

Short communication

Anisakis simplex, a relevant etiologic factor in acute urticaria

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Anisakis simplex, a parasite of fish and cephalopods, can induce IgE-mediated reactions. This study aimed to determine the etiologic role of *A. simplex* in patients affected by urticaria/angioedema (AE) or anaphylaxis. We studied 100 adult subjects suffering acute episodes of urticaria/AE, by anamnesis, prick tests with *A. simplex* and fish-mix extracts, and total and specific IgE to both *A. simplex* and cod. The following criteria of *A. simplex* allergy were considered: 1) urticaria/AE within 6 h after fish ingestion; 2) specific IgE to *A. simplex*; 3) positive prick test to *A. simplex* extract; 4) exclusion of other suspected causes. Double-blind, placebo-controlled food challenge was not carried out because ethical considerations forbid challenge with a parasite. Specific IgE to *A. simplex* (>0.7 kU/l) was found in 22 subjects, but only eight were diagnosed as having *A. simplex* allergy. Other allergens were involved in 37 patients, and 55 cases were considered idiopathic. Specific IgE to fish (>0.7 kU/l) was found in two patients, but only one was diagnosed as having fish allergy. We concluded that *A. simplex* is an important etiologic factor in acute urticaria. We suggest that it should be considered in cases of urticaria/AE or anaphylaxis, especially after fish ingestion.

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Foods may be contaminated by a wide variety of substances (preservatives, bacteria, parasites, etc.) which can elicit hypersensitivity reactions simulating food allergy. *Anisakis simplex* (Ascaridoidae) is a fish parasite that causes anisakiasis or anisakidosis (human infection) (1–3). It can also induce IgE-mediated reactions, with several clinical manifestations ranging from urticaria/angioedema (AE) to anaphylaxis, when a parasitized fish is ingested (4–6).

This study aimed to determine the etiologic role of this parasite in patients affected by urticaria/AE and its importance in comparison with other well-known allergens.

Material and methods

Subjects

The subjects comprised 100 patients (63 women) older than 18 years, with a mean age of 37.38

(ranging: 18–75), referred to us for at least one acute outbreak of urticaria/AE of less than 1 week of evolution. Sixteen had atopic antecedents. In 28 of them, other organs were also involved.

Anamnesis

All patients were asked about personal and family atopic antecedents and tolerance of foods, drugs, contactants, physical causes, insect bites, etc., in order to detect the major causes of urticaria/AE/anaphylaxis (7).

Antigen

A. simplex extract was prepared by the procedure of Desowitz et al. (8) with some modifications (4, 5). Larvae were collected from muscle tissue of *Phycis blennoides* (Brünich, 1768). Protein concentration, measured by Lowry's method (9), was 5 mg/ml, with bovine serum albumin (BSA) as

standard. Larvae were kindly identified by Dr David Gibson, of the Natural History Museum, London, UK, as *A. simplex* (Rudolphi, 1809) third-stage larvae.

Prick tests

Skin prick tests (SPTs) were performed on the volar aspect of each subject's forearm with allergy pricker lancets (DHS, Madrid, Spain) with 0.05 mg/ml of *A. simplex* extract and commercial extracts of cod and fish mix (Bencard, Bayer, Madrid, Spain).

Histamine 10 mg/ml and saline solutions were used as positive and negative controls, respectively. The SPTs were read after 15 min. Those with a wheal diameter 3 mm larger than the negative control were regarded as positive.

Furthermore, if other causes were suspected (other foods, drugs, Hymenoptera, etc.), they were also investigated by prick/intradermal tests, serum specific IgE measurements, and challenge tests when required.

Total serum IgE

Total IgE determinations were performed by the radioallergosorbent test according to the manufacturer's instructions (Pharmacia Diagnostics, Uppsala, Sweden).

Specific IgE determination

Specific IgE determinations were performed by radio-immunoassay (CAP System, Pharmacia Diagnostics, Uppsala, Sweden). For this purpose, commercially available immunoCAPs of *A. simplex*, cod, and other allergens suspected by history were used. Results higher than 0.7 kU/l were considered positive.

Criteria of A. simplex allergy

In order to analyze the clinical relevance of the *A. simplex* sensitization, we considered the following criteria:

- 1) urticaria/AE or anaphylaxis within 6 h after fish ingestion (10)
- 2) specific IgE antibodies to *A. simplex*
- 3) positive SPT with *A. simplex* extract
- 4) exclusion of fish allergy or other suspected causes.

Results

Prick tests

Fourteen patients presented positive SPTs with *A. simplex* extract. In two of them, specific IgE

detection by CAP was negative. Fish-mix extract gave positive results in three cases.

Total IgE

Total IgE ranged from 2 to 1770 kU/l with a median of 98.5 kU/l. Results higher than 100 were observed in 51 patients.

Specific IgE

Specific IgE antibodies to *A. simplex* were found in 22 subjects with a median of 15 kU/l. Atopic antecedents were observed in four of them. Total IgE results in these 22 CAP-positive subjects ranged from 15 to 1770 with a median of 164 kU/l. The mean age of this group was 45.77 years. Two of the three patients with positive SPT with fish mix also had specific IgE to cod: 1.73 and 74 kU/l, respectively.

A. simplex allergy criteria

Of the 22 patients with specific IgE antibodies against *A. simplex*, 11 had eaten fish in the previous 6 h. Three of them were discarded because the SPT with *A. simplex* extract were negative and because other etiologic agents were established in two of them: fish and Hymenoptera venom. These three patients had low levels of specific IgE antibodies to *A. simplex* (1.94, 1.02, and 1.41 kU/l, respectively).

Therefore, only eight patients (patients 1–8 in Table 1) who fulfilled the mentioned criteria were diagnosed as having allergy to *A. simplex*. None of them had atopic antecedents. The ages of these eight patients ranged from 37 to 63 years (mean 53.12). Medians of specific IgE to *A. simplex* were significantly higher in these patients (36.75 kU/l) than in the other subjects with positive CAP to *A. simplex* (3.3 kU/l). On the contrary, no relevant differences were found in medians of total IgE in these two groups (182 vs 164).

Table 1. Characteristics and IgE determinations in *A. simplex*-allergic patients

Patient no.	Sex	Age (years)	Atopy	Total IgE	Specific IgE
1	F	55	NO	26	44.5
2	M	59	NO	245	37.6
3	M	52	NO	103	19.9
4	F	37	NO	1770	100
5	F	62	NO	121	18.2
6	M	45	NO	243	35.9
7	F	52	NO	69	9.16
8	F	63	NO	1189	49

Although all patients were prick tested with fish-mix extract, only three were positive and only one was diagnosed as having fish allergy.

Table 2 shows the list of final diagnoses in all 100 patients studied. If we include *A. simplex* as a "food" allergen (although it is not a food), it would represent 32% (8/25) of the "food"-allergic patients.

Discussion

Acute urticaria is extremely common, affecting up to 20% of the population at some time in their lives (7). Food allergy was found to be the most frequent cause in our patients with 17 cases. Drugs were implicated in 14. Only eight patients were diagnosed as having *A. simplex* allergy. In 55 patients, affected by only urticaria/AE, no etiologic factor was found, as in previous reports (11).

A recent French multicenter study (12) found food allergy to be the cause of 10.2% of anaphylactic shocks. The most frequently implicated food allergens were egg, fish, and crustaceans. However, the most frequent foods involved in allergic reactions depend on the dietary habits and the age of the studied population (13, 14). In our study, the implicated foodstuffs were fruits and/or nuts in nine patients, shellfish in seven and fish in only one. This means that the clinical relevance of *A. simplex* in acute urticaria is, at least, similar to that of other well-known allergens.

The severity of symptoms is also important in *A. simplex* allergy. Two patients had anaphylactic shock and five gastrointestinal symptoms with intense abdominal pain. Only one patient presented exclusively cutaneous symptoms. Of cases of anaphylaxis (more than one organ involved), 25% were due to *A. simplex* allergy and 21.42% to food allergens.

Since all the patients were older than 18 years (range: 18–75, mean 37.38), it is interesting to note that the mean age of *A. simplex*-allergic patients was 53.12 years, while it was 27.41 years for the remaining patients with food allergy. None of the patients with allergy to *A. simplex* had atopic antecedents, while 7/17 patients diagnosed as having food allergy reported such antecedents. This confirms our previous assumption (6) that although food allergy is most frequent in atopic patients and children, *A. simplex* induces allergic reactions more frequently in nonatopic middle-aged adults.

Fish is one of the most commonly implicated foods in food sensitization in populations in which fish is a staple food. Spain is one of the countries with the highest fish consumption (89 g per person per day) (15). The mean frequency of fish consumption among our patients was 2.54 times per week, and all of them ate fish at least once a week.

Table 2. Causes of urticaria/AE/anaphylaxis in 100 patients

	Food		Drugs		Other	
Fruits	3	NSAIDs intolerance	7	Hymenoptera		3
Nuts	2	Radiocontrast	2	Cholinergic		3
Fruits and nuts	4	Pyrazoles	1	Idiopathic		55
Fish	1	β -lactams	3	<i>A. simplex</i>		8
Shellfish	7	Mercurochrome	1			
Total	17	Total	14	Total		69

However, in our study, allergy to *A. simplex* was more frequent than fish allergy (8 to 1) and sensitization (CAP > 0.7 kU/l) much higher (22 to 2). The prevalence of fish allergy was lower than expected (12, 13) but similar to that observed by Joral et al. in northern Spain (14). These data could be related to the frequent infection of fish in our area (16).

We found two problems in the diagnosis of *A. simplex* allergy: the difficulty in determining whether the fish ingested was infected by this nematode and ethical objections to performing a challenge test with a parasite (17). When an unequivocal anamnesis was confirmed by positive SPTs and high levels of specific IgE were found, the diagnosis was clear. However, we found an important group of doubtful cases with no relevant positive CAPs, as in previous reports (18–21). While we await the results of further studies to clarify the diagnostic procedure, assessment of the evolution of suspected patients, after a fish-free diet trial, is our best diagnostic approach.

We conclude that *A. simplex* is a relevant etiologic factor in acute urticaria, and it should be considered in cases of urticaria/AE/anaphylaxis after fish ingestion. Fish infection is widespread; therefore, prevalences similar to that of this study could be found in other areas with similar fish consumption and fish infection rates. It is also important to note that these eight patients diagnosed as having *A. simplex* allergy would have been previously labeled as idiopathic because *A. simplex* was not identified as the inciting agent.

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