INTRODUCTION

Food allergy is a complex area of medicine. up to 20% of population have adverse reaction to food and claim to be of food allergy or food intolerance ***(Zuo et al., 2007)***.

The percentage of food allergy is much higher in some functional diseases of the gastrointestinal (GI) tract such as irri bowel syndrome. However, the role played by true food allergy in the pathogenesis of IBS are still controversial and there are no well- established tests to identify food allergy in this condition ***(Niec et al., 1998; Jones et al., 1982).***

Previously, food allergy was believed to be associated with an IgE-mediated immune response to a particular allergen in the diet. Therefore, the standardized skin prick testing and RAST testing were frequently used to diagnose food allergy, ***(Roudebush, 1995; Spergel and Browen-whitehorn, 2005).***

Fortunately, accumulating data in recent years have indicated that IgG-mediated immune response, which characteristically gives a more delayed response following exposure to a particular antigen, is of great importance in food allergy ***(Crowe and Perdue, 1992; Awazuhara et al., 1997).***

Zar et al., 2005 have shown elevated IgG titres in IBS patients also ***Atkinson et al., 2004*** have demonstrated that food

elimination based on IgG antibodies – not IgE- may be effective in reducing IBS symptoms.

Prick skin testing examines IgE-mediated reactions. IgE-mediated reactions occur within seconds to hours after ingestion of food causing hives or anaphylaxis. Patch testing examines for non-IgE mediated reactions. These reactions are often delayed, occurring hours to days after ingestion of food. Many patients with non-IgE mediated reactions have difficulty in identifying the food causing the reactions. Patch testing was first done in 1890 for reactions for perfumes, dyes and metals. Patch testing for foods have been done since 1990 in Europe and in the US since 2000 ***(Park and Camilleri, 2006; Huang and Shih, 2010).***

Aim of the Work

The aim of this work is to investigate the value of skin prick test and atopy patch test in the diagnosis of food allergy as a causative factor in patients with IBS.

FOOD ALLERGY

Food allergy is an abnormal immune response to certain food(s) that the body reacts to as harmful. Prevalence of food allergies has been estimated to be 5-6% in infants and children and 3.7 % in adults ***(Sicherer and Sampson, 2010).***

Though reasons for this are poorly understood, the prevalence of food allergies and associated anaphylaxis appears to be on the rise. Risk factors associated with food allergy include: family history of asthma and allergies, genetic predisposition to allergic disease, elevated allergen-specific serum immunoglobulin levels (IgE concentrations), and being younger than 3 years of age. There are eight foods that account for 90% of all food-allergy reactions cow's milk, egg, peanut, tree nuts (for example, walnuts, pecans, almonds, and cashews), fish, shellfish, soybeans, and wheat ***(Sicherer et al., 2003)***.

Epidemiology

Frequency

General surveys report that as many as 25-30% of households consider at least 1 family member to have a food allergy ***(Altman and chiaramonte, 1996)***. This high rate is not supported by controlled studies in which oral food challenges are used to confirm patient histories. The prevalence of food

allergies has been estimated to be 5-6% in infants and children and 3.7 % in adults ***(Sicherer and Sampson, 2010).***

However, variations in prevalence are reported according to methods (self-report, testing, physician evaluation), geographic region, and foods included in assessments.

Based upon available studies, estimations of the rate of food allergies in children have been summarized as follows for common food allergens: cow milk, 2.5%; eggs, 1.3%; peanuts, 0.8%; wheat, 0.4%; and soy, 0.4%. ***(Sicherer and Sampson, 2010)***.

Mortality/Morbidity

Severe anaphylactic reactions, including death, can occur following the ingestion of food ***(Bock et al., 2007).*** Symptoms observed in a food-induced anaphylactic reaction may involve the skin, gastrointestinal tract, and respiratory tract. Frequently observed symptoms include oropharyngeal pruritus, angioedema (eg, laryngeal edema), stridor, dysphonia, cough, dyspnea, wheezing, nausea, vomiting, diarrhea, flushing, urticaria.

Fatalities result from severe laryngeal edema, irreversible bronchospasm, refractory hypotension, or a combination of three. Peanuts, tree nuts, fish, and shellfish are the foods most often implicated in severe food-induced anaphylactic reactions,

though anaphylactic reactions have been reported to a wide variety of foods. Fatalities caused by reactions to milk are increasingly noted ***(Bock et al., 2007)***.

Risk factors or associations for fatal food-induced anaphylaxis include: (1) the presence of asthma, especially in patients with poorly controlled disease; (2) previous episodes of anaphylaxis with the incriminated food; (3) a failure to recognize early symptoms of anaphylaxis; and (4) a delay or lack of immediate use of epinephrine to treat the allergic reaction ***(Pumphrey and Gowland, 2007)***. Teenagers and young adults appear to be overrepresented in registries of food allergy fatalities and present a special risk group.

Pathophysiology:

The gastrointestinal mucosal immune system is exposed to numerous antigens. Thus, an intact and immunologically active gastrointestinal barrier is critical to suppress immune reactivity to foreign antigens and to protect the gastrointestinal tract against pathogens. The gut contains epithelial cells joined by tight junctions, a thick mucus layer, lumenal and brush border enzymes, bile salts, and extreme pH conditions. ***(Cianferoni and Spergel, 2009)***.

In the gut, the innate immune system (natural killer cells, polymorphonuclear leucocytes, macrophages, epithelial cells,

and toll like receptors) works together with the adaptive immune system (intraepithelial and lamina propria lymphocytes, Peyer's patches, IgA, and cytokines) to provide an active barrier to foreign antigens ***(Cianferoni and Spergel, 2009)***.

Two percent of the food antigens that are absorbed and transported throughout the body do not cause clinical symptoms because of oral tolerance, which may result from T cell anergy. Intraepithelial cells are inefficient antigen presenting cells; they present allergens on the major histocompatibility complex as the first signal to T cells, but they lack the second signals (CD-28 and ICAM-1) needed to stimulate an active immune response. Consequently, the partially activated T cells become anergic or tolerant ***(Mahmoudi, 2008)***.

Furthermore, dendritic cells in Peyer's patches express interleukin IL-10 and IL-4, which favour the generation of tolerance, and regulatory T cells secret the immunosuppressive cytokines IL-10 and tumour necrosis factor-beta, which are also important for oral tolerance ***(Dahan et al., 2007)***.

Several types of regulatory T cells contribute to the development of oral tolerance: Th3 cells, which are a population of CD4 cells that secrete transforming growth factor-beta; Tr1 cells, which secrete IL-10; CD4 CD25 regulatory T cells, which

express the transcription factor FoxP3; CD8 suppressor T cells; and gamma-delta T cells ***(Cianferoni and Spergel, 2009).***

Allergic reactions to food are mediated by IgE-, non-IgE-dependent, or mixed mechanisms. Cell-mediated responses to food allergens may also mediate allergic responses, particularly in disorders with delayed or chronic symptoms. For example, food protein - induced enterocolitis syndrome (FPIES), a gastrointestinal food allergy, appears to be mediated by T-cell elaboration of the cytokine tumor necrosis factor (TNF)-alpha ***(Sicherer et al., 1998)***.

Persons with atopic dermatitis that flares with ingestion of milk have been noted to have T cells that, in vitro, express the homing receptor cutaneous lymphocyte antigen, which is thought to home the cell to the skin and mediate the response ***(Abernathy et al., 1995)***. Celiac disease is the result of an immune response to gluten proteins in grains.

Food allergens:

The two types of sensitisation to food allergens are class-1, which occurs in the gastrointestinal tract, and class-2, which occurs in the skin or respiratory tract ***(Breiteneder and Mills, 2005)***. Class-1 allergens are water-soluble glycoproteins, 10-70 kDa in size, and are stable to heat, acid, and proteases. Examples include caseins in milk, vicillins in peanuts, ovomucoid in eggs,

and non-specific lipid transfer proteins in apples (Mal d 3) or corn (Zea m 14) ***(Sicherer and Sampson, 2006)***.

Class-2 allergens are heat labile, susceptible to enzymatic degradation, and difficult to isolate. A limited number of these allergens have been identified: the Cupin superfamily, the Prolamin superfamily, and the pathogenesis-related proteins of the plant defence system ***(Breiteneder and Mills, 2005).***

Food allergens are typically glycoproteins of 10-70 kDa that bind to high affinity IgE receptors (FcRRI and FcRRII). Specific antigen exposure induces cross-linking of food allergen specific IgE and FcRRI on mast cells and basophils (Sicherer and Sampson 2009). The cells then degranulate and release histamine, prostaglandins, and leukotrienes, which produce clinical symptoms. Mast cells were thought to be the primary effector cells, but studies have shown that basophils also play a major role in acute food allergy symptoms ***(Lee and Burks, 2006).***

Subsequent allergen exposure binds and cross links IgE antibodies on the cell surface, resulting in receptor activation and intracellular signaling that initiates the release of inflammatory mediators (eg, histamine) and synthesis of additional factors (eg, chemotactic factors, cytokines) that promote allergic inflammation. The effects of these mediators

on surrounding tissues result in vasodilatation, smooth muscle contraction, and mucus secretion, which, in turn, are responsible for the spectrum of clinical symptoms observed during acute allergic reactions to food.

The glycoproteins are usually water soluble and resistant to denaturation by heat and degradation by proteases ***(Arshad et al., 2006)***.

These characteristics facilitate the absorption of these allergens across mucosal surfaces. Numerous food allergens are purified and well-characterized, such as peanut Ara h1, Ara h2, and Ara h3; chicken egg white Gal d1, Gal d2, and Gal d3; soybean-Gly m1; fish-Gad c1; and shrimp-Pen a1. Closely related foods frequently contain allergens that cross react immunologically (ie, lead to the generation of specific IgE antibodies detectable by skin prick or in vitro testing) but less frequently cross react clinically ***(Sicherer, 2001)***.

Recently, delayed allergic reactions to meat proteins have been attributed to reactions to carbohydrate moieties ***(Commins et al., 2009).***

Cross-reaction between food and inhalant allergens:

Cross-reactive allergens between food and inhalant allergens are common. Patients with allergic rhinitis/ conjunctivitis

due to birch and, to a lesser extent, other Betulaceae (hazel, alder) pollen are frequently allergic to tree nuts, fruits and vegetables, including apples, carrots and potatoes. Most patients develop mild symptoms but anaphylaxis may occur from these cross-reacting foods. Some birch or hazel pollen allergens cross-react with those of apple, other fruits ***(Pastorello et al., 1996)***. or various nuts ***(Hirschwehr et al., 1992).***

Most patients with food hypersensitivity are severely allergic to pollens. Some Compositae pollen allergens (mugwort) cross react with foods of the Ombelliferae family (celery, in particular) ***(Bauer et al., 1996)***. Although IgE antibodies to food allergens are highly prevalent in patients allergic to Betulaceae and Compositeae pollens, only a proportion of patients present food allergy symptoms.

Ragweed (*Ambrosia*) or grass pollen ***(Garcia et al., 1995)*** sensitive individuals may present symptoms when eating banana or melon. Cross-reactive antigens have been identified between latex and banana, chestnut or kiwi fruit ***(Moller et al., 1998)***.

Although it is common to find positive skin tests and IgE antibodies to a range of legumes in peanut allergic patients, only a small percentage of the individuals also have clinical responses to legumes other than peanut. Such reactions are often less severe than to the peanut itself ***(Burks et al., 1999)***.

However, recent concern has been raised for lupine, another member of the legume family, which appears to induce systemic reactions in peanut allergic patients.

Molecular biology-based approaches have also improved knowledge about cross-reactivity among allergens. The identification of allergens in fruits and vegetables showed IgE cross-reactivities with the important birch pollen allergens, Bet v 1 and Bet v 2 (birch profilin) ***(Hoffmann et al., 1999)***.

Many other cross-reactive antigens have also been identified and characterised. Depending on the main cross-reactive allergen, different symptoms may be observed. Bet v 1 in apples, cherries, peaches and plums primarily causes mild symptoms such as the oral allergy syndrome. However, Bet v 1 associated with other allergens may cause generalized symptoms. Sensitization to Bet v 2 is more often associated with generalized symptoms, in particular urticaria and angioedema.

Lipid-transfer proteins are relevant to apple and peach allergens and, considering their ubiquitous distribution in tissues of many plant species, could be a novel pan-allergen of fruits and vegetables ***(Pastorello et al., 1999).***

Clinical disorders

Gastrointestinal reactions

Pollen food syndrome is an IgE-mediated allergic reaction. Patients with a history of seasonal allergic rhinitis experience symptoms more frequently during pollen season. They develop itching or tingling of the lips, tongue, palate, and throat following the ingestion of certain foods. Angioedema of the lips, tongue, and uvula may occur and, in rare instances, can lead to a severe systemic reaction such as laryngeal oedema ***(Mahmoudi, 2008).***

The syndrome is primarily caused by fruit and vegetable epitopes that cross-react with pollen allergens. As the allergens responsible for these reactions are easily broken down by heat or gastric enzymes, most patients experience allergic symptoms only in the oral and pharyngeal mucosa ***(Sampson, 2004)***.

Gastrointestinal anaphylaxis, another IgE-mediated allergic reaction, typically presents as vomiting, nausea, abdominal pain, and diarrhoea after ingestion of a food allergen ***(Sampson, 1999).***

The allergic eosinophilic esophagitis (AEE), and allergic eosinophilic gastroenteritis (AEG) can be mediated by IgE- or non-IgEdependent mechanisms. The symptoms vary according to the degree of eosinophil infiltration into the oesophagus,

stomach, and intestinal walls. Approximately half of the patients have peripheral eosinophilia; however, a diagnosis cannot be made on that basis ***(Liacouras and Markowitz, 1999).***

AEE may manifest as gastroesophageal reflux symptoms such as dysphagia, nausea, vomiting, and epigastric pain (heartburn), particularly in children **(*Sampson, 2004).***

Most patients who have AEE exhibit other allergic signs such as eczema, rhinitis, or asthma. The pH probe results are generally normal. A patient with gastroesophageal reflux and a negative pH probe result should undergo endoscopy and a biopsy ***(Mahmoudi, 2008)***.

An elemental diet, which contains no potential allergens, or an oligoantigenic diet, which removes common allergenic foods, may be required to determine the role of food in a patient's allergy. The long-term prognosis for AEE has not been clearly delineated, but patients who are not treated appropriately may develop Barrett's esophagitis ***(Rothenberg, 2004)***.

The AEG symptoms include vomiting, abdominal pain, and diarrhoea; the disorder can occur at any age, including early infancy ***(Rothenberg, 2004)***. Depending on the extent and location of the inflammatory involvement, patients may present with blood in the stool, iron deficiency anaemia, and protein losing enteropathy ***(Rothenberg, 2004)***. Increased numbers of

TH2 cells have been found in the peripheral blood and infiltrated into the intestinal mucosa of patients with AEG ***(Beyer et al., 2002).***

Food protein-induced proctocolitis is a non-IgE-mediated allergic reaction that occurs in infants. Cow's milk and soy protein-based formulas are usually responsible for this reaction. Mucus and blood in the stool of breastfed infants can be attributed to food allergens, primarily cow's milk, ingested by the mother. These infants typically appear healthy and grow well, but are identified as having food protein-induced proctocolitis by gross or microscopic blood in their stool. The bleeding resolves when the allergen is excluded from the mother's diet ***(Sampson, 2004)***.

Food protein-induced enterocolitis syndrome is a non-IgEmediated allergic reaction and typically manifests in the first few months of life, with severe projectile vomiting, diarrhoea, and failure to thrive ***(Nowak-Wegrzyn et al., 2003).***

The symptoms are most commonly provoked by cow's milk or soy protein-based formulas; however, solid foods such as rice can also cause these symptoms. In adults, shellfish (e.g. shrimp, crab, and lobster) hypersensitivity may provoke a similar syndrome, with delayed onset of severe nausea, abdominal cramps, and vomiting.