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Editorial

When do allergic reactions to *Anisakis simplex* occur?

Ever since the first reports of the clinical manifestations induced by stage 3 *Anisakis simplex* larvae in man subsequent to the ingestion of parasitised fish, two clearly differentiated disease conditions became evident: on the one hand, so-called anisakidosis, caused by larval parasitisation of the digestive tract and exceptionally of other organs, clinically manifested through episodes of abdominal pain with or without associated vomiting and diarrhoea that might mimic the clinical features of gastric peptic ulcer disease, ileitis, appendicitis, acute abdomen or even intraabdominal tumours. These manifestation correlate with the ingestion of raw or undercooked fish, in which the *Anisakis simplex* larvae are still alive and viable and are able to attach themselves to the gastrointestinal wall with generation of an *in situ* inflammatory reaction responsible for the clinical symptoms. On the other hand, it was later observed that some patients, without foregoing or associated digestive complaints, evidenced episodes of urticaria, angioedema or severe anaphylactic reactions in association to the ingestion of fish or seafoods, apparently without relation to the ingested foodstuff being cooked or not. In this context, it has been interesting to learn about the heat-stability of some *Anisakis simplex* antigens. These reactions were shown to be mediated by specific IgE-class antibodies induced by certain definite parasite antigens; thus, they were true allergic reactions to *Anisakis simplex*.

Later studies, however, demonstrated that when subjects with episodes of urticaria or anaphylaxis with or without overt digestive symptoms were endoscopically explored, *Anisakis* larvae could be seen firmly attached to the gastric wall or traversing its mucosa. Extraction of all the larvae was usually followed by the disappearance of the allergic symptoms the patient had been evidencing. Further to this, in oral challenge studies with freeze-killed or lyophilised *Anisakis simplex* larvae in patients who had evidenced clinical allergic reactions and had positive skin tests and specific IgE antibodies to *Anisakis simplex* the allergic symptoms did not reappear. Conjunctival challenge tests with *Anisakis simplex* extracts did however yield positive results in patients who had had clinical symptoms of allergic reaction and positive skin and laboratory tests.

For all these reasons, it seemed obvious that the mechanism or mechanisms whereby *Anisakis simplex* larvae can elicit allergic sensitization should be reassessed. A first approach was provided by patients evidencing a mixed clinical picture, i.e. digestive disease associated to evident allergic reaction, and in whom the extraction of the larvae induced the remission of the allergic features. Also, insistent questioning about the past clinical history in patients who had had allergic symptoms very often disclosed previous ingestion or raw

or insufficiently cooked fish, such as for instance vinegar-marinated anchovies. This is a widely consumed delicacy in many areas of Spain, and *Anisakis simplex* larvae have been shown to withstand the action of vinegar for several months, or at least for a longer period than the one usually stipulated for consumption of anchovies. A trend is also currently seen to consume raw or undercooked fish courses as a consequence of certain culinary habits. And yet, those patients with prior clinical manifestations who were allowed to reintroduce cooked fish in their diets have fully tolerated its ingestion without evidencing new episodes of allergic reaction.

It should also be remembered that the incidence of allergic reactions is quite uneven throughout Spain: high incidences are reported in northern Spain and in the central regions of the Iberian Peninsula, while such cases are scarce in the eastern seaboard (the "Levante" region). Besides the different origin of the fish consumed depending on the different fishing grounds where the fishery fleets work, which may entail higher or lesser degrees of infestation of the consumed fish, local usages and customs as to the alimentary habits may also influence these varying incidences.

It is quite possible that the *Anisakis simplex* larvae that have been killed while cooking the fish may traverse the digestive tract without inducing any complaint whatsoever, as in the first place they cannot attach themselves to the mucosa and thus induce abdominal complaints, and in the second place the antigens released do not arrive at the circulating blood in amounts sufficient for triggering an allergic reaction. However, the ingestion of live larvae may provide the opportunity for them to penetrate the digestive tract mucosa. They may then cause digestive symptoms, depending on the number of larvae that become attached and on the associated inflammatory reaction, and in those individuals who have furthermore become immunologically sensitised because of the passage of antigens into the blood through the mucosa perforated by

the larvae generalised allergic reactions may also be triggered.

Anisakis simplex larvae are not adapted to the human organism, and neither do they evolve in it to their adult parasite form. For this reason, even though they may attach themselves to the gastrointestinal mucosa, the usual course seems to be that after some days or weeks they become spontaneously detached and are evacuated, migration to tissues distant from the digestive tract being exceptional.

In my personal opinion, for sensitization to occur and allergic reactions to develop it is necessary that the antigens enter the bloodstream in appreciable concentrations. This may occur when the parasite perforates the gastrointestinal mucosa, and also when antigens are artificially deposited onto highly vascularised areas, the latter being the case in conjunctival challenge tests.

It is possible that allergic reactions may occur after the ingestion of dead *Anisakis simplex* larvae, ingested with sufficiently cooked fish; in such a case, the possibility of preexisting changes in the gastrointestinal mucosa should be assessed. Such reactions, however, should represent a very low fraction of the total number of cases.

In the present issue several of the studies are published that were presented at a meeting dedicated exclusively to the problem of *Anisakis simplex*-induced reactions. This meeting was one in the series of annual ones under the general title "From Research to The Clinic", and was held at Vienna in 1999. At that meeting, the results were presented of a multicenter study organised by the Spanish Allergy Society, SEAIC, in which over 50 Spanish hospitals participated both in its clinical and in its research aspects. I would like to express here my gratitude for their efforts, for the importance of the studies performed and for the significance of the results achieved to all the groups participating in that study and to the working teams that presented the results achieved after three years of hard work dedicated to this research.