

EDITORIAL

Anisakiasis: immunity, allergy or both? Lessons on the natural role of immunoglobulin E from a nematode infestation

Anisakis simplex is a nematode of the Anisakidae family, Ascaridoidea superfamily, Ascaridida order, which can parasitize many different kinds of fish or cephalopods like, i.e. codfish, hake, sardine, salmon, red mullet, tuna, mackerel, horse mackerel, squid, etc. In its adult stage it parasitizes sea mammals like whales, seals, dolphins and sea lions. Analysis of fish from the Atlantic ocean revealed an infestation rate between 40 and almost 100% [1,2].

A. simplex can cause different diseases in humans [3]: human anisakiasis is caused by infection with the larval form of *A. simplex* and is due to invasive larvae and an inflammatory response to it. The human being acquires the larvae by eating raw or undercooked seafood (smoked fish, salted sea food, pickled or similarly prepared sea fish) or cephalopods, which contain the third stage larvae of *A. simplex*. Anisakis larvae can be invasive, penetrating the host stomach or the intestinal wall. Acute anisakiasis is probably caused by an inflammatory and/or allergic reaction in the digestive tract mucosa with abdominal pain and eosinophilic infiltration. Chronic anisakiasis results from abscesses or eosinophilic granulomas caused by parasite invasion. This later form can mimic appendicitis, gastroduodenal ulcer, gastroenteritis and colitis, inflammatory bowel disease, and intestinal obstruction [3,4]. Anisakiasis should be considered as a cause in eosinophilic gastrointestinal disorders such as eosinophilic gastroenteritis [5]. Other organs, like lungs, spleen, pancreas and liver are rarely affected. The disease was first reported in The Netherlands and has since been reported rather frequently in Japan [6,7]. Changes in eating habits have caused an increase in cases reported in Europe, mainly from France and Spain [8,9].

In 1990 Kasuya *et al.* pointed out the allergenic potential of *A. simplex* and emphasized the need to consider it as an aetiological factor in urticaria related to the consumption of fish [10]. Indeed, urticaria, angioedema and anaphylaxis have been associated repeatedly with consumption of fish infested with *A. simplex* from different parts of the world [4,11]. Even occupational asthma has been described, in one patient due to extensive handling of infested fish, in another patient due to the use of *A. simplex*-contaminated fish powder to feed chickens [12].

The preparation and storage of fish is important for the potential to elicit an immune reaction upon infestation or an allergic reaction to some anisakis protein [4]. Heating for

10 min over 65°C or freezing (minus 20°C for 24 h) destroys the infectivity of the larval stage, while the allergenicity for skin tests and serology is retained. Thus, even cooked fish contains the nematode in an allergenic form, but cannot cause an infestation.

Both serological assays as well as skin tests have been developed to detect IgE specific for *A. simplex*. Surprisingly, the incidence of positive reactions was found to be 16% in Spanish blood donors, which seems to be very high compared with the still rather low incidence of true allergic reactions to *A. simplex* [13]. Skin tests with extracts of the nematode give a similarly high positive reaction. For the diagnosis of anisakiasis it became a problem, that many people have high IgE titres in the absence of obvious allergic reactions to seafood. Attempts to distinguish between true allergic and only sensitized individuals by immunoblotting did not give clear results [14].

The paper by Daschner *et al.* in this issue of *Clinical and Experimental Allergy* describes a sequential analysis of specific and total IgE in patients which complained about typical symptoms of acute anisakiasis, namely abdominal cramps, vomiting and diarrhoea, after ingestion of raw or undercooked fish [13]. Simultaneously, most of them had also allergic reactions (mainly urticaria, angioedema, but also anaphylaxis). This study addresses two crucial questions of an IgE-mediated immune response to *A. simplex*. Why do so many people have high *A. simplex*-specific IgE titres, and why do so many people with specific IgE to *A. simplex* not have an allergic reaction after eating the frequently contaminated seafood?

The patients described had already elevated specific IgE against *A. simplex* at their first visit. After 1 month total and specific IgE were measured again: both had significantly increased in the great majority of patients ($n=41$, 85–90%) by three- to fourfold. Thus, sequential measurement of specific and total IgE may be a useful tool to diagnose acute anisakiasis, which is otherwise hard to diagnose in the presence of a high percentage of so-called false positive IgE.

Is the IgE against *A. simplex* now an allergic or an immunological reaction? Daschner *et al.* [13] favour the idea of an immunological reaction: the patients in their study had actually a *fresh infestation* with the larvae of *A. simplex*. They had gastrointestinal symptoms and in nine of 22 patients, who underwent gastroscopic examinations, at

least one larva of *A. simplex* could be identified. Quite interestingly, both specific and unspecific IgE increased dramatically, even in the few patients without allergic symptoms. Eating well-cooked fish, containing the allergens, but unable to propagate, does probably not cause such a rise of total and specific IgE (however, such a formal control has not yet been done). Thus, the data give a human example of a 'natural', not necessarily allergic IgE response against a nematode: IgE was increased only by live larvae, and not by *A. simplex* protein. The ratio in between the raised specific and unspecific IgE remained actually constant: further data might reveal to what extent the ratio of specific/unspecific IgE is relevant for the development of 'allergic' symptoms (i.e. urticaria) in the individual patient, as not all patients had allergic symptoms.

The high prevalence of *A. simplex*-specific IgE in the Spanish population would thus indicate that many people were actually infested by live *A. simplex*, most of them probably without developing symptoms. Their immune response (including IgE) worked silently and eliminated the nematode. The data emphasize the concept that one main biological function of IgE lies in the defence of parasites, in particular nematodes [15].

A further puzzle of anisakiasis is the frequent exposure to this allergen, which is heat stable, without causing any symptoms in sensitized persons: Daschner *et al.* suggest that most acute allergic reactions appear only after ingestion of live parasites (gastroallergic anisakiasis, having allergic and gastrointestinal symptoms), while pure allergic reactions to anisakis allergen, which occur without gastrointestinal symptoms, are actually rare [13]. This implies, that sensitized patients can continue to eat fish (which frequently contains the *A. simplex* allergen), if it is well cooked. Thus, the gastrointestinal tolerance to food protein (even if it is derived from a nematode) may still work, even if specific, functional IgE and the relevant allergen (which is not completely digested, as allergic reaction is possible) is present. Such a situation is actually not exceptional, as bakers with baker's asthma rarely have problems eating wheat. It might be that only the live nematode is able to provoke an allergic reaction, possibly by causing an inflammatory response as well [16].

There are different advantages to living in a coastal area: besides the romantic view of the sea, the pride of the navy, one has also the opportunity to study the immune response to *A. simplex*, as long as people like to eat fresh, under-cooked fish. Human anisakiasis and its immunological reactions to it have features, which make us inlanders from Switzerland (who get only frozen sea fish) envy those fascinating possibilities to study the relationship between allergy and immunity: (1) it is rather common in humans; (2) it might be feasible to make a predictive study and to evaluate the effect of nematode infestation on the

immune response and subsequent clinical symptoms to other allergens; (3) it would be a big challenge to find out, which kind of 'factor' induced the rise in total IgE in these patients; (4) what in the nematode elicits this 'factor'; (5) most patients did not develop an eosinophilia, thus the immune reaction seems to be restricted to IgE, but some do, and what is the difference from patients with eosinophilia?; (6) what type of T-cell immunity will develop to *A. simplex* antigens, which cytokines are involved?, etc.

Although clinicians and researchers in inland areas may miss the chance to participate in this research, we may have some comfort in the fact that we all get some nematode proteins for free if we eat sea fish.

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