Travelling with *Anisakis* Allergens

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The ability of *Anisakis* L3 larvae to infect humans and provoke gastrointestinal disorders was first recognized more than 50 years ago. However, it was not until the early 1990s that infections by this genus of nematodes were found to cause allergic reactions ranging from urticaria to anaphylaxis [1, 2]. More recently, it has been reported that the immunological/inflammatory changes brought about by previous infections involving this parasite can potentiate NSAID-induced upper gastrointestinal bleeding [3]. *Anisakis* allergens are frequently classified as food allergens because they are present in sea fish [4]. However, *Anisakis*-induced allergy differs from food allergy because it does not require an atopic predisposition and because for presentation of clinical symptoms the *Anisakis* allergens must enter the tissues of the alimentary tract at certain locations (e.g. the submucosa of the stomach) [5]. The hypothesis that *Anisakis* only provokes allergic symptoms when it parasitizes the alimentary tract was confirmed in provocation studies showing that patients with allergy to *Anisakis* tolerate ingestion of *Anisakis* allergens [6–8]. However, the possibility that the induction of IgE antibodies also requires infection by the parasite was suggested by epidemiological studies showing that such antibodies only occur in populations at risk (i.e. those consuming raw or undercooked sea fish) [9].

Historically, laboratory-based diagnosis of *Anisakis* IgE sensitization has mainly been done with whole parasite extracts (e.g. ImmunoCap and Western blot) [10], defined antigens recognized by monoclonal antibodies [11], and, more recently, recombinant allergens [12]. To date, 12 *Anisakis* allergens (Ani s 1 to Ani s 12) have been officially recognized by the WHO/IUIS Allergen Nomen-

clature Subcommittee (<http://www.allergen.org/>). Two of these, Ani s 2 (paramyosin) and Ani s 3 (tropomyosin), are considered pan-allergens with low specificity [13], which makes them unsuitable as specific targets for immunoassays. The remaining group includes 3 major allergens (Ani s 1, Ani s 7, and Ani s 12) and 7 minor allergens (Ani s 4, Ani s 5, Ani s 6, Ani s 8, Ani s 9, Ani s 10, and Ani s 11).

In a recent issue of the *International Archives of Allergy and Immunology*, Caballero et al. [14] focused on the importance of using component-resolved diagnosis to reveal IgE sensitization to *Anisakis* to avoid problems related to specificity while maintaining good sensitivity. The study was carried out by comparison of the specific IgE responses in sera from symptomatic and asymptomatic patients in Italy and Spain against a panel of 4 recombinant *Anisakis* allergens (Ani s 1, Ani s 5, Ani s 9, and Ani s 10; response measured by dot blot assay) and a purified native allergen (Ani s 4; response measured by Western blot). The authors reported differences in IgE recognition patterns between the two populations under study, as well as a predominance of gastrointestinal over allergic symptoms in the Italian population. These observations underline the importance of using selected allergenic components for the accurate diagnosis of *Anisakis*-induced IgE sensitization in different populations. Differences in IgE reactivity in sera from patients infected with *Anisakis* may reflect interindividual variations in immunological responses or a different frequency of exposure, as reported for other allergens [15]; however, such differences may also be due to a bias in patient selection when comparing different populations. In the study by Cabal-

lero et al. [14], the higher frequency of patients with high levels of anti-*Anisakis* IgE antibodies (CAP class 6) in the Spanish population may at least partly explain the higher reactivity of the sera. However, the observation that some allergens (e.g. Ani s 4) are preferentially recognized by sera from Italian patients is consistent with the authors' conclusion that some *Anisakis* allergens are differentially recognized in the two populations.

Regarding component-resolved diagnosis, although Caballero et al. [14] investigated the presence of IgE antibodies to the major allergen Ani s 1, they did not test the IgE response to Ani s 7, the main *Anisakis* allergen and a possible marker of infection [16]. Ani s 7 has repeatedly been recognized as the most important *Anisakis* allergen as it is the only one recognized by more than 90% of patients [12, 17, 18]. Moreover, unlike for Ani s 1, the percentage of patients with IgE antibodies to Ani s 7 was

consistently high in patients with acute *Anisakis* infections (gastroallergic anisakiosis) or with *Anisakis* sensitization associated with chronic urticaria [19]. Although the molecular basis of Ani s 7 allergenicity has not yet been investigated, it is probably associated with the distinctive cysteine-rich tandem repeats in the allergen structure [18]. The presence of such antigenic epitopes may enhance the antigenicity of Ani s 7 relative to that of other *Anisakis* allergens. Consistent with this hypothesis, in a recent study carried out in Croatia, where *Anisakis pegreffii* is also prevalent [20, 21], all members of a population of 10 positive asymptomatic individuals produced antibodies to Ani s 7, but only 3 presented IgE antibodies to Ani s 1 [22]. The Ani s 7 allergen is now commercially available [23], and the usefulness of different allergen combinations for anti-*Anisakis* IgE determinations can therefore be tested under field conditions.

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