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PREVALENCE OF SENSITIZATION TO ANISAKIDAE AMONG LEONESE ASTHMATICS

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Anisakis simplex has been reported as a frequent cause of IgE-mediated urticaria or anaphylaxis, and exceptionally as a cause of occupational asthma. Some

authors have also observed *Anisakis simplex* hypersensitivity in patients with eosinophilic gastroenteritis or chronic urticaria. However, because of the high prevalence of sensitization to this nematode among the general population, it is difficult to attribute to it a causal relationship in the latter two conditions.

We have studied 135 patients aged between 6 and 73 years with persistent asthma. Through prick tests with a standardised *Anisakis simplex* extract and quantitation of the specific serum IgE, we have detected a 26% frequency of sensitization to this nematode (35/135). The atopic status did not appear to have any influence in this sensitization: 21.7% (15/69) were atopics, and 30.3% (20/66) non-atopics. We also studied 37 blood donors aged between 35 and 65 years as a control sample. The sensitization rate among the control subjects was 11.8% (4/37), much lower than the 33.8% one (22/65) among the age-matched asthmatics. The anti-*Anisakis simplex* IgE levels in the patient group were significantly higher than those in the blood donor control subjects ($p < 0.004$).

Our data suggest that, in our environment, asthmatic patients are sensitized to *Anisakis simplex* to a higher degree than the general population, although this fact cannot be attributed to the atopic status. The possible aetiopathogenetic role of *Anisakis simplex* antigens or of other cross-reacting antigens in persistent asthma should be investigated in future studies.

Key words: Persistent asthma. Parasites. *Anisakis simplex*. General population. Specific IgE.

PREVALENCIA DE SENSIBILIZACIÓN A ANISÁKIDOS EN ASMÁTICOS LEONESES

Anisakis simplex ha sido descrito como causa frecuente de urticaria o anafilaxia mediadas por IgE, y excepcionalmente como causa de asma ocupacional. También algunos autores han observado sensibilidad a *Anisakis simplex* en pacientes con gastroenteritis eosinofílica o urticaria crónica. No obstante, debido a la alta prevalencia de sensibilización a este nematodo en la población resulta difícil atribuir una relación causal con estas últimas enfermedades.

Hemos estudiado 135 pacientes con asma persistente y edades entre 6-73 años detectando, mediante

prick-test con un extracto estandarizado de Anisakis simplex e IgE específica sérica, una frecuencia de sensibilidad a Anisakis simplex del 26% (35/135). El estado atópico no pareció influir en ello: 21,7% atópicos vs 30,3% no atópicos (15/69 vs 20/66). También estudiamos 37 donantes de sangre como muestra control de edades entre 35-65 años. La tasa de sensibilización a Anisakis simplex obtenida en los controles fue 11,8% (4/37), en contraste con el 33,8% (22/65) en el grupo de asmáticos –emparejados en rango de edad–. Los niveles de IgE anti-Anisakis simplex en el grupo de pacientes fueron significativamente más elevados que en el grupo de donantes ($p < 0,004$).

Nuestros datos sugieren que, en nuestro medio, los asmáticos se hallan más sensibilizados a Anisakis simplex que la población general, no pudiendo atribuir este hecho al estado atópico. El posible papel etiopatogénico en el asma persistente de antígenos de Anisakis simplex, u otros alérgenos con reactividad cruzada, debería ser evaluado en futuros estudios.

Palabras clave: Asma persistente. Parásitos. *Anisakis simplex*. Población general. IgE específica.

Anisakis simplex is a nematode that is exceedingly well known as a cause of anaphylaxis^{1,2}; it will usually cause symptoms only when there are viable larvae capable of breaching the digestive tract wall. For this reason, the new term "gastroallergic anisakiasis" has been coined in an allusion to the well-known disorder of gastrointestinal anisakiasis, in which *A. simplex* passes the digestive tract wall and causes only digestive symptoms but no allergic manifestations³. Contrary to other forms of food-induced anaphylaxis, in gastroallergic anisakiasis the parasite must pass through the digestive mucosa, so that the allergic symptomatology may be delayed (hours). Symptoms usually occur also sporadically after the ingestion of fish because (a) not all fish are contaminated, and (b) the parasite larvae may die in the course of freezing and cooking, and the larval proteins in the digestive lumen will be unable to trigger allergic reactions by themselves in most patients. For these reasons, it is not uncommon for allergic manifestations to occur after the ingestion of poorly cooked fish or of fish in semi-preserve, such as anchovies in vinegar⁴.

Extensive series of gastrointestinal anisakiasis have been published in Japan and Corea⁵, where consumption of raw fish is frequent and gastric cancer is ende-

mic, so that digestive endoscopies are performed as a routine examination. It is perhaps for this reason that only isolated cases have been observed in Spain. However, allergy to *A. simplex* does not appear to be so frequent in Asiatic countries, an observation that is difficult to explain.

The role of the parasite as a cause of alimentary anaphylaxis has been well studied; however, it is also suspected to be the cause of other manifestations such as eosinophilic gastroenteritis⁶ or chronic urticaria. To assume the responsibility of the parasite in these entities encounters the obstacle of the high frequency of sensitization among the general population. Moreover, inhaled *Anisakis simplex* proteins have also been demonstrated to cause occupational asthma in workers manipulating fish or fish flour⁷.

Several years ago, we detected a high rate of *Anisakis simplex* sensitization among adult asthmatics beyond the third decade of life⁸; for this reason, we decided to study a larger group of patients within that age range and assess what occurred in comparison to a control group.

Methods

The study population comprised 134 patients aged from 6 to 73 years (mean age 39.1 years, SD 17.4 years) who were seen at our Allergology Outpatient Clinic because of persistent asthma. In the same period, serum samples were collected from 37 healthy blood donors aged between 35 and 65 years (mean age 48.1 years, SD 4.49 years).

Prick tests were performed on all patients with a panel of airborne allergens that are common in our environment, including grasses, *Plantago*, mites, *Alternaria*, *Aspergillus*, and cat and dog danders (ALK-Abelló). Other allergens were tested when a clinical suspicion of involvement existed. The tests were classed as positive when the wheal diameter was $\geq 50\%$ that of the positive 10-mg/ml histamine control. In both the patients and the controls the total serum IgE and the specific IgE to *Anisakis simplex* were determined (CAP System, Pharmacia); the specific IgE was classed as positive when its level exceeded 0.7 kU/l.

Statistics

The Kruskal-Wallis test was used for comparing the specific IgE levels among the various age groups, Student's t-test for comparing ages between the groups of asthmatics, and the Mann-Whitney test for comparing the total IgE le-

vels between groups of asthmatics and the specific IgE levels between asthmatics with a history of urticaria.

Results

Prevalence of sensitization among asthmatics and control donors

In the asthmatic patient group, 26% of the subjects (35/135) evidenced positive specific IgE to *Anisakis simplex*. The prevalence was greater among the older age groups: 33.8% (22/65) for the 35 to 65 years age group (Fig. 1). In contrast, in the healthy blood donor group only 11.8% of the subjects (2/37) had positive specific anti-*Anisakis simplex* IgE.

The statistical analysis showed that the patient group had higher anti-*A. simplex* IgE levels than the blood donor group ($p < 0.004$).

Prevalence of sensitization: differences between asthmatics

The atopic status did not increase sensitivity to the parasite: 21.7% of the group of atopic asthmatics (15/69) were sensitized, versus 30.3% (20/66) among the non-atopic asthmatics (Fig. 2).

There were no statistically significant differences between the two groups regarding the specific anti-*A. simplex* IgE levels.

As expected, the atopic asthmatics were younger ($p = 0.0013$) and their total serum IgE levels were higher ($p < 0.0001$).

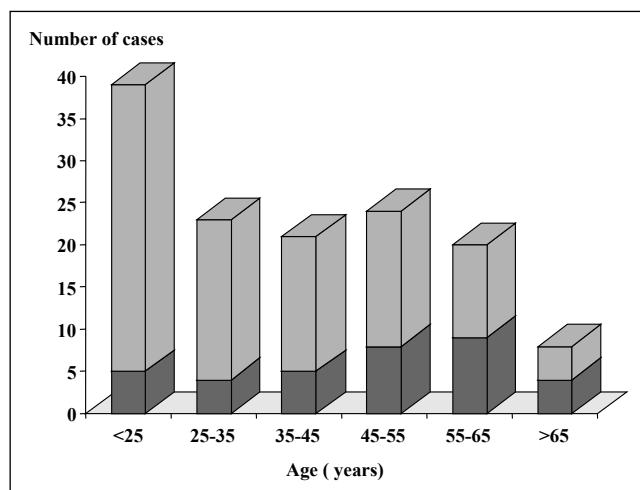


Fig. 1. *Anisakis* sensitization in asthmatics, by age groups.

Correlation to skin symptoms: differences between asthmatics

Asthmatics with urticaria were more often sensitized to *A. simplex* (40%; 14/35) than the patients with no skin symptoms (21%; 21/100) (Fig. 3). The statistical analysis showed that the anti-*A. simplex* IgE levels were higher in the group of asthmatic patients who also had urticaria episodes ($p < 0.01$).

Discussion

In the present study, the frequency of sensitization to *Anisakis simplex* among adult asthmatics was greater than the one observed in a group of healthy blood donors. This finding is not easily explained through the atopic status in both groups, firstly because the differences are much too marked, and secondly because the rate of sensitization to *A. simplex* was higher among the non-atopic asthmatics (Fig. 2).

Two studies have been published in which an increased number of rhinitides and airborne allergen sensitizations occurred among patients with moderate helminthiasis. In the first of them it was observed that *Ascaris* infestation in the childhood population in East Germany did not block the allergic responses; quite to the contrary, the presence of anti-*Ascaris* IgE was associated to a greater frequency of rhinitides and airborne allergen sensitizations⁹. In the second study, Venezuelan children with a heavy parasitic burden received antihelminthic therapy, and a parallel increase of the airborne allergen sensitivities was observed after this treatment. The authors concluded that the helminthic infestation increases the synthesis of IgE

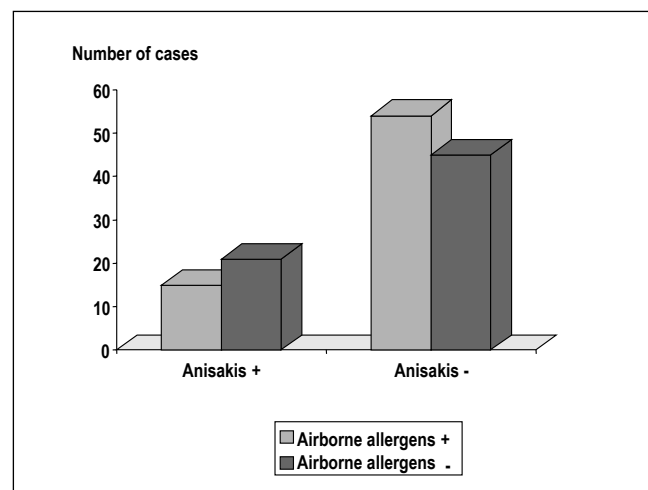


Fig. 2. Sensitivity to *Anisakis* and airborne allergens.

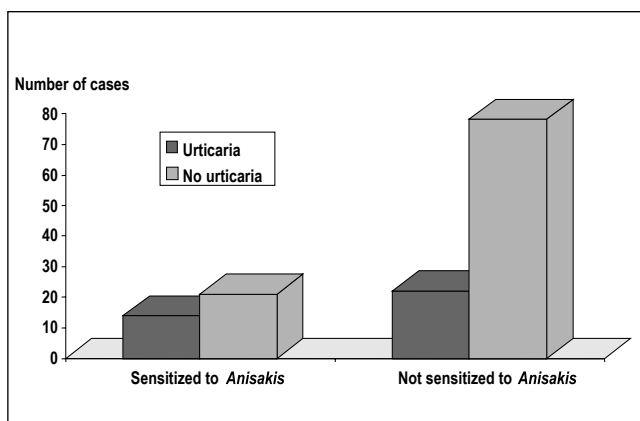


Fig. 3. Presence of urticaria in the two groups of asthmatics.

and improves the specific IgE response when the parasite burden is small¹⁰. It has been speculated that low-degree parasitic infestations might alter the interleukin balance favouring a Th2 response. However, when the parasitisation pressure is greater, it might suppress the allergic response by saturating the Fcε receptors in the mast cells with polyclonal IgE and inhibiting the synthesis of specific IgE. Man is not a natural host for *A. simplex*; this parasite does not complete its life cycle in man, but it does invade the gastrointestinal wall and induces intense immunologic responses, so that the *A. simplex* "offer" in our environment could be considered to represent a low-grade parasitic pressure from the immunological point of view.

A further possibility might be that we are faced with a ubiquitous airborne allergen that is present even outside the occupational environment. Fish flour may be found in important proportions in fodders destined mainly for fowl and piglets (a single fodder factory may process over 100 Tm of fish flour every month). The province of León is predominantly a cattle-farming one, with a number of composite fodder factories, and a sizeable proportion of the rural population raises cattle for personal consumption. A further sensitization pathway, alternative to that of fish ingestion, might well be the inhalational one; its relative relevance has not yet been assessed.

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ANTI-ANISAKIS IgE. EVOLUTION WITH DIET AND OVER TIME

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The total IgE response to the fish nematode Anisakis simplex in allergic humans ranges between 260 and 1058 kU/l, and the specific IgE between 2.3 and >100 kU/l however the evolution of these IgE antibodies over time in patients following a fish and seafood-free diet is unknown.

We report the results of the 18-month follow-up of seven adult patients aged 54.1±15.7 years with a diagnosis of allergic anisakiasis (skin and respiratory symptoms and, in one case, anaphylaxis). All of them were treated with diet, with absolute deprivation of fish and seafood for three months and relative privation (deep-frozen fish not more than once weekly) for a further six months.

The levels of anti-Anisakis IgE antibodies at the beginning of the study ranged between 11.3 and 10 kU/l (mean, 59.7±37.4 kU/l). A significant fall in these levels was observed by the sixth month of follow-up (38.6±27.5 kU/l; p = 0.18). Although the antibody levels did never become negative, by the eighteenth month of follow-up