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H.知的財産権の出願・登録状況

特になし

厚生労働科学研究費補助金　（食品の安心・安全確保推進研究事業）
科学的知見に基づく食物アレルギー患者の安全管理とQOL向上に関する研究
分担研究報告書

食物アレルギーへの理解促進を目的としたゲーム教材試作案の開発

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研究要旨

食物アレルギーに関する理解促進を目的として、食物アレルギー患者にとっての食物選択時の「危機」をコミュニケーション，いわゆるリスクコミュニケーションによって回避できるようになり、食物アレルギー患者としての疑似体験ができる教材開発を試みた。カードゲーム形式により、試作品が完成した。次年度以降、ゲーム性を高めつつ、アレルゲン除去が可能になるようなルールを添加し、より食物アレルギー患者の食物選択の疑似体験ができるようにし、完成させる。また、学校現場などでの試用により、評価をすることが必要不可欠と考えられた。

A．はじめに

食物アレルギーについてすべての人々が理解をしているわけではなく、学校現場などでは「いじめ」につながっている状況などを耳にする。また、食物アレルギー患者においては、幼少時には、食物選択をその保護者が主として行っているが、十代以降は、患者本人が食物を選択する機会が増える。食物アレルギー患者にとっての食物選択時の「危機」をコミュニケーション，いわゆるリスクコミュニケーションによって回避できるようになり、食物アレルギー患者としての疑似体験ができる教材開発を試みた。

リスクコミュニケーションのツールとして、ゲーミングシミュレーションを利用した教材（媒体）が開発され[1]、著者は、健康危機管理分野においてとそのプログラムの開発と評価を行ってきた[2-4]。ゲーミング・シミュレーションは，学習者が能動的であり，提供された論題の全体像を経験し，それは構成要素が一つ一つ別々ではなく同時に与えられ，プレイ後の議論や分析において無遠慮な発言や断定的な主張ではなく役割によって構造化されることなどがある。教育目的としては，動機づけと興味づけ，情報の提供または強化，意思決定やコミュニケーションなどの技能開発，態度変容，そして知識，態度やリーダーシップ能力などの評価が挙がっている[5]。また，現実の問題状況についてゲームという仮想的状況のなかで役割が与えられ，異なった世界観をもつ主体間でのコミュニケーションを可能とし，多様な意思決定のあり方，解釈のあり方について学習するための手段となりえるとされている[6]。

B．研究方法

教材利用の目的は食物アレルギー患者にとって食物選択時に起こる「危機」への対応として、どのように食事を選択すればよいのか、またどのようなアレルゲンがあるのか、食物アレルギー患者としての疑似体験による理解促進である。教材開発では、ゲーミングシミュレーションの研究やこれまで健康危機分野でゲーム開発を行ってきた研究協力者、そして、食物アレルギー患者を抱えるＮＰＯ団体との議論によった。

C．研究結果及び考察

ゲームはカードゲーム方式をとった。カードは「料理（献立名）」カードと「アレルゲン」カードの２種類である。

ゲームのストーリーとして、１週間の月曜から金

曜までのウィークデーの昼ごはんのメニューを決めていく。しかし、プレーヤー全員が何らかのアレルゲンをもった食物アレルギー患者のため、「バランスよく食べること」「アレルゲンは食べてはいけない」ことが決められている。手持ちの料理カードに書かれている総得点が高い人が勝利する。

「料理」カードの献立として、固定的に一対一対応（同じ献立名でも材料が異なる場合がある）にならないものを採用する。また献立名から容易にアレルゲンが含まれていることが予測できないものを採用する。そして、身近な献立とするために、国民栄養調査などを参考にする。また、食事には、そのシチュエーションも重要（デートや誕生日など）であるため、さまざまな料理を採択することとした。そして、そのデザインは視覚情報で料理を示すデザインをさける。

D．今後の課題と展望

試作品に対して今後反映させ、また改善する点として、ひとつの献立に対してアレルゲン数を２つなどと絞らないこと、アレルゲン除去ができるシチュエーションを設定することが考えられた。

次年度には試作品から完成させ、次年度以降学校などでの試用から評価を行うことが必要不可欠である。

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F．健康危険情報

なし

G．研究発表・学会発表

なし

H．知的財産権の出願・登録状況

なし

Ⅲ．研究成果の刊行に関する一覧

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Benhamou AH, Caubet JC, Eigenmann PA, Nowak-Węgrzyn A, Marcos CP, Reche M, Urisu A.	State of the art and new horizons in the diagnosis and management of egg allergy	Allergy	65	283-289	2010
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Ito K, Urisu A.	Diagnosis of food allergy based on oral food challenge test	Allergol Int	58	467-474	2009

Ⅳ．研究成果の刊行物・別冊

REVIEW ARTICLE

State of the art and new horizons in the diagnosis and management of egg allergy

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Abstract

Egg allergy is one of the most frequent food allergies in children below the age of three. Common symptoms of egg allergy involve frequently the skin as well as the gut and in more severe cases result in anaphylaxis. Non-IgE-mediated symptoms such as in eosinophilic diseases of the gut or egg-induced enterocolitis might also be observed. Sensitization to egg white proteins can be found in young children in absence of clinical symptoms. The diagnosis of egg allergy is based on the history, IgE tests as well as standardized food challenges. Ovomucoid is the major allergen of egg, and recent advances in technology have improved the diagnosis and follow-up of patients with egg allergy by using single allergens or allergens with modified allergenic properties. Today, the management of egg allergy is strict avoidance. However, oral tolerance induction protocols, in particular with egg proteins with reduced allergenic properties, are promising tools for inducing an increased level of tolerance in specific patients.

Prevalence

IgE-mediated food allergy is common among children and egg white, together with milk and peanuts, is one of the foods most frequently incriminated below the age of 3 years. The estimated prevalence of egg allergy has been reported to vary, depending on method or definition. Self-reported prevalence values of egg allergy of up to 7% have been demonstrated, while challenge-confirmed egg allergy has shown lower estimates, up to 1.7% (1). An estimated point prevalence of 1.6%, confirmed by challenge, was reported from Norway and Denmark (2, 3), and a similar prevalence of 1.3% was reported from the United States (4). Egg allergy also accounts for a high prevalence in childhood in France and Japan (5, 6). Egg allergy is the most common food allergy in children with atopic dermatitis. Egg allergy was found to be present in about two-thirds of children with positive food challenges made for allergy work-up of atopic dermatitis (7).

Symptoms (clinical presentation)

Initial allergic reactions to egg are usually observed during the first year of life. The most common symptoms are IgE-mediated erythema, urticaria and eczematous rash occurring in 90% of the children (8). Furthermore, gastrointestinal symptoms, abdominal pain and vomiting (mostly in conjunction with other immediate-type symptoms) occur in 40–50% of cases following egg ingestion. In addition, egg is one of the most common food allergens in allergic eosinophilic esophagitis (AEE) and allergic eosinophilic gastroenteritis (AEG) that might be IgE-mediated, cell-mediated or both (9). AEE is seen most frequently during infancy through adolescence, whereas AEG can occur at any age, including young infants. Food protein-induced proctocolitis and food-induced enterocolitis, also reported to be egg-induced, are other gastrointestinal disorders and appear to involve a non-IgE, cell-mediated mechanism (10, 11).

Anaphylactic reactions to egg are not commonly reported, even in children. However, the reaction severity has been associated with asthma, suggesting that asthma care should be a critical target for supervision of children with food allergy (12). In rare cases, egg has caused fatal reactions because of anaphylaxis (13).

Ingestion of cooked or baked egg can be tolerated by some children who react to raw egg, whereas other children react both to raw as well as heated egg (14–18).

Egg white components

Egg white is the major source of allergens in egg. Egg white contains 23 different glycoproteins, most of which have been purified. Ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin/conalbumin (Gal d 3) and lysozyme (Gal d 4) have been identified as the major allergens (Table 1) (19). Although ovomucoid comprises only 10% of the total egg white protein, it has been shown to be the dominant allergen (19, 20). Ovomucoid has several unique characteristics, such as stability against heat and digestion by proteinases. It also appears to be allergenic in minute quantities.

Sensitization

Initial sensitization to food is generally accepted to take place via the gut mucosa or cutaneous exposure (21). Sensitization to food in infants is often transient and low levels of IgE antibodies to egg can occur without any symptoms (22), highlighting the fact that allergen-specific IgE is a marker of allergic sensitization and not of allergic disease. Reactions occurring on first known ingestion or skin contact with egg are not uncommon (23). In a prospective study of 107 young children who not previously ingested egg but were sensitized to egg white, oral food challenges to egg were performed at a median age, 15 months (range; 12–24 months). The egg challenge resulted in an immediate or early reaction (within 6 h) in 56/107 (52.3%) children (24). The presence of IgE antibodies to egg has been demonstrated in infants with atopic dermatitis before the introduction of egg into the diet (24, 25). Sensitization may thus theoretically occur either by transplacental transfer of egg allergen (26) or through breast milk (27). In addition, experience with occupational asthma to inhaled egg proteins that may be followed by breakdown in previously established oral tolerance to ingested egg, suggests a possible inhalation route for primary sensitization to egg allergens (28, 29).

The pattern of allergic sensitization in a large cohort of infants with atopic eczema, participating in an international study multicenter was recently published and showed a predominance of sensitization to egg in each country, with a global rate of sensitization to egg white of 42% (30). The pattern of sensitization to egg white in the individual countries was paralleled by the pattern of sensitization to peanut. Sensitization to egg white is considered to be a risk factor for development of peanut allergy; 20% of children with AD and egg white sensitization will ultimately develop peanut allergy. In an ongoing clinical trial, headed by Dr G. Lack in London, investigating prevention of peanut allergy [LEAP study; Learning Early About Peanut allergy], infants between the ages of 4 and 10 months and with AD and detectable serum egg white IgE antibody levels are randomly assigned to peanut avoidance until 3 years of age or to early introduction of a peanut-containing snack three times per week (equivalent to about 6 g of peanut protein per week). The primary endpoint of the study is the proportion of children who develop peanut allergy by age 5 years in each study group. The study will reach completion in 2013.

A strong association between sensitization to egg during infancy and sensitization to inhalant allergens later in childhood has been observed by several groups (31–35). Sensitization to egg in infancy, and particularly in combination with atopic dermatitis, should thus be considered a risk marker for predicting future inhalant allergy. The mechanism of this association has not been elucidated.

Common vaccines, such as influenza vaccine, that are cultured in fertilized chicken eggs may contain small amounts of egg allergen, and immunization with these vaccines might cause adverse effects in children with egg allergy (36). Egg allergy is therefore still considered a contraindication to immunization against influenza, particularly in individuals with a history of egg anaphylaxis. However, it has been clearly demonstrated that minute amounts of egg proteins possibly present in the MMR vaccine do not provoke allergic reactions in egg-allergic individuals, implying that this vaccine is not contraindicated in egg-allergic individuals (37).

Diagnosis

Challenge

An accurate history is the key element in the diagnostic process of egg allergy. The double-blind placebo-controlled food challenge (DBPCFC) test remains the golden standard for the confirmation of food allergy although, in clinical practice and especially in infants, open challenges are useful. Challenge methods often vary from study to study and challenge availability varies from country to country. Standardized guidelines would facilitate comparison of the

Table 1 Major egg white allergens

Allergen	Common name	Constitute* (%)	Mw (kDa)	pI	Carbohydrate (%)	IgE binding activity		Allergenic activity	Test code (*in-vitro* tests)
						Heat-treated	Digestive enzyme-treated		
Gal d 1	Ovomucoid	11	28	4.1	~25	Stable	Stable	+++	f233
Gal d 2	Ovalbumin	54	45	4.5	~3	Unstable	Unstable	++	f232
Gal d 3	Ovotransferrin/conalbumin	12	76.6	6.0	2.6	Unstable	Unstable	+	f323
Gal d 4	Lysozyme	3.4	14.3	10.7	0	Unstable	Unstable	++	k208

*Percent of egg white proteins.

outcome and results between studies. A Position Paper for this purpose has been presented by the European Academy of Allergology and Clinical Immunology (38). Challenge tests always imply a potential risk to the allergic child and should thus only be performed by trained allergists in clinics with adequate facilities. Besides, challenge tests are time-consuming and not considered practical in the primary care setting. The diagnosis is therefore often assessed by quantitative IgE tests but always needs to be correlated to a convincing history (39). It should be emphasized that if a child tolerates egg in the diet on a regular basis without any immediate reaction, then this child is not egg allergic, even if high levels of egg white-specific IgE antibody are detected in serum. In clinical practice, food challenges are used both for initial diagnosis as well as monitoring of food allergy resolution. This is already the trend in milk and egg allergy but needs further support for everyday practice.

Skin prick tests

Skin prick tests (SPT) are frequently used in screening for egg-specific IgE and should be performed by trained personnel. The diagnostic accuracy of SPTs is dependent on the quality of the extract, which should be standardized. In children with atopic dermatitis and egg allergy, SPT shows a good sensitivity and NPV, but poor specificity and PPV (40). As a consequence, a negative test essentially excludes an IgE-mediated egg allergy, whereas a positive test does not predict clinical reactivity accurately. Few studies correlated the results of the prick skin test with the outcome of an oral egg challenge. In a study by Sporik et al. (41), positive skin reactions to egg ≥7 mm (mean wheal diameter) were associated with an adverse reaction on a formal open challenge, indicating that a wheal diameter equal to or greater was 100% specific in defining the outcome of challenge. For 3 mm diameter, the specificity was reduced to 70% for egg, and positive challenges were observed in children with a negative skin reaction.

In vitro IgE tests

IgE antibodies to egg white proteins can be measured in serum by standardized assay systems, used in clinical routines. As for SPT, the quality and performance criteria for the assay need to be considered. The test is principally dependent on the egg allergen preparation, composition, quality and stability. Commercially purified egg white single proteins often contain significant quantities of contaminating protein, which may lead to erroneous interpretation of test results (19).

In vitro IgE antibody tests provide standardized, quantitative measurements of egg-allergen-specific IgE, and a relation between the concentration of egg-specific IgE antibodies and the probability of reaction during an ingestion food challenge can be determined. Threshold values of egg-specific IgE (cutoff values) to predict the outcome in challenge have been defined in several studies, showing various predictive values. Crespo et al. (42) challenged children with egg allergy after 2.5 years of egg elimination, and the outcome of the challenges were correlated with the egg-specific IgE antibody levels. A likelihood ratio of 6.3, if the concentration of egg-specific IgE was 1.2 kU_A/l, made the investigators draw the conclusion that challenges could be delayed in children with egg-specific IgE concentrations greater than 1.2 kU_A/l. The studies by Sampson (43) suggested the diagnostic decision point for egg white IgE to be 7 kU_A/l, with 95% of the children having a clinical reaction. A similar value, 7.4 kU_A/l, was recently reported by Ando et al. (44). Although different values have been demonstrated in other studies, the predictive cutoff values are constantly lower in small children and increasing by age (8, 45–48). For children under 2 years of age, egg white IgE level ≥ 2 kU_A/l has 95% PPV (49).

The range of cutoff levels observed might depend not only on differences in age, but also on the type of symptoms, other clinical characteristics of the cohorts such as prevalence and/or various challenge procedures and the type of food given during the challenge. Future studies utilizing patients with well-characterized clinical phenotypes and with standardized challenge protocols, including foods preparation, should give better comparable results and useful predictive information (50).

In children with low levels of egg-specific IgE, those with the smaller SPT responses to egg were shown to be more likely to pass a challenge test to egg than children with larger wheal responses. In children with egg white IgE levels < 2.5 kU_A/l, the skin test wheal diameter of egg white commercial extract equal or smaller than 3 mm was associated with a 50% pass rate during the supervised oral egg challenge. Thus, on these occasions, a combination of the two tests might provide additional information to the clinician in determining the timing of egg challenge (51).

The studies mentioned earlier set cutoff levels for the diagnosis of egg allergy and did not evaluate the egg-specific IgE levels in relation to the severity of the challenge reaction. This was recently investigated by retrospectively reviewing clinical data on symptoms at a standardized oral food challenge to egg and egg-specific IgE levels. Analyses showed statistical differences in egg-specific IgE levels for patients with severe, moderate or absent reactions at challenge, highest for patients with severe reactions and decreasing with the severity of reaction.

This indicates that the level of egg-specific IgE might be a help to assess the potential risk of a reaction to egg (48).

Ovomucoid in the diagnosis of egg allergy

Ovomucoid is heavily glycosylated and contains three well-separated domains, which have been investigated with regard to allergenicity (52). Each domain bears unique epitopes that are recognized by IgE antibodies from egg-allergic patients. Analysis of sera from egg-allergic patients showed that IgE antibodies reacted with all three domains but significantly more to the second ovomucoid domain (20). However, further investigations could demonstrate a higher IgE-binding to the pepsin digests of ovomucoid in egg-allergic patients who did not outgrow their allergy, compared to patients who developed tolerance (53). Previous studies have suggested that

the allergenicity could be explained by the fact that ovomucoid demonstrates a higher stability against protease digestion and heat compared with other egg white components (14, 19). Significant differences in IgE antibodies to ovomucoid were found in patients, depending on the reactivity to raw and cooked eggs, where low levels of IgE antibodies to ovomucoid were associated with tolerance to cooked eggs (14). Furthermore, quantification of ovomucoid antibodies could be useful in guiding the physician in the decision whether to perform a challenge or not. Recently published data suggest that a concentration of IgE antibodies to ovomucoid higher than approximately 11 kU_A/l (positive decision point) indicates a high risk of reacting to heated (as well as raw) egg. At the same time, a concentration lower than approximate 1 kU_A/l (negative decision point) means that there is a low risk of reaction to heated egg, even if the patient might well react to raw egg (44).

New diagnostic tools for egg allergy

Recent advances in technology, improved purified allergens and specific epitopes open up new opportunities and better defined diagnosis of food allergy. Component-resolved diagnostics using microarray technology has recently been evaluated in the diagnosis of egg allergy. The clinical performance of an allergen microarray, containing a panel of clinically relevant egg components, has been evaluated for IgE detection in children with challenge-proven egg allergy. The results showed performance characteristics comparable to current diagnostic tests, both *in vitro* IgE-test and SPT (54). The advantages of the microarray assay allow for characterization of several allergen components simultaneously. Furthermore, the small volume obtained by capillary blood sampling makes the microarray assay suggestive for testing in small children.

Point-of-care (POC) tests for small children, requiring small volumes of capillary whole blood and with results within 30 min, could be particularly suitable in primary care settings. A new POC test with a panel of ten allergens, including egg white, has recently been evaluated and published, with an overall sensitivity and specificity of 92% and 97%, respectively (55). Measurements of IgG_4 and the ratios of IgE/IgG_4 have also been shown to be useful in following the development of tolerance and outgrowing of egg allergy in the research studies (56, 57). However, at this time, measurement of IgG_4 has not been validated sufficiently to be used in clinical practice.

Management/therapy

Today, the standard therapy for egg allergy is strict avoidance, access to self-injectable epinephrine and adequate pharmacotherapy in the event of an accidental ingestion. Basic food, such as egg, is widely used in many processed foods and difficult to avoid. This difficulty in egg avoidance and the risk of dietary failures have been shown to affect the quality of life for egg-allergic children as well as their families (58).

Oral desensitization to different foods has earlier been reported with a limited number of patients and various results of tolerance achievement (59, 60). In recent years, more promising articles have been published on achieving clinical tolerance to egg by oral immunotherapy (OIT), or sometimes called specific oral tolerance induction (SOTI).

Food allergy seems to result in a failure to establish or maintain oral tolerance (61). In order to achieve tolerance, the offending food is administered orally in small doses, which are increased slightly up to an amount equivalent to the usual daily oral intake. Thereafter, the food is given daily in a maintenance dose (62, 63). New preparations of heated and ovomucoid-reduced egg white, which is hypoallergenic enough to eat for approximately 95% of egg-allergic subjects, are currently under investigation and might be effective and safe for patients under OIT (Fig. 1). The individual pattern

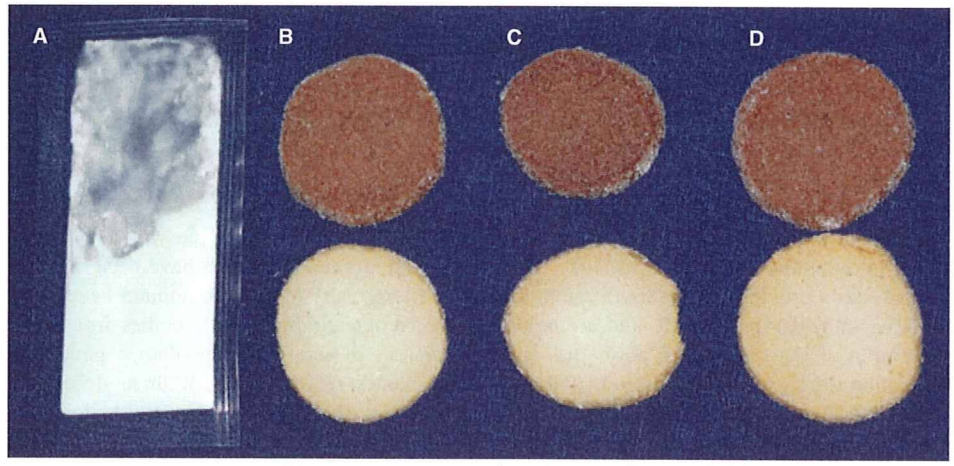

Figure 1 (A) Freeze-dried egg white, (B) Cookie including heated & ovomucoid-reduced egg white, (C) Cookie including heated egg white, (D) Cookie without egg white.

of clinical reactions seems to vary between patients and type of allergen. In some patients who obtained tolerance by OIT, the allergic symptoms were found to re-occur after a period of avoidance, indicating a short-term and not lifelong tolerance to egg (62, 64). As a consequence, regular egg ingestion might be necessary to maintain the established tolerance for those patients.

Children with successful oral immunotherapy to egg were shown to have lower baseline levels of IgE antibodies to egg compared to nonresponding children. In addition, the levels of egg-specific IgE decreased over time in children with successful OIT. However, this study also showed that egg-specific IgE decreased in children who developed natural tolerance during elimination diet (63).

Furthermore, other studies have demonstrated an increase over time in IgG and IgG_4 antibodies to egg during oral immunotherapy (61, 65, 66).

Immunologic changes associated with ingestion of extensively heated egg in children with egg allergy were recently published by Lemon-Mulé et al. (56). Children reacting to heated egg had significantly larger egg white-induced SPT, greater levels of IgE antibodies to egg white, ovalbumin and ovomucoid and higher OVA-IgE/IgG_4 and OVM-IgE/IgG_4 ratios, compared with children tolerant to heated and unheated egg. Continued ingestion of heat-treated egg for tolerant children showed a decrease in OVA-IgE/IgG_4 and OVM-IgE/IgG_4 ratios from baseline at 3, 6 and 12 months, respectively. These results suggest that ingestion of heated egg by tolerant children might hasten the development of tolerance to unheated egg. The authors found that only extremely increased levels of IgE antibodies to ovomucoid (> 50 kU_A/l) were highly predictive of heated egg reactivity. This might be explained by the so-called matrix effect (67, 68), because of the fact that the heated egg used in the study was baked with wheat matrix. Kato et al. (69) previously showed a decreased solubility of ovomucoid when egg was mixed with wheat flour and wheat gluten and heated, suggesting that ovomucoid forms complexes with gluten leading to aggregation and insolubilization.

Resolution/persistence

The prognosis of egg allergy in young children is generally good and shown to resolve in 50% by age 3 years and in 66% by age 5 years (49). However, results from a recent study suggest a longer duration of allergy, predicted resolution in 4% by age 4 years, 12% by age 6 years, 37% by age 10 years and 68% by age 16 years. Moreover, children with egg-specific IgE greater than 50 kU_A/l were unlikely to develop egg tolerance (70).

Monitoring egg-specific IgE levels has been found to be useful in predicting when patients will develop clinical tolerance. A relationship between the degree of decrease in egg-specific IgE concentration over time and the probability of developing tolerance has been demonstrated, showing that a greater decrease in egg-specific IgE levels over a shorter period was indicative of a greater likelihood of tolerance development (71). Application of this model might help the clinician in the timing of challenge and in offering information to the patient and the family regarding the prognosis of the allergic disease.

Significantly higher levels of specific IgE antibodies to ovomucoid were demonstrated in children with persistent egg allergy. Children with high levels of IgE antibodies binding to pepsin-treated ovomucoid were thus less likely to outgrow their egg allergy compared to children who developed tolerance (53). In addition, sera from children with persistent egg allergy recognized more linear epitopes on ovomucoid. Four sequential IgE-binding sites on ovomucoid have been identified, differentiating children with persistent egg allergy from those with transient egg allergy (72). The presence of IgE antibodies to specific sequential epitopes may therefore be useful as a screening tool for persistent egg allergy.

High ratios of IgG_4/IgE antibodies to ovalbumin were also associated with a faster achievement of clinical tolerance in egg-sensitized children with eczema, who had been able to introduce egg in their diet. As a consequence, IgG_4/IgE ratios may be a valuable marker for identifying sensitized children able to continue with allergen exposure (57).

Future perspectives

The goals for the future are

- Prediction of tolerance when the diagnosis of egg allergy has been established:
  - by measuring antibody titers of specific egg white proteins in various forms (heated or unheated).
  - by determining whether combinations of tests to specific egg white proteins in various forms could predict tolerance to eggs.
  - by determination of IgE/IgG ratios.
- Efficient induction of tolerance to egg in egg-allergic individuals:
  - by studying efficient tolerance induction protocols with heated and partially heated egg-containing food products.
  - by establishing safe and efficient mucosal and systemic immunotherapy protocols.
- Prevention of development of egg allergy or progression to allergic symptoms in high risk individuals for allergy:
  - by identifying at-risk individuals with appropriate (egg-specific) tests.

In conclusion, egg allergy is not only most common in children suffering from food allergies, but sensitization to egg protein is a complex, only partially characterized phenomenon found in allergy-prone individuals. Addressing various aspects of egg allergy and antibody response to egg sensitization will allow most fascinating studies with a direct impact in order to prevent allergic manifestations in childhood.

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REVIEW ARTICLE

Oral Allergy Syndrome

Yasuto Kondo[1] and Atsuo Urisu[2]

ABSTRACT

Oral allergy syndrome (OAS) is defined as the symptoms of IgE-mediated immediate allergy localized in the oral mucosa, and the characteristics depend on the lability of the antigen. Another term used for this syndrome is pollen-food allergy (PFS); the patient is sensitized with pollen via the airways and exhibits an allergic reaction to food antigen with a structural similarity to the pollen (class 2 food allergy). In addition to PFS, latex-fruit syndrome is also well-known as the disease exhibiting OAS. In treating the condition, it must be noted that most but not all symptoms of PFS are those of OAS. In many cases, antigens become edible by heating, but some are resistant to heating. Also, since the exacerbation of atopic dermatitis is occasionally observed after the intake of cooked antigens in asymptomatic individuals, careful inquiry of the history is important in designing the treatment. Immunotherapy against the cross-reacting pollen has also been attempted in PFS.

KEY WORDS

allergen, allergic rhinitis, food allergy, latex allergy, pollen

DEFINITION

Oral allergy syndrome (OAS) is a condition characterized by IgE-mediated immediate allergic symptoms restricted to the oral mucosa, which may involve itching, stinging pain, and vascular edema of the lips, tongue, palate, and pharynx with a sudden onset, occasionally accompanied by itching of the ear and feeling of tightness of the throat. Usually, these symptoms gradually resolve. A typical example of OAS is oral mucosal symptoms that appear when a patient with birch pollen allergy has eaten a food of the family Rosaceae (apple, cherry, peach, etc.).

HISTORICAL CONFUSION

There used to be controversy over the definition of OAS. In 1987, Almot *et al.*[1] first reported allergic symptoms induced by eating a food yielding a positive skin test that are primarily oral mucosal symptoms which occasionally spread to the entire body as OAS. They did not mention whether the patients had pollinosis, and the causative foods included shellfish, fish, and eggs. At that time, the term OAS did not attract much attention, but a report by Ortolani *et al.*[2] in 1988 directed attention toward it. Since the symptoms observed after patients with birch pollinosis ate fruits and vegetables were in agreement with those of OAS reported by Amlot, they reported 262 pollinosis patients who developed symptoms localized to the oral mucosa caused by the ingestion of fruits and vegetables as cases of "OAS", making the term OAS international.

OAS has become widely known with a new definition, i.e., localized oral symptoms due to a labile allergen observed after patients with pollinosis have eaten a fruit or vegetable. This historical background led to confusion among researchers concerning the definition. In 1994, Liccardi *et al.*[3] reported oral symptoms without generalized symptoms caused by the ingestion of eggs or egg-containing foods in a patient with no pollinosis as OAS. In response to this, Kelso[4] stated that the condition might have been usual egg allergy rather than OAS, because the patient had a history of egg-induced hypotension. Liccardi *et al.* responded that the hypotension record was inappropriate as it was based on the self-judgment of the patient, and argued that no generalized symptom was observed on any of the confirmation challenge test using egg.

To avoid such confusion related to the term OAS, food allergy due to a cross-reaction between pollen antigen and fruit or vegetable antigen has been called the more specific term "pollen-food allergy syndrome (PFS)[5,6]".

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Table 1 Characteristics of class 1 and 2 food allergy

	Class 1	Class 2
Sensitization to allergens	Gastrointestinal tract	Respiratory exposure
Age of peak prevalence	Early childhood	After school age
Symptoms	Rapid onset of gastrointestinal responses (nausea, abdominal pain, cramp, vomiting, diarrhea); other target organ responses (e.g., skin, respiratory tract) often involved	Mild pruritus, tingling, and/or angioedema of the lips, palate, tongue or oropharynx; occasional sensation of tightness in the throat and rarely systemic symptoms
Typical foods	Egg, milk, wheat, peanut, fish	Fruit, vegetable
Stable or labile in presence of heat, acid, and proteases	Stable	Labile
Diagnosis	Clinical history and positive SPT responses or CAP-RAST results	Clinical history and positive SPT responses (prick-plus-prick method)
	Oral challenge-positive on double-blinded food-challenge test	Oral challenge-positive with fresh food, negative with cooked food
Treatment	Elimination diet	Elimination diet
		Foods may become edible by heating
		Immunotherapy to treat the pollen-induced rhinitis may improve PFS

Table 2 Major fruits and vegetables reported to show cross-reactivity with pollen

Pollen	Food
Birch	Rosaceae (apple, pear, sweet cherry, peach, plum, apricot, almond), Apiaceae (celery, carrot), Solanaceae (potato), Actinidiaceae (kiwifruit), Betulaceae (hazelnut), Anacardiaceae (mango), Chili pepper, etc.
Japanese cedar	Solanaceae (tomato)
Mugwort	Apiaceae (celery, carrot), Anacardiaceae (mango), spice, etc.
Grass	Cucurbitaceae (melon, watermelon), Solanaceae (tomato, potato), Actinidiaceae (kiwifruit), Rutaceae (orange), Fabaceae (peanut), etc.
Ragweed	Cucurbitaceae (melon, watermelon, cantaloupe, zucchini, cucumber), Musaceae (banana), etc.
Plane	Betulaceae (hazelnut), Rosaceae (apple), lettuce, corn, Fabaceae (peanut, chickpea)

CHARACTERISTICS OF OAS: CLASS 1 AND CLASS 2 ALLERGY

Food allergens that induce OAS rapidly dissolve in the oral cavity and are readily broken down by digestive enzymes such as those in gastric juice. Since these food allergens differed in properties from known food allergens that are resistant to digestive enzymes and induce sensitization via the intestine, allergy to proteins in fruits and vegetables cross-reactive with pollen antigen in individuals sensitized by the antigen via the airway began to termed class 2 food allergy[7] to distinguish it from food allergy caused by conventional intestinal sensitization (class 1 food allergy) (Table 1, 2).

DISEASES EXHIBITING OAS

PFS mentioned above is a typical disease that exhibits OAS. In addition to PFS, latex-fruit syndrome (LFS; allergy to fresh fruits or vegetables after sensitization with latex-inhalation antigen in latex powder) has been reported as disease exhibiting OAS. Clinically, also, some patients yielding a positive skin test complain of oral discomfort immediately after the ingestion of egg on the oral challenge test but show no spread of allergic symptoms to the entire body if they continue eating it.

PFS IS NOT EQUAL TO OAS

While the majority of symptoms of PFS are indeed mild, such as the OAS, caution is necessary, because systemic and severe reactions may be observed by some pollen-related food allergens (Api g 1, Gly m 4). The antigens that cause PFS have been extensively studied, particularly in Western countries, and they will be discussed in the next section.

ANTIGENS CAUSING OAS

In Europe, more than 70% of patients with birch pollinosis are allergic to pollen-related food allergens such as the apple, cherry, and hazelnut. Major allergens responsible for these symptoms belong to a group exhibiting high-level homology with Bet v 1, a major antigen of birch pollen (Table 3). The next most frequent is the food allergen showing a high-level homology with Bet v 2 (profilin), another birch pollen antigen. Bet v 5 and 6 are also reportedly involved in cross-reactivity, but most cross-reactivity is related to Bet v 1, and the involvement of other antigens is negligible.[8]

Table 3 Major pollen/latex and class 2 food allergens

Pollen/latex allergens		Class 2 food allergens			
Bet v 1 homolog's (Group belonging PR-10)					
Aln g 1 (alder)	Bet v 1 (birch)	Api g 1 (celery)	Ara h 8 (peanut)	Cor a 1 (hazel)	Dau c 1 (carrot)
Car b 1 (hornbeam)	Cas s 1 (chestnut)	Fra a 1 (strawberry)	Gly m 4 (soybean)	Mal d 1 (apple)	Pru ar 1 (apricot)
Cor a 1 (hazelnut)	Que a 1 (white oak)	Pru av 1 (sweet cherry)	Pyr c 1 (pear)	Sol t 1 (potato)	Vig r 1 (mung bean)
Profilin					
Art v 4 (mugwort)	Bet v 2 (birch)	Ana c 1 (pineapple)	Ara h 5 (peanut)	Api g 4 (celery)	Cap a 2 (bell pepper)
Cyn d 12 (Bermuda grass)	Hel a 2 (sunflower)	Cit s 2 (sweet orange)	Cor a 2 (hazel)	Cuc m 2 (muskmelon)	Dau c 4 (carrot)
Ole e 2 (olive)	Phl p 12 (timothy)	Gly m 3 (soybean)	Lit c 1 (lychee)	Lyc e 1 (tomato)	Mal d 4 (apple)
Hev b 8 (latex)		Mus xp 1 (banana)	Pru av 4 (sweet cherry)	Pru p 4 (peach)	Pyr c 4 (pear)

Data from http://fermi.utmb.edu/SDAP/.

Bet v 1 GROUP

Bet v 1 (PR-10) is one of the pathogenesis-related (PR) proteins, which increase in plants when they are exposed to stress. Many foods have been reported to contain this protein, and the cross-reactivity is considered to be derived from the high-level homology of amino acid sequences in this group. The IgE-binding activities of these allergens are readily lost through heat or enzyme treatment. Also, the p-loop (AA41-52) region has been reported to be particularly important in the IgE epitope of Bet v 1.[9]

While many of the symptoms caused by antigens of PR proteins are those of OAS, antigens of celery (Api g 1) and soybean (Gly m 4), which belong to the same group as Bet v 1, have been reported to induce marked systemic symptoms.

Api g 1

Celery allergy is common in Europe (Primarily Switzerland, France, and Germany). In Switzerland, it is reported to be a major cause of food-induced anaphylaxis,[10] and about half of the patients have been reported to show systemic allergic reaction.[11,12] Its allergenicity is not changed markedly by heating. Pollen of birch and mugwort is known to be cross-reactive to celery, and is considered to be a sensitizing antigen.[13] While celery allergens include Api g 4 and Api g 5, the major allergen is Api g 1, which belongs to the above-mentioned PR-10. However, the reason why Api g 1 is stable against heating unlike other allergens belong to the same group as Bet v 1 has not been sufficiently clarified. Wangorsch *et al.*[14] reported that Api g 1 has 2 isoforms, that Api g 1.01 shows a stronger IgE-binding capacity than Api g 1.02, and that this difference is derived from the fact that the binding site of Api g 1.01 in the above p-loop region is Lys44 while that of Api g 1.02 or Bet v 1 is Glu45, and suggested the importance of this region.

Gly m 4

In 2002, Kleine-Tabbe *et al.*[15] reported that 20 patients with birch pollinosis developed allergic symptoms including serious ones after the initial ingestion of soybean protein food. Notable symptoms included swelling of the face (17 patients), OAS (14), dyspnea (6), urticaria (6), and drowsiness (5). They also reported that soybean starvation-associated message 22 (SAM22: Gly m 4), which belongs to PR-10, showed an IgE-binding capacity in 85% (17/20) of the patients. A follow-up study by Mittag *et al.*[16] confirmed that Gly m 4-specific IgE was positive in 21 of 22 birch pollinosis patients who developed soybean allergy, and that it inhibited the binding of IgE to soybean protein by 60% or more in 9 of 11 patients, indicating that Gly m 4 was the major allergen. Moreover, as the binding of IgE to soybean protein was inhibited by 80% or more by the addition of birch pollen protein in 9 of the 11 patients, they suggested that birch pollen is primarily responsible for the common antigenicity of the two. According to their report, Gly m 4 was not detected in fermentation products such as miso and soy sauce or roasted soybean, but its content was 9 ppm in tofu, 11 ppm in soy flakes, 70 ppm in a dietary powder among soybean-containing food despite its variation with the total soybean content. They also reported that Gly m 4 concentration was markedly affected by the cooking method and that it was reduced by 30-minutes and not detected after 4-hour heating. Three patients with alder/birch pollinosis who developed OAS (1 case) or anaphylaxis (2 cases) after the intake of soymilk have been reported, and an involvement of Gly m 4 is suspected[17] in Japan, too.

Table 4 Lipid transfer protein (LTP); major allergens belonging to PR-14

Inhaled allergens		Food allergens		
Tree	Weed	Fruits/vegetables		Beans/nuts/seeds
Cas s 8 (chestnut)	Art v 3 (mugwort)	Aspa o 1 (asparagus)	Bra o 3 (cabbage)	Cor a 8 (hazelnut)
Pla a 3 (plane tree)	Par j 1 (pellitory)	Cit l 3 (lemon)	Cit s 3 (sweet orange)	Jug r 3 (English walnut)
	Par j 2 (pellitory)	Fra a 3 (strawberry)	Lac s 1 (lettuce)	
	Par o 1 (pellitory)	Lyc e 3 (tomato)	Mal d 3 (apple)	
		Pru ar 3 (apricot)	Pru av 3 (sweet cherry)	
Heb b 12 (latex)		Pru d 3 (European plum)	Pru p 3 (peach)	
		Vit v 1 (grape)	Zea m 14 (maize, corn)	

Data from http://fermi.utmb.edu/SDAP/.

PROFILIN GROUP

Profilin is considered to be an allergen involved in a wide range of cross-reactivities among plants, and patients sensitized with it react with a variety of plants and foods. For example, it is considered responsible for the cross-reactions between birch/mugwort pollen-celery-spices, grass pollen-celery-carrots, and tree pollen-hazelnut. The cross-reactivity of IgE is considered to be due to a structural similarity rather than similarity at the amino acid sequence level.[18] There major IgE epitope have been identified in birch profilin.[19]

Asero *et al.* performed skin tests in 200 pollinosis patients using purified palm profilin (Pho d 2) and observed positive reaction in one-third of the patients. They were also positive for pollen from a wide range of plants, more than half of them exhibited OAS with symptoms of fruit allergy, and no symptom was induced by cooked or processed foods.[20]

CROSS-REACTIVE CARBOHYDRATE DETERMINANTS (CCD)

Carbohydrates that act as cross-reacting antigens among various plants or invertebrates are collectivity called cross-reactive carbohydrate determinants (CCD).

Carbohydrates with an IgE-binding capacity have also been reported in plant proteins with no allergenicity. They are, for example, bromelain of pineapple, horseradish peroxidase (HRP), polyamine oxidase of corn, ascorbic acid oxidase of Cucurbita pepo, and phytohemagglutinin of haricot bean. Many CCDs are monovalent and do not form bridges of IgEs on the mast cells, and so they are generally considered not to induce histamine release. However, it has been revealed that about half of individuals positive for Ole e 1, a major antigen of Olive pollen, show IgE antibodies to this carbohydrate, and that this carbohydrate induces histamine release in them.[21]

Recently, van Ree *et al.*[22] reported that α1,3-fucose and β1,2-xylose, which are N-linked glycans, have IgE-binding capacities. Individuals are considered to be sensitized when exposed to pollen and thereafter develop cross-reaction to foods. However, only limited individuals with IgE antibodies to CCDs actually develop clinical symptoms, and whether they develop symptoms is speculated to depend on the difference in the glycan number or affinity of IgE antibodies.[23]

LIPID-TRANSFER PROTEINS (LTP) GROUP

Antigens belonging to the LTP family have been reported to exist in a wide variety of fruits, vegetables, and pollen (Table 4).

LTP, belonging to PR-14, exhibit an antigenicity resistant to heating or digestive enzymes and cause fruit allergy even without pollinosis, and the symptoms are not only OAS but also involve severe systemic symptoms at a relatively frequent rate. Therefore, they are presently considered to be non-pollen-related allergens (class 1 food allergens) that act by intestinal sensitization.[24] However, there are data that suggest that LTP is responsible for food allergy associated with pollinosis (class 2 food allergy) in some patients.

Mugwort is known to be a major cause of pollinosis in Mediterranean coastal areas, and Art v 3 is a mugwort pollen antigen belonging to the LTP group. According to a report on cross-reaction between Art v 3 and LTP from peach or apple,[25] whether the cross-reaction was due to sensitization primarily by pollen or peach was unclear. To study this relationship, Pastorello *et al.*[26] collected 17 patients with peach allergy and compared 10 who had not developed pollinosis and 7 with pollinosis. The 10 patients with no pollinosis reacted with mugwort pollen LTP and peach LTP, but the 7 pollinosis reacted with proteins other than

LTP. Next, the reactions of IgE with mugwort pollen LTP and peach LTP were examined using pooled serum from 10 patients by immunoblot inhibition. IgE binding to the peach 9-kDa band (LTP) was totally inhibited by a small amount of peach LTP but only by 100 times amount of mugwort LTP, whereas a small amount of both mugwort and peach LTP totally inhibited the IgE-binding to mugwort LTP. Therefore, they concluded that this cross-reactivity was primarily due to sensitization by peach LTP (peach class 1 allergy). In contrast, Lombardero *et al.*[27] considered that the report by Pastorello *et al.* was biased based on the fact that the patients were mostly those with peach allergy, and performed reevaluation by collecting 24 patients with mugwort pollinosis. They reported that more than 70% of the patients were positive on the skin test to mugwort LTP. They subsequently evaluated the cross-reactivity of mugwort LTP with peach LTP by ELISA inhibition, and reported that IgE binding with peach LTP was inhibited by the addition of mugwort LTP in 3 of 6 studied patients but that IgE binding with mugwort LTP was not inhibited by the addition of peach LTP, suggesting that the common antigenicity of mugwort and peach LTP was primarily due to mugwort pollen in some patients (class 2 food allergy).

OAS IN JAPAN

In Japan, also, there have been reports of OAS due to foods of the family Rosaceae in patients hypersensitive to birch pollen in Hokkaido and Alnus sieboldiana (family Betulaceae, genus Alnus) pollen in Hyogo Prefecture.[28,29]

The frequency of OAS in patients with Japanese cedar pollinosis is lower than that in those with birch pollinosis (75%), being reported to be 7-17%.[30,31] According to questionnaire surveys performed in Japanese cedar pollinosis patients, melon and kiwifruit induced allergy in many of them.

According to our oral questionnaire survey concerning foods causing fruit and vegetable hypersensitivity in patients with Japanese cedar pollinosis (17 respondents with pollinosis and fruit allergy), melon (12/17), kiwi (9/17), tomato (9/17), watermelon (7/17), and pineapple (6/17) were frequently ingested. However, in such a questionnaire survey, reactions to materials with pharmacological actions contained in foods may be misinterpreted by the respondents as allergic symptoms, and food allergy unrelated to Japanese cedar pollinosis may be reported; therefore, the competitiveness for IgE antibody between cedar pollen and fruit or vegetable antigen must be demonstrated.

At first, we identified the main allergens of tomato fruit,[32] then demonstrated the cross-reactivity between tomato fruit and Japanese cedar pollen by RAST inhibition, and further identified the protein responsible for the cross-reactivity by immunoblot inhibition.[33] As a result of comparing the amino acid sequences of these proteins, we clarified the presence of regions showing close agreement, i.e., Cry j 2 of Japanese cedar pollen and PG2A of tomato fruit, and reported the possible involvement of these regions in the competitiveness for IgE. Concerning the common antigenicity of tomato and Japanese cedar pollen, there is a report that symptoms considered to be OAS appeared after the oral ingestion of tomato in a dog model of Japanese cedar pollinosis, establishing the cross-reactivity between Japanese cedar pollen and tomato fruit antigens.[34]

TREATMENT FOR OAS

In PFS due to birch pollinosis, birch pollen-specific immunotherapy has been reported to be effective for the treatment of OAS to related foods.[35,36] Food tolerance and negative skin tests have also been reported to persist for 30 months,[37] and food skin tests converted to positive with the reactivation of OAS symptoms in all patients.

Foods that cause OAS should be avoided, in principle, but pollen-associated foods are often edible when heated. Therefore, the unnecessary elimination of foods should be avoided through close evaluation of the history of allergy due to cooked foods and oral challenge test. There is also a report that symptoms of OAS were significantly alleviated using antihistamines compared with a placebo.[38] Antihistamines might partially relieve symptoms of oral allergy syndrome.

However, some pollen-related foods such as celery and soybean may lead to severe symptoms although they belong to the Bet v 1 group. In LFS, the antigenicity of some foods is not lost by heating, and they tend to cause severe symptoms.

Naturally, PFS may also cause generalized symptoms and even anaphylaxis if a large amount of antigen has been ingested. Therefore, in case of emergency, patients with a history of anaphylaxis should carry a portable epinephrine injection kit, antihistamines, and oral steroids with a medical certificate.

Even if cooked food allergens did not elicit oral allergy syndromes, they may cause T-cell-mediated late-phase reactions (deterioration of atopic eczema) in some birch pollen-allergic patients with atopic dermatitis. Because thermal processing affected their conformational structure and not the primary amino acid sequence. Therefore, the judgment of whether the intake of cooked foods may be permitted should not be made on the basis of the presence or absence of immediate hypersensitivity alone.[39]

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