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DIAGNOSTYKA

Food allergy: epidemics of the 21st century?

SUMMARY

Food allergy is an adverse reaction to food that is caused by a specific immune response. Food allergy is a common disorder. **Alergia pokarmowa jest reakcją organizmu na białka pokarmowe o podłożu immunologicznym.**

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Introduction

Food allergy is defined as “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.” (1)

The most common food allergens in children include cow’s milk, hen’s egg white, soy, wheat, peanut, tree nuts, and fish. In the adults the most common food allergens include: peanut, tree nuts, fish, and shellfish. In addition, mild oral symptoms (so called pollen-food allergy syndrome or oral allergy syndrome) caused by raw fruits and vegetables occur in a large subset (25-75%) of children and adults with pollen allergy. The manifestations of food allergy are diverse and range from mild hives to anaphylaxis and chronic gastrointestinal symptoms (reviewed in Table 1). (2)

Food allergy is estimated to affect “more than 1-2% but less than 10%” of the general population in the USA. (3) The wide estimate of the affected population reflects the challenges of determining food allergy prevalence with certainty due to the limited accuracy of the self-reported symptoms and the diagnostic allergy tests that rely on the detection of the IgE sensitization to the specific foods. The gold standard of food allergy diagnosis, the double-blind, placebo-controlled oral food challenge (DBPCFC) cannot be easily applied to epidemiologic studies due to limited availability and high cost. (4) The issue is further complicated by the non-IgE-mediated food allergic reactions (also referred to as food hypersensitivity reactions) that are usually manifesting with isolated and chronic/intermittent gastrointestinal symptoms. These non-IgE-mediated food allergies usually occur in the setting of an undetectable food-specific IgE antibody (by serum measurement or prick skin test) and their diagnosis requires a confirmatory endoscopy and intestinal biopsy as well as empiric elimination diet and re-challenge with the offending food. Nevertheless, the literature on epidemiology of food allergy has been steadily growing over the past two decades and has accumulated robust evidence regarding the scope of this problem.

Food allergy has emerged as a major public health problem in the westernized societies in the past two decades. In the US, a recent study from the Centers for Disease Control reported an 18% increase in food allergy prevalence from 1997 to 2008 in children under 18 years of age. (5) In the US, Canada, and UK, prevalence of peanut allergy in young

children tripled over the same time period. (6) Food allergy is the leading cause of anaphylaxis and the emergency department admissions for allergic reactions, over the past two decades there was an increase in the emergency department visits due to food allergy. (7) **Public perception and common**

misconceptions about food allergy

Ingestion of foods can induce a number of adverse reactions (reviewed in the table 2). Patients may casually refer to any adverse food reaction as “food allergy”; up to 20% of the interviewed subjects report some “food allergy”. (8) However, only a fraction of those perceived adverse reactions has an immunologic etiology and the reported symptoms alone don’t provide a reliable estimate of food allergy frequency. The new US guidelines summarize a self-report rate of about 13% compared with about 3% when testing and or DBPCFC is performed. (1) The pediatric study by Bock (9) found 28% reported symptoms (parent or doctor reports), but only 28% of those with complaints were verified on OFC. In the study by Young et al, (8) 19% of the complaints were verified on challenges. It is important to discern the different pathophysiology of adverse food reactions because over-diagnosis of food allergy may result in global malnutrition or specific nutrient deficiencies. **Prevalence of food allergy in**

the USA

In the US, the seminal population-based study was conducted by S. Allan Bock. (9) and estimated the prevalence of adverse reactions to foods in children under age 3 years to be between 6% and 8%. This study included children from a birth cohort, utilized frequent telephone contact with the parents and the pediatricians and supervised oral food challenges (OFCs). This study did not distinguish between immediate (classic, IgE-mediated) and non-IgE-mediated gastrointestinal food allergies. Liu et al (10) took advantage of the serologic testing (IgE to milk, egg, peanut, and shrimp) performed during the National Health and Nutrition Examination Survey (NHANES) in the United States from 2005 to 2006. Estimates of clinical food allergy risk were based on previous studies correlating clinical outcomes to food-specific IgE concentrations. (11) The overall food allergy prevalence was estimated at 2.5%. In the children age 1 to 5 years, clinical allergies to milk, egg, and peanut were estimated at 1.8% each. Branum and Lukacs (5) reported that in 2007, on the basis of the National Health Interview Survey response to the query, “During the past 12 months has [child] had any kind of food or digestive allergy?”, 3.9% of US children were affected and that the prevalence of food allergy increased by 18% between 1997-2007. Analyses of data from 2441 mothers in the 2005/2007 US Infant Feeding Practices Study II, (12) which followed newborns to age 1 year and defined probable food allergy as doctor-diagnosed or immediate food-related symptoms (likely urticaria/angioedema), found a rate of 6% (milk, 3.8%; soy, 1.4%; fruit, 1.2%; peanut, 0.6%; wheat, 0.5%).

In telephone surveys, shellfish allergy was reported at a significantly higher rate among black/African American subjects than white subjects (3.1% vs 1.8%). (13) Non-Hispanic blacks also had increased risks of having serologic results indicating likely food allergy in the NHANES study (odds ratio, 3.1). (14) Boys appear to be at higher risk than girls, and perhaps women more than men. (13)

Mechanism

IgE-mediated

Mixed*

Cell-mediated

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General

Anaphylaxis; FDEIA **

Gastrointestinal

Immediate GI symptoms

Pollen food allergy syndrome

Eosinophilic esophagitis /

gastroenteritis

Celiac disease; Enteropathy

FPIES***

Allergic proctocolitis

Respiratory

Bronchospasm

Asthma

Heiner's syndrome****

TABLE 1 Classification of food allergy based on the involvement of IgE antibody in the pathophysiology of food allergy

*Mixed pathophysiology involves both cell-mediated and IgE-mediated mechanism

**FDEIA: Food-dependent, exercise-induced anaphylaxis

***FPIES; food protein-induced enterocolitis syndrome

****Heiner's syndrome: pulmonary hemosiderosis reported in association with milk and buckwheat allergy

Prevalence of food allergy in the UK and Western Europe

The prevalence of food allergy in the general population was estimated as 1% to 2% on the basis of a study by Young et al. (8) Venter et al (15) reported on the rate of food allergies among a birth cohort of 969 children on the Isle of Wight, UK, evaluated at age 3 years. Percent testing positive among 642 tested were as follows: peanut (2%), egg (1.4%), sesame (1.4%), wheat (1.3%), milk (0.5%), and cod (0.5%). The cumulative percentage of complaints of adverse food reactions was 34% at 3 years, with 8% having a current complaint. Using unmasked OFCs and a clear history, the cumulative incidence was 6%, and using DBPCFCs, 5%; the primary triggers were milk, egg, and peanut.

Osterballe et al (16) evaluated 1272 young adults age 22 years in Denmark, by using questionnaires, skin prick tests (SPTs), and OFCs. By questionnaire, 20% reported adverse reactions to non-pollen-associated foods, which after OFC (performed in 42 cases among 165 with complaints) resulted in a prevalence of 1.7%.

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In the European Community Respiratory Health Survey, in which 4522 young adults from 13 countries were tested with up to 24 foods,(17) the most common food sensitizations included: hazelnut, peach, shrimp, wheat, apple, sesame, carrot, kiwi, celery, corn, tomato, rice, and buckwheat (from 7.2% to 2.8%), peanut (2.6%); banana, walnut, sunflower, soy, poppy, melon, mustard, milk, egg, and fish (from 2.5% to 0.2%).

Pollen-food allergy syndrome

Among pollen-allergic individuals, 74% reported symptoms (majority had oral symptoms), to the pollen-associated foods (e.g., fruits and vegetables). (16) In a study of a birth cohort of 562 children from Denmark (18) evaluated periodically with interviews, SPT, food-specific IgE, and OFC (offered for suspicion of allergy or positive tests without ingestion) to age 6 years, overall, 3.7% had positive food challenges to 1 or more foods.

Oral allergy syndrome/pollen food-related allergy clearly fulfills the definition of food allergy but is often not focused on when statistics are offered regarding food allergy. In a study of young adults in Denmark, 16.7% reported this type of allergy.(16)

Prevalence of nut, sesame and shellfish allergy

A number of large population-based studies have addressed the prevalence of peanut and other food allergies. (19) (Table 3) Three studies used a random calling method with administration of a survey, two studies utilized allergy testing and OFCs, and one was a retrospective study in a specialist referral population. (6;20-22) All of these studies estimated that peanut allergy affects more than 1% of children in Canada, the United States, Australia, and the UK.

Toxic / Pharmacologic

Non-Toxic/ Intolerance

Food poisoning

Scromboid fish poisoning

Histamine

Tyramine

Caffeine

Alcohol

Latose intolerance due to lactase deficiency

Galactosemia

Pancreatic insufficiency

Gallbladder / liver disease

Panic, anxiety

Depression, anorexia, bulimia

Hiatal hernia

Gustatory rhinitis

Auriculotemporal syndrome*

Blepharochalasis**

TABLE 2 Differential diagnosis of food allergy: selected non-immune mediated adverse food reactions

*Auriculotemporal syndrome (Frey's syndrome): transient uni or bilateral facial flushing or sweating following ingestion of spicy or flavored foods, infants and children with history of forceps delivery and damage to auriculotemporal nerve.

** Blepharochalasis an inflammation of the eyelid that is characterized by exacerbations and remissions of eyelid edema, which results in a stretching and subsequent atrophy of the eyelid tissue resulting in redundant folds over the lid margins. It typically affects only the upper eyelids, and may be unilateral as well as bilateral.

Meta-analyses and large scale reviews

A systematic review of the world literature by RAND Corp was performed by using pre-specified criteria and concluded that food allergy affected from 1% to 2% up to 10% of the population. (3) Two large meta-analyses were published by the EuroPrevall program. (23) (24). These meta-analyses showed significant heterogeneity between studies regardless of food item or age group. The EuroPrevall working group searched MEDLINE and EMBASE for articles from 1990 to 2005 and identified 51 articles that fulfilled inclusion criteria out of the 934 articles initially identified from a wide search strategy. Considering studies of allergy to "any food" where multiple foods were assessed, the overall prevalence rates were 12% self-reported in children and 13% in adults (based on 23 studies), 3% for all ages on the basis of testing and history (6 studies), and 3% for all ages on the basis of studies that included DBPCFC (6 studies). The studies had marked heterogeneity: rates of self-reported allergy varied from 3% to 35%. The rates of self-report, symptoms with sensitization, and rates based on OFC were as follows, respectively: peanut (0.75%, 0.75%, not available), milk (3.5%, 0.6%, 0.9%), egg (1%, 0.9%, 0.3%), fish (0.6%, 0.2%, 0.3%), and shellfish (1.1%, 0.6%, not available). Higher prevalence among children was seen; for example, 6% to 7% children self-reported milk allergy compared with 1% to 2% adults. Zuidmeer et al (24) reviewed the prevalence of plant food allergies to fruits, vegetables, legumes, tree nuts, wheat, cereals, soy, and seeds. Among the 6 studies including OFC, prevalence ranged from 0.1% to 4.3% each for fruits and tree nuts, 0.1% to 1.4% for vegetables, and <1% each for wheat, soy, and sesame. The prevalence of reported symptoms exceeded prevalence of sensitization except for wheat and soy among adults.

Food allergy and other allergic disorders

Food allergy is associated with other allergic disorders, including atopic dermatitis and asthma in childhood, anaphylaxis, and eosinophilic esophagitis, reviewed in table 4.

Is food allergy increasing in prevalence?

There are several studies in which similar methods were applied over time, that showed a 2-3-fold increase in peanut allergy and peanut-IgE sensitization in children in the US, UK, Canada, and Australia over the past 10-20 years. Multiple studies show rates of peanut allergy over 1% in young children.

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In a study from the same clinic in China performed in 1999 and 2009, rates increased from 3.5% to 7.7%

($P = .017$). (25) Branum and Lukacs reported on several US national databases in which information could be compared over time. (5) Based on the response to, “During the past 12 months has [child] had any kind of food or digestive allergy?” there was an 18% increase from 1997 to 2007. On the basis of diagnostic coding in US national ambulatory care surveys, ambulatory care visits tripled between 1993 and 2006 ($P < .01$).

Eosinophilic esophagitis (EoE) is an inflammatory disease of the esophagus characterized by eosinophilic infiltration of the esophageal mucosa. (26) Symptoms of EoE include gastroesophageal reflux, abdominal pain, growth failure, and dysphagia. Dysphagia is a more common presentation in adults and older children. Esophageal food impactions necessitating urgent endoscopic removal of the food and esophageal strictures requiring endoscopic balloon dilations may complicate EoE. The incidence of EoE (defined as minimum of 24 distal esophageal eosinophils per high power field (HPF), epithelial basal zone hyperplasia, and absence of eosinophilia in any other gastrointestinal segment) increased from 9.1 cases/100,000 children in 2000 to 12.8 cases per 100,000 in 2003, and the prevalence has increased from 9.9 per 100,000 in 2000 to 43 per 100,000 in 2003.(27) Similar trends have been observed in adults with EoE residing in Olten County, Switzerland. (28;29) Criteria for the diagnosis of EE consisted of typical history, typical endoscopic abnormalities, and histologic infiltration of the esophageal epithelium by 24 or more eosinophils per HPF, after excluding gastroesophageal reflux disease clinically and endoscopically. Annual incidence of 1.7 cases per 100,000 inhabitants was noted (range 0–8), with a marked increase in newly diagnosed cases in the past few years. EoE is a chronic disease and the prevalence steadily increased from 2 per 100,000 in 1989 to 30 per 100,000 at the present time.

Food

General

Children <5 years of age

Adults

Cow's milk

0.4% - 0.9% (14;23)

0.5%* (Israel)(52) -3.8%(US, UK)(12) (15) (14)

Hen's egg white

0.2%(14)

~2% (14) (15)

Soybean

0;0.7% (24)

1.4%

0 - 0.7%*(24)

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Wheat

0;1.2% (24)

~0.5%(12) (15)

0-1.2% (24)

Peanut

0.75%(23)- 1.3% (14)

0.2% (Israel)(53) -1.9 % (US, Canada, UK) (20);(6;53);

0.7% (6;20)

Tree nuts*

0.6%-1.1% (6;20)

1.1% (6); 1.6% (20)

0.5%(6); 1%(20)

Sesame/seeds

Overall, 0.1%(20) (6); <1%*(24)

0.6%(15)

Fish

Overall, 0.3%; 0.5% (23) (20)

(6)

0.2%(20) (6); 0.5%(15)

~ 0.6%(20);(6)

Shellfish

0.6%(23); 2%(14); (6;20)

0.5% (20) (6)

Age 14-16 y, 5.2% (Singapore)(22)

1.7%(20); 2.5% (6)

Fruits

up to 4.2% (SPT); up to 8.5% (symptoms)(24)

0.4%* (UK)(15)

Vegetables

0.1 to 0.3%*, up to 2.7% (SPT); up to 13.7% (symptoms)(24)

1.2% (12)

Oral allergy (raw fruits/vegetables)

Age 22 y, 17% (Denmark)(16)

TABLE 3 Prevalence of allergy to specific foods **Food-induced anaphylaxis**

Food is the most common trigger of anaphylaxis in the community.(30) In the United States, comparison in Minnesota from 1983 to 1987 and 1993 to 1997 potentially show a 71% to 100% increase.(30-32) Studies focusing on pediatric food-related ambulatory and emergency department visits or food-induced anaphylaxis suggest increases as well.(5;33;34) Data from 34 emergency departments in the US National Electronic Injury Surveillance System were analyzed for food-related adverse events over August and September 2003. (34) There were 20,281 emergency department visits, 2333 episodes of anaphylaxis, and 520 hospitalizations for food allergy reactions in the United States over this 2-month period. For adults, shellfish was the most common trigger, whereas egg, fruits, peanuts, and tree nuts were more common triggers for young children. In 117 pediatric patients presenting with anaphylaxis to 1 hospital in Melbourne, Australia, food was responsible for 85% of reactions, and peanut (18%), cashew (13%), and milk (11%) were the most common triggers. (35) Two US emergency department-based cohort studies and the US National Hospital Ambulatory Medical Care Survey estimated 203,000 emergency department visits per year (for 2001-2005; 38% pediatric), including 90,000 as probable anaphylaxis. (36)

There are no studies to address directly the prevalence of fatal food-allergic reactions. However, the series of cases of fatal anaphylaxis identified the important risk features including age (adolescents and young adults), delayed use of epinephrine, and co-morbid asthma. (31) (37;38) (35) (39) **Risk factors**

Epidemiologic risk factors for food allergy may include genetic risks (familial associations, HLA, and specific genes), association with atopy (eg, atopic dermatitis), timing of exposure to allergen, route of exposure (eg, topical/respiratory exposure may be sensitizing), reduced consumption of ω -3 polyunsaturated fatty acids, and the hygiene hypothesis. (40) Another risk may be antacid medications that alter digestion and may allow increased immune exposure to ingested proteins.(41) Vassallo and Camargo (42) reviewed the mechanisms for the

hypothesized link between vitamin D and food allergy. Recent epidemiologic study findings, such as the observations that season of birth is a risk factor, (43) that food-induced pediatric anaphylaxis is more common in northern areas of the United States,(44) and that maternal intake of vitamin D during pregnancy was associated with a decreased risk of food sensitization,(45) support this hypothesis.

Summary

Although the exact prevalence and incidence of food allergies remain uncertain, food allergies are common and have significant impact on life quality. Rates of food allergy vary geographically, reflecting various genetic, environmental and dietary factors.

□

Disorder

Food allergy frequency

Comments

Atopic dermatitis (AD)

30-40% of children with moderate to severe persistent AD, not controlled with optimal medical therapy (meticulous skin care and top

Most common food allergens in children include: milk, egg white, soybean, wheat, peanut, tree nuts, fish. (46) When food is ingested

Asthma

Several studies have indicated that having food allergy may be a risk for problematic asthma, and having asthma may be a risk for s

Frequency of peanut allergy was increased among the children admitted with severe asthma-exacerbations(49)

Anaphylaxis

Foods are the most common triggers of anaphylaxis outside the hospital in children and adults.

Serum tryptase is not a reliable marker for food-induced anaphylaxis. Risk factors for fatal food-induced anaphylaxis include: age (

Eosinophilic esophagitis (EoE)

Overall, it is estimated that in 50% of subjects with EoE food allergens play a role.

In young children with EoE, response to an elemental diet is >95%.(50;51)

TABLE 4 Frequency of food allergy among other allergic disorders
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