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Invited review article

Recent advances of *in vitro* tests for the diagnosis of food-dependent exercise-induced anaphylaxis

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ABSTRACT

Food-dependent exercise-induced anaphylaxis (FDEIA) is a special form of IgE-mediated food allergy and exhibits allergic symptoms in combination of causative food-intake and triggers such as exercise. As the causative foods and the condition of triggers vary among patients, diagnosis of FDEIA is not always easy. Serum food-specific IgE tests, which are widely used in the diagnosis of FDEIA, have rather low sensitivity, because the tests mostly utilize crude extracts of foods. Concept of using defined allergen molecules has been proposed as the term "component-resolved diagnostics" for diagnosis of IgE-mediated allergy. Use of purified allergens such as recombinant omega-5 gliadin turned out to highly improve its sensitivity and specificity of the tests in the diagnosis of wheat-dependent exercise-induced anaphylaxis (WDEIA). Recently, CD203c expression-based basophil activation test (BAT) is reported to be useful in identifying adult patients with WDEIA and predicting causative allergens in WDEIA, when combined with appropriate allergens. Detection of serum allergen levels possibly gives useful information whether food challenge tests have been performed with sufficient strength.

Contents

1. Introduction

Food-dependent exercise-induced anaphylaxis (FDEIA) is a distinct clinical entity characterized by development of systemic allergic reaction triggered when ingestion of food is followed by physical exercise. The clinical symptoms include generalized urticaria, angioedema, respiratory disturbance and anaphylactic shock. Patients usually eat causative foods without any symptoms, but triggers such as exercise elicit the symptoms. Presentation of the symptom is extremely variable with respect to the threshold of amount of food ingested and intensity of exercise [1,2]. In many case reports strenuous exercise, such as running and playing tennis, trigger anaphylaxis after ingesting specific food. However, milder exercise often induces the symptoms. Some observations indicate that symptoms may also occur if the food is ingested soon after the completion of exercise. Moreover, patients may not show allergic reaction each time they are subjected to the exercise. The causative foods vary, including shellfish, wheat products, vegetables, fruits, nuts, egg, mushrooms, corn, garlic, and pork/beef. In Europeans, tomatoes, cereals, and peanuts are the most frequent

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causative foods, whereas wheat and seafood are the most frequent in Japan. Triggers in FDEIA include general conditions, drugs, alcohol, and atmospheric conditions in addition to foods and exercise. Among these triggers non-steroidal anti-inflammatory drugs have been well known.

Frequency of FDEIA events varies from patient to patient and ranges from singular episode to multiple episodes. Severity of allergic reaction also varies in each event from localized urticaria to anaphylactic shock. Thus, diagnosis of FDEIA and determination of causative foods are not always easy to establish, especially in cases with wheat-dependent exercise-induced anaphylaxis (WDEIA). Wong et al. reported that the diagnosis of idiopathic urticaria or idiopathic anaphylaxis had primarily been given to four of the patients with WDEIA before WDEIA was diagnosed in these patients [3].

Although wheat is the most frequent causative food in Japan, an outbreak of a new subtype of FDEIA caused by hydrolyzed wheat protein (HWP) has recently been observed [4]. Patients with this new subtype were sensitized percutaneously to HWP by using HWP-supplemented soap. To date more than 1800 patients sensitized by HWP, who developed allergic symptoms after ingesting wheat products, have been accumulated by the Special Committee for the Safety of Protein Hydrolyzate in Cosmetics of the Japanese Society of Allergology [5].

2. Detection of serum food-specific IgE

Detection of serum food-specific IgE has been widely used in the diagnosis of immediate type allergic reactions to foods. This is a valuable supplementary test with ease for identifying causative allergens in the patients with food allergies. The methods to identify specific IgE in serum include the ImmunoCAP (CAP; Phadia KK, [at present Thermo Fisher Scientific]) [6], the IMMULITE 3gAllergy (IMMULITE; Siemens Healthcare Diagnostics) [7], the multiple-antigen simultaneous test (MAST; Hitachi Chemical Co.) [8], and the fluorescence allergosorbent test (Mitsubishi Chemical Medience Co.) [9]. It is noteworthy that these immunoassay systems usually employ crude extracts from natural food-stuffs to detect the allergen-specific IgE, thus the sensitivity and specificity of these tests are not always satisfactory in identifying true immediate type allergic patients.

2.1. Probability curve

Many studies have attempted to establish correlations between serum- food-specific IgE and results of food challenge tests (probability curve) and thus the clinicians can predict the likelihood that a patient will react on ingestion of the food, such as egg, milk, wheat, soy, fish, and peanut [10–17]. These reports have been performed using CAP system, therefore the obtained results cannot be applied to results from other assays, because the food-specific IgE values are arbitrary and varies dependent on different assays [18]. The results obtained by these IgE assay systems may not be comparable between tests. Further limitations should be understood when these IgE tests are used for diagnosing FDEIA, since all above presented reports have been obtained from children with food allergy. Patients with FDEIA have relatively low titers of food-specific IgE in their sera, and ingestion of causative food and physical effort are necessary to induce anaphylaxis. Thus, a probability curve is not available for FDEIA. For example, in wheat-dependent exercise-induced anaphylaxis (WDEIA), which is the most frequent subpopulation in FDEIA, wheat CAP recognized only 41.0% and gluten CAP recognized only 43.5% of the patients [2]. In addition, false positive results in serum food-specific IgE tests are often seen in patients with atopic dermatitis. Positive rates of wheat CAP and gluten CAP were 35.1% and 24.0%, respectively, in the 74 adult patients with atopic dermatitis who exhibit no immediate type allergic reaction to wheat (data not presented).

2.2. Component-resolved diagnostics (CRD)

Attempts to isolate and purify disease-eliciting allergens from the natural allergen sources for diagnostic purposes have been performed, and a huge number of allergens have been identified with the capacity to bind IgE antibodies and elicit allergic reactions. With the introduction of recombinant DNA technology in the field of allergen characterization, an increasing number of recombinant allergens with immunological properties comparable with the natural allergens have become available. Recombinant allergens can be produced with consistent quality and reproducibility, which make possible to be standardized. Using recombinant allergens it is possible to measure biochemical, immunological and biological reaction to the defined allergen molecules. The concept of using defined allergen molecules has been proposed as the term "component-resolved diagnostics (CRD)" for diagnosis of immediate type allergy (Fig. 1) [18].

Wheat protein consists of salt-insoluble protein and salt-soluble non-gluten protein. The latter mainly contains water-soluble albumins and water-insoluble globulins. The former are called gluten which can be further fractionated into two categories of proteins in according to solubility in 70% ethanol. The ethanol-soluble proteins are named gliadins and the ethanol-insoluble proteins are glutenins. Of these wheat proteins ω-5 gliadin and high molecular weight glutenin subunit (HMW-glutenin) were identified as major allergens for WDEIA by analyzing gluten component proteins with immunoblotting [19,20]. On the basis of this observation, recombinant ω-5 gliadin protein was produced, applied to CAP system and demonstrated that the sensitivities of recombinant ω-5 gliadin CAP was 80% for the patients with WDEIA but those of wheat CAP and gluten CAP were 48% and 56%, respectively. They also demonstrated that the specificity of recombinant ω-5 gliadin CAP was 68% when cut-off value was set at 0.35 kUa/l, but improved to 96% when this was set at 0.89 kUa/l [21]. Several studies have focused diagnostic value of the recombinant ω-5 gliadin CAP in adult patients with wheat-induced anaphylaxis and demonstrated its usability [22,23]. Since a probability curve using recombinant ω-5 gliadin CAP was recently reported [24], it would be helpful to make a probability curve using recombinant ω-5 gliadin CAP in diagnosing WDEIA. More recently, HMW-glutenin was produced and examined its usability to identify patients with WDEIA. As a result detection of specific IgE against recombinant HMW-glutenin (recombinant HMW-glutenin CAP, commercially not available) was found to be highly useful for diagnosis of WDEIA when combined with the recombinant ω-5 gliadin CAP as indicated in Table 1 [25]. In addition, the recombinant HMW-glutenin CAP was found to be rather useful in the patients under 20 years old.

The CAP constructed with the recombinant wheat proteins are found to be incompetent for identifying the new subtypes of WDEIA sensitized by HWP in Japan [4]. More than 90% of the patients with conventional type of WDEIA can be detected positively, whereas only 16% of the patients showed positive results even with a combination of recombinant ω-5 gliadin CAP and recombinant HMW-glutenin CAP. This indicates that major epitope recognized by serum IgE from the patients with HWP-type WDEIA is different from that recognized by serum IgE from conventional type WDEIA. Recently, the wheat protein recognized by the patients with HWP-type WDEIA has been identified as γ-gliadin and its epitope as QPQQPFP [26]. Interestingly, the epitope was identical to that determined in European patients sensitized with HWP [27].

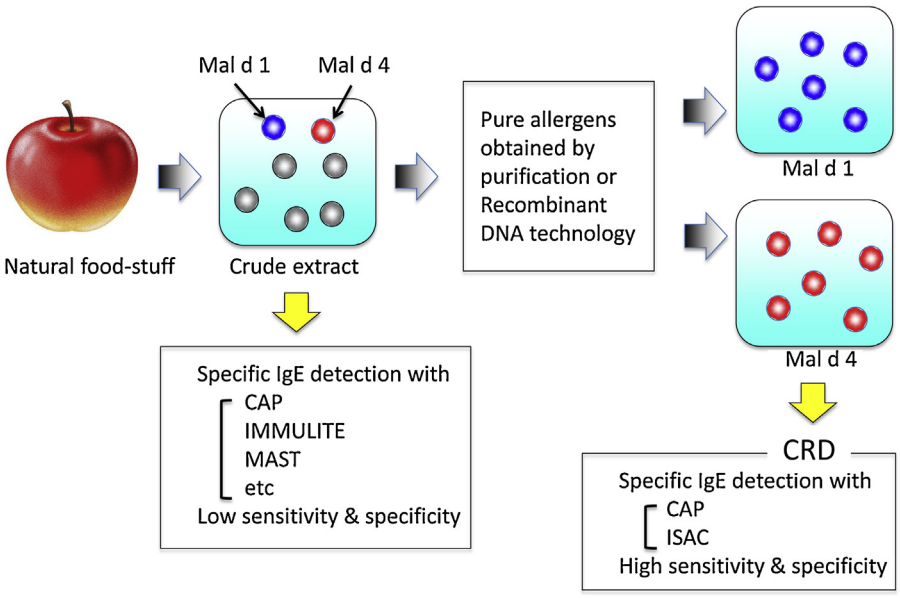

Fig. 1. Concept of CRD. When purified allergens or recombinant allergens were used for the specific IgE detection, sensitivity and specificity of the tests highly improves compared with the tests using crude extracts.

Oral allergy syndrome (OAS) is another complicated IgE-mediated food allergy, which mainly exhibits oral mucosal allergy (itch, redness, tingling, swelling occuring in the mouth, lips, and throat mostly within 15 min after ingestion) against multiple foodstuffs [28]. The foodstuffs range a variety of fruits and vegetables. Most of the patients are associated with pollinosis. A typical example of OAS appears in a patient with birch pollen pollinosis who has eaten a fruit of the family Rosaceae. IgE against birch pollen-allergens cross-react to certain fruits of the family Rosacea (apple, cherry, peach, *etc.*), and the allergens have been identified such as pathogenesis-related proteins and profilin [29,30]. However, these allergens often cross-react to vegetables or spices beyond the family species, because their homolog proteins widely distribute in these foodstuffs. The use of recombinant proteins of these allergens enabled us to understand the cross-reactivity among unrelated plant species. In this concept, ISAC (Thermo Fisher Scientific), which offers semi-quantitative measurement of IgE against an array of 112 allergenic components from 50 different allergen sources, are commercially available (Fig. 1) [31].

3. Basophil activation test (BAT)

The BAT is an *in vitro* assessment of allergic response that requires only a small amount of whole blood. The test currently uses flow cytometry to detect upregulation of certain cell surface molecules, such as CD63 and CD203c, after allergen stimulation in order to identify activated basophils. CD203c is ectonucleotide pyrophosphatase/phosphodiesterase 3, which is constitutively expressed and upregulated by activation on the cell membrane of basophils. CD63 is lysosomal-associated membrane glycoprotein-3, which is secreted through degranulation of basophils. A comparative study using either CD63 or CD203c indicated higher sensitivity for the CD203c test as an *in vitro* diagnostic tool for bee allergy and latex allergy [32,33]. On the other hand, another comparative study showed only a slight, but not statistically significant, higher sensitivity of the CD203c test [34]. To date, evidences have accumulated indicating usefulness of the test in children with various food allergies [35–39] as well as in the patients with pollen-associated food allergy syndrome [40–45].

Currently, a commercial kit for quantification of CD203c expression on basophils, Allergenicity kit® (Beckmann Coulter, Fullerton, CA, USA), which identifies basophils as CD3-negative and CRTH2-positive fractions from whole blood samples, is available and measures fluorescent intensity of CD203c that is enhanced by cross-linking of surface-bound IgE of basophils. The CD203c expression-based BAT is highly useful in identifying adult patients with WDEIA and predicting causative allergens in WDEIA. Chinuki et al. have recently demonstrated that the CD203c expression-based BAT can clearly distinguish two phenotypes of WDEIA, conventional type WDEIA and HWP-type WDEIA, by using culprit wheat allergens [4]. They also reported that the CD203c expression-based BAT is useful in determining allergenicity of allergens, such as HWPs [46].

Table 1
Positive rate (%) of allergen-specific IgE tests (CAP) with wheat proteins.

CAP	WDEIA ($n=54$)	WDEIA over 20[a] ($n=38$)	WDEIA under 20[b] ($n=16$)	AD[c] ($n=16$)	Healthy ($n=12$)
wheat	31.4	31.5	31.2	87.5	0
gluten	37.0	39.4	31.2	18.7	0
ω-5gliadin	79.6	94.7	43.7	0.0	0
HMW-glutenin	18.5	7.8	43.7	12.5	0
ω-5gliadin and/or HMW-glutenin	94.4	97.3	87.5	12.5	0

Referred from reference [24] with modification.
[a] Patients who are over 20 years old.
[b] Patients who are under 20 year old.
[c] Patients with atopic dermatitis who had positive IgE antibodies to wheat > 0.34 (kUa/L) but no episodes of immediate-type allergic reactions to wheat.

4. Histamine release test (HRT)

The HRT is an *in vitro* test to evaluate amount of histamine released from peripheral blood basophils after reaction with allergens. The test is considered to be the most reliable methods to reflect sensitization by allergen-specific IgE antibodies in a living body [47]. Currently, a commercial kit, HRT Shionogi kit® (Shionogi & Co., Ltd., Osaka, Japan), which covers five different allergens, egg white, cow's milk, wheat, soybean and rice, is available in routine examination [48]. The threshold of the test is related to outcomes of oral food challenge tests and is useful in determining food allergy when cutoff value was appropriately determined [49]. Utility of the HRT has not well established in identifying adult patients with FDEIA, because sensitivity and specificity of the test has not fully investigated. The low sensitivity of the test might be due to inappropriate preparation of allergens. In addition, it is also disadvantage of the test that basophils from certain patients do not react to the relevant allergens (non responders), and the basophil reactivity to relevant allergens can be reduced within 48 h after blood sampling from some patients, resulting in lower reaction than real values.

5. Monitoring of serum allergen levels during food challenge tests

Combined challenge test with causative food intake and exercise is often performed to identify the patients with FDEIA. The challenge test is the most reliable when allergic symptoms are elicited. Since aspirin is a well-known trigger in inducing symptoms in combination with food-intake, even in the patients with FDEIA who had no previous history of aspirin hypersensitivity, a combination challenge of food and aspirin-pretreatment and/or triple combination challenge of aspirin-pretreatment, food and exercise can be performed. However, these tests may often result in a false-negative challenge, because symptoms are not always elicited by the challenge tests depending on the patient's conditions.

In the food-challenge tests for FDEIA, absorption of enough amounts of allergens from gastrointestinal tract is essential for eliciting allergic symptoms. Matsuo et al. established a gliadin-specific sandwich enzyme-linked immunosorbent assay and found that immunoreactive gliadins appears in the sera of patients with WDEIA during the wheat challenge test combined with exercise concurrently with allergic symptoms [2,50]. An enhancement of serum gliadin levels was also demonstrated in combined challenge testing with wheat and aspirin, indicating that aspirin facilitates allergen absorption from the gastrointestinal tract. The exercise-induced enhancement of allergen absorption was seen in healthy subjects. Considering these facts, Kohno et al. demonstrated that monitoring serum gliadin level is a good marker to check whether challenge tests have been performed with sufficient strength [51]. Negative challenge testing with high gliadin level can eliminate diagnosis of WDEIA but that with low gliadin level might be false negative testing and need re-testing.

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