

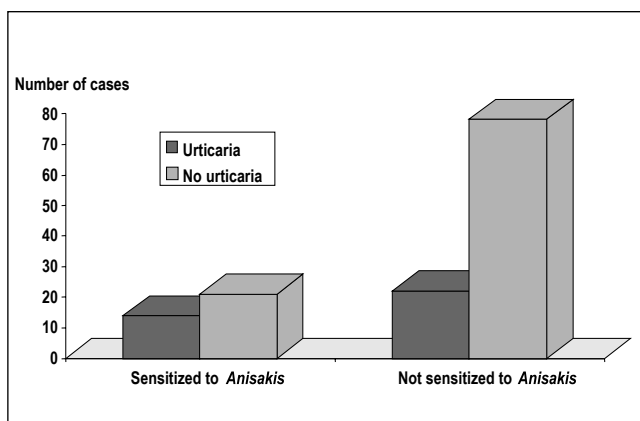


Fig. 3. Presence of urticaria in the two groups of asthmatics.

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.

References

1. Kasuya S, Hamano H, Izumi S. Mackerel-induced urticaria and *Anisakis*. *Lancet* 1990; 335: 665.
2. Audicana M, Fernández de Corres L, Muñoz D, Del Pozo MD, Fernández E, García M, et al. *Anisakis simplex*: una nueva fuente de antígenos alimentarios. Estudio de sensibilización a otros parásitos del orden Ascaridoidae. *Rev Esp Alergol Inmunol Clin* 1995; 10: 325-331.
3. Alonso A, Moreno-Ancillo A, Daschner A, Lopez Serrano MC. Dietary assessment in five cases of allergic reactions due to gastroallergic anisakiasis. *Allergy* 1999; 54: 517-520.

4. Arduoso Lovera DD, Quirce Gancedo S, Díez Gómez ML, Cuevas Agustín M, Eiras Martínez P, Sánchez Cano M, et al. Hipersensibilidad inmediata al parásito del pescado *Anisakis simplex*. Estudio de reactividad cruzada. *Rev Esp Alergol Inmunol Clin*, 1996; 11: 280-286.

5. Kakizoe S, Kakizoe H, Kakizoe K. Endoscopic findings and clinical manifestation of gastric anisakiasis. *Am J Gastroenterol* 1995; 90:761-763.

6. Gómez B, Tabar AI, Tunon T, Larrinaga B, Álvarez MJ, García BE, et al. Eosinophilic gastroenteritis and anisakiasis. *Allergy* 1998; 53: 1148-1154.

7. Armentia A, Lombardero M, Callejo A, Martín Santos JM, Gil FJ, Vega J, et al. Occupational asthma by *Anisakis simplex*. *J Allergy Clin Immunol* 1998; 102: 831-834.

8. Estrada JL, Gozalo F. Sensitization to *Anisakis simplex*: an unusual presentation. *Allergol Immunopathol* 1997; 25: 95-97.

9. Dold S, Heinrich J, Wichmann HE, Wjst M. Ascaris-specific IgE and allergic sensitization in a cohort of school children in the former East Germany. *J Allergy Clin Immunol* 1998; 102: 414-420.

10. Lynch NR, Hagel I, Pérez M, di Prisco MC, López R, Álvarez N. Effect of antihelminthic treatment on the allergic reactivity of children in a tropical slum. *J Allergy Clin Immunol* 1993; 92: 404-411.

ANTI-ANISAKIS IgE. EVOLUTION WITH DIET AND OVER TIME

F. Gozalo Reques, J. L. Estrada Rodríguez and M. J. Álvarez Puebla

Allergy Section. León Hospital. León, Spain.

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

mean reductions greater than 70% of the pre-diet baseline values had been achieved (14.7 ± 4.7 kU/l; $p=0.28$). These data show that the anti-Anisakis IgE antibodies persist in the circulation for over 18 months in spite of the diet; although they evidence a significant decrease as from the sixth month, this decrease becomes particularly striking after the twelfth month. This serological evolution might have clinical impact when deciding the type and duration of the diet in the management of this condition.

Key words: Allergy. Anisakis. Diet. Parasites. Specific IgE.

IG E ANTI-ANISAKIS. EVOLUCIÓN A TRAVÉS DE LA DIETA Y EL TIEMPO

La respuesta IgE total de humanos alérgicos al nematodo del pescado *Anisakis simplex* oscila entre 260-1058 KU/l y la de IgE específica desde 2,3 y > 100 KU/l. Sin embargo, se desconoce la evolución de dichos anticuerpos IgE a lo largo del tiempo en pacientes sometidos a dieta exenta de pescado y marisco.

Presentamos el seguimiento durante dieciocho meses de siete pacientes adultos diagnosticados de anisakiasis alérgica (síntomas cutáneos, respiratorios, digestivos y, en un caso, anafilaxia) de $54,1 \pm 15,7$ años de edad. Todos fueron tratados con dieta de privación absoluta de pescado durante 3 meses y con privación relativa (pescado congelado 1 vez/semana) otros seis meses más.

Los anticuerpos IgE anti-Anisakis al comienzo del estudio oscilaron entre 11,3-100 KU/l ($59,7 \pm 37,4$). Al sexto mes de seguimiento se objetivó una disminución significativa de los niveles ($38,6 \pm 27,5$ KU/l; $p=0,18$) y, aunque en ningún caso se llegaron a negativizar, al decimotercero mes se alcanzaron reducciones medias superiores al 70% del valor basal pre-dieta ($14,7 \pm 4,7$ KU/l; $p=0,28$). Estos datos demuestran que los anticuerpos IgE-anti-Anisakis persisten en la circulación más de 18 meses, a pesar de la dieta, y si bien a partir del sexto mes tales anticuerpos experimentan un descenso significativo, es a partir del décimosegundo mes cuando es especialmente llamativo. Esta evolución serológica podría tener repercusión clínica a la hora de establecer la duración y tipo de dieta en el tratamiento de esta enfermedad.

Palabras clave: Alergia. Parásitos. *Anisakis*. Dieta. IgE específica.

The prevalence of fish and seafood parasitised by nematodes of the *Anisakis* type has increased relentlessly in recent years in northern Spain, and as a consequence also the occurrence of allergic anisakiasis cases among the general population. This disorder has been reported to be the most frequent cause of recurrent urticaria among fish consumers who are not allergic to fish¹. Some years ago, our group investigated the prevalence of IgE-mediated *Anisakis* sensitization among patients with rhinitis and asthma and put forward the hypothesis of a possible non-digestive sensitization². More recently, the protagonism of *Anisakis* as a cause of occupational asthma and conjunctivitis has been demonstrated^{3,4}. Even so, the allergens in *Anisakis* are potent enough to cause anaphylaxis⁵. This nematode has a common allergenic profile consisting of four 30-45 kDa IgE-binding bands, although it is at present not known whether the exclusively digestive form of anisakiasis might be mediated by different antigens⁶.

The humoral response in humans who are allergic to these parasites is mediated by IgE and IgG isotypes⁷. Experimental studies of the kinetics of the immune response to these antigens carried out on mice have disclosed early responses based on the IgM isotype, and late responses mediated by IgG₁, IgG₃ and IgA isotypes^{8,9}. In *Anisakis*-sensitive patients, the humoral responses range between total serum IgE values of 260 to 1,058 KU/l (mean, 667 KU/l), in the case of the specific IgE between 2.3 and over 100 KU/l, and for the specific IgG between 16 and over 100 KU/l⁷.

Reliable biologically-standardised extracts are currently available for the *in vivo* diagnosis of allergic anisakiasis¹⁰, but the quantitation of the serum anti-*Anisakis* IgE antibodies by the ELISA method still provides potentially

Table I. Clinical data

Age (years)	Patient	Gender	Symptoms
63	FGD	M	Anap
26	MGV	M	U+Ang
76	IMY	F	Ang
55	DYE	M	Ang+Dig
43	AFM	F	U+Dig
49	SPD	F	Pru
48	AAM	M	U+Ast
51.4 ± 15.7			
Anap: anaphylaxis; U: urticaria; Ang: angioedema; Dig: digestive; Pru: pruritus; Ast: asthma.			

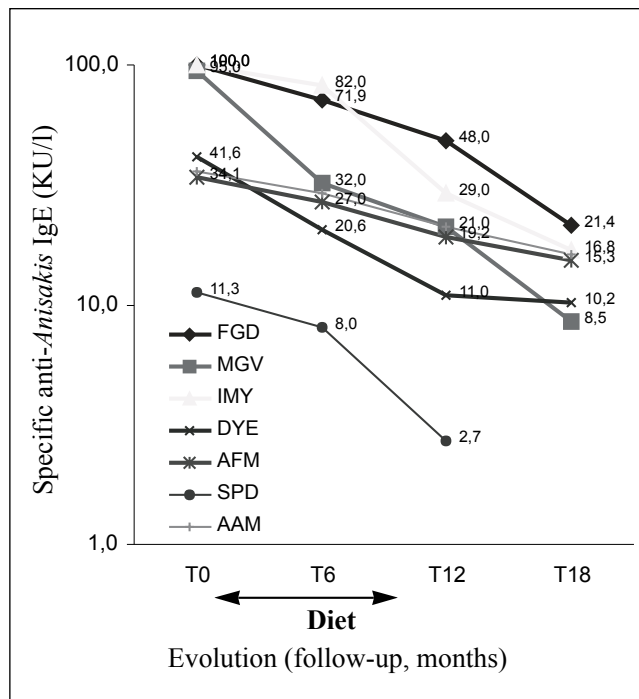


Fig. 1. Evolution over time of the specific anti-Anisakis IgE levels.

useful information in the follow-up of patients who are sensitive to this parasite, even though the evolution of those IgE antibodies over time in patients treated with a fish-and-seafood-free diet is unknown.

Methods

Seven patients who had been diagnosed of allergic anisakiasis at our hospital clinic, with ages ranging between 26 and 76 years (54.1 ± 15.7 years, mean $\pm$ SD) were treated with absolute fish deprivation diet (from the first to the third month after diagnosis) and then with relative deprivation diet (deep-frozen fish once weekly, between the fourth and the tenth month), and followed up at six-monthly intervals as from the time of diagnosis. The clinical manifestations included diverse symptoms such as urticaria, angioedema, pruritus, bronchospasm, digestive symptoms (epigastric pain, abdominal bloating/pain, postprandial heaviness) and, in one case, anaphylaxis (Table I).

Blood samples were collected in all cases for quantitation of anti-Anisakis IgE (Pharmacia, Sweden) at the time of diagnosis (T0) and at six-monthly intervals (T1, T6, T12 and T18). For the purpose of the calculations, when a given IgE value exceeded 100 kU/l a value of 100 kU/l was assigned.

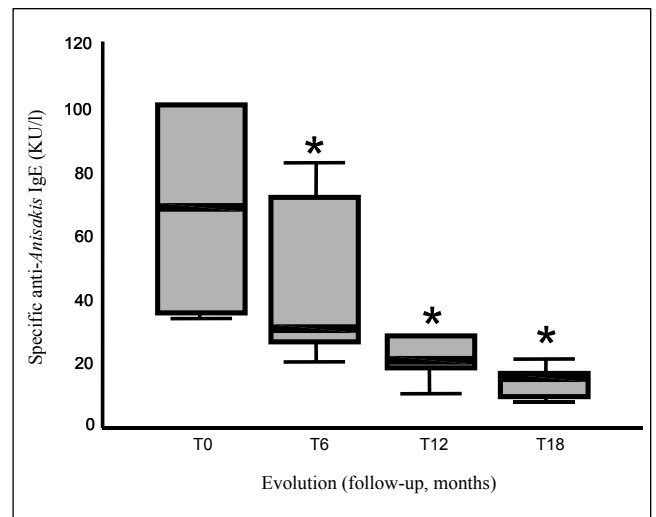


Fig. 2. Evolution over time of the specific anti-Anisakis IgE levels.

Statistics

The Wilcoxon test was used for comparing the specific IgE levels at the different time points.

Results

Figure 1 graphically presents the evolution of the specific IgE levels of each of the patients over time. In Figure 2 the medians (thick horizontal lines) and the interquartile ratio (IQR, shaded area) of the specific IgE levels at the four time points in the follow-up (T0, T6, T12 and T18) are presented. At the time of diagnosis, the dispersion range of the IgE levels was quite large (T0, 11.3 to 100 kU/l; 59.7 ± 37.4); however, from the 6th month of follow-up onwards the reduction of the serum specific IgE levels was statistically significant (38.6 ± 27.5 kU/l; $p = 0.18$).

By the end of the 12th month the IgE antibody levels had decreased even more significantly (T12, 21.7 ± 14.3 kU/l; $p = 0.18$), and although they in no case became negative within the follow-up period, by the end of the 18th month mean reductions greater than 70% of the pre-diet baseline values had been achieved (T18, 14.7 ± 4.7 kU/l; $p = 0.28$).

As our experience shows, the anti-Anisakis IgE antibodies persist in the bloodstream for over 18 months in spite of a fish-and-seafood-free diet of several months' duration. Even though these antibodies evidence a significant fall from the sixth month of follow-up onwards, the decrease is particularly striking beyond the 12th month (Figs. 1 and 2).

Similar to other long-lasting, IgE-mediated food allergies (e. g., fish protein allergy), it is quite possible that these antibodies never completely disappear, particularly considering our socio-cultural environment in which a diet lacking fish and seafood is quite poorly tolerated by the population. Even so, and again according to our experience, a considerable proportion of the patients are able to tolerate without medication, from the 6th month onwards, limited amounts (once-weekly servings) of deep-frozen fish or seafood, and after the 12th month the vast majority tolerates them.

References

1. Montoro A, Perteguer MJ, Chivato T, Laguna R, Cuéllar C. Recidivous acute urticaria caused by *Anisakis simplex*. *Allergy* 1997; 52: 985-991.
2. Estrada Rodríguez JL, Gozalo Reques F. Sensitization to *Anisakis simplex*: an unusual presentation. *Allergol Immunopathol* 1997; 25: 95-97.
3. Armentia A, Lombardero M, Callejo A, Martín Santos JM, Gil FJ, Vega J, et al. Occupational asthma by *Anisakis simplex*. *J Allergy Clin Immunol* 1998; 102: 831.
4. Añíbarro B, Seoane FJ. Occupational conjunctivitis caused by sensitization to *Anisakis simplex*. *J Allergy Clin Immunol* 1998; 102: 331-332.
5. Rosel Rioja L, del Pozo Gil MD, Lobera Labairu T, Ibarra Cucalón V, Blasco Sarramán A, Oteo Revuelta JA. Allergy to *Anisakis simplex*. Report of 2 cases and review of the literature. *Rev Clin Esp* 1998; 198: 598-600.
6. Sugane K, Sun SH, Matsuura T. Radiolabelling of the excretory-secretory and somatic antigens of *Anisakis simplex* larvae. *J Helminthol* 1992; 66: 305-309.
7. Del Pozo MD, Moneo I, de Corres LF, Audicana MT, Muñoz D, Fernandez E, et al. Laboratory determinations in *Anisakis simplex* allergy. *J Allergy Clin Immunol* 1996; 97: 977-978.
8. Iglesias R, Leiro J, Ubeira FM, Santamarina MT, Sanmartín ML. *Anisakis simplex*: antigen recognition and antibody production in experimentally infected mice. *Parasite Immunol* 1993; 15: 243-250.
9. Perteguer MJ, Cuéllar C. Isotype-specific immune responses in murine experimental anisakiasis. *Zentralbl Veterinarmed [B]* 1998; 45: 603-610.
10. Gozalo Reques F, Estrada JL, García M, Díez J, de Barrio M, Tornero P, et al. Evaluation of the biological activity of an *Anisakis simplex* extract. *Allergy* 1998; 53: 197.