Immediate food hypersensitivity among adults attending a clinical immunology/allergy centre in Singapore

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ABSTRACT

Introduction: The patient characteristics, clinical features and causative foods in 74 consecutive adult patients with immediate food hypersensitivity were studied.

Methods: A retrospective review of 74 consecutive adults who presented during the study period from July 1, 1994 to April 30, 2002 was performed.

Results: There were 35 male and 39 female patients, with a mean age of 36.3 +/– 10.9 (range, 19-66) years. The most common causative foods were seafood crustaceans, molluscs and bird's nest. Prawn and crab were the most commonly implicated crustacean, and limpet the commonest culprit mollusc. The main symptoms were periorbital angioedema (64.9 percent), dyspnoea/wheezing (44.6 percent) and urticaria (44.6 percent). 66 percent of the patients developed anaphylaxis. 34 (45.9 percent) had concomitant allergic rhinoconjunctivitis, asthma, eczema or combinations of these atopic diseases. Only six (8.1 percent) patients had a family history of food allergy. Skin prick tests (SPT) to commercially-prepared food allergens were positive in 22 of 36 patients (61.1 percent) tested. SPT to the fresh, cooked or canned food products were positive in 11 of 20 (55 percent) cases where the food allergen was not commercially available. Open food challenges were required for diagnosis in two patients who had negative SPT.

Conclusion: The most common food allergens in our patients were seafood crustaceans, molluscs and bird's nest. More than half of the patients had concomitant allergic rhinitis, asthma and/or eczema. The pattern of food allergy in Singapore differs from Caucasian populations, likely to be because of different regional dietary patterns and methods of food preparation.

Keywords: food allergens, food hypersensitivity, radioallergosorbent test, skin tests

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INTRODUCTION

Immediate hypersensitivity reactions to food, commonly referred to as IgE-mediated reactions, have been more commonly reported in children than adults. Sensitisation to cow's milk, egg, wheat, soy, peanut, tree nuts and fish during infancy and childhood have been well-reported, with most children "growing out" of their allergy to milk and egg by the age of five years. In Singapore, bird's nest is the most common cause of food-induced anaphylaxis in children. The patterns and causes of immediate hypersensitivity to food in adults have not been reported locally. We describe 74 consecutive adults with immediate hypersensitivity to food presenting to a clinical immunology/allergy centre in Singapore.

METHODS

This is a retrospective review of 74 consecutive adults who presented during the study period from July 1, 1994 to April 30, 2002. They were evaluated based on the clinical history of the presenting symptoms and the temporal relationship to food intake. Where the meal was prepared by the patient or his/her family, the contents of the meal including the method of preparation, spices or condiments used, were recorded in detail. In instances where the reaction occurred after a meal prepared at a hawker stall, restaurant or other eating establishments, the same information was obtained from the source where the food was prepared, as far as possible. Other clinical

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Table I. Summary of clinical characteristics and putative foods.

	No. of patients (n=74)	%
Sex		
Male	35	47.3
Female	39	52.7
Racial distribution		
Chinese	49	66.2
Malay	5	6.8
Indian	8	10.8
Others	12	16.2
Type of reaction		
Angioedema	48	64.9
Dyspnoea/wheeze	33	44.6
Urticaria	33	44.6
Pruritis	28	37.8
Nasal symptoms	20	27.0
Abdominal pain	14	18.9
Anaphylaxis	49	66.2
Personal history of atopy		
Allergic rhinitis	28	37.8
Asthma	15	20.3
Atopic eczema	10	13.5
Drug allergy	18	24.3
Family history		
Allergic rhinitis	11	14.9
Asthma	10	13.5
Atopic eczema	8	10.8
Food allergy	6	8.1

information obtained included the type of reaction, severity, clinical manifestations, number of previous episodes and personal and family history of other atopic diseases including allergic rhinitis, asthma and atopic eczema. Anaphylaxis was defined as a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance following the clinical criteria as proposed by the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium.[1]

The putative food was determined from clinical history followed by measurement of allergen specific immunoglobulin E (IgE) levels using the Pharmacia UniCAP system (Pharmacia, Sweden), skin prick test (SPT) using allergen extracts (Greer Laboratories, Lenoir, NC, USA) or prick-to-prick test with the fresh, cooked, or canned food products. Although the prick-to-prick test was originally recommended for fresh fruit and vegetables presumably because of the lability of the commercial allergen, it is common clinical practice in paediatric and adult allergy clinics to make extracts "in-house" for prick-to-prick tests, although this has not been validated. Positive tests were defined as CAP specific IgE ≥ 0.7 kU/L, or mean SPT wheal diameter 3 mm greater than the negative control.

Food challenges were not carried out to confirm the diagnosis when a consistent history was supported by positive SPT or CAP specific IgE. An open food challenge (OFC) was performed when the SPT and specific IgE were negative, achieving a maximum dose equivalent to 8 g of dried food or to the normal daily intake in a serving. Single-blind, or double-blind, placebo-controlled food challenges (SBPCFC and DBPCFC, respectively) were undertaken when the SPT and/or CAP specific IgE levels was negative and the symptoms were vague or atypical of immediate food hypersensitivity.

RESULTS

There were 74 adults with IgE-mediated food allergy (FA) of whom 35 (47.3%) were male and 39 (52.7%) female. The mean age of all patients was 36.3 ± 10.9 (range, 19–66) years. There were 49 Chinese (66.2%), five Malays (6.8%), eight Indians (10.8%), and 12 (16.2%) of other racial denominations (eight Caucasians, two Indonesians and two Sikhs). This is summarised in Table I. The most common clinical manifestations were angioedema (48, 64.9%) dyspnoea or wheeze (33, 44.6%), and urticaria (33, 44.6%). 49 cases (66.2%) were defined as anaphylactic reactions, of which hypotension was documented in nine (18.4%) cases. This is summarised in Table I. The median duration between ingestion of the allergenic food and onset of the acute reaction was 60 (interquartile range, 30–120) minutes.

54 patients (73.0%) were allergic to one, 14 (18.9%) to two, and one (1.4%) to three different food types. The most common causative foods were seafood crustaceans (25, 33.8%), molluscs (14, 18.9%) and bird's nest (seven, 9.5%). Prawn (21.7%), crab (16.2%), and lobster (8.1%) were the most commonly implicated crustaceans. Limpet was the most commonly implicated mollusc. Allergy to fish, peanut, tree nuts, vegetables and fruit were uncommon. There were no cases of oral allergy syndrome (pollen-fruit syndrome) or latex-fruit syndrome. This is summarised in Fig. 1.

34 (45.9%) patients had concomitant allergic rhinoconjunctivitis (28, 37.8%), asthma (15, 20.3%), eczema (10, 13.5%) or combinations of these atopic diseases. All the patients with asthma had asthma which was well-controlled during the episode of FA. Of 23 patients with positive SPT to local environmental aeroallergens, the most common were *Dermatophagoides farinae (D. farinae)* (20/22, 90.9%), *Dermatophagoides pteronyssinus (D. pteronyssinus)* (15/16, 93.8%) and cockroach (9/10, 90.0%). The remaining patients with rhinoconjunctivitis or asthma declined SPT for

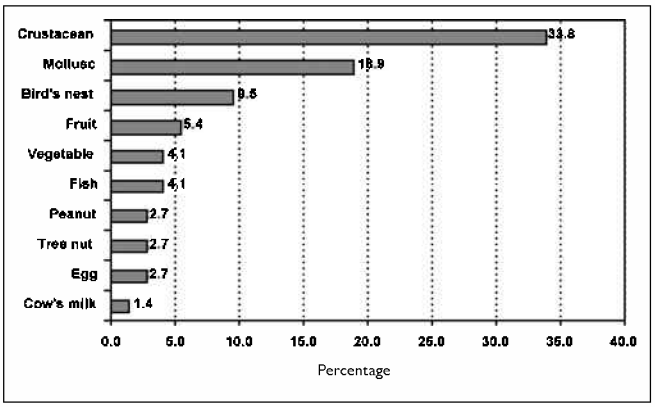

Fig. 1 List of commonly implicated foods.

aeroallergens. Of the 39 patients with allergy to seafood crustaceans or molluscs, 11/12 tested (91.7%) showed positive SPT to house dust mite and three of four (75.0%) showed positive SPT to cockroach. A family history of rhinoconjunctivitis, asthma and eczema were present in 11 (14.9%), ten (13.5%) and eight (10.8%) of all patients respectively. Only six (8.1%) patients had a family history of FA.

58 patients underwent SPT for food allergens. Of 36 patients tested with the corresponding commercial glycerinated extract, SPT was positive in 22 (61.1%) patients. Of 20 patients with prick-to-prick tests using fresh, cooked or canned food because commercial extracts were not available, 11 (55.5%) were positive. 14 patients did not undergo SPT for various reasons: six because the initial reaction was anaphylactic and hence the patients were not keen, eight refused further evaluation. Serum specific IgE levels were measured in two patients with anaphylaxis. In the first patient with peanut anaphylaxis, serum specific IgE to peanut was elevated at 14.4 kU/L. In the second patient with allergy to limpet, specific IgE levels to shrimp, lobster, squid, mussel and oyster were each less than 0.35 kU/L. Three patients underwent OFCs. Two patients responded positively: the prick-to-prick test was negative to canned limpet in one and SPT negative to commercial shrimp allergen in the other.

DISCUSSION

The spectrum of adverse reactions to food include IgE-mediated, mixed IgE and non-IgE mediated, and non-IgE-mediated mechanisms.[2] However, although this classification is applicable to both children and adults, there are distinct differences in the causes and natural history of IgE-mediated FA between them. Much more is known about FA in children than adults. IgE-mediated FA is generally more common in children than adults, with prevalence reported as 6%–8% of infants in the first year of life[3] compared to 1%–2% in adults.[4–6] However, recently, it has been shown that the prevalence of FA is increasing, affecting up to 3.7% of adults.[7]

The most common food allergens in childhood in Caucasian populations are cow's milk (2%–3% incidence in the first year of life),[8] egg (prevalence 2.4% at two years of age),[9] peanut (prevalence 0.5%–0.6% at four years of age),[10] fish, shellfish, wheat and soy. About 35% of children with moderate to severe atopic dermatitis/eczema syndrome (AEDS) have food-sensitive eczema,[11] and 6%–8% of asthmatic children have food-induced wheezing.[12] The majority of food allergic children (about 85%) lose their sensitivity to most allergenic foods (egg, milk, wheat, soya) within the first three to five years of life, as demonstrated in children with AEDS. Even peanut allergy, once thought to be life-long, may resolve in about 20% of peanut-allergic children younger than two years who achieve tolerance by school age.[13] Although recurrences have been reported, children with peanut-specific IgE levels of 5 kU/L or lower have been shown to have at least a 50% chance of outgrowing their allergy, with recurrences being relatively uncommon.[14]

The majority (85%) of cow's milk and egg allergy in childhood resolve by the age of five years. In Singapore, bird's nest has been found to be the most common cause of food-induced anaphylaxis in children.[15] The pattern of food sensitisation in our atopic children less than five years of age shows that sensitisation to shellfish and peanut was most common, followed by milk and egg, thus indicating exposure to these allergens at an early age. This pattern of sensitisation is similar to other studies despite the fact that the causes of clinical FA are different.[15,16] In contrast, the causes of IgE-mediated FA in adults appear to be highly variable with geography, dietary patterns and inhalant allergies contributing to these. The common allergenic foods in adults include peanuts, tree nuts, fish, shellfish, fresh fruit and vegetables. FA in adults is commonly associated with sensitisation (IgE cross-reactivity) to other allergens, particularly inhalants. This includes pollen-associated FA, bird-associated egg allergy, house dust mite-related FA and latex-associated FA.[17] Pollen-associated FA commonly presents with symptoms and signs limited to the oropharynx, hence the term oral allergy syndrome.

As a result of the many different types of foods causing IgE-mediated FA in adults, the performance characteristics (sensitivity, specificity, positive and negative predictive values) of commercially-available glycerinated food extracts for SPT and food-specific IgE levels are also highly variable when compared to the outcomes from DBPCFC, the gold standard in the diagnosis of IgE-mediated FA.[18] In contrast, well-defined positive and negative predictive values for allergenic foods in childhood both for SPT[19,20] and specific IgE levels[21,22] have been established.

In our study, SPT was positive in 61.1% using the glycerinated extracts, and positive in 55.5% using the fresh, cooked or canned food suggesting that most of the time skin tests did not appear to correlate with the history of an immediate hypersensitivity reaction. There may be several reasons for this. Firstly, the suspected food from history may not have been the correct putative food, especially when the reaction occurred during oriental restaurant meals comprising several consecutive dishes with several ingredients. Secondly, the reaction may not have been IgE-mediated but occurred from non-IgE mediated mechanisms. Thirdly, although skin prick tests are generally sensitive and specific with negative predictive value exceeding 95% for reliable extracts,[23] these predictive values for food extracts vary depending on the type of food and between different extracts. Apart from cow's milk, egg, wheat, soy and peanut where predictive values of SPT have been studied in infants and children, there have been no similar validation studies in adults. Fourthly, because the types of allergenic foods in adults are different from children because of a more varied diet, prick-to-prick testing has been used for which some allergen extracts (e.g. limpet) are not commercially available. This, however, is unvalidated for most foods with no proper comparisons made with DBPCFC, although recent European paediatric studies have also used fresh cow's milk, egg and soy rather than commercial extracts.[20,24] Thus, one of the limitations of this study was that DBPCFC was not carried out in all patients who had negative skin tests or specific IgE tests and it can be argued that FA may have been "over-diagnosed" in some of these patients.

IgE-mediated FA in children has a good prognosis in that the majority resolves with a period of dietary elimination. FA in adults, however, appears to persist although there have been no longitudinal studies to date of the natural history of IgE-mediated FA in adults following a period of dietary elimination. The pattern of food allergens in our study population appears to be similar to that reported from geographical areas where there is a high consumption of seafood, including the Mediterranean.[25] One of the unusual findings in our centre was that of a relatively large number of adults with allergy to limpet, a gastropod mollusc. This has so far only been reported in Japan[26] and Spain,[27] where the putative limpets were of different genera. The other unusual finding was that of bird's nest allergy, similar to that reported in our paediatric population.[15] All our patients with bird's nest allergy reported their first reaction during adolescence or adulthood.

IgE-mediated FA to peanut, tree nuts, fruit and vegetable was much less common in our study compared to studies from Western populations. The paucity of peanut allergy is unusual because peanut is commonly used in Chinese, Malay and Indian cooking either in the main dish or in sauces. Similarly, the per-capita consumption of peanuts in China and the United States is essentially the same, but there is virtually no peanut allergy in China.[28] This has been attributed to the Chinese eating predominantly boiled or fried peanuts, and Americans eating almost exclusively dry-roasted peanuts. The higher heat of dry roasting (180°C) and the processes of maturation and curing have been shown to increase the allergenicity of peanut proteins.[29–31]

The consumption of fruits and vegetables is probably not different than that in Western populations. However, the low prevalence of grass and tree pollen inhalant allergies and immediate hypersensitivity to latex locally may partly explain the paucity of allergy to fresh fruit. House dust mite is a common aeroallergen in Singapore and patients with allergic rhinitis and asthma are mostly sensitised to *Blomia tropicalis, D. pteronyssinus* and *D. farinae*.[32] Local healthy oriental adults without inhalant allergy have also been shown to demonstrate positive SPT to *D. farinae* in 52.4%.[33] Hence, the rates of sensitisation are high in both healthy adults and those with inhalant allergies. The high prevalence of FA to seafood crustaceans and molluscs in our study may be associated with the high prevalence of house dust mite allergy. The muscle protein, tropomyosin, has been implicated as the cross-reacting allergen between shrimp, other crustaceans and molluscs, and non-edible arthropods such as insects (cockroach and chironomids), arachnids (house dust mites) and even nematodes. The IgE recognition by shrimp-allergic individuals of identified and/or similar amino acid sequences homologous to the major shrimp allergen, Pen a 1 epitopes in mite, cockroach and lobster tropomyosins are the basis of the in vitro cross-reactivity among invertebrate species.[34] Another recent study on Orthodox Jews with allergic rhinitis or asthma who had never eaten shrimp demonstrated that IgE antibody reactivity to shrimp can occur, with subjects allergic to house dust mite and/or cockroach showing substantial IgE antibody reactivity to Pen a 1. Based on inhibition with cockroach and/or dust mite extracts, this reactivity appeared to be due to cross-reacting tropomyosins.[35] Cross-reactivity between limpet and the house dust mite, *D. pteronyssinus* has also been demonstrated.[36] In our study, of the 39 patients with allergy to seafood crustaceans or molluscs, 91.7% showed positive SPT to house dust mite and 75.0% showed positive SPT to cockroach.

There were several limitations to this study. Firstly, this was a retrospective study based on referrals to a clinical immunology/allergy clinic. Thus, the pattern of putative foods may not be representative of the types of food allergies among adults in Singapore. The more severe, systemic reactions may have been over-represented. Secondly, the diagnosis of FA was not based

on DBPCFC which is the gold standard for diagnosis. It can thus be argued that FA may have been over-diagnosed in this cohort, given the limitations of clinical history and in vitro skin tests. Thirdly, the use of prick-to-prick tests in foods other than fruit and vegetables has not been standardised.

The most common allergens in our patients with IgE-mediated FA were crustaceans, molluscs and bird's nest. More than half of the patients had concomitant allergic rhinitis, asthma and/or eczema. A family history of atopy was often present. The low prevalence of pollen and latex allergy may be related to the paucity of allergy to fruit, and high prevalence of house dust mite allergy associated with allergy to shrimp and limpet.

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