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Total IgE in respiratory allergies and infections by intestinal parasites

Dear Editor,

The paper published by Medeiros et al.[1] meets all of the journal's editorial prerequisites, such as Ethics Committee approval and sample size calculations to obtain a "convenience sample" adequate for a valid statistical analysis. It has contributed information to the subject, but further comments are necessary to better explain the issue.

The antigenic determinants in parasites vary depending on their stage of development, from egg, through embryo and larva to the adult worm. The adult parasite has countless antigens capable of inducing humoral and cellular immune response, generally with polyclonal stimulation, but the presence of IgE antibodies to *Ascaris* provides no indication of which antigens or from which phase they have resulted.

The authors claim, without offering any references, that "Infected atopic individuals show exacerbation of allergic symptoms immediately after anti-helminthic therapy." Whether this is a personal experience or one reported by other authors, what would be the approach to take in cases of infection by parasites in asthmatics to avoid exacerbations due to anti-helmintic treatment?

In an editorial on the article in question, Sorensen & Sakali,[2] pointed out the high prevalence of parasitic infection in the cohort of atopic patients and the lack of certain controls that would have been of interest if included, in order to determine whether parasitic infections offer protection against allergic manifestations, or vice-versa.

Parasitic geohelminth infections are accompanied by elevated IgE levels in serum, especially when larvae are migrating through tissues or when parasites are lodged within tissues, a fact which has been recognized since the end of the sixties, after the discovery of IgE antibodies.

Eosinophila only occurs during the acute phase of Ascaris infection. In Table 1 of their article, the authors provide figures for total and serum IgE, anti-Ascaris IgE and eosinophil counts in blood for their sample of 101 individuals with asthma and/or allergic rhinitis, from Recife, PE, in 2002, without separating the 34% with positive parasitology results for geohelminths in feces from those who did not have parasites at the time of examination. The proportion of anti-Ascaris IgE in total serum IgE did not take account of parasitic load nor of the proportion of IgE antibodies specific to domestic mites, such as those of the geni *Dermatophagoides* and *Blomia*, which are common allergens in the tropics.

In earlier work, we did not observe any correlation between eosinophils counts in blood, total IgE in serum and intensity of infections by *Ascaris*, *T. trichuris* or ancylostoma.[3,4] Positive skin tests for allergens from domestic dust and *D. farinae* were not associated with the presence of parasitic infection.[3]

The highest total IgE levels observed in serum occurred in cases of combined infection by *Ascaris* and *trichuris* (geometric mean: 1,114 UI/mL) rather than in cases of isolated infections by these intestinal worms (geometric means: 428 UI/mL and 471.4 UI/mL, respectively).[3]

Medeiros et al.[1] observed that just 34% of their allergic patients had helminthiasis, 16% with *Ascaris*, 12% with *T. trichuris* and 6% with other intestinal worms that were not listed. Despite the low percentage of patients infected by Ascaris, anti-Ascaris IgE was positive in 73% of the sample, probably demonstrating the low specificity of the test.

The subset of allergic patients without parasites (66%) should not have been analyzed together with those who were infected, but could have served as a basis for comparison of the variables total IgE, specific IgE for *Ascaris* and for inhalant allergens and for eosinophil counts.

Nevertheless, they would only have provided a basis for comparison if the exposure conditions in the environment were known (for example, presence of allergens and eggs in dust at home/school), duration of infection, previous infections by Ascaris or other intestinal worms, parasitic load, which are just some of the large number of variables that should have been controlled for.

The relationship between infection by Ascaris and atopic disease may be more complex if we consider the possibility of allergic sensitization of IgE through respiratory mucosa due to inhalation of the eggs of intestinal worms contained in dust in homes were individuals infected by intestinal worms are living.

It is not known whether IgE levels normalize after patients are purged of parasites, which compromises the interpretation of any assessment of IgE in relation to present or

previous parasitosis, since reinfection is probable if the patient returns to the same conditions of hygiene and sanitation.[3,4]

Anti-Ascaris IgE contributed to total serum IgE for the whole sample. The authors should have separated those infected from those uninfected by Ascaris and other intestinal worms, if they were to have demonstrated the value of IgE assay for the diagnosis of ascariasis and its relationship with allergic diseases.

The sensitivity of the parasitology test in feces is low (40%), but to state that the same is true in Brazilian laboratories is far from true.[5]

Ascaris-specific IgE levels > 0.35 kU/L only denote an amnestic response to antigens of this and other parasites or cross-reaction with other proteins, such as tropomyosin and chitin, but not an active parasite infection. The authors should not conclude, from the data provided, that the presence of anti-Ascaris IgE would be of greater use than the parasitology test in feces for the diagnosis of ascariasis in atopic patients.

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Authors' reply

Dear Editor,

The relationship between parasitosis and allergy is complex and of great interest. We are grateful to Prof. Nelson Rosário's letter because it gives us the opportunity to provide further explanation and avert the possibility that readers interpret our results improperly or make inferences that our study design does not support.

Anti-Ascaris specific IgE is obtained from extract of the entire worm body, in which there are a myriad of antigens, but whose immunologically representative allergens are the primary ABA1 and tropomyosin, which are probably responsible for the resistance to reinfection that has been linked with high levels of this antiparasitic IgE.[1]

It is possible that there may be a later cross-reaction with allergens that share a similar tropomyosin, but this is a speculation that has yet to be proven clinically. High levels of anti-Ascaris IgE may be an expression of defense, resulting in reduced parasitic load and reduced oviposition rate or may be a continuous immunoresponse in response to ingestion of infected eggs, since this response to the parasite is independent of polyclonal total IgE stimulation, which was observed predominantly among atopic patients.[2]

On the subject of eradication of parasitosis, it is necessary to stress that this must always be performed, since it benefits many aspects of both individual and public health. Nevertheless, there is the worry that eradication of intestinal worms, by liberating allergens and reducing interleukin-10 levels, could exacerbate asthma and other allergic diseases.[3] Nevertheless, despite this immediate possibility, a long-term study demonstrated that periodic anthelmintic treatment resulted in improvement of the symptoms of asthmatic patients.[2]

Skin and/or mite-specific IgE tests were positive in all of our patients, which means that it is out of the question that the influence of these allergens is a factor that could explain why some of our patients had extremely elevated IgE levels, although it could be a contributing factor. With reference to eosinophila, the literature is consistent in demonstrating that levels are elevated in the tissular phase of the parasite cycle, which is more common during the acute phase, but can also take place during the chronic phase, if tissues are infested by the adult worm or larvae. Furthermore, eosinophila does not exhibit correlation with total IgE levels.

In practice, the sensitivity of feces examination for parasites is indeed low. A high quality study carried out in Brazil demonstrated positivity of just 55% in the first sample, increasing to 74% with the second sample and 80% with three samples.[4] This being so, negative results in this test for children in our sample living in poor socioeconomic conditions are not sufficient to allow us to state that they are free of parasitosis, especially not with reference to low parasitic load infections, since it was not possible to perform serial testing for all patients.

Our study design was cross-sectional and we only enrolled individuals with a diagnosis of asthma and/or allergic rhinitis and positive allergy test results for at least one aeroallergen. It was not our objective to explain the relationship between respiratory allergy, atopic disease and intestinal parasitosis, but to investigate total IgE levels, which reach

extremely elevated levels in some patients and, especially in developing countries may be caused by intestinal parasitosis. This is why patients were not categorized as cases or controls, and why the dependent variable (total IgE) was included in the statistical analysis as a continuous variable, which is to say that it was not broken down into more or less elevated levels, and this is the reason why multiple linear analysis was adopted. The theoretical model proposed to explain total IgE levels in these patients with respiratory allergy was that intestinal parasitosis (detected both by parasitology in feces and by anti-Ascaris IgE) could be responsible for the extremely elevated total IgE levels, rather than being exclusively the result of the allergic process.

The suggestion made by the letter's author that allergic patients with parasitosis should not have been analyzed together with those free from parasites would only make sense if the study had a case-control design (with allergic patients with parasitosis as cases and those without as controls) or a cohort design (in which, after a period of observation of the allergic patients, they would be classed as either with or without intestinal parasitosis). The objective in both cases would be to compare individuals with respiratory allergies who had or did not have intestinal parasitosis. In such a case, since the dependent variable would be categorical, the statistical analysis would have to be via multiple logistic regression. That suggestion, however, would only apply to a different research scenario and, even with a cohort study, it would prove complicated to obtain certain variables suggested by our correspondent, such as duration of infection, previous infections, parasitic load and the conditions of exposure in patients' environments. How much time and resources would be required to guarantee the reliability of those data?

The author's letter refers to the "large number of variables that should have been controlled for". We would remind him that, in research, it is not possible for researchers to cover all possible explanations for a phenomenon – there are some possibilities that are unknown, even with current knowledge. That would be possible within the paradigm of modern science (complexity – there are multiple versions of reality within different linguistic domains of explanation).[5]

Returning to anti-Ascaris IgE , our study simply demonstrated, for the sample in question, that anti-Ascaris IgE positivity may have been an explanatory factor for elevated total IgE levels in these patients. Nevertheless, whether the anti-Ascaris IgE detected in our sample was the result of past or present ascariasis infection or some type of cross-reaction, is a question that could only be answered by a differently designed study. At no point was it stated that anti-Ascaris IgE confirms a diagnosis of ascariasis, that was an interpretation made by the author of the letter to the editor. In fact the conclusion of our study was that, in endemic countries, total IgE should be analyzed in the context of parasitic infection. In this context, anti-Ascaris IgE may be a marker of previous contact with the parasite or even with another geohelminth and should be investigated.

The explanatory model chosen for the study is simple, with few variables, but we recognize that complex thinking is capable of contextualizing while still recognizing the singular - what is "visible" to the researcher – since the model of reality is (still) elaborated by the researcher.[6]

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