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Topic 2: Commonly Known Allergenic Sources (IgE-mediatd and non IgE-mediated Food Allergens as well as Environmental allergens):

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INTRODUCTION

Foods are essential nutritional sources to maintain the human life activity. Especially, appropriate nutrition is important for children who are growing and developing. However, foods occasionally cause hypersensitive reactions among a certain group.

Foods are composed of proteins, carbohydrates and lipids. The allergens in foods are usually proteins. The sole exception is a transfer RNA, a minor allergen, in shrimp (P. indicus) (Nagpal 1987). Food allergens are derived from animal or vegetable sources. In theory, any foods have the potential to produce allergic reactions. However, 90% or more of all serious allergic reactions to food are, actually, accounted by eight foods and the food groups. These foods are cow's milk, hen's egg, fish, crustacea (shrimp, crab, lobster), peanuts, soybean, tree nuts (almonds, walnuts, cashews, etc.) and wheat (Hefle 1996).

The kinds of foods likely to cause hypersensitive reactions are different depending on age and race.

In infant and young children, hen's egg, cow's milk, fish, soybeans, peanut and nuts, and wheat are dominant allergens. In contrast, hypersensitive reactions to fruit, vegetable, fish, buckwheat, crustacea and mollusk are common in older children and adults.

In general, the major food allergens that have been identified are proteins or glycoproteins that have molecular masses ranging from 10 to 60 kDa and are stable to treatment with heat, acid and proteases (Tayler 1996).

The major food allergens in human are discussed below.

FOOD ALLERGENS FROM ANIMALS

1. Eggs

Hen's egg is one of the most common foods that induce hypersensitive reactions in young children.

Egg white contains more than 20 kinds of proteins. Ovomucoid (*Gal d* 1), ovalbumin (*Gal d* 2), ovotransferrin (*Gal d* 3) and lysozyme (*Gal d* 4) have been identified as main allergens in the egg white.

Ovomucoid is a glycoprotein with a molecular mass of 28 kDa and have trypsin inhibitor activity. Its amino acid sequence contains 186 residues (Kato 1987). There are three tandem domains, which show homology in amino acid sequence with each other. Ovomucoid is the most stable to treatment by heat and digestive enzymes such as pepsin, trypsin and chymotrypsin.

Ovalbumin is a monomeric phosphoglycoprotein with a molecular mass of 43 to 45 kDa and the amino acid sequence consists of 385 residues. The most abundant protein in egg white is ovalbumin. Johnsen and Elsayed (Johnsen 1990) demonstrated that a peptide of amino acid sequences 323-339 has IgE-binding activity.

Ovotransferrin (conalbumin) has a molecular mass of 77 kDa with 686 amino acid residues.

Lysozyme is a 14.3-kDa protein with 129 amino acid residues.

Egg yolk is considered less allergenic than egg white (Anet 1985), though IgE antibodies to chicken gamma-globulin, apovitellin I and contaminating egg white proteins can be demonstrated.

Many egg-hypersensitive patients show positive skin tests or specific IgE antibody to chicken meat, but most can eat chicken meat without any adverse reactions.

2. Cow's milk

Cow's milk generally represents the first foreign food proteins encountered by infants. It is one of the most common food allergens in young children and has been implicated in a variety of hypersensitive reactions (Hill 1986.). Cow's milk contains at least 20 protein components that may trigger antibody response.

The milk protein fractions are subdivides into casein and whey proteins. The casein fraction is precipitated from skim milk by acid at pH 4.6 and is composed of five basic caseins (α, αs, β, κ, and γ). The whey fraction contains α-lactalbumin, β-lactoglobulin, serum albumin, immunoglobulins, and a small amount of various proteins (lactoferrin, transferring, lipases, esterase, etc). The most dominant allergenic proteins in cow's milk are αs1-casein (23 kDa) and β-lactoglobulin (18 kDa). These proteins may be recognized to be not-self for infants due to the absence of these proteins in mother's milk.

Nakajima-Adachi et al (Nakajima-Adachi 1998) have reported that the dominant IgE epitope is an amino acid sequence 181-199 at the C terminal of alpha s1-casein. Beta-lactoglobulin has 6 IgE-binding epitopes, of which peptide 4 (amino acid residue 97-108) is considered to be the main determinant (Ball 1994). Alpha-lactalbumin (14 kDa) and bovine serum albumin (67 kDa) are minor allergens in cow's milk.

3. Fish

Parvalbumin (*Gad c* 1; Allergen M) (12.3 kD), a major allergen of cod (Aukrust 1978), have been isolated from the myogen fraction of the white meat. Parvalbumin controls the flow of calcium in and out of cells. It is stable to heat treatment and resistant to proteolytic digestion. This protein is considered involved in the cross-reactivity among the fish. *Gad c* 1 shares approximately 34% homology in amino acid sequence with similar proteins from hake, carp, pike, and whiting (Elsayed 1975). Individuals with fish allergy sometimes develop hypersensitive reactions to the fish species that they first eat. This phenomenon is explainable by the presence of cross-reactive protein such as parvalbumin. However, even fish-allergic patients who have multiple positive skin tests to various fish species cannot eat all fish species. The protein fraction or fractions responsible for clinical symptoms may be labile to manipulation such as heating. There might be different IgE-epitopes on parvalbumin among fish species. Otherwise, unidentified allergens might be present in fish meat. Actually, Shiomi et al have reported that fish collagen in the acid-soluble fraction has IgE-binding activity. The fish collagen is not extractable in the salt-soluble fraction in which parvalbumin is found.

Gad c 1 is an acidic protein (pI 4.75) with a molecular weight 12,328 Da, and is composed of 113 amino acid residues (Elsayed 1970). Gad c 1 contains at least five IgE-binding determinants (Elsayed 1983).

Ag-17-cod, protamine sulfate, and surimi 63 kDa protein have been reported as minor allergens.

4. Crustaceans

Two allergenic proteins were isolated from shrimp by Hoffman et al (Hoffman 1981). Antigen I was found in raw shrimp and shell extract and was heat-labile protein with molecular mass of 45 kDa. Antigen II was a heat-stable glycoprotein with molecular mass of 38 kDa, composed of 341 amino acid residues and 4% carbohydrate.

Nagpal et al (Nagpal 1989) has reported two IgE-binding polypeptides, allergen SA-I with a molecular weight of 8.2 kDa and SA-II with a molecular mass of 34 kDa.

Pen a 1 (36 kD) is a major allergen isolated from the brown shrimp and comprises 312 amino acid residues and 2.9% carbohydrate. *Pen a* 1 is a shrimp tropomyosin since it demonstrates significant homology in amino acid sequences with tropomyosin from various species (Daul 1994). Considerable cross-reactivity among crustacea has been demonstrated by skin test, RAST, and RAST inhibition assays (Waring 1985). However, no oral challenge studies have been performed to determine the extent of symptomatic cross-reactivity among the different crustacea.

Pen a 1 is probably the same protein with antigen II and SA-II.

FOOD ALLERGENS FROM PLANT

1, Legumes

There are two major legumes that cause allergic reactions. The first one is peanuts. Peanuts are one of the most allergenic foods in children and adults. Children in the U.S.A are often exposed to peanuts at an early age, usually in the form of peanut butter. Peanut-allergic patients sometimes show severe hypersensitive reactions such as anaphylaxis and seldom outgrow the intolerance.

Ara h 1 was identified as a major allergen by Burks et al (Burks 1991). *Ara h* 1 has molecular mass of 63.5 kDa and is stable to treatments with heat and digestive enzymes. This protein has 23 linear epitopes, of which 4 epitopes show IgE-binding activity to IgE from more than 80% of peanut-allergic patients (Burks 1997).

Moreover, *Ara h* 2 (17 kDa) (Burks 1992) and *Ara* h 3 (14 kDa) have been identified as major allergens.

Soybeans are the other members of the legume family that cause hypersensitive reactions, predominantly in infants and young children.

Although legumes show extensive cross-reactivity by in vitro methods such as RAST inhibition and skin testing, most peanut-allergic patients can ingest other legumes with no adverse reactions (Bernhisel-Broadbent 1989)

Soybeans contain multiple allergens. Soybean globulin fractions 11S, 7S and 2S have IgE-binding activity as indicated by Shibasaki et al (Shibasaki 1980). The 2S fraction had the highest potency inhibiting RASTs for all fractions. When the fractions were heated to 80□ for 30 min, the inhibitory activity of the 2S fraction was enhanced, where the others decreased to 39 to 75% of that of the native globulin.

Gly m Bd 30K has been identified as a major allergen by Ogawa et al (Ogawa 1991). This protein corresponded to the oil-body-associated protein described by Kalinski et al (Kalinski 1990). Gly m Bd 30k possesses 30% sequence homology to *Der p* 1, major dust mite allergen, which is also a thiol protease (Ogawa 1993). This allergen has 5 linear IgE-epitopes (Helm 1998.).

Alpha subunit of β-conglycinin and Gly m Bd 28K have also IgE-binding activity.

2. Cereals

Cereals include wheat, barley, rye, oats, corn (maize) and rice. Rice is reportedly one of offending foods of atopic dermatitis in Japan. Matsuda et al (Matsuda 1988) have identified a 16 kDa rice protein as one of the major allergens in rice seeds. Subsequently, when cloned and sequenced, several proteins with a molecular mass of 14-16 kDa have 80% or more identities in DNA sequence and belong to the same multigene family (Izumi 1992). IgE-binding of the 16 kDa rice protein could be inhibited by preincubation of sera with not only rice extract, but also extracts of wheat, corn, Japanese millet, and Italian millet, suggesting that this protein is responsible for the cross-reactivity among cereal grains in the Poaceae family (Urisu 1991). Indeed, the 16 kDa rice protein shows significant homology to the alpha-amylase/trypsin inhibitor family from wheat and barley (Izumi 1992).

Wheat flour induces allergic reactions by ingestion and inhalation. The bronchial constriction by inhalation of the flour is noted as Baker's asthma, one of the occupational asthma. Gómez et al (Gómez 1990) have identified a 15kDa salt-soluble allergen in wheat flour using sera from baker's asthma. The corresponding allergen with a molecular mass of 14.5 kDa has been found in barley flour (Barber 1989). These allergens are glycosylated monomeric subunits of alpha-amylase/trypsin inhibitors (Sánchez-Monge 1992)

3. Buckwheat

Buckwheat is one of "the notorious foods" to trigger severe hypersensitive reactions such as generalized urticaria, asthma, and anaphylaxis even by ingestion of a small amount of buckwheat flour.

Yanagihara and colleagues (Yanagihara 1980) described some allergens with molecular mass of approximately 100 kDa, 50 kDa, and 17 kDa as the major allergens of buckwheat seed. In contrast, Yano et al (Yano 1989) reported that a buckwheat component with a lower molecular mass of 8-9 kDa had the greatest IgE-binding activity. At least 14 buckwheat proteins are capable of binding to IgE as demonstrated through immunoblotting assay using 15 patients' sera. Protein bands with molecular masses of 24, 26, 60-70 kDa were recognized by IgE from more than 50% of the patients tested. All of the patients' IgE bound to the 24-kDa protein (BW24KD) (Urisu 1994). Homology search of the N-terminal amino acid of BW24KD demonstrated the 37.9 to 48.3% identity with a globulin from dicot species (garden pea, soybean, upland cotton, mouse-ear cress, rape, pumpkin, cucurbit, sunflower), 51.7% identity with a globulin from monocot species (rice, oat), and 31.0% identity with a protein from the Douglas fir conifer. These are all storage proteins, 11S or 12S globulins, consisting of a heavy A chain and a light B chain, and processed from a common precursor polypeptide. The N-terminal amino acid sequences of BW24KD correspond to the B chain of the proteins.

4. Fruit and vegetable

Fruit and vegetable allergens are generally not stable to denaturation by heat and enzyme-digestion. Commercially available antigens for diagnosis are not reliable because of their loss of allergenicity. Prick to prick tests using fresh fruit or vegetable is recommended for skin test.

The symptoms caused by fruits and vegetables are mainly oral allergy syndrome (OAS), in which offending foods trigger local symptoms, usually in the form of oral itching, lip swelling, and labial angioedema, but also glottis edema, or in rare cases, systemic anaphylactic reactions. OAS is dominantly seen in adults and complicated with pollinosis. This association between OAS and pollinosis is considered to be due to the shared allergens between fruit/vegetable and pollens. These cross-reactions have been described between watermelon and ragweed pollen (Enberg 1987); celery and mugwort pollen (Wüthrich 1990); potato and grass pollen (Calkhoven 1987); and apple and birch pollen (Ebner 1991). Ebner et al. provided the first conclusive demonstration that antigens in birch pollen and apple share allergenic epitopes (Ebner 1991). Indeed, there is 64.5% homology in the amino acid sequence between *Bet v* 1, a major allergen of birch pollen, and *Mal* d 1, a major allergen of apple (Vanek-Krebitz 1995.). Many of these cross-reactions are caused by pathogenesis-related proteins and profilins.

Recently, the prevalence of pollinosis has been reported to be steadily increasing all over the world. If this phenomenon is true, fruit and vegetable allergy might be increased. Further study is needed.

Hypersensitivity to fruits and vegetables, especially avocado, banana, chestnut, fig, and kiwi, is sometimes associated with latex allergy. This association is termed latex-fruit syndrome (Brehler 1997), of which the development is triggered by the cross-reactive proteins between fruits/vegetables, and latex. These shared proteins include pathogenesis-related (PR) -2 type proteins (β-1,3-glucanase) (Yagami T1998), PR-3 type proteins (basic (class I) chitinases) (Diaz-Perales 1998 Chen 1998) and PR-4 type proteins (chitinases similar to potato Win proteins) (Hänninen 1999 Van Damme 1999).

Lipid transfer proteins (LPTs) (PR-14 type proteins), named for their ability to transfer phospholipids from liposomes to mitochondria, form a family of 9 kDa polypeptides that is widely distributed throughout the plant kingdom. Most of these molecules contain 8 conserved cysteines forming 4 disulfide bridges, which make them highly resistant to harsh temperature and pH changes (Kader 1996). LPTs are the most important allergens of the Prunoideae, such as peach, apricot, plum and cherry, when no pollinosis is involved (Pastorello 1994).

EMERGING FOOD ALLERGENS

Hypersensitive reactions to ingestion of kiwi fruit (Fine 1981) and avocado fruit (Blanco 1994) have been reported since these exotic fruits have become more common as food in western countries. The prevalence of kiwi fruit and avocado allergy seems to be low in food allergic individuals. Nevertheless, IgE mediated reactions after ingestion of these fruits can mainly induce OAS, although uncommonly followed by anaphylactic shocks. These allergies are associated with latex allergy as mentioned above. The two major kiwi allergens are Actinidin (*Act c* 1) (Pastorello 1998) and a 43 kDa-Allergen (Act c 2) (Möller 1997).

A 32 kDa major avocado allergen, Per a 1, was purified and cloned by Sowka et al (Sowka 1998).

INHALATION OF FOOD ALLERGENS

Generally, the sensitization to foods occurs in gastrointestinal tract in which foods are fragmented by digestive enzymes. Therefore, the stability against digestive enzymes is one of the characteristics of food allergens (Astwood 1996). In some food allergies, however, individuals become sensitized through the respiratory route (Breiteneder 2000). One is the case of OAS. As mentioned above, the sensitization to foods such as fruits and vegetables possibly occurs through inhalation of pollens with cross-allergenicity. Another mechanism of sensitization is mediated by the inhalation of the foods themselves, particularly following occupational exposure in the food-processing industry.

Inhalation of several food allergens induces occupational asthma through the respiratory rout. Milk proteins have been implicated in the development of occupational asthma in two individuals. The causative allergenic protein is casein in one case (Rossi 1994) and alpha-lactalbumin in another case (Bernaola 1994).

Bird-egg syndrome is unique egg allergy in the respect that patients are sensitized through inhalation of bird serum antigens. Subsequently, they show hypersensitive responses to ingestion of chicken egg yolk. The responsible allergen is alpha-livetin, serum albumin of 70 kDa (Szepfalusi 1994). This protein is also present in the yolk of the chicken egg.

Flour or organic dusts from legumes sensitize and trigger asthma through inhalation. Offending legumes previously described were soybean (Anto 1989), caster bean (Ordman 1955), green bean (Igea 1994) and green coffee bean (Karr 1979).

Fish and crustacea are involved in occupational asthma, particularly in the seafood industry (Malo 1993)

Baker's asthma is caused by inhalation of wheat, rye and barley flour especially in individuals working in the baking industry. Gomez et al (Gomez 1990) identified the major allergens associated with baker's asthma as members of the alpha-amylase inhibitor family from wheat endosperm. The major barley allergen, a 14.5 kDa barley endosperm protein was cloned by Mena et al (Mena 1992). This protein corresponds with a glycosylated monomeric member of a multigene family of inhibitors of alpha-amylase/trypsin from cereal grains.

NON IGE-MEDIATED FOOD ALLERGIES

Gastrointestinal food hypersensitivity such as food-induced enterocolitis syndrome, food-induced eosinophilic protocolitis and food protein-induced enteropathy is generally seen in young infants who present protracted vomiting and diarrhea. Cow's milk, egg and soybean proteins are most often responsible. Celiac disease is more severe enteropathy leading to malnutrition. Total villous atrophy and dominant cellular infiltrate are associated with sensitivity to gliadin, the alcohol-soluble portion of gluten found in wheat, oat, rye and barley.

Measurement of specific IgE antibody is not useful in diagnosis of these non-IgE mediated food allergy. Elimination dietary tests and oral challenge tests are relevant for diagnosis of these non-IgE mediated food allergy. Furthermore, intestinal biopsy is required for definitive diagnosis.

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