Food Allergy In Children: Symptoms, Diagnosis And Research

Abdellatief A. Sulieman, Hayat A. Hassan, Hui-Ming Zhou

Abstract: Food allergy is a major health issue for the human body in industrialized countries and has increased significantly in the past decade. Food intolerance must be distinguished from food allergies and, furthermore, these allergies should be classified into either immunoglobulin E (IgE), Non-IgE, or a mixed response. The clinical attributes vary from life-threatening anaphylaxis to milder IgE-mediated responses, atopic dermatitis, and gastrointestinal symptoms. Milk, soybean, egg, wheat, and peanut allergies are common in children, whereas peanut, tree nuts, fish, and shellfish allergies are common in adults. The digestive allergies, skin allergies, and respiratory allergies are the most common allergies among children. Diagnostic work up must be guided by the clinical history, and consumption of fortified gluten-free bakery products instead of wheat products is necessary for celiac disease (CD) patients. Most current allergen detection methods are immunoassays, such as ELISA. Skin testing and food-specific IgE done by standard methods are very useful. Combination of skin prick test and patch test is useful tool for the diagnosis of food hypersensitivity in children with atopic dermatitis.

Keywords: Food allergy, allergens, diagnosis, symptoms, children, celiac disease, immunoassays.

1 INTRODUCTION

During the first year of life, the infant diet is the most powerful determinant of the growth and development of the child, and food allergy is the most common health problem. The epicutaneous immunotherapy and therapeutic approaches are still important future research goals. The prevalence of food allergy in children from Europe and the United States is considered to be 3-8% [1, 2], and the figures remain similar to those in Asia. Recently, Australian study reported that food allergy in 12 months'age children found a prevalence of 8.9% for egg, 3% for peanut and 0.8% for sesame allergy [3]. Unfortunately, there is no curative treatment available for food allergic patients. Food allergy is defined as an abnormal response to a food triggered by your body's immune system and can involve several body systems including the skin, gastrointestinal and respiratory tracts, and cardiovascular system. It is not felt to play a role in chronic respiratory symptoms. The immunological response is mediated by the antibody immunoglobulin E(IgE), the major mediator of asthma, urticaria and rhinitis, which is classified as immediate allergic reactions [4]. Food hypersensitivity can be divided in clinical terms into food allergy and non-allergic food hypersensitivity such as lactose intolerance. Food allergy can then be further subdivided into IgE-mediated food allergy to foods such as milk, egg or peanuts, and non-IgE-mediated food allergy such as gluten intolerance (celiac disease) and systemic allergic contact dermatitis (Fig. 1).

- *Abdellatief A. Sulieman, Hayat A. Hassan, Hui-Ming Zhou*
- *State Key Laboratory of Food Science and Technology, School of Food Science and Technology, Jiangnan University, Wuxi, PR China.*
- *Department of Cereal Science and Technology, National Food Research Center, Ministry of Agriculture and Forestry, Khartoum North, P.O. Box. 213, Sudan.*
- *lotfiabba@yahoo.com; dafaallahdongos@hotmail.com Tel: +86 15961799718*

Until recently, most allergy guidelines recommended strict avoidance of all forms and amounts of allergens from the diets of allergic children. Food or digestive allergies, skin allergies, such as eczema, and respiratory allergies, such as hay fever are the most common allergies among children [5]. The ability to incorporate extensively heated egg in baked products, such as cakes significantly liberalizes the diet and may help to reduce anxiety over accidental ingestions. There is also the potential for altering the natural history of the disease and accelerating acquisition of tolerance to egg [6]. Food allergy in young children is usually caused by milk (2.5%), egg (1.3%), peanut (0.8%), tree nuts (0.2%), fish (0.1%), and shellfish (0.1%) with the overall prevalence being 6% [7], but a recent study by [8], using strict clinical criteria, stated that most children with egg allergy (EA) will outgrow their allergy by early school age. There is evidence that having a food allergy can impact the quality of life of food allergic children and their families [9]. A lack of information providing to the parents at time of diagnosis may increase anxiety and uncertainty in how to manage risk and safety for their child [10]. Moreover, the diagnosis of food allergy may be problematic as well, given that non-allergic food reactions, such as food intolerance and intoxication are frequently confused with food allergy [11]. The significance of food allergy research has been increasing in the United States (US), particularly among pediatric populations. Recent national survey estimates report a prevalence of 3.9% of food allergies among children 18 years or younger, affecting approximately 3 million children [2]. Different reports claim prevalence of food allergy at 13% for children and 7% for adults in the US, in Europe the claimed prevalence is at 0.3-7% for children and 2% for adults [12]. Some studies investigating birth weight as a potential risk factor for allergic disease have demonstrated an increased risk of atopic disease (allergic reactions) among preterm and otherwise low birth weight (LBW) children [13]. Children with food allergy have a lower quality of life than diabetic children, and their condition also affects the wider family quality of life [14-16]. Robison [17] reported that early weaning and the development food allergy in infants have actually found a potential protective effect in early weaning. Other individuals suffering from non-IgE-mediated food allergy or intolerances also experience a negative impact

on their quality of life, and in some specific cases such as celiac disease have recognized long-term health risks [18].

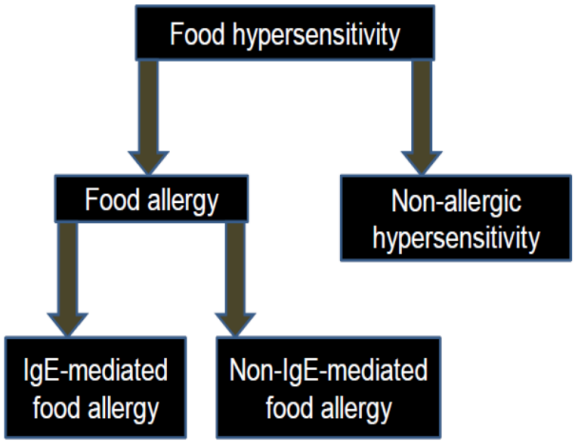

Fig. 1. *Types of food allergy in children.*

2. Food Allergens in Children

Allergens have been studied extensively, and are found to come from protein families (plant and animal proteins) with a range of biological functions [19]. In addition, allergens are protein components, not the fat or carbohydrate components of these foods that lead to sensitization and allergy. Some water-soluble glycoproteins, such as caseins in milk, parvalbumin in fish, vicillins in peanut and ovomucoid in egg, are resistant to denaturation by heat or acid and, thus can remain intact after processing, storage, cooking and digestion [20]. There are 8 foods that appear to be responsible for 90% of all food allergic reactions. Milk, eggs, peanuts, wheat, soybean, and tree nuts are the foods most often implicated food allergic in children [21], whereas in adults, peanuts, tree nuts (walnuts and pecans), fish and shellfish are the most common culprits (Fig. 2).According to several studies, food allergens are typically water-soluble glycoprotein resistant to heating and proteolysis. These characteristics facilitate the absorption of these allergens across mucosal surfaces.

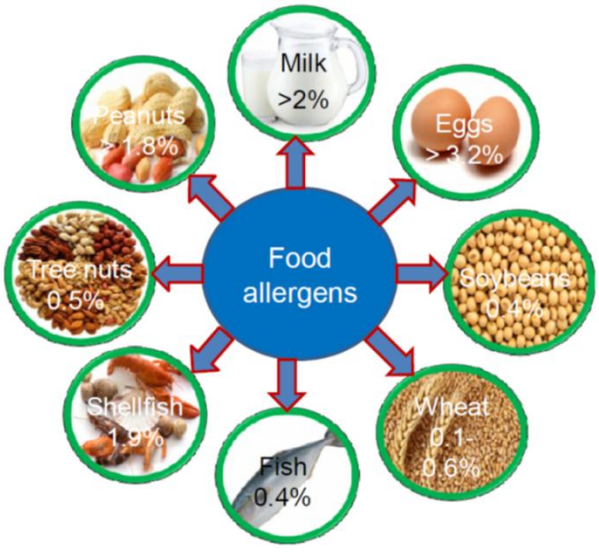

Fig. 2. *Food allergens with estimated prevalence in children.*

2.1 Peanut

Peanut allergy is one of the most common allergen in Western countries with an estimated prevalence of up to 1.8% [19, 21, 22], as well as it is becoming apparent in African and Asian countries. Clinical symptoms of peanut allergy mainly involve the oral cavity, skin, and gastrointestinal tract and occasionally include respiratory symptoms [21, 23]. In Japan, peanut is ranked among the top five items causing anaphylaxis [24]. Several proteins have been identified as peanut allergens, and the use of recombinant allergens has offered improve possibilities for a more specific and simplified peanut diagnosis [25], [26], [27]. According to [28], there are three methods of reducing allergenicity of peanuts: physical methods, chemical methods, and biological methods. Many children who have milk and egg allergies are potential candidates for subsequently developing allergies to other highly sensitizing food, such as peanuts during childhood [29]. Boiled peanuts are less allergenic in children than the roasted form. Therefore, the form of the food and timing of its preparation are necessary factors.

2.2 Milk

Cow's milk allergy (CMA) is common in childhood with a prevalence rate of around 2.5%, and needs specific dietary interventions [30, 31]. The percentage of parents that believe their child has cow's milk allergy (or any other food allergy), however, amounts to between 5% and 20% [32, 33]. In general, cow's milk allergens are caseins, whey proteins β-lacto-globulin, α-lacto-albumin, bovine serum albumin and bovine immunoglobulin. Signs and symptoms of CMA are non-specific and often difficult to objectify. Due to diagnostic burdens, the number of children treated for CMA is probably two to three times higher than justified [34]. Some studies have found that introduction of extensively heated milk appears to accelerate the development of tolerance in children compared to unheated food protein [35].

2.3 Egg

Egg allergy was defined as children with a previous convincing clinical reaction to egg within the past 12 months or evidence of current sensitization consistent with a > 95% likelihood of clinical reactivity [36, 37]. Patel and Volcheck [38] detected a prevalence of egg allergy in 4% of children by age 4 years, 12% by 6 years, 37% by 10 years, and 68% by 16 years, but children who did not have resolution of their allergy had higher egg-specific IgE levels. It is interpreted that food protein is thought to be denatured, with the heat labile protein undergoing a conformational change secondary to the high heat of cooking rendering it to be non-allergenic to some patients. Tolerance to extensively heated egg is usually demonstrated at formal open food challenge (OFC) under medical supervision, given the potential for anaphylaxis [39]. However, some guidelines support a home introduction protocol for selected egg-allergic children without a prior history of asthma.

2.4 Soybean

The prevalence rate of soybean allergy in children is estimated at around 0.3% to 0.4% [21]. Manifestations range from immediate reactions like urticaria to non-IgE responses such as atopic dermatitis and gastrointestinal

(GI) symptoms as a result of soybean protein intolerance. Reactions are usually mild, however, isolated cases of death have been reported because of soybean allergy. In contrast, soybean oil and soybean lecithin can be safely ingested by patients with soybean allergy [40]. Historically, estimates of soybean allergy prevalence have been based on perceived allergy or sensitization in pediatric populations. Recent unpublished clinical observations from a Dutch clinic indicated that many of the soybean milk-allergic patients can tolerate soybean flour, suggesting that soybean allergy is sometimes associated with some specific types of soybean products [41]. These individuals allergic to soybean milk and certain types of soybean protein isolate but able to tolerate soybean flour seem less relevant for the purposes of risk assessment of soybean in wheat flour although this soy-allergic subpopulation merits further studies.

2.5 Wheat

Wheat is responsible for numerous diseases, which are called gluten related disorders [42]. According to the most recent classification, gluten disorders are divided into three main groups: allergic, auto-immunological (celiac disease, dermatitis herpetiforms) and possibly immune-mediated (gluten sensitivity) [43]. Although wheat is one of the most common food allergens in children, the natural history of the IgE-dependent allergy to wheat has been rarely discussed in the literature [44], [45], [46], [47], [48]. Recent IgE mediated allergic reactions due to commodity contamination of wheat have led the Canadian Food Inspection Agency (CFIA) to encourage manufacturers and importers of grain-based products to inform consumers and transition towards the inclusion of precautionary labeling on their products containing cereal grains (e.g. oat and barley), to indicate the potential presence of wheat at low level [49]. Celiac disease is a non-IgE-mediated small intestine immunologic reaction to gluten in genetically susceptible individuals [50]. The symptoms of celiac disease malabsorption including diarrhea, bloating, weight loss, and growth failure in children. Laboratory testing can reveal anemia and vitamin deficiencies. Testing for celiac disease should take into account whether a patient is consuming a gluten-free diet and the probability of disease. Celiac disease is now recognized as a systemic disease that may affect persons of any age, race, and ethnic group, which may not always involve the gut, and which manifests itself with a wide range of symptoms and complications [51]. Most of the children that were allergic to soybean also had another allergic condition such as asthma, peanut allergy, rhinitis or dermatitis [52].

2.6 Shellfish and Fish

Shellfish allergies are among the most common and serious types of food allergies on a worldwide basis [53], [54], [55], [56], [57], [58]. Shellfish allergy is the most common among all allergenic foods in the Asian population [55]. The prevalence of shellfish and fish allergies is mostly dependent on the availability of seafood in the locality. Shellfish and fish allergies can be important causes of severe acute hypersensitivity reactions, including fatal anaphylaxis (2). Furthermore, although children can develop tolerance to most common food allergens, the potential for persistence of seafood allergy should be considered when counseling families regarding its expected clinical course [20]. Moreover, epidemiological studies informed that up to 43% of fish-allergic people may also be allergic to shellfish [50]. This is likely due to their increased atopic predisposition guiding to development of multiple types of IgE, which are leading to various types of food allergies and may not be due to cross-reactivity.

2.7 Tree Nuts

Tree nuts are including walnut, hazelnut, pecan, almond, cashew, pistachio, and Brazil nut.The prevalence rate of tree nut allergy is 0.5% in the US in the unselected population survey on tree nuts and peanuts [59], and hazelnut allergy is common in Europe [60]. Tree nut allergies were thought to be lifelong, however, a study done in a tertiary allergy referral center showed that 9% of patients including those who had previous severe reactions outgrew their allergies [61].

3. Symptoms and Diagnosis of Food Allergy in Children

3.1 Symptoms

The most common symptoms of food allergy involve skin (urticaria, angioedema, itching, morbiliform rash, erythema), gastrointestinal (nausea, vomiting, abdominal pain, diarrhea) and respiratory system (acute rhino-conjunctivitis, wheezing, coughing, stridor) with the most severe in the form of anaphylaxis [62]. In young children, food allergy can present as a food aversion due to underlying symptoms of lip tingling, abdominal pain or nausea, which non-verbal child cannot express [63]. Table 1 shows the most common symptoms of food allergy in children.

Table 1. *Classification and symptoms of food allergy in children*

IgE- mediated	Non-IgE- mediated	Mixed IgE- & non-IgE-mediated
Skin		
Urticaria	Dermatitis herpetiforms	Atopic dermatitis (eczema)
Angioedema	Contact dermatitis	
Erythema		
Itching		
Acute angioedema		
Gastrointestinal system		
Nausea	Blood and/or mucus in stools	
Vomiting	Infantile colic	
Colicky abdominal pain	Abdominal pain	
Diarrhea	Food refusal or aversion	
Angioedema of the lips, tongue and palate	Gastroesophageal reflux disease	
Oral pruritus	Loose or frequent stools	
	Constipation	
	Perianal redness	
	Pallor and tiredness	
Respiratory system		
Upper: Nasal, itching, sneezing, rhinorrhea or congestion; **lower:** Cough, chest tightness, wheezing or asthma		Asthma
Oral allergy syndrome	Food protein-induced entero-colitis syndrome (FPIES)	Eosinophilic oesophagitis (EOE)
Acute gastrointestinal spasm	Food protein-induced procto-colitis syndrome (FPIPS) Food protein-induced enteropathy syndrome- celiac disease	Eosinophilic gastritis Eosinophilic gastroenteritis
Other		
Symptoms of anaphylaxis or other systemic allergic reactions		

Sources: *Sampson [80], NICE [102]*

3.2 Diagnosis

The medical history and examination are recommended to aid in diagnosis. A detailed history of the reaction to each incriminated food is essential for proper diagnosis [64]. Tests for food-specific IgE are recommended to assist in diagnosis, and medically monitored feeding is considered the most specific test and gold standard for diagnosing food allergy [65]. Testing "food panels" using food-specific IgE and/or skin prick testing without considering history is often misleading and not recommended [66, 67]. Skin prick tests are realized through pricking the patient skin with the needle containing small amount of the allergen extract, are regarded as a safer way of allergy diagnosis, but unfortunately less reliable. The sensitivity of skin prick test greater than 95%, but the specificity is only 50% [68, 69]. Combined skin prick and patch testing are a useful tool for the diagnosis of food hypersensitivity in children with atopic dermatitis [70], [71], [72]. Several tests are not recommended to show food allergy, including food-specific IgG/ IgG4, total IgE, applied kinesiology, and electro-dermal

testing [73]. The differential diagnosis of IgE-mediated food allergy should be done with entities that present similar symptoms but are not related to food: diseases with vomiting and diarrhea in children. In addition, the differential diagnosis also needs to include non-immunological food intolerance syndromes (cow's milk intolerance) and reactions by toxic agents, which contaminate or were generated during food processing [74]. In vitro diagnostic methods include quantification of specific IgE antibodies using assays such as the Immuno-CAP (Phadia, Termo Scientific, Sweden). For fish allergy, a diagnostic level of IgE that can predict clinical reactivity in the US population with > 95% certainty was identified as 20 KUA/l [63], although diagnostic decision points for specific serum IgE to other species of fish or shellfish are still needed. However, the problem of serological and clinical cross-reactivity between different fish and shellfish species has not yet been solved. There is a high co-occurrence of food allergy with other atopic diseases, including atopic dermatitis, asthma, and allergic rhinitis [75, 76].

3.2.1 Diagnosis of Anaphylaxis

Three different diagnostic criteria were described for the diagnosis of anaphylaxis: sudden illness with involvement of the skin, mucosal tissue, and the sudden respiratory symptoms. Skin or mucosal symptoms and signs, respiratory symptoms, or gastrointestinal symptoms, as well as reduced blood pressure [77].

3.2.2 Diagnosis of Atopic Dermatitis (Eczema)

Atopic dermatitis is clinically defined by the presence of pruritus, and a relapsing eczematous rash typically found over flexor surfaces [78, 79]. In children with atopic dermatitis, skin symptoms significantly diminished after an elimination diet. According to [80], exclusive breast feeding in newborn infants reduced the development of atopic dermatitis (eczema) 7-fold compared to infants receiving cow's milk.

3.2.3 Diagnosis of Asthma

In children capable of doing spirometry, asthma was diagnosed in the presence of reversible airway obstruction [81] or improvement in asthma symptoms after inhaled steroid or leukotriene modifier agent therapy, which is a potent bioactive known to play an important role in asthma, in addition to produce local effect on cutaneous blood vessels [82, 83].

3.2.4 Diagnosis of Rhinitis

Allergic rhinitis is clinically defined by the occurrence of symptoms such as rhinorrhea, nasal obstruction, nasal itching, and sneezing in children with aeroallergen sensitivity [84]. Pediatric allergy specialists made the diagnosis of accompanying allergic diseases.

3.2.5 Diagnosis of Accompanying Food Allergies

Children were diagnosed as having IgE-mediated food allergy when they fulfilled both of the following two criteria [85]: A consistent of symptoms that developed in the early phase after the ingestion of implicated food. The presence of the implicated food sIgE is shown by positive titers of sIgE or positive skin prick test of the implicated food. In particular, children with moderate-to-severe atopic dermatitis appear to have a significant risk approximately 35% of food allergy [86]. There are no similar studies in adults, and therefore the prevalence of co-occurring food allergy in adults with atopic dermatitis is unknown.

4. Methods of Allergens Detection

In general, protein or peptide detecting methods are to be preferred over DNA detection methodologies by usually polymerase chain reaction (PCR) [87]. DNA is stable against thermal process and pH alteration that often happening during industrial food manufacturing, it is an ideal target for the specific allergen detection with low risk of cross-reactivity phenomena [88]. Experiments of PCR are fast, simple to manage and to incorporate into analysis. Moreover, recent examples of real-time PCR application were stated for the identification of sesame, hazelnut, pistachios, fish, almonds and mustard allergens in commercial food products [88], [89], [90], [91], [92]. However, despite all the advantages, PCR should only be used where no other protein detection technology is available. On the other hand, for validation of cleaning processes, or for ingredient or final product testing, enzyme-linked immune-sorbent assays (ELISA) are the current method of choice as the technique is generally quantitative and sufficiently sensitive for this purpose (Fig. 3), and ELISA are 4 types: direct, indirect, competition and sandwich (Fig. 4), in addition to the general procedure of ELISA is also identified in Fig. 4. Most current allergen detection methods are immunoassays [such as aptamer, immuno-affinity capillary electrophoresis (IACE) with laser-induced fluorescence (LIF)], utilizing antibodies raised against the target food or food protein extracts to broadly identify the allergenic food [93]. Separation techniques that are used for direct detection and quantification of allergens comprise LC-MS and CE-MS with UV or fluorescence detection [94], [95], [96]. Due to the potential co-elution of other compounds present in the sample matrix, separation techniques are typically coupled with MS for unambiguous allergen detection to avoid the negative effect.

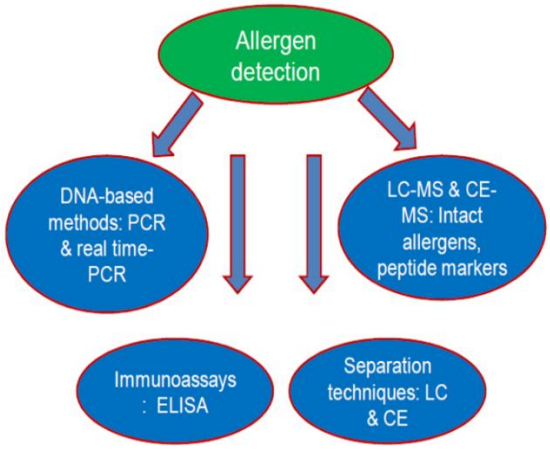

Fig. 3. *Analytical methods used for the allergen detection and quantification in food products.*

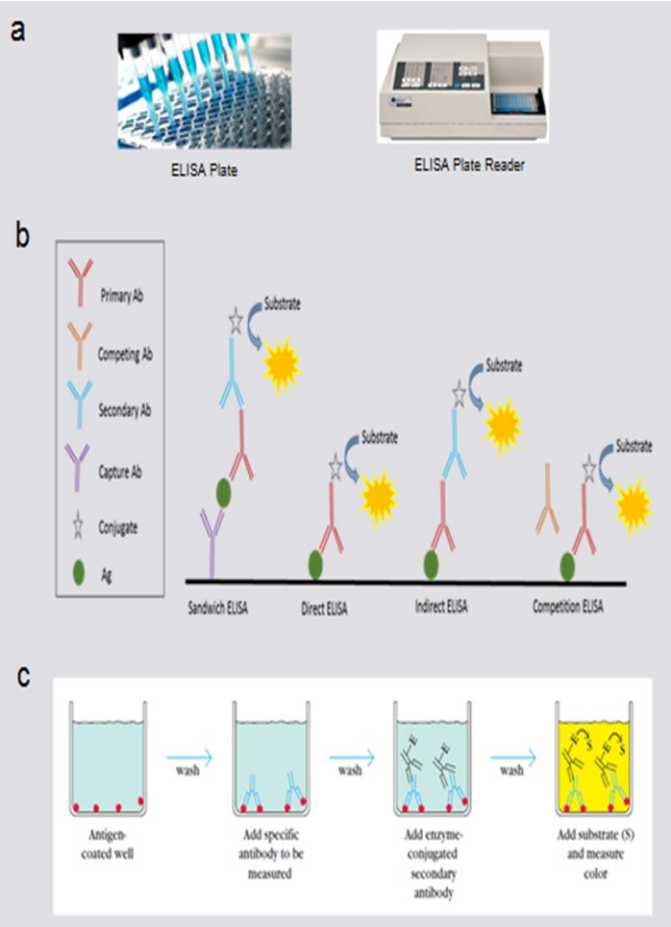

Fig. 4. *ELISA plate and ELISA Plate Reader (a), ELISA types (b) and general procedure of ELISA (c).*

5. Research and Future Challenges in Food Allergy

As presented in Table 2, the prevalence of food and skin allergies increased in children under 18 years from 1997-2011 in the United States. Moreover, the prevalence of skin allergies decreased with age, while the prevalence of respiratory allergies increased with age (Table 3) [97]. According to study of [97], Hispanic children had a lower prevalence of food allergy, skin allergy and respiratory allergy compared to children of other race or ethnicities. Therefore, Non-Hispanic black children were more likely to have skin allergies and less likely to have respiratory allergies compared with non-Hispanic white children. On the other hand, the family income is play an important role in the prevalence of food and respiratory allergy in children, thus children with higher poverty level had the highest prevalence rates [98].

Table 2. *Percentage of children (0-17 years of age) with reported allergic condition in the United States (1997 to 2011)*

Period from 1997-2011	Children allergy (%)		
	Food allergy	Skin allergy	Respiratory allergy
1997-1999	3.0	7.5	17.5
2000-2002	3.1	8.0	17.7
2003-2005	4.0	9.7	17.4
2006-2008	4.5	10.0	16.5
2009-2011	5.2	12.5	17.3

Source: *Jackson et al. [97], National Child Health Services, NCHS data brief, No: 121.*

Table 3. *Percentage of children (0-17 years of age) with reported allergic condition by age group in the United States (2009 to 2011)*

Allergy type	Children age (%)		
	0-4 years	5-9 years	10-17 years
Food allergy	5.0[a]	5.1[a]	5.0[a]
Skin allergy	14.2[a]	13.1[b]	11.0[c]
Respiratory allergy	11.0[c]	17.5[b]	21.5[a]

[a, b and c] *Significant differences among age groups. Source: Jackson et al. [97], National Child Health Services, NCHS data brief, No: 121.*

Children are increasingly acknowledged to have rights in the determination of medical decisions that affect them. This has encouraged research to be undertaken with children themselves to understand their own views on the impact of a disease on their experiences and relationships. It has become increasingly important for researchers and healthcare professionals to understand how the perceptions, experience, and impact of chronic diseases might influence a patient's interpretation and response to it, so that we, in turn can respond more appropriately. Related to this, the role of psycho-educational interventions in facilitating adaptation to chronic diseases has received growing recognition and is in keeping with policy developments advocating greater involvement of patients in their own care [22, 40]. Such a model may be used to explain both physiological and psychological phenomena, and their interaction, and consequently provide a shared language as a basis for multidisciplinary studies in food allergy. Longitudinal studies are necessary when the goal is to investigate cause and effect. Identification of biomarkers those are predictive of poor growth in children with allergy and atopic diseases, in addition to development of novel methods for identifying diet-responsive and non-responsive phenotypes. There are therapies not allergen, especially

attractive due to many patients have multiple food allergies. These approaches include immunotherapy with modified food proteins, peptide bacterial adjuvants, traditional Chinese medicine, probiotics, and others [99, 100]. A number of tests are currently underway to investigate the most effective strategies for avoiding food allergy in children and a number of diagnostic approaches, such as basophil activation techniques and allergenic epitope analyzes [101]. At present, Euro-prevall is conducting a birth cohort study in food allergy that includes clinical and psychological measures. Some studies may also lead to novel treatment options in the future.

6. Conclusion

In conclusion, allergy disease begins early in the first years of life. It is the result of mutual interaction among genetic factors, environmental factors and immunological (physiological) factors. Current preventive measurements for allergic children include allergens avoidance, better management of allergic reactions and choosing the most appropriate foods. Furthermore, practice implications could include additional care, vigilance for food allergy symptoms and diagnosis among children, and avoidance of all types of allergens (milk, eggs, peanuts, wheat…ect), as well as preparation of nutritious gluten-free products for celiac disease (CD) patients. Combined skin prick test and patch test is a useful tool for the diagnosis of food hypersensitivity in children with atopic dermatitis. Presently, the methods of choice for precise and sensitive allergen detection in the food products are ELISA, real-time PCR and LC-MS. On the other hand, immunotherapy is a future hope for persistent to detecting and treating of food allergy in children and adults.

Acknowledgments

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