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Invited review article

Food allergy: Past, present and future

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Abbreviations:
IgE, immunoglobulin E; DBPCFC, double-blind placebo-controlled food challenge; OIT, oral immunotherapy; RAST, radioallergosorbent test; Ara h 2, Arachis hypogaea component protein #2; Cor a 9 and 14, Corylus avellana component proteins #9 and #14; TLR, toll-like receptor; OFC, oral food challenge

ABSTRACT

Hippocrates is often credited with first recognizing that food could be responsible for adverse symptoms and even death in some individuals, but it was not until the seminal observations by Prausnitz that the investigation of food allergy was viewed on a more scientific basis. In the first half of the 20th century, there were periodic reports in the medical literature describing various food allergic reactions. In the mid- to late- 1970's, the studies of Charles May and colleagues began to penetrate the medical world's skepticism about the relevance of food allergy and how to diagnose it, since standard skin testing was known to correlate poorly with clinical symptoms. With May's introduction of the double-blind placebo-controlled oral food challenge, the study of food allergy became evidence-based and exponential strides have been made over the past four decades in the study of basic immunopathogenic mechanisms and natural history, and the diagnosis and management of food allergies. Today IgE- and non-IgE-mediated food allergic disorders are well characterized and efforts to treat these allergies by various immunotherapeutic strategies are well under way.

Historical background

Although the first account of food allergy is generally attributed to Hippocrates, the Chinese emperors Shen Nong (~2735 BC) and Huang Di (2698-2598 BC) provided advice in “Shi Jin-Jing” (“Interdictions concerning food”) for pregnant women to avoid certain foods, e.g. shrimp, chicken and meats, and for individuals with certain skin lesions (possibly atopic dermatitis lesions) to avoid certain foods.[1] In Hippocrates' writings (460–377 BC), he referred to the presence of “hostile humors” (now known as IgE antibodies) in some men that made them “suffer badly” following ingestion of cheese.[1] An often quoted line from a poem of Titus Lucretius Cato (98–55 BC), “*What is food to one, to another is rank poison*,”[1] strongly suggests an understanding of adverse reactions to foods over 2000 years ago. In the 17th century case reports of food hypersensitivity reactions began to appear in the medical literature[1]; Jean Baptiste van Helmont reported asthmatic attacks following the ingestion of fish in *Oriatrike* published in 1662. Later Robert Willan described urticaria following the ingestion of almonds, mushrooms, fish, crab, lobsters and mussels, and “*urticaria febralis*” (fatal anaphylaxis) following ingestion of mussels and lobsters in his *Treatise on Dermatology*, (a multi-volume publication; 1798–1808).

While various reports of reactions to foods appeared periodically in the medical literature, the classic experiment of Prausnitz in 1921 initiated the scientific investigation of food allergy and established the immunologic basis of allergic reactions.[2] In his experiment, Prausnitz injected serum from a fish-allergic patient, Kustner, and a non-allergic control subject into his own skin, and on the following day he injected fish extract into the same areas. A positive local reaction (Prausnitz–Kustner test) proved sensitivity could be transferred by a factor in serum (now known to be IgE antibodies) from an allergic to a non-allergic individual. In a similar experiment four years later, Freeman passively sensitized his middle nasal turbinate with serum from an egg allergic patient and demonstrated the induction of rhinitis (rhinorrhea and sneezing) shortly after the ingestion of an egg the following day.[3]

Other early studies of food allergy focused on radiologic changes associated with immediate hypersensitivity reactions in the gastrointestinal tract. In one of the first of these reports, hypertonicity of the transverse and pelvic colon and hypotonicity of the

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cecum and ascending colon were noted in a patient with wheat allergy following the ingestion of wheat.[4] In a later fluoroscopic study, Rowe and colleagues[5] compared the effect of barium contrast material containing food allergens with standard barium contrast material in 12 food-allergic children. They noted prolonged gastric hypotonia and retention of the allergen test meal, prominent pylorospasm, and subsequently increased or decreased peristaltic activity of the intestines.

In a novel series of experiments over 70 years ago, Walzer and his colleagues in New York utilized sera from food-allergic patients to passively sensitize volunteers and demonstrate that "immunologically" intact antigens can cross the gastrointestinal mucosal barrier and disseminate rapidly throughout the body. The investigators passively sensitized skin on the arms of a large cohort of normal adults with serum from a fish allergic patient and similarly a large cohort of normal children with serum from an egg allergic patient, as well as with control non-allergic serum.[6,7] Twenty-four hours later the adults and children were fed fish and eggs, respectively, and within about 90 min, nearly 90% of the study subjects developed a large wheal and flare response at the site on their arm sensitized with "allergic sera," but not at the site with "non-allergic, control sera." Using similar passive sensitization, colonic mucosa of patients who had previously undergone an ileocolostomy was injected with sera from food allergic patients and normal controls.[8] Serum from the allergic patient was injected at the distal (non-contiguous) site of the ileocolostomy opening and 24 h later the study subjects ingested the food allergen. Within 10–15 min, they developed hyperemia at the sensitized distal colonic site followed shortly thereafter by pallor and edema, and prolonged, copious mucus secretion and petechia at the injection site. Walzer and his colleagues also studied the effects of stomach acidity on food allergen uptake. They demonstrated that increased stomach acidity and the presence of other food in the gut decreased antigen absorption, while decreased stomach acidity, such as from today's H2-blockers and proton pump inhibitors, and ingestion of alcohol increased antigen absorption.[9]

In the late 1930's, six patients with gastrointestinal food allergy or wheezing exacerbated by the ingestion of a food allergen and control subjects were evaluated by gastroscopy.[10] Thirty minutes after a food allergen was placed on the gastric mucosa, patients with gastrointestinal food allergy developed markedly hyperemic and edematous patches with overlying thick gray mucus and scattered petechiae at the site of allergen placement, similar to the findings reported earlier by Walzer and colleagues in passively sensitized intestinal mucosal sites.[9] Only mild hyperemia of the gastric mucosa was noted in patients with wheezing provoked by food ingestion. Fifty years later a study confirmed these earlier observations in a cohort of 30 patients with gastrointestinal food allergy, and established an IgE-mediated mechanism for these reactions.[11] These investigators demonstrated that food-allergic patients had significant food-specific IgE antibodies and increased numbers of intestinal mast cells in the gastric mucosa compared to normal controls, and significant decreases in stainable mast cells and tissue histamine following a positive food allergen response.

In 1912, Schloss introduced the concept of using extracted protein from foods for scratch testing in the diagnosis of food allergy,[1] but by then there were already calls for curbing the growing practice of "*scratching the skin with a few food tests and putting the patient on a weird and impracticable diet which usually accomplishes no result…*"[1] In 1950, Loveless demonstrated that the patient's history and presence of positive skin tests were often insufficient to diagnose food allergy in her report of the first blinded, placebo-controlled food trials in patients with milk allergy.[12] In a later report of 89 children being evaluated for milk allergy, Goldman and colleagues recommended that the diagnosis of food allergy could only be established when withdrawal of the food (milk) from the diet led to complete resolution of symptoms and three successive challenges with the food (milk) duplicated the presenting symptoms.[13] Due to the potential severity of reactions developing during food challenges, this approach was not widely accepted. In the mid-1970's, Charles May and his colleagues reported on the use of the double-blind, placebo-controlled oral food challenge (DBPCFC),[14] which has emerged as the accepted "gold standard" for the diagnosis of food allergy. A consensus document (Practall) attempting to standardize the DBPCFC was published in 2012 by the American Academy of Allergy & Immunology and the European Academy of Allergy and Clinical Immunology.[15]

Even before Prausnitz's classic experiment demonstrating that a transferable factor, i.e. IgE, was likely involved in the pathogenesis of food allergy, physicians began experimenting with immunotherapeutic approaches to treat food allergy. The first report of successful oral immunotherapy (OIT) was published in the *Lancet* in 1908 and described the successful treatment of a child with egg-induced anaphylaxis.[16] A few scattered case reports followed including a report by Keston, which provided very limited details on a "*…method as outlined above has been effective in desensitizing about fifty patients with allergic symptoms,*"[17] and reports by Edwards[18] and Unger[19] that were equally vague on outcomes, e.g. "*Twelve of thirteen patients attempted have been successfully desensitized by the oral method.*"[18]

Recent past and present history

In the early 1980's, the landscape of food allergy was very different from today: food allergy was less prevalent, there was little public awareness of the problem, most clinicians were highly skeptical of the diagnosis, and there was little active research going on, primarily because many investigators did not consider the field to be "*a real science*." Skin testing and food-specific serum IgE values (radioallergosorbent tests [RASTs]) were seen as unreliable diagnostic tools, given their poor correlation with oral food challenge (OFC) outcomes.[20] Thirty-five years ago the perceived prevalence of food allergy in the United States was similar to what is reported today, i.e. about 20%, but the actual prevalence then was thought to be less than 1%[21] compared to more recent estimates today of 3.5%–5% of the general population[22] and 8% of the pediatric population.[23] Some have referred to the increase in food allergy and atopic dermatitis as the "*second wave of the allergy epidemic*,"[24] as suggested by the National Health Interview Survey in the US (Fig. 1). Severe food-allergic reactions were rare 35 years ago, but now represent the single leading cause of anaphylaxis treated in American emergency departments, and data from the USA and Australia indicate that there has been a marked increase in hospitalizations due to food allergy in the past two decades, as depicted in Figure 2.[25] The reason for this rapid rise in food allergy among industrialized countries around the world remains an open question.[26]

Many of the same diagnostic tools used today to diagnose food allergy were utilized 30 years ago, but these tools have been refined. Patient history and skin testing remain the cornerstone for diagnosing food allergy. However, the characteristics of food allergic disorders (Table 1) and food allergic symptoms (Table 2) have been more precisely defined, which has improved the diagnostic accuracy of the medical history and its utility in guiding appropriate laboratory studies.[27] Until the mid-1990's, most allergists rarely utilized *in vitro* food-specific IgE measurements (RASTs) in their food allergy work-up because of poor sensitivity and specificity in identifying symptomatic food allergy.[20] However, with the advent of a quantitative *in vitro* assay, it was shown that there was a direct correlation between the quantity of food-specific