

## CLINICAL REPORT

# Acute Allergic Reactions to *Anisakis simplex* After Ingestion of Anchovies

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***Anisakis simplex* is a seafish nematode, which is responsible for the well-known human infection (anisakiasis) and can induce IgE-mediated reactions. IgE sensitization to *Anisakis simplex* can be frequent in particular countries and should be suspected in patients with acute allergic symptoms after ingestion of fish. The etiological role of *Anisakis simplex* was evaluated in 49 adult subjects with acute allergic symptoms after ingestion of anchovies. Serum-specific IgE and prick tests to anchovy were negative in each patient. Specific IgE reactions to *Anisakis* were positive in 45 patients and skin tests in 43. Only 3 patients with allergy to the nematode were atopic. However, IgE responses to *Anisakis* were also observed in habitual consumers of raw fish, without any clinical manifestations, suggesting that the relevance of results of conventional tests has to be interpreted on the basis of clinical aspects. Key words: allergy; *Anisakis simplex*; anchovy.**

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Allergic reactions after ingestion of seafoods parasitized by *Anisakis simplex* have been reported in the past decade, especially in the Spanish population, whose main risk factor appears to be the frequent consumption of raw or undercooked fish (1). In Italy, to our knowledge, there has only been one report showing the high frequency of IgE sensitivity to the nematode in a risk population of fishermen/fishmongers (2).

In the past few years, we have observed numerous cases of acute urticaria following the ingestion of anchovies (*Engraulis encrasicolus*), which are frequently consumed in our geographical area and usually eaten raw or pickled. The role of IgE-sensitization to *Anisakis simplex* was assessed in patients consecutively observed during the past year.

## MATERIAL AND METHODS

The study included a total of 49 patients with acute allergic symptoms, developing after the ingestion of anchovies and

without any further triggering or causal factors, who were consecutively admitted to the Unit of Dermatology of the University Hospital of Bari (Apulia, Southern Italy) from June 2000 to June 2001. Anamnesis was directed not only to rule out other causes responsible for the symptoms, but also to evaluate personal histories of atopy, clinical characteristics of symptoms and fish-eating habits.

The study population also comprised 33 controls grouped as:

- 24 individuals who never ate raw or undercooked fish during their lifetime, of whom 5 were non-atopic healthy subjects, 9 were non-atopic patients with physical urticarias, and 10 had a personal history of atopy (atopic dermatitis, allergic asthma and/or rhinitis);
- 9 regular consumers of raw-fish products with no antecedents of atopy or any allergic reactions.

After an adequate washout period from active treatments, *in vivo* tests were performed in both patients and controls:

- skin-prick tests (SPTs) with common aeroallergens (Stallergenes Italia, Saronno, Varese, Italy);
- SPT with extract of *Engraulis encrasicolus* (provided by Lofarma, Milan, Italy);
- SPTs with two different *Anisakis* extracts (1 mg/ml): the first was commercially available and obtained from International Pharmaceutical Immunology (I.P.I., Madrid, Spain), the other extract was prepared for the occasion by Lofarma, Milan, Italy.

SPTs were read after 15 min; histamine hydrochloride (10 mg/ml) and normal saline solution were used as positive and negative controls, respectively. Tests with a wheal diameter > 3 mm than the negative control were considered positive.

Moreover, total serum IgE levels were assessed by the radioallergosorbent test in accordance with the manufacturer's instructions (Pharmacia Diagnostics, Uppsala, Sweden). Serum-specific IgE was determined against *Engraulis encrasicolus* and *Anisakis simplex* using the CAP system (Pharmacia Diagnostics, Uppsala, Sweden). IgE levels higher than 0.35 kU/l were regarded as positive.

## RESULTS

The patients included 25 males and 24 females, mean age 44.7 years (range: 18 to 70). A personal history of atopy was found in only 5/49 cases (10.9%). Of these patients, 46 reported the consumption of raw or pickled anchovies and 3 reported having eaten cooked anchovies prior to the onset of symptoms. Clinical manifestations included: urticaria/angioedema syndrome alone in 52% of cases, urticaria/angioedema associated with gastrointestinal symptoms in 33%, anaphylaxis (respiratory disturbances with hypotension up to anaphylactic shock) in 13%, and anaphylaxis with gastrointestinal complaints

in 2%. Symptoms developed after a variable period of time from the ingestion of anchovies (30 min to 24 h, mean 5 h) and faded away within 3 days of active treatments, which comprised antihistamines, corticosteroids and epinephrine, depending on the severity of symptoms.

SPTs with aeroallergens gave negative results in all cases with the exception of 7 patients, who had a positive reaction to *Dermatophagoide s pteronyssinus*. The SPTs with anchovy extract were negative in all cases, as well as the serum IgE levels to this seafood. The SPT with *Anisakis simplex* was positive in 43/49 (88%) patients; there was an absolute concordance between the two different extracts used. Serum-specific IgE levels to *Anisakis* were detected in 45/49 (92%) patients, with a mean value of 28.4 kU/l (range 0.8 to 118 kU/l, median value 15 kU/l); most values belonged to class III (3.5–17.5 kU/l; n = 18) and class IV (> 17.5 kU/l; N of patients: 20). However, there was no correlation between specific IgE levels and the severity of symptoms. Sensitization to *Anisakis simplex* was observed in only 3 of the 5 atopic patients; levels of specific IgE were variable (37 kU/l, 17 kU/l and 3 kU/l, respectively). Of the 6 patients with negative SPTs, 4 had specific IgE levels of less than 0.35 kU/l and the other 2 had only low levels. In total, *in vitro* and *in vivo* tests were concordant in 47/49 cases. High total serum IgE levels (> 100 kU/l) were found in 33 cases and showed a considerable dispersion rate of values (range 12.4 to 2212 kU/l, mean 431.3 kU/l). There was a good correlation between specific IgE levels and total IgE levels ( $r = 0.94$ ).

On the whole, IgE sensitization to *Anisakis simplex* was found in 45 out of the 49 (92%) cases evaluated. Only one of these patients experienced symptoms after ingestion of cooked anchovies, whereas, in all the others, symptoms occurred after having eaten raw and especially pickled anchovies. Thirty-one of these patients reported a habitual consumption of raw or undercooked fish, with pickled anchovies being the most frequent.

In the controls, *in vivo* and *in vitro* tests to *Anisakis simplex* and anchovy gave negative results in all the groups studied with the exception of the group of regular consumers of raw/undercooked fishes (at least once a week), in whom SPTs with *Anisakis simplex* were positive in 5/9 cases (55%), with anti-*Anisakis* IgE levels > 0.35 kU/l in 4/9 cases (44%) (range 1.15 to 11 kU/l, mean value 4.19 kU/l, median value 2.5).

## DISCUSSION

*Anisakis simplex* is a nematode of the Anisakidae family, which can infect humans through ingestion of raw or undercooked fish contaminated by third-stage larvae. Human infection by *Anisakis simplex* (anisakidosis) appears to be very frequent in Japan, where the consumption of raw fish dishes is very common, but it has

also been reported in Europe, especially in Spain (3). The nematode can also induce IgE-mediated reactions, responsible for the development of urticaria angioedema syndrome and anaphylaxis (4–6).

In the light of the results derived from anamnesis and tests in our study population, the role of an IgE-mediated reaction to *Anisakis simplex* could be implicated in 45 out of the 49 cases evaluated. Most of these patients (90%) experienced symptoms after ingestion of raw and especially pickled anchovies. This peculiar eating habit can represent an important risk factor for transmission of live larvae and consequently for IgE sensitization (7). In only one case with positive *in vivo* and *in vitro* tests, the onset of symptoms occurred after consumption of cooked anchovies. This suggests the possibility, even if almost rare, that, in sensitized individuals, an allergic reaction may develop also after ingestion of dead larvae (8, 9); this possibility may be promoted by concomitant gastrointestinal conditions which alter the absorption of allergens (10).

In the remaining 4 patients who had eaten anchovies, the role of both *Anisakis simplex* and anchovy itself was excluded; in these cases, scombroid-fish poisoning (11), related to the presence in the fish of contaminant histidine-decarboxylating bacteria, could be hypothesized.

In agreement with the foregoing assumptions, IgE-mediated reactions to *Anisakis* seem to develop more frequently in middle-aged, non-atopic patients (12). In particular, a personal history of atopy was present in only 3 of the 45 cases with IgE-hypersensitivity to *Anisakis*.

*Anisakis* allergy should be taken into account in populations in which the consumption of raw or undercooked fish is habitual and the rate of fish infection is high. The true impact of *Anisakis* as a cause of acute allergic syndromes can be underestimated owing to some confounding situations, such as the suspicion about the fish as an etiological factor and the possibility of a relatively long period of latency from fish ingestion to the development of symptoms (13). In our patients, the period of latency was almost variable, ranging from 30 min to 24 h (mean 5 h). This great variability is probably dependent on multiple factors (7): time needed to the invasion of digestive mucosa and to the secretion of some allergens or immunogenic substances by the live larvae, concomitant conditions that are apt to interfere with mucosal absorption of allergens.

The study of our control population demonstrated also an association between IgE sensitivity to *Anisakis simplex* and the habitual consumption of raw/undercooked fish, without allergic symptoms. This observation suggests that serum-specific IgE levels and SPTs are not specific for the assessment of *Anisakis* allergy. In regular consumers of raw/undercooked fish, these tests can indicate previous exposure to larvae of the nematode and probably help to recognize a potential

risk for allergy (14). However, the possibility of false-positive reactions, owing to cross-reactivity with other parasites, cannot be ruled out (15, 16). Considering the ethical objections to performing a challenge test, it is mandatory to improve the specificity of tests for the diagnosis of *Anisakis* allergy through an intensive study of allergens and the use of more sophisticated procedures. While awaiting these results, it seems important to take into consideration this clinical entity, for diagnostic and prophylactic reasons, and to highlight that the positive results of conventional *in vivo* and *in vitro* tests should be supported by clinical aspects in order to be regarded as relevant.

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