The many faces of food allergy

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Food allergy is a common problem in medical practice. Because of its diverse manifestations, confusion exists regarding whether certain symptoms are caused by food allergy. Major target organs involved in food allergy reactions include: the skin, the upper and lower respiratory tracts and the gastrointestinal tract. In this article, various manifestations of food allergy are discussed along with their pathophysiologic mechanisms.

Key words: Food allergy, Food hypersensitivity, Manifestation, Pathophysiology, Diagnosis.

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Objective: To review various presentations and clinical syndromes associated with / or caused by food allergy.

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การแพทย์ เป็นปัญหาที่พบบ่อยในชีวิตปฏิบัติ โรคหนึ่งมีอาการแสดงได้ในหลายระบบของร่างกาย และอาการแสดงแตกต่างกันในแต่ละบุคคล การวินิจฉัยการแพทย์จึงเป็นปัญหาที่สำคัญสำหรับทั้งแพทย์และผู้ป่วย

การแพทย์มีอาการแสดงหลักๆ ใน 3 ระบบคือ ระบบมิติหนึ่ง, ระบบทางเดินอาหาร และระบบทางเดินหายใจ กลไกการเกิดแสดงต่างกันตามชนิดของโรค สามารถแบ่งได้เป็น IgE-mediated, Mixed IgE- and non–IgE-mediated และ Non-IgE-mediated reactions

บทความนี้ได้นำเสนอความรู้เกี่ยวกับการแพทย์ ในด้านอาการแสดง และอาการซึ่งเกิดจาก การเกิดโรค รวมทั้งนำเสนอกลุ่มอาการและโรคต่างๆ ที่เกี่ยวเนื่องกับการแพทย์
Hippocrates, "Father of Medicine" first described adverse reaction to food over 2000 years ago. Other Greek scholars recorded adverse reactions to cow's milk in the first and second centuries. However, it was not until the 20th century that significant advances were made in the understanding of food allergy.

Because food allergy has diverse manifestations and involves different organ systems, confusion exists in the medical community as well as in the public regarding whether food allergy is the cause of certain symptoms. In the following review, clinical manifestations of food allergy classified according to their pathophysiologic mechanisms are discussed.

Pathophysiologic classification

Because of the complex pathophysiologic mechanisms, it is more appropriate to classify food allergy reactions into three groups: IgE-mediated, Mixed IgE- and non-IgE-mediated or Partially IgE-mediated, and Non-IgE-mediated, rather than two strictly separate IgE-mediated and non-IgE-mediated mechanisms. Non-IgE-mediated reactions are generally more difficult to diagnose. Physicians should be familiar with different presentations of food allergy in order to make appropriate diagnosis.

Clinical manifestations

Major target organs involved in food allergy reactions include the skin, the upper and lower respiratory tracts and the gastrointestinal tract. Manifestations of food allergy vary greatly with symptoms ranging from itchy mouth to fatal food-induced anaphylaxis.

Cutaneous manifestations IgE-mediated reactions:
Urticaria and Angioedema

Food-induced acute urticaria and angioedema are well recognized adverse reactions to food. The causative food is usually obvious because of the close temporal association between eating the food and the development of symptoms. Contact urticaria is usually obvious as well. An example is hives and swelling of the hands while peeling shrimp in patients with shrimp allergy. Although it is common that acute urticaria has food allergy among its etiology, chronic urticaria and angioedema are rarely caused by food allergy. In a review of 554 patients with chronic urticaria, only 1.4% of cases were attributable to food ingestion. Food additives such as dyes and preservative have been implicated in chronic urticaria, but are rarely confirmed by appropriate challenges.

Mixed IgE- and non-IgE-mediated reaction: Atopic dermatitis

Atopic dermatitis is one form of eczema. This disorder generally begins in infancy and is characterized by extremely pruritic skin lesions, chronically relapsing course, and distinctive distribution. The pathogenic role of allergy in atopic dermatitis has been long debated. Recent studies delineated the role of allergen-specific IgE antibodies and other inflammatory cells in the pathogenesis of atopic dermatitis. Langerhans cells, professional antigen presenting cells in the skin, are increased in lesions of atopic dermatitis. They possess allergen-specific IgE antibodies on their surface and promote \( T_\alpha \) response to allergens. Infiltrating T lymphocytes in acute eczematous lesions express predominantly
T\(_{h1}\) cytokines, IL-13\(^{(4)}\) This is in contrast to classic "delayed" cell-mediated responses, such as the tuberculin response which is T\(_{h1}\) type response. Several well-controlled studies have concluded that food allergy plays a significant adverse role in atopic dermatitis.\(^{(4-6)}\) By utilizing double-blind placebo-controlled food challenges, clinically significant food allergy is present in 33% of typical pediatric atopic dermatitis patients.\(^{(5)}\) In some children with atopic dermatitis and food allergy, non-IgE-mediated mechanism is suggested. A double-blind, placebo-controlled food challenge performed in 139 children with atopic dermatitis and suspected food-related clinical symptoms showed that around 10% of positive challenge results were not IgE mediated. Wheat challenge results were more often positive among the apparently non-IgE-sensitized children, while hen's egg challenge results were more often positive in the IgE-sensitized group.\(^{(7)}\) Therefore any child with persistent moderate-to-severe atopic dermatitis deserves evaluation for possible food allergy, especially those with skin symptoms resistant to conventional treatment.

Non-IgE-mediated reactions: Dermatitis herpetiformis

Dermatitis herpetiformis is a chronic, intensely burning, pruritic vesicular skin disease associated in most instances with a subclinical gluten-sensitive enteropathy and IgA deposits in the upper dermis. It is characterized by a chronic, intensely pruritic papulovesicular rash symmetrically distributed over the extensor surfaces and buttocks. Granular (85 % to 90 %) or linear (10 % to 15 %) deposits of IgA, PMNs, and C3 accumulate in the dermoeidermal junction of both involved and uninvolved skin. The histology of the intestinal lesion is virtually identical to that seen in celiac disease, although villous atrophy and inflammatory infiltrates are generally milder and often clinically insignificant.\(^{(8)}\)

Gastrointestinal manifestations IgE-mediated reactions: Immediate gastrointestinal hypersensitivities and Oral allergy syndrome

Immediate gastrointestinal hypersensitivity reactions consist of nausea, vomiting, abdominal pain, and diarrhea that typically develop within minutes to 2 hours after ingestion of the responsible food. It is important to note that some infants may present with intermittent vomiting and failure to thrive rather than immediate symptoms.

The oral allergy syndrome (OAS) is a form of contact allergy that is confined almost exclusively to the oropharynx. It rarely affects other target organs or causes anaphylaxis. The symptoms include pruritus, tingling and angioedema of oropharyngeal area, for example, lips, tongue, palate, and throat, and occasionally a sensation of pruritus in the ears, or tightness in the throat. It is caused by local IgE-mediated mast cell activation. OAS is most commonly associated with the ingestion of various fresh fruits and vegetables.\(^{(9,10)}\) The patients usually tolerate these foods in cooked form.

Mixed IgE- and non-IgE-mediated reactions: Allergic eosinophilic esophagitis, gastritis, and gastroenteritis

This group of disorders is characterized by infiltration of the esophagus, stomach, and/or intestinal walls with eosinophils, basal zone hyperplasia in the absence of vasculitis. Peripheral eosinophilia can be
found in about 50% of patients. Clinical symptoms correlate with the extent of eosinophil infiltration.\(^{(11, 12)}\) Eosinophilic infiltration of mucosal layer causes malabsorption and diarrhea, while the infiltration in muscular layer leads to symptoms of obstruction. Infiltration of the serosal area results in eosinophilic ascites. The underlying immunopathogenesis of these disorders is poorly understood. Some patients may also develop IgE-mediated food allergy.

Allergic eosinophilic esophagitis is seen most frequently during infancy and adolescence. The patients with gastroesophageal reflux, intermittent emesis, food refusal, abdominal pain, dysphagia, irritability, sleep disturbance, and failure to respond to conventional reflux medication. One study of children less than 1 year of age with gastroesophageal reflux found that 40% had cow’s milk-induced reflux.\(^{(13)}\) Therefore in children with reflux not responding to medication, food allergy evaluation should be considered.

Allergic eosinophilic gastritis also is more common between infancy and adolescence. The presentation include postprandial vomiting, abdominal pain, anorexia, early satiety, hematemesis, failure to thrive, and gastric outlet obstruction. Resolution of symptoms may require 3 to 8 weeks after the elimination of the responsible food allergens.\(^{(14)}\)

**Non-IgE-mediated reactions: Dietary protein enteropathy, enterocolitis and proctitis**

A well recognized dietary protein enteropathy is celiac disease, which is characterized by extensive loss of absorptive villi and hyperplasia of the crypts, leading to malabsorption, chronic diarrhea, steatorrhea, abdominal distention, flatulence, and weight loss or failure to thrive. In contrast to gluten-induced celiac disease, patients with cow’s milk induced enteropathy usually present at a younger age, have less severe villus injury, and outgrow the protein sensitivity, generally by 3 years of age. The universal symptom of dietary protein-induced enteropathy is diarrhea, usually associated with early satiety, emesis, and failure to thrive.\(^{(15, 16)}\) Malabsorption, anemia and protein-losing enteropathy can also be associated with this disorder. The clinical presentation of enteropathy is usually more gradual than enterocolitis or proctitis. As noted previously, cow’s milk protein is most commonly implicated, although other food protein such as soy, egg, wheat, rice, and chicken can also be a cause. Serum IgE, and skin tests to the protein are generally negative. Clinical remission is usually achieved in 7 to 10 days after elimination of the causative food. Long-term follow-up showed that 80% of patients who are allergic to cow’s milk will tolerate the offending protein by 2 years of age, with nearly 100% recovery by 3 years.\(^{(17)}\)

Patients with dietary protein enterocolitis are usually between 1 week and 3 months of age. The causative dietary proteins are generally cow’s milk or soy protein. Clinical manifestations are relatively acute, consisting of vomiting, diarrhea, rectal bleeding, and dehydration with metabolic acidosis. Hypotension may occur in younger infants. The severity of the symptoms often lead to concerns about possible sepsis. The stools contain mucous, with polymorphonuclear leukocytes and eosinophils. Symptoms resolve within 72 to 96 hours after elimination of the offending protein from the diet. Even though the presentation in some patients may mimic anaphylaxis, this clinical syndrome is not IgE-mediated and is not classified
as an anaphylaxis because the markers of immediate hypersensitivity are lacking. Food-specific IgE and skin tests are negative. The long-term responses to open food challenge suggest that 50 % of involved infants can tolerate the offending protein by 18 months of age and 80 % by age 3 years. The pathophysiology of this disorder is incompletely understood. Fecal TNF-alpha was found in increased concentrations after positive milk challenge responses in patients with enterocolitis. (16)

Dietary protein proctitis mostly occurs in infants. Typically, the patients present at 2 to 6 weeks of age with blood streaked in stool. The patients appear well despite the bloody stool. Weight gain and growth are normal. Neither emesis nor abdominal distention are seen. It should be noted that more than half of the reported infants have been extensively or exclusively breastfed. Thus, breast feeding does not rule out the possibility of food allergy. Colonoscopic examinations have revealed inconsistent gross features ranging from focal erosions to linear erosions and friability, which may be prominent in the sigmoid colon. Focal epithelial erosions are common. As with the other non-IgE-mediated syndromes, the elimination of the offending protein from the diet leads to a clinical resolution within 72 to 96 hours, in both formula and breast-fed infants. Nearly all of these infants will tolerate an unrestricted diet at 9 -12 months of age. There is no long term sequelae after a follow-up for more than ten years. (16)

Respiratory manifestations IgE-mediated reaction: Rhinitis

Children with atopic disorders and food allergy frequently experience nasal symptoms during oral food challenges. In double-blind placebo-controlled food challenges of 480 children referred for evaluation of adverse food reactions, about 16 % experienced respiratory symptoms (sneezing, rhinorrhea, nasal obstruction, wheezing, cough, or ocular signs) during the challenges, but only 2 % of symptoms were confined to the respiratory tract. (20) Rhinitis accounted for 70 % of the respiratory symptoms observed in children undergoing double-blind placebo-controlled food challenges. (21) It should be noted that rhinorrhea or nasal congestion typically occurs in association with other clinical manifestations (i.e., cutaneous or gastrointestinal symptoms) during allergic reactions to foods or food challenges, and rarely occurs in isolation. (20, 21) In addition, rhinitis induced by food allergy is more frequently observed in infants and young children than in adults.

Mixed IgE- and non-IgE-mediated reaction: Asthma

Asthmatic reactions caused by airborne food allergens have been reported in susceptible individuals who are exposed to vapors or steam emitted from cooking food, especially fish. (22) Respiratory symptoms may be provoked by food in a subset of patients with asthma. These usually are associated with other clinical manifestations (e.g., cutaneous, gastrointestinal). The patients with asthma related to food allergy were generally younger. Children with atopic dermatitis, especially those with food reactions confirmed during blinded food challenges, are a higher risk group for food-induced asthma. (23, 24) Subclinical bronchial involvement is also suggested by a study assessing nonspecific bronchial hyperresponsiveness (BHR) in patients with food allergy who did not have asthma. The study demonstrated that BHR is a frequent finding (53 %) in nonasthmatic patients with food allergy which may be due to a subclinical inflammatory process in
the bronchi. (25)

**Non-IgE-mediated reactions: Food-induced pulmonary hemosiderosis (Heiner's Syndrome)**

Heiner's syndrome is a rare syndrome characterized by recurrent episodes of pneumonia associated with pulmonary infiltrates, hemosiderosis, gastrointestinal blood loss, iron deficiency anemia, and failure to thrive in infants and young children. (26) It is most often associated with hypersensitivity to cow's milk. (27) The immunologic mechanisms responsible for this disorder are not known. Laboratory findings reveal peripheral blood eosinophilia and multiple serum IgG-precipitating antibodies to cow's milk proteins. (26) The patients recover after elimination of the causative food, usually cow's milk. Re-challenge may cause massive hemorrhage and therefore is not generally recommended.

**Conclusion**

Food allergy can result in various clinical symptoms in different target organs. In this article, food allergy reactions are discussed and grouped according to the pathophysiologic mechanisms. Becoming familiar with diverse manifestations of food allergy will enable physicians to select the appropriate investigations and make proper diagnosis of this complex disease.

**References**

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กิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์

ท่านสามารถได้รับการรับรองอย่างเป็นทางการสำหรับกิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์ กลุ่มที่ 3 ประเภทที่ 23 (ศึกษาด้วยตนเอง) โดยศูนย์การศึกษาต่อเนื่องของแพทย์ จุฬาลงกรณ์มหาวิทยาลัย ตามเกณฑ์ของศูนย์การศึกษาต่อเนื่องของแพทย์แห่งประเทศไทย (ศนผ.) จากการอ่านบทความเรื่อง “การแพทย์ darm” โดยแต่ละคำสำคัญต่างๆ พร้อมกับคำสำคัญที่อ่านได้ถูกต้องโดยใช้แบบฟอร์มคำสำคัญที่ค่ายคำาน แล้วใส่ลงในหน่วยของเป้า (ไม่ต้องติดแสดงปี) จำนวนห้าคำสำคัญต่างกัน ดังนี้

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เลขที่ภูมิ 10330

จุฬาลงกรณ์มหาวิทยาลัยขอความเสียใจที่จะส่งรายละเอียดคำสำคัญหลักหนึ่งเรื่องเกี่ยวกับกิจกรรมการศึกษาต่อเนื่องอย่างเป็นทางการ ดังกล่าวแต่ข้าพเจ้าสำหรับท่านที่เป็นสมาชิกจุฬาลงกรณ์มหาวิทยาลัยเจ้าหน้าที่ สำหรับท่านที่ยังไม่เป็นสมาชิกและท่านที่สนใจจะเป็นสมาชิกจุฬาลงกรณ์มหาวิทยาลัยสำหรับชมสาระเรื่อง 2545 (พื้นที่ 200  บาทต่อปี) ทางจุฬาลงกรณ์มหาวิทยาลัยได้ดำเนินการส่งรายละเอียดคำสำคัญจากการอ่านบทความเรื่องให้คัดแผละบัน เดือนมกราคม 2545 จนถึงเดือนธันวาคม 2545 โดยสามารถส่งคำสำคัญได้เฉลี่ยเดือนละหนึ่งฉบับ 2546 และจะส่งหลักเรื่องของข้อมูลเรื่องที่ส่งไปให้ท่านสมาชิกได้เข้าร่วมกิจกรรมการศึกษาต่อเนื่องที่จัดโดยจุฬาลงกรณ์มหาวิทยาลัย จำนวนเกณฑ์ต่อปีที่ด้านมา โดยจะส่งให้ในเดือนมกราคม 2546

คำถาม - คำตอบ

1. The followings are major organ systems involved in food allergy reactions except:
   a. central nervous system
   b. respiratory tract
   c. skin
   d. gastrointestinal tract

คำตอบ สำหรับบทความเรื่อง "การแพทย์ darm"

จุฬาลงกรณ์มหาวิทยาลัย ปีที่ 46 ฉบับที่ 6 เดือนมิถุนายน พ.ศ. 2545

รหัสการศึกษาต่อเนื่อง 3-15-201-2000/0206-(1013)

ชื่อ - นามสกุลผู้ขอ CME credit     .......................................................... เพื่อใช้เป็นหลักฐานวิชาชีพการรพ.

ที่ปรึกษา ..........................................................

1. (a) (b) (c) (d) 4. (a) (b) (c) (d)
2. (a) (b) (c) (d) 5. (a) (b) (c) (d)
3. (a) (b) (c) (d)
2. Which disorder is classified as "non-IgE-mediated" food allergy?
   a. atopic dermatitis
   b. allergic eosinophilic esophagitis
   c. oral allergy syndrome
   d. dietary protein enteropathy

3. The common causes of dietary protein enterocolitis are:
   a. cow's milk, soy
   b. cow's milk, egg
   c. seafood, rice
   d. egg, soy

4. Food-specific IgE antibody testing is helpful in which disorder?
   a. dermatitis herpetiformis
   b. dietary protein enterocolitis
   c. atopic dermatitis
   d. Heiner's syndrome

5. Which is not true regarding food allergy?
   a. Oral allergy syndrome is most commonly caused by ingestion of fresh fruits and vegetables
   b. Gastroesophageal reflux can be a presentation of allergic eosinophilic esophagitis
   c. Protein losing enteropathy can be caused by dietary protein enteropathy
   d. Chronic urticaria is most commonly associated with seafood allergy