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Research Article

Anisakis simplex, a New Hero in the Anaphylaxis Scene

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Article Information

Received date: Apr 12, 2017
Accepted date: May 24, 2017
Published date: May 31, 2017

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Keywords Anaphylaxis; Adults; Elderly people; *Anisakis simplex*; Cofactors; Emergency department

Abbreviations AS: *Anisakis simplex*; NSAIDs: Non-Steroid Anti-Inflammatory Drugs; BAB: Beta-Adrenergic Blockers; ACE: Angiotensin-Converting Enzyme Inhibitors; PPI: Proton-Pump Inhibitors; ED: Emergency Department

Abstract

Introduction: Anaphylaxis occurs worldwide and recent data from developed countries indicate a continued increase, not only in children but also in adults. In children, food allergens are the most frequent elicitors. In adults, besides food, hymenoptera venoms and drugs are frequent causes of anaphylaxis. Milk and egg are the most frequent foods involved in small children and adolescents. In the last decades, fish parasite *Anisakis simplex* is considered to be an important cause of food allergy among adults in Spain and Japan. At present, *Anisakis simplex* is one of the most important hidden food allergens in adults who suffer from anaphylaxis in these geographical areas.

Methods: This retrospective, case-based and time series study was conducted over a sixteen years period, from January 2000 to December 2016, in patients studied in our Department and diagnosed of anaphylaxis induced by *Anisakis simplex*. The diagnosis was confirmed with a combination of clinical data, skin tests and specific IgE determinations.

Results: A mean population prevalence of 3 cases per 100.000 inhabitants and year was recorded. The ratio of females to males was 2.5:1 and the median age was 59 years (range 18 - 88 years). Most anaphylaxis cases (65%) were treated in Emergency rooms, 12.5% of them were hospitalized and 1% admitted in Intensive Care Unit. Most patients were undertreated with H1-receptor antagonists (antihistamines) and steroids, and only 34% received injected adrenaline.

Conclusion: This study shown that *Anisakis simplex* induces most allergic reactions in non-atopic middle-aged adults in northern Spain. Drug cofactors (NSAIDs, ACE-inhibitors and beta-blockers) are involved in most of the patients studied. In emergency departments, digestive signs were not taken into account as an additional organ affected, and subsequently most patients were not treated with adrenaline. It is expected that more cases of allergy to *Anisakis simplex* in sea-fish consumption areas could appear.

Introduction

Anaphylaxis is a rapid onset and dangerous syndrome characterized by urticaria and angioedema, collapse, shock, bronchoconstriction and severe gastrointestinal symptoms. Anaphylaxis is usually the clinical manifestation of an immediate hypersensitivity reaction with vital risk.

Although the term anaphylaxis was introduced as far back as 1902 by Portier and Richet, only in recent years has a general definition of clinical criteria been published [1].

Anaphylaxis occurs worldwide and recent data from developed countries indicate a continued increase, not only in children but also in adults. The World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis alert health care professionals about patient-related factors that increase the risk of severe or fatal anaphylaxis [1]. Incidence rates ranging from 3.2 to 30 per 100,000 inhabitants per year have been estimated, with large differences observed between most of the studies reviewed [2,3].

Most patient factors that increase the risk of severe or fatal anaphylactic episodes are similar worldwide. They include age-related factors, concomitant diseases, cardiovascular diseases, mastocytosis or clonal mast cells disorders and severe atopic diseases. In addition, some concurrent medications such as Beta-Adrenergic Blockers (BAB) and Angiotensin-Converting Enzyme (ACE) inhibitors can also increase the risk. Described cofactors that amplify or facilitate anaphylactic episodes are exercise-induced anaphylaxis, concomitant ingestion of ethanol or Non-Steroid Anti-Inflammatory Drugs (NSAIDs) and Proton-Pump Inhibitors (PPI) that enhance intestinal permeability and allergen absorption. In addition, the habit of eating raw fish may interfere with the integrity of the intestinal mucosa, thus predisposing to more severe symptoms such as anaphylaxis [4].

Anaphylaxis trigger(s) should be identified by obtaining a detailed history of the episode. Many of the specific triggers for anaphylaxis are universal; however some important geographic variations have also been reported. Foods are the most common trigger in children, teens and young adults. Insect stings and drugs are relatively common triggers in middle aged and elderly adults. Idiopathic anaphylaxis is also relatively common in the last age groups.

In 1990, Kasuya et al. [5] pointed out the allergenic potential of *Anisakis simplex* (AS) and emphasized the need to consider it as an etiologic factor in urticaria related to the consumption of fish. After studying a case of anaphylaxis caused by AS [6], our group reported several patients with immediate hypersensitivity developed after parasitized fish ingestion using a new home made allergen extract [6-9]. *Anisakis simplex* allergic reactions have been recognized as one of the most common causes of anaphylaxis in the adult population in Spain. *Anisakis*-associated hypersensitivity cases have been particularly noted in northern Spain. In the allergic cases from this region, the consumption of cooked hake (*Merluccius merluccius*) predominates, closely followed by cooked or raw anchovies *(Engraulis encrasicholus)* [7]. It is becoming apparent that AS is the most important hidden food allergen in the adult population suffering acute urticaria and anaphylaxis of the Basque Country in northern Spain, and this recognition has now spread to other regions in Spain [7-10]. It is also the etiological factor which is most commonly associated with urticaria for any specific food allergy in the adult population and comprises as much as 10% of the anaphylaxis previously diagnosed as idiopathic [7-9]. Although food allergy is most frequent in atopic patients and children, *Anisakis simplex* also induces allergic reactions in non-atopic middle-aged adults.

There is evidence that purified allergens from AS are potent enough to cause anaphylaxis in some individuals even as a result of a Skin Prick Test (SPT) with an extract of the parasite and that allergens are also present in the flesh of fish in areas close to the larvae [11]. These findings indicate that parasite antigens and allergens can be present in the edible fish muscle and might cause allergic symptoms [7,12]. Some authors have suggested that *Pseudoterranova decipiens* larvae, especially those found in the United States are less invasive and less pathogenic than are *Anisakis simplex* larvae [13].

Material and Methods

This retrospective, case-based and time series study was conducted on all patients presenting to a single Allergy Department of Basque Country over a sixteen year period from January 2000 to December 2016. The study hospital was a university affiliated tertiary referral teaching hospital in Vitoria, Spain, a city of 250.000 inhabitants and an influenced area of 300.000. We enrolled a total of 585 patient presentations with urticaria and 133 with anaphylaxis. Thirty-two last anaphylactic patients (recorded from 2011) were analyzed in detail in addition to 6 cases that experienced a previous episode of anaphylaxis to *Anisakis*. The Local Ethical Committee and Institutional Committee on Human Investigation confirmed that clinical data were obtained through electronic clinic history without a deviation of habitual clinical practice.

The patients studied were referred to the Allergy Department from Emergency Rooms (ER) of hospitals with an identical protocol in case of anaphylaxis as well as by their general practitioner. All subjects were recorded in the Allergy Department and data about age, gender, complaint and vital signs during the episode were obtained from clinical electronic records. Subjects were examined by an allergy physician and final diagnosis was reported after a detailed clinical history confirmed by SPT and specific IgE.

Exclusions

Patients were excluded if there was insufficient documentation to clearly define an allergic reaction induced by *Anisakis simplex* and in the case of sensitization to the fish´s own proteins.

Definitions

Clinical data were collected from the Allergy Department of Vitoria (Spain) because for the last 20 years, the Allergy Department of University Hospital Araba has been involved in active research of this topic. A total of 585 episodes of AS-induced urticaria and 133 episodes of AS-induced anaphylaxis were reviewed from 2000 to 2016. In a previous publication [8] we confirmed the diagnosis with a combination of clinical, skin tests and specific IgE determinations. A clinical detailed history with data provided from ER and allergic assessment followed by SPT with the culprit agents involved were carried out in all cases. Following the protocol previously described, in all cases commercially available AS extracts were tested forming part of a series of food allergens (and in some cases drug allergens and/or others such as hymenoptera venoms). In those patients with positive SPT results to AS, a determination of tryptase, total and specific IgE was carried out to confirm a true allergic response.

The diagnosis of AS allergy was based on the following criteria: (a) a compatible history of anaphylaxis following fish consumption, (b) positive SPT, (c) positive specific IgE against AS (ImmunoCAP), considering positive values >0.7 kU/l and (d) a lack of reaction to AS host fish proteins and/or other possible cross reacting antigens such as crustaceans, snails, cockroach, dust mites and other insects [8,9].

Results

During the study period, a total of 718 patients (585 urticaria and 133 anaphylaxis) met the inclusion criteria remained for analysis. The patient's medical records were missing or unavailable in 5 cases and further 6 cases were studied separately because a previous episode of anaphylaxis induced by AS was diagnosed. A total of 127 new cases of anaphylaxis remained for analysis. This number represented a mean population prevalence of 3 cases per 100,000 inhabitants and year (10.1 cases/year over a sixteen year study period). A total of 133 cases of anaphylaxis were recorded in this period and a total of 585 cases of urticaria were attributed to AS in the same time. These data are represented in Figures 1 and 2.

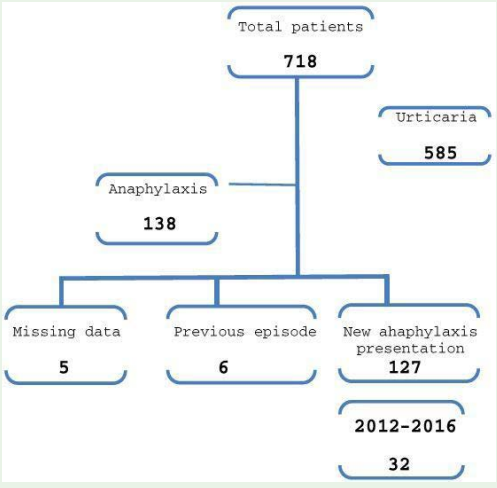

Figure 1: Organization chart.

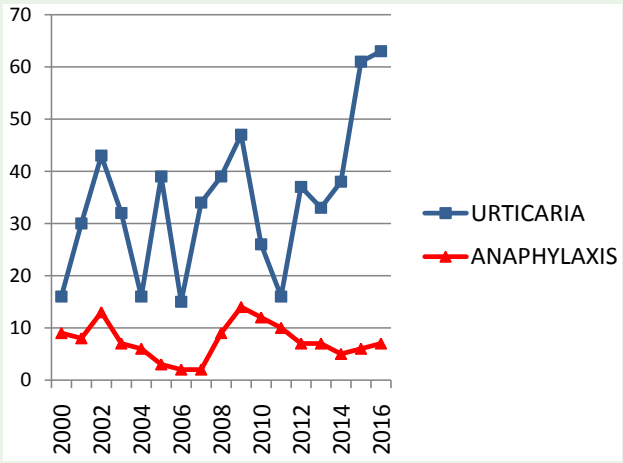

Figure 2: The anaphylaxis data.

Thirty two last patients recorded from 2011, were analyzed in addition to the 6 cases that experienced a previous episode of anaphylaxis to *Anisakis simplex*. Nine of the 32 anaphylaxis patients were male; the ratio of females to males was 2.5:1. The median age for patients with anaphylaxis was 59 years (range 18 - 88 years). Fourteen (44%) of those were under 60, 16 (50%) were aged 60-80 and 2 (6%) were 80 years or older.

Twenty six patients had severe, potentially life threatening anaphylaxis. Twenty one patients (65%) were treated in ER, 4 (12.5%) of them were hospitalized and 1 admitted to Intensive Care Unit (1%). Eight patients were treated in their Outpatient Health Center and 2 at their home.

Six patients had a new episode of anaphylaxis, whereas they were previously diagnosed of *Anisakis* allergy. Their median age was 55 years and all of them were female.

Clinical features

Cutaneous features were present in 94% of all patients. The prevalence of cutaneous (30/32), gastrointestinal (22/32), respiratory (21/32), cardiovascular (hypotension 19/32) and neurological (13/32) features is recorded in table 1. Among digestive symptoms, vomiting was the most involved. Respiratory dyspnea and laryngeal edema were also described. A traumatic brain injury was recorded in one case in the context of anaphylactic shock.

The first signs of an allergic reaction usually appear within 30–120 minutes after ingestion of infected fish but can take up to six hours.

In 5 cases, a drug allergic reaction was suspected and finally ruled out. All of them were woman and the drugs suspected were: NSAIDs in all cases and in 2 of them other additional drugs could be involved because they were taken simultaneously (a beta-lactam and Omeprazole).

Causative agents, fish involved

The reported causative agent was recorded in 90% of cases. The most common suspected causes of anaphylaxis were hake and

Table 1: Incidence of cutaneous, mucosal, respiratory, cardiovascular, neurological and/or gastrointestinal features of last patients presenting with anaphylaxis.

	Anaphylaxis (n=32)	Anaphylaxis previously diagnosed (n=6)
Cutaneous features		
Pruritus	16	4
Urticaria	18	2
Angioedema	13	1
General erythema	6	2
Total (any cutaneous feature)	30	6
Respiratory features		
Rhinitis/conjuntivitis	0	0
Oxygen desaturation	8	
Dyspnea/wheeze	7	1
Laryngeal oedema	7	
Cyanosis	2	
Total (any respiratory feature)	21	1
Cardiovascular features		
Hypotension	19	
Neurological features		
Loss of consciousness	10	2
Sphincter relaxation	2	
Traumatic brain injury	1	
Total (any neurological feature)	13	2
Digestive features		
Epigastralgia	7	4
Nausea	8	3
Vomiting	14	1
Diarrhea	7	
Total (any digestive feature)	22	4

Table 2: Fish involved in last cases of anaphylaxis.

	Anaphylaxis (n=32)				Anaphylaxis previously diagnosed (n=6)			
		C	Not C	F		C	Not C	F
Anchovies (*Engraulis encrasicholus*)	11	3	9		2	1	1	
Hake (*Merluccius merluccius*)	15	14	1		2	2		1
Monkfish (*Lophius piscatorius*)					2	1		
Horse mackerel (*Trachurus trachurus*)	1	1						
Cod (*Gadus morhua*)	5	5						
Total cooked		23				7		
Total not cooked			10				1	

anchovies (Table 2). In most cases hake was ingested cooked and anchovies uncooked.

Co-morbid conditions

The prevalence of atopy and asthma in patients with anaphylaxis induced by *Anisakis* was 12.5% and 9% respectively. One patient had a known pre-existing *a frigore* urticaria (24 year old female) and another patient had had a gastric by-pass operation.

Fifteen per cent of patients (6 cases from 38 episodes of anaphylaxis from 2011) had a known pre-existing allergy to the causative agent (*Anisakis simplex*). The fish involved in these cases were cooked fish (hake) and other species were anchovies and monkfish. In 1 case the patient confirmed the ingestion of raw fish.

Concurrent cofactors involved

Fifteen patients (47%) with anaphylaxis were taking drugs considered as cofactors in this study. Nine patients took a drug as cofactor, 5 patients took two drugs at the same time and 1 patient three active drugs.

In the previously diagnosed anaphylaxis group 2 out of 6 patients were taking drugs considered as cofactors. An elevated tryptase level was detected in other patient of this group (Table 3).

Tryptase and treatment

Tryptase determinations were recorded in hospital in eight patients (25%) with anaphylaxis. The mean value was 21 µg/L in the moment of anaphylactic episode. At allergic assessment, all cases recorded a normal basal value of tryptase (mean value 4.2 µg/L) except one case from the previously diagnosed anaphylaxis group with a basal value of 15.6 µg/L.

Most patients (31/32) were treated with H1-receptor antagonists (antihistamines) and steroids. Only 11 patients received injected adrenaline (34%), 9 intramuscularly and 2 patients by continuous infusion. Five patients (15%) had received Salbutamol saline inhaled via nebulizer with supplemental oxygen. Vasopressors were required in 2 cases.

Allergic study: skin tests, IgE and other causes discarded

Each case was diagnosed by suggestive anamnesis, positive SPT with *Anisakis simplex* extract and specific IgE detection in serum (CAP System). The possibility of sensitization to the fish´s own proteins was ruled out using the above mentioned tests that were negatives in all patients selected. Six other causes had been referred to our clinic because of drugs (5/32) or other foods (1/32). These allergens were also ruled out by SPT, *in vitro* and challenge tests. Drugs involved were NSAIDs in 5 cases, 1 of them also with beta-lactam and other one with Omeprazole. The other food suspected was strawberries.

Table 3: Co-factors involved in anaphylaxis cases.

Drugs		
	Anaphylaxis (n=32)	Anaphylaxis previously diagnosed (n=6)
IBP	5	1
AINEs	8	1
IECAs	9	1
Total not Co-factors involved	17	4
Total 2 Co-factors involved	5	1
Total 3 Co-factors involved	1	0

Discussion

The WAO Guidelines focus on a systematic approach to basic management of anaphylaxis emphasizing two points:

1. Recognition of characteristic symptoms (in more than one body organ system usually).
2. The primary role of adrenaline (epinephrine) in a rapid treatment [1].

Anisakis induced anaphylaxis is a re-emerging global disease caused by consumption of fish contaminated with L3 *Anisakis* larvae. This zoonotic disease is characterized by severe gastrointestinal and/or allergic symptoms which may be misdiagnosed as appendicitis, gastric ulcer or other food allergies. Digestive signs are also present in 68% (22/32) of patients diagnosed of anaphylaxis and probably these symptoms were not taken into account as an additional organ involved. This event can explain an important conclusion of our revision: that most patients (66%) were not treated with adrenaline. Similar results have been described in infant population, however in adults the percentages of treatment with adrenaline were higher [1,14].

This is the most extensive series of anaphylaxis record for the only cause that is *Anisakis simplex*. According to the present report and in agreement with other authors, it is important to highlight the importance of allergy study (skin tests and specific IgE quantification) to confirm an allergic mechanism and to recommend preventive measures.

Unlike other food allergies, which are typically first observed in babies and young children, allergy to *Anisakis* may not become apparent until adulthood [1]. Paradoxically, the patients reported a tolerance to the ingestion of the same kind of fish between and after the allergic episodes and attribute the episode to other allergens. Managing *Anisakis simplex* allergy includes strict avoidance of sea-fish and cephalopods, but this can be difficult because the adult population is not prompt in changing their fish consuming habits. In addition, it is possible to find *Anisakis* in hidden, substituted, confusing labels and contaminated foods.

Risk factors for severe or fatal food allergic reactions to hidden allergens in foods are namely: early age, multi-sensitivity, presence of uncontrolled asthma, previous serious food reactions, epinephrine not immediately available and eating out of the home. Atopic allergic diseases are familiar and genetically based. However, most patients diagnosed as allergic to AS can not be classified simply as merely being atopy-susceptible patients, but are instead adults of mid-dle age, without a previous history of atopic dermatitis, asthma, or rhinitis [6-9]. An Italian study, demonstrate that atopic subjects had a lower risk of *Anisakis* allergy than non-atopic subjects, and showed AS sensitization associated with consumption of uncooked seafood (anchovies and squid) and increasing age [15]. In a previous study of food induced anaphylaxis, logistic regression analysis revealed that age and specific IgE level were the unique risk factors associated with AS [7]. In many cases, patients did not suspected fish or AS allergy but drug (analgesic and/or antibiotic) allergy. Obviously, they were not used to suspecting fish as a culprit allergen because they have tolerated it all their lives.

Anisakis simplex represents a hidden food allergen, and reports from France, Italy, Portugal, and Spain, are show that allergy in Europe is not confined to the Basque Country but is also present in Japan, where more *Anisakis* IgE sensitization than to fish proteins has been diagnosed [12]. It is possible that prevalence of AS allergy is different depending not only on genetic differences but also on fish consumption habits.

In our population, 15% of cases were recurrent anaphylaxis; consequently, particular attention should be paid to prevention and care of this population. This is consistent with previous findings in pediatric and adult's series of anaphylaxis, and represents a potentially avoidable proportion [14]. This is exemplified by study of 32 fatal cases of food allergy reported in the USA, who were found to have existing food allergy before the fatal event [16]. However, other authors describe higher rates of recurrence in subtypes with an increased prevalence of atopy (food, idiopathic, latex) than in drugs and *Anisakis* [17].

Anaphylaxis reaction was elicited by the parasites antigens, and no influence was demonstrated by the fish´s own proteins. Although cooking or freezing kills the parasite, these treatments do not destroy the allergenic ability of AS extract [6-8]. Hake *(Merluccius merluccius)* was the first fish involved in the first patient diagnosed and continues to be the fish most involved in our patients. In the Basque country, it is very popular to eat hake and it seems that more research is required to evaluate the risk of other fish in other countries.

It is worth highlighting the severity of symptoms: 1 patient suffered a near-fatal respiratory arrest and admitted to Intensive Care Unit, 65% had to be treated by emergency services and two of them were hospitalized.

Seafood consumption has been popular worldwide because of its palatability and promoted nutritional advantages. The largest consumer is China followed by Japan, some European countries (Spain and Portugal among others) and North America. Americans ate an average of 15.8 pounds of fish and shellfish per capita by year [18]. In adult population, it is difficult to change fish consumption habits and some contradictory dietary guidelines for allergic patients have been proposed previously. In our Department, we insist on the training of subjects to avoid accidental consumption of parasite by teaching the patients to recognize worms and not to consume small fish (such as anchovies) or hypaxial tissue (ventral muscles next to the abdominal cavity) in large fish and do not eat fish at restaurants [6-9]. These recommendations were based on AS fish parasitology studies, and characteristic of *Anisakis simplex* allergens associated with the triggering of allergic episodes (thermo stability, resistance to pepsin, pathogen associated molecular patterns, presence of HLA binding motifs, protein structural features, etc.) [7].

It is worth noting that prior to 1995, the 718 patients described had been labeled idiopathic. It is known that acute idiopathic urticaria is a mild and frequent pathology but anaphylaxis must be investigated in depth [6]. The diagnosis of idiopathic anaphylaxis provides an opportunity to identify patients with mastocytosis and also to identify previously unrecognized triggers such as galactose alpha-1,3 galactose or omega-5 gliadin. Our results confirm that *Anisakis simplex* parasite has a place in the anaphylaxis scenario as a hidden food allergen. In most cases, the professionals who care for the patient in the acute phase are not an allergist but an emergency or intensive care physician, and the medical history of this patient is crucial in establishing the diagnosis of urticaria, angioedema or anaphylaxis because this usually reveals antigenic exposure during the previous few hours.

There are few studies of food allergy or anaphylaxis in elderly patients [1]. Another interesting contribution of our work is to include elderly people in risk population of anaphylaxis, not only because of subclinical cardiovascular diseases and the medications used to treat them, but also because *Anisakis* allergy is more frequent in this age range (56% more than 60 years old). Elderly people usually consume drugs acting as cofactors (NSAIDs, hypotensive drugs, PPI) and also are characterized by including more fish in their dietary habits.

Our results confirmed the usefulness of carrying out an allergy study that includes *Anisakis simplex* as an etiological factor involved in adults with anaphylactic episodes. A positive study helps to choose the safest foods for allergic patients. In those cases of AS allergy, our recommendations can be used safely but studies on the safety of fish from aquaculture would be desirable.

Three "pearls" to summarize:

1. *Anisakis simplex* anaphylaxis is present in middle age and elderly patients without a previous history of atopy.
2. Drug allergy is suspected in 15% of cases and cofactors are present in 46% of cases.
3. Digestive symptoms are not taken into account and subsequently most patients were not treated with adrenaline.

Acknowledgements

The authors are grateful to Darren Mathew Patrick Kurien for his review of English

References

1. Simons FE, Ardusso LR, Bilò MB, El-Gamal YM, Ledford DK, Ring J, et al. World Allergy Organization anaphylaxis guidelines: summary. J Allergy Clin Immunol. 2011; 127: 587-593.
2. Weiler JM. Anaphylaxis in the general population: A frequent and occasionally fatal disorder that is underrecognized. J Allergy Clin Immunol. 1999; 104: 271-273.
3. Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: A population-based study. J Allergy Clin Immunol. 1999; 104: 452-456.
4. Polimeno L, Loiacono M, Pesetti B, Mallamaci R, Mastrodonato M, Azzarone A, et al. Anisakiasis, an underestimate infection: effect on intestinal permeability of Anisakis-simplex-sensitized patients. Foodborne Pathog Dis. 2010; 7: 809-814.
5. Kasuya S, Hamano H, Izumi S. Mackerel-induced urticaria and Anisakis. Lancet. 1990; 335: 665.
6. Audicana MT, Fernández de Corres L, Muñoz D, Fernández E, Navarro JA, del Pozo MD. Recurrent anaphylaxis caused by Anisakis simplex parasitizing fish. J Allergy Clin Immunol. 1995; 96: 558–560.
7. Audicana MT, Kennedy MW. Anisakis simplex: from obscure infectious worm to inducer of immune hypersensitivity. Clin Microbiol Rev. 2008; 21: 360-379.
8. Audicana MT, Ansotegui IJ, de Corres LF, Kennedy MW. Anisakis simplex: dangerous dead and alive? Trends Parasitol. 2002; 18: 20-25.
9. Audicana M, García M, Del Pozo MD, Moneo I, Díez J, E. Fernández, et al. Clinical manifestations of allergy to Anisakis simplex. Allergy. 2000; 55: 28-33.
10. Añíbarro B, Seoane FJ, Múgica MV. Involvement of hidden allergens on food allergic reactions. J Investig Allergol Clin Immunol. 2007; 17: 168-172.
11. Solas MT, García ML, Rodriguez-Mahillo AI, Gonzalez-Munoz M, de las Heras C, Tejada M. Anisakis antigens detected in fish muscle infested with Anisakis simplex L3. J Food Prot. 2008; 71: 1273-1276.
12. EFSA Panel on Biological Hazards (BIOHAZ). Scientific opinion of risk assessment of parasites in fishery products. EFSA Journal. 2010; 8: 1543.
13. Deardorff TL, Overstreet RM. Seafood-transmitted zoonoses in the United States: the fishes, the dishes, and the worms. In book: Microbiology of Marine Food Products. D.R.Ward and C.Hackney (Ed.). 1990; 211-265.
14. Braganza SC, Acworth JP, Mckinnon DR, Peake JE, Brown AF. Paediatric emergency department anaphylaxis: different patterns from adults. Arch Dis Child. 2006; 91: 159-163.
15. Foti C, Fanelli M, Mastrandrea V, Buquicchio R, Cassano N, Conserva A, et al. Risk factors for sensitization to Anisakis simplex: a multivariate statistical evaluation. Int J Immunopathol Pharmacol. 2006; 19: 847-851.
16. Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol. 2001; 107: 191-193.
17. Alonso MA, García MV, Hernández JE, Moro MM, Ezquerra PE, Ingelmo AR, et al. Recurrence of anaphylaxis in a Spanish series. J Investig Allergol Clin Immunol. 2013 ; 23: 383-391.
18. United States Department of Commerce. National Oceanic and Atmospheric Administration. Available in: http://www.noaa.gov/