Uterine Contractions Are Known Side Effects of Venom Immunotherapy

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In a recent article in this journal we noted with some amazement the claim by Karakurt et al [1] that, to the best of their knowledge, their case report of uterine contractions as a side effect of bee venom immunotherapy was the first such report. Uterine contractions are not at all an unusual side effect of Hymenoptera venom immunotherapy (VIT) and they can also occur during allergic Hymenoptera sting reactions, particularly in women around menopause. Although not many case reports have been published, uterine contractions have been a widely recognized side effect of VIT since the introduction of this therapy, and are mentioned in many textbooks [2-4].

What is remarkable about the recently published case by Karkurt et al [1] is that the patient developed hypoparathyroidism after thyroidectomy. Regrettably, exact documentation of the so-called "rapid-onset hypocalcemia" following VIT is missing, as is information on pre-VIT calcium levels on at least 2 occasions and the patient's normal calcium range. The most plausible explanation for the hypocalcemia in this case, particularly with reference to the authors' statement "on the third occasion, we administered the injection after a calcium infusion and no contractions were observed", is that the treatment of the hypoparathyroidism was not adequate. Nevertheless, this observation indicates that serum calcium, and possibly calcium metabolism, should be tested in women who experience uterine contractions during VIT.

The final sentence "Such a side effect is increasingly important, as VIT can now be administered during pregnancy" is somewhat intriguing. According to European guidelines, VIT should not be started during pregnancy [5], although, it can be continued as maintenance therapy during pregnancy if it was previously well tolerated. To our knowledge there have been no reports to date suggesting premature delivery because of uterine cramps due to VIT. In the past 25 years, we have treated more than 3000 patients with VIT in our clinic; several of these became pregnant during therapy and we have never observed any specific problems.

In our experience, antihistamines and corticosteroids have no effect on uterine contractions due to Hymenoptera stings or VIT injections, contrasting with intramuscular adrenaline at a dose of 0.1 mg per 10 kg body weight, which has a rapid effect on uterine and intestinal cramps [6]. Further studies are needed to show whether hypocalcemia is really the main cause of uterine cramps in this situation and whether calcium infusions are the treatment to recommend.

References

1. Karakurt F, Kargili A, Bozkurt B, Kasapoglu B, Ikizek M. Uterine Contractions: An Unusual Side Effect of Venom Immunotherapy. J Investig Allergol Clin Immunol. 2010; Vol. 20(5): 431-432
2. Müller U. Insect Sting Allergy: Clinical picture, diagnosis and treatment. Gustav Fischer, Stuttgart/New York. 1990, page38-39.
3. Golden DBK Insect allergy. In Middleton's Allergy principle and practice (Adkinson Jr. NF, Yungiger JW, Busse WW et al. eds). Mosby 6. edition, 2003; Vol. 2, p. 1478
4. Müller U. Insect Sting Allergy. In Allergy and Allergic Diseases, Kay AB, Kaplan A, Bousquet J, Holt P eds, Blackwell Publishing, 2008:2010-2024
5. Bonifazi F, Jutel M, Bilo BM, Birnbaum J, Müller U and the EAACI interest group on insect venom hypersensitivity. Prevention and treatment of Hymenoptera venom allergy: guidelines for clinical practice. Allergy. 2005; 60:1459-70.
6. Kemp SF, Lockey RF, Simons FER, on behalf of the WAO ad hoc committee on Epinephrine in Anaphylaxis. Allergy. 2008;63:1061-70

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Low Immunoglobulin E Response in Gastro-Allergic Anisakiasis Could Be Associated With Impaired Expulsion of Larvae

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We read with interest the article "Multiple Acute Parasitization by *Anisakis simplex*" by Jurado-Palomo et al [1], which described a patient with acute parasitism involving over 200 *A simplex* larvae attached to the gastric mucosa. This case of gastro-allergic anisakiasis is particularly interesting because of a well-documented poor immune response with consistently low specific and total immunoglobulin (Ig) E levels. The authors proposed that the patient might have an immune deficiency or alternatively a downmodulation of the immune response due to such a great number of larvae.

We would like to propose a third hypothesis, based on an evolutionary interpretation, which we believe is consistent with the case description. IgE, its receptors, and cellular responses have evolved as a defense mechanism against metazoan parasites [2], and it has even been proposed that allergy to common aeroallergens might have evolved in the absence of parasites to which humans have been exposed

in their evolutionary history [3]. A recent article described how patients with gastro-allergic anisakiasis expel *A simplex* larvae more readily than those with gastric anisakiasis without urticaria [4]; it even proposed that urticaria might be an immunopathological visible side effect of a defense response against the invading larvae.

In the case described by Jurado-Palomo et al [1], after an initial urticarial reaction, the patient continued to experience gastric symptoms and the larvae were obviously not expelled. We propose that a possibly genetically determined low IgE response in this patient could be the primary reason for the lack of a sufficient local IgE-mediated "weep and sweep" response against the invading larvae; this in theory might be a beneficial type 2 T helper cell (T_H2)–mediated effect that evolved in response to helminth infections with an enteric phase [2]. This would provide strong support for the possible beneficial effect of the vigorous IgE response seen in the majority of patients with gastro-allergic anisakiasis, where we have learned that larvae are mainly expelled without the need for further gastroscopic procedures [5].

Furthermore, the patient had no history of atopic disease. In this respect, it has been proposed that the reduced frequency of alleles promoting an overly active T_H2 inflammatory response in nontropical populations could be due to the fact that they no longer confer a survival advantage because of the reduced environmental parasite load [3]. In this special case it could be argued that the patient studied has lost her genetically determined capacity to deal with *A simplex*, a member of the Ascaridae family, which also includes other common human parasites such as *Ascaris lumbricoides* and *Toxocara canis*.

References

1. Jurado-Palomo J, López-Serrano MC, Moneo I. Multiple parasitization by Anisakis simplex. J Investig Allergol Clin Immunol. 2010;20:437-41.
2. Fitzsimmons CM, Dunne DW. Survival of the fittest: allergology or parasitology? Trends Parasitol. 2009;25:447-51.
3. Le Souëf PN, Candelaria P, Goldblatt J. Evolution and respiratory genetics. Eur Respir J. 2006;28:1258-63.
4. Daschner A, Cuéllar C. The hidden sense of symptoms: Urticaria can be beneficial. Med Hypotheses. 2010;75:623-6.
5. Alonso-GómezA, Moreno-Ancillo A, López-Serrano MC, Suarez-de-Parga JM, Daschner A, Caballero MT, Barranco P, Cabañas R. Anisakis simplex only provokes allergic symptoms when the worm parasitises the gastrointestinal tract. Parasitol Res. 2004;93:378-84.

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New Pathways in Defense Against Metazoan Parasites; Interleukin (IL)-25–Dependent Cell Population That Provides IL-4, IL-5, and IL-13 at the Onset of Helminth Expulsion

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We read with interest the Letter to the Editor "Low IgE response in gastro-allergic Anisakiasis could be associated with impaired expulsion of larvae" by Daschner et al [1] regarding our description of a patient who presented acute anisakiasis due to the presence of more than 200 larvae attached to the gastric mucosa. We speculated that the poor immunoglobulin (Ig) E response observed during follow-up could reflect some kind of immune deficiency or could be caused by modulation induced by the parasite itself as a mechanism to evade the immune response [2]. Daschner et al propose that "the possibly genetically determined low IgE response in this patient could be the primary factor for the fact that no sufficient local IgE-mediated "weep and sweep" response against the invading larvae was produced, a postulated beneficial T-helper type 2 (T_H2) mediated effect evolved in response to helminth infections with an enteric phase" [1].

Immune responses in helminth infections and allergy share many important features, such as a T_H2-dominated cytokine milieu. Upregulation of interleukin (IL) 4, IL-5, IL-13, total IgE, and eosinophilia are part of the host immune response against the parasite and hallmarks of acute helminth infections and allergic disease [3]. It is clear that a T_H2 response is essential for the expulsion of gastrointestinal helminths; however, each of the immunological effector mechanisms induced following infection with these parasites may not be required or may be insufficient, although together they operate to expel gastrointestinal helminths [4].

In our opinion, the hypothesis of Daschner et al [1] is interesting, but it seems to be somewhat IgE-dependent. In fact, T_H2 responses seem to be responsible for worm expulsion, but multiple effector mechanisms operate against gastrointestinal nematodes and T_H2 cytokines induce gut inflammatory responses, including mast cell or goblet cell responses and changes in gut physiology. Some authors even think that traditionally accepted mechanisms of resistance such as eosinophilia and IgE responses may not play as important a role in protection as previously thought [5]. Fallon et al [6] recently reported that IL-25 seems to be essential in helminth expulsion and that a T and B cell–independent, IL-25–regulated cell class is responsible for worm expulsion. Furthermore, IL–25 deficient mice showed inefficient *Nippostrongylus*

brasiliensis expulsion that was corrected after exogenous recombinant IL-25 administration.

We summarize these observations as "some kind of immune deficiency", because a low T_H2 response must be considered a kind of immune deficiency and because defense against parasites should be considered a relevant part of the immune response.

We should bear in mind the important work of Amano et al [7], who proved that, in experimental infection by Anisakis simplex, the specific IgE response is strongly regulated. In fact, specific IgE antibody titers were higher in rats infected with 1 larva, and rats inoculated with 5 or 20 larvae showed lower specific IgE levels, implying that only low-level infection leads to effective IgE synthesis. Our finding of an ineffective IgE response could reflect this type of regulation induced by an excess of larvae.

References

1. Daschner A, Rodero M, Cuellar C. Low immunoglobulin E response in gastro-allergic Anisakiasis could be associated with impaired expulsion of larvae. J Investig Allergol Clin Immunol. 2011;21:330-32.
2. Jurado-Palomo J, López-Serrano C, Moneo I. Multiple acute parasitization by Anisakis simplex. J Investig Allergol Clin Immunol. 2010;20:437-41.
3. Flohr C, Quinnell RJ, Britton J. Do helminth parasites protect against atopy and allergic disease? Clin Exp Allergy. 2009;39:20-32.
4. Lawrence CE. Is there a common mechanism of gastrointestinal nematode expulsion? Parasite Immunol. 2003;25:271-81.
5. Onah DN, Nawa Y. Mucosal immunity against parasitic gastrointestinal nematodes. Korean J Parasitol. 2000;4:209-36.
6. Fallon PG, Ballantyne SJ, Mangan NE, Barlow JL, Dasvarma A, Hewett DR, McIlgorm A, Jolin HE, McKenzie AN. Identification of an interleukin (IL)-25-dependent cell population that provides IL-4, IL-5, and IL-13 at the onset of helminth expulsion. J Exp Med. 2006;203:1105-16.
7. Amano T, Nakazawa M, Sugiyama H, Secor WF, Oshima T. Specific antibody patterns of Wistar rats inoculated with third stage larvae of Anisakis simplex. J Parasitol. 1995;81:536-42.

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