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A PATIENT WITH SALMON ROE ALLERGY SHOWING TAXONOMY-UNRELATED CROSS-REACTIVITY WITH SEA URCHIN ROE

In Japan, salmon (*Oncorhynchus keta*; phylum Chordata, family Salmonidae) eggs (salmon roe [SR]) are commonly eaten raw in dishes such as sushi, and the number of patients who develop severe allergies after initial SR intake has been increasing in recent years. In Western countries, one patient developed unexpected anaphylaxis after consuming rainbow trout (*Oncorhynchus mykiss*; family Salmonidae) roe,[1] and another adult developed anaphylactic symptoms after initial SR intake.[2] On the basis of the induction of allergy by initial SR intake, there is a possibility that SR allergy develops through sensitization due to cross-reactivity with other foods. However, the source of such SR sensitization remains unclear.[3]

We encountered a patient with allergy to SR who developed a cross-reactive allergic reaction to the eggs of sea urchins (phylum Echinodermata; sea urchin roe [UR]), which are distantly taxonomically related. There have been no previous reports of cross-reactivity between the Chordata and Echinodermata phyla. We confirmed the cross-reactivity between them by inhibition enzyme-linked immunosorbent assay (ELISA) and immunoblotting.

The patient first developed SR allergy at 4 years of age. He had previously tolerated chicken eggs and had also eaten fish meat, including salmon and the roe of other kinds of fish (herring and pollock roe), without any reaction. Immediately after first ingesting an SR egg, he became pale, experienced abdominal pain, vomited, and had diarrhea. His SR specific IgE antibody level was subsequently found to be high (91.9 UA/mL) using the ImmunoCAP test (Phadia AB, Uppsala, Sweden). At the age of 10 years, because he wished to eat UR, which is a popular sushi dish, we planned an oral challenge after skin prick tests. The oral challenge was performed without discontinuing the oral administration of pranlukast for his underlying asthma. Because the skin prick test result was positive (wheal diameters: UR extract, 3 mm; 10 mg/mL histamine, 4 mm; and saline, 0 mm), a very small amount (corresponding to 0.1 mg) of UR was orally administered using the open challenge method after preparing for his admission. He developed abdominal pain 15 minutes after the challenge, excreted soft feces, and experienced itching around his eyes. The oral challenge test result was regarded as positive, and the test was terminated. The above symptoms disappeared without any treatment. We subsequently realized that we could have obtained more objective data if we had measured plasma histamine levels.

To examine the cross-reactivity between SR and UR, we performed an inhibition ELISA study with the patient's sera, as described in a previous report.[3] Extracts from UR, salmon meat, SR,

Disclosures: Authors have nothing to disclose.

Funding Sources: This research was supported by a grant from the Ministry of Health, Labour, and Welfare and the Cabinet Office of Japan, 2010.

doi:10.1016/j.anai.2011.06.007

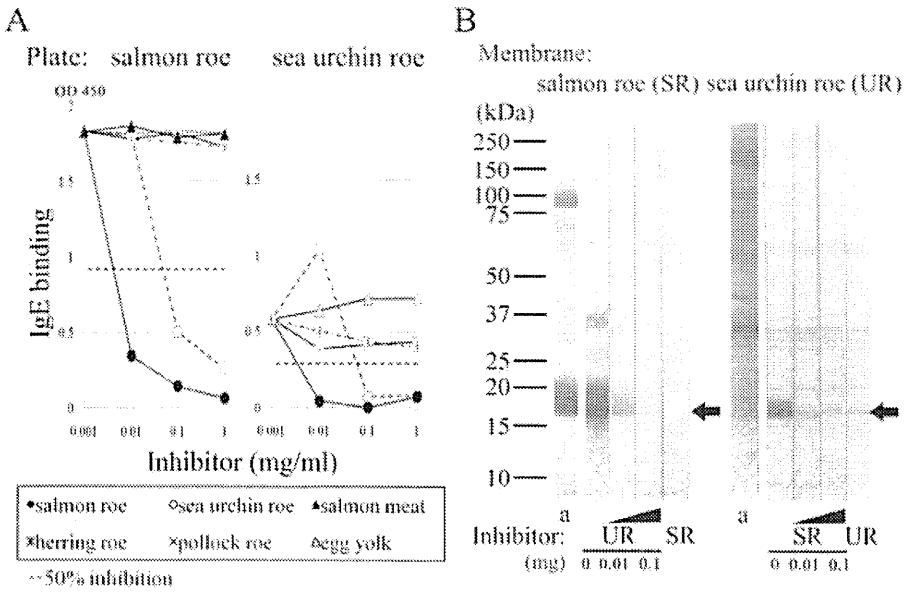

Figure 1. Inhibition assay and immunoblot results. A, Inhibition enzyme-linked immunosorbent assay between salmon roe (SR) and sea urchin roe (UR). Preincubation of the patient's serum with heterogeneous SR or UR extract induced more than 50% inhibition of the IgE specific to each extract. Other kinds of fish roe and chicken yolk did not affect IgE binding to either extract. B, Inhibition immunoblot between SR and UR. IgE specific to low-molecular-weight proteins (arrows) isolated from the 2 extracts mutually inhibited each other. Lane a: Amido black stained.

herring roe, Alaskan pollock roe, and chicken egg yolk were obtained in the previously reported manner.[3] Specific IgE to SR and UR almost completely inhibited each other's binding. Interestingly, other kinds of fish roe were not only poor inhibitors of IgE specific to UR, to which they were not taxonomically related, but also poor inhibitors of IgE specific to SR, to which they were closely related taxonomically (Figure 1A). This finding suggested that there was no correlation between taxonomy and allergenicity. Then, we attempted to identify the relevant allergen by performing an inhibition immunoblot study. Sodium dodecyl sulfate–polyacrylamide gel electrophoresis was performed in a 4% to 12% NuPAGE Novex Bis-Tris Mini Gel (Invitrogen, Carlsbad, California) under reducing conditions. Immunoblotting of the proteins and the detection of bound serum IgE were performed as previously reported.[4] Specific IgE to 2 proteins of approximately 18 kDa that were isolated from UR or SR (1 protein was isolated from each roe) mutually inhibited each other (Figure 1B). We performed amino acid analysis of the N-terminal of the 18-kDa UR protein and identified an 18-kDa egg cortical vesicle protein (NP_999641). A search revealed homology with the complement C1q-like protein 4 precursor (ACM08719) of Atlantic salmon (*Salmo salar*) with a Basic Local Alignment Search Tool (BLAST) expected value of 2×10^{-7} (−10). Both proteins belong to the C1q family, and a member of this family has been reported to be localized in mature eggs in the prespawning ovary.[5] These findings suggest that the homology of these proteins could cause cross-reactivity.

There have been 3 case reports of UR allergy.[6–8] As allergens, 2 high-molecular-weight proteins (118 kDa[7] and 160 kDa[8]) have been reported, and the latter was identified as major yolk protein. However, these reports did not mention cross-reactivity. In Figure 1B, the patient's IgE did not react with these proteins. Therefore, the 18-kDa protein was considered to be a novel allergen that displays the unique characteristic of cross-reacting with SR.

This is the first study, to our knowledge, to demonstrate unexpected cross-reactivity between the Echinodermata and Chordata phyla. It is important to bear in mind that cross-reactivity can occur in taxonomically unrelated species.

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Allergology International. 2011;60:221-236
DOI: 10.2332/allergolint. 11-RAI-0329

REVIEW ARTICLE

Japanese Guideline for Food Allergy

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ABSTRACT

Food allergy is defined as "a phenomenon in which adverse reactions (symptoms in skin, mucosal, digestive, respiratory systems, and anaphylactic reactions) are caused in living body through immunological mechanisms after intake of causative food."

Various symptoms of food allergy occur in many organs. Food allergy falls into four general clinical types; 1) neonatal and infantile gastrointestinal allergy, 2) infantile atopic dermatitis associated with food allergy, 3) immediate symptoms (urticaria, anaphylaxis, etc.), and 4) food-dependent exercise-induced anaphylaxis and oral allergy syndrome (i.e., specific forms of immediate-type food allergy).

Therapy for food allergy includes treatments of and prophylactic measures against hypersensitivity like anaphylaxis. A fundamental prophylactic measure is the elimination diet. However, elimination diets should be conducted only if they are inevitable because they places a burden on patients. For this purpose, it is highly important that causative foods are accurately identified. Many means to determine the causative foods are available, including history taking, skin prick test, antigen specific IgE antibodies in blood, basophil histamine release test, elimination diet test, oral food challenge test, etc. Of these, the oral food challenge test is the most reliable. However, it should be conducted under the supervision of experienced physicians because it may cause adverse reactions such as anaphylaxis.

KEY WORDS

elimination diet, food allergy, IgE-mediated type, non-IgE-mediated type, oral food challenge test

1. DEFINITION OF FOOD ALLERGY

The Japanese Pediatric Guideline for Food Allergy 2005,[1,2] published in 2005, defines food allergy as "a phenomenon in which adverse reactions (symptoms in skin, mucosal, digestive, respiratory systems, and anaphylactic reactions) are caused in living body through immunological mechanisms after intake of causative food."

2. EPIDEMIOLOGY OF FOOD ALLERGY

2.1. PREVALENCE OF IMMEDIATE-TYPE FOOD ALLERGY

Food allergy is common among infants aged 0-1 years and decreases with aging, which indicates that tolerance develops with aging. The estimated prevalence in Japan is 5-10% among infants and 1-2% among schoolchildren. The prevalence of food allergy, reported from various countries, is shown in Table 1.

2.2. CAUSATIVE FOODS

Eggs, dairy products, wheat, buckwheat, shrimp and peanuts are the common causative foods of immediate-type food allergy, indicated by the national surveys of food allergy during 1998-1999, conducted by the Review Committee on the Countermeasure for the Food Allergy of the Ministry of Health and Welfare (Fig. 1). As shown in Figure 2, patients aged less than 1 year of age account for 29.3%, and those aged $\leq$8 years account for 80.1%. The number of patients decreases with aging. Patients aged $\geq$20 years account for 9.2%. This is not a small number. Eggs, dairy products and wheat are 3 major allergens among those aged $\leq$6 years, while shrimp, fish, and

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Received 20 January 2011.

Table 1 Prevalence of food allergy reported from various countries

Year	Reporter	Country	Subject	Number of subjects	Methods	Diagnosis	Prevalence	Journal
1994	Young E	UK	All ages	7,500 households	Interview + DBPCFC	Food intolerance	1.4-1.8%	Lancet
1994	Jansenn JJ	Netherlands	Adults	1,483 persons	Questionnaire + DBPCFC	Food allergy, food intolerance	0.8-2.4%	J Allergy Clin Immunol
1999	Kristjansson I	Sweden, Iceland	Children (aged 18 months)	652 persons	Questionnaire + DBPCFC	Food allergy	2.00%	Scand J Prim Health Care
2001	Kanny G	France	All ages	33,110 persons	Questionnaire (two-step survey)	Food allergy	3.52%	J Allergy Clin
2004	Zuberbier T	Germany	All ages	4,093 persons	Questionnaire + DBPCFC	Food allergy	3.60%	Allergy
2005	Imai	Japan	School children	8,035,306 persons	Questionnaire	Food allergy	1.30%	J Jpn Pediatr Soc
2005	Rance F	France	School children	2,716 persons	Questionnaire	Food allergy	4.70%	Clin Exp Allergy
2005	Pereira B	UK	School children (aged 11 years)	757 persons	Questionnaire + Open challenge test	Food allergy	2.30%	J Allergy Clin Immunol
			School children (aged 15 years)	775 persons	Questionnaire + DBPCFC	Food allergy	2.30%	
2005	Osterballe M	Denmark	3 years old	486 persons	Questionnaire + Food challenge test	Food allergy	2.30%	Pediatric Allergy Immunol
			Aged ≥3 years	301 persons	Questionnaire + Food challenge test	Food allergy	1.00%	
			Adults	936 persons	Questionnaire + Food challenge test	Food allergy	3.20%	
2005	Penard-Morand C	France	School children (aged 9-11 years)	6,672 persons	Questionnaire	Food allergy	2.10%	Allergy
2006	Venter C	UK	1-year-old children	969 persons	Questionnaire + Open challenge test	Food allergy	5.50%	J Allergy Clin Immunol
					Questionnaire + DBPCFC	Food allergy	2.20%	
2006	Venter C	UK	6-year-old children	798 persons	Questionnaire + Open challenge test	Food allergy	2.50%	Pediatric Allergy Immunol
					Questionnaire + DBPCFC	Food allergy	1.60%	

fruits are common among those aged >6 years (Table 2).

3. PATHOLOGY, SYMPTOMS AND CLINICAL TYPES OF FOOD ALLERGY

3.1. PATHOLOGY OF FOOD ALLERGY

IgE is often involved in food allergies (IgE-mediated food allergy).[3] In some patients, symptoms develop via immunological mechanisms not involving IgE (non-IgE-mediated food allergy).[4] Both IgE-mediated and non-IgE-mediated reactions may be involved in the development of food allergies (mixed type food allergy).

Food provides essential nutrients for humans. The antigenicity of foods is reduced when they are digested into low-molecular substances. However, even in adults with mature digestive functions, the antigenicity remains to some extent after foods are absorbed into the living body. Orally ingested foods are foreign substances (non-self). If antigenicity remains, they should be immunologically eliminated, but are not eliminated. Healthy individuals have mechanisms for preventing allergic reactions to foreign food antigens, including a physicochemical barrier during food digestion and absorption in the digestive tract and an immunological barrier to reduce the antigenicity of foods absorbed in the digestive tract. The former includes digestion into low-molecular substances by digestive enzymes (e.g., pepsin) and denaturation by gastric acid. The latter includes the inhibition of

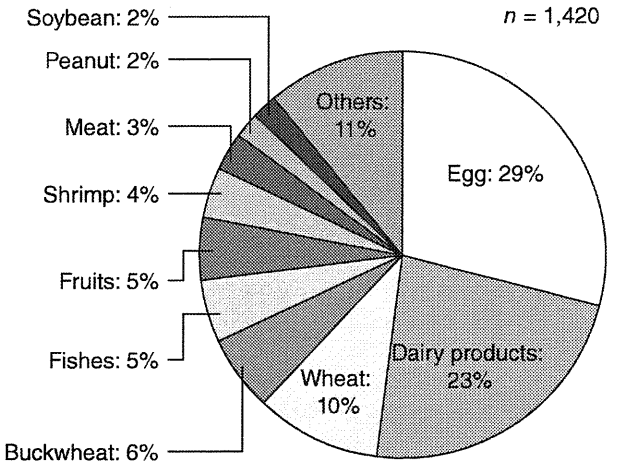

Fig. 1 Causative foods of immediate-type food allergy (national surveys by the Ministry of Health and Welfare during 1998-1999).

absorption of food antigens via secretory IgA and the establishment of oral immunotolerance to suppress allergic reactions to food antigens ingested from the digestive tract.[5]

In patients with food allergy, oral immunotolerance, which is normally established against orally ingested food antigens, may not be established or may be compromised after establishment. However, it is unknown why oral immunotolerance is not established in patients with food allergy.

Food allergy is common in infants because physical, biochemical and immunological barriers are underdeveloped during infancy.

3.2. SYMPTOMS OF FOOD ALLERGY

Symptoms of food allergy include skin, digestive, nasal, ocular, respiratory and systemic symptoms (Table 3).

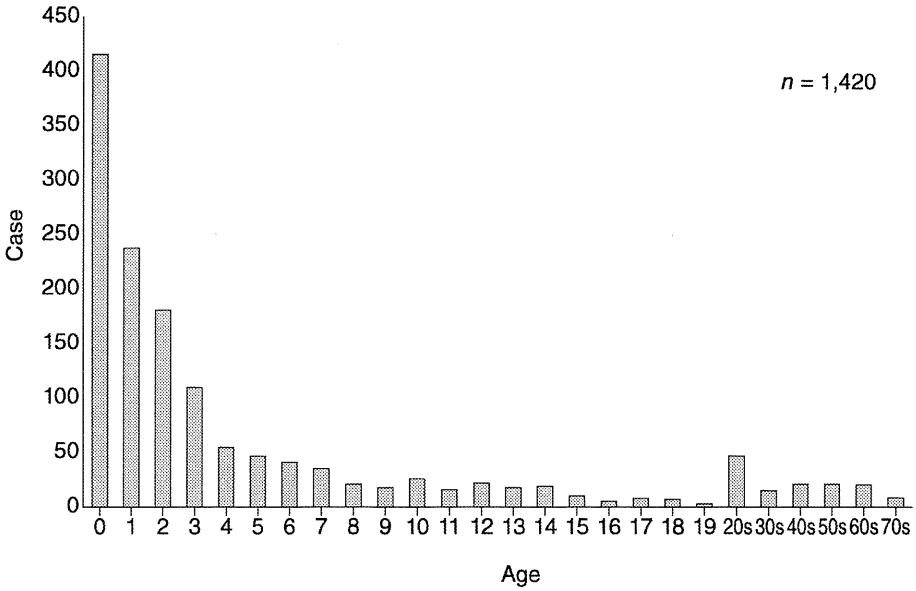

Fig. 2 Age distribution of immediate-type food allergy (national surveys by the Ministry of Health and Welfare during 1998-1999).

Table 2 Causative foods of immediate-type food allergy by age

	0 year (n = 416)	1 year (n = 237)	2-3 years (n = 289)	4-6 years (n = 140)	7-19 years (n = 207)	>20 years (n = 131)
No. 1	Egg	Egg	Egg	Egg	Buckwheat	Seafood
	47.4%	30.4%	30.8%	25.0%	14.0%	16.0%
No. 2	Dairy products	Dairy products	Dairy products	Dairy products	Shrimp	Shrimp
	30.8%	27.8%	24.2%	24.3%	13.0%	14.5%
No. 3	Wheat	Wheat	Wheat	Wheat	Wheat	Buckwheat
	9.6%	8.4%	12.1%	8.6%	10.6%	12.2%
Total	87.8%	66.6%	67.1%	57.9%	37.6%	42.7%

Table 3 Symptoms of food allergy by organ

Organ	Symptoms
Digestive system	Oral discomfort, lip swelling, abdominal pain, nausea and vomiting, diarrhea
Respiratory system	Sneezing, rhinorrhea, nasal congestion, coughing, wheezing, dyspnea, chest tightness, laryngopharyngeal edema
Eyes	Conjunctival hyperemia and edema, blepharedema, and lacrimation
Skin	Erythema, urticaria, angioedema, itch, burning sensation, blister, eczema
Nervous system	Headache
Urinary system	Hematuria, proteinuria, nocturnal enuresis
Systemic	Anaphylaxis

3.2.1. Skin Symptoms: Skin Symptoms Are Most Common in Food Allergy

(1) Urticaria and angioedema: Acute urticaria and angioedema are common. Rash often occurs within several minutes after ingestion, accompanied by itch.

(2) Atopic dermatitis: Atopic dermatitis is not caused by a single factor. There are various exacerbation factors. Many papers have been published regarding the involvement of food allergies. Reports of its incidence vary widely, depending on the methods used to select subjects (e.g., selection based on severity, history, specific IgE antibodies, or skin test results), methods used for the oral challenge test (open food challenge, double-blind, placebo-controlled food challenge (DBPCFC), and test timing, i.e., before or after the remission of skin symptoms).

3.2.2. Digestive Symptoms

(1) Immediate-type gastrointestinal allergy: Nausea, vomiting, abdominal pain, colic and diarrhea occur during food ingestion or at about 2 h after food ingestion. These are often accompanied by skin and airway symptoms. Some infants present with intermittent vomiting and poor weight gain. Most affected infants ($\geq$95%) are positive for specific IgE antibodies against causative foods and in a skin test.

(2) Oral allergy syndrome (OAS)[6]: OAS is caused by contact urticaria in the oral mucosa. IgE antibodies are involved. Itch, redness, tingling, swelling, etc., often occur in the mouth, lips, and throat mostly within 15 min after ingestion. Some patients present with systemic symptoms, such as throat constriction, generalized urticaria, cough, wheezing, dyspnea, and anaphylactic shock. These may be caused by food antigens absorbed from the oral mucosa and distributed throughout the body. OAS occurs in infants, schoolchildren, and adults. Common causative foods are fruits (kiwi, banana, melon, peach, pineapple, apple, etc.) and vegetables. OAS is often complicated by pollinosis. OAS complicated by pollinosis is called pollen-associated food allergy syndrome or pollen-food allergy syndrome (PFS). Reportedly, in Hokkaido (Japan), 16% of patients with birch pollinosis develop OAS due to fruits, such as apple.

(3) Eosinophilic gastroenteritis: Eosinophilic gastroenteritis is a rare disease with eosinophil infiltration in the intestinal mucosa from the esophagus to the rectum. Abdominal pain, nausea and diarrhea occur. Eosinophilic gastroenteritis is accompanied by malabsorption, protein leakage and iron deficiency anemia caused by intestinal hemorrhage. While an infiltration of eosinophils is usually localized to the mucous membrane, it may spread to submucosa or muscle layer, being complicated by eosinophilic ascites. Food allergy is involved in 25-50% of these cases.

(4) Neonatal and infantile gastrointestinal allergy: In Europe and America, several disease types have been reported, which mainly present with digestive symptoms and occur among newborns and infants, and in which IgE is not involved.[7,8] Many Japanese patients also fall into these categories regarding their symptoms and test results. However, some patients do not fall into any of these disease types. Thus, the Guideline Committee for Food Allergy in the Japanese Society of Pediatric Allergy and Clinical Immunology bracket together these food allergies, which mainly present with digestive symptoms and occur among newborns and infants, into "neonatal and infantile gastrointestinal allergy." Many patients are negative for IgE antibodies and are positive for an allergen-specific lymphocyte stimulation test (ALST). Thus, this disease may be mainly caused by the hyperreactivity of cellular immunity.

About 70% of patients develop symptoms during the newborn period, while some do at several months after birth. Half of neonatal patients develop symptoms until 7 days after birth. Symptoms may develop after the first milk ingestion on the day of birth. Common symptoms are vomiting, bloody stool, diarrhea, and abdominal fullness. Other symptoms include shock, dehydration, sluggishness, hypothermia, acidosis, and methemoglobinemia. Of note, some patients present with fever and positive CRP. Differential diagnosis of these patients from those with severe infections, such as bacterial enteritis, is difficult. Some patients develop neonatal transient eosinophilic colitis, which causes bloody stool immediately after birth (before nursing). This disease may occurs in utero.[9]

The most common causative food is cow's milk.

Table 4 Classification of food allergy

Clinical type		Age of onset	Common causative foods	Tolerance acquisition (remission)	Possibility of anaphylactic shock	Mechanism of food allergy
Neonatal and infantile gastrointestinal allergy		Neonatal and infantile period	Cow's milk (powdered milk for infants), soybean, rice	(+)	(±)	Mainly non IgE-mediated type
Infantile atopic dermatitis associated with food allergy†		Infancy	Egg, cow's milk, wheat, soybean, etc.	(+) in many cases	(+)	Mainly IgE-mediated type
Immediate-type (urticaria, anaphylaxis, etc.)		Infancy-adulthood	Infants-young children: egg, cow's milk, wheat, buckwheat, fishes, etc. School children-adults: crustacean shellfish, fish, wheat, fruits, buckwheat, peanut, etc.	Egg, cow's milk, wheat, soybean, etc.(+) Others (±)	(++)	IgE-mediated type
Specific type	Food-dependent exercise-induced anaphylaxis (FEIAn/FDEIA)	School age-adulthood	Wheat, shrimp, squid, etc.	(±)	(+++)	IgE-mediated type
	Oral allergy syndrome (OAS)	Infancy-adulthood	Fruits, vegetables, etc.	(±)	(+)	IgE-mediated type

† Some cases are complicated by digestive symptoms, such as chronic diarrhea, and hypoproteinemia. Foods are not involved in all cases of infantile atopic dermatitis.

Modified from Food Allergy Management Guideline 2008.

Others include soybean milk and rice. Some cases were fed by mother's milk or hydrolyzed whey formula.

Diagnosis is made based on i) development of digestive symptoms after causative food ingestion, ii) improvement and disappearance of symptoms by eliminating causative foods (positive elimination test), and iii) positive food challenge test.

To treat gastrointestinal allergy caused by cow's milk in an early stage, therapeutically effective products, such as amino-acid-based formula and extensively hydrolyzed formula, are preferably used.

The prognosis is relatively favorable. About 70% of patients acquire tolerance at 1 year of age, and about 90% acquire tolerance by their second birthday.

3.2.3. Respiratory Symptoms

Upper respiratory tract symptoms include symptoms of allergic rhinitis, such as nasal discharge, nasal congestion, and sneezing. Lower respiratory tract symptoms include symptoms of airway narrowing (wheezing) and laryngeal edema.

The Heiner syndrome is characterized by pulmonary hemosiderosis caused by milk,[10] Heiner syndrome a rare disease, which causes hemoptysis due to alveolar hemorrhage and features chronic cough, dyspnea, wheezing, fever, and bloody sputum, resulting in iron deficiency anemia. Precipitating antibodies against cow's milk proteins are detected in the sera of affected infants.

3.2.4. Ocular Symptoms

Symptoms of allergic conjunctivitis, such as conjunctival hyperemia and edema, blepharedema, and lacrimation, may occur.

3.2.5. Systemic Symptoms

(1) Anaphylaxis: Severe allergic symptoms occurring in multiple organs are called anaphylaxis. The most severe symptoms result in shock accompanied by decreased blood pressure and impaired consciousness. Causative agents of anaphylaxis, besides foods, include medicines, blood transfusion, bee, and latex. Food allergy is the most common cause. Food-induced anaphylaxis is an immediate reaction, in which IgE antibodies are involved. While symptoms usually occur within several minutes after ingestion, they occasionally occur 30 min or later. Symptoms may occur either in monophasic or biphasic. In Europe and America, causative foods of anaphylaxis include peanuts, nuts and seeds, seafood, eggs, and cow's milk. In Japan, they include eggs, cow's milk, seafood, shellfish, buckwheat, and peanuts in this order.

(2) Food-dependent exercise-induced anaphylaxis (FEIAn or FDEIAn): FEIAn is induced by exercise after food ingestion (mostly within 2 h after ingestion), but does not occur after either food ingestion or exercise alone. Nonsteroidal antiinflammatory drugs, such as aspirin, are an exacerbation factor. FEIAn occurs in an IgE-mediated manner.

The prevalence of FEIAn in schoolchildren and students is 0.0085%, i.e., one incidence per 12,000 per-

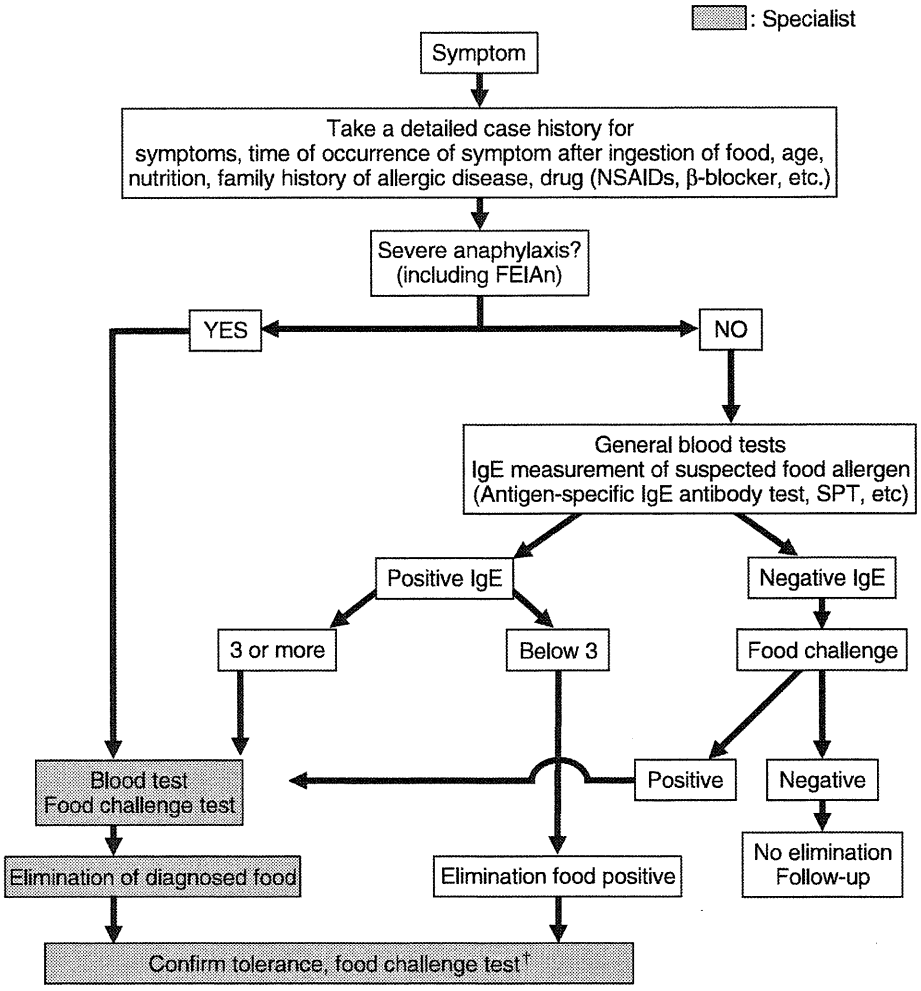

Fig. 3 Procedure for Diagnosis of Food Allergy (for "Immediate Type Reaction"). NSAIDs, non-steroidal antiinflammatory drugs; FEIAn, food-dependent exercise-induced anaphylaxis; SPT, skin prick test.
†Generally, patients who demonstrate immediate type reaction in later childhood are less likely to acquire tolerance.
Adapted from reference 12.

sons. FEIAn is most common among junior high school students, and is more common in males than in females (male-female ratio, 4 : 1). Common causative foods are shellfish (55%) and wheat products (45%).[11]

Definitive diagnosis can be made by presuming the causative foods through history taking, allergy testing, and checking hypersensitivity in a provocation test with food challenge followed by exercise loading. Few patients have a positive provocative test. In patients with negative results, consider administering aspirin before the food challenge.

3.3. CLINICAL TYPES OF FOOD ALLERGY

Four representative clinical types of food allergy are shown in Table 4, a revision to "Food Allergy Management Guideline 2008".[12]

"Neonatal digestive symptoms" in the Food Allergy Management Guideline 2008 was altered to "neonatal and infantile gastrointestinal allergy" after approval by the Guideline Committee for Food Allergy in the Japanese Society of Pediatric Allergy and Clinical Immunology.

Atopic dermatitis during infancy is often associated with food allergy, of which symptoms become immediate type and is usually resolved with aging. This type atopic dermatitis is called "infantile atopic dermatitis associated with food allergy." Common causative foods are eggs, cow's milk, wheat, and soybeans.

The food allergy which promptly develop after ingestion of causative food are "immediate-type food allergy which is common in young children to adulthood." The causative foods are buckwheat, peanuts, fish, curastacean shellfish, and fruits. Tolerance ac-

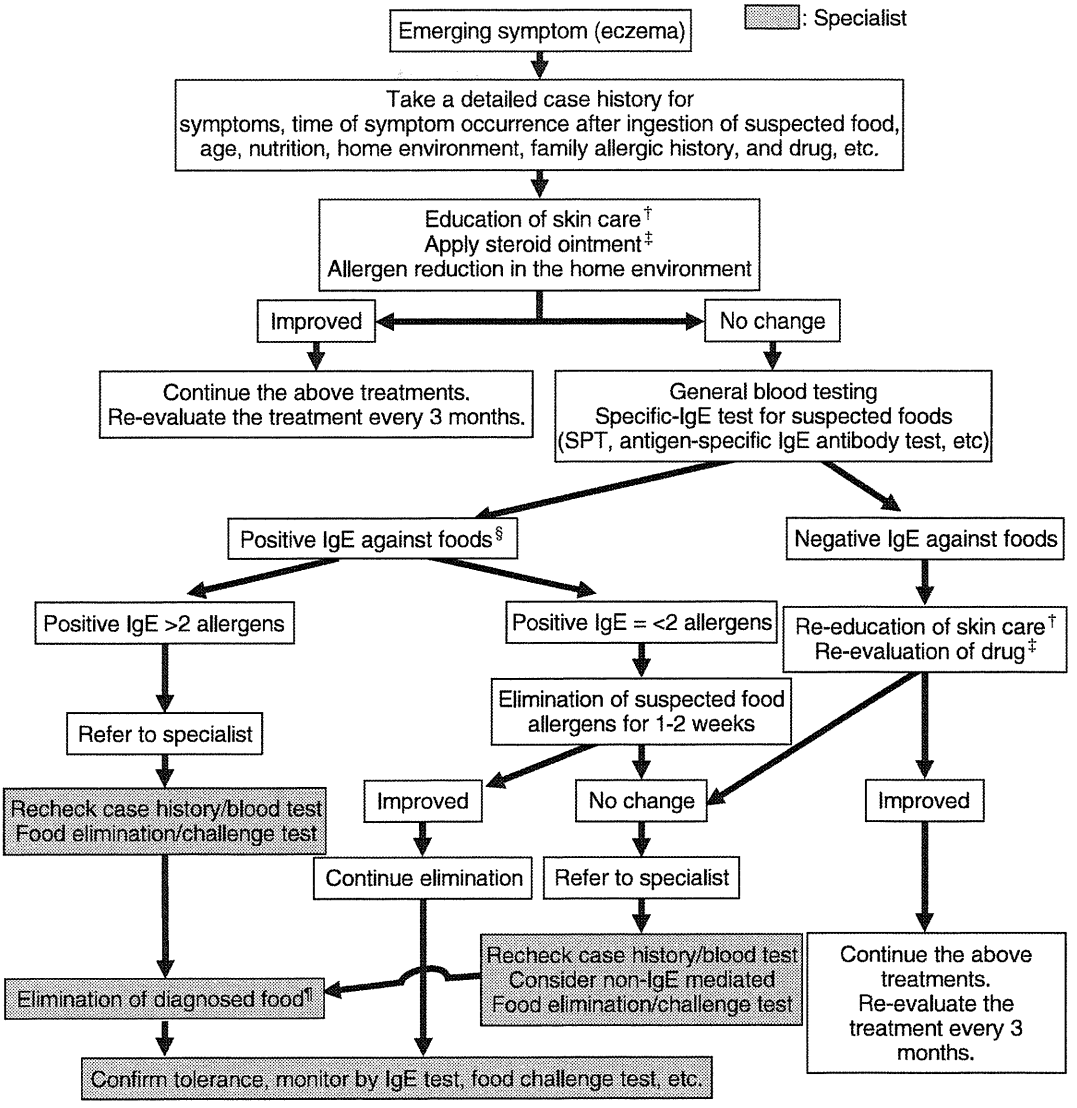

Fig. 4 Procedure for Diagnosis of Food Allergy (for "Infantile Atopic Dermatitis associated with Food Allergy"). SPT, skin prick test.

† Skin care. Cleaning with soap and moisturizing is essential for skin care.

‡ Drug treatment. Steroid ointment is the essential treatment for infantile atopic dermatitis.

§ SPT is useful for a baby under six months of age because an IgE antibody tends to become negative.

¶ Precautions for practicing the elimination diet. Monitor child's growth and development. Always look for the possibility of ceasing the elimination diet.

Adapted from reference 12.

quisition may be less common compared with food allergy in infants.

"Food-dependent, exercise-induced anaphylaxis" and "oral allergy syndrome" are specific forms of immediate-type food allergy.

4. DIAGNOSIS AND CHALLENGE TEST OF FOOD ALLERGY

The flowcharts of food allergy diagnosis are shown in Figure 3, 4.[12]

4.1. HISTORY TAKING

In history taking, causative foods and their intakes, time from food intake to onset of symptoms, reproducibility, other causative conditions (exercise, medication, etc.) and time when last symptoms occurred, should be recorded. Food diaries are useful for history taking.

4.2. EXCLUSION OF FACTORS INFLUENCING SYMPTOMS OTHER THAN DIETS

For chronic nonimmediate symptoms (e.g., atopic

Table 5 Cutoff values of specific IgE antibody titers, which enable food allergy diagnosis even if no challenge test is conducted

1) Sampson (JACI 2001)				(U_A/mL)
Specific IgE	Egg white	Cow's milk	Peanut	Fish
Diagnositic decision points	7	15	14	20
2) Komata (JACI 2007)				
Age	<1 year	1 year		≥2 years
Egg white	13.0	23.0		30.0
Cow's milk	5.8	38.6		57.3
3) Ando (JACI 2008)				
Challenge diet	Raw egg white		Heated egg white	
Specific IgE	Egg white	Ovomucoid	Egg white	Ovomucoid
Positive decision point	7.38	5.21	30.7	10.8

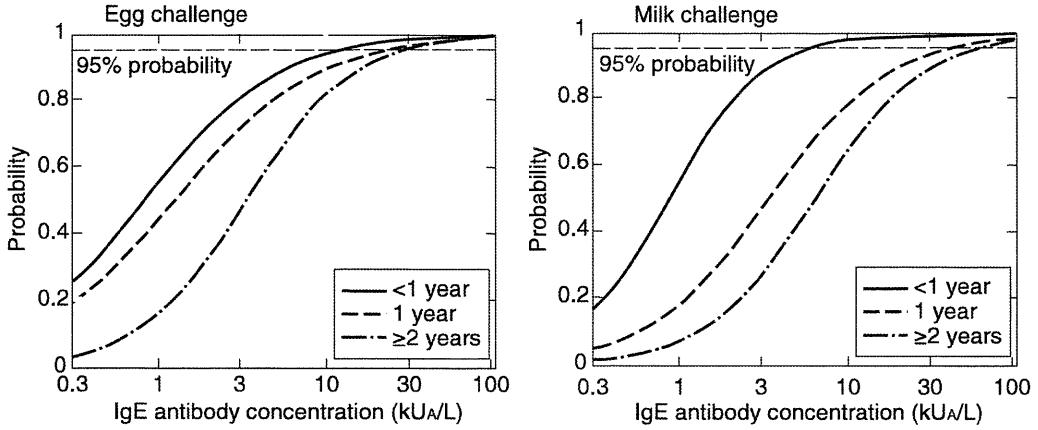

Fig. 5 Probability curves of egg white-specific and cow's milk-specific IgE antibody titers by age. Specific IgE antibody titers indicate the rate of positive immediate reaction (probability) in the food challenge test. However, these values should be used as reference, because they vary by reporters.

dermatitis), factors other than diet causing or exacerbating symptoms should be removed by indoor environmental improvement, proper skin care, pharmacotherapy, etc.

4.3. SKIN TEST

A skin prick test (SPT) is recommended for examining the causes of food allergy. Intradermal tests using food antigens are not recommended because they are more likely to yield false positive results and cause anaphylactic reactions than SPT. However, for patients with a history of symptoms or high antigen specific IgE antibody levels, even SPT should be avoided because it may cause systemic symptoms.

Reportedly, an atopy patch test is useful for predicting nonimmediate reactions in the diagnosis of causative food of atopic dermatitis. However, no consensus has been reached on this finding.

Before testing, the use of agents such as antihistaminics, antiallergic drugs, and steroids should be avoided because these influence *in vitro* tests.

SPT-negative patients present with no immediate-type food allergy at the possibility of 95% or more. While a positive SPT indicates the presence of antigen-specific IgE antibodies, this result alone does not substantiate the diagnosis of food allergy. However, even if the antigen-specific IgE antibodies in blood is negative, a positive SPT may provide a clue to the diagnosis of food allergy. Of note, during early infancy, some patients negative for antigen-specific IgE antibodies in blood may give positive results in SPT.

Vegetables and fruits, which cause oral allergy syndrome, are unstable allergens. Thus, employ a prick-prick test using fresh vegetables and fruits (a needle used to prick food is used to prick the skin).

4.4. ANTIGEN-SPECIFIC IgE ANTIBODIES IN BLOOD

The presence of specific IgE antibody titers suggests antigen sensitization and do not necessarily indicate the induction of hypersensitive reactions. However, for some antigens (eggs, cow's milk, and peanuts), it is possible to depict the probability curves indicating correlations between specific IgE antibody titers and the positive rates of immediate reactions in food challenge tests. Furthermore, some reports suggest specific IgE antibody titers, with which food allergy can be diagnosed without food challenge tests (Table 5, Fig. 5).[13-16] However, since the values differ with reports, they should only be used as reference values.

Wheat and soybean-specific IgE antibody titers are correlated with positive predictive values in challenge tests. However, even if titers are above 100 UA/mL, positive rates do not exceed 95%. Wheat-specific IgE antibody titers are correlated with positive predictive values in challenge tests. Even if titers are above 100 UA/mL, positive rates are around 75%. Antibody titers which are predicted that positive rates in challenge tests are $\geq$95% cannot be calculated. IgE antibody titers specific for omega-5 gliadin show positive predictive values of 90% for Class 3 and almost 100% for Class 4 or above. However, the diagnostic sensitivity is around 77%, thus wheat allergy cannot be ruled out even if results are negative.[16]

Reportedly, a titer of 65 UA/mL of soybean-specific IgE antibody shows a positive predictive value of 86% in a challenge test. Antibody titers are weakly correlated with positive rates in challenge tests. A titer of 20 UA/mL of fish-specific IgE antibody shows a positive predictive value of 100% in a challenge test, but this has not been sufficiently reexamined.

These positive and negative predictive values were calculated using immediate reactions as parameters, thus they cannot be applied to nonimmediate reactions.

Reportedly, the incidence of induced symptoms requiring treatment becomes higher as specific IgE antibody titers increase. Many reports show that specific IgE antibody titers do not reflect provocation thresholds or the severity of induced symptoms in challenge tests.

4.5. BASOPHIL HISTAMINE RELEASE TEST

A basophil histamine release test is used to measure the amount of histamine released from peripheral blood basophils after reactions with allergens. This is an *in vitro* test which most accurately reflects specific IgE antibodies in the living body. "HRT Shionogi®," covered by health insurance, can be used for clinical laboratory tests. This kit allows simultaneous tests of response to egg white, cow's milk, wheat, soybean and rice. HRT Shionogi® greatly differs in its diagnostic usefulness depending on antigens. This kit is very useful for eggs, cow's milk, and wheat. The diagnostic sensitivity of immediate reactions is 93.0% for egg white (Class 4), 93.9% for cow's milk (Class 3 or above), and 93.8% for wheat (Class 4). Thus, this kit, combined with the above specific IgE antibody titers, is useful for conducting antigen detections without challenge tests in patients at higher risk of severe symptoms. However, this kit is less diagnostically useful for soybean and rice.

4.6. ELIMINATION TEST

Eliminate potential causative foods for about two weeks. Then, observe whether symptoms are improved. In infants receiving mother's milk or mixed feeding, eliminate the potential causative foods from the mother's diet.

4.7. ORAL FOOD CHALLENGE TEST[17,18]

An oral food challenge test is the most reliable in identifying the causative foods of food allergy. However, this test carries a risk of anaphylaxis in patients,[17] so it is important to ensure safety. Preferably, the food challenge tests should be conducted by physicians skilled in the treatment of food allergy and management of anaphylaxis. For treatment at outpatient departments or clinics, prepare for immediate hospitalization. Criteria for facilities are determined to conduct food challenge tests as healthcare services provided by health insurance. Thus, make a notification according to them.

4.7.1. Objectives

(1) Identification of the causative foods of food allergy:

i) Challenge tests, conducted following elimination tests if food allergy may be involved in atopic dermatitis, etc.

ii) Determination of causative allergens if immediate reactions are predominant symptoms.

iii) Challenge tests, conducted when sensitization to foods of interest was demonstrated by positive specific IgE antibodies, but the presence of induced symptoms is unknown because the foods are not consumed.

(2) Determination of tolerance acquisition.

4.7.2. Ensuring Safety

(1) Conduct tests under the supervision of physicians and nurses.

(2) Prepare agents for emergency, such as adrenaline (epinephrin) (Bosmin®, Adrenaline Syringe®), steroids, antihistaminics, bronchodilators (inhaled β2 stimulants, aminophylline), and transfusion sets.

(3) Postpone the test if symptoms such as fever and diarrhea occur.

(4) Start with small dosage and increase gradually.

(5) If symptoms occur, discontinue tests to conduct treatment if needed.

Table 6 Induced symptoms and their grades in an oral challenge test

Grade	Skin	Digestive system	Respiratory system (mucous membrane)	Circulatory system	Nervous system
1	- Mild small erythema - Wheal (≤3) - Itch of eczema	- Mild nausea - Discomfort and itch in the mouth and pharynx	-	-	-
2	- Localized erythema - Wheal (3-10) - Slight exacerbation of eczema - Increased scratching	- Vomiting (once or twice) or diarrhea - Temporary abdominal pain	- Sneezing - Rhinorrhea and nasal blockade - Scratching of the nose and eyes - Cough (<10 times)	-	- Mild depression
3	- Systemic erythema and wheal - Marked itch - Angioedema	- Vomiting (≥3 times) or diarrhea - Persistent abdominal pain	- Cough (≥10 times) - Wheezing - Hoarseness and barking cough - Dysphagia	- Tachycardia (increase of ≥15 times/min) - Ill complexion	- Decreased activity level or dysphoria
4	Same as the above	- Frequent vomiting and diarrhea	Add the following to the above: - Dyspnea - Reduced wheezing - Cyanosis	- Arrhythmia - Slight pressure decrease - Coldness of limbs - Sweating	- Vertigo - Agitation and confusion
5	Same as the above	Same as the above	Add the following to the above: - Respiratory arrest	- Severe bradycardia - Severe hypotension - Cardiac arrest	- Unconsciousness

4.7.3. Preparation

(1) Prepare for tests (staff, equipments, medicines, etc.) considering the risks of anaphylaxis.

(2) Explain objectives, methods, risks, and measures for hypersensitivity, etc., and obtain informed consent in written form.

(3) Before tests, discontinue the use of agents, which influence test results, such as antiallergic drugs, histamine H1 receptor antagonists, β2 stimulants, theophylline, oral disodium cromoglicate, Th2 cytokine inhibitors, leukotriene receptor antagonists and steroids.

4.7.4. Administration Methods

(1) Open test: Both the examiners and the subjects know the content of the challenge food. If the symptoms are subjective, reexamine in a blind manner.

(2) Single-blind food challenge: Examiners know the content of the challenge food, while the subjects do not. For blinding, mix a challenge food with masking stuff, such as juice, puree, oatmeal and hamburger. Powdered foods may be used as challenge tests. A challenge test is conducted using a placebo (e.g., masking food alone or a mixture of masking food and food other than what is in the challenge test), in addition to the challenge test of interest, on a different day.

(3) DBPCFC (double-blind placebo-controlled food challenge test): Both subjects and examiners who assess symptoms are blinded to the challenge test. The challenge test should be prepared by controllers other than examiners. In addition to challenge tests using foods of interest, a test using a placebo should be conducted.

4.7.5. Protocol of Challenge Test

(1) Administration method: Provocation thresholds in food challenge tests cannot be predicted even when based on a combination of history and data of various tests. Thus, divide the total amount of challenge diet into 3-6 portions and gradually increase the amount fed. To ensure safety, conduct a preliminary challenge test with a small dose. If negative results are obtained, a challenge test using a standard dose may be needed on a different day.

(2) Administration intervals and total challenge dose: Safety can be improved by increasing the administration intervals, thus it will be more likely to prevent unnecessary dose-up before symptoms develop. Foods are given at intervals of 15-30 min because of the time restriction of challenge tests. Within the scheduled observation period, make note of possible signs of induced symptoms such as mild redness and small wheals around the mouth and mild cough. Make flexible judgments such as prolonging the observation period or reducing the dosage as

needed. The total challenge dose is determined as a sufficient amount based on intake per meal according to age.

(3) Observation period after the last intake: Immediate reactions mostly occur within 1-2 h after intake. Thus, even if no symptoms occur, patients should remain in hospitals for about 2 h after the last intake. Explain to patients that symptoms may occur within 24 h. Then, instruct them about what measures to take before going home. If nonimmediate reactions are predicted, prolong the observation period as needed, e.g., one-day hospitalization.

(4) Classification of induced symptoms (Table 6): Not all symptoms are prerequisites. Severity is classified based on the most severely affected organ. For example, if respiratory symptoms of Grade 3 and gastrointestinal symptoms of Grade 1 are noted, the severity is Grade 3.

5. PREDICTION, PROPHYLAXIS, AND NATURAL HISTORY OF FOOD ALLERGY

5.1. PREDICTION OF FOOD ALLERGY

Although a few of studies have reported that the measurement of cord blood total IgE level, combined with a family history of allergy, is useful in predicting the development of allergic disorders, the measurement of cord blood total IgE level is not sensitive enough to predict the development of allergic disorders. Therefore, the measurement of cord blood total IgE level is not recommended for screening test.

5.2. SUBJECTS AND METHODS OF THE PROPHYLAXIS OF FOOD ALLERGY

There is no evidence that the incidence of childhood allergic diseases is reduced by eliminating food allergens from the mother's diet during pregnancy. Thus, dietary restriction during pregnancy is not recommended.

There have been many reports that eliminating food allergens from the diets of breast-feeding mothers does not reduce the incidence of allergic diseases after infancy. Thus, dietary restriction during breast-feeding is not recommended as a prophylactic measure for food allergy. If mothers and their children undergo dietary restriction during lactation, the incidence of atopic dermatitis temporarily declines, and specific IgE levels significantly are decreased. However, these effects are temporary. In addition, dietary restriction continued from late gestation through lactation has no long-term prophylactic effects. There is no evidence that an elimination diet reduces the incidence of childhood allergic diseases over long periods. In addition, there are case reports from showing poor weight gain in pregnant women and impairment in fetal growth due to nutritional deficiency during pregnancy. Thus, caution should be exercised for elimination diets.

5.3. NATURAL HISTORY OF FOOD ALLERGY

5.3.1. Food Allergy and Allergic March

Childhood allergic diseases exhibits a natural history, in which various diseases, such as food allergy, atopic dermatitis, asthma and allergic rhinitis, develop with aging. This natural course is called allergic march. Food allergy occurs at an early stage.

5.3.2. Tolerance of Food Allergy

Most patients with food allergy, which developed during infancy, become tolerant with aging to be able to eat causative foods. High remission rates are noted for eggs, cow's milk, wheat, and soybeans. However, the reported age of remission varies, mainly due to subject differences. Allergies to peanuts, nuts, sesame, and fish, which may continue for a long time, also remit although at lower rates.

6. THERAPY OF FOOD ALLERGY

Therapy of food allergy includes treatments to improve hypersensitivity due to causative foods (anaphylaxis, etc.) and those to prevent hypersensitivity (eliminate causative foods).

6.1. TREATMENTS TO IMPROVE HYPERSENSITIVITY DUE TO CAUSATIVE FOODS

6.1.1. Treatments at Medical Institutions

Oral administration of a histamine H1 receptor antagonist (antihistaminics) is effective for local urticaria. An intramuscular injection of adrenaline (epinephrine) (1 : 1,000) (Bosmin® or Adrenaline syringe®; 0.005-0.01 mL/kg for children to a maximum of 0.3 mL, 0.2-1 mL for adults) is the first choice for anaphylaxis. Injections can be repeated every 10-15 min. The anterolateral part of the thigh is the preferred injection site because of rapid absorption. Reportedly, immediate adrenaline injection (within 30 min) after the onset of symptoms is important for patients with the potentially fatal prognosis of anaphylaxis.

The timing of adrenaline injection is still controversial. Histamine H1 receptor antagonist can be orally administered to patients in Grades 1 and 2 as described in Table 6. Intramuscular adrenaline injection is required for patients in Grade 3 or above. For patients with a history of severe anaphylactic symptoms (Grade 4 or above), such as respiratory symptoms, decreased blood pressure, and impaired consciousness, adrenaline should be injected even if no symptoms occur after intake of causative food.

Place a patient with anaphylactic shock in the supine position with the lower limbs raised by 15-30 cm (shock posture). Perform oxygen inhalation for dyspnea (<95% SpO_2). In patients with laryngeal edema, administer adrenaline, inhaled corticosteroid, and intravenous steroid. In patients with bronchoconstriction, conduct β2 stimulant inhalation.

Steroids, such as methylprednisolone (Solu-

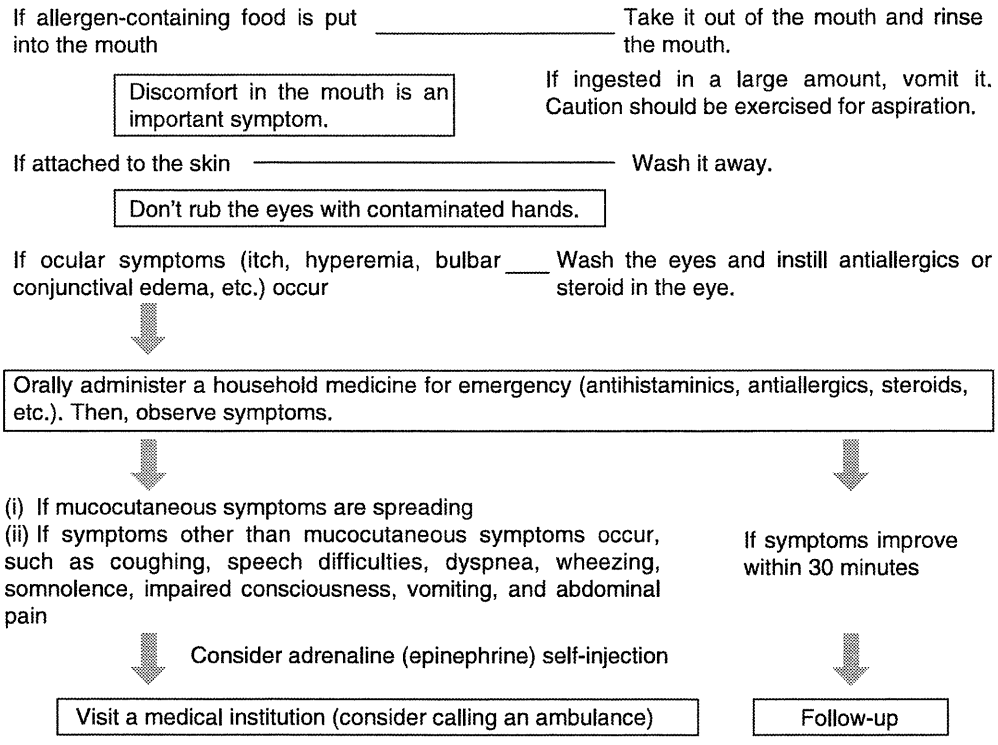

Fig. 6 Treatment out of medical institutions.

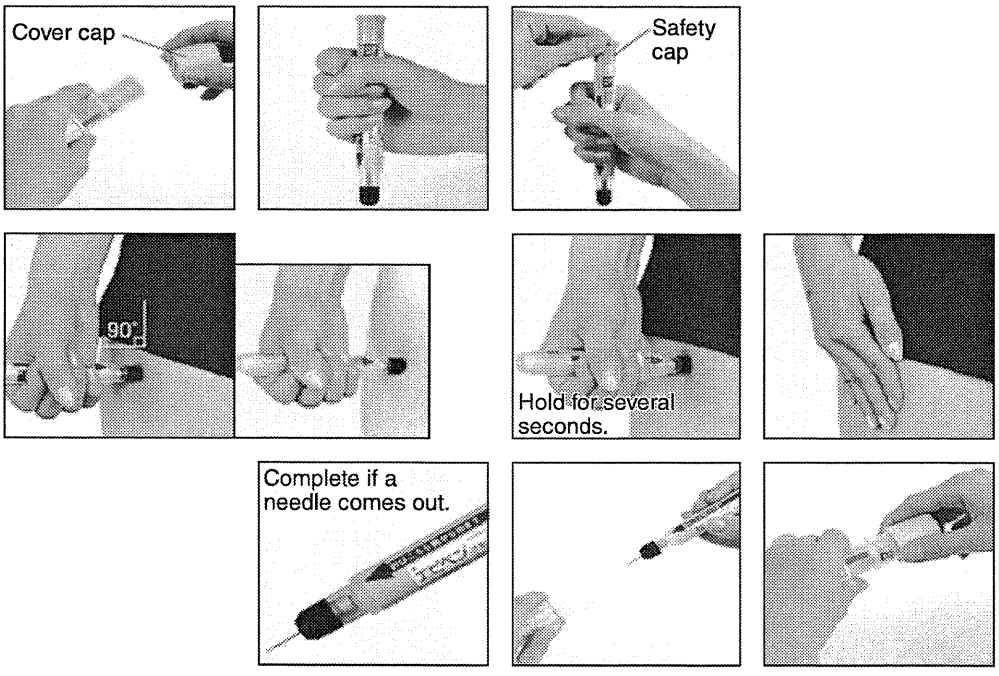

Fig. 7 Injection of Epipen®. Caution should be exercised for thumb positioning to prevent accidental injection on the thumb. Thigh muscle is the recommended injection site.

Medrol®, 1-2 mg/kg) and hydrocortisone (5-10 mg/kg), are intravenously injected.

Dual response may occur. Thus, even if patients with anaphylaxis recover after ambulatory treatment, they should be observed for at least 4 h.

6.1.2. Measures at Places Other than Medical Institutions (Fig. 6)

Instruct patients with a history of anaphylaxis to carry medicines for the first-aid treatment of hypersensitivity (histamine H1 receptor antagonists, oral corticosteroids [prednisolone], or adrenaline for self-injection [Epipen®]). For patients with food allergy complicated by asthma, inhaled β2 stimulants are also needed.

According to the "Guidelines for the Treatment of Allergic Diseases in Schools",[16] there is no legal problem with school staff injecting Epipen® if patients cannot inject it themselves. However, there are many other problems with injection, so staff should receive technical training. In March 2009, the Ministry of Health, Labour and Welfare issued a notification that ambulance staff can inject Epipen® if patients carry it. Epipen® (0.15 mg of Epipen® injection for 15-30 kg body weight; 0.3 mg for ≥30 kg body weight) can be prescribed only by qualified physicians who received training. Before prescription, patients and their guardians should receive technical training (Fig. 7).

Measures for accidental ingestion are shown in Figure 6. First, cause the patient to bring up an accidentally ingested food by beating the back. At this time, caution should be exercised for aspiration. Then, rinse the mouth. If ocular symptoms occur after rubbing the eyes with hands exposed to causative foods, wash the eyes and administer eye-drops such as antihistaminics or steroids. In addition, orally administer household medicines for emergency, prescribed by physicians, such as histamine H1 receptor antagonists and steroids. If symptoms are exacerbated or symptoms occur in multiple organs, immediately consult a medical institution. At this time, consider calling an ambulance and using an Epipen®.

If anaphylactic shock is suspected, place the patient in the shock position with the lower limbs raised by about 30 degrees. Then, wait for an ambulance. Start resuscitation to help patients in cardiopulmonary arrest.

6.2. TREATMENT TO PREVENT HYPERSENSITIVITY

The elimination of causative foods is the most reliable prophylactic method of hypersensitivity caused by food allergy. However, this places various burdens on patients and their guardians. Ensuring safety by causative food elimination, preventing nutritional disorders, and improving the quality of dietary life are essential for diet therapy. For these purposes, consider eliminating minimal causative foods.

6.2.1. Minimal Elimination Diet

(1) Correctly identify causative foods.

To minimize the number of causative foods to be eliminated, it is important to identify causative foods correctly (see the method to identify causative foods).

(2) Even if the food is positive for specific IgE antibodies and in a skin prick test, do not eliminate the foods if it is negative in an oral challenge test.

(3) Periodically check tolerance to foods that patients tend to outgrow.

Tolerance to buckwheat, peanuts, nuts, fish, shellfish, sesame, etc., is unlikely to develop. On the other hand, allergies to eggs, cow's milk, soybeans, etc., often remit with aging. Do not continue the elimination diet, but rather conduct a challenge test once or twice a year to determine continuance of symptoms. Even if infants have allergies to peanuts and fish, a part of them may develop tolerance.

(4) Not all the foods with cross-reactivity with allergenic ones should be eliminated.

Wheat and rice are both gramineous plants and cause cross-reactivity in terms of IgE-binding capacity. However, most patients with wheat allergy can eat rice. Alternate kinds of beans and fish may be consumed even if a single species of them cause symptoms.

(5) Don't eliminate all foods even if they are of the same biological lineage.

The burden on patients can be reduced by determining elimination in reference to the degree of allergenicity of foods belonging to the same biological lineage.

The allergenicity of egg white is reduced by heating. Thus, about half of patients, for whom raw eggs should be eliminated, can consume heated eggs.

The allergenicities of fermented foods (e.g., miso and soy sauce) are reduced. Thus, many patients can consume them even if they are hypersensitive to soybeans and tofu. The allergenicity of natto (fermented soybeans) is also reduced compared with soybeans.

Fruits (e.g., apples and tomatoes) can be often consumed because their allergenicities are reduced by heating and processing. For example, most patients can consume tomato juice and ketchup even if they cannot consume fresh tomatoes. About 90% of patients with milk allergy can eat beef without hypersensitive reactions.

6.2.2. Elimination Diet without Nutritional Problem

(1) Instruction of alternative foods.

Elimination diet therapy may cause nutritional poblem in affected children. Caution should be exercised particularly for patients with allergy to multiple foods. Instruct them about suitable edible foods, as

Table 7 Specific raw materials, for which labeling is mandated or recommended

	Specific raw materials	Reasons for selection
Mandatory	Egg, milk, wheat, shrimp, crab	Allergies to these foods are common.
	Buckwheat, peanut	Caution should be exercised because of severe and life-threatening symptoms.
Recommended	Abalone, squid, salmon roe, orange, kiwi fruits, beef, walnut, salmon, mackerel, soybean, chicken, pork, matsutake mushroom, peach, yam , apple, banana	Allergies to these foods are less common. Thus, further surveys are needed for the ministerial ordinance to designate them.
	Gelatin	Many public comments demand independent labeling as "gelatin." Many specialists also request this labeling.

Adapted from Food Sanitation Act, revised in June 2008.

well as eliminated foods, for nutritional management. Here, dietitians familiar with food allergy play a major role.

(2) Use of alternative foods.

Alternative foods for patients with food allergy include low allergenic foods and allergen-free or allergen-reduced foods, produced using low allergenic food materials.

Low allergenic foods include stuff using peptides and amino acids, reduced in molecular sizes by enzyme treatment. For example, hydrolyzed casein formula (New MA-1®), hydrolyzed whey formula (MA-mi®, Milfee HP®), amino acid formula (Elemental Formula®), etc., are available.

Commercially available main allergen-free packaged foods include those in which 25 food allergens are not used as raw materials. Allergen-reduced foods include low allergenic rice.

(3) Assessment of growth and development.

The growth and development of children must be assessed. Measure weight and height over time and graph them on charts. Growth graphs in maternal and child health handbooks are useful.

6.2.3. Check Food Labels before Purchase

Table 7 shows 7 items for which labeling is mandated and 18 items for which labeling is recommended. Instruct patients to check food labels before purchase.

6.3. ANTIGEN SPECIFIC ORAL IMMUNOTHERAPY OF FOOD ALLERGY

Tolerance is more likely to develop to orally administered antigens. Antigen specific oral immunotherapy has also been initiated to treat food allergy. Elimination diet therapy is a negative treatment, while this immunotherapy is called active treatment, with the goal of causing remission of food allergy. The effects of oral immunotherapy have been recognized, but problems with safety and permanent tolerance remain.[19]

7. SOCIAL MEASURES FOR FOOD ALLERGY

Hand instructions (medical certificates), which indicate foods to be eliminated, to guardians. Instruct staff of kindergarten and schools to have a discussion based on the instructions. Use the instruction table attached to the "Guidelines for the Treatment of Allergic Diseases in Schools" for management (Table 8).[16]

8. POINTS TO REMEMBER IN TREATING ALLERGIES COMPLICATED BY OTHER DISEASES

8.1. ATOPIC DERMATITIS

The exacerbation factors of atopic dermatitis vary with age. Atopic dermatitis, associated with food allergy, is common among infants and decreases with aging.

The basic therapy of atopic dermatitis, associated with food allergy, is the same as that outlined in the Guidelines for the Management of Atopic Dermatitis 2009. The following comprehensive therapies are essential.

8.1.1. Pharmacotherapy

This entails the proper use of topical steroids or Protopic ointment® (for children aged ≥2 years), histamine H1 antagonists for itching, antimicrobials to treat skin infection.

8.1.2. Skin Care

Ensure that skin is protected by bathing and showering, applying moisturizer, using bandages or supporter, etc.

8.1.3. Diet Therapy (e.g., Eliminating Causative Foods) and Measures Against Causative and Exacerbation Factors

Many patients with atopic dermatitis associated with food allergy are simultaneously involved in other causative and exacerbation factors. Thus, measures other than eliminating causative foods are often taken.

Causative foods, including the exacerbating foods of atopic dermatitis and the causative foods of immediate-type allergy, should be eliminated.

Table 8 Food allergy and anaphylaxis in certificate for school life management (for allergic diseases)

Name _____ Male/Female Birthday (age)_____(___) School name _____ Grade/Class_____ Date of submission:_____

Certificate for school life management (for allergic diseases)

Food allergy (+/-)
Anaphylaxis (+/-)

Disease type and treatment

A. Type of food allergy (if you have food allergy)
1. Immediate-type
2. Oral allergy syndrome
3. Food-dependent exercise-induced anaphylaxis

B. Type of anaphylaxis (if you have a history of anaphylaxis)
1. Food (causative food:)
2. Food dependent exercise induced anaphylaxis
3. Exercise-induced anaphylaxis
4. Insects
5. Medicines
6. Others

C. Causative foods/Grounds for diagnosis: Circle the number of causative food and describe grounds for diagnosis in <>.

1. Egg < >
2. Cow's milk/Dairy products < >
3. Wheat < >
4. Buckwheat < >
5. Peanut < >
6. Nuts and seeds < > ( )
7. Shellfishes (shrimp and crab) < >
8. Fruits < > ( )
9. Fish < > ( )
10. Meat < > ( )
11. Others 1 < > ( )
12. Others 2 < > ( )

[Grounds for diagnosis] Describe all relevant items in <>.
(i) History of marked symptoms
(ii) Positive for food challenge test
(iii) Positive for IgE antibody test

D. Prescriptions for emergency
1. Oral medicines (antihistaminics and steroids)
2. Adrenaline self-injection "Epipen®"
3. Others ( )

Points to remember for school life

A. School meals
1. No need for management
2. Consult with guardians for decision.

B. Classes and activities regarding foods and food materials
1. No need for considerations
2. Consult with guardians for decision.

C. Exercise (gymnastics, extracurricular activities, etc.)
1. No need for management
2. Consult with guardians for decision.

D. Overnight extracurricular activities
1. No need for considerations
2. Caution should be exercised for meals and events.

E. Other considerations/Management items (optional)

[Emergency contact number]

*Guardians
TEL:

*Contact medical institution
Name of medical institution:
TEL:

Date of description

Name of physician

Name of medical institution

Adapted from http://www.gakkohoken.jp./book/bo0002.html.

Table 9 Points to remember in referral to food allergy specialists

1. Accurate diagnosis by an oral food challenge test
2. Instructions on diets, including elimination and alternative diets
3. Instructions on elimination diet, requested by nursery, kindergarten, school, etc.
4. Nutrition guidance to discontinue elimination diet and to gradually introduce usual diet
5. Instructions on adrenaline (epinephrine) self-injection for anaphylaxis

Examine whether specific IgE antibody-positive foods can be consumed, referring to the degree of sensitization at the time of initial intake. Carefully start feeding from small amounts based on the results of oral challenge test.

Infants with severe atopic dermatitis, positive for various food antigen specific IgE antibodies, may suffer from malnutrition and growth disorder, including hypoproteinemia and poor weight gain. Some patients may develop hypersensitivity because they are positive for IgE antibodies specific for various food antigen, and may suffer from malnutrition because they cannot consume baby foods. Although rare, some infants suffer from atopic dermatitis caused by unnecessary excessive dietary restrictions, delayed start of baby foods, and inappropriate folk medicine.

Early intervention is desired to prevent severe atopic dermatitis. Specifically, points to remember include: (i) appropriate application of steroid ointment and skin care at an early stage for favorable management; (ii) appropriate diet therapy, aimed at minimal elimination diets and nutrition management by edible foods; (iii) check of growth (weight and height) and development; and (iv) mental support for guardians, especially mothers.

8.2. BRONCHIAL ASTHMA

Remember that anaphylactic shock is common among patients with food allergy complicated by bronchial asthma.

8.3. ALLERGIC RHINITIS

OAS is established through sensitization to pollen, and is developed after intake of foods that share cross reactivity with pollen. Thus, OAS is often complicated by pollinosis. At the consultation, examine nasal symptoms. In patients with pollinosis, examine abnormalities in the mouth after ingestion of fruits and vegetables.

9. *POINTS TO REMEMBER IN REFERRAL TO SPECIALISTS*

Table 9 summarizes the issues to consider when making a referral to a specialist.

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Available online April 9, 2011.
doi:10.1016/j.jaci.2011.03.012

IgE to Gly m 5 and Gly m 6 is associated with severe allergic reactions to soybean in Japanese children

To the Editor:

Soybean is 1 of 8 foods believed to cause a majority of food-induced allergic reactions in children.[1,2] However, the prevalence of soybean allergy in Japan might be higher than in Europe and the United States, with soybean reported as the fifth most common food allergen causing anaphylaxis.[3] Soybeans contain about 40% protein, the majority of which is composed of the 2 storage proteins β-conglycinin and glycinin, which have been recently designated Gly m 5 and Gly m 6.[4] Four other proteins are officially accepted as allergens, and at least an additional 12 have been reported as IgE-reactive proteins.[5] Data regarding soybean allergens associated with clinical symptoms in children are limited. In this study we have examined the IgE reactivity pattern to 5 soybean and 3 cross-reactive allergens in a group of children with and without soybean allergy. Furthermore, we have investigated the clinical usefulness of analyzing specific IgE antibodies to Gly m 5 and Gly m 6.

There were 74 subjects (range, 0.6-16.3 years), of whom 33 were given diagnoses of soybean allergy (symptomatic group) based on challenge outcome (n = 29) or clinical history after intake (n = 4; 3 experienced apparent skin symptoms and 1 experienced anaphylaxis). The symptomatic group was further divided into subjects with severe symptoms (n = 14) and mild symptoms (n = 19). Severe symptoms were defined as a combination of skin, respiratory, or gastrointestinal symptoms, whereas mild symptoms were defined as isolated skin symptoms, oral symptoms, or both (Table I). The remaining 41 subjects were sensitized to soybean without any symptoms from soybean (nonsymptomatic group). Tolerance in the nonsymptomatic group was either confirmed by means of food challenge (n = 22) or a history of daily ingestion of soybean products (n = 19). Food challenges were conducted in accordance with the Japanese guidelines.[6]

IgE reactivity to 8 different allergens was tested in an in-house, qualitative multiplexed immunoassay, essentially as reported elsewhere.[7] The 8 allergens included in the setup were Gly m 5, Gly m 6, rGly m 4, soybean Kunitz trypsin inhibitor (Sigma-Aldrich, St Louis, Mo), soybean agglutinin (Vector Laboratories, Peterborough, United Kingdom), Cross-reactive carbohydrate determinants (CCDs) purified from digested bromelain (essentially MUXF3), profilin from timothy pollen (rPhl p 12), and lipid transfer protein from peach fruit (rPru p 3). Native Gly m 5 and Gly m 6 were essentially purified according to the method of Thanh and Shibasaki.[8] All recombinant allergens, as well as the CCD reagent, were produced at Phadia AB (Uppsala, Sweden).

IgE antibody levels to soybean, Gly m 5, and Gly m 6 were analyzed in serum by using ImmunoCAP (Phadia AB), all of which were commercially available. The lower limit of quantitation of the tests was 0.10 kU_A/L. The Fisher exact test was used to determine differences regarding the prevalence of IgE reactivity analyzed by using the multiplex assay (categorical data). The Spearman rank correlation test was used in the analysis of associations between IgE concentrations. The relationship between IgE concentrations and clinical status outcome was analyzed by using logistic regression analysis. Odds ratios were estimated by using regression models, and 95% CIs were generated according to the Wald test.

Among the children in the symptomatic group with mild symptoms, all had skin symptoms, and 3 had oral symptoms (Table I). Respiratory symptoms, mostly coughing and wheezing, were the most frequent symptoms (n = 12) in the severe group. The multiplex immunoassay showed that among the children in the symptomatic group, 67% had IgE reactivity to Gly m 5 (49% in the nonsymptomatic group), 58% to Gly m 6 (39% in the nonsymptomatic group), 21% to Gly m 4 (20% in the nonsymptomatic group), and 6% to soybean agglutinin and soybean trypsin inhibitor (7% and 10%, respectively, in the nonsymptomatic group). The number of subjects with IgE reactivity to lipid transfer protein, profilin, and CCDs varied between 12% and 15% (7% to 17% in the nonsymptomatic group). No significant difference in the frequency of IgE reactivity between the symptomatic and nonsymptomatic groups was observed for any of the allergens included in the study. However, a tendency toward a higher frequency of IgE reactivity in the symptomatic group was noted for both Gly m 5 and Gly m 6 ($P = .16$ for both). Therefore quantitative analysis of IgE to Gly m 5 and Gly m 6 was performed to investigate the true prevalence.

Analysis with ImmunoCAP demonstrated that all children had IgE levels to soybean, Gly m 5, and Gly m 6 of greater than 0.1 kU_A/L, except one in the nonsymptomatic group. The IgE levels to both Gly m 5 and Gly m 6 correlated with the IgE levels to soybean ($r_S = 0.89$ and $r_S = 0.86$, respectively). The IgE levels to soybean and Gly m 5 were significantly higher in the symptomatic group than in the nonsymptomatic group ($P < .01$). With respect to the specific IgE levels in the 2 groups, the risk of being allergic to soy increased significantly with increasing levels of IgE. For IgE to soybean, the odds increased 1.51-fold (95% CI, 1.10-2.08), and for IgE to Gly m 5, the odds increased 1.48-fold (95% CI, 1.08-2.02) per logarithmic unit increase, respectively. Significant differences were noticed between the severe and nonsymptomatic groups in IgE levels to soybean, Gly m 5, and Gly m 6 (Fig 1). The IgE responses to soybean, Gly m 5, and Gly m 6 were not statistically different between the children with mild symptoms and the nonsymptomatic children. Significant differences in the IgE levels to soybean were detected between the mild and severe symptom groups but not in the IgE levels to Gly m 5 and Gly m 6.

Knowledge about specific soybean allergens associated with clinical symptoms is restricted to a few publications. Many studies demonstrating IgE reactivity to soybean proteins in sera from soybean-sensitized subjects have been published, but the patient material has generally been small and often with an unclear diagnosis. In this study we have examined IgE reactivity to 5 soybean and 3 cross-reactive allergens in sera from 74 Japanese children. To the best of our knowledge, this group, consisting of symptomatic and nonsymptomatic subjects, is the largest defined clinical sample tested with the aim of identifying important soybean allergens.