Allergol Immunopathol (Madr). 2018;xxx(xx):xxx-xxx

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

ORIGINAL ARTICLE

Immunomodulation of allergic response in children and adolescents: What we can learn from lymphatic filarial infection

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Received 24 March 2017; accepted 13 September 2017

KEYWORDS
Lymphatic filariasis;
Intestinal parasites;
Neglected diseases;
Child;
Adolescent;
Allergic diseases

Abstract
Background: Although it is well known that allergic diseases involve a strong Th2 immune response, with production of high levels of specific IgE allergen, knowledge on the association between filarial infection and allergies, among paediatric patients is scarce.
Objective: To evaluate the allergic response patterns in cases of filarial infection by comparing peripheral eosinophils, total IgE levels, immediate hypersensitivity and cytokine levels in children and adolescents in Brazil.
Methods: This was an exploratory study with three groups: (I) with filarial infection and without allergic diseases; (II) without filarial infection and with allergic diseases; and (III) without filarial infection and without allergic diseases. The prick test and specific IgE tests for aeroallergens were performed using five antigens. Peripheral eosinophils and total IgE were also evaluated. IL-4 and IL-5 were determined using whole-blood culture stimulated by three antigens.
Results: Eosinophilia and elevated levels of total IgE ($\geq$400 IU/dl) were observed in all groups. The prick test was positive in 56.6% of the cases. Group I presented hypersensitive responses similar to the allergic disease groups. In the whole-blood culture stimulated by *Dermatophagoides pteronyssinus*, average IL-4 production did not differ significantly among the groups, but IL5 production resulting from stimulation was greater in the allergic disease groups ($p < 0.05$).

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https://doi.org/10.1016/j.aller.2017.09.023

Please cite this article in press as: Aguiar-Santos AM, et al. Immunomodulation of allergic response in children and adolescents: What we can learn from lymphatic filarial infection. Allergol Immunopathol (Madr). 2018. https://doi.org/10.1016/j.aller.2017.09.023

Conclusions: The allergic response pattern in group with filarial infection was similar to that of the groups with and without allergic diseases, but the response to IL-5 in the culture stimulated by *D. pteronyssinus* was an exclusive characteristic of the allergic group.

Introduction

Lymphatic filariasis is caused by the nematodes *Wuchereria bancrofti*, *Brugia timori* or *Brugia malayi*.[1] It evolves as a chronic disease, particularly due to its Th2-type immune response. This response includes increased production of IL-4, IL-5 and IL-3, along with presence of eosinophilia and IgE production.[2] These characteristics are quite similar to those of schistosomiasis.[3]

Although it is well known that allergic diseases involve a strong Th2 immune response, with production of high levels of specific IgE allergen, knowledge on the association between filarial infection by *W. bancrofti* and allergies is scarce, particularly in relation to paediatric patients.[4,5] During the course of filarial infection, in which the disease may become chronic, the host's immune response seems to be modulated towards a regulatory profile through regulatory T cells that produce IL-10 and TGF-β, and through production of IgG4 antibodies via B cells. This process makes the host tolerant to the parasite, thus decreasing the tissue damage caused by an excessive inflammatory immune response.[6,7]

It needs to be considered that a similar phenomenon might also regulate the allergic response. In this regard, individuals infected by *Schistosoma mansoni* and by *Trichuris trichiura* may present low incidence of allergies.[8–10] Thus, the interaction between helminth infections and allergic disease remains unclear.[8–11] Divergences in opinions regarding this interaction may be due to several factors, such as the parasite species, the parasite load, the time elapsed since infection and the host's age, immune response or genetics.[6]

In addition, some authors have reported the existence of cross-reactivity between helminth antigens and the usual allergens.[6,12,13] This cross-reactivity may involve epitopes of antibodies produced by B cells.[2,6] Strong antigenic similarity between tropomyosins from *Onchocerca volvulus* and from *Dermatophagoides pteronyssinus* (*Dpt 10*), which are associated with increased IgE and IgG4 antibody production in subjects with chronic filarial infection, has been demonstrated.[6]

A bibliographical survey identified gaps in knowledge regarding this relationship between filariasis and allergy, particularly in children, and this motivated the present investigation. Research on the association between skin response to allergens and lymphatic filarial infection will provide support for the Global Programme to Eliminate Lymphatic Filariasis, with regard to understanding the frequency of occurrences of allergic diseases in populations after mass treatment.[14] We evaluated the allergic response using cases of filarial infection as a model, through analysis on peripheral eosinophils, total IgE levels, immediate hypersensitivity reactions and IL-4 and IL-5 cytokine levels in children and adolescents, in an area in Brazil that is endemic for lymphatic filariasis.

Methods

This study was conducted among individuals living in the municipalities of Recife, Olinda and Jaboatão dos Guararapes, in Brazil, where lymphatic filariasis is endemic.[15] These municipalities present similar socioeconomic conditions characterised by precarious conditions of sanitation, sewage disposal, wastewater management and water supply. Such conditions favour the creation of artificial breeding sites for vectors. Environmental factors interact strongly with socioeconomic factors, thereby contributing towards maintaining the endemicity of lymphatic filariasis.[16] These attributes relate to socioeconomic conditions and to the characteristics of the quality of the urban infrastructure and environment that affect health and contribute to other health problems such as intestinal parasites.[17]

This was an exploratory study involving children and adolescents younger than 16 years of age. The sample size calculation was based on the frequency of positivity in skin tests for aeroallergens found in asthmatic and asymptomatic patients according to Godinho et al.[18] The sample size thus calculated was sufficient to detect differences between the groups, according to the estimates made using the STATA 9.1 software. To compare proportions between the groups regarding the results from skin tests for aeroallergens, the following assumptions were made: proportions of 15% positivity in the non-asthmatic group and 80% positivity in the asthmatic group; alpha value = 0.05 (two-tailed); power = 90%; and group I to group II ratio = 1. From these assumptions, the sample size required in each group would be 14 individuals. In the end, a sample composed of 20 participants in each group was studied, i.e. a total of 60 individuals.

The exclusion criteria comprised use of diethylcarbamazine (in the last 24 months), corticosteroids (in the last 30 days) or antihistamines (in the last 10 days). Subjects harbouring intestinal parasites (*A. lumbricoides*, Ancylostomatidae, *T. trichiura*, *S. mansoni* or *Strongyloides stercoralis*) were also excluded.

Initially, screening tests were performed to allocate the subjects to one of the three study groups:

Group I – with filarial infection and without allergic diseases **(WFNA)**.
Group II – without filarial infection and with allergic diseases **(NFWA)**.

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