

Educational Clinical Case Series

Shellfish allergy in children

Kandyil RM, Davis CM. Shellfish allergy in children.
Pediatr Allergy Immunol 2009; 20: 408–414.
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Food allergies affect approximately 3.5–4.0% of the world's population and can range from a mere inconvenience to a life-threatening condition. Over 90% of food allergies in childhood are caused by eight foods: cow's milk, hen's egg, soy, peanuts, tree nuts, wheat, fish, and shellfish. Shellfish allergy is known to be common and persistent in adults, and is an important cause of food induced anaphylaxis around the world for both children and adults. Most shellfish-allergic children have sensitivity to dust mite and cockroach allergens. Diagnostic cut-off levels for skin prick testing in children with shrimp allergy exist but there are no diagnostic serum-specific immunoglobulin E (IgE) values. All patients with symptoms of IgE-mediated reactions to shellfish should receive epinephrine autoinjectors, even if the initial symptoms are mild. In this study, we review three cases of clinical presentations of shellfish allergy in children.

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Key words: shellfish allergy; fish allergy; food hypersensitivity; case presentations; anaphylaxis

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Accepted 2 June 2009

Food allergies affect approximately 3.5–4.0% of the worldwide population and can range from a mere inconvenience to a life-threatening condition (1). Immediate or Type 1 hypersensitivity responses to food result when immunoglobulin E (IgE) antibodies are made to specific proteins that occur naturally in allergenic foods (1). Individuals with food allergies can also react adversely to skin contact with foods or the ingestion or inhalation of foods that most consumers can safely ingest (2).

The sea has been a major source of food for human populations since the beginning of time. Edible seafood can be categorized into three phyla: Chordata, Mollusca, and Arthropoda. The Chordata phylum includes finned fish, with the major component consisting of the class Osteichthyes (salmon, tuna, cod, hake) (3). The Mollusca phylum is also known as molluscan shellfish and consists of three classes, gastropods (snails and abalone), bivalves (scallops, clams, mussels, oysters), and cephalopods (squid, octopus). The Arthropoda phylum consists of the class crustacea and is also known as crustacean shellfish, including shrimp, crab, lobster, prawn, and crawfish (3).

Shellfish allergy is known to be a common cause of food hypersensitivity and is most often

persistent (4–7). It occurs in adults more commonly than in children (4). The description of shellfish allergy in children in the literature is limited. In this study, we review three clinical cases of shellfish allergy in children.

Case 1: Toddler with hives and angioedema with ingestion of shrimp

A 22-month old Latin-American male with history of milk allergy, reactive airway disease, and eczema was referred for allergy evaluation. He had no history of allergic rhinitis symptoms. About 2 weeks prior to his visit, his father gave him one shrimp seasoned with oil, pepper, and garlic. There was no known previous exposure to shrimp. He immediately had swelling of his eyes and hives on his face without difficulty in breathing. He was given diphenhydramine and his symptoms subsided within 24 hours. At this visit, serum-specific IgE showed levels of 12.6 kU/L to shrimp, 12.3 kU/L to milk, 0.55 kU/L to egg white, 0.72 kU/L to wheat, 0.41 kU/L to soybean, 0.61 kU/L to peanut, and <0.35 kU/L to codfish. Though milk-specific IgE was high, he had been tolerating whole milk for 6 months prior to this visit. Based on history and specific IgE results, his parents were told to

strictly avoid shrimp and other shellfish in his diet, without need to avoid fish or milk. Autoinjectable epinephrine was prescribed. He had no further episodes of angioedema or hives.

Case 1: Discussion

This case represents a typical Type I IgE-mediated food hypersensitivity reaction to shellfish. Typical symptoms can include throat and lip pruritus, urticaria or angioedema, gastrointestinal symptoms, rhinoconjunctivitis, bronchospasm, and anaphylaxis (8). The above case is relatively mild given the absence of gastrointestinal symptoms, bronchospasm, or hypotension. Although shellfish reactions are the most common cause of food induced anaphylaxis (9), mild reactions are common in young children.

The prevalence of food allergy in children in the USA is estimated to be 6–8% (4). The most common food allergens and their relative prevalence in the USA in decreasing order are: milk (2.5%), egg (1.3%), tree nuts (0.8–1%), peanut (0.8%), wheat (0.4%), soy (0.4%), tree nuts (0.2%), and fish (0.1%) (4, 7, 10). Shellfish allergy is estimated to affect at least 250,000 people in the USA (10).

The prevalence of seafood allergy in the USA was determined by a random telephone survey including participation of a total of 5529 households, representing a census of 14,948 individuals across all age ranges (4). Seafood allergy was defined based on either self-reported diagnosis of allergy by a physician or the self-reported presence of convincing symptoms (hives, urticaria, angioedema, trouble breathing, oral pruritus, and throat closing). Based on this study, prevalence rates in adults are significantly higher than in children, respectively, in all categories including: any seafood allergy (2.8% vs. 0.6%), shellfish allergy (2.5% vs. 0.5%), and fish allergy (0.5% vs. 0.2%). Boys are affected more than girls (0.8% vs. 0.5%), as seen in Case 1 (4). Highest rates are reported by African Americans (4, 11, 12).

The most common reported shellfish allergies, in decreasing frequency are: shrimp, crab, lobster, clam, oyster, and mussel. Symptoms are individually variable and ranging from mild rashes and hives to life-threatening anaphylactic shock (4). One of the limitations of the data from this prevalence study is the likely under-representation of lower socio-economic classes as they may not have phones and would not have been able to participate in the study. In addition, African-American, Hispanic, and Asian ethnic groups were also underrepresented.

Shellfish allergies are among the most common and serious types of food allergies on a world-wide basis (5, 13–17). The prevalence rate of shellfish allergy for parent-reported adverse food reactions in Hong Kong pre-school children was higher than in the USA, with a prevalence of 1.28% in the total population, comprising 15.8% of children with food adverse reactions. Shellfish allergy is among the most common among all allergenic foods in the Asian population (13, 14). Meta-analysis of publications from Sweden, USA, France, the Netherlands, Iceland, Mozambique, Portugal, and Germany of self-reported allergies since 1990 revealed an overall prevalence rate of 0–10% for self-reported shellfish allergy and 0–1.4% for symptomatic allergy with IgE-specific sensitization (16). More prevalence data is needed in Hispanic populations as shellfish allergy occurs in this group, as illustrated in Case 1.

Classically, shellfish allergy in children presents as an IgE-mediated reaction as described in Case 1, with hives and angioedema within minutes of exposure, which may proceed to frank anaphylaxis (15). The most important component of the management of shellfish allergy is the complete avoidance of shellfish and other crustacea. If there is a history of suspected or proven IgE-mediated systemic reactions to foods, injectable epinephrine should be given to patients and/or caregivers to carry with them and they should be instructed in its use (8).

Double blind placebo controlled oral food challenge remains the gold standard for diagnosis of food allergy (15). Clinical diagnostic tests aid in the differentiation of patients who have favorable probability of tolerating foods during food challenges compared with those who are likely to react. Detection of food-specific IgE antibodies to certain foods has been shown to be predictive of symptoms of IgE-mediated food allergy (18). Diagnostic decision points have been delineated for serum-specific IgE to common food allergens including egg, milk, peanut, wheat, soybean, fish, and tree nuts (18, 19). These are not always accurate in predicting clinical reactivity, however, and host factors probably contribute to the expression of clinical reactivity. For example, in this case, this toddler's milk-specific IgE was greater than the 95% positive predictive value for a child <2 yr old (5 kU/l) and this child did not have clinical reactivity. All of the other foods to which this child had testing were well below the positive predictive value for reactivity (8). Ninety-five percent positive predictive values have been

determined for skin prick tests to crude extracts from *Penaeus monodon* (seawater shrimp) and commercial shrimp extracts. A mean wheal diameter of 22.5 mm and 20 mm for skin prick testing to the crude and commercial extracts, respectively, provides 95% predictive probability for a positive oral challenge to shrimp (20). Currently no predictive values for serum-specific IgE to shrimp, crab, or lobster exist. Diagnostic decision points for serum-specific IgE to shellfish (including shrimp, crab, lobster) are needed and would greatly assist in decision making in clinical practice and identification of shellfish allergy in patients.

Case 2: Toddler with eczematous flare with ingestion of shellfish

A 20-month old Caucasian boy with severe eczema since infancy was referred by his dermatologist for allergy evaluation. At the time of the office visit, he was not avoiding any foods and was eating shrimp, fish, milk, peanuts, eggs, and soy without any obvious clinical reactions but he had uncontrolled eczema. At that time his serum-specific IgE was 41.9 kU/L to shrimp, 11.6 kU/L to milk, 27.5 kU/L to peanut, 1.73 kU/L to egg white, 6.46 kU/L to soy and <0.35 kU/L to fish. He was told to avoid milk, peanuts, shrimp and all other shellfish and his eczema improved dramatically. Repeat-specific IgE at 3 yr of age was 28.7 kU/L to shrimp, 1.13 kU/L to codfish, 4.26 kU/L to milk, and 4.03 kU/L to peanut. Despite a mild increase in fish-specific IgE, he had been eating flatfish at home without any reactions. He continues to avoid shellfish, milk, and peanuts. Of note, this patient also had severe dust mite allergy noted at the first office visit, with specific IgE > 100 kU/l for both *Dermatophagoides farinae* and *D. pteronyssinus*. Dust mite avoidance was reviewed with the family.

Case 2: Discussion

Shellfish allergy in children can also be present as a combined IgE and non-IgE mediated reaction as illustrated in Case 2 with a worsening of eczema (8). About one-third of children with eczema also have food allergies which can worsen or exacerbate the eczema and cause a 'flare' (21). In people with eczema and food allergies, strictly avoiding food allergens may help reduce or eliminate symptoms. Common food triggers for eczema include eggs, milk, peanuts, soybean, wheat, and shellfish, such as crab, shrimp, and clam. In a recent study of 114 Chinese children

with atopic dermatitis, the most common foods causing sensitization by skin prick testing were egg yolk (53%), egg white (42%), shrimp (35%), peanuts (31%) and crab (29%) (22). As illustrated in Case 2, a child with shellfish allergy may present with eczema exacerbations after ingestion of shellfish. Shellfish allergy frequently coexists with other food allergies in children with severe eczema. Shrimp and other shellfish, if ingested by the patient's family, should be considered in the evaluation of childhood eczema with possible food allergy triggers. If the child has a shellfish allergy, strict avoidance may result in fewer eczema flares.

Sensitization to dust mite allergens occurs frequently in pediatric patients with clinical reactivity to shellfish. Ninety-four percent of shrimp-allergic children with positive oral food challenges had sensitization to *D. pteronyssinus* and 96% had specific IgE to *D. farinae* (20). The allergenic protein in shellfish is tropomyosin. It is a heat-stable protein that is essential for muscle contraction in vertebrates and invertebrates (3). Tropomyosins in invertebrates are 34–41 kDa proteins that share high homology in their amino acid sequences and are responsible for the majority of IgE-mediated allergies to shellfish (23, 24). Interestingly, tropomyosins in vertebrates are not allergenic. The molluscan shellfish allergens, such as oyster (Cra g 1, Cra g 2), abalone (Hal m 1), snail (Tur c 1), and squid (Tod p 1) have been identified as tropomyosins (1, 25, 26). Cross-reactivity to tropomyosin from other molluscan shellfish species has been observed with sera from patients allergic to oysters, suggesting that individuals with allergies to molluscan shellfish should avoid eating all species of molluscan shellfish (1).

Among crustacean shellfish, the major allergen Pen a 1 is found in brown shrimp (*Penaeus aztecus*), which is a highly valued commercial species in the USA found from the coastal New Jersey waters down to Texas and the Gulf Coast as well as the Caribbean Ocean (27, 28). Eighty-five percent of shrimp-allergic individuals studied show reactivity to Pen a 1 (27, 28). Another shrimp allergen, Pen m 1, is found in the black tiger shrimp (*Penaeus monodon*), which is the single most widely distributed and marketed shrimp in the world, and is found in various Southeast Asian countries (28, 29). Lit v 1, another shrimp allergen, is found in Pacific white leg shrimp (*Litopenaeus vannamei*), which is found primarily in Mexico and Ecuador. A small amount of white leg shrimp is now farmed in the USA, primarily in Texas (28). All of the aforementioned crustacean shellfish allergens are

classified as tropomyosins. To date, at least 10 different tropomyosins in crustacean shellfish and six different tropomyosins in molluscan shellfish have been identified (24). Recently, in addition to tropomyosins, three new classes of shrimp allergens have been identified, including arginine kinases (Pen m 2 and Lit v 2), sarcoplasmic calcium-binding proteins (SCP and Lit v 4), as well as myosin light chain (Lit v 3) (30–34).

Cross-reactivity between crustaceans and between crustaceans and mollusks is thought to be due to tropomyosin (35). This case demonstrates the fact that crustaceans do not cross-react with vertebrate fish (8). While 50–67% of those allergic to fish are at risk for a reaction to a second species of fish, 38–80% of those allergic to crustacean shellfish are at risk for a reaction with other crustaceans (4, 36) and approximately 40% may react clinically upon ingestion (4, 37). Among individuals with mollusk shellfish allergy, 50% report reactions to more than one type of mollusk (4, 38). Between 10–15% of patients allergic to any shellfish are allergic to both crustaceans and mollusks (4). Tropomyosin also acts as a panallergen and causes cross-reactions between crustaceans, mollusks, dust mites and insects such as cockroaches and grasshoppers (20, 39, 40). As illustrated in Case 2, many patients with shellfish allergy may also have dust mite allergy and vice versa due to the cross-reactivity of tropomyosin. Patients with shrimp allergy should be evaluated for allergy to dust mites. Of note, patients may become sensitized to shrimp and other cross-reacting foods while receiving immunotherapy for dust mites (41).

Case 3: Adolescent with reactions to aerosolized shellfish

A 16 yr old African-American girl with history of allergic rhinitis had tongue/lip/eye swelling, urticaria, within 20 min after eating shrimp. Her symptoms progressed over 4 days to include difficulty breathing, at which point she presented in the emergency room and was admitted to the hospital. Serum-specific IgE during hospitalization was 13.8 kU/L to shrimp, 0.56 kU/L to crab, 7.93 kU/L to lobster, 1.44 kU/L to langoust, 15.6 kU/L to crawfish. Specific IgE was <0.35 kU/L to 24 types of flatfish and mussels. She was advised to avoid all shellfish, and to avoid fish due to potential cross-contamination given the severity of her reaction. She was seen in clinic 6 months later and reported lip/facial swelling with urticaria several times per month, particularly on Fridays when shellfish or fish was

served at her school. She did not eat food served by the cafeteria on these days, but ate in the cafeteria. Her symptoms extended on Fridays several hours after lunchtime and sometimes to Saturdays. She also had a similar episode of lip/facial swelling and urticaria when walking by the seafood (shellfish and fish) section at a local grocery store. Her lip swelling resolved with diphenhydramine. She now brings her own lunch to school, eats it in the nurse's office, and is symptom free. Of note, her skin prick test was positive for *D. farinae* and *D. Pteronyssinus* and, therefore, dust mite avoidance was reviewed with the family. She carries autoinjectable epinephrine with her at all times.

Case 3: Discussion

Case 3 underscores the point that adolescent shellfish-allergic patients may have severe symptoms which are more similar to the clinical presentation in the adult population. In adults, symptoms of shellfish allergy can result from ingestion, contact, or inhalation. In one report, of a group of 30 shrimp-allergic patients, the most frequently reported sign was generalized itching (90%). In the same study, 61% had urticaria, 52% had angioedema of lips and tongue, 42% had pulmonary symptoms, 35% had gastrointestinal symptoms, and 13% had shock-like symptoms (1, 42, 43). In the USA telephone study mentioned previously, 60–70% of adult patients with shellfish allergy experienced urticaria/angioedema and greater than 50% reported dyspnea or throat tightness with exposure to shellfish. Consistent with this, 50% of the reactions prompted evaluation by a physician or care in an emergency room. Despite severe symptoms, epinephrine was administered to only 16% (1). Epinephrine should be administered to any patient with a history of suspected or proven IgE-mediated systemic reactions to foods (8).

Anaphylaxis and death is the most severe life-threatening consequence of having a shellfish allergy. Risk factors for anaphylaxis include other atopic diseases and occupational allergy to shellfish. Anaphylaxis is an important cause of death in the USA and causes approximately 150 deaths per year (17). Food-related anaphylaxis represents 13–51% of all emergency department food-allergic events (44, 45). Emergency rooms in the USA treat 30,000 food-related anaphylactic reactions per year, and of these, 2000 result in hospitalizations (17). Analysis of food-allergic and anaphylactic events was performed via the National Electronic Injury Surveillance System

utilized in emergency rooms across the USA (44). In this study, shellfish was the most frequently implicated food in anaphylaxis in persons > 6 yr of age. In this study, prevalence of shellfish allergy in 6–18 yr old children approximated 37%. Shrimp and/or crab ingestion initiated > 35% of emergency room food-allergic events. This was more than triple the rate for peanuts (44). Up to 43% of food-related events involving anaphylaxis involved children or teenagers (44). Age of onset of shellfish allergy is less than 18 yr for 40% of individuals with shellfish allergy (4). Fifty-eight percent report multiple reactions, typically with 2–5 episodes, and 15–20% of people experience more than six reactions and the course of shellfish allergy appears persistent in most cases (4). Case 3 is an example of a typical shellfish-allergic patient with a history of multiple episodes. She belongs to the African American ethnic group in the USA which is most likely to experience shellfish allergy (11, 12). Shellfish is also an important cause of food induced anaphylaxis in Asia (14), Singapore (46) and Italy (47).

This case is also an illustration of the potential for clinical symptoms of shellfish allergy with minimal exposure through inhalation. Patients with occupational exposure to shellfish can develop dermatologic symptoms from direct handling of the shellfish. In a population of snow crab-processing workers, 15.6% had occupational asthma, 76% had rhinoconjunctivitis and 35% had associated urticaria (48, 49). Although allergic reactions to foods occur most commonly after ingestion, inhalation of foods can also be an important underlying cause of these reactions. For example, published reports have highlighted the inhalation of allergens from fish, shellfish, seeds, soybeans, cereal grains, hen's egg, cow's milk, and many other foods in allergic reactions (50–53). Symptoms have typically included respiratory manifestations such as rhinoconjunctivitis, coughing, wheezing, dyspnea, and asthma. In some cases, anaphylaxis has been observed. There is a danger of aerosolization and cross-contamination in restaurants and/or cafeterias as they may use the same pans, grill, oil, and servingware to prepare shellfish as they do for other food items (54). As illustrated in this case, the fish market or the fish/meat counter at the grocery store is a place where aerosolization and cross-contamination can occur, as the shellfish may come in contact with other meats and foods. Fish protein can become airborne during cooking and cause an allergic reaction (52). In the face of IgE-mediated sensitization to shrimp and history of anaphylaxis, reactions to

aerosolized food protein are possible and should be considered in patient counseling.

Once the diagnosis of shellfish allergy is established through the history and evidence of IgE sensitization, the family should be educated on careful label reading and potential hidden sources of shellfish. Foods to avoid include: clams, crab, crayfish/crawfish, lobster, oysters, abalone, shrimp, prawn, scallops, mussels, and sea urchins. Patients should be careful when eating fried foods at any restaurant that serves seafood. Many establishments use the same oil to cook french fries as they do to fry shrimp and clam. Other foods, such as Worcestershire sauce, steak sauce, fried rice, egg rolls, salad dressings, seafood muffaletta sandwiches, and vitamin supplements (containing coral calcium) often contain shellfish for flavoring so patients should avoid these as well (55). Injectable epinephrine should be prescribed for both home and school and should be available at all times to treat any anaphylactic reactions (8).

Label reading is very important to avoid the accidental ingestion of shellfish. The Food Allergy Labeling Consumer Protection Act (FALCPA) was passed in 2004 and went into effect in 2006. It requires labels to be marked such that a 7-yr old can read and understand the ingredients. It specifies that all allergens should be declared even if they are in the spices or flavorings. Under FALCPA, a major food allergen includes egg, fish, tree nuts, wheat, peanuts, soybeans, and crustacean shellfish defined as crab, lobster, or shrimp (56).

Shellfish allergy can present at any time during childhood with a range of symptoms, from mild reactions consisting of urticaria or eczematous exacerbations to anaphylaxis. Because of the cross-reactivity of dust mite, cockroach and shellfish allergens, patients with a history of dust mite or cockroach allergy are at risk for shellfish hypersensitivity. Pediatric shellfish allergy is a very important cause of food induced anaphylaxis around the world.

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CME questions

1. The most common reported shellfish allergies in decreasing frequency are:
 - a. Lobster, shrimp, crab, oyster and mussel
 - b. Shrimp, lobster, crab, clam and oyster
 - c. Oyster, shrimp, crab, lobster, and mussel
 - d. Shrimp, crab, lobster, clam and oyster
2. Sensitization to the following allergens are seen commonly in shellfish-allergic children
 - a. Dog and dust mites
 - b. Cockroaches and molds
 - c. Dust mites and cockroaches
 - d. Dog and molds
3. All of following are allergens found in crustacean shellfish EXCEPT:
 - a. arginine kinase
 - b. serine protease
 - c. myosin light chain
 - d. tropomyosin
4. Patients with allergy to crustacean shellfish are most likely to have allergy to:
 - a. Codfish
 - b. Salmon
 - c. Oyster
 - d. Tuna
5. The most frequently reported symptom of shellfish allergy is:
 - a. urticaria
 - b. angioedema
 - c. wheezing
 - d. shock

Answers:

1. d
2. c
3. b
4. c
5. a