

## Does parasitic infection protect against allergy?

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**I**mmunoglobulin E (IgE) plays a central role in the pathogenesis of immediate hypersensitivity reactions because of its capacity to bind specifically to high-affinity IgE receptors on mast cells or basophiles by the alpha chain of Fc epsilon receptor type I (Fc-epsilon RI- $\alpha$ ).<sup>1</sup> In addition to its ability to activate mast cells and basophiles, IgE can bind to the low-affinity IgE receptor (CD23, or Fc-epsilon RII) on B cells to augment cellular and humoral immune responses in allergic disease.<sup>2</sup>

Moderate to highly elevated IgE concentrations have been linked to IgE-mediated allergic disease, especially food allergy and one of its main manifestations, atopic dermatitis. In newborns and asymptomatic young infants, elevated IgE concentrations are an indicator of the likelihood of the development of allergic disease and they are a prognostic indicator in adults with certain types of chronic allergic diseases. Serum IgE concentrations are highly variable, however when IgE levels are compared between allergic and non-allergic individuals, the average IgE concentration of the allergic individuals is almost always higher than that of the non-allergic individuals. Recent data suggest that mast cells can contribute to eosinophil-mediated inflammatory responses. Activation of mast cells can occur by antigen and immunoglobulin E via the liberation of proteases, leukotrienes, lipid mediators, and histamine contributing to tissue inflammation and allowing recruitment of eosinophils to tissue.

Elevated IgE concentrations can also be seen in certain infections like HIV infection and chronic hepatitis, in immunodeficiency diseases affecting regulatory T

lymphocytes, in the rare hyper-IgE syndrome with recurrent infections and in some parasitic diseases.

In parasitic infections, increased IgE concentrations occur during metazoan phases, with an apparent association between increasing levels of tissue invasion and increasing levels of IgE. The most common known parasites to be associated with increased serum IgE levels include visceral larva migrans (*Toxocara canis*), intestinal capillariasis (*Capillaria philippinensis*), schistosomiasis, ancylostomiasis, and echinococcosis.

The increased IgE concentrations are the result of both parasite-specific and nonspecific IgE production.<sup>3,4</sup> One mechanism proposed to explain the increase in total IgE levels is the

secretion by parasites of factors that stimulate IL-4 production, leading to increased IgE levels.<sup>5,6</sup> Whether or not this increase in IL-4 production may also promote the production of specific IgE against common allergens is not clear, but it is conceivable that it may occur in at least some patients. When intestinal parasitic disease is successfully treated with antiparasitic drugs, the serum levels of IgE have been noted to decrease considerably over time. However, when anti-parasite IgE antibodies coexist with anti-allergen IgE, the effect of the decrease in anti-parasite and total IgE concentrations on the manifestations of inhalant allergy is variable and still controversial.

A protective effect of parasitic infections against IgE-mediated allergy manifestations is suggested by observation in developing countries with a high burden of parasitic infections. In these countries, the prevalence of atopic diseases is much lower than industrialized nations. Parasitic infections correlate with enhanced helminth-induced IL-10 production, which in turn was inversely associated with allergic sensitization. These findings suggest that the anti-inflammatory properties of IL-10 induced by helminth infection may attenuate the allergic response or promote tolerance.<sup>7</sup> Such an inverse relationship with reduced skin prick sensitivity has been demonstrated for

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helminth infections including ascariasis, trichuriasis, and hookworm.<sup>8</sup>

It has also been postulated that large quantities of IgE resulting from parasitic infection saturate mast cell IgE receptors, preventing the attachment of sufficient allergen-specific IgE to produce positive skin tests to airborne allergens. This finding is consistent with the finding of Nielsen et al., that histamine released from basophiles of patients infected with *Toxocara canis* or *Ascaris suum* was related to the ratio of parasite-specific IgE to total IgE in serum. In fact, stimulation of an intense polyclonal IgE response may be a mechanism by which parasites attempt to evade the protective effects of parasite-specific IgE antibodies.<sup>9</sup>

An inhibition of allergic manifestations in parasitic diseases is further supported by an increase in the manifestations of allergy after treatment of the parasitic disease as reported by some authors.

Elsewhere in this journal, Medeiros et al. report on the relationship between allergic diseases including rhinitis, atopic dermatitis and specially asthma and intestinal *Ascaris* infestations in a young patient population in Northern Brazil.<sup>10</sup> A total of 101 male or female patients with asthma and/or allergic rhinitis aged 12 to 21 years were selected for evaluation. All patients had evidence of sensitization to aeroallergens proven by high specific IgE antibodies detected *in vitro* or skin testing. Parasitic infestation was assessed by the classical stool analysis method and specific anti-*Ascaris* IgE titers. Eosinophilia was present in almost 50% of the subjects, and anti-*Ascaris* IgE was positive in 73% of the individuals, although parasitological stool examination yielded positive results in only 34% of study subjects.

A key observation in this study was the unusual high prevalence of parasitic infections in a cohort of atopic patients. This observation stands in contrast to the observation of decreased atopic diseases in areas of a high prevalence of parasitic infections.<sup>11,12</sup> While a number of controls that would have been of interest were not included in this study, the report by Medeiros et al. suggests that further investigation into the real role of parasitic infections in allergic disease is warranted to determine if parasitic infection offers a protection against allergic disease manifestations or if the outcome of the association between both diseases is rather dependent on local condition of exposure and sensitization in the area of study, as discussed eloquently by the authors of this report.

What conclusions for the practicing pediatrician can we draw from the Medeiros report?

Diagnostically the authors of the study suggest that the quantification of anti-*Ascaris* IgE can be more useful than the parasitological stool examination in patients with respiratory allergy and high total IgE levels, although we

do not know exactly how long after parasite eradication the anti-*Ascaris* IgE antibodies persist. Certainly, the presence of concomitant eosinophilia suggests active parasite infestation. When elevated IgE concentrations and eosinophilia are present in patients without allergic manifestations like atopic dermatitis, rhinitis and or asthma and/or without evidence of IgE sensitization to food or inhalant allergens, a parasitic infestation needs to be actively sought and ruled out. The Medeiros study further points out that in patients with parasitic infestations and allergic symptomatology, the coexistence of specific anti-parasite and anti-allergen IgE antibodies needs to be considered and studied.

For the management of parasitic disease and a coexisting respiratory allergy, the Medeiros report clearly suggests that at least in some patient populations, parasitic infestation and elevated total and specific anti-parasite IgE antibodies do not offer a significant protection against the development of allergy. Therefore, appropriate management of the parasitic infection and of the respiratory allergies should be performed simultaneously as required, without fears that treatment of one condition may exacerbate the other.

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