Fish and shellfish allergy: Presentation and management differences in the UK and US—analysis of 945 patients

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Background: Seafood allergy (SA), including allergy to shellfish (crustacean and mollusks) and fish, is among the 4 most common food allergies causing anaphylaxis, but there are limited data showing SA clinical management in different countries.
Objective: We sought to characterize a large cohort of patients with fish and shellfish allergy and to facilitate standardization of future care for this increasingly common allergic disease.
Methods: We performed a retrospective, observational, noninterventional study from 945 patients from 2015 to 2019 in 7 hospitals in the United States and the United Kingdom to evaluate SA. A chi-square test was used to detect differences in family history, medical history, and current symptoms between patients in 2 countries.
Results: Underdiagnosed anaphylaxis in patients with SA was associated with underuse of epinephrine (adrenaline) autoinjectors in both countries. Oral food challenge was used only when skin or serologic test results were negative. Asthma and allergic rhinitis were more common in the US patients with SA, but eczema was more common in UK patients with SA ($P < .001$). Respiratory, gastrointestinal, and neurological symptoms were higher in UK patients with SA than in US patients with SA ($P < .001$).
Conclusions: In international multicenter cohorts of patients with fish and shellfish allergy, there are opportunities for improvement in management. Physician identification of anaphylaxis, use of diagnostic oral food challenges, and anaphylaxis treatment with epinephrine are areas with significant knowledge gaps in need of improvement in the United Kingdom and the United States. There is an opportunity for the development of unified, standardized diagnostic protocols for SA with distribution for allergists and trainees. (J Allergy Clin Immunol Global 2024;3:100309.)

Key words: *Seafood allergy, fish allergy, shellfish allergy, total IgE, fish specific IgE, shellfish specific IgE, oral food challenge, anaphylaxis, epinephrine (adrenaline) autoinjectors*

Seafood allergy (SA), including allergy to shellfish (crustacean and mollusks) and fish, is one of the most common food allergies causing anaphylaxis in adults and children.[1-3] Although seafood plays an important role in human nutrition and health, there is limited data showing the clinical management of SA in different countries. Being a good protein source, seafood can also be a hidden allergen or subingredient in many foods, inducing allergic reactions.[3] The 2 most important seafood groupings are fish and shellfish.[3] The prevalence of shellfish allergy seems to be higher than the prevalence of fish allergy, with an estimate of up to 3% in the adult population and a fin fish allergy prevalence of approximately 1%.[1,2]

A good patient history, diagnostic analysis of specific IgE (sIgE) antibody reactivity, and oral food challenge (OFC) can be used to distinguish between a true SA and other adverse reactions generated by toxins or parasites contaminating ingested seafood.[3-5] There have been few advances in the understanding of SA in the past few decades, so there is a need to understand differences in disease expression in different populations.[4]

We present a detailed characterization of the largest international multicenter cohort of patients with SA allergy, focusing on demographics, presentation, diagnostic testing, management/outcomes, and treatment, with the aim of understanding the differences in these populations. This will be useful for improving and standardizing care for this common allergic condition. This study ultimately aims to establish the basis for harmonization of the diagnostic process among allergy centers globally and a shared diagnostic, management, and treatment plan for patients with SA in different countries.

METHODS

We performed a retrospective study to evaluate SA in different countries. Data from 945 patients were obtained from a database

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Abbreviations used
AAI: Epinephrine (adrenaline) autoinjector
ED: Emergency department
GI: Gastrointestinal
OFC: Oral food challenge
SA: Seafood allergy
SPT: Skin prick test
sIgE: Specific IgE

within 5 years (2015-2019) in 7 hospitals in 2 countries: the United States and the United Kingdom.

Four UK allergy/immunology centers (Lancashire Teaching Hospitals; Guy's and St Thomas', London; Addenbrooke's, Cambridge; and Sheffield Teaching Hospitals) and 3 US allergy/immunology centers (Houston, Tex; St Petersburg, Fla; and Stanford, Calif) collected data from 251 and 694 patients referred to their services, respectively, between January 1, 2015, and December 31, 2019, with a history of suspected fish and/or shellfish allergy.

All data collected were obtained for solely clinical reasons, and no identifiable patient information was available to clinicians who were not part of the clinical team. Ethical approval for this retrospective, observational, noninterventional review/study was not required in UK sites according to UK law, but in the United States, the study was approved by the Baylor College of Medicine Institutional Review Board (H-23905).

All patients received standard clinical care and were selected on the basis of a history of clinical reaction to seafood. Data were retrieved from the medical records and submitted in a standardized spreadsheet for analysis. This spreadsheet included information on the patient's age, sex, comorbidities, family history of atopy, symptoms during the index reaction, type of fish/shellfish causing the reactions, total IgE, and serum sIgE antibodies and skin prick tests (SPTs) to fish and shellfish. The ethnic groups included White (Caucasian American and White British), non-White (African American, Hispanic American, Asian American, Native American, British Asian), and unknown. US cohorts were chosen and categorized on the basis of presence of only shellfish or fish allergy.

The manufacturers of SPT solutions used for fish and shellfish included Allergopharma (Buckinghamshire, UK), ALK Abello (Hørsholm, Denmark), Allergy Therapeutics (Worthing, UK), and Stallengenes Greer (Lenoir, NC). Tested species included the following fish: codfish, salmon, tuna, mackerel, carp, hake, sardine, and haddock and shellfish (shrimp, crab, lobster, oyster, mussel, squid, scallop, and clams). A positive SPT result was defined as a diameter of wheal increase of 3 mm or more compared with the negative control when read at 15 to 20 minutes in the context of a histamine 10 mg/mL (positive control) and saline (negative control) SPT result.

Total IgE and sIgE antibodies to fish (cod, salmon, tuna, carp, mackrel, haddock, sardine, plaice, tilapia, halibut, and anchovy) and shellfish (shrimp, crab, lobster, oyster, mussel, scallop, squid, and clam) were analyzed with the ImmunoCAP system (Phadia/Thermo Fisher Scientific, Uppsala, Sweden). Total IgE level was considered elevated if values were more than 80 ku/L, and for sIgE, if values were more than 0.35 kUA/L. These are the reference range units of total IgE and sIgE cutoffs from the ImmunoCap system. Only patients with negative SPT results and/or negative sIgE to fish or shellfish underwent OFC with the suspected culprit and with patient's agreement for OFC by signing a consent form. Sensitization to house dust mite and cockroach was proved by either positive SPT result or serum sIgE more than 0.35 kU/L.

Treatments given/provided for reactions were assessed, including epinephrine before hospitalization or in the emergency department (ED). The management plan with referral to an allergy specialist, recommendations for patients (avoidance of fish, shellfish, or both and the anaphylaxis management plan), and the epinephrine autoinjector prescriber (ED/general practitioner/specialist) were analyzed.

Fish- and/or shellfish-associated reactions were assessed using the World Allergy Organization Anaphylaxis Guidelines,[6,7] and reaction severity was graded using the Brown Anaphylaxis Grading Scale[8]: Brown anaphylaxis grading is as follows: grade 1—mild reaction affecting skin and subcutaneous tissues only; grade 2—moderate reaction with features suggesting respiratory, cardiovascular, or gastrointestinal (GI) involvement, including dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain; grade 3—severe reaction resulting in hypoxia (cyanosis or oxygen saturation as measured by pulse oximetry [SpO_2] ≤92%), hypotension (systolic blood pressure <90 mm Hg), or neurological compromise (including confusion, collapse, loss of consciousness, or incontinence).

For open OFCs, the suspected seafood was given in gradually increasing doses until an age-appropriate serving was reached. A challenge was ceased at the first clinical manifestations of an allergic reaction, preventing more severe reactions, as well as determining the eliciting threshold dose. Open oral challenges were performed with cod, salmon, or mackerel (for fish allergy) and with shrimp (for shellfish allergy). Fish or shellfish proteins were administered in the same escalating doses, as by EuroPreval protocol,[9] every 15 minutes (interval between doses).

One gram of fish/shellfish protein is equivalent to 5 g of cooked fish/shellfish. For fish: The incremental doses of cooked Atlantic cod/salmon/mackerel containing 3, 60, and 600 μg; 6, 12, and 120 mg; and 1 g fish protein were given, followed by 10, 30, and 60 g (equivalent to 2, 6, and 12 g fish protein) given every 15 minutes. The cumulative dose of fish was 101.138 g. For shrimp in the United Kingdom: 7 doses containing 3, 60, and 600 μg; 6, 12, and 120 mg; and 1 and 3 g followed by 30 and 50 g cooked shrimp, equivalent to 0.2, 0.6, 6, and 10 g shrimp protein were administered every 15 minutes. The cumulative dose of shrimp was 84.138 g.[9] In the United States, shrimp were given with dose doubling every 15 minutes, starting with 0.5 g of protein (2 g shrimp weight) until a 8-g protein (32-g shrimp weight) dose was reached (a total cumulative dose of 15.5 g protein [62 g shrimp weight]).[10] The shrimp OFCs were performed only at the allergy/immunology center in Houston, Tex, and Sheffield and London Hospitals UK sites.

Statistical methods

The study was performed on historical patient data as provided by the participating sites. Patients were included if there was a physician diagnosis of fish or shellfish allergy. All data were combined into a single database, which allowed patients to be counted in various categories in a fully automated way. For every category we considered, the number of patients in that category can be assumed to be distributed according to a binomial

TABLE I. Characteristics of seafood allergic patients in the United Kingdom and the United States

Clinical site	Country	Total patients	Sex		Median age at diagnosis (y)	Shellfish allergy (n)	Fish allergy (n)	Eczema (n)	Asthma (n)	Allergic rhinitis (n)	Urticaria (n)
			Male	Female							
Preston	UK	43	17	26	41.1	37	22	16	19	25	2
Sheffield	UK	122	52	70	37	109	90	32	45	67	20
London	UK	20	5	15	34.5	20	6	9	9	15	1
Cambridge	UK	66	26	40	37.4	62	10	NA	NA	NA	NA
Houston	US	48	31	17	7.2	42	9	25	31	44	17
St Petersburg	US	79	40	39	10	34	21	44	40	67	NA
Stanford	US	567	326	241	18.8	271	296	NA	312	258	NA
Total	NA	945	497	448		575	454				

NA, Not applicable/available.

distribution that can be approximated by a normal distribution, given the large number of patients.

For each category (family history, medical history, and current symptoms), we applied a chi-square test to detect differences between the 2 countries. As a criterion, we used a critical P value of .001, corresponding to a confidence level/interval of 99.9%.

The primary comparison is among the fish only, shellfish only, and both fish- and shellfish-allergic patients in the clinical presentation in 2 countries (the United Kingdom and the United States). In addition, we analyzed clinical differences between the various food allergen types in the United Kingdom and the United States.

RESULTS

Patients

The total cohort of 945 patients was composed of 52.6% males (497) and 47.4% females (448). However, the individual site characteristics showed that the males predominated in 57.2% (397 of 694) of the US patients, whereas the females predominated in 60.2% (151 of 251) of the UK patients (Table I). In the entire cohort, the mean age in males was 19 years (range, 0-81) and in females 26 years (range, 0-90). The mean age was 38 years (range, 16-81) in the UK cohort, with no difference in the mean age in males and females at the time of diagnosis. Meanwhile, the US cohort showed the mean age of 15 years in males (range, 0-55) and 20 years in females (range, 0-90) at the time of diagnosis.

The ethnic composition of all the patients was non-White at 67.8% (n = 641), White at 14.6% (n = 138), and unknown ethnicity at 17.6% (n = 166). The comparison of sites shows 29.9% (75) White, 4.4% (11) non-White, and 65.7% (165) unknown in the UK cohort, whereas the figures were 9.1% (63), 90.8% (630), and 0.1% (1), respectively, in the US cohort (Table II).

Family history. In terms of family history, of those 73.7% (n = 185 of 251) of UK patients for whom data were available, 2.7% (n = 5) had a history of food allergy in their families, 14.6% (n = 27) had allergic rhinitis, 14% (n = 26) had asthma, and 9.2% (n = 17) had eczema. In comparison, of those US patients for whom data were available (n = 48, Houston), the results were significantly different from the United Kingdom (99.9% CI, $P < .001$). Sixteen percent (n = 8) had food allergy in their families, 70.8% (n = 34) had allergic rhinitis, 64.5% (n = 31) had asthma, and 25% (n = 12) had eczema.

Patient comorbidities. The investigation of past medical history among the 73.7% (n = 185) of UK patients for whom data were available demonstrated that 57.8% (n = 107) had allergic rhinitis, 39.5% (n = 73) had asthma, 30.8% (n = 57) had eczema, and 12.4% (n = 23) had chronic urticaria. Of all 694 US patients, 55.2% (n = 383) had asthma and 53.2% (n = 369) had allergic rhinitis. Of 567 US patients at Stanford University Hospital, 92.5% had other food allergies besides fish and/or shellfish. Except for allergic rhinitis ($P = .26$), the UK and US results were significantly different from each other at the 99.9% CI level ($P < .001$)

Relationship between fish and shellfish allergy

In the whole cohort, there were 3 groups of patients: only fish allergic, comprising 35.7% (n = 337), only shellfish allergic, comprising 48.5% (n = 458), and both fish and shellfish allergic, comprising 12.4% (n = 117). In the US cohort, 48.8% of patients had shellfish allergy alone (n = 339 of 694) and only 1.15% (n = 8) had mixed shellfish and fish allergy. The UK cohort showed that 47.4% of patients had shellfish allergy alone (n = 119 of 251) and 43.4% (n = 109 of 251) had both shellfish and fish allergy.

Fish allergy. The prevalence of fish allergy alone was 45.8% among US patients (n = 318 of 694), compared with only 7.6% in the UK cohort (n = 19 of 251), whereas both fish and shellfish allergy were found in 1.15% (n = 8) in the US cohort and in 43.4% (n = 109 of 251) in the UK cohort.

The ratio of shellfish to fish allergy in the total combined UK/US cohort was 1.35. This means that there were 35% more people allergic to only shellfish than only fish in the cohort. The country group comparison showed that fish allergy was significantly less common in the UK patients compared with the US patients (7.6% vs 45.8%), whereas mixed fish and shellfish allergy dominated in the UK patients (43.4% vs 1.5%). There was no significant difference in shellfish allergy between the 2 countries (47.4% and 48.8%). In the United Kingdom, patients who were only shellfish allergic or those with both fish and shellfish allergies were 5-fold more common than those with only fish allergy. In fact, the significant difference in combined allergy to fish and shellfish in the United States and the United Kingdom could be explained by selection bias, because US cohorts were chosen on the basis of the presence of only shellfish or fish allergy.

In 3.5% of patients with negative SPT and sIgE testing results (n = 33 of 945), OFCs with suspected culprit allergens were not

TABLE II. Ethnicity of seafood allergic patients in the United Kingdom and the United States

Clinical site	Country	Non-Hispanic White (n)	Hispanic (n)	Black (n)	Asian (n)	Unknown (n)
Preston	UK	39	0	0	4	0
Sheffield	UK	0	0	0	0	122
London	UK	11	0	1	0	8
Cambridge	UK	25	0	1	5	35
Houston	US	6	22	19	0	1
St Petersburg	US	44	12	20	3	0
Stanford	US	13	509	0	16	29

performed, because of patients/parents' choice or reluctance. So, the diagnosis was made on the basis of a convincing clinical history.

Clinical manifestation and severity of reactions

Clinical manifestations were incredibly varied, both in nature and in severity. They ranged from mild oral allergy syndrome and the most common acute urticaria/angioedema, followed by respiratory and GI symptoms to life-threatening anaphylaxis (Table III).

Symptom evaluation. For allergic reactions, among 185 UK patients from whom data were available, 42.7% (n = 79) had respiratory symptoms, 37.3% (n = 69) acute hives, 52.4% (n = 97) acute angioedema, 11.3% (n = 21) eye and nasal symptoms, 32.4% (n = 60) GI symptoms, 4.3% (n = 8) symptoms from the central nervous system, and 4.9% (n = 9) vascular shock. Of 127 US patients (Houston, St Petersburg) from whom data were available, 42.5% (n = 54) had acute angioedema, 40.1% (n = 51) acute urticaria, 19.6% (n = 25) respiratory symptoms, 11.8% (15) eye and nasal symptoms, 6.3% (n = 8) GI symptoms, and 1.6% (2) vascular shock. No neurological symptoms were documented in the US cohort. Not all of the patients above were classified as having anaphylaxis because there was only 1 symptom present and this symptom was not respiratory in nature.

Only for the respiratory, GI, and neurological symptoms was there a significant difference between the 2 countries, with UK patients experiencing more respiratory, GI, and neurological symptoms ($P < .001$).

Severity of reactions. Among all 694 US patients, anaphylaxis was diagnosed in 22.9% (n = 159), compared with 15.1% (n = 28) in 185 UK patients.

On the basis of the Brown Anaphylaxis Grading Scale, in 79 US patients (St Petersburg), 73.4% (n = 58) had mild reactions, 19% (n = 15) moderate, and 7.6% (n = 6) severe reactions. Even though 55.7% (103 of 185) of UK patients and 19.6% of US patients (25 of 127) had 2 or more organs/systems involved in the reaction, they were not clinically diagnosed with anaphylaxis.

ED admission, hospitalization, and treatment

In terms of ED admission and subsequent hospitalization, 26% of UK patients (48 of 185) were admitted to the ED and of those, 52.5% (n = 25) were hospitalized. Of those 48 patients seen in the ED, shellfish-associated allergy prevalence was higher than fish allergy (31 vs 17); 54.2% of all patients seen in the ED were treated with epinephrine (adrenaline). Of the 185 patients, 63.8% (n = 118) used antihistamines as first line of treatment. Of the 48 US patients from whom data were available, 18.7% (n = 9) were admitted to the ED, and of those, 55.5% (n = 5) were given epinephrine (adrenaline). Of all patients, 45.8% used antihistamines, as a first line of treatment.

After a severe reaction/anaphylaxis associated with fish/shellfish allergy was experienced, an epinephrine (adrenaline) injector (AAI) was prescribed to 73.5% (136 of 185 UK patients), with 23.8% (44 patients) prescribed either by the ED physician or by their general practitioner. Forty-nine percent (92 patients) were prescribed by the allergist in the allergy clinics on subsequent patient review. Of 48 US patients, 8.3% were given an AAI, with 75% prescribed by the referring physicians and 25% by the allergy clinic. Of the US patients seen in the centers included in this cohort, none had prescriptions provided by ED physicians.

SPTs

Of 231 UK patients from whom data were available, 79.6% (184) had positive SPT result to at least 1 fish or shellfish allergen. These data were not available from the US sites.

Shellfish sIgE

The UK cohort analyses showed that 61% of patients (n = 153 of 251) had positive sIgE to at least 1 shellfish allergen, and in most, it was shrimp (more than 90%) followed by crab and lobster. In the mollusks group, mussels, squid, and scallop, followed by oysters, were positive. Meanwhile of those US patients for whom data were available (18.3%, n = 127, Houston and St Petersburg), 59% were positive to at least 1 shellfish allergen, with similar spreading of species as in the United Kingdom. There was no correlation between the level of sIgE to shellfish and severity of reaction. Moreover, the range of sIgE varied from 0.72 to 91.8 kuA/L in mild reactions, 0.49 to 100 in moderate, and 1.7 to 45.7 kuA/L in severe.

Fish sIgE

Of those UK patients for whom data were available (73.7%, 185 of 251), 52.4% had positive sIgE to at least 1 fish allergen. More frequent positivity was found to cod (more than 70%), followed by salmon, mackerel, and tuna. Among 645 US patients (St Petersburg and Stanford) for whom data were available, 5.4% (n = 35) had positive sIgE to fish allergen, and of them mostly to salmon (25.7%), followed by cod (20%), tuna (17.4%), tilapia

TABLE III. Clinical presentation symptoms in patients with SA in the United Kingdom and the United States

Clinical site	Total no. of patients	Respiratory		Urticaria		Angioedema		GI		Eye/nasal		Neurological		Vascular shock	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%
Preston	43	23	53	13	30	29	67	19	44	3	7	2	5	6	14
Sheffield	122	50	41	50	41	58	48	36	30	17	14	3	2	1	1
London	20	6	30	6	30	10	50	5	25	1	5	3	15	2	10
Cambridge	66	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Houston	48	9	19	17	35	19	40	1	2	6	13	0	0	0	0
St Petersburg	79	16	20	NA		NA		7	9	9	11	NA	NA	2	3
Stanford	567	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

NA, Not available/applicable.

(14.2%), trout (11.4%), halibut (5.7%), and catfish, flounder, red snapper, and mackerel (2.9% each).

Sensitization/allergy to house dust mite and cockroach

From available data, 41.6% in UK patients (77 of 185) and 58.3% in the US cohort (28 of 48) were sensitized to house dust mite. There was a high level of sensitization to cockroach in 50% of US patients (24 of 48), but these data were not available in the UK cohort.

OFC

Open OFCs were performed in only some of Sheffield and London Hospitals UK site patients and the Houston US site. The results were positive to crab (n = 2), shrimp (n = 2), and cod (n = 1), and negative to shrimp (n = 2) and mackerel (n = 1). Of London patients, 45% (9) demonstrated positive OFC to some shellfish (mostly shrimp, followed by crab).

DISCUSSION

We present the largest cohort of fish- and shellfish-allergic patients to date (n = 945), with analysis of demographic data and differences in fish and shellfish allergy clinical features, treatment of reactions, and subsequent management in the United Kingdom and the United States. Although patients in both the United Kingdom and the United States presented to the ED with respiratory symptoms or more than 1 system involved in a reaction to seafood, 25% of ED providers in the United Kingdom did not recognize these reactions as anaphylactic and did not give a prescription of epinephrine (adrenaline), the only current effective treatment for anaphylaxis. (Data were unavailable for the US patients.) An allergic response with respiratory symptoms and a reaction with 2 or more symptoms are defined as anaphylaxis.[6-8] Reasons for lack of diagnoses of anaphylaxis to seafood may include lack of education of the symptoms necessary in the diagnosis of anaphylaxis, physician hesitancy to treat with epinephrine (adrenaline), or the lack of recognition of the life-threatening nature of SA. Because millions of adults and children have symptoms consistent with shellfish allergy, and approximately 50% of all shellfish-allergic adults have visited an ED for severe reactions, with 10% in the previous year,[1,2] the gap in the administration of correct treatment for SA must be addressed.

Prevalence

The prevalence of fish or shellfish allergy in many countries has been hypothesized to be associated with food habits and increased average consumption amounts, with subsequent development of sensitization and/or allergy. Fish consumption has been associated with higher rates of development of fish allergy,[11] and shellfish allergy is higher in the United States in adults living in ocean-adjacent (shoreline) counties as compared with those living in nonshoreline counties.[1] There was a male and female predominance noted in the UK and US cohorts, respectively. This may reflect the male predominance of food allergy in children versus the female predominance in adults.[12,13] The predominance of non-White patients in the United States has been confirmed in patients with SA.[14] The UK racial/ethnic SA patient demographics should be recorded, so that inequities can be better defined.

Prevalence of fish or shellfish allergy may also be associated with the age of involved patients, particularly in the United Kingdom because only adult patients were involved compared with the US sites where pediatric patients were involved. Adults presumably eat higher amounts of shellfish than do children. The average age of diagnosis of SA in the United States is 17.7 years.[1,2] Later consumption of seafood may explain primarily sensitization to shellfish and fish, which is more likely to occur later in life.[15]

Family history

The differences in the primary family history of the patients between the 2 countries could be linked to the fact that the most involved US patients were children, and so their parents could easily state their own medical family history, whereas adult patients in the United Kingdom may have been removed from their own parents' medical history of atopy.

Clinical symptoms

From the data available, the rate of respiratory symptoms was more than twice higher in the UK cohort than in the US cohort, and the rate of documented GI symptoms was significantly higher in the UK compared with US patients. These findings might explain the high rate of underdiagnosed anaphylaxis in UK patients if initial GI symptoms (when they are followed by combination with 1 symptom from another system) are neglected by physician assessment of the fish/shellfish-allergic reactions.

However, this is evidence for an educational need in the United Kingdom regarding treatment of fish/shellfish-allergic reactions and use of World Allergy Organization anaphylaxis criteria, which include GI symptoms in grade 2 reactions, an indication for epinephrine treatment.

Severity of reactions

The high rate of underdiagnosed anaphylaxis in patients with fish and shellfish allergy was associated with the underuse of adrenaline AAI where indicated (by paramedics, EDs, and patients, who had an available autoinjector). Provision of proper management and treatment of patients with severe reactions associated with fish and shellfish allergy needs improvement. These circumstances dictate the necessity of providing education for physicians (including ED) in the field of anaphylaxis diagnosis and management.

There is also a need to emphasize the crucial role of physicians in providing anaphylaxis management plans and education for patients with anaphylaxis, including causative allergen avoidance recommendations and training for the use of autoinjectors.

Testing and diagnosis

sIgE tests do not correlate with the severity of reactions in food allergy. This could be due to either poor patient and physician history, non-IgE reactions, or lack of sIgE testing identification of the correct allergen causing the reaction. There is limited evaluation of sIgE binding and the clinical correlation to sIgE total protein and component testing levels for multiple seafood allergens. We found differences between the United States and the United Kingdom and within the countries between centers, possibly due to local dietary habits. There have been efforts to identify specific allergens that are most clinically relevant, but more research is paramount to understand the clinical relevance of seafood allergen sIgE levels. Ruethers et al[16] compared 3 commercial ELISA tests for fish allergens and demonstrated that only 26% to 61% of fish extracts of the 57 fish species were detected, whereas none of the 9 cartilaginous fish was detected. In the 3.5% of patients with diagnosis by history alone without SA confirmation by testing, there were other food culprits for the reaction, cofactor(s) or some fish or shellfish allergens undetectable by *in vivo* or *in vitro* testing. Moreover, some patients were reluctant to undergo further investigation with OFC procedures, which is the criterion standard test for food allergy. This might demonstrate a gap in ability to detect all seafood allergens with sIgE testing.

Treatment with epinephrine in the ED

Underuse of epinephrine AAIs in the ED in patients with severe symptoms associated with suspected fish/shellfish allergy is a significant issue. Moreover, there are still quite high levels of postponed prescription of AAIs by general practitioners even when the clinical manifestation fits with anaphylaxis criteria. Only approximately 55% of patients were treated with epinephrine (adrenaline) in both the UK and the US EDs, and so education on the use of epinephrine is needed.

OFCs

In this study, OFCs were not a priority for physician diagnosis of fish/shellfish allergy. Despite OFCs being the diagnostic standard for food allergy, there are no standardized protocols for fish and shellfish allergies. Moreover, in everyday clinical practice, the avoidance of the suspected culprit allergen(s) (based on positive SPT result or sIgE or in many cases on clinical history) is frequently recommended and used in practice rather than OFC. There are cross-reacting allergens in multiple fish and shellfish species, including tropomyosin, that need further evaluation by OFC to determine the clinical significance of these allergens. Cockroach and dust mite allergy are cross-reactive with shellfish allergen tropomyosin.[10] Parvalbumin, enolase, and aldolase may also contribute to clinical cross-reactivity in fish and chicken meat.[17-20] The danger of hidden seafood allergens in food raises the need to emphasize the importance of labeling subingredients such as flavoring on food products[21,22] to provide more detailed information about all food allergens in dishes and ingested items for customers in public food establishments.

This was a retrospective, observational, noninterventional study, with the purpose of evaluating differences in fish and shellfish allergy in 2 separate countries (the United Kingdom and the United States). Despite obtaining the largest cohort of fish- and shellfish-allergic patients to date, the database was quite heterogeneous, which led to restrictions in the evaluations of each parameter from all patients and missing data; however, we focused on the estimation in group-selected patients where data were available. This may have resulted in bias, which is inherent in a retrospective study. One center described the symptoms from organs/systems (skin, respiratory, GI, central nervous system), whereas another one evaluated symptom severity (mild, moderate, severe). For many patients, testing was performed only to the suspected food, leading to heterogeneity. This study demonstrates the need for united protocol/algorithms for fish and shellfish diagnostic procedures, management, and treatment recommendations.

Conclusion

Underdiagnosed anaphylaxis in patients with SA and underuse of epinephrine AAIs for severe SA reactions are universal features of treatment in both the United Kingdom and the United States. Physicians should be aware of SA-associated anaphylaxis, and education and training are crucial. There is an open window for development of unified, standardized OFC protocols for fish and shellfish allergy and wide distribution of protocols, so allergists and trainees can learn these techniques. More information is needed on the clinical relevance of sIgE and component testing in SA. Development of new molecular (recombinant) allergen tests for different fish and shellfish species is necessary for more precise diagnosis and personalized recommendations for patients with SA. SA is a heterogeneous disease, needing more accurate testing and appropriate treatment of severe reactions.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: K. Nadeau reported receiving grants from the National Institute of Allergy and Infectious Diseases, the National Heart, Lung, and Blood Institute, the National Institute of Environmental Health Sciences, and Food Allergy Research and Education; serving as director of the World Allergy Organization; serving as advisor for Cour Pharma; serving on the National Scientific Committee of the Immune Tolerance Network and the National Institutes of Health clinical research centers; being cofounder of Before Brands,

Latitude, Alladapt, and IgGenix outside the submitted work; and having patents for an oral formula for decreasing food allergy risk and treatment for food allergy, for granulocyte-based methods for detecting and monitoring immune system disorders issued, for methods and assays for detecting and quantifying pure subpopulations of white blood cells in immune system disorders, and for microfluidic device and diagnostic methods for allergy testing based on detection of basophil activation pending. S. B. Sindher is funded by the National Institute of Allergy and Infectious Disease, Consortium for Food Allergy Research (CoFAR), Regeneron, DBV Technologies, Aimmune Therapeutics, Novartis, and Sanofi, and is an advisory member for AstraZeneca. P. Sriaroon is funded by Food Allergy Research and Education. C. M. Davis receives research contract funding from DBV Technologies, Regeneron, and Aimmune Therapeutics, grant funding from the National Institute of Allergy and Infectious Disease (grant no. R34AI157948) (CoFAR and Consortium of Eosinophilic Gastrointestinal Disease Researchers), and the Food Allergy Research and Education. The rest of the authors declare that they have no relevant conflicts of interest.

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