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Total IgE level in respiratory allergy: study of patients at high risk for helminthic infection

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Abstract

Objective: Eosinophilia and increased serum IgE levels are indicators of atopy; however, other factors can also play a key role, such as intestinal parasitic infections. This study assesses the relationship between total serum IgE, eosinophil count, and anti-Ascaris IgE in individuals with asthma and/or allergic rhinitis.

Methods: A cross-sectional study was carried out in adolescents with asthma and/or allergic rhinitis. The patients had their total serum IgE, anti-Ascaris IgE and eosinophil count measured.

Results: A total of 101 patients aged 12 to 21 years were assessed. Median IgE level was 660 IU/mL (P_{25-75} 243.5-1500), and the eosinophil count corresponded to 510 cells/mm³ (P_{25-75} 284-811). Anti-Ascaris IgE was positive in 73% (74/101) of the individuals, but parasitological stool examination yielded positive results in only 33.7% (34/101). The correlation coefficients were the following: 0.34 ($p = 0.001$) between total IgE level and eosinophil count, 0.52 ($p < 0.001$) between total IgE level and anti-Ascaris IgE, and 0.26 ($p = 0.01$) between eosinophil count and anti-Ascaris IgE. The final multiple linear regression model pointed out that anti-Ascaris IgE contributed to a total serum IgE level with a coefficient of determination (adjusted R^2) of 0.25 ($F = 12.35$; $p < 0.001$). This effect occurred regardless of eosinophil count and of the presence of intestinal helminthic infection.

Conclusion: In patients with respiratory allergy and increased total serum IgE levels living in areas where there is a high risk for helminthic infections, the quantification of anti-Ascaris IgE can be more useful and more insightful than the parasitological stool examination.

J Pediatr (Rio J). 2006;82(4):255-9: IgE, eosinophils, allergy, helminthic infection, ascariasis.

Introduction

In general, eosinophil count and total serum IgE levels are high in allergic diseases.¹ The association between increased total serum IgE levels in cord blood, eosinophilia in the third month of life and positive prick test results at 18 months may have a predictive value for atopy and asthma.¹

A total serum IgE level greater than 200 IU/mL in individuals with family history of atopy suggests possible development of allergic disease in the future.² Nevertheless, other factors have an impact on total IgE levels, as IgE is not only an expression of atopy, but it can also indicate chronic parasitic infection, especially by geohelminths, which stimulate the production of polyclonal IgE.^{3,4} Moreover, it has been observed that polyclonal IgE synthesis by intestinal helminths may reduce allergic reactivity in populations with high rates of parasitic infection, representing one possible explanation to the hygiene hypothesis in allergic diseases.⁵

Increased total IgE levels in a patient with respiratory allergy can be influenced by intestinal parasites, and this can be determined by parasitological stool examination and by the measurement of anti-Ascaris IgE levels, which are important for the daily clinical practice. Therefore, the aim of the present study was to assess the relationship between total IgE levels, eosinophil count, and anti-Ascaris IgE levels in adolescents with asthma and/or allergic rhinitis.

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Methods

A cross-sectional study was carried out at the Research Center for Allergy and Immunology at Hospital das Clínicas of Recife, affiliated to Universidade Federal de Pernambuco. Parents or surrogates signed an informed consent form allowing for their children's participation in the study. The study was approved by the Research Ethics Committee of Universidade Federal de Pernambuco, Brazil.

Considering the prevalence of asthma in the city of Recife and that 25% of asthmatic patients have total serum IgE levels greater than 1,500 IU/mL,⁶ a convenience sample of 89 patients was calculated in order to have alpha and beta errors of 5% and 20%. A 10% increase in the sample size was allowed in order to account for possible loss to follow-up.

A total of 101 male or female patients with asthma and/or allergic rhinitis aged 12 to 21 years were selected. Respiratory allergy was diagnosed in those patients with asthma and/or allergic rhinitis with total IgE levels greater than those expected for age, with specific IgE to aeroallergens greater than 0.35 IU/dL and/or with skin tests showing immediate hypersensitivity to mites greater than 3 mm (compared to the negative control). All patients presented with sufficiently remarkable symptoms to make them seek the city's referral center for allergy. Asthma was defined as recurrent history of dyspnoea, chronic cough, wheezing, chest tightness or discomfort, with symptom improvement after bronchodilator use.⁷ Patients with history of sneezing, rhinorrhea, itchy nose, and nasal congestion were regarded as having allergic rhinitis.

The exclusion criteria were: use of oral corticosteroid or antibiotics in the last 30 days prior to the study, use of fluticasone, or other inhaled corticosteroid in an equivalent dose, greater than 500 mcg/day, as well as the presence of any other chronic disease in addition to asthma and/or allergic rhinitis.

After anamnesis and physical examination, blood and stool samples were collected from patients. Total serum IgE level was measured by the Pharmacia UniCAP System (Pharmacia Upjohn Uppsala, Sweden), and a complete blood count was performed to determine the number of eosinophils. Presence of intestinal parasites was assessed by the examination of fresh stool specimens using Hoffman and Baermann-Moraes methods.⁸ Specific IgE to *Ascaris lumbricoides* was quantified by the enzyme immunoassay technique using Pharmacia UniCAP System (Pharmacia Upjohn Uppsala, Sweden),⁹ according to which a specific IgE level greater than 0.35 IU/dL (class 1) was regarded as positive.

The relationship between total serum IgE, anti-Ascaris IgE and eosinophil count was evaluated by Spearman's rank correlation coefficient, due to the non-normal distribution of variables. Multiple linear regression models

were built using total serum IgE as dependent variable, anti-Ascaris IgE and eosinophil count as independent variables, and the presence of intestinal parasites as control variable. Continuous variables were log-transformed to satisfy the normality assumption for the multiple linear regression analysis. The models were based on stepwise forward selection, with inclusion of anti-Ascaris IgE, eosinophil count and intestinal parasitic infection, respectively.¹⁰ The variables with $p < 0.20$ were selected for inclusion in the multiple model; after being included, the variable remained in the model and was used for the adjustment of subsequent models. All data were stored and analyzed using SPSS for Windows, version 8.0 (SPSS Inc., Chicago, Illinois).

Results

The sample consisted of 101 patients, 56% (57/101) of whom were male. The mean age was 14.9 ± 2.36 years. With regard to respiratory allergy, asthma was predominant in 24% (25/101) of patients, whereas 33.7% (34/101) had allergic rhinitis and 41.5% (42/101) showed coexistence of asthma and allergic rhinitis. The parasitological stool examination yielded positive results for geohelminths in 33.7% (34/101), and *Ascaris lumbricoides* was the most prevalent parasite, with a rate of 47% (16/34), followed by *Trichuris trichiura*, with 35.3% (12/34).

Table 1 - Median levels of total IgE, anti-Ascaris IgE and eosinophil count in 101 adolescents with asthma and/or allergic rhinitis (Recife, PE, 2002)

Variables	Median	P ₂₅₋₇₅
Total IgE (UI/mL)	660	243.5-1,500
Anti-Ascaris IgE (IU/mL)	2.1	0-5.2
Eosinophils (mm ³)	510	284-811

Table 1 shows the total serum IgE and anti-Ascaris IgE levels and the eosinophil count.

The correlation coefficients between total IgE and eosinophil count, total IgE and anti-Ascaris IgE, and eosinophil count and anti-Ascaris IgE were 0.34 ($p = 0.001$), 0.52 ($p < 0.001$) and 0.26 ($p = 0.01$), respectively.

Table 2 shows the final multiple linear regression model. Anti-Ascaris IgE contributed to the total serum IgE, and this effect occurred regardless of eosinophil count and of the presence of intestinal helminthic infection. The coefficient of determination (adjusted R^2) was 0.25 ($F = 12.35$; $p < 0.001$).

Table 2 - Final multiple linear regression model for total serum IgE (IU/mL) in 101 adolescents with asthma and/or allergic rhinitis

Variables	B (CI)	F statistics	p
Anti-Ascaris IgE (IU/mL)	4.17 (2.45, 7.08)	29.09	< 0.001
Eosinophils (mm ³)	1.41 (0.85, 2.40)	1.83	0.15
Intestinal parasitic infection	0.08 (-0.12, 0.29)	0.63	0.34

CI = confidence interval.

Discussion

Elevated total IgE levels and eosinophils are not only associated with allergies but also with helminthic infections,^{11,12} and this is why we chose to assess this relationship in the present study.

In this study, 49.5% (50/101) of patients with respiratory allergy showed eosinophil counts within the normal range suggesting the participation of other cells in the allergic inflammatory process.¹³ However, it should be recalled that the absence of peripheral eosinophilia does not rule out the possibility of eosinophilic inflammation of the lung tissue.^{13,14} Serum eosinophils are more dependent on interleukin-5 (IL-5) for their maturation and survival, whereas tissue eosinophils are more responsive to the granulocyte and macrophage colony-stimulating factor (GM-CSF) originating from innate immunity or derived from the Th1 axis.¹⁴ Besides that, eosinophil count can be normal in peripheral blood but active and filled with active granules with major basic protein, eosinophil cationic protein and other mediators.^{14,15} Another explanation for normal serum eosinophil count in 50% of these patients could be the presence of a mild inflammatory process, without any effects at the peripheral blood level, which may result from the use of medications to control the allergy or from the down-regulation of the number of eosinophils in circulating blood, and is a common finding in chronic intestinal parasitic infections.¹⁶ After the migration of intestinal larvae, there is a remarkable reduction in eotaxin, which is essential for chemotaxis and eosinophilia in these patients.¹⁷

The role of total IgE in the severity or persistence of bronchial hyperreactivity must be reassessed. Currently, total IgE is a weak indicator of allergic respiratory disease.³ Very high total serum IgE levels can result from polyclonal activation due to chronic infection by geohelminths,¹⁸ which can probably confirm the hypothesis that intestinal parasitic infection can prevent atopy or reduce its severity.¹⁸⁻²⁰ Individuals from areas where *Ascaris lumbricoides* is endemic show remarkable expression of

Th2 cytokines.²¹ Infected atopic individuals show exacerbation of allergic symptoms immediately after anti-helminthic therapy. An adequate and chronic parasitic infection, mainly early in life, can modulate the immune response and reduce allergic inflammation and its pathophysiological effects.

Another possibility is that individuals with a strong genetic predisposition to atopy, who are more likely to be hypersensitive to environmental allergens, also have stronger resistance to geohelminthic infections.²²

Copper et al.¹⁸ have shown that geohelminths can stimulate specific antibody production but also an exaggerated nonspecific polyclonal IgE synthesis. Consequently, these parasites are associated with high circulating levels of total IgE, which is an escape mechanism, may result in the saturation of mast cells Fcε IgE receptors and in the inhibition of allergenic reactivity and also of any defense action of specific IgE against the parasite.²⁰

The time at which parasitic infection occurs, the possibility of scarce parasite load or of larval forms, or frequent and repeated anti-helminthic therapy should be taken into consideration when interpreting stool examination for parasites,²² and its sensitivity in some cases can be as low as 40%.²³ In this study, positivity was around 40% and did not influence the total serum levels of IgE. By assessing intestinal parasitic infections and the levels of serum IgE in atopic and non-atopic patients, Nyan²³ could not find any relationship between parasitic disease and increased levels of total serum IgE.

On the other hand, when analyzing anti-Ascaris IgE in these patients, it was observed that it contributed to explain up to 25% of serum IgE levels. Dold et al.²⁴ also observed that the presence of anti-Ascaris IgE was associated with high levels of total serum IgE, even though they did not investigate parasitic infection.

Tropomyosin has been identified as a molecule that can be found in several invertebrates and can produce cross-reactions with mites, cockroaches, shrimp, mollusks

and intestinal parasites, including *Ascaris lumbricoides*. Therefore, such possibility should not be overlooked.^{11,12} However, the influence of this protein on cross-reactions with anti-*Ascaris* IgE still needs to be further investigated. Furthermore, there was a high prevalence of ascariasis in the analyzed sample, and therefore, anti-*Ascaris* IgE must represent hypersensitivity of the patients in this study to recent or past infection by *Ascaris lumbricoides*. Recently, some reports have shown that IgE and specific antiparasite IgG4 are markers of resistance and susceptibility of humans to ascariasis.²⁵

Immune and allergenic responses to intestinal parasitic infections vary and can be either acute or chronic. Usually, there is a specific response to the parasite in the acute phase, characterized by pronounced eosinophilia and high levels of specific IgE.²⁶ On this occasion, allergic syndromes can be observed, such as urticaria-like rashes or episodes of bronchospasm caused by larval migration across the lung tissue. At this stage, serum and tissue eosinophilia occur, in an attempt to deter or even eliminate the parasite. Thus, the high level of specific IgE plays an important role in increasing eosinophil recruitment to the site of invasion. Serum polyclonal IgE levels will be extremely high only at a later stage, after the host has been infected several times,²⁶ when the relationship between the host and the parasite seemingly reaches a plateau, however, parasitic infection does not cease to exist, but larval migration is reduced to a minimum. At this stage, helminths may induce suppressor T cells and contribute to reduce allergic responses towards environmental allergens, to a remarkable production of interleukin 10 (IL-10) and of transforming growth factor beta (TGF- β), which, in its turn, reduce the number of serum eosinophils.²⁶⁻²⁸ Lima et al.¹⁷ studied mice chronically infected by *Ascaris suum* and observed a reduction in eosinophil count and in eosinophil peroxidase in the airways, as well as a marked reduction in IL-4 and IL-5 in the bronchoalveolar lavage.

Since 1987, very high levels of anti-*Ascaris* IgE have been found in allergic patients in tropical regions.²⁹ In non-atopic patients, anti-*Ascaris* IgE was negatively correlated with increased levels of total IgE,³⁰ which suggests that polyclonal IgE response against helminths is a prevalent characteristic in atopic individuals.

In children with predisposition to atopy, IgE response was associated with a protective response against helminths. The relationship between anti-*Ascaris* IgE and total IgE was up to nine times greater in atopic children with helminthic infection than in those children with parasitic infection but without allergy, which supports the hypothesis that predisposition to atopy can be a selective evolutionary advantage.³¹

In short, there is reasonable evidence that helminths and other infectious agents can induce nonspecific

proliferation of activated B cells, resulting in very high levels of total IgE, which must be frequent in poor countries and in undernourished populations.³² The immune response to intestinal parasitic infection is initially characterized by the production of specific IgE followed by the increased synthesis of polyclonal IgE. It has been postulated that both specific IgE and polyclonal IgE can prevent the development or relieve the symptoms of allergic diseases by blocking the cell receptors of this immunoglobulin.³³

This study suggests that the quantification of anti-*Ascaris* IgE can be more useful than the parasitological stool examination in patients with respiratory allergy with very high total IgE levels, in whom the past or present history of parasitic infection is a possible explanation. Although it is not within the scope of this study, the behavior of anti-*Ascaris* IgE in the clinical context of specific diagnosis of ascariasis has not been sufficiently explored. Therefore, this specific IgE should be further investigated.

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