INTRODUCTION AND AIM OF THE WORK

The incidence of food allergy in children is approximately 6%. It is more common and prevalent in children under 3 years of age than in older children *(Sampson and Leung, 2004)*.

Allergic sensitization to foods in infancy is a risk factor for respiratory tract allergic disease including asthma, later in life. Asthma is a significant risk factor for life-threatening food-allergic reactions. Among patient who experienced life-threatening food hyper-sensitivity reaction, the vast majority had a history of asthma. Acute food-induced respiratory reactions are typically accompanied by cutaneous and gastrointestinal symptoms as a component of systemic anaphylaxis. There are also circumstances when isolated rhinitis or asthma is induced by foods, but these are uncommon *(John, 2003)*.

Fish has always been an important source of dietary protein, especially in coastal regions. Recently, as transport by unbroken cold chain became routine and the demand for meager food increased, geographical restrictions are not longer an issue and fish is now consumed by a large part of population. In parallel to this development, the number of persons

with fish hypersensitivity has augmented, and allergy to fish is counted among the most common food allergies *(Sampson, 2000)*.

In industrialized countries, about 0.1-0.3 of the general population have fish allergy whereas the prevalence in food Allergic children and adults have been found to be at 2.3% to 30.4% depending on the study cohorts *(Faeste and Plassen, 2008)*.

The edible fish include more than 20000 species; however, the most commonly consumed belong to only a few orders of the ray-finned fish (Actinoptergii). Fish-sensitive patients are often Allergic to multiple species of fish and are therefore advised to avoid consuming fish in general *(Hansen et al., 1997)*. Clinical cross-reactivity was found to be about 50-70% *(Helbling et al., 1999)*.

The aim of this work is to study the sensitivity to fish among allergic Egyptian infants and children in a trial to outline the significance of this antigen in exacerbation of allergic disorders.

FOOD ALLERGY

Definition:

Food allergy is defined as an abnormal immunological reaction to food proteins that causes an adverse clinical reaction. Food allergy needs to be distinguished from other types of adverse reactions to food, including:

- Food intolerance (eg, lactose malabsorption);
- Pharmacological reactions to food components (eg, vasoactive amines);
- Food poisoning (eg, food-borne bacterial gastroenteritis); and
- Toxic reactions (eg, to staphylococcal enterotoxin).It is estimated that about a quarter of the population will have an adverse reaction to food (of which food allergy is just one type) during their lifetime, especially during infancy and early childhood.

(Allen et al., 2006)

Epidemiology and prevalence:

Food allergies have become a major health concern in industrialized, westernized countries in the past two decades. Surveys suggest that between 5% and 25% of adults believe that they or their children are afflicted with a food allergy *(Sampson et al., 2005),*

but the true prevalence is far less. It has been estimated that in general population approximately 4-6% of children and 1-3% of adults experience food allergy. There is some evidence to suggest that prevalence has increased over the last 10 years *(Gupta et al., 2007).*

Food allergy is more prevalent in patients with Atopy. 30% of children with severe atopic dermatitis (AD) and 10% of those with asthma are found to have food allergies *(Jost et al., 2003).* Sensitization in infancy generally occurs first to food allergens, predominantly egg white and cow's milk. The combined results of double-blind placebo-controlled food challenges performed in the United States (primarily in children) showed that eight foods were responsible for 93% of reactions. These foods listed in order of frequency are eggs, peanuts, milk, soy, tree nuts, fish, crustaceans and wheat. In adults and older children, peanuts, crustaceans, tree nuts, and fish (in order of frequency) were reported to be responsible for the majority of fatal anaphylactic reactions *(Grammer et al., 2009).*

Early childhood allergies to milk, egg, soy, and wheat are usually resolved by school age (approximately 80%), whereas peanut, tree nuts and

seafood allergies are generally considered permanent *(Sicherer et al., 2006).*

Pathogenesis:

Food allergy represents an abnormal response of the mucosal immune system to antigens delivered through the oral route. The healthy gastrointestinal mucosal immune system encounters enormous quantities of antigen on a daily basis and generally suppresses immune reactivity to harmless foreign antigens (food proteins and commensal bacteria), although it is fully capable of mounting a brisk protective response against dangerous pathogens. The process by which the gastrointestinal immune system avoids attacking harmless antigens is termed "oral tolerance" *(Worbs et al., 2006).*

Food allergy might result from a failure in oral tolerance to food while they are being ingested (class 1 food allergy) or from a sensitization to allergens recognized instead during respiratory exposure (class 2 food allergy). Class 1 food allergy is typically related to food proteins, generally stable to digestion, which is encountered by infants or children at a presumed immunological immaturity. In contrast, class 2 food allergy is the result of a sensitization to protein susceptible to enzymatic degradation, encountered in the respiratory tract, such as pollens, resulting in an

IgE antibody production that recognize homologous epitopes on food proteins of plant origin (i.e. pollen-food related syndrome) *(Egger et al., 2006).*

Gut barrier:

The gastrointestinal mucosal barrier is a complex of physical (mucus, acid, enzymes, bile salts, and epithelial cell tight junctions) and immunologic structures both "innate" (natural killer cells, polymorphonuclear leukocytes, macrophages, epithelial cells, and toll-like receptors), and "adaptive" (intraepithelial and lamina propria lymphocytes, Peyer's patches, secretory immunoglobulin type A [sIgA], and cytokines)-which all serve to destroy antigens and to render antigens non immunogenic **(Dubois et al., 2005).** Alteration of the gut barrier might lead to food allergy. Developmental immaturity of components of the gut barrier (enzymatic activity and sIgA) might account for the increased prevalence of food allergy in infancy. Despite the evolution of this barrier, about 2% of ingested food antigens, both particulate and soluble, are adsorbed by the follicle associated epithelium (M cells), overlying Peyer's patch and the intestinal epithelial cells, respectively, and transported throughout the normal mature gut, but they infrequently induce clinical symptoms, because tolerance develops in most individuals *(Mansueto et al., 2006).*

Food additives are substances added to food to preserve flavor or improve its taste and appearance. Food additives have been thought by many people, including physicians, to be a precipitating cause of acute allergic-type reactions and a cause of exacerbations of asthma. There are more than 2500 substances that the FDA lists as food additives in the United States. The incidence of reactions to food additives is unknown but is generally overestimated by the public. The prevalence of allergic reactions to foods is much higher than the reactions to any of the food additives. European studies have extrapolated the prevalence as <0.5% of the total population and only as high as 2% reporting of challenges listed prevalence of adverse reactions as 0.01% to 0.23% *(Spergel and Fiedler, 2005).*

In European studies, artificial food colors have been blamed for ≥15% of chronic urticaria cases, whereas in the United States this high percentage has never been substantiated. Tartrazine (food dye yellow #5) has been reported to cross-react with aspirin in aspirin-sensitive asthmatics *(Jost et al., 2003).*

Properties of food allergens:

Typically, food allergens are glycoproteins that are relatively resistant to digestion and cooking. A large number of food allergens have now been

identified and characterized (eg, β-lactoglobulin in cows milk, ovomucoid [Gal d 1] in egg and Arachis hypogaea allergen 1 [Ara h 1] in peanut). On each of these proteins, specific epitopes (structural components of the antigen molecule) have been mapped that interact with food-specific IgE antibody or T cell receptors. Further characterization of these epitopes is essential for developing food vaccines or genetically modified hypoallergenic foods *(Allen et al., 2006).*

Mechanism:

Food hypersensitivity IgE–mediated reactions are the result of mast cell and basophil mediator release. Food-specific IgE bound to mast cells or basophils via the high-affinity FceRI is cross-linked by the food allergen, resulting in the release of preformed mediators such as histamine and newly preformed mediators such as leukotrienes and prostaglandins. These result in smooth muscle contraction, vasodilatation, microvascular leakage and mucus secretion. Eosinophils, monocytes and lymphocytes are recruited to the area affected in the late phase response and release a variety of cytokines and inflammatory mediators *(Gouta et al., 2008).*

Clinical manifestations:

Manifestations of food allergy depend on the organ systems involved. Reactions can be isolated, in

combination, or as part of a generalized anaphylactic reaction.

1. Skin manifestations represent the most often observed clinical symptoms in food allergy. Immediate symptoms are urticaria, angioedema and sudden erythema (flush). Delayed symptoms which can be observed are exanthema and exacerbation or worsening of eczema (most often atopic dermatitis). Atopic dermatitis and urticaria/angioedema represent the most often observed skin manifestations triggered by foodstuffs *(Breuer et al., 2006).*

2. Gastrointestinal symptoms:

Pollen-food allergy syndrome:

Pollen-food allergy syndrome(or oral allergy syndrome): is an IgE-mediated food adverse reaction, elicited by a variety of plant-derived food proteins, especially concentrated in the peel, which cross react with airborne allergens, including birch, ragweed, and mugwort pollens. It is characterized by mild pruritus, tingling, and/or angioedema of the lips, tongue, palate or oropharynx, occasional sensation of tightness in the throat, and rarely systemic symptoms, because the allergens responsible for these reactions are easily broken down by heat or gastric enzymes, and thus are not absorbed by the gastrointestinal mucosa. Reactions

to all related food are rare, but sensitivity to more than one is common. Diagnosis is based on clinical history, positive skin prick test responses to fresh food and relevant airborne proteins, and, if necessary, on an oral challenge, positive with fresh food and negative with cooked food *(Mansueto et al, 2006)* .

Gastrointestinal anaphylaxis:

This is a form of IgE-mediated gastrointestinal hyper-sensitivity, which often accompanies allergic manifestations in other target organs and results in a variety of symptoms which generally develops within minutes to 2 hours of consuming the responsible food allergen and consists of nausea, abdominal pain, cramps, vomiting, and diarrhea. In food allergic children with atopic dermatitis, frequent ingestion of a food allergen appears to induce partial desensitization of gastrointestinal mast cells resulting in less pronounced symptoms, such as occasional minor complaints of poor appetite and periodic abdominal pain *(Adkinson et al., 2008).*

Allergic eosinophilic oesophagitis:

It is an IgE- or non-IgE-mediated, or both, food adverse reactions, seen most frequently during infancy through adolescence, characterized by gastroesophageal reflux, excessive spitting- up or emesis, dysphagia,

intermittent abdominal pain, failure to respond to conventional reflux medications, and peripheral blood eosinophilia. Diagnosis is based on clinical history, skin prick tests, endoscopy with biopsy, elimination diet and challenge. Patients who are not appropriately treated might develop fibrosis, with subsequent esophageal stricture, and Barrett's oesophagitis *(Katzka et al., 2006).*

Allergic eosinophilic gastroenteritis:

This is a mixed IgE and non IgE mediated food adverse reactions, being diagnosed more frequently in adults,

abdominal pain, blood loss in the stools, iron-deficiency anemia, and protein-losing enteropathy, with a peripheral blood eosinophilia. Clinical history, skin prick tests, endoscopy with biopsy, and elimination diet and challenge, are required for the diagnosis *(Chehade et al., 2006).*

Food protein-induced enterocolitis, proctocolitis, and enteropathy:

It is a non-IgE mediated (T cell-mediated) disorders with different clinical pictures.

Allergic Proctocolitis:

Infants may present between 1 day and 3 mo of age with spots or streaks of blood and mucus in stool and occasional mild diarrhea. Increased numbers of white blood cells in stool and peripheral eosinophilia may be present. Typically, a patchy, mild colitis is present; nodular lymphoid hyperplasia occurs in ≈25% of cases. Most often, proctocolitis results from hypersensitivity to cow's milk; soy sensitivity is less common. This disorder also occurs in exclusively breast-fed patients and occasionally abates with maternal diet modification with elimination of milk products. Non–breast-fed infants can be treated with protein hydrolysate formulas. Occasionally, an amino acid–based formula may be required.

Food-Induced Enterocolitis:

Protracted vomiting and diarrhea begin between 1 wk and 3 mo of age. Less severe reactions can occur in older children and adults. Stools contain occult blood, neutrophils, and eosinophils. jejunal biopsy demonstrates flattened villi, edema, and inflammatory cells. Symptoms resolve within 72 hr of removal of the offending food and recur within 1–6 hr of reintroduction. The blood neutrophil count increases by at least 3.5 × 109/L at 4–6 hr after a food challenge. Older infants may develop a poorly characterized syndrome of anemia, hypoproteinemia, and failure to

thrive when weaned from nursing or formula to ordinary cow's milk. Eosinophilia is common. Casein hydrolysate or amino acid–based formulas successfully treat most patients.

Food-Induced Enteropathy:

Malabsorption, protracted diarrhea, vomiting, and failure to thrive caused by food hypersensitivity occur most often in the 1st mo of life. Small bowel biopsy shows patchy villus atrophy with mononuclear cell inflammatory response. Reaction to food challenge as well as resolution of symptoms on removal of the offending food may take several days to weeks.

(Kliegman et al., 2007)

In these patients, skin prick test responses are negative. Endoscopy and biopsy are often required. Elimination of food proteins leads to the clearing of symptoms in 24-72 h. Challenge induces recurrent vomiting or bleeding within 72 h (*Heine, 2004).*

Celiac disease:

Celiac disease (or gluten-sensitive enteropathy) is a more extensive enteropathy leading to malabsorption, associated with sensitivity to gliadin, found in wheat, rye and barley. Diagnosis is based on celiac IgA, anti-gliadin and anti-transglutaminase antibodies detection, endoscopy and biopsy, elimination diet, with resolution of symptoms and food challenge, if necessary *(Van Heel and West , 2006).*

3. Respiratory manifestations

Acute respiratory symptoms caused by food allergy generally represent isolated IgE-mediated reactions, whereas chronic respiratory symptoms represent a mix of IgE- and cell-mediated reactions. Isolated rhinoconjunctivitis is rarely the result of a food-induced allergic reaction, although it frequently occurs in association with other food allergy symptoms *(Sampson, 2004).*

Respiratory symptoms consist of rhinoconjunctivitis, laryngeal edema, cough, and bronchospasm. Food-induced respiratory symptoms,

specifically asthmatic reactions, are a risk factor for fatal and near-fatal anaphylactic events *(Bock et al, 2001).*

Considerable epidemiological data suggest a link between asthma and food allergy. Food can induce bronchospasm, and food allergy has been implicated as a risk factor for life threatening asthma. Asthma also seems to be a risk factor for a life threatening food allergy. The mechanism underlying this connection is unclear, but the co-existence of food allergy should be considered in any child with asthma, especially if there a history of atopic dermatitis, elevated serum IgE level or both *(El-Gamal and Hossny, 2006).*

Rhinitis and nasal symptoms are commonly seen in patients who have reactions during food challenges. Just as it is uncommon to have isolated food-induced asthmatic symptoms, it is very unusual to have nasal symptoms as the only manifestation of an acute allergic reaction *(Duggan et al, 2008)*

4. Anaphylaxis:

Food allergy is one of the most common causes of systematic anaphylaxis and anaphylactoid reactions, with an annual incidence of four cases per million populations and estimated 500 deaths annually. In