can be quantified and qualitatively evaluated using the UniCAP system, a type of ImmunoCAP (Lopata et al., 2004).

The common antigen present in hen's egg yolk and other avian antigens responsible for bird-egg syndrome is recognised as s, which corresponds to chicken serum albumin (Szepfalusi et al., 1994; Williams, 1962). Serum albumin belongs to a group of protein fraction known as livetins in the egg yolk. Livetins are water soluble glycoproteins that are derived from blood serum proteins of the hen. Furthermore, radioallergosorbent (RAST) test inhibition experiments had demonstrated inhibition of IgE binding to livetins of hen's egg yolk by avian antigens from different bird species. This result indicates that serum proteins from different bird species have highly conserved epitopes which allow specific IgE antibodies to cross react (Mandallaz et al., 1988). The clinical relevance of serum albumin in bird-egg syndrome had been established by immunological methods in order to validated it as a food allergen designating the allergen name Gal d 5 (Quirce et al., 2001).

An individual develops allergy to hen's egg yolk following exposure to birds, where sensitisation to inhalant avian allergens takes place resulting in respiratory allergy symptoms. The cross reacting allergen which is responsible for producing both respiratory and gastrointestinal allergy symptoms in bird-egg syndrome is identified as chicken serum albumin present in bird antigens and in the egg yolk as well.

10. Diagnosis of egg allergy

Different diagnostic techniques are used for successful diagnosis of egg allergy. Similar to other allergic conditions, the foremost step in egg allergy diagnosis is assessment of the medical history of the patient for potential evidence for clinical reactivity to eggs and physical examination. This helps to determine whether the patient has experienced adverse reactions to eggs and the potential involvement of the immune system (Metcafe and Sampson, 1990; Sicherer, 1999). The medical history examination essentially takes into consideration the allergic conditions the patient's parents are/were exposed to and evaluates these information with the current symptoms, the type and the amount of food ingested and the timing of the reaction. The physical examination involves testing for gastrointestinal symptoms and detection of atopic features in the body. The next step involves the use of *in vitro*

or *in vivo* tests such as SPT and ImmunoCAP specific IgE blood tests (formerly known as radioallergosorbent tests or RAST) (Bock et al., 1977; Chinoy et al., 2005). These tests assist in determining if the patient possesses egg allergen specific antibodies in their immune system. Although these tests provide an estimation of allergen specific IgE in the patient, which positively correlates to the clinical reaction (wheal formation), they fail to fully ascertain diagnosis of clinical symptoms of egg allergy. Increasing levels of IgE may predict the presence of an allergy, however, there is no universal agreed level of IgE to confirm the condition as the IgE levels can differ between different individuals. This may also be due to the discrepancies between the testing method, testing criteria and prevalence of the allergy between studies. However, a recent study conducted by Sicherer et al. (2014) has further confirmed the significant predictive capacity of IgE as a marker in egg allergy. They also report of a web-based calculator that uses an algorithm, which is based on novel findings egg specific IgE, that may allow clinicians to predict the likelihood of the resolution or persistence of the disease. Supplementary studies on IgE as a reliable egg allergy marker may provide useful information for the development of effective diagnostic approaches.

In addition to SPTs and ImmunoCAP tests, elimination diets and oral food challenges can be used for the diagnosis of egg allergy. In an elimination diet diagnosis, once the patient is suspected of being allergic to eggs, a diet excluding eggs is followed to study the ability of the patient to maintain the diet without any hypersensitive reactions over a period of time (Sicherer, 2013). In an oral food challenge, the patient is asked to eat/ingest a small amount of egg to reproduce the hypersensitivity symptoms. It is also done in a dose dependant manner where the egg ingestion is increased until the symptoms are observable. Oral food challenge can be done openly, single-blinded, double-blinded placebo controlled, with the latter being considered the gold standard in diagnosis of major food allergies because it provides information such as the amount of food needed to cause an allergic reaction and the extent of the patient's reaction (Rance et al., 2009). However, the safety of oral food challenge has not been well established or scrutinised and may not be ideal if the patient is known to be anaphylactic to eggs, therefore much care should be taken when implementing this method. Overall, medical history and physical examination, SPTs or ImmunoCAP tests and oral food challenge combined together provides successful diagnosis of egg allergy (Fig. 4), which can lead to the implementation of treatment strategies for the condition.

11. Treatment of egg allergy

As for other food allergies, currently there is no temporary or permanent cure for egg allergy. Upon successful diagnosis for egg allergy, the most effective treatment is strict dietary avoidance of eggs and products containing traces of eggs. Eggs are an important source of nutrients and thus strict avoidance may cause malnutrition or eating disorders. The egg yolk is known to carry numerous health benefits, but since it is impossible to fully separate the egg yolk from the egg white without allergen contamination, complete avoidance of the egg is the only option, which results in reduced or no uptake of this important nutrient source (David et al., 1984; Friedman, 1996). As a part of avoidance of eggs, it is important to educate patients how to identify potential egg allergens or traces of eggs in various food products such as cakes, biscuits, cereal and breads, as well as educate them about foods/supplements that can potentially replace eggs in their diet. This may include involvement of a dietician for patients with dietary limitations, such as vegetarians and multiple food allergic patients, to ensure proper intake of vital nutrients.

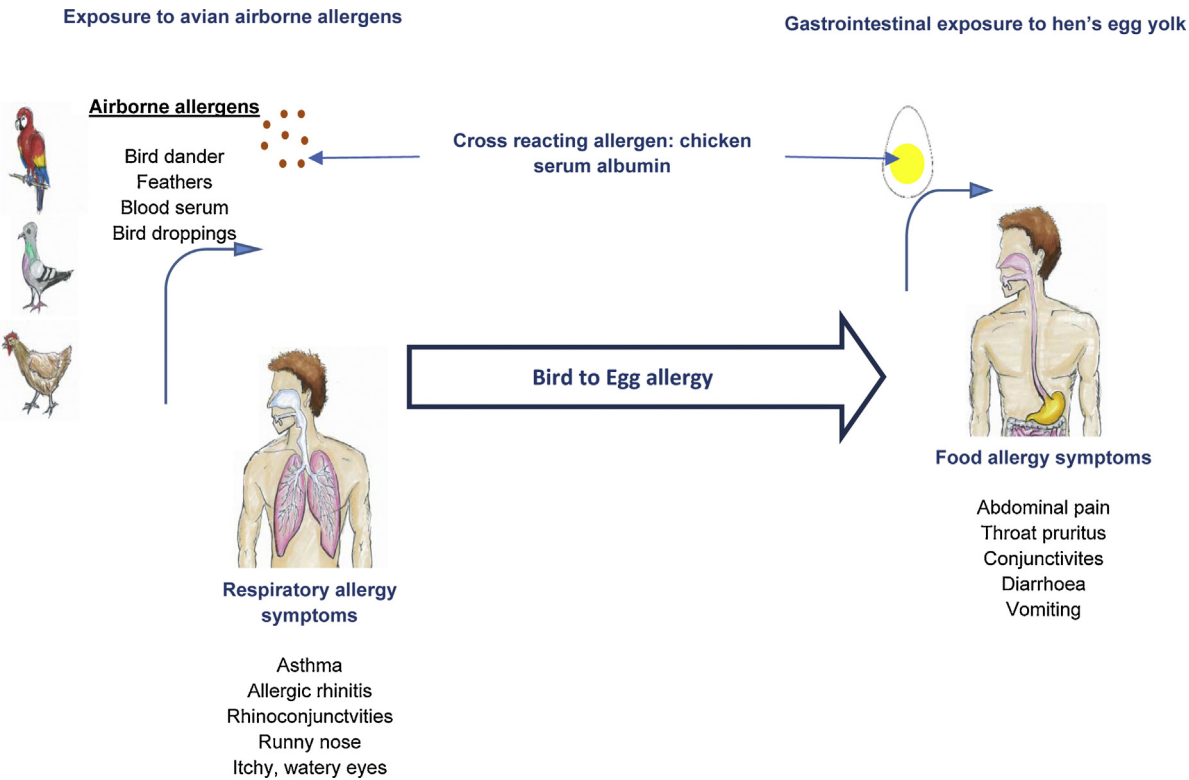


Fig. 3. An illustration of the bird-egg syndrome.

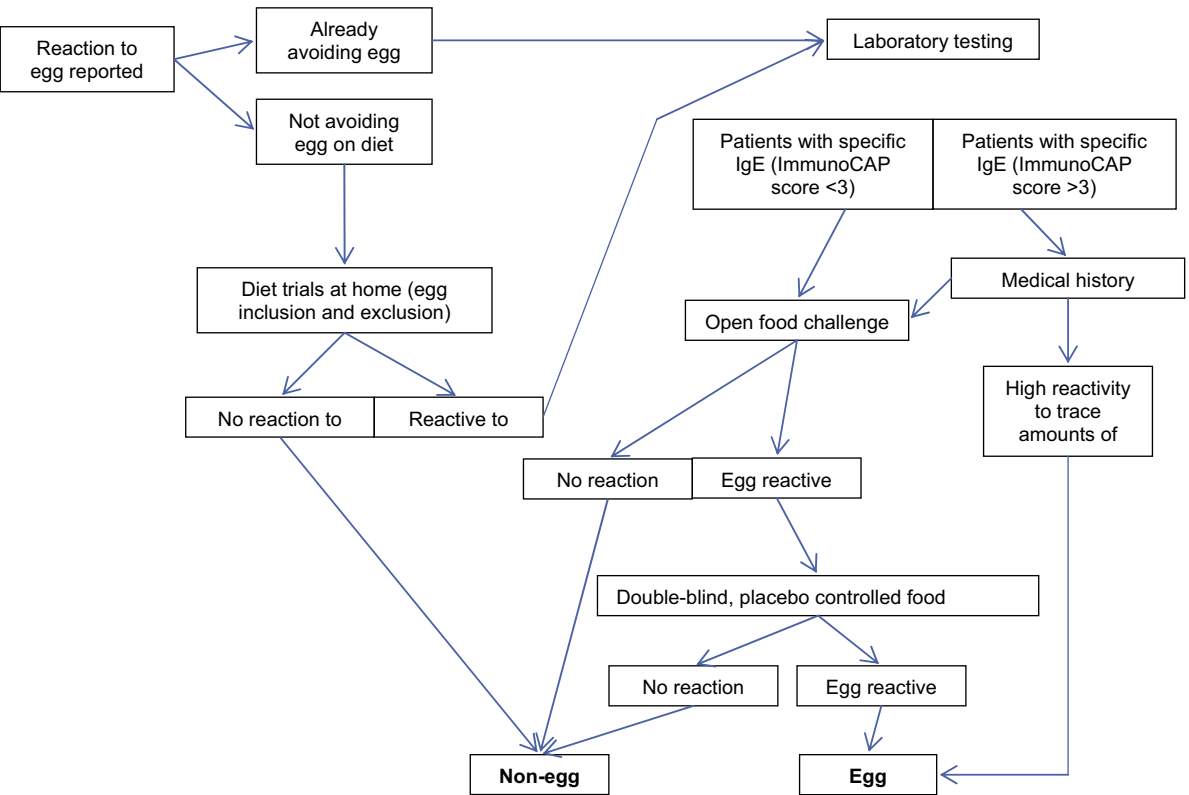


Fig. 4. A typical diagnosis procedure of egg allergy. Once a suspected a reaction to egg is reported a patient undergoes the appropriate steps shown in this figure. Figure adapted and modified from Eggesbø et al. (2001).

In addition to dietary avoidance, egg allergic patients are required to avoid vaccines and medications derived from eggs. For example, influenza vaccine is developed in chicken extra embryonic fluid and used extensively worldwide every year (Caubet and Wang, 2011). Although the majority of egg allergic patients may not have adverse effects upon administration of influenza vaccine (Chung et al., 2010), it is important to take caution to avoid severe or anaphylactic reactions in the individuals that may well react to the egg allergens (Zeiger, 2002). These patients should receive the vaccine via a desensitisation protocol upon diagnosis with a positive skin test. Yellow fever vaccine is another vaccine derived from chicken egg, with few reported cases of anaphylaxis upon administration (Kelso et al., 1999). Moreover, there are reported cases of anaphylaxis due to the use of lipid emulsions and pharmaceutical products derived from eggs (Artesani et al., 2008; Buchman and Ament, 1991; Hofer et al., 2003). Occurrence of egg allergens in our daily diet, vaccines and other pharmaceutical products complicates strict avoidance of eggs. Therefore, alternatives are required to treat patients in case of accidental exposure to the egg allergens.

In allergic conditions such as asthma, specific immunotherapy (SIT) is used to induce tolerance to the allergens. This method essentially involves administration of small amounts of allergens to patients in, with slight increments, to induce tolerance to that particular allergen. A study conducted by Buchanan et al. (2007) indicates that oral immunotherapy (OIT), a form of SIT, may provide a promising treatment strategy for patients without anaphylactic history to eggs. The authors suggest that OIT may even cause a shift in food allergy treatment paradigm from allergen avoidance to active immunotherapy. This is further supported by a recent study in which OIT showed successful desensitisation to eggs, however tolerance was maintained only in 1/3 of the study population following discontinuation of the egg diet (Caminiti et al., 2015). However, extreme care should be taken during immunotherapy to avoid potential anaphylactic reactions. In case of an accidental exposure to egg allergens, and acute anaphylaxis, the most common treatment is administration of the hormone and neurotransmitter epinephrine (Kemp et al., 2008; Sampson, 2004; Wasserman and Watson, 2011). Upon administration of epinephrine at the right dosage and appropriate route, peripheral vasodilatory effects and bronchoconstriction caused by histamines and other chemical mediators released by allergic reactions are reversed, conditions such as urticaria, erythema and angioedema are reduced and further release of chemical mediators are suppressed. Currently, epinephrine is available for self-administration by auto-injectors such as EpiPen. In summary, allergen avoidance, SIT and administration of epinephrine provide temporary relief from egg allergic reactions. However, these methods can be costly and may have negative effects on the lifestyle of the patient. Therefore, it is imperative to investigate and research on permanent and affordable ways to treat egg allergy.

12. Future perspectives in egg allergy research – cracking the egg problem

Various research teams around the world are involved in finding answers or cures for different types of allergies. Development of hypoallergenic variants of the egg allergens is given utmost priority by many egg allergy researchers, because hypoallergens may be used in immunotherapy to desensitise egg allergic patients. In fact, a group from University of Guelph in Canada has studied the efficacy of an engineered ovomucoid third domain at desensitizing a murine model (Rupa and Mine, 2006). This hypoallergenic third domain has been produced by directly targeting the IgE binding sites of that domain. A similar approach has been tested in 2004 by an Australian research team in which they successfully developed a

T-cell reactive hypoallergenic variant of the latex allergen, Hev b 6.10, by targeting the disulphide bridges of that allergen (Drew et al., 2004), therefore it can be suggested that similar methods can be used for the development of hypoallergenic variants of egg allergens. In addition to the aforementioned methods, it has been recently reported that allergen conjugation with reducing sugars through the Maillard reaction may help attenuate allergic reactivity to allergens (Rupa et al., 2014). Production of IgE reactive recombinant variants of egg allergens is also important in diagnostic methods such as SPT and treatment methods such as SIT (Dhanapala et al., 2015; Valenta et al., 2011). Although the current results seem promising, all of the research conducted on hypoallergen and IgE reactive recombinant allergen production requires clinical trials before administration to patients.

The focus of egg allergy research should not be limited to the aforementioned strategies and invention of drugs/vaccines. The advanced molecular and genetic techniques used in other medical research and life sciences can be utilised for tackling egg allergy from the root of the cause. A team in New Zealand has developed a transgenic calf lacking the milk allergen β -lactoglobulin using RNAi technology (Jabed et al., 2012). Similar methods can be used in egg allergy research providing promising methods of egg allergy treatment or management. The advancement of techniques such as CRISPR (clustered regularly interspaced short palindromic repeats) (Sander and Joung, 2014) based genome editing may also allow precision engineering of the chicken genome to edit/change the IgE binding epitopes to produce transgenic hens capable of producing hypoallergenic eggs. If any of the current research on egg allergy proves successful in the future, a large number of families will benefit by being less apprehensive about eggs or egg contaminated products.

Conflict of interest

There is no conflict of interest

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