Current Practice

Food allergy in children

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Introduction
Paediatricians and general practitioners often encounter children with food allergy (FA). However, most medical professionals confuse food intolerance with true FA. Manifestations of FA vary with the underlying immune reaction and symptoms could be complex. Diagnosis is not easy and the available diagnostic tests are expensive and difficult to perform. This article will facilitate understanding the rationale behind using different tests to diagnose FA and the impact of correct diagnosis on the management of these children.

What is food intolerance?
Food intolerance is defined as non-immunological adverse reactions. In certain reactions, such as intolerances to lactose, caffeine and tyramine, well defined patho-physiological processes are involved[1]. However, the pathophysiology is not clear in food intolerances such as irritable bowel syndrome and other functional gastrointestinal disorders[2]. There are natural substances/chemicals in food that cause food intolerance. Monosodium glutamate (additive number-620/621) occurs naturally in tomatoes and mushrooms[3]. Certain individuals manifest allergy like symptom with ingestion. Vasoactive amines such as tyramine and histamine occur naturally in pineapple, cheese, chocolate, avocado, bananas, citrus food and red wine, known triggers of migraine[4]. When some fish are improperly stored, gut bacteria in fish convert naturally occurring histidine into histamine and cause allergy like symptoms[5].

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What is food allergy?
Immune reactions to food which are reproducible and absence of symptoms with avoidance of the given food indicate FA. There are many studies published on prevalence of FA. It has been speculated that there is a tendency for increase in prevalence of FA even among Asians since their economies grow and populations adopt a more westernised lifestyles[6]. In most studies the method employed varies from self-reporting questionnaires to more tedious double blind placebo controlled food challenges (DBPCFC)[7,8]. The chief drawback in most of these trials that have used DBPCFC to evaluate FA prevalence is the small sample size. Prevalence is overestimated with surveys using self-reported questionnaires because of over-reliance on lay perceptions on allergy[9,10]. According to Gupta *et al* self-reported prevalence of FA is 8% in the United States of America (USA)[9]. However, prevalence of FA, confirmed with food challenges and other immunological tests (e.g. skin prick testing, specific IgE levels), is reported to be 2.5% in a population based health survey in the USA[11]. The EuroPrevall FA survey based on questionnaires has reported a prevalence of 9% in certain administrative districts[10].

In Sri Lanka, there is no information on prevalence of FA or intolerance to date. We need more research in this area to reinforce the knowledge and preparedness among health care professionals and the public on managing FA.

Classification of food allergy
FA is classified immunologically into 3 main groups (Table 1). In non-IgE mediated FA, T cell responses are predominant and generally histological evidence and development of clinical features on exposure are needed for diagnosis.

Table 1: ***Classification of food allergy***

IgE mediated	Non-IgE mediated	Mixed
Urticaria / angioedema	Food protein induced entero-colitis syndrome	Eosinophilic gastroenteritis
Bronchospasm/ laryngospasm /rhinitis	Food protein induced proctocolitis	Eosinophilic oesophagitis
Diarrhoea/ vomiting		
Oral allergy syndrome		
Anaphylaxis		

IgE mediated FA

Gut is continuously exposed to foreign substances. The mucosal immune system builds up an immune reaction to reject some (pathogenic bacteria and toxins) while not reacting to gut commensals and most food proteins[12]. This immune exclusion of certain proteins will avoid many antigens getting absorbed through the gut. However, this complex mechanism of development of tolerance to food proteins is still not well understood and interaction of immune system with foreign proteins at early stages of life may determine the tendency for future allergic reactions with re-exposure[5,13]. Although any food can cause sensitization, only a few bring about allergic reactions in the majority. Cow's milk, fish, egg, wheat and shellfish are the most common among children[14]. However, they could develop tolerance to some of these allergens eventually. Thus, the spectrum of allergens in adults is different to those of children. In adults, tree nuts (hazel nut, pistachio, cashew, walnut etc.), peanuts, fish and shellfish are the commonest[15]. In Asian countries, certain FAs (chick pea, eggplant) are unique to specific regions[16,17].

In IgE mediated allergy onset of symptoms is immediate (within the first two hours) and reproducible upon exposure to the same allergen. Target organs are the skin, respiratory and gastrointestinal systems. Any combination of symptoms can occur and the most severe reactions lead to anaphylaxis. Cutaneous symptoms are the commonest (80%)[18]. Symptoms of the respiratory system alone are unlikely with food allergy and could occur as a part of a systemic reaction[18].

Anaphylaxis is initiated by binding of antigen to mast cell or basophil bound IgE in a sensitized individual. This leads to the release of tryptase and other chemo-attractants causing eosinophilic activation, smooth muscle spasms and increase in vascular permeability[19]. Although the commonest route is via ingestion, anaphylaxis is reported with skin contact of vomitus/food or inhalation of food particles[20]. Symptoms are most commonly related to skin, respiratory and cardiovascular systems. However, severe anaphylaxis can occur without any cutaneous manifestations[21]. Unlike drug/venom anaphylaxis, in food induced anaphylaxis respiratory symptoms predominate and isolated cardiovascular symptoms are rare[19]. Compared to venom/drug induced anaphylaxis gastrointestinal symptoms are common in food induced anaphylaxis (41%)[19]. Generally, symptoms could be uniphasic (symptoms do not recur during the same episode), biphasic (recurrence of symptoms about 8 hours after previous reaction) or protracted (symptoms last for hours or days)[19,22]. Diagnosis is primarily clinical. High serum tryptase levels could indicate anaphylaxis. Tryptase levels starts to rise within minutes and gradually revert to normal within the next 6-24 hours. Ideally blood samples should be collected within 5 hours[19].

Food dependent exercise induced anaphylaxis is rare in both children and adults. Symptoms occur typically 2 hours following intake of the trigger food with exercise. Wheat and shellfish are the commonest triggers and tomatoes, cheese, alcohol and peanuts are less common triggers[23].

Oral food allergy syndrome is generally seen in older children and adults. It is due to cross-reacting allergens of pollen (ragweed, grass) and raw fruits/vegetables (banana, apple, tomatoes)[24]. Individuals who are sensitized with pollen and having symptoms of rhinitis will react to fruits/vegetables with cross reacting allergens upon oral exposure[25]. Common symptoms are itchiness or swelling of mouth, throat, tongue etc. Itchy ears are reported[25]. Generally reactions are localized, but anaphylaxis has been reported in 2%[25].

Diagnosis of IgE mediated food allergy

A detailed history is the key to diagnosis of FA and investigations play a supportive role. FA is suspected when typical symptoms occur within a short time after ingesting food. Eczema could be triggered by FA[26] and children who are resistant to therapy can be tested for FA. Performing commercially available "food sensitivity panels" without a clear history could be misleading[27]. Certain in-vivo tests could be hazardous.

SPTs, measuring sIgE antibody levels and food challenges are useful in diagnosing IgE-mediated FA. Though food challenge is risky and inconvenient to perform it is yet the gold standard of the diagnosis of FA[27].

***sIgE levels in serum*:** Accurate methods (Immuno-Cap assay) are available both in a limited number

of private and government sector institutions in Sri Lanka. sIgE levels cannot differentiate between true allergy and sensitization but is helpful if the history is suggestive. On the other hand sIgE can be negative in the presence of a clear history. In such instances, oral food challenge is useful[28].

Skin prick testing (SPT): SPTs are done with commercially prepared allergens or real food items. Using fresh food items rather than commercial preparations is preferable since commercial preparations may become less sensitive with time. Similar to sIgE, sensitization and true allergy cannot be differentiated with SPT alone[28]. Individuals who are sensitized may or may develop symptoms on exposure. However, the size of the wheal/reaction correlates to the likelihood of true allergy[29]. Measurement of sIgE levels is preferable to SPT when the risk is high for anaphylaxis, in severe skin disease, while on continuous medication and with dermographism.

Oral food challenges[30]: Medical supervision is essential when food challenges are done. Currently there are no accepted standardized protocols to perform or to interpret DBPCFCs. All foods in question should be stopped for a minimum of 2 weeks before the challenge. Challenge could be performed in the open form in infants and in the single-blinded/double-blinded fashion in older children to minimise patient and physician bias. Once significant improvement with elimination is noted, challenge could be initiated. During this period symptomatic medications should be avoided as much as possible.

Management of IgE mediated FA

Withdrawal of the allergen from the diet and also avoiding skin contact or inhalation are important aspects of management of FA. Information needs to be conveyed to the patient and parent regarding avoidance of allergens. The family needs advice on how to check the food labels and facts on cross reacting food items. Cross reactivity among some food allergens are listed in table 2. It is due to specific antibody reaction not only to the primary allergen but also to different homologous allergens. Parents and patients should be aware of alternative terms of certain allergenic food items, e.g. sweet cream, casein indicate the presence of milk protein.

Table 2: ***Cross reacting allergens***[31]

Primary allergen	Cross reacting food items
Cashew	Other tree nuts e.g. walnut, pistachio
Shellfish	Cross reaction with other shellfish. Reaction with mollusks is less well defined.
Fish	Significant cross reactivity between other vertebrae species. Individual evaluation needed to determine tolerance.
Cow's milk	Goat's milk (90%), sheep milk (90%). Less cross reactive with camel milk.
Hen's egg	Duck and turkey eggs
Peanut, soy	Cross reactivity with other legumes uncommon

They should be told how to avoid unintended contamination of foods especially when they eat away from home. Contamination could occur while serving or cooking. Parents and children should be educated about management of anaphylaxis outside the hospital. Prompt recognition and administration of adrenaline are important. Australian Society for Clinical Immunology and Allergy (ASCIA) has published guidelines for proper prescription of adrenaline auto-injectors in management of severe FA outside hospital[32] (Table 3).

Table 3: ***Prescription of adrenaline auto-injectors for use in non-medical settings for emergency/first aid treatment of potentially life-threatening severe allergic reactions***[32]

Following is a list of situations where an auto-injector is prescribed. However, this is not comprehensive. o History of anaphylaxis o Food allergy and co-existing, unstable or moderate to severe, persistent asthma (Most food allergy related fatalities occur in those with unstable asthma) o Underlying mast cell disorder Auto-injector could be **sometimes** recommended. History of a generalized allergic reaction with one or more of the following, o Teenagers who will eat away from home or while not under parent supervision o Specific allergic triggers such as sea food, pea nuts and tree nuts. Allergic reactions occur even with small amounts and risk is not reduced with cooking. o Limited access to emergency medical care o Prolonged travel abroad
Dose: Children 10-20kg: EpiPen Jr (0.15 mg) Children over 20kg and adults: EpiPen (0.3 mg)

When a child is having FA, most family members are inclined to consume a restricted diet and they change their purchasing habits. Therefore, nutritional evaluation and advice, preferably by a dietitian, is essential. Use of immunotherapy in management of IgE-mediated FA is still under evaluation because the risks are high when compared to benefits of therapy[28].

Frequency of re-evaluation (e.g. serial sIgE levels) on follow up of these children depends on the food involved the child's age. Re-introducing foods into the diet could be considered when the child shows signs of tolerance clinically and immunologically. Most children with milk, egg, soy and wheat allergy tend to outgrow their allergy eventually[27]. They could be started on the cooked form first and then small amounts of raw foods. Re-introduction as soon as they are showing signs of tolerance increases the quality of life and avoids potential nutritional deficiencies.

Non-IgE mediated FA

Diagnosis of non-IgE mediated FA could be challenging. It may not be easy to make a diagnosis solely on history and examination. Manifestations of non-IgE mediated FA are shown in table 4. Food protein induced proctocolitis (FPPC), food protein induced enterocolitis (FPIES), eosinophilic gastrointestinal diseases (EGIDs) and food protein induced enteropathy are some of them. Several diagnostic tests are recommended in non IgE mediated FA including DBPCFC, patch testing, intradermal testing, elimination diet and endoscopic biopsy.

FPPC is benign and transient. Commonest trigger is cow's milk[33]. Rarely even exclusively breast fed babies develop proctocolitis since maternally ingested cow's milk proteins are present in breast milk[34]. Resolution of allergic symptoms when the food in question is excluded from the diet and re-appearance of symptoms with re-introduction suggests the diagnosis.

FPIES[35] is rare and presents with profuse vomiting with or without diarrhoea. Oral food challenge can establish the diagnosis. However, if reactions are severe, e.g. previous hypotensive episode to suspected food, absence of symptoms with elimination is adequate to make the diagnosis.

EGIDs are a diverse group of gastrointestinal diseases and are classified under mixed variety in which both IgE and non-IgE mechanism are responsible. Generally they are diagnosed by endoscopic biopsy. Eosinophilic oesophagitis is diagnosed if the biopsy contains more than 15 eosinophils/high power field in the oesophageal biopsy[36]. In EGIDs, elimination is useful in determining the allergenic food.

Table 4: ***Manifestations of non-IgE mediated/mixed food allergy***

Food protein induced proctocolitis (FPPC)	Food protein induced enterocolitis (FPIES)	Food protein induced enteropathy	Eosinophilic oesophagitis
Blood and mucus stools in a relatively healthy infant	Usually diagnosed in early infancy	Uncommon disorder	Both IgE and non-IgE mechanisms are responsible.
No systemic symptoms or weight loss. Negative stool cultures	Repeated vomiting and/ or diarrhoea within 24 hrs following exposure	Chronic diarrhoea/steatorrhoea, weight loss	Poor appetite, vomiting, weight loss
Symptoms improve with elimination and reappear with re-introduction	Only gastrointestinal symptoms are seen Symptoms disappear within 24 hrs when trigger food is withdrawn	Most often due to milk allergy. Resolution is seen with allergen elimination. Strict elimination diet. Virtually all grow out of it by 2-3 years	Oesophageal biopsy showing >15/hpf eosinophils support the diagnosis

Misconceptions on food allergy

Aetiology of chronic urticaria is attributed to FA and extreme measures are taken by patients to avoid food. Chronic urticaria is rarely due to true FA and unnecessary avoidance of food could lead to nutritional deficiencies and growth retardation[37]. Many parents believe that the commonest trigger of asthma is food and they put their children on an intense restrictive diet. Another misconception is that some parents do not realize that certain FAs could be fatal. They should be made aware of preventive measures and emergency action plans to prevent fatalities.

Prediction of future reactions

Severity of previous reactions, level of sIgE level or wheal size of SPT cannot predict severity of future reactions[38]. However, high level of sIgE at the onset is associated with a lower rate of development of tolerance[30].

Conclusions

It's important to differentiate true FA from intolerance. Although the majority of the FAs result in minor symptoms, certain allergies could be fatal. Therefore, early recognition and treatment of severe reactions and prevention of FA are vital. Investigation and management of FA is a neglected area in healthcare in a resource poor country like Sri Lanka. However, improving facilities for investigations and prescription of adrenaline auto-injectors are important aspects in preventing fatalities. Furthermore, compared to Western countries, Sri Lankans have a unique diet and may have unusual or different FAs. Thus, large population studies to uncover the trends and prevalence of FA are needed.

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