

UNIT NO. 3

THE ROLE OF FOOD ALLERGY IN ALLERGIC AIRWAY DISEASES

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ABSTRACT

Food allergies have been increasing over the last decades, in parallel with a general increase of allergy worldwide. However, epidemiological studies on food allergy are difficult to perform (especially when using questionnaires), and contain a number of pitfalls because of a considerable amount of false negative and false positive results. This is mainly because food can induce a number of abnormal reactions which are not food allergic reactions (i.e. food intolerance, aversion). The prevalence of food allergy is lower than inhalant allergy (such as house dust mite allergy). Only a few population based studies on food allergy in Asia have been published, showing higher prevalence in young children than in older children or adults. Clinical manifestations are variable, but are usually skin symptoms (urticaria, angioedema). Other symptoms can be rhinitis, asthma, and gastro-intestinal symptoms (FTT, vomiting and diarrhea). Symptoms resulting from other organs (especially psychological or neurological symptoms) are usually not due to food allergy. Diagnosis of food allergy is based on history – clinical examination, allergy testing (IgE and skin prick testing) and provocation testing. The double-blind placebo-controlled food challenge (DBPCFC), (performed in a hospital setting, under strict observation and with all emergency facilities available) is still the golden standard for the diagnosis.

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DEFINITION OF FOOD ALLERGY

Any abnormal reaction that results from the ingestion of food is considered an adverse food reaction. A number of types of adverse reactions are distinguished. The terminology is not always clear, as different researchers use different definitions. Usually, adverse reactions to food are divided into three groups: food intolerance, food allergy (including IgE-mediated reactions) and food aversions or phobias. Most researchers consider the term “food allergy” as an abnormal reaction from the human body in which the immune system is involved. The term “food allergy” is here used for all abnormal immunological reactions, not only for the IgE-mediated reactions. This definition is therefore different from all other allergic reactions, in which the involvement of IgE is pivotal. Any abnormal reaction to food in which the immune system is not involved is not considered as food allergic reactions.

Food Intolerance

Food intolerances are the most common type of adverse reactions to foods. It is a general term describing an abnormal physiologic response to an ingested food. A number of underlying causes have been identified which may be due to either the food or the host. Usually, the symptoms are diarrhea, tummy pain and vomiting. The most common types are:

a. Intolerance caused by toxic contaminants of food

Examples: high histamine in scombroid fish poisoning, toxins from bacteria, such as Salmonella, Shigella and Campylobacter.

b. Intolerance caused by pharmacologic properties of the food

Examples: alcohol, caffeine in coffee, tyramine in aged cheeses or food poisoning by foods containing heavy metals or pesticides.

c. Intolerance caused by infected food

Examples: food containing bacteria, parasites or viruses (such as rotavirus infection, by drinking contaminated water)

d. Intolerance caused by characteristics of the host

Example: metabolic disorders, such as lactase deficiency, causing intolerance to milk.

Food Allergy

Food allergy is more common in young children. This type of reaction may occur after only a small amount of the food is ingested (is non-dependent from the amount of food, although large amounts may induce more severe reactions), and is unrelated to any physiologic effect of the food.

Usually, food allergy is caused by an underlying IgE-mediated hypersensitivity reaction, but other types of immunological reactions have been identified.

Food allergic reactions include:

1. IgE-mediated reactions
2. Non-IgE-mediated reactions

Various types of non-IgE-mediated food allergic reactions have been identified, including cellular-mediated mechanisms (involving T lymphocytes, these reactions have a delayed onset), mixed types (involving IgE and cells, such as in eczema) and other mechanisms constituting a large variety of reactions. Of some, the underlying mechanisms are unknown. In some, immune complexes or complement are involved.

Food Aversion

Food aversions or food phobias are psychological reactions that may mimic food allergy. Moreover, some children who are food allergic will refuse the foods that cause allergic reactions.

Sometimes, distinguishing food allergy from food aversion is very difficult, and parents should not persist to give food that has caused symptoms in their children. Typically, real food aversion cannot be reproduced when the child ingests the food in a blinded fashion.

Apart of the above different types of adverse food reactions, a number of chronic diseases can mimic food allergy. There is a long list of diseases, of which the most common are: diseases of the gastrointestinal tract (pyloric stenosis, hiatus hernia, diseases of liver, gallbladder, and pancreas) and enzyme deficiencies or metabolic diseases.

MECHANISMS OF FOOD ALLERGY

IgE-Mediated Food Allergy

This type of reaction occurs in genetically predisposed patients and is the result of an excessive production of food-specific IgE antibodies. These antibodies bind (through receptors) on different cells, such as mast cells, basophiles, and other cells. After the food allergens reach the food-specific IgE antibodies on mast cells and basophiles, various mediators such as histamine, prostaglandins, and leukotrienes are released. These mediators then induce different symptoms of immediate hypersensitivity. The activated mast cells may also release various cytokines that play a part in inflammatory reactions (also called late-phase reactions).

Non-IgE-Mediated Food Allergy

A large variety of non-IgE-mediated types of FA have been described. However, these types are much less documented than the IgE-mediated type, and, therefore, the scientific evidence supporting this mechanism is limited. The most important types of non-IgE-mediated food allergic reactions are:

- Type III reactions involving immune complexes (= soluble antigen-antibody complexes that affect functioning of different organs) have been described. However, there is little support from systematic studies that these complexes are able to mediate FA.
- Type IV reactions (i.e. cell-mediated reactions, as called delayed type of hypersensitivity) have been suggested in several disorders where the clinical symptoms do not appear until several hours after intake of the suspected food. This type of immune response may contribute to some food allergic reactions (such as enterocolitis) but significant supporting evidence of a specific cell-mediated hypersensitivity disorder is lacking.
- Mixed types involving IgE and cellular hypersensitivity reactions have been suggested and some researchers consider these mixed types of reactions to be involved in atopic dermatitis. Recently a role of Th17 (a newly discovered type of T helper lymphocytes, that can drive inflammatory reactions) has been attributed into this type of reactions.

SYMPTOMS OF FA, AND SYMPTOMS THAT ARE NOT CAUSED BY FA

The most common clinical presentation of an IgE-mediated FA is the sudden appearance of urticaria (hives), within minutes after intake of a food, such as peanuts, seafood or fish. In more severe cases, there is also presence of angioedema, presenting as swelling of lips or eyes. When the FA is really very severe, symptoms of difficult respiration (asthma, difficult breathing) and even anaphylactic shock (drop in blood pressure and coma) can appear, being potentially fatal and needing urgent treatment.

Table 1: Sequences of a typical “full blown” IgE-mediated food allergic reaction

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- Itch (neck, trunk)
 - Urticaria (spreading over the whole body)
 - Swelling of lips – eyes
 - Swelling of tongue – itchy throat
 - Difficult breathing – wheezing + rhinitis (sneezing) + conjunctivitis
 - Fainting – coma – anaphylactic shock
-

SYMPTOMS OF IgE-MEDIATED FOOD ALLERGY

Skin and respiratory food allergic reactions

The skin is the most commonly affected target organ in IgE-mediated FA. The ingestion of food allergens can induce either immediate cutaneous symptoms or aggravate chronic symptoms (such as eczema). Acute urticaria and angioedema are the most common manifestations of FA, generally appearing within minutes of ingestion of the food allergen.

If respiratory symptoms appear, it is usually in association with skin symptoms, and rarely as isolated symptoms of FA. Symptoms may include peri-ocular erythema (rash surrounding the eyes), itchy eyes, tearing, nasal congestion (blocked nose), sneezing, runny nose, cough, voice changes, and wheezing and difficult breathing.

A very well described entity in this group is The Oral Allergy Syndrome (OAS). OAS is considered a form of contact urticaria induced by exposure of the oral and pharyngeal mucosa to food allergens, being a consequence of a cross-reactivity between certain foods and inhaled allergens. The syndrome is classified by some researcher under the group of gastrointestinal symptoms of FA. Affected patients may present with rapid onset of symptoms with increasing severity, from mild itching of the lips, mouth and throat, to lip and tongue swelling, to severe angioedema of the throat (pharyngeal mucosa) up to life-threatening emergencies, such as anaphylaxis.

OAS is an important alarm manifestation in subjects at risk for severe allergic reactions. Generally, OAS is related to plant-derived foods only, but also severe reactions to animal-derived foods may be preceded and accompanied by local oral symptoms. The triggering food may be dependent on geographically different nutritional habits and may thus vary

from place to place. Patients with allergic rhinitis to certain airborne pollen (especially birch, mugwort and ragweed) are frequently afflicted with OAS (Europe, USA, seldom in Asia).

Patients with birch pollen sensitization often have symptoms following the ingestion of stone fruits and pip fruits, but also after vegetables such as carrots or celery, nuts, and legumes. Patients with ragweed pollen sensitization may experience allergic symptoms following contact with certain melons (watermelon, cantaloupe, honeydew, etc) and bananas.

Other examples are:

- Allergy to seafood in patients with house dust mite allergy
- Allergy to vegetables and fruits in patients with latex allergy (such as in children with spina bifida)

Gastrointestinal symptoms of FA

IgE-mediated gastrointestinal symptoms of FA include immediate gastrointestinal hypersensitivity and allergic eosinophilic gastroenteritis.

Immediate gastrointestinal hypersensitivity

This type of hypersensitivity may accompany allergic symptoms in other organs. The symptoms vary but may include nausea, abdominal pain, abdominal cramping, vomiting, and/or diarrhea. Symptoms may resemble those of a gastrointestinal infection and need to be distinguished from it. Complete elimination of the suspected food allergen for up to two weeks will lead to resolution of symptoms. Diagnosis is usually made by a food challenge, although positive skin prick tests suggest FA. Foods that have been associated with immediate gastrointestinal hypersensitivity are milk, egg, peanut, soy, cereal and fish.

Allergic eosinophilic gastroenteritis

This type of FA is a mixed IgE-mediated and non-IgE-mediated type of FA. It is a disorder characterized by infiltration of the gastric and/or intestinal wall with eosinophils and raised numbers of eosinophils in the blood. Patients presenting with this syndrome frequently have postprandial nausea and vomiting, abdominal pain, diarrhea, failure to thrive or weight loss. Diagnosis is difficult, and is usually based upon an appropriate history and a gastrointestinal biopsy demonstrating a characteristic eosinophilic infiltration. However, multiple biopsies may be needed because the eosinophilic infiltrates may be quite patchy. Patients with this disease usually have other atopic symptoms (eczema), including multiple food allergic reactions, elevated IgE levels, positive skin prick tests and elevated blood eosinophils. Other symptoms are anemia and low levels of proteins in the blood (hypoalbuminemia). An elimination diet of up to 12 weeks may be necessary before complete resolution of symptoms occurs.

A separate entity, related to eosinophilic gastroenteritis, is the eosinophilic oesophagitis (sometimes with gastritis), which is a chronic allergic inflammatory condition of the esophagus, which most often results in dysphagia, bolus impaction, heartburn

or chest pain. Of particular importance is the differentiation from other inflammatory diseases of the esophagus, especially gastro-esophageal reflux disease. Biopsies from the proximal to the distal esophagus demonstrating >15-20 eosinophils per field help to make the diagnosis. Besides avoidance of the responsible food allergens, common treatment regimens in children and adults involve also the ingestion of topical corticosteroids.

SYMPTOMS OF NON-IGE-MEDIATED FOOD ALLERGY

A large variety of non-IgE-mediated food allergic disorders has been described. Usually, these disorders are much less documented than the IgE-mediated type of FA. Among the many disorders, the most important are:

Dietary protein enterocolitis (also called protein intolerance)

This is a rare disease of young infants, usually starting between the ages of 1 week to 3 months. The typical symptoms are isolated to the gastrointestinal tract and consist of recurrent vomiting and/or diarrhea. The symptoms can be severe, causing dehydration. The disease is usually associated with a non-IgE-mediated allergy to cow's milk or soy milk; while in older infants, egg has been reported to be responsible for the disease. Elimination of the offending food allergen generally will result in improvement or resolution of symptoms within 72 hours. Skin prick tests or determination of specific IgE in the blood are negative. Diagnosis is based on an oral food challenge, which can result in severe symptoms. The disease usually settles by the age of 18-24 months.

Dietary protein proctitis - colitis

This disease usually presents during the first months of life and is often secondary to cow's milk or soy protein hypersensitivity, affecting the large intestinal and terminal intestinal segment. Infants with this disorder often do not appear ill, have normally formed stools, and generally are discovered because of the presence of blood in their stools. It is accepted, without well-controlled studies that the disease resolves by age 6 months to 2 years of allergen avoidance.

Celiac disease

Celiac disease is an extensive enteropathy leading to malabsorption and failure to thrive. Total villous atrophy (destruction of small intestine) and an extensive cellular infiltrate are associated with sensitivity to the alcohol-soluble portion of gluten found in wheat, oat, rye, and barely, also called gluten intolerance. Gluten is found mainly in foods but may also be found in products we use every day, such as stamp and envelope adhesive, medicines, and vitamins. Because the body's own immune system causes the damage, celiac disease is considered an autoimmune disorder. However, it is also classified as a disease of malabsorption because nutrients are not absorbed. Celiac disease is also known as celiac sprue, non-tropical sprue, and gluten-sensitive enteropathy. It is a genetic disease, meaning it runs in families. Sometimes the

disease is triggered — or becomes active for the first time — after surgery, pregnancy, childbirth, viral infection, or severe emotional stress. Patients often have presenting symptoms of diarrhea or “steatorrhea” (fatty stools), abdominal distention and flatulence, weight loss, and occasionally nausea and vomiting. However, a person with celiac disease may have no symptoms. People without symptoms are still at risk for the complications of celiac disease, including malnutrition. The longer a patient goes undiagnosed and untreated, the greater the chance of developing malnutrition and other complications. Anemia, delayed growth, and weight loss are signs of malnutrition: the body is just not getting enough nutrients.

SYMPTOMS THAT ARE (USUALLY) NOT CAUSED BY FOOD ALLERGY

FA usually manifests itself through reactions from the skin (urticaria, eczema), the respiratory tract (rhinitis, asthma) or the gastrointestinal tract (vomiting, diarrhea). Diseases from other organs (kidney, brain, heart, etc) are usually not due to food allergy, especially neurological or psychological disorders. However, often parents believe that FA is involved in their child's problems. Neurological, psychological or psychiatric diseases are usually not caused by FA. These include: sleep or learning problems, hyperactivity, autism and migraine.

Manifestations of the skin, the respiratory tract and the gastrointestinal tract are the most common symptoms of food allergy. Symptoms resulting from other organs (especially psychological or neurological symptoms) are usually not due to food allergy!

FOODS THAT CAUSE FOOD ALLERGY AND THEIR GEOGRAPHIC ASPECTS

In theory, worldwide, all foods can cause food allergy, as foods contain proteins that are considered foreign by the human immune system and might induce IgE production in all human beings with an underlying, genetically-determined allergic constitution. However, most food allergic reactions are caused by a limited number of foods, are age specific and have their own geographical distribution. In general, in young children, FA is mainly caused by cow's milk, hen's egg, soy, and wheat. In older children, FA is usually caused by seafood, peanut, fish, and fruits or vegetables (cfr. OAS).

Food Allergy in Asia

Only a few population based studies on FA in Asia have been published. Prevalence of FA in Asian children were found to be 4% in Singapore and rural China, to as high as 12% in Seoul, Korea and Japan. The exact reason for this wide range in prevalence is not known, but could mirror that these differences are related to survey methodologies rather than to a true difference. Furthermore, it has been observed that certain specific foods consumed mainly in the Asian region have resulted

in allergies that are unique for their respective populations.

An example of this is that allergy to bird's nest from swiftlets has been described in the Chinese population in Singapore, Malaysia and Hong Kong. It is one of the most common causes of severe FA, leading to anaphylaxis in Singapore children. Bird's nest is a popular Chinese delicacy believed to have health benefits. Similarly, royal jelly, another food that is very popular amongst the Chinese, has also been reported to trigger asthma and anaphylaxis in Hong Kong and in ethnic Chinese in Australia. Buckwheat causing anaphylaxis has been observed in Japan, Korea and China. Buckwheat is consumed in large quantities by these populations in the form of noodles or soba. Similarly, chickpeas, a staple food in children living in India and chestnuts in Korea have been described as common triggers immediate hypersensitivity in these populations. These patterns of food allergies in populations of East Asia are not commonly recognized elsewhere. It is more likely that exposure rather than genetic factors are responsible for these observations.

Fish allergens

The fish from tropical waters consumed in Asia are quite different from temperate fish. Consumption practices are also quite different. Fish is a weaning food amongst many populations in Asia. This contrasts with the western diet, where fish is regarded as a highly allergenic food, and national guidelines on allergy prevention have recommended to avoid fish till the age of three years. There is an impression that fish allergy in Asia is less common than in the western world, but this has not been substantiated by systemic study. Hence, the allergenicity of tropical fish is comparable with cod. The reason(s) that fish allergy is not highly prevalent in tropical Asia, despite high consumption and exposure in early life is not obvious.

Peanut Allergy

To date, there have been no published reports on population based prevalence studies on peanut allergy in Asia, but the impression amongst clinicians practicing in Asia is that it is still uncommon, although increasing. In Singapore, a peanut allergy survey showed that the prevalence of peanut allergy was 0.3%, or about a third of those reported in western populations. The notion that peanut allergy is not as prevalent in Asia is also substantiated by hospital-based studies on anaphylaxis. Studies from Singapore have shown that severe peanut allergy resulting in anaphylaxis was very uncommon. These data are similar to those from Thailand and Hong Kong where no cases of peanut allergy were recorded. This apparent low prevalence rate of peanut allergy in Asian populations is not likely due to lack of exposure, but more likely due to immune tolerance.

Crustacean Shellfish Allergy

In contrast to the low prevalence of peanut and fish allergy, crustacean shellfish appears to be an important cause of food allergy in Asia. In terms of severity, hospital-based studies on anaphylaxis show that crustacean shellfish are one of the most important food triggers in Singapore, Thailand and Hong Kong. Interestingly, this phenomenon appears to be reversed in

Western populations with less severe crustacean shellfish allergy in comparison to peanut or fish allergy. Only a few or no cases of crustacean shellfish-induced anaphylaxis were reported in hospital-based surveys in children in UK and Italy, and children and adults in Australia. Instead, peanut triggered anaphylaxis predominates in these populations.

Like fish, crustacean shellfish is a major component of the East Asian diet. However, unlike fish allergy, this increased exposure may explain the high prevalence of shellfish allergy in this region. Since exposure to fish and peanuts has not resulted in high prevalence of allergy to these food allergens in Asia, it is tempting to speculate an alternative hypothesis for the high prevalence of shellfish allergy. The high prevalence of inhalant dust mite and cockroach allergies in tropical and subtropical Asia may contribute to cross reacting allergens through the allergen tropomyosin (cfr. OAS). This hypothesis is supported by the correlation of sensitization to shrimp and cockroach allergens in Singapore children, as well as population studies on unexposed Jews who observed Kosher dietary rules, which showed that sensitization to shrimps was related to cross reacting tropomyosin allergens in house dust mites.

DIAGNOSIS OF FOOD ALLERGY

Medical history and physical examination

The evaluation of FA must begin with a carefully taken and focused medical history and physical examination. The true value of a medical history is largely dependent on the parent's (or child's) recollection of symptoms and the examiner's ability to differentiate disorders provoked by FA and other disorders. The history may be directly useful in diagnosing FA in acute events (such as acute anaphylaxis or acute urticaria). However, problems arise when the reaction is delayed (such as in some non-IgE-mediated reactions), or occurs after several foods are ingested. An example of this is that in children with eczema, less than 50% of the reported food allergies (suspected by parents) could be substantiated by provocation tests. Moreover, if reactions occur less than two or three times weekly, keeping a food diary is cost-effective and may suggest an offending agent.

Several pieces of information are important to establish that a food allergic reaction occurred:

1. Identification of the food that have provoked the reaction
2. The quantity of the food ingested (FA can occur after minimal amounts were ingested)
3. The length of time between ingestion and development of symptoms (FA usually within minutes)
4. A detailed description of all the symptoms
5. If similar symptoms developed on other occasions when the food was eaten
6. If other factors are necessary (e.g. some types of FA occur preferentially after exercise)
7. The length of time since the last reaction

A diet diary has been frequently utilized as an adjunct to the medical history. Parents (or children) are asked to keep a chronological record of all foods ingested over a specified period of time and to record any symptom they experience in the child during this time. The diary can then be reviewed to determine if there is any relationship between the foods ingested and the symptoms experienced. However, uncommonly this method will detect an unrecognized association between a food and a patient's symptoms. But as opposed to the medical history, information can be collected on a prospective basis that is less dependent on a patient's or parent's memory.

An elimination diet is frequently used both in diagnosis and management of FA. If a certain food is suspected of provoking the FA, it is completely eliminated from the diet. The success of an elimination diet depends on several factors, including the correct identification of the allergen(s) involved, the ability of the patient to maintain a diet completely free of all forms of possible offending allergen, and the assumption that other factors will not provoke similar symptoms during the study period. The likelihood of all these conditions being met is very low. Therefore, elimination diets are rarely diagnostic of FA, particularly in chronic disorders such as eczema. Moreover, it is very difficult to avoid food totally, as sensitization can also occur through touching or smelling of food, and in infants, who are totally breast fed, mother's milk can contain traces of food that the mother took (and traces of food can be sufficient to induce FA).

Skin prick testing and determination of specific IgE (RAST or CAP test)

Skin prick testing (SPT) and IgE determination in the blood by RAST or CAP only evaluate the IgE-mediated mechanisms, and give no information on non-IgE-mediated food allergic reactions. Usually, SPT are highly reproducible and often utilized to screen patients for suspected IgE-mediated FA.

For SPTs, a drop of the food extracts and appropriate control SPT (i.e. histamine as positive control and saline as negative control) are applied on the skin and the skin is gently lift up in the drop, using a small needle (prick or puncture technique). A food allergen eliciting a wheal reaction (=a swelling, and not an erythema of redness of the skin) of at least 3mm greater than the negative control is considered positive, and anything else is considered negative. However, there are two important remarks on SPT. First, a positive SPT to food indicates the possibility that the child has symptomatic reactivity to that specific food but is not a proof (in general, the positive predictive accuracy seems to be less than 50%). It means that the child has specific IgE in the blood, but this can also be found in healthy children. Second, a negative SPT confirms the absence of an IgE-mediated reaction (overall negative predictive accuracy is greater than 95%), but does not mean that the food cannot induce non-IgE-mediated reactions. Furthermore, both these remarks are only justified if appropriately standardized and good quality food extracts are utilized.

The SPT should be considered an excellent means of excluding IgE-mediated FA, but is only suggestive of the

presence of clinical FA. There are minor exceptions to the general statement:

- 1) A positive SPT to a food ingested in isolation which provokes a serious systemic anaphylactic reaction may be considered diagnostic.
- 2) Children less than one year of age may have IgE-mediated FA without a positive SPT, or with minimal SPT positivity, and children less than two years of age may have smaller wheals. Usually, in young children a positive SPT is considered a SPT that has a wheal of $\frac{3}{4}$ of the histamine reaction, dependent of medical history.
- 3) IgE-mediated sensitivity to several fruits and vegetables (apples, bananas, kiwi, pears, melons, carrots, celery, etc) are frequently not detected with commercial reagents, presumably secondary to the liability of the responsible allergen in the food.

An intradermal test (injection of the allergen in the skin)

This test is a more sensitive tool than the SPT, but is far less specific when compared to oral provocation tests, and results in a large number of false positive results. Furthermore, there are no studies on the sensitivity and specificity of an intradermal test in children, and it is even assumed that healthy children easily can show positive intradermal tests. In one study, no patient who had a negative SPT but a positive intradermal test to a specific food had a positive oral challenge to that food. In addition, intradermal skin testing increases the risk of inducing a systemic reaction compared to SPT, and should not be used in children.

Determination of specific IgE (by RAST or CAP method) in the blood is often used to screen for IgE-mediated FA. In general, these measurements performed in high quality laboratories provide information similar to SPT, although it seems from a number of studies that SPT are more sensitive, especially in young children. Comparison of SPT and specific IgE determination is shown in the following table:

Table 2: Comparison of SPT and specific IgE determination

SPT	IgE
sensitive (young children)	less sensitive than SPT
less specific than IgE	specific
cheap	expensive
immediate results	wait for results (according to lab)
need normal skin	for all patients
antihistamines suppress SPT	no effect of any medication
not very painful	painful
patient (and parents) can see the result	patient has to be informed by doctor

The double-blind placebo-controlled food challenge

The double-blind placebo-controlled food challenge (DBPCFC) is the golden standard to diagnose adverse reactions to food, including FA. Moreover, it is the only test to diagnose non-

IgE-mediated FA, as all other tests for non-IgE-mediated FA lack sensitivity and specificity. The DBPCFC has been utilized successfully by many investigators in both children and adults. The foods to be tested are based upon history and/or SPT (or specific IgE) results.

This test is the best means of controlling for the variability of chronic disorders (such as eczema) any potential temporal effects, and acute exacerbations secondary to reducing or discontinuing medications. Particularly psychogenic factors and observer bias are eliminated. The use of native fresh food for challenge is the most reliable way, although these foods need to be administered blindly, usually through a gastric tube. Alternatively, lyophilized foods (in capsules) can be administered, but sometimes the patient receives insufficient challenge material to provoke a reaction (especially in cases of non-IgE-mediated FA) or the lyophilization of the food antigens has altered the allergic potency of relevant allergens (e.g. fish).

A contra-indication for a DBPCFC is a history of an obvious severe reaction to a specific food, as the challenge might induce severe reactions (example: a clear history of anaphylactic shock due to peanuts or seafood).

Practical approach to diagnosing food allergy

The diagnosis of FA is a complex process utilizing a careful history, physical examination, SPT (or specific IgE determination), appropriate exclusion diet, and, if necessary, a DBPCFC. Any other test has no value in the diagnosis. These tests include: food-specific IgG or IgG4 (commonly advised and very expensive), determination of food-antigen-complexes in the blood, and other blood tests assessing the immune system. Moreover, intradermal tests or intracutaneous tests with allergen have never been shown to be of value in diagnosing FA.

It is very important that the medical care provider makes an unequivocal diagnosis of FA. Nowadays, there are still too many children are labeled "food allergic" based on non-scientific criteria or suspicion. If these practices continue, over $\frac{1}{4}$ of the population will continue to alter their eating habits, which is based on misconception of FA, and which may induce other problems as stigmatization, social isolation (children are not allowed to attend birthday parties) and, even worse, unnecessary malnutrition caused by extensive and useless diets.

PROGNOSIS OF FOOD ALLERGY: PERSIST OR GROW OUT?

FA in young children is usually a favorable dynamic process in terms of long-term prognosis, as most youngsters will grow out of their FA. This is mainly the case for IgE-mediated allergy for cow's milk, soy and egg. Usually, infants grow out of a cow's milk or soy allergy by the age of two years, and most of them grow out of an allergy to hen's egg by the age of four years. This is also the case for non-IgE-mediated allergies of infancy. However, recent studies on severe allergy to cow's milk and hen's egg have shown less favorable results. Children with a severe allergy to

these food might have persistent symptoms till puberty and it was shown that those children will additional allergies and high concentrations of IgE in the blood are the ones who tended to have persistent allergy to cow's milk or eggs. The slow rate of achieving tolerance to food reported in these recent studies is alarming, but the studies emphasize that most of the children became tolerant, and reappraisal is therefore crucial, even into teenage years.

Allergies to other foods may have a persistent character. Studies have shown that FA to peanuts (80%), tree nuts, seafood and fish can persist for a life time and that most children will not grow out of this type of FA. In adults the prognosis of a FA is even less favorable.

Whereas symptomatic FA is very specific in most patients, i.e. they do not react to more than one member of a botanical family or animal species, this is not the case in other patients, particular in pollen-related food allergy (i.e. OAS). Here, cross-reactions can even occur between phylogenetically distantly related species such as birch and kiwi or soy. Therefore, usually, due to this high variety of reactions, OAS persists during adulthood. Moreover, certain factors place some individuals at increased risk for more severe or persistent reactions to food:

1. A history of a previous severe anaphylactic reaction
2. A history of asthma, especially of poor controlled asthma
3. An allergy to peanuts, nuts, fish and seafood
4. Patients on medications such as beta-blockers or ACE-inhibitors (usually in adults)
5. Possibly being female

TREATMENT OF FOOD ALLERGY

If a food is identified, the only proven therapy is the strict elimination of the food of the child's diet. However, avoidance of foods is very difficult, as contact may occur because the food is hidden in commercially prepared foods or contact may also occur through smelling. Various case reports were published of patients experiencing severe reaction by smelling peanuts (in airplanes) or fish. Therefore, it is important to continue research on active treatment of food allergy, focusing on the induction of tolerance to foods (i.e. switch of the immune system from Th2-type to Th1-types immune reactions) and on effective treatment of severe reactions.

Various studies are ongoing on different types of immunotherapy to foods, including studies on sublingual immunotherapy (SLIT) with foods, such as peanuts. Nowadays, however, it is still too early to recommend these treatments, but in the near future effective desensitization programmes might become available for those children suffering from severe FA.

Several medications have been used in an attempt to protect children with FA. Among them are oral cromolyn, antihistamines, ketotifen, corticosteroids and prostaglandin synthetase inhibitors. Some of these medications modify FA symptoms in a therapeutic approach, but overall they have minimal efficacy or unacceptable side effects, especially when used long-term. However, the use of epinephrine is vitally important in acute anaphylaxis, and the prompt administration of epinephrine when symptoms of systemic reactions to foods develop cannot be overemphasized. In these cases Epipen (0.3mg) and Epipen Jr. (0.15mg) should be given intramuscularly immediately in a dose of 0.01 mg/kg.

Role of patient-parent education

Patient and parent education and support are essential for food allergic children. In particular, parents and older children who are prone to severe food allergic reactions must be informed in a direct but sympathetic way that these reactions are potentially fatal. In addition, when eating away from home (in schools or restaurants), food-sensitive children should feel comfortable to request information about the contents of prepared foods. Schools should also be equipped to treat anaphylaxis in allergic students (which has already been recommended by the American Academy of Pediatrics Committee of School Health in USA). Children older than seven years can usually be taught to inject themselves with epinephrine, and for younger children, parents and caregivers should be appropriately instructed. Physicians must be willing to explain and, with the parents, help instruct school personnel about these issues. In the home, it should be considered to eliminate the foods that can cause FA in children, or if this is not practical, warning stickers should be placed on foods with the offending food allergens. A variety of support groups, including parent groups of children with FA, can help provide information, advocacy, and education.

LEARNING POINTS

- **The following aspects of food allergy in children is covered.**
 - **The epidemiology of food allergy, especially in Asian countries.**
 - **The definition, the differential diagnosis and the distinction between food allergy and other adverse reactions to food.**
 - **The main manifestations of food allergy.**
 - **How to make a correct diagnosis of food allergy.**
 - **The prognosis of childhood food allergy.**
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