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20

Soybean and Allergy

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1. Introduction

Food allergies can affect both people and animals, and the number of food allergies not only in human but also in animals has increased. Food allergies can affect a patient's quality of life and lead to a loss of pleasure in eating. There are many kinds of food in the world, and it is possible for all people to have food allergies. The kinds of food allergy differ depending on country, nationality, age, and religion. For example, peanut allergy is common in western countries, but in Asia, it does not occur as frequently. And the incidence of egg allergy in children is higher than that in adults. Not all food allergies in childhood continue into adulthood; in some cases, the symptoms often improve with age, so-called allergy march. In case where food is restricted by religion, the number of its foods allergy must be rare. Food allergies of childhood have close relation to growth and development; this is a serious problem for not only patients but also their families and educational institutions. In some countries, information regarding and measures against food allergy are inadequate. Because religion, economy, education, and nationalities are different, addressing these inadequacies will require large amounts of time and effort. Overcoming food allergy is difficult, but food allergy of childhood often improve with grow up. There are some puzzling aspects of food allergy in childhood; some contaminated foods, plural food allergies and foods that are impossible or difficult to avoid (ex. flour). It needs to measure for people with food allergy, especially, in case of disaster and war. Regardless of religion, economy, education, or nationality, children cannot easily avoid allergens. Their families and other related people must maintain their living environment, and it is important to prepare some kinds of foods without allergens in these cases. Food allergies in adults often appear as a result of occupational problems. Our study showed that some cases of occupational disease were caused by foods; these included a patient working in a bakery with a flour allergy, a green grocer with a vegetable and fruit allergy, a noodle shop worker with a flour allergy, a cook with a fruit allergy, etc (Sugiura K & Sugiura M. 2010a). Occupational food allergies affect a patient's life and occupation. The avoidance of foods that cause allergic reactions during only meals can not resolve the problem of occupational food allergy; if other workers in the same office do not understand the allergy, a patient's symptoms are going to progress, finally food allergy causing them to resign from their work. Economic and productivity loss due to food allergy are huge; a response is therefore needed to problems of allergy in the office and on social ground (Sugiura K & Sugiura M. 2010a).

Recently, the number of pets with food allergies has been increasing. Basically, food allergy in pets is similar to that in humans with regard to symptoms, examinations, treatment, and safety measures. Because animals do not speak, it is often difficult to diagnose animal food allergy. Most of the food allergies in animals show as red spots, scratching, runny nose,

congestion, wheezing, and so on. A previous report showed that dogs with adverse reactions to foods suffer from dermatological symptoms (Proverbio D,et al. 2010). If pets repeatedly show some symptoms or do not recover from these symptoms, they should be examined in a veterinary clinic.

Soybean is one of the most consumed grains in the world, and soybean allergy is a very important problem in the medical and food fields. Soybean allergy is a subject that has been investigated by many scientists. However, soy sauce allergy without soy and flour allergy have not been discussed. We have previously reported four cases of soy sauce allergy (Sugiura K & Sugiura M. 2010b), and at that time we recognized that the topic of soy sauce allergy must be studied. Our theme is soybean and allergy. We explored this theme here-in based on three categories: general information about allergies, allergies to soybean products, and soy sauce allergy. We also approached and provided general information about allergies and food allergy, including the different kinds of allergy, the causes of allergic reactions, the diagnosis of allergies and treatment, soy products allergy and cases of soybean allergy and soy sauce allergy, including a discussion of examination tests, treatment, and safety measures. The globalization of manufacturing and production of materials that include soybean products has grown, and consumption of soy will continue to increase all over the world, because soybean products are generally healthy and have good effects on the human body; people are interested in these products. In the case of production and manufacturing occurring in different countries, the problems of food allergies are complicated. The reasons for this complication are, the kinds of food allergy, the ratio of people with food allergies and the different criteria regarding the listing of ingredients on packaging, all being different depending on the country, people, and religion. Many food companies use foreign factories for manufacture because of cutting personnel costs. These companies need to educate the foreign people working at these factories about issues regarding to food allergy. An international standard for the labeling of ingredients could be useful for patients, letting people know whether it is safe to eat foods in foreign countries. The methods or procedures for treating food allergies are different depending on the physician, institute and country. International criteria for the labeling of ingredients, not only soybeans but also other foods products, on package, as well as for the diagnosis and treatment of food allergies are needed, because tradition, culture and customs related to food are different. First, we describe the basics of allergy and food allergy, then discuss soy sauce and soy sauce allergy.

2. Allergy

2.1 Introduction

The term 'allergy', coined in 1906, derives from two Greek words: *allos,* meaning "foreign" or "strange", and *ergo*, meaning "to act" (von Pirquet, C. 1906). Allergies are complicated immunological reactions and appear as morbid symptoms in individuals who suffer from them. Allergic symptoms are shock, urticaria, skin rash, contact dermatitis, asthma, nephritis, etc. The mechanisms of allergy have been studied, but they have not been completely analyzed and defined. Here, we described the mechanisms of allergy as they have been illuminated thus far. Allergies are caused by many cells and mediators, and the main trigger of allergies is exposure to allergens. An allergen is a specific material which induces an allergic reaction in some individuals, and varies depending on the case. Allergic reactions are often caused not by just one allergen but by plural allergens. All materials in

the world have the potential to be allergens; generally, the higher frequently of contact or exposure to the materials, the more likely they are to become allergens. Allergic reactions often affect quality of life, childhood growth and development, occupation, economy, morale, etc. Economic loss due to occupational allergy is a huge issue; more attention needs to be given to allergy-preventive measures (Sugiura K & Sugiura M. 2010a).

2.2 Mechanisms of allergies

Allergic reactions have been divided into five types based on pathophysiology. Type I allergies is mediated by IgE antibody (immediate allergy). Type II is antibody-mediated (cytotoxic) allergy. Type III is immune complex allergy. Type IV is cell-mediated allergy (delayed-type allergy). Type V allergies is mediated by antibody against receptors. Type I allergy is often identified as food allergy. This immediate-type allergy is described in a later section. First, we present immunoglobulin II, III, IV and V type allergies. There are various factors essential to allergic reactions; here, we discuss the involvement of immunoglobulin, antigen, eosinophils, macrophages, basophiles, Langerhans cells, lymphocytes, immuno-complex, etc., in the various allergic processes.

2.2.1 Immunoglobulin (antibodies)

Immunoglobulin play essential roles in allergic reactions and immune responses to infections by viruses, bacteria, microbes, etc. When vertebrates are exposed allergens, bacteria, microbes, etc., they produce an antibody, which is a glycoprotein, to protect themselves. These antibodies are always present in the tissue; if we are exposed to or infected with these foreign materials, they respond to the invasion. Antibody has three functions: agglutination, opsonization and neutralization. Antibodies bind allergens (antigens) to form antigen-antibody complexes (agglutination). Macrophages easily recognize and phagocyte these complex via the Fc region of the antibody (opsonization), because macrophages understand these complexes as non-self. The macrophages present the antigen's information to the T cells, and further immunological reactions develop. T cells present the antigen's information to B cells, which produce new, specific antibodies. Therefore, antibodies activate complements, the activated complements bind antigens and assist in further opsonization. When bacteria infect tissue, the activated complements destroy the bacterial cell membranes. The binding of bacteria with activated complements results in bacteriolysis and loss of infectious properties. Antibodies play some essential roles in immunological or allergic reactions. In the case of venom (ex. insect, snake), venom-binding antibodies do not exercise toxicity and do not invade tissue or cells (neutralizing).

There are five kinds of antibodies: IgA, IgD, IgE, IgG and IgM. Antibodies have a basic y-shaped structure, composed of Fc and Fab regions (Figure 1). Fc is the crystallizable region. Some cells (ex. mast cells, macrophages) have Fc receptors; these cells recognize and phagocyte via this region. The Fc region play roles in the immunological systems; this region is essential for the three functions of antibodies, i.e., agglutination, opsonization and neutralization. Fab is the antigen-binding region, which binds to the allergen. Antibody can also be divided into a variable and constant region. The variable region differs depending on the target antigen; because the arrangement of amino acid in the Fab region can change, B cells can produce an antibody against each antigen. The constant region is consistent

across all immunoglobulins. The structures of the five antibody types are shown in Figure 2: IgD, IgE and IgG are monomers, IgA is a dimer, and IgM is a pentamer.

Immunoglobulin A (IgA) plays important roles in the immune systems of mucous membranes, its molecular weight is 170 kDa. This antibody has two sub-classes, and this antibody comprises about 15 % of immunoglobulins. The half-life of this antibody is 7 days. Secretary type IgA transits via the colostrum (first mother's milk after birth), and protects the digestive tracts of newborns from bacteria, viruses, etc. Giving colostrum to newborns is important from a medical viewpoint. The structure of IgA is a dimer of immunoglobulin (Figure 2).

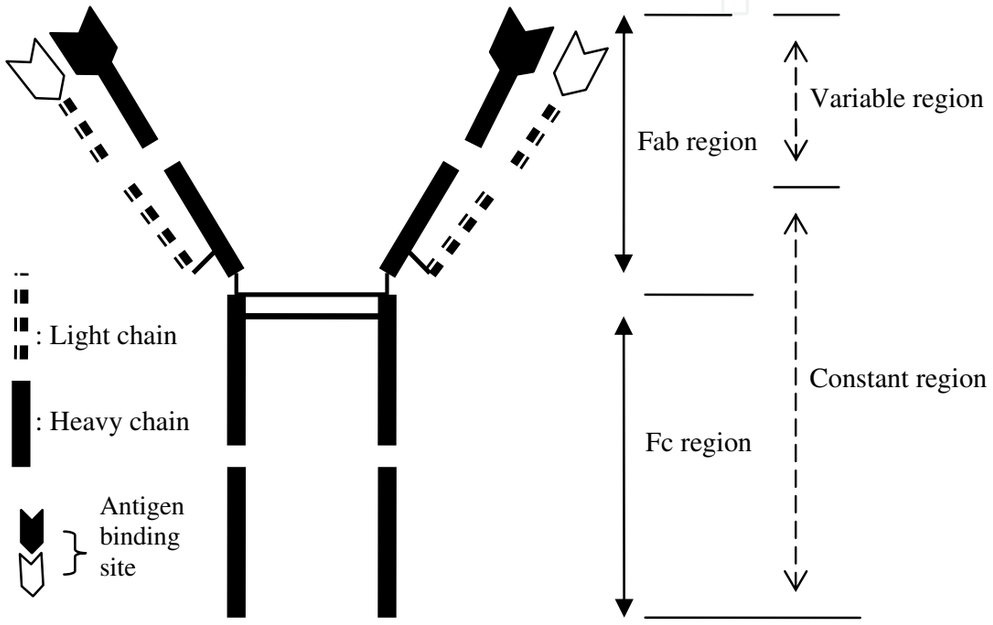


Fig. 1. The structure of an antibody

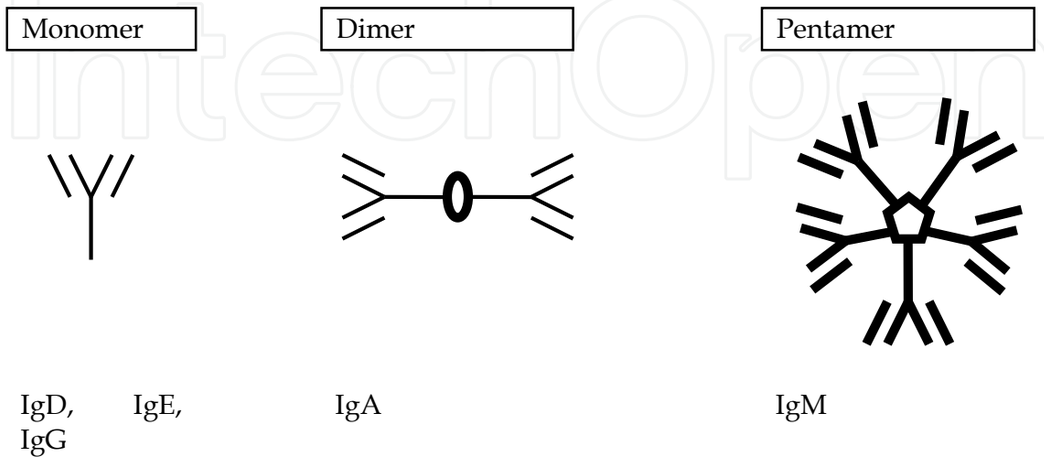


Fig. 2. Structures of the five types of immunoglobulin

Immunoglobulin D (IgD) is on the surface of B cells, and this antibody comprises less than 1% of immunoglobulin. Its molecular weight is 180 kDa and its half-life is 2.8 days. The significance of this antibody is unknown, but IgD is often measured and increased in cases of myeloma and monoclonal gammopathy. This antibody is a monomer. As monomers, IgE and IgG have essentially the same structure (Figure 2). Immunoglobulin G (IgG) comprises about 75% of immunoglobulins, and has a molecular weight of 150 kDa (Figure 2). This antibody has four sub-classes. The half-life of this antibody is 25 days. Only this antibody has the ability to pass through the placenta. Mother's IgG goes to the baby via transitional milk (after colostrum, but before mature milk), and this antibody plays essential roles in the immunity of newborns. About 2-3 months after birth, the level of this antibody in mother's milk drops, and newborns begin to produce it themselves. IgA and IgG are essential for the immunity of newborns. Immunoglobulin M (IgM) has a pentamer structure (Figure 2) and a molecular weight of 900 kDa, making it the largest immunoglobulin. Its half-life is 5 days. The level of this globulin is higher in females than males. When people are exposed to allergens, IgM is the first antibody produced in the body. Only IgG and IgM have the function of activating complements; other antibodies—IgA, IgD and IgE—cannot do this.
IgE was discovered by Ishizaka (Ishizaka K & Ishizaka T. 1967). This antibody has a molecular weight is 200 kDa and a half-life of 2 days. As mentioned above, we will describe the role of the IgE antibody in type I "food" allergy last, at the end of the next section. Only IgG and IgM can activate complements, other antibody, IgA, IgD and IgE can not do this.

2.3 Types of allergic reaction

2.3.1 Type II allergy

Type II allergy is specific reactions when IgG and IgM are activated against allergens bound to the individual's own cells; thus, the lymphocytes attack the body's own cells. The diseases of type II allergies include idiopathic thrombocytopenia (ITP), malignant anemia, rheumatism, Good pasture's syndrome, myasthenia gravis, etc.

2.3.2 Type III allergy

The mechanism of type III allergy is that immune complexes are deposited on the tissue; then the tissue with these complexes is damaged by the activated complements. There are two mechanisms for type III allergies, arthus reactions and serum sickness. Arthus reactions are caused in a local area whereas serum reactions result in systemic disorder. The diseases of this allergy are hypersensitivity pneumonitis, arthus reaction, systemic lupus erythematosus and poststreptococcal acute glomerulonephritis.

2.3.3 Type IV allergy

Type IV allergy is a delayed-type hypersensitivity in response to foreign allergens. Important cells in this immune process are M cells in the intestinal mucosa and Langerhans cells (LCs) in the skin. In the case of digestive organs, exposure to allergens occurs via the mucous membrane. The mechanism of delayed-type hypersensitivity reactions has been proven: when people are exposed to foreign allergens, M cells in the Peyer's patches capture the antigens and deliver them to antigen-presenting cells (APCs), and these APCs present the antigen's information to T lymphocytes (T cells). T cells contact B lymphocytes (B cells), and B cells produce antibodies which react to specific allergens. Various kinds of antibodies and chemical mediators are produced which attack tissue, and inflammation cells (eosinophils, lymphocytes, monocytes, mast cells, plasma cells, etc.) cluster at the exposure

points due to signals from these chemical mediators. These mediators, antibodies and cells attack the antigens and organs, and the attacks appear as delayed hypersensitivity reactions. Peyer's patches, located at the lower ileum, comprise the immune system of the mucous membranes of the gastrointestinal tract.
The human skin is also exposed to allergens; one cutaneous APCs is Langerhans cells (LCs), which present in the epidermal layer. LCs capture antigens and present the antigen's information to the cell surface. LCs are capable of movement; they migrate from the skin to lymph nodes via lymph vessels with (Sugiura K, et al. 2003). Mature LCs, known as Birbeck granules, have an interesting and unique character. There are two kinds; tennis racket-shaped or coffee-bean shaped atypical granules (tennis racket-shaped granules can become coffee-bean shaped granules) (Shamoto M. 1970). Mature LCs migrate and present the antigens' information to T cells. T cells contact B cells, and B cells produce antibodies against the specific allergens. These antibodies cause delayed hypersensitivity reactions at the skin. Our study showed that LCs started migration one hour after exposure to allergens. Allergic contact dermatitis, sarcoidosis, multiple sclerosis, etc. are type IV allergy diseases.

2.3.4 Type V allergy

In type V allergy, antibodies against certain receptors attack (stimulate) the body's own cells having these receptors as ligands, and then these cells secrete mediators (ex. thyroid hormone). Self-antibodies acts like the allergen and combine ligand. Grave's disease is based on type V allergy.

2.3.5 Type I allergy

Food allergies comprise the type I allergy, which are signaled by (immediate IgE-mediated reactions such as urticaria. Type I allergy symptoms occur within 30 minutes of exposure and often threaten a patient's life (ex. anaphylactic shock). The mechanisms of IgE-mediated allergic reactions have been demonstrated: when people are exposed to foreign allergens, specific T cells against allergens produce IL-4 cytokines, which causes B cells to produce a specific IgE antibody against the particular allergen. When people are exposed to allergens again, mast cells and basophiles with IgE receptors (FcεRI), monocytes, lymphocytes and platelets with IgE receptors (FcεR II) bind with specific IgE antibodies and allergens, then these cells degranulate, liberating chemical mediators. Chemical mediators cause allergic reactions (permeability of blood vessels, twitching of smooth muscle, etc.), which appear within 10-30 minutes from exposure to allergens. There are many cases of IgE abnormalities: allergy, parasite infection, liver disorder, collagen disease, nephritic syndrome, chronic lymphocytic leukemia, etc. IgE antibodies attack antigens and the body's own cells, and immunological reactions increase with more and more exposure; these attacks often manifest as allergic reactions.

3. Food allergy

3.1 Introduction

Adverse reactions to foods are classified into two categories: food allergies and food intolerance (Cianferoni A & Spergel JM. 2009). These categories are divided into two and three subcategories, respectively. The frequency of food allergy has been reported, with varying results in different countries; the prevalence rate of food allergy is about 5% in

three-year-old children in Japan (Ebisawa M. 2006); the prevalence in children was reported to be 3-5% in France (Kanny G, et al. 2001) and 3.5-4 % in the USA (Sicherer SH, et al. 2004); 6 % of one-year-olds in Iceland were reported to have food allergy (Kristinsdóttir H, et al. 2011) and 11 % of Ghanaian school children were reported to develop adverse reactions to foods (Obeng BBet al. 2010). In the case of delayed-hypersensitivity foods allergy, because the frequency of this food allergy is lower than that of the immediate type. A frequent clinical symptom of food allergy is eruptions on the skin, which cause itching or irritation. Food allergies are classified as IgE-mediated allergies, non-IgE-mediated allergies, and mixed allergies. Food allergies are often caused by IgE-mediated and most food allergies are immediate allergy. The symptoms occur within 15-30 minutes of exposure to allergens. Most food allergens are glycoproteins, which have molecular weights ranging from about 10,000 to 60,000. The properties of these allergens are heat stability and resistance to proteolysis enzymes. If these allergens are cooked or digested, most of their antigenic qualities persist and cause allergic reactions. Japanese food allergy management guidelines is classified 5 categories; newborn infant's digestive symptoms, infantile atopic dermatitis associated with food allergy, an immediate-type reaction, food-dependent exercise-induced anaphylaxis (FDEIA)(Kidd JM 3rd, et al. 1983) and oral allergy syndrome (OAS) (Kondo Y & Urisu A. 2009). These allergies are related with IgE-mediated allergy. Generally, the antigenic quality of heated foods is lower than that of raw foods. Anyone who is concerned about having a food allergy or develops gastro-entero disturbances should eat heated foods.

When a food allergy is diagnosed, differential diagnoses should be considered, especially food intolerance. Food intolerance is characterized by the interaction between foods that contain chemical agents and a host who does not have the ability to resolve them. Food intolerance is not an immunological reaction, which is caused by food contents such as pharmacological active agents (ex. histamine, serotonin and caffeine), salicylic acid compounds (ex. tomato, potato and strawberry), or food additives (ex. paraben and benzoic acid) and by a characteristic of the host such as a metabolic or psychological abnormality (ex. lactose intolerance). Adverse effects due to soy sauce should be caused by soy sauce allergy and soy sauce intorelance. Histamine is related with both soy sauce allergy and soy sauce intorelance. For the diagnosis of a food allergy, the serum-specific IgE levels must be investigated, and skin test (prick test, scratch test or patch test) and oral challenge test must be performed. A diagnosis can be made based on the results of the examination, a clinical examination, the patient history (past history, present history and family history) and the patient's symptoms. Serum IgG is often not measured, because IgG is not always useful for the diagnosis of food allergy. Prick and scratch tests are used to diagnose immediate allergies, and these tests are performed on the forearm or back. After 20 minutes of prick or scratch test, physicians evaluate the results using their own criteria. However, the evaluation of prick and scratch tests is done differently depending on the physician, institute and country, these differences can cause confusion among physicians and patients, especially with respect to the prick test. If the prick test is performed using foods containing histamine or serotonin, these agents could modify some results of the prick test, and the prick test should be evaluated using plural criteria. We presented our criteria for evaluating the results of prick test, and then our criteria resulted in decreasing the number of false-positive reactions and reflecting clinical symptoms. The patch test is the main method for studying delayed-hypersensitivity reactions. The patch test is performed on the back or forearm. The evaluation of results read at 48 and 72 hours after removing allergens. The

International Contact Dermatitis Research Group (ICDRG) advocated that uniform criteria be adopted to evaluate the results of the patch test (Wilkinson JD & Shaw S. 2004). If international standards for the prick test were established, the confusion regarding prick test results would be eliminated. There are three kinds of oral challenge food tests: open, single-blind and double-blind tests. Basically, method of open test is that patients ingest small amounts of foods that may cause allergic reactions, and physicians then observe and evaluate the patient's reactions.

There are two interesting conditions resulting from food allergies: food-dependent exercise-induced anaphylaxis (FDEIA) (Kidd JM 3rd, et al. 1983) and oral allergy syndrome (OAS) (Kondo Y & Urisu A. 2009). These two conditions are IgE-dependent allergic reactions. Because the frequency of the shock symptoms of FDEIA is higher than that of OAS, people must know and it needs enlightenment about this disease. One common trigger of FDEIA is exercise, especially after allergens have been consumed. The kinds of exercise that can trigger FDEIA are different depending on the case, but they include running, tennis, basketball, baseball, golf, cycling, cleaning, etc. Some individuals can precipitate FDEIA just by walking after a meal. Other triggers of FDEIA are drugs (ex. aspirin) and the patient's status (physical condition). Present illness (episode of this disease) is important for the diagnosis. Most FDEIA occurs at 20-40 minutes after eating; patients should rest of 2-3 hours after meals. Some students develop allergic symptoms during physical education class after lunch. Teachers must be aware of this condition, and patients must obtain and know how to use an Epipen®. The Epipen®is an injection of epinephrine, which is a vasoconstrictor, and it is portable. An Epipen® injection causes vasoconstriction and results in a rise in blood pressure. This drug is a single use injection by own self. In the provocation test of FDEIA, an urgent treatment is often required.

OAS refers to contact urticaria of the mucosa (oral cavity, lip, throat, nose, esophagus, and trachea). This condition usually occurs within 20 minutes of the exposure to allergens. This allergy has become more prevalent in recent years, and the number of OAS has been increased. Most OAS allergens are fruits and vegetables. Some OAS patients have allergies to some kinds of pollen, which can cause cross-reactions (Table 1). The cross-reactions between pollen and vegetables or fruits are caused by PR-10 protein or profiling (Kondo Y & Urisu A. 2009). It is interesting that some cases of OAS are complicated with allergic conjunctivitis, allergic rhinitis, or latex allergy. The mechanism by which this occurs is likely a cross-reaction to these antigens.

Pollen	Foods
alder	melon, kiwi, soy, apple, peach mango, avocado, orange, potato, tomato, nut, carrot
white birch	melon, apple, peach, pear, almond, walnut. nut, peanut, potato, kiwi, celery, orange
orchard grass, timothy grass	tomato, flour, melon, rice, watermelon, potato, onion
hogweed	banana, watermelon, melon
Japanese cedar, cypress	tomato

Table 1. These pollens caused cross-reactions with foods.

3.2 Provision for foods allergy

The therapies for allergic reactions are different depending on the symptoms. The most important therapy for a food allergy is to avoid or eliminate the allergens. Individuals with food allergies and their family or caregivers must be attentive to the allergy at home or at school. At home, contamination during cooking is the most frequent cause of allergic reactions, there is a strong possibility of contamination because multiple people are involved in preparing and serving the school lunch at school. The mistaken distribution of foods at lunch time and in class is also an important cause. A child with a food allergy may suffer persecution if other children around him or her do not understand the food allergy. Children, teachers and the patient's family need to understand the psychological dimensions of food allergies. Therefore it is important that the patient's family, teacher and home doctor have a good relationship. Notices in the school are food restriction, bring lunch, and avoid allergens. Food allergy guidance and foods without allergens are essential for patients and their families. Depending on the allergen, a food allergy can be a significant burden for the patient and his or her family and can have a significant economic cost. Food restriction sometimes causes nutritional or eating disorders and can result in abnormal growth. If the patients have severe allergic reactions, and especially if the patients develop immediate allergy (shock), it is important for the patient to be able to inject epinephrine (Epipen®) by themselves. When people with severe allergic reactions are exposed to allergens, they usually inject this drug into their thigh by themselves before suffering shock. In Japan, processed foods using 7 materials (milk, egg, peanut, flour, buckwheat, shrimp and crab) must be labeled by law. And then, eighteen other foods (abalone, apple, banana, beef, chicken, gelatin, kiwi fruit, mackerel, matsutake mushroom, orange, peach, pork, salmon, salmon roe, soy, squid, walnut and yam) are not restricted but labeling is recommended. Because many foods today are widely distributed, common methods of labeling processed foods are needed worldwide. There are many kinds of foods allergy, in the case of flour allergy, it is difficult to avoid the allergen completely, because flour is often used not only in foods but also other items (ex. soap, shampoo, cosmetics). Processed foods and seasonings sometimes contain flour. The ingredients of these foods must be confirmed before they are consumed. International food labeling standards are useful for people with food allergies.

4. Soy products allergy

4.1 Introduction

Soybean allergy is 2% of food allergy. Leading cause of food allergy is eggs, the 2nd cause is milk, the 3rd cause is flour and the 10th cause is soybean (Rodrigo MJ, et al. 1990). There are many kinds of soy products, soy milk, tofu, natto. When we grind soybean and filter it, soybean changes soy milk. Coagulated soy milk is tofu. Soy oil is extracted from soybean. Fermented soybean is natto, soy sauce and soybean paste (miso). Roasting soybean is soy powder (Figure.3).

4.2 Classification according to types of soy allergy

Recently, we distinguish food allergy as a mechanism of pathogenesis. There are 6 parts of food allergy, class 1 allergy, class 2 allergy, inhalant allergy, contact urticaria, protein contact dermatitis and others.

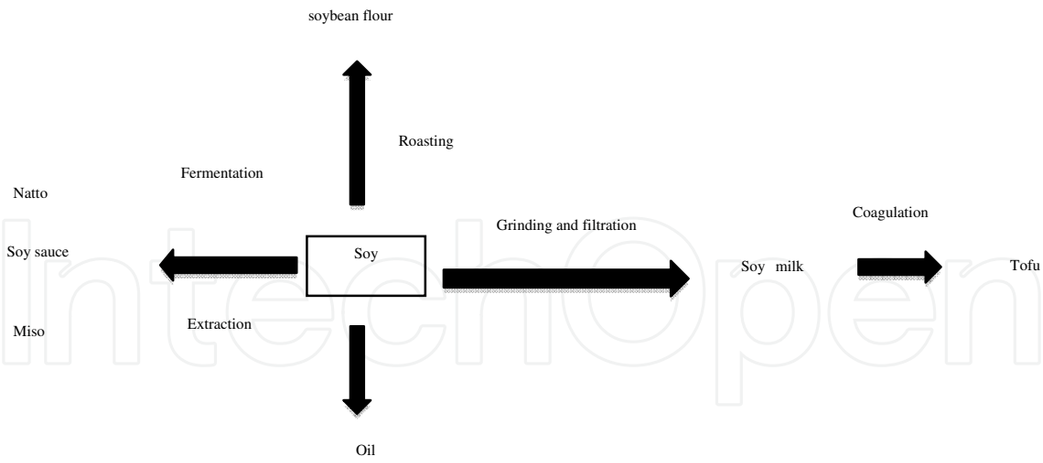


Fig. 3. Soy is processed into a wide variety of products

4.2.1 Class 1 allergy

Class 1 allergy is quote-unquote archaic food allergy. In this type, sensitized antigens equal to pathogenic antigens. Symptoms are urticaria, diarrhea, vomitting and anaphylactic shock. Basement of pathogenesis is an antigen permeability of mesentery and incomplete immune tolerance in infants. Class 1 allergy almost heal naturally expect some antigens as crabs, shrimp, buckwheat noodles. Main causative antigens are soybean, eggs, milk and flour. Causative antigens have digestive tolerance and fever tolerance. The structure is small molecular weight and contain s-s band.

4.2.2 Class 2 allergy

Transmucosaland percutaneous sensitization of pollen and latex tap, then similar molecules of food from vegetable sources trigger food allergy. Usually, adults with a pollen allergy and / or latex allergy cause this type of allergy, and natural healing is a rare occurrence. Symptoms are itching of the mouth and pharynx, frog and anaphylactic symptoms like facial edema, airway constriction dyspnea. Main causative antigens are vegetable, fruits, soybean and walnuts. The character of causative antigens is food protein from vegetable sources and water-soluble low molecular protein. Digestive resistibility of digestive enzyme isn't involved in this allergy because the allergens are assimilated by the mouth not the digestive canal (Table 2).

4.2.3 Inhalant allergy

Someone may sensitize soy protein when they inhale it, then they inhale soy protein again and soy protein evokes asthma attack. Over 20 patients passed away because they worked unloading the equipment from the ship in Barcelona, Spain, from 1981 to 1987 (Ikeda I & Ogawa T. 2000).

4.2.4 Contact urticaria

Some cases induce contact urticaria when they contact soy product such as tofu with hands or some body parts. They suffer from local parts urticaria that is only contact area with soy products (Amin S & Maibach HI. 1997). There is a staging of contact urticaria syndrome

(Iijima S. 2008). Stage 1 is local urticaria and dermatitis, stage 2 is generalized urticaria, stage 3 is bronchial asthma, rhinitis, conjunctivitis, orolaryngeal symptoms and gastrointestinal symptoms. Stage 4 is anaphylactic reactions.

	Class 1 allergy	**Class 2 allergy**
Causative food	Tofu, soy sauce, boiled soybean, soy sauce, bean paste (miso)	soymilk
Age	young children	adults
IgE RAST of soy (blood test)	high score	low score or negative
Source of sensitizing antigens	food	pollen
Pathway of sensibilization	oral sensitization	inhalation sensitization contact sensitization
Induction allergens	as same as induction allergens	cross-reaction between pollen and food
Symptoms	urticaria, diarrhea, vomitus anaphylactic shock.	oral allergy syndrome

Table 2. Class allergy and class 2 allegry

4.2.5 Protein contact dermatitis (PCD)

PCD is an allergic skin reaction induced by proteins of ether animal or plant origin. When they contact the causative protein, they have a chronic eczema and an acute urticaria occurring within 15-30 minutes. Prick or scratch test usually show positive, and patch test results are often negative.

4.2.6 Others

Some cases have both class 1 and class 2 allergies. When they eat freeze-dried bean curd or snacks including soybean, they suffer from orolaryngeal symptoms (class 2 allergy) at first, then urticaria, gastrointestinal symptoms and anaphylactic reactions (class 1 allergy).

4.3 Allergens

Table 3 shows main allergens of soy bean. Ogawa (Ogawa T, et al. 1993) reported Gly mBd was a main allergen of class 1. Soy 7s globulin is also a main allergen of class 1 (Ogawa T, et al. 1995). In Japan, we have an eating habit of soy. Therefore, there are a lot of studies of class 1 allergy. In the United States and Europe, they don't have an eating habit of soy, so they study about class 2 allergy and inhalant allergy. Main allergens of Barcelona asthma are Gly m1 and Gly m2, and main allergens of class 2 allergy are oleosin, SAM 22 (Gly m4), soy profilin (Gly m3). Soy milk contains a lot of Gly m4 and tofu dose not contain Gly m4 so much.

classification of soy allergy	molecular size	classification
Soy 7s globulin	68kDa 66kDa 50kDa	class 1
glycin A3 subunit	43kDa	class 1
Gly m Bd30K	30kDa	class 1
Gly m Bd28K	28kDa	class 1
oleosin	23-24kDa	class 2
Kunitz-type soybean trypsin inhibitor	18-20kDa	class 1
SAM 22 (Gly m4)	17kDa	class 2
soy profilin (Gly m3)	13kDa	class 2
Gly m1	7.5kDa	inhalant antigen
Gly m2	8kDa	inhalant antigen
2S albumin	9kDa 5kDa	class 1?

Table 3. Main allergens of soy bean

4.4 Tests

4.4.1 Blood tests

When we suspect our patients suffer from soybean allergy, we study IgE RAST of soy. We also study IgE RAST of pollen such as Japanese white birch, Alnus japonica, Japanese cedar and Japanese cypress, IgE RAST of fruits and vegetables such as apples, strawberries, carrots and celeries.

4.4.2 Skin tests

We conduct prick tests using tofu, soy milk, some fruits and vegetables. Histamine dihydrochloride is a positive control and saline is a negative control. We also conduct a 48-hour closed patch testing. Prick test results are usually positive, and patch test results often negative as PCD.

4.5 Treatments

Soy-free diet is important for class 1 allergy, soy milk, fruits and vegetables-free diet is important for class 2 allergy. They should protect their hands with gloves when they contact soybean product in PCD patients(Table 4). They suffer from class 1 allergy and class 2 allergy, they should take medicines such as anti-histamine internal medicine. If they have eczematous symptoms, they need to put on steroid ointment.

Tipe of food	processed food
grain	fried noodles, popcorn, macaroni, spaghett, instant noodle
potato and amyloid processed products	mashed potatoes, crisps, french fries
nuts and seeds processed products	fried almond, peanuts
pulse	red bean paste, kidney beans, peas, green peas, broad beans, bean sprout, soy beans, Tofu, fried tofu, a fried bean curd cake with vegetables and other ingredients in it, freeze-dried tofu, fermented soy beans, soy pulp, tofu skin, soybean flour, soymilk, gelatin
fish and shellfishseafood	tsukudani that preserved small fish, shellfish, konbu, etc. boiled down in soy sauce and sugar, fish sliced open that seasoned with mirin, soy sauce, etc. and dried in the sun, smoked fish, fish preserved in miso
meat processing products	meat with miso, soy sauce and oils
oils and fats	margarine, soybean oil, sesame oil and safflower oil contain with soy, bean- jam- filled wafers, oiled beans, agar- agar cubes, other delicacies in sugar syrup
sweets	a bar of sweet jellied adzuki- bean paste, a bun with a bean- jam filling, a rice ball coated with sweetened red beans, soybean flour, or sesame and salt, cubic rice crackers, fried dough cookies, Japanese sponge cake, chocolates
preference beverage	cocoa, coffee
seasoning	curry roux, white sauce, mayonnaise, dressings, a seasoned powder for sprinkling over rice, miso, soy sauce

Table 4. Soy products

4.6 Countermeasures

Moriyama reported some soy products improve hypoallergenic products (Moriyama T & Ogawa T. 2010). They attempt using hypoallergenic soybean paste (miso), hypoallergenic soy milk, hypoallergenic boiling soy and hypoallergenic soy cookies.

5. Soy sauce allergy

5.1 The history of soy sauce

Soy sauce originated from preserved foods in ancient China about 3000 years ago. The introduction of preserved foods from China into Japan occurred in about 500 A.D. Grains, especially soy, are easer to preserve than foods such as fish, duck, deer, and other meat and are suitable for Japanese-style cuisine. Preserved grain foods had developed in Japan because Japanese have been agricultural people and cultivated some kinds of grain. A Japanese Buddhist monk introduced the process of making miso (soybean paste), miso was developed in Japan. Some Japanese people in the Kamakura or Muromachi period (about 1200 - 1500 A.D.) found that the fermented solution obtained from preserved soy or miso was delicious. Both preserved soy and the fermented solution were then used for cooking, and soy sauce, fermented solution would be soy sauce. First, only noblemen (Buddhist monks, the samurai classes and court nobles) ate soy sauce, because soy sauce was a expensive food. The first soy sauce shop opened in about the 1580s in Japan, and then soy sauce began to be used for cooking by the public. The term 'soy sauce' started being used during the same period. The soy sauce trade started in about 1700 with the growth of the economy and commerce. In the Edo period (about 1700 A.D.), industrial production of soy sauce began, and mass production began in about 1900 A.D. (the Taisho period). Since the beginning of the 19th century, soy sauce began being exported abroad, and soy sauce has now become a global product due to the popularity of Japanese food worldwide. Soy sauce is now exported to over 100 countries.

5.2 Soy sauce

Soy sauce '醤油' is a traditional Japanese sauce made from fermented soybeans. Soy sauce is called 'shoyu' in Japan, and is made from soy, flour and salt (Kobayashi M. 2005). Soy sauce has 5flavors: tasty, salty, sweet, acidic and bitter, and the delicious of soy sauce are composed by striking a balance among these 5 flavors. Glutamic acid is a key to the taste. The concentration of salt in the soy sauce is about 16-18%, and the pH (potential of hydrogen) is about 5. This concentration of salt (about 16-18%) is high. Organic acids cause acidity and soften the saltiness. Three microbes, malt bacteria, lactic acid bacteria and yeast, play important roles in producing soy sauce. Japanese foods (washoku, 和食) are now being consumed worldwide, and soy sauce is thus widely consumed. The reason why Japanese foods are popular worldwide is because Japanese cuisine is known to be healthy. Soy sauce has been considered a healthy food which is anti-allergic, inhibits allergic reactions (Kobayashi M, et al. 2004 a), promotes the secretion of gastric juice (Kojima T. 1954), and improves anemia (Kobayashi M, et al. 2006) and hypolipidemia (Kobayashi M, et al. 2008). There are five kinds of soy sauce: koikuchi, usukuchi, tamari, siro and saisikomi shoyu. There are uses for each of these soy sauces. Koikuchi shoyu is the most consumed soy sauce in Japan; about 75 % of this shoyu is produced by honjouzo (production process). There are three production processes, honjouzo, kongoujouzo and kongou. The ingredients and additives used in this process are salt, alcohol, amino acid, glucose and sugar. The source, quality and volume of these substances are different depending on the kind of soy sauce being made or the companies that make them. Shoyu is made by brewing soybeans. Some of the production stages are shown in Figure 4.

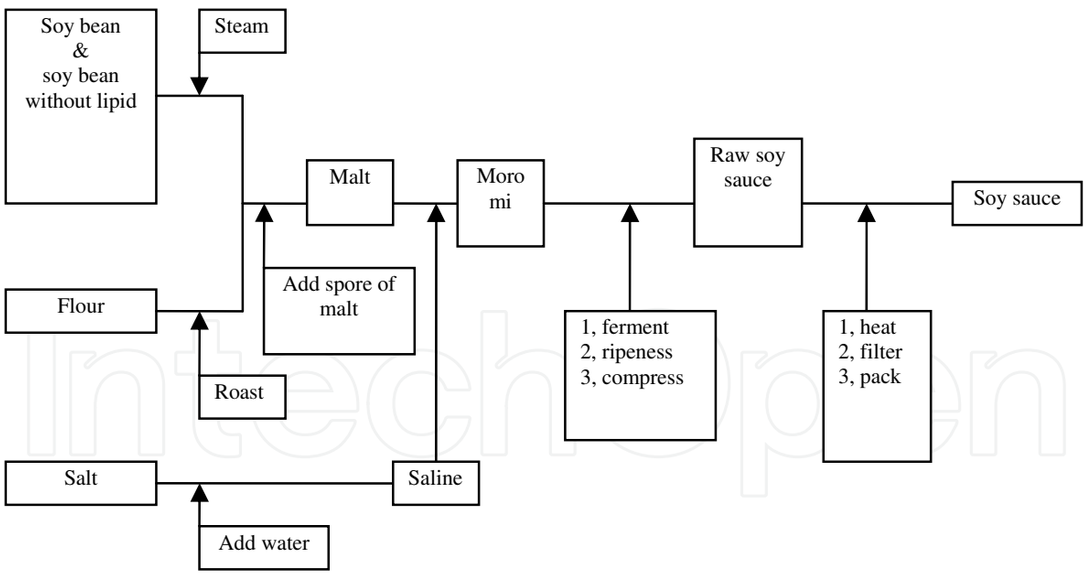


Fig. 4. This figure shows the process of honjouzou.

These processes take about 6-8 months. The same amount of soybeans (including soybeans without lipids) and flour are used. The soybeans (including soybeans without lipids) are steamed, and the flour is roasted. The kinds of soy and flour used depend on what type of soy sauce is being made or the soy sauce companies. The soybeans(including soybeans without lipids) and flour are mixed, and mold is added to this mixture. The mixture is then

mixed for a few days, and turns into malt. Saline is put into the malt, which changes it to moromi. The moromi is then turned into raw soy sauce by three steps (fermentation, ripening and compression). Raw soy sauce change soy sauce products throgh three process. The other 4 sauces (usukuchi, tamari, siro and saisikomi shoyu) are produced by different methods. The features of the other four sauces are as follows. About 15% of the soy sauce produced is uskuchi soy sauce. This sauce originates from the Kansai area. There is a greater amount of salt in usukuchi sauce, at about 10%, than koikuchi. Tamari, manufactured in the Chubu area of Japan, is often used for sashimi or sushi. Saisikomi is used in the Kyushu area, in western Japan, and is made from soy, flour and soy sauce. Siro is light in color and tastes sweet. This sauce is produced in the Hekinan area of Aichi, Japan. In Japan, except for soy, there are some other kinds of primary materials of shoyu sauce; fish, kelp, millet, rice, barnyard grass, etc. In these sauces, fish sauce smelled particular and unique. You can see or eat fish sauce when you go to East Asia. In the future, because of this increased consumption, the number of adverse effects, such as allergic reactions, may increase.

5.3.1 Introduction of soy sauce allergy

In Japan, some people develop irritation, cellulites or dermatitis around the lips after using soy sauce. The source of these symptoms is a possible soy sauce allergy, histamine poisoning, soy allergy, flour allergy, etc. Allergies to soy products and flour products are often caused by soy and flour, respectively. In particular, a major allergen of soybean is Gly mBD 30k (Tsuji H, et al. 1995) and Gly mBD 28k (Bando N, et al. 1998), but it is not detected in fermented soy products because of the heating used for production. However, allergens of fermented soy and flour foods were not detected, and fermented soy products are hypoallergenic foods (Kataoka S. 2005) because allergens of soy and flour should be degrade during fermentation (Kataoka S. 2005, Kobayashi M, et al. 2004 a,b). Why does irritation, cellulites, or dermatitis around the lips occur after using soy sauce? What allergens cause these symptoms? When cellulites and dermatitis around the lips occur, the person should be tested prick test and determine the volume of histamine. These symptoms are likely caused by a soy sauce allergy or histamine poisoning.

5.3.2 Cases of soy sauce allergy

We present eight cases of persons who developed allergic reactions after using their soy sauces. Case 1: A 35-year-old female who had been suffering from cellulites, dermatitis around the lips and coughing since 2004. Case 2: A 51-year-old female who has suffered swelling of the lips since November, 2008 (Figure 5). Case 3: A 10-year-old female who, since infancy, sometimes developed cellulites and scales after meals. Case 4: A 46-year-old female who had developed dermatitis around the lips with itching after meals since April, 2009. Case 5: A 10-year-old female exhibiting cellulites, scales with itching and dermatitis around the lips (Figure 6), and whose mother was the case 4 patient; both used the same soy sauce. Case 6: A 41-year-old female who suffered scales and swelling on her lips. Case 7: A 39-year-old female cook who developed swelling of the lips while working. Case 8: A 34-year-old female who sometimes suffered scales and swelling on her lips after meals. The average age of the 8 patients was 33.25 years. Their symptoms improved after they changed the brand of soy sauce they used. The eight patients did not develop any symptoms when they used salt, alcohol, amino acid, glucose and sugar.



Fig. 5. This figure showed Case 2; swelling of her lips.

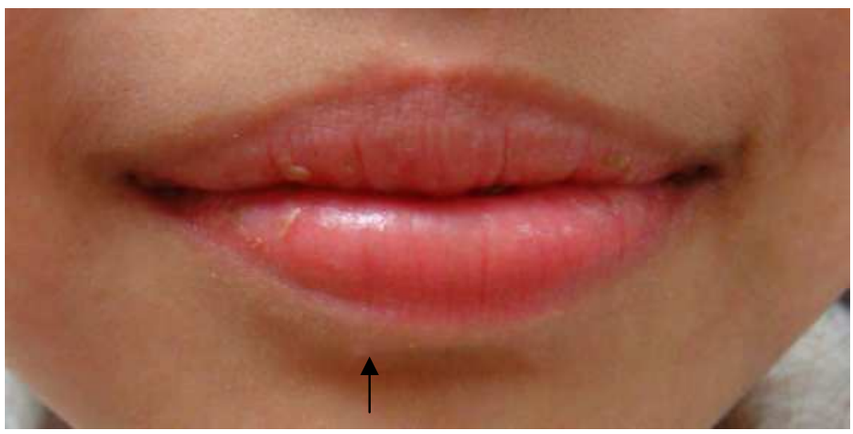


Fig. 6. This figure showed case 5; Allow indicated cellulites, scales with itching and dermatitis around lips.

5.3.3 Materials and methods for studying soy sauce allergy

5.3.3.1 Materials and methods for the prick test

Using prick tests and laboratory tests are essential for investigating allergies. The prick test is often used to study immediate allergy. We use Lancet needles (Leti, Madrid, Spain)for these tests. To conduct a prick test, we prick the substances suspected of causing patient's allergic reaction, and then we prick the patient's skin using the same needles. To read the results correctly, control substances and control people are needed. Generally, control substances are negative and positive controls, and control people are healthy without allergy. 15-20 minutes after the prick test, the results are evaluated using established criteria. Typical (conventional) criteria are 5-mm wheals with erythema (Roll A, et al. 2006), wheals 5 mm larger than in the negative control (Kivity S, et al. 2005), a mean diameter of two wheals that was 3 mm larger or more than the mean diameter of the negative control (Douglass JA and O'Hehir RE. 2006), half or more of wheals induced by histamine (Lee S, et al. 2001), 3-mm-diameter or larger wheals (Abi Berger. 2002, Brockow K & Romano A. 2008, S Kirschner, et al. 2009) and wheals with diameters 3 mm larger than the wheals of the negative controls (Lopes MI, et al 2006, Fereidouni M, et al. 2009, Christopher W Calabria & Larry Hagan. 2008, Baral VR & Hourihane JO. 2005). In our method, a wheal with a

diameter 3 mm smaller than the average wheal diameter of the controls with 21 mm or larger flare or wheals with diameters 3 mm larger than the average wheal ((maximum + minimum wheal diameter) / 2) diameter of the controls is considered to be a positive reaction. The A/H ratio (Sang-Ha Kim, et al. 2006)is the ratio of allergen-induced wheal size (A) to histamine-induced wheal size (H). A score of 1 indicates an A/H ratio of 0.1 to 1 with a flare of less than 21 mm. A score of 2 is an A/H ratio of 0.1 to 1 with a flare of 21 mm or more. A score of 3 is an A/H ratio of 1 to 2, a score of 4 is an A/H ratio of 2 to 3. And a score of 5 is an A/H ratio of 3 or more. A score of 2 or more was determined to be a positive reaction. The criteria varies among physicians, countries and institutes, and some criteria have often shown pseudo-positive reactions when substances containing histamine are tested. Because our method was not sufficient for evaluating results, we used both our method and A/H ratio as our new criteria. Therefore, we read the results of a prick test using soy sauce, and then positive reactions in both our method and A/H ratio are considered to be positive reactions in our criterion (Sugiura K & Sugiura M. 2011). Our criterion could decrease the number of pseudo-positive reactions.

Our volunteers without food allergies were four females as negative controls. The 4 controls 24, 27, 35 and 40 years old; the average age was 31 years. We obtained written consent for study participation from 12 persons (8 patients and 4 volunteers) before prick testing. We performed the prick test on their back or forearms. We used 15 sauces to investigate soy sauce allergy, including one barnyard grass sauce, one flour sauce, one garlic sauce, one kelp sauce, one millet sauce, one nam pla (Thai fish sauce), one rice sauce, one sardine sauce and 7 soy sauces. We used saline as the negative control and histamine chloride 1% aq as the positive control. These fifteen sauces were the commercial products from different companies, and there were one tamari sauce, one usukuchi sauce and 5 koikuchi sauces among the 7 soy sauces.

5.3.3.2 Laboratory test

We measured the percentage of eosinophils, IgE RIST and specific IgE against soy and flour by the capsulated hydrophilic carrier polymer-radioallergosorbent test (CAP-RAST) (ImmunoCAP®, Phadia KK, Tokyo). The concentration of IgE was divided into 6 classes; class 0 is less than 0.34 IU/ml, class 1 is 0.35-0.69 U/ml, class 2 is 0.7-3.49 IU/ml, class 3 is 3.5-17.49 IU/ml, class 4 is 17.5-49 IU/ml, class 5 is 50.0-99.99 IU/ml and class 6 is 100 IU /ml and more. The results evaluated as positive are class 2 and more.

5.4 Results of the laboratory test and prick test

5.4.1 The results of the laboratory test

The average percentage of eosinophils in patients was 3.35% (1%～5%), and that of serum IgE was 190 IU/ml. The values for specific IgE against soy in all cases were class 0; one patient was classified in class 2 for specific IgE against flour. The average percentage of eosinophils in the control volunteers was 0.45%, and the average of serum IgE was 91.75 IU/ml. The specific IgE against soy and flour in all volunteers received a score of 0.

5.4.2 The results of the prick test

We compared the results using our criteria with those using the 6 conventional criteria and A/H ratio described above. We observed positive reactions in 9 colors and various patterns (Table 5, Sugiura K & Sugiura M. 2011). It was interesting that some positive reactions by the conventional criteria described negative reactions by our method and A/H ratio, and

cases with negative reactions by conventional criteria did not show any positive reactions by our criteria (that is, there were no cases with false-negative reactions). Figure 7 showed positive reactions by the conventional criteria, but by our new criteria judged negative reactions. The positive ratio of the controls according to our new criteria was lower than that of the controls according to the conventional criteria (Table 6). Both the conventional and

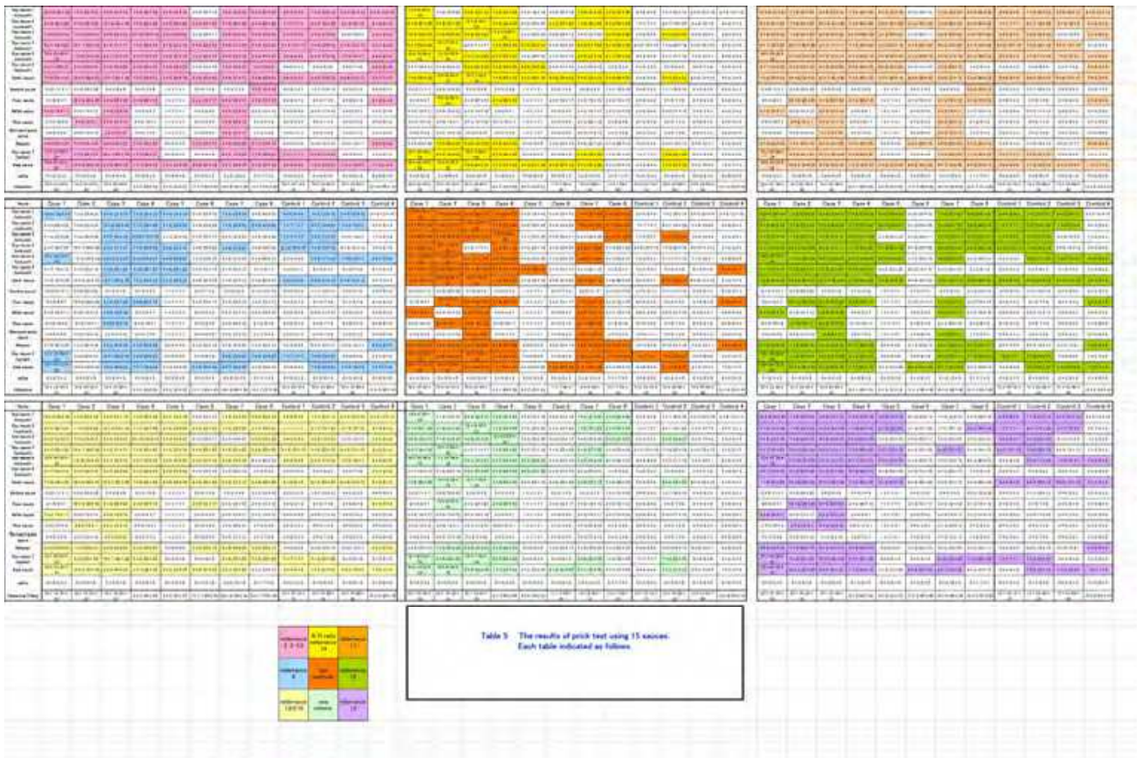


Table 5. The results of prick test using 15 sauces. Each table indicated as follows.

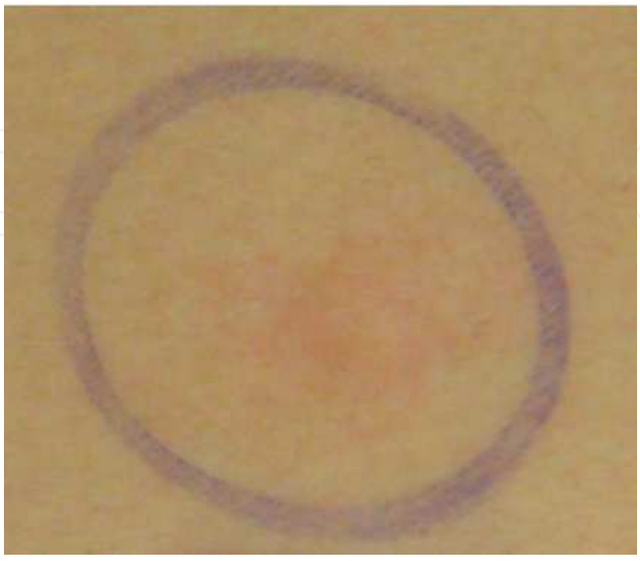


Fig. 7. This reaction show negative or positive reaction.

new criteria described that some soy sauces that contained 10 mg/100 g or more histamine showed higher positive ratios in patients; however, the positive ratio by our new criteria was lower than that by the conventional criteria in the controls (Table 6). The positive ratios of the prick test using soy sauce in this study had different results between the conventional and new criteria (Table 6). We speculated that the concentration of histamine would be closely related to the type of shoyu (for example, koikuchi, usukuchi), but we did not see any significant relations. Some soy sauces containing extremely high concentrations of histamine may cause positive reactions, but there was no relation between the positive ratio and the concentration of histamine in our study.

Conventinal Criteria	Our new Criteria		Conventinal Criteria	Our new Criteria	
Positive ratio of patients (%)	Positive ratio of patients (%)	Sauces	Positive ratio of controls (%)	Positive ratio of controls (%)	Histamine (mg/100g)
46.87	25	**Flour sauce**	15.62	0	4.6
57.81	37.5	**Soy sauce 6 (koikuchi)**	12.5	0	5.1
65.62	37.5	**Nanplar**	21.87	0	7.1
71.87	62.5	**Soy sauce 7 (tamari)**	46.87	25	13.5
68.75	62.5	**Soy sauce 3 (koikuchi)**	56.25	25	27.6
85.93	62.5	**Garlic sauce**	84.37	25	29.4
85.9	62.5	**Kelp sauce**	78.12	25	30.2
79.68	62.5	**Soy sauce 5 (koikuchi)**	75	0	41.3
78.12	62.5	**Soy sauce 1 (koikuchi)**	78.12	0	50.5
87.5	75	**Soy sauce 2 (usukuchi)**	78.12	0	54
85.93	50	**Soy sauce 4 (koikuchi)**	59.37	0	75.2
21.87	0	**Sardine sauce**	0	0	not detected (Minimum limit of determination; 0.5mg/100g)
25	0	**Millet sauce**	0	0	not detected (Minimum limit of determination; 0.5mg/100g)
23.43	0	**Rice sauce**	0	0	not detected (Minimum limit of determination; 0.5mg/100g)
3.12	0	**Barnyard grass sauce**	3.12	0	not detected (Minimum limit of determination; 0.5mg/100g)

*Request for this to Japan Food Research Laboratories authorrized by Japaneze government
*Certificate of analyisis: No. 10024724001-10024724015
*We made this table based on the results provided by the Japane Food Research Laboratory.
*Each of there soy sauces were different brand

Table 6. The contrecation of histamine and positive ratio of prick test

5.4.3 Determination of histamine in each sauce

Histamine is an important factor for studying soy sauce allergy. Because the concentration of histamine in soy sauce is high and a false-positive skin reaction could be present, the results of a skin prick test must be evaluated strictly.

There are a variety of histamine-containing foods (Wantke F, et al 1993, BJ Vlieg-Boerstra, et al. 2005) change to (Wantke F, et al. 1993, BJ Vlieg-Boerstra, et al. 2005) in the world. The histamine-containing foods are cheese, sausages, fish, wine and soy products, and the histamine-releasing foods are strawberries, chocolate, tomatoes, peanuts and additives. Histamine-releasing foods act on mast cells for degranulating. Because histamine sometimes causes adverse reactions such as histamine poisoning, the concentration of histamine in the foods is provided on food packaging. Food Standards Australia and New Zealand (FSANZ) show that the concentration of histamine must be 20 mg/100 g or less, and codex standards

for hygiene and handling demonstrate that any fish used for human consumption must not contain a concentration of histamine of 20 mg /100 g or more. There is currently no rule regarding the acceptable concentration of histamine in soy sauces. The histamine in soy sauce comes during the brewing of soy (BJ Vlieg-Boerstra, et al. 2005, KW Chin, et al. 1989). The concentration is various depending on the kind of sauce, the manufacturing company and the preservation conditions.

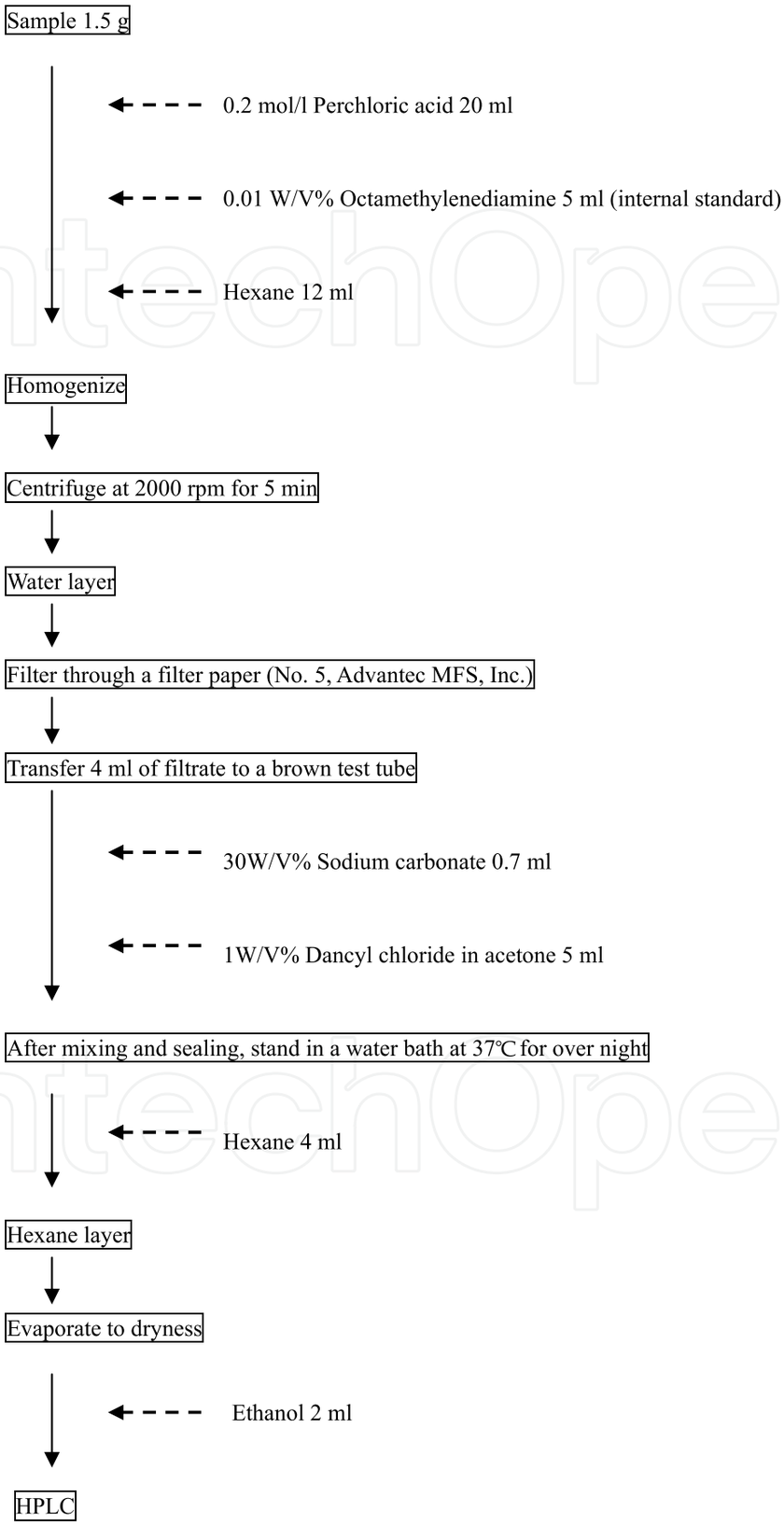
We asked the Japan Food Research Laboratories (Tokyo) to determine the volume of histamine in 15 sauces. They used high-performance liquid chromatography (HPLC) for their testing, as shown in Table 7. The minimum limit of determination by this method was 0.5 mg/100 g.

5.4.4 The volume of histamine in the sauces

We tested various colors of soy sauce; those containing histamine expressed a deep color (Figure 8). No histamine was detected in the millet *(kibi)*, barnyard grass, sardine and rice sauces, all of which are lighter-colored than the sauces containing histamine. The concentrations of detected histamine in the tested sauces are described in Table 5. In those results, three soy sauces contained 50 mg/100 g and more, which is a high concentration of histamine. These soy sauces were soy sauce 4 at 75.2 mg/100 g, soy sauce 2 at 54.0 mg/100 g and soy sauce 1 at 50.5 mg/100 g. The minimum concentration of histamine was detected in the flour sauce, 4.6 mg/100 g. Seven sauces contained histamine at concentrations of 20 mg/100 g or more. In the case of soy sauce, the positive ratio of the prick test with concentrations of 50 mg/100 g and more of histamine was high. In fact, the level of toxicity or poisoning by histamine is low; the concentration of histamine that will cause food poisoning is 50 mg/100 g or more (Gilbert RJ, et al. 1980, Lehane L & Olley J. 2000, Brink B, et al. 1990). Because soy sauces containing high concentrations of histamine could cause adverse effects and affect medical tests, we need a new world standard for the concentration of histamine in soy sauces.



Fig. 8. The color of the tested soy sauces. The bottle at the far left contains distilled water. 4th, 5th, 6th and 8th from left side are barnyard grass, rice sauces, millet *(kibi)* and sardine.


Sample 1.5 g
0.2 mol/l Perchloric acid 20 ml
0.01 W/V% Octamethylenediamine 5 ml (internal standard)
Hexane 12 ml
Homogenize
Centrifuge at 2000 rpm for 5 min
Water layer
Filter through a filter paper (No. 5, Advantec MFS, Inc.)
Transfer 4 ml of filtrate to a brown test tube
30W/V% Sodium carbonate 0.7 ml
1W/V% Dancyl chloride in acetone 5 ml
After mixing and sealing, stand in a water bath at 37℃ for over night
Hexane 4 ml
Hexane layer
Evaporate to dryness
Ethanol 2 ml
HPLC

<Condition for HPLC>

Pump: LC-10ADvp [Shimadzu Co., Ltd.], Detector: UV Spectrophotometric Detector SPD-10Avp [Shimadzu Co., Ltd.]
Column: Mightysil RP-18GP, Φ4.6 mm×150 mm [Kanto Chemical Co., Inc.]
Column temperature: 45℃,Mobile phase: Acetonitrile-Methanol – 0.01 mol/l Acetic acid (2:3:2 V/V/V)
Flow rate: 1.0 ml/min,Wave length: 254 nm
(This table is based on the information provided by the Japan Food Research Laboratory)

Table 7. Analytical Method for Histamine

6. Conclusion

Irritation of the lips and the skin can occur around the mouth after a meal containing soy sauce, but physicians do not always have any idea what the origin of these symptoms is. We hope our study contributes to awareness about these symptoms and soy sauce allergy. Our challenges were that the allergen of soy sauce allergy without soy and flour allergy is unknown, and there is no established method for evaluating the results of prick tests.

First, we suspected that unknown substances made during fermentation were the source of allergic symptoms. When cellulites or dermatitis around the lips occurs, a soy sauce allergy is suspected, and clinicians investigate patient's symptoms. What materials cause soy sauce allergy? Previous reports described that no allergens were detected in fermented soy products and that some allergens were lost in the process of fermentation (Kataoka S. 2005, Kobayashi M, et al. 2004 a,b). We found that soy sauce allergy was caused by unknown substances generated during fermentation, as our cases did not have positive reactions on skin tests or show a negative class of specific IgE to soy or flour (score 0). One problem with soy sauce is that it is often of poor quality and contains unknown substances. There often are sediments of soy sauce that are affecting its quality. These sediments are proteins produced by the molding of malt that are not always obvious. We speculated that these sediments might cause soy sauce allergy, and thus when examining soy sauce allergy, one must investigate not only soy allergy but also allergies to other materials (flour, salt, additives) as well as histamine poisoning. Making a differential diagnosis of soy sauce allergy and histamine poisoning requires knowledge about a patient's present illness and past history as well as performance of a skin test that is strictly evaluated. If histamine poisoning is the origin of symptoms, other foods containing histamine may have caused the symptoms. In fact, when patients eat some foods contained histamine, they do not appear allergic symptoms. It is difficult to diagnose correctly using the conventional prick test criteria, because soy sauces contain histamine that affects the results. Ideally, the volume of histamine should be determined, and the prick test should be given to healthy volunteers at the same time it is given to the persons suspected of having allergies. If the patients show positive reactions and control volunteers show negative reactions, it can diagnose that test materials must be origin of allergy. The results must be read by the strictly evaluation.

The consumption of soy sauce is increasing, and hence the number of cases with soy sauce allergy could increase. Companies that manufacture soy sauce should educate people about the advantages of healthy eating, the acceptable concentration of histamine, histamine poisoning and allergic reactions. Histamine poisoning presents like an allergic reaction, with

the subject experiencing vomiting, diarrhea, urticaria, hypotension, headache, flushing, itching, etc (Steve L Taylor. 1986). Histamine is produced during the fermentation of soy, and we studied the concentration of histamine in soy sauce, which is different depending on the sauce. The concentration is related to the soy sauce color, with most soy sauces with deep color containing a high concentration of histamine and soy sauces with light color containing low concentrations of histamine (Figue. 8, Table 6). It is important to study the concentration of histamine when a soy sauce allergy is suspected. Consideration of how the histamine level will affect the results of a prick test is also important. The conventional criteria for evaluating prick test results are not suitable for soy sauce allergy, because the variety of results by these criteria can confuse both patients and physicians. We note that the conventional criteria have the possibility of not reflecting clinical symptoms and of including false-positive reactions. Our criteria are suitable for the evaluation of prick tests using soy sauce, because the number of false-positive reactions can be decreased (Sugiura K & Sugiura M. 2011). It is important for patients to know whether what they are experiences is a food allergy, and thus whether they can eat a given food. The International Contact Dermatitis Research Group (ICDRG) (Wilkinson JD & Shaw S. 2004) provided criteria for patch testing (used for testing delayed-hypersensitivity allergies), but there are no appropriate criteria for the prick test using foods containing histamine; if people have false-positive reactions according to the conventional criteria, they must eat a soy-sauce-free diet. This is unfortunate, as they may not actually have to eliminate soy sauce from their diet. Not only the results of the prick test but also clinical findings are essential for diagnosing an allergy, and thus globally correct criteria for diagnosis are needed. Our new criteria are useful and superior for prick tests using soy sauce.

In this chapter, patients with soy sauce allergy who do not have allergies to soy, flour or additives are described, including their symptoms with figures, laboratory data, the results of skin tests, treatment and their condition at present. We recommend a new criterion for prick tests using soy sauce for the accurate diagnosis of soy sauce allergy.

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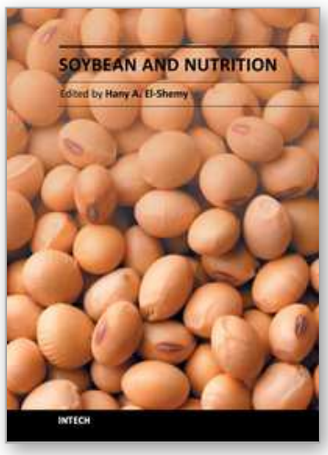
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Worldwide, soybean seed proteins represent a major source of amino acids for human and animal nutrition. Soybean seeds are an important and economical source of protein in the diet of many developed and developing countries. Soy is a complete protein and soy-foods are rich in vitamins and minerals. Soybean protein provides all the essential amino acids in the amounts needed for human health. Recent research suggests that soy may also lower risk of prostate, colon and breast cancers as well as osteoporosis and other bone health problems and alleviate hot flashes associated with menopause. This volume is expected to be useful for student, researchers and public who are interested in soybean.

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