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## **Practical experience of allergy to egg proteins clinical manifestation**

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## **Abstract**

Food allergy occupies a significant place among disorders that impair the quality of patients' lives, bringing a large number of restrictions to their diet and lifestyle. Therefore, the purpose of this study is to examine the clinical features of allergy to chicken eggs with the determination of key trends in diagnosis and treatment. A descriptive and comparative analysis of three cases was carried out with a large-scale assessment of specific Immunoglobulins E (IgE), determined by the enzyme-linked immunosorbent assay. It becomes clear, that due to the high prevalence of allergy to white and yolk of chicken eggs in the general population (among the Polish population including), chicken eggs have severe allergenic characteristics and may display various symptoms that may be problematic to differentiate. The patients from the presented cases were characterized by a severe course of the disease – minimal consumption of chicken eggs led to the development of urticaria, swelling of the eyelids, and bronchospasm, which required urgent administration of adrenaline and hospitalization. For the purpose of diagnosis, patients with anaphylactic reactions are highly restricted, because methods of skin prick testing, and provocation tests (oral and nasal) are contraindicated. In this regard, molecular diagnostics and the determination of specific immunoglobulins E for ovalbumin, ovomucoid, and other glycoproteins are recommended. This research can lead to the creation of purified recombinant allergens for use in the process of diagnosis and treatment, as well as in the food industry, also, it emphasizes the introduction of preventive measures for the development of anaphylaxis.

## Introduction

Currently, most allergies are related to food products, and according to the estimates of the World Allergy Organization (WAO), more than 10% of people worldwide suffer from food allergies.<sup>1</sup> Despite the necessity of consuming food to maintain life and health, it remains particularly unclear why the human body identifies certain foods as harmful, which is the basis for the development of intolerance to them. Nevertheless, significant progress has been made in understanding the mechanisms of allergic reactions. According to E. Johansson and T.B. Mersha,<sup>2</sup> it was even shown that the risk of the disease in a child is up to 80% if there are hereditary factors.

Zambrowicz *et al.*<sup>3</sup> pay attention to chicken eggs as a source of necessary nutrients that have a beneficial effect on human health; there are also biologically active compounds that affect metabolic processes, especially in the cardiovascular system and muscles. These nutrients include proteins, lipids (including high-density lipoproteins), carotenoids, and other biologically active compounds exhibiting antioxidant, antimicrobial, immunomodulatory, anti-inflammatory, and pro-inflammatory properties.<sup>4</sup> Chicken eggs also contain essential B vitamins, fat-soluble vitamins, trace elements, choline, and a relatively small amount of saturated fatty acids compared with other food sources of animal origin.<sup>5</sup> Therefore, the high nutritional value of chicken eggs makes them a valuable component of dietary nutrition not only for people with an increased need for proteins (such as children and the elderly), but also for the general population.

Chicken eggs, which are a rich source of useful substances, occupy one of the first places among food allergens. A recent study among European countries showed that in Łódź (Poland), among children aged 7 to 10 years, allergies to chicken eggs account for 5% of all food allergies and give way to cow milk and peanuts.<sup>6,7</sup> Most allergens are contained in the egg white, but the yolk also contains substances with allergenic activity.<sup>8</sup> Thus, allergy to chicken eggs occupies an important place in the context of food sensitization, which forces patients to resort to dietary restrictions and deprives them of the opportunity to consume this product, which has a number of useful properties. S.H. Sicherer *et al.*<sup>9</sup> stratified patients with allergy to chicken eggs as “highly allergic” and “not highly allergic”,

which allows to individualize the approach to therapy for each patient depending on the severity of clinical manifestations.

Therefore, there is promise and significance in exploring the issue of food allergy within the framework of variations in clinical presentations, leading to the development of treatment and diagnostic strategies rooted in a comprehensive understanding of the underlying principles of etiopathogenesis. Therefore, the task of this study is to investigate the clinical features of this food allergy on the basis of three clinical cases and other published investigations, as well as to determine promising research directions.

## **Materials and Methods**

At the beginning of the study, three clinical cases that demonstrate a variety of clinical manifestations of an allergy to chicken eggs were selected. All patients were hospitalised in the National Medical Institute of the Ministry of Internal Affairs (Department of Allergology) between 2021 and 2022.

In the first case patient M., 45 years old, who has been allergic to chicken eggs from early childhood, still has attacks of bronchial asthma in the kitchen where chicken broth is cooked. At the same time, small amounts of chicken yolk, which can remain and dry on poorly washed dishes, can cause symptoms of anaphylaxis: swelling of the face, eyelids, and lips, as well as symptoms of generalized urticaria and bronchospasm, which needs the administration of adrenaline. In the second case, 13-month-old patient I., after eating 4 teaspoons of scrambled eggs almost immediately developed generalized urticaria, bilateral swelling of the upper eyelids, cough, and shortness of breath. In the third case, 8-month-old patient K. ate a small piece of omelet and after 30 seconds she developed shortness of breath, swelling of the upper eyelids of both eyes, and swelling of the face. These symptoms lasted approximately 6-7 hours.

All of them were physically examined, and for the next diagnostic intervention, blood serum was collected for the determination of specific Immunoglobulin E (IgE) in kilounits per liter (kU/L) to chicken egg white, chicken egg yolk, ovalbumin, ovomucoid, conalbumin, and lysozyme. For this,

the Enzyme-Linked Immunosorbent Assay (ELISA) technique was applied to the Phadia 100 analyser. Patients were also examined for complete blood count, urine analysis, Electrocardiogram (ECG), chest x-ray, but these diagnostic procedures were not presented in the study, since their results had no practical value for making a diagnosis of food allergy.

All patients were treated with an elimination diet, but based on the results of an immunological study, none of them responded adequately to treatment. Patients also continued to present respiratory symptoms, which could also be life-threatening. The patients were given new therapeutic recommendations, but this information was not covered during this follow-up, since the subjective status of the patients was not re-evaluated and immunological tests were not carried out to determine the titer of specific immunoglobulins E.

The article also used descriptive methods and methods of comparative analysis, which were used to search for and determine the characteristics of chicken egg allergens and their role in the clinical manifestation of patients with food allergies, the share and role of immunotherapy, current trends and the establishment of diagnostic methods, as well as the prospects for further research.

## **Results**

Among the known components of eggs, five are distinguished by strong genetic properties and are considered the main allergens of chicken eggs. These are glycoproteins: ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin (Gal d 3), lysozyme (Gal d 4) and albumin (Gal d 5).<sup>10</sup>

Table 1 provides information on chicken egg allergens contained in two databases: Allergen WHO (World Health Organization) / IUIS (International Union of Immunological Societies) and Allergome. According to the recommendations of the WHO/IUIS subcommittee, allergens are indicated by the first three letters of the generic name of the organism from which the allergen originates and the first letter of its species name. In the case of chicken egg allergens, this is the abbreviation Gal d (*Gallus domesticus*) (Table 1).

During the examination of all mentioned patients, the determination of specific IgE to chicken egg white, chicken egg yolk, chicken meat, chicken proteins (ovalbumin, ovomucoid, ovotransferin, lysozyme) was used in order to answer a number of questions: i) is intolerance to chicken eggs or meat associated with the development of an allergic reaction? ii) to which of the components (protein or yolk) is there this intolerance? iii) what specific protein does this intolerance exist for?

As can be seen from Table 2, patient M. had high titers of antibodies to chicken white, yolk, and meat, so it was inappropriate to determine indicators for particular proteins, since their result was expectedly high and it would not affect either the diagnostic or treatment tactics. Despite the use of a strict elimination diet for 40 years of life (that is, the diagnosis of allergy to chicken eggs was made at the age of 5), the patient still has not only an allergic condition but also continues to have life-threatening clinical symptoms. In most children, allergy symptoms can disappear between the ages of 2 and 5 years (although patients I. and K. present symptoms of food allergy even before the age of 1 year), and sometimes they persist up to 10 years or even appear only in adulthood and on the example of patient M., this disease can accompany the entire life.<sup>11,12</sup>

Allergy symptoms can be represented by damage to various organ systems and varying degrees of severity. It can manifest as signs of gastrointestinal disorders (such as abdominal pain, vomiting, diarrhoea, meteorism), skin itching and/or atopic dermatitis, urticaria, rhinitis and/or conjunctivitis, in more severe cases – asthma and swelling of the larynx.<sup>11</sup> A. Bongiovanni<sup>12</sup> observed that in patients with cutaneous manifestations, this hypersensitivity is very common and sometimes very intense. According to the EuroPrevall study, in which 12049 infants were included, among whom 0.7% had an egg allergy, while the presence of eczema at the time of examination and in the anamnesis increased the risks of allergy more than 9 times, rhinitis symptoms – 3 times, and atopic dermatitis disease – more than 1.5 times. Taking antibiotics in the first days of life also played a role, which is probably mediated by the effect on the intestinal microbiota. The researchers also note that the age of introducing eggs into the diet was not associated with egg allergy.<sup>13</sup> It is interesting that the examined

patients did not have previous atopic reactions, and the development of allergy debuted with episodes of anaphylaxis.<sup>14</sup>

People with an allergy to chicken eggs often have urticaria, especially in its two forms – acute and contact. In the study by H. Ünsal *et al.*<sup>15</sup> in which 102 children were included, urticaria was observed in the second place after manifestations of allergy to chicken eggs in the form of atopic dermatitis (65.6%) – 18.6%. Contact urticaria is especially common in children and after ingestion of eggs, occurs mainly around the mouth and is sometimes accompanied by erythema. It is noteworthy that in the same study, children demonstrated attention to warmed (92.3%) and baked eggs (87.2%), which also correlated with the perception of the yolk. The patients from the described clinical cases had a high level of immunological reactivity, due to which they could not tolerate any chicken egg proteins, even after thermal exposure, and the severity of allergic reactions did not depend on the amount of these proteins.

It is worth mentioning the rare forms of allergy to chicken egg proteins, which can get not only through food consumption. Respiratory symptoms (such as hay fever, bronchial asthma, rhinitis) and conjunctivitis are characteristic not only among children, but also among adults – this is sometimes observed in workers of the food industry and poultry farms who came into contact with aerosols containing egg powder or liquids from components of chicken eggs, which is clinically similar to baker's asthma to wheat allergens, and only some of these patients also develop food allergies.<sup>16,17</sup> Another consequence of inhalational allergy can be bird-egg syndrome, specifically of adults (especially women), although it can also occur in childhood, which was mentioned earlier. Bird-egg syndrome refers to a rare form of allergy characterized by hypersensitivity reactions to avian proteins, particularly those found in bird eggs. This syndrome typically manifests as respiratory symptoms such as hay fever, bronchial asthma, rhinitis, and conjunctivitis upon exposure to aerosols containing egg powder or liquids from components of chicken eggs. Workers in the food industry or poultry farms who come into contact with such aerosols are at risk of developing this syndrome, which can resemble baker's asthma caused by wheat allergens. Bird-egg syndrome may also occur in individuals



with egg allergies who develop respiratory symptoms upon exposure to avian proteins, even without ingesting eggs. In addition to respiratory symptoms, individuals with bird-egg syndrome may experience other allergic reactions, such as Oral Allergy Syndrome (OAS), which presents as swelling of the lips and itching of the oral mucosa, sometimes accompanied by abdominal pain and vomiting. Rare cases have also been reported where bird-egg syndrome is associated with ulcerative colitis, a form of inflammatory bowel disease. In such cases, eliminating eggs from the diet can lead to significant improvement in symptoms, highlighting the importance of testing for food hypersensitivity and adhering to a hypoallergenic diet in the management of inflammatory bowel diseases.<sup>16,17</sup>

Sometimes people with egg allergies also develop OAS, which is usually seen in people with allergies to fruits, vegetables, and nuts, and the most important symptoms of this syndrome are swelling of the lips and itching of the oral mucosa, sometimes abdominal pain and vomiting.<sup>18</sup> Rare cases include ulcerative colitis (*colitis ulcerosa*) – in this case, it is worth mentioning the following clinical situation: the patient L., 44 years old, who suffered from ulcerative colitis for 20 years, was tested for a possible food allergy, and one of the *in vitro* tests with chicken eggs gave a positive result. The patient followed an egg-free elimination diet and saw immediate improvement, and 9 months later, at her last examination, she considered herself completely cured. Thus, testing for food hypersensitivity and adherence to a hypoallergenic diet can have a significant place in the diagnosis and treatment of inflammatory bowel diseases, which has been confirmed in scientific studies.<sup>19</sup>

The first stages of the diagnostic tactic often include elimination diets, which involve removing one or more food groups from the diet; however, this strategy can lead to problems, as children may experience weight loss, eating disorders, and stunted growth resulting from malnutrition.<sup>20</sup> However, in the described cases, dietary restrictions are of a forced nature, since the consumption of food products containing chicken eggs and/or meat can pose a threat to health and life, so this is the first step in solving the issue of food intolerance. At the same time, it is worth mentioning other diagnostic methods that can be used to establish a diagnosis of food allergy, in the case that the disease has a

mild or moderate course of severity, and there are no contraindications to these procedures. *In vivo* diagnostics, such as a Skin Prick Test (SPT), involves applying a small amount of a target allergen to the epidermis using a needle or scarifier, which allows the allergen solution to penetrate into the body.<sup>21</sup> The severity of the reaction is then assessed by calculating the diameter of the affected area, which is considered a qualitative indicator, as there is currently no unified way of interpreting these data.<sup>22</sup> Also, this method is associated with significant risks due to the unpredictability of the results, taking into account the direct impact on the patient caused by allergens, which was reported in a number of case reports – therefore, for the subsequent treatment of anaphylaxis, it is necessary to have appropriate equipment and consumables, such as epinephrine, an artificial pulmonary ventilation kit.<sup>23,24</sup> An additional problem that arises during SPT is the insufficient representation of allergen extracts due to biological variability of allergen sources, which often leads to false-negative results.<sup>21</sup>

*In vivo* methods include Oral (OPT) and Nasal Provocation Tests (NPT), which demonstrate good results in examining adult patients with food allergies.<sup>25</sup> A Double-Blind, Placebo-Controlled Food Challenge (DBPCFC) is the gold standard for confirming the diagnosis of food allergy, although it is time-consuming and not without risk, it is possible to conclude that such research methods are more specific than SPT and have a tropic effect with the development of gastrointestinal and respiratory reactions.<sup>26</sup> It is worth noting that in this case report study, a 21-year-old patient with an allergy to chicken eggs also underwent immunological testing (such as Polycheck, ALEX multiplex test, ISAC, ImmunoCAP), where she received positive titers of IgE to Gal d 1, Gal d 2 and negative IgE for Gal d 3, Gal d 4 and Gal d 5. In the study by J. Kido et al.<sup>25</sup> which included 103 children with suspected chicken egg allergy, a diagnostic program was performed that included an OPT, molecular diagnostics, and SPT. D.V. Maltsev<sup>26</sup> came to the conclusion that these methods should be performed with the usage of both raw and heated eggs, with OPT demonstrating more pronounced results in the case of a reaction to raw eggs without a reaction to heated ones, unlike SPT and IgE tests.

The possibility of using allergenic molecules in the last decade initiated a new phase of diagnostics, which is now called Precision Allergy Molecular Diagnostic Applications (PAMD@), this made it possible to improve the management of patients with food allergies.<sup>27, 28</sup> In the described cases, the use of molecular diagnostic methods plays an important role, as it is minimally invasive, highly accurate and allows monitoring the effectiveness of the therapeutic measures. Returning to the data in Table 2, it is possible to conclude that patient I. had no dynamics of titers of diagnostic antibodies after the elimination diet therapy. In patient K., the dynamics turned out to be positive, but insufficient in combination with a history of anaphylaxis, which requires the continuation of strict dietary restrictions. Thus, unmet medical requests for the efficient treatment of food allergies represent a significant challenge for today's society. The development of allergy diagnostics has greatly benefited from advancements in the molecular identification of allergens. For such patients, as described in this study, it is necessary to develop diagnostic and therapeutic procedures that would be safe to use and available to patients of different ages and social categories.

## **Discussion**

In typical cases of chicken egg allergy, symptoms appear before the age of two years, which is several months later than with cow milk allergy, which affects 1-4% of the general population of European countries, but this percentage may be higher in children with atopic tendencies.<sup>11</sup> According to W. Balińska-Miśkiewicz, allergens Gal d 1-4 more often cause allergic reactions in children, while Gal d 5 and Gal d 6 more often cause allergic symptoms in adults. In the presented three cases, it was the Gal d 1 and Gal d 2 allergens that played a key role in the development of an allergic reaction, and actually anaphylaxis.<sup>29</sup>

It can be assumed that heat treatment causes denaturation of chicken egg proteins, and such changes in conformation can significantly affect the allergenic structure of the protein, which will prevent contact with antibodies of the IgE class and mediate the development of an allergic reaction. The data

was presented by de Silva *et al.*<sup>30</sup> that boiling an egg for at least 10 minutes reduces its allergenic effect by more than 75%, frying or baking – even more, so most children with allergy symptoms after eating raw or semi-raw eggs tolerate fried eggs and baking well, and heat treatment of food contributes to the destruction infectious agents.<sup>31,32</sup> However, as it was mentioned earlier, among the indicated patients, heat treatment of food products did not protect against the development of symptoms of the disease. However, knowledge about the structure can be used to obtain proteins with reduced allergenic properties, which was discovered during experimental studies.<sup>33,34</sup> This could help create egg analogs for the food industry to enable food allergy patients to expand their diet without fear of provoking a paroxysm of the disease.

According to research by Lunhui *et al.*,<sup>8</sup> the egg white is more allergenic than the yolk, although it also has allergenic properties; this allows to avoid an excessively restrictive diet, which contributes to the improvement of the quality of life of patients in their family.<sup>8</sup> Among the described patients, a reaction to both chicken protein and egg yolk was observed under the conditions of the development of severe symptoms, which suggests the reactivity of the body to all components of the egg, which requires the complete exclusion of this food product and its derivatives from the diet. It is worth paying attention to the phenomenon of cross-reactions. Different researchers presented their cases, that while diagnosing an allergy to chicken egg allergens, it is necessary to take into account the possibility of cross-allergic reactions between allergens obtained from egg white and yolk, as well as between eggs of different species of birds, such as turkeys, ducks, geese, quails, and even seagulls. Cross-allergic reactions between allergens from different bird tissues are the basis of the state called bird-egg syndrome, which is characterized by the coexistence of food allergy to eggs and meat and inhalation allergy to bird feathers. Patients were not tested for cross-reactivity, but this study would be useful in the context of clarifying dietary and professional restrictions to protect them from developing allergic reactions.<sup>34-36</sup>

Dona and Suphioglu<sup>27</sup> presented a detailed systematic review of other aspects of allergy diagnosis. This process begins with a thorough analysis of the patient's environmental factors and symptoms,

followed by a physical examination. Allergy diagnosis and treatment is often problematic because the condition is multifactorial and symptoms and timing of onset can be confusing to doctors – this is due to food symptoms that can be signs of both IgE-mediated Food Allergy (IFA) and non-IFA, malabsorption syndrome, psychological rejection, and other medical disorders.<sup>37-39</sup> The key point is that a true allergic reaction to a food product occurs after consumption of a particular food, and allergic symptoms appear within minutes or hours after consumption.<sup>25</sup> In the example of the described patients, the diagnosis of IFA does not cause any doubts.

Currently, there are no temporary or permanent therapeutic methods that would completely cure allergies. In the case of a confirmed diagnosis of allergy, especially allergy to eggs, according to Caffarelli *et al.*,<sup>40</sup> the main therapeutic approach is to strictly exclude the allergen from the diet or minimize contact with it. And for the patients with anaphylactic reactions in these cases, it was the only outcome. Usage of pharmacotherapy is aimed at alleviating symptoms by blocking allergy mediators, as in the case with antihistamines. Parisi *et al.*,<sup>41</sup> however, note that this treatment is not etiologic, because it does not stop the production of specific IgE antibodies. In addition, drugs like anti-leukotriene blockers (that stabilize mast cells) and anti-inflammatory corticosteroids can induce the development of immunosuppression with undesirable side effects. Parisi *et al.*,<sup>42</sup> in the described cases, note that no data were presented on the use of other medications, except for adrenaline, which would be useful to investigate in subsequent studies.

Although such severe cases are rare in European countries, anaphylaxis is a life-threatening condition and it requires the use of epinephrine, which, according to recommendations, is administered intramuscularly, and must be previously prescribed by physicians in the amount of 2 auto-injector pens.<sup>43,44</sup> Allergen-Specific Immunotherapy (ACIT or AIT) is recognized as the most effective and safest method of treatment and alleviation of allergy symptoms, and the results of clinical studies indicate that immunotherapy can not only alleviate allergic symptoms, but also prevent the development of allergies. This therapy consists of the regular and long-term introduction of allergen extracts in order to achieve a tolerance to the allergen.<sup>45-47</sup> The first stage of therapy is called induction

of desensitization, the effectiveness of which depends on the dose of extracted allergens in the form of subcutaneous injections, tablets, aerosols, or sublingual drops. This means that the minimum dose of the administered extract should be sufficient to effectively control symptoms. Therapeutic efficacy increases over time, as significant improvement is usually observed only after at least three months of therapy, which may continue for several years.<sup>43</sup> Therefore, it is extremely important to communicate realistic expectations to patients.

Nevertheless, immunotherapy is associated with a significant risk of anaphylaxis, which requires special care and vigilance by medical personnel. Oral immunotherapy appears to be preferentially used in patients who do not report previous symptoms of systemic or gastrointestinal anaphylaxis, whereas sublingual and epicutaneous ways of distribution in particular may be more preferentially used in patients at risk of anaphylaxis.<sup>48-50</sup> Therefore, there is a need for safer reagents for immunotherapy, such as highly purified recombinant hypoallergens, which would minimize the risk of anaphylaxis. This highlights the importance of investigating safe recombinant allergens and hypoallergens in the context of immunotherapy.<sup>47</sup> The usage of recombinant DNA technology, where individual proteins are expressed separately in bacterial and/or yeast host systems, it is possible to obtain allergens with a higher degree of purity, free from other allergens, and with preservation of T-cell epitopes and immunogenicity.<sup>48</sup> Changing the conformational epitopes of B cells while preserving the epitopes of T cells allows for reducing IgE reactivity, creating hypoallergens.<sup>51-53</sup> There are also many approaches to protein modification, including molecular fusion or fragmentation, random or point mutations, and the formation of chimeric and mosaic structures, all of which can be used to reduce the risk of adverse allergic reactions.<sup>54,55</sup> Patients of the described clinical situations could become candidates for AIT, however, considering the severity of the course, high immunoreactivity, early childhood, and the imperfections of this method of treatment, unfortunately, these patients currently have no other treatment alternatives except strict dietary restrictions and constant access to the use of adrenaline.

Thus, identifying details about cross-reactivity, primary sensitization, and hazards should be included in the diagnostic search for patients with chicken egg allergy. Pitfalls in this process can be the severity of the patient's condition, availability, and associated costs, which prevent widespread use. The lack of safe and well-standardized recombinant IgE-reactive allergens and their hypoallergenic variants, the lack of long-term population studies with a comprehensive approach to egg allergy, and the lack of safe and well-standardized diagnostic and therapeutic approaches are among the limitations of the current study.

## **Conclusions**

Chicken eggs have strong allergenic properties, which leads to a high percentage of allergy to chicken eggs (both white and yolk) in the general population. Food allergy can be the first manifestation of atopic march in childhood patients; however, the development of this condition is quite likely in adulthood, especially in the presence of a burdensome family and professional history. The main allergenic components of chicken egg are glycoproteins ovomucoid (Gal d 1), and ovalbumin (Gal d 2). Symptomatically, allergy is very polymorphic. Most often, the clinical picture in patients is represented by skin manifestations, although the presented clinical cases show that an allergic reaction can develop into a life-threatening condition (anaphylaxis) that requires immediate administration of epinephrine, which patients should be taught.

Diagnosis and treatment of allergies are often problematic due to the need for detailed differential diagnosis between different clinical conditions, but in cases of anaphylaxis the diagnosis of IgE-mediated food allergy has no doubt. The development of allergy diagnostics has greatly benefited from the improved molecular identification of allergens and determination of specific IgE – it is safe and available for patient, who are contraindicated skin prick tests and other risky methods. Currently, there are also no temporary or permanent therapeutic methods that would allow the complete cure of allergies; however, allergen-specific immunotherapy is currently recognized as the most effective and

safe, but it is not developed for patients with food allergies. Innovations in molecular diagnostics will lead to safe and reliable diagnostic methods as well as improved pharmacological and immunological reagents for use in immunotherapy.

It is important to give a chance for a safe cure and life for patients with severe clinical manifestations of allergy to chicken eggs. The development of preventive measures, the creation of hypoallergenic chicken egg protein for therapeutic use, as well as the stratification of patients according to the severity of clinical manifestations and levels of specific antibodies, which could provide adequate tactics for the management of such patients, may be promising areas for the next research.

## References

1. Allergen-component Diagnostics Food-pollen Allergy. 2022. Available from: <https://www.worldallergy.org/component/content/article/allergen-component-diagnostics-food-pollen-allergy?catid=17&Itemid=101>
2. Johansson E, Mersha T. Genetics of food allergy. *Immunol Allergy Clin North Am* 2021;41:301-19.
3. Zambrowicz A, Dąbrowska A, Bobak Ł, Szołtysik M. Egg yolk proteins and peptides with biological activity. *Postepy Hig Med Dosw* 2014;68:1524-9.
4. Chen YP, Li D, Zhang XC, et al. Azacytidine-induced hypomethylation delays senescence and coloration in harvested strawberries by stimulating antioxidant enzymes and modulating abscisate metabolism to minimize anthocyanin overproduction. *Food Chem* 2023;407:135189.
5. Godovanets OI, Kotelban AV, Hrynkevych L, et al. Potential effectiveness of poly-vitamins and probiotics among preschool children living within iodine deficiency territory to caries prevention. *Pesq Bras Odontopediatria Clín Integr* 2020;21:1-11.



6. Savage J, Johns C. Food allergy: epidemiology and natural history. *Immunol Allergy Clin North Am* 2015;35:45-59.
7. Lyons SA, Clausen M, Knulst AC, et al. Prevalence of food sensitization and food allergy in children across Europe. *J Allergy Clin Immunol Pract* 2020;8:2736-46.e9.
8. Lunhui H, Yanhong S, Shaoshen L, et al. Component resolved diagnosis of egg yolk is an indispensable part of egg allergy. *Allergol Immunopathol* 2021;49:6-14.
9. Sicherer S, Abrams E, Nowak-Wegrzyn A, Hourihane J. Managing food allergy when the patient is not highly allergic. *J Allergy Clin Immunol Practice* 2022;10:46-55.
10. Chokshi N, Sicherer S. Molecular diagnosis of egg allergy: an update. *Exp Rev Molec Diagn* 2015;15:895-906.
11. Leech S, Ewan P, Skypala I, et al. BSACI 2021 guideline for the management of egg allergy. *Clin Experim Allergy* 2021;51:1262-78.
12. Bongiovanni A, Parisi GF, Scuderi MG, et al. Gastroesophageal reflux and respiratory diseases: Does a real link exist? *Minerva Pediatr* 2019;71:515-23.
13. Samady W, Warren C, Wang J, et al. Egg allergy in US children. *J Allergy Clin Immunol Practice* 2020;8:3066-73.e6.
14. Grimshaw KEC, Roberts G, Selby A, et al. Risk factors for hen's egg allergy in Europe: EuroPrevall birth cohort. *J Allergy Clin Immunol Pract* 2020;8:1341-8.e5.
15. Ünsal H, Dal S, Akarsu A, et al. Phenotypes of persistent hen's egg allergy in children and adolescents. *Turk J Pediatr* 2023;65:3-12.
16. Jeebhay M, Baatjies R. Occupational inhalant allergy in food handling occupations. *Curr Opin Allergy Clin Immunol* 2022;22:64-72.
17. di Palma E, Gallucci M, Cipriani F, et al. Asthma and food allergy: which risks? *Med* 2019;55:509.
18. Sicherer S, Warren C, Dant C, et al. Food allergy from infancy through adulthood. *J Allergy Clin Immunol Practice* 2020;8:1854-64.

19. Campmans-Kuijpers M, Dijkstra G. Food and food groups in Inflammatory Bowel Disease (IBD): the design of the Groningen Anti-Inflammatory Diet (GrAID). *Nutr* 2021;13:1067.
20. Kostecka M, Kostecka-Jarecka J, Kostecka J, et al. Parental knowledge about allergies and problems with an elimination diet in children aged 3 to 6 years. *Child* 2022;9:1693.
21. Foong R, Dantzer J, Wood R, Santos A. Improving diagnostic accuracy in food allergy. *J Allergy Clin Immunol Practice* 2021;9:71-80.
22. Almeida A, Perger E, Gomes R, et al. Objective evaluation of immediate reading skin prick test applying image planimetric and reaction thermometry analyses. *J Immunol Method* 2020;487:112870.
23. Pitsios C, Dimitriou A, Stefanaki E, Kontou-Fili K. Anaphylaxis during skin testing with food allergens in children. *Euro J Pediatr* 2010;169:613-5.
24. Hernández-Moreno K, Diez L. Systemic reaction after performing a food prick-to-prick test. A case report. *Rev Alergia Mexico* 2017;64:126-9.
25. Kido J, Nishi N, Matsumoto T. The oral provocation test for raw egg in patients with hen egg allergy. *Int Arch Allergy Immunol* 2018;177:40-4.
26. Maltsev DV. Efficiency of a high-dose intravenous immunoglobulin therapy in children with Autism Spectrum Disorders associated with genetic deficiency of folate cycle enzymes. *J Global Pharma Technol* 2019;11:597-609.
27. Dona D, Suphioglu C. Egg allergy: diagnosis and immunotherapy. *Int J Molec Sci* 2020;21:5010.
28. Steering Committee Authors, Review Panel Members. A WAO – ARIA – GA2LEN consensus document on molecular-based allergy diagnosis (PAMD@): Update 2020. *World Allergy Org J* 2020;13:100091.
29. Balińska-Miśkiewicz W. Molecular diagnosis of food allergy – Do we know more? *Postepy Hig Med Dosw* 2014;68:754-67.

30. de Silva D, Halken S, Singh C, et al. Preventing food allergy in infancy and childhood: Systematic review of randomised controlled trials. *Pediatr Allergy Immunol* 2020;31:813-26.
31. Sokołowicz Z, Kačániová M, Dykiel M, et al. Influence of storage packaging type on the microbiological and sensory quality of free-range table eggs. *Animals* 2023;13:1899.
32. Mine Y, Wei Zhang J. Identification and fine mapping of IgG and IgE epitopes in ovomucoid. *Biochem Biophys Res Commun* 2002;292:1070-4.
33. Dhanapala P, Withanage-Dona D, Tang M, et al. Hypoallergenic variant of the major egg white allergen Gal d 1 produced by disruption of cysteine bridges. *Nutr* 2017;9:171.
34. Moghtaderi M, Nabavizadeh S, Hosseini Teshnizi S. The frequency of cross-reactivity with various avian eggs among children with hen's egg allergy using skin prick test results: fewer sensitizations with pigeon and goose egg. *Allergol Immunopathol* 2020;48:265-9.
35. Lee J, Gantulga P, Lee C, et al. A preliminary study on cross-reactivity of heat-treated quail and hen's egg white proteins in young children. *Nutr* 2021;13:2172.
36. Langeland T. A clinical and immunological study of allergy to hen's egg white. VI. Occurrence of proteins cross-reacting with allergens in hen's egg white as studied in egg white from turkey, duck, goose, seagull, and in hen egg yolk, and hen and chicken sera and flesh. *Allergy* 1983;38:399-412.
37. LoVerde D, Iweala O, Eginli A, Krishnaswamy G. Anaphylaxis. *Chest* 2018;153:528-43.
38. Hemmer W, Klug C, Swoboda I. Update on the bird-egg syndrome and genuine poultry meat allergy. *Allergo J Int* 2016;25:68-75.
39. Gargano D, Appanna R, Santonicola A, et al. Food allergy and intolerance: a narrative review on nutritional concerns. *Nutr* 2021;13:1638.

40. Caffarelli C, Giannetti A, Rossi A, Ricci G. Egg allergy in children and weaning diet. *Nutr* 2022;14:1540.
41. Parisi GF, Leonardi S, Ciprandi G, et al. Cetirizine use in childhood: An update of a friendly 30-year drug. *Clin Mol Allergy* 2020;18:2.
42. Parisi GF, Leonardi S, Ciprandi G, et al. Antihistamines in children and adolescents: a practical update. *Allergol Immunopathol (Madr)*. 2020;48:753-62.
43. Nucera E, Inchingolo R, Nicotra R, et al. Influence of antihistamines on basophil activation test in food allergy to milk and egg. *Diagnost* 2020;11:44.
44. Patriarca G, Schiavino D, Pecora V, et al. Food allergy and food intolerance: diagnosis and treatment. *Intern Emerg Med* 2009;4:11-24.
45. Muraro A, Worm M, Alviani C, et al. EAACI guidelines: Anaphylaxis (2021 update). *Allergy* 2022;77:357-77.
46. Kraft M, Dölle-Bierke S, Turner P, et al. EAACI Task Force Clinical epidemiology of anaphylaxis: experts' perspective on the use of adrenaline autoinjectors in Europe. *Clin Trans Allergy* 2020;10:12
47. Schapovalova O, Gorlova A, de Munter J, et al. Immunomodulatory effects of new phytotherapy on human macrophages and TLR4- and TLR7/8-mediated viral-like inflammation in mice. *Front Med* 2022;9:952977.
48. Turmagambetova AS, Sokolova NS, Bogoyavlenskiy AP, et al. New functionally-enhanced soy proteins as food ingredients with anti-viral activity. *Virus Dis* 2015;26:123-32.
49. Mandziy ZP, Boichuk OH, Myhovykh VV. Correction of iron deficiency in the clinical picture of internal medicine. *Emerg Med (Ukraine)* 2021;17:64-70.
50. Muraro A, de Silva D, Halken S, et al. Managing food allergy: GA2LEN guideline 2022. *World Allergy Org J* 2022;15:100687.

51. Sahiner U, Giovannini M, Escribese M, et al. Mechanisms of allergen immunotherapy and potential biomarkers for clinical evaluation. *J Personal Med* 2023;13:845.
52. Marcucci F, Isidori C, Argentiero A, et al. Therapeutic perspectives in food allergy. *J Trans Med* 2020;18:302.
53. Lam H, Tergaonkar V, Ahn K. Mechanisms of allergen-specific immunotherapy for allergic rhinitis and food allergies. *Biosci Rep* 2020;40:BSR20200256.
54. Durham S, Shamji M. Allergen immunotherapy: past, present and future. *Nat Rev Immunol* 2023;23:317-28.
55. Pavón-Romero G, Parra-Vargas M, Ramírez-Jiménez F, et al. Allergen immunotherapy: current and future trends. *Cells* 2022;11:212.

**Table 1.** Chicken egg allergens in yolk and white.

	<b>Abbreviation</b>	<b>Name</b>		<b>Abbreviation</b>	<b>Name</b>
1	Gal d 1	Ovomucoid	9	Gal d Clusterin	Clusterin
2	Gal d 2	Ovoalbumin	10	Gal d IgY	Immunoglobulin Y
3	Gal d 3	Ovotransferin	11	Gal d PGDS	Lipocalin type prostaglandin D-synthase
4	Gal d 4	Lyzocyme C	12	Gal d OIH	Serine Protease Inhibitors
5	Gal d 5*	Alpha-livetin	13	Gal d Ovomucin	Ovomucin
6	Gal d 6*	YGP42	14	Gal d Phosvitin*	Casein Kinases
7	Gal d Apo I*	Apovitellenin-1/-4	15	Gal d RFBP	Riboflavin-binding Protein
8	Gal d Apo IV*	Apovitellenin-4			

\*allergens contained in the yolk of chicken eggs.

Source: created by the authors.

**Table 2.** Titers of specific Immunoglobulin E (IgE) (kU/l) before and after elimination diet

	Patient M., 45 years		Patient I., 8 months		Patient K., 13 months	
	Before	After	Before	After	Before	After
Chicken egg white	ND	30.4	43.75	54.8	17.4	2.84
Chicken egg yolk		18.3	0.51	0.35	ND	
Chicken meat		100	ND			
Gal d 1		ND	1.06	0.81	8.73	1.87
Gal d 2			0.25	0.32	0.09	0.02
Gal d 3			ND		ND	0
Gal d 4						0.07

ND, Not Determined; the reference value is up to 0.35 kU/L

Source: created by the authors.