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Parasites and allergy: observations from Brazil

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Abstract

Brazil is a middle-income country undergoing the epidemiological transition. Effects of changes in daily life habits, and access to clean water, sanitation and urban services on a growing urban population have contributed to a double burden of both infectious and non-communicable chronic diseases. Studies have indicated that parasite infections may modulate the human immune system and influence the

development of allergic conditions such as asthma. However, there is no consensus in the published literature on the effects of parasitic infections on allergy, perhaps as a consequence of factors determining the epidemiology of these infections that vary between populations such as age of first infection, duration and chronicity of infections, parasite burden and species, and host genetic susceptibility. In this review, we discuss the observations from Brazil concerning the relationship between parasite infections and allergy.

Keywords: Parasite, co-infection, allergy/atopy, immune modulation, asthma.

Introduction

Allergic diseases, autoimmune diseases, and atopy have increased considerably in prevalence globally since the 1970s [1–9]. Allergic reactions are consequent to complex interactions between genetic predisposition and environmental exposures resulting in allergic inflammation and associated with diseases such as allergic rhinitis and allergic asthma [10, 11]. Atopy is typically associated with a heightened tendency to produce IgE antibodies in response to common allergens and is accompanied by skin prick test (SPT) reactivity [12, 13]. Atopy is an immunological phenomenon used to define a disease as allergic (e.g. allergic or atopic asthma) [12].

In Brazil, asthma is an important cause of morbidity and mortality with a significant economic impact, being responsible for about 350,000 hospitalizations annually [14, 15]. The increased prevalence of immune-mediated diseases has been associated with immune dysfunction and impaired tolerance mechanisms. These immunological alterations have been attributed to a reduction in biodiversity and reduced exposures to a variety of microorganisms and their products [16, 17], consequent to the effects of economic development and industrialization and their associated effects including indoor and outdoor pollution, the increased utilization of chemicals in households, improved hygiene and sanitation, access to infant immunization and widespread use of antibiotics [17–19]. The putative effects of reduced exposures to microbes and their products on immune development and an

increased risk of inflammatory diseases are described by the hygiene hypothesis [18], relabeled more recently as the biodiversity hypothesis [4, 5, 17].

The concept of a reduced biodiversity includes effects on all living organisms in all ecosystems including terrestrial, marine and other aquatic ecosystems and related ecological complexes [17].

In Brazil, public health initiatives over the past 80 or so years have led to a decrease in the proportion of total deaths caused by infectious diseases from 50% to 5% [20, 21]. Such initiatives have included routine universal immunization of infants and children against an ever increasing number of infectious diseases [22, 23]. In addition, sanitary reform, and social and economic changes have permitted the control or eradication of childhood diarrhea and cholera [24], hepatitis A, Schistosomiasis, *Toxoplasma gondii*, *Herpes simplex*, and EBV infections, among many formerly endemic infectious diseases [21]. Similarly, improvements in sanitation and access to anti-parasitic drugs have had dramatic effects on the prevalence of soil transmitted helminth parasites (STH), mainly *Ascaris lumbricoides* (*A. lumbricoides), Trichuris trichiura (T. trichiura)*, and hookworm (*Ancylostoma duodenale* and *Necator americanus*), that were formerly highly prevalent in regions of Brazil with poor access to sanitation and clean water [25]. The potential effects of a reduction in STH prevalence on asthma and atopy have been explored in some detail recently [26].

It has been suggested that parasites such as STH may induce immune regulatory mechanisms in the host and ameliorate aberrant immunological responses that are considered to underlie atopic [27, 28] and autoimmune diseases [29]. The host inflammatory response to parasitic helminths such as STH and schistosome parasites and that documented for atopic conditions have many parallels including a systemic eosinophilia and elevated serum IgE, both of which are hallmarks of a type 2 immune response [30–32]. An ecological study of all municipalities in Brazil reported lower rates of hospitalization for asthma in areas endemic for *Schistosoma mansoni* or STH [14], indicating that endemic infections with these parasites might contribute to a reduced prevalence and or severity of asthma.

Impact of sanitation on prevalence of parasitic infections and allergy in Brazil

Coverage of control strategies for STH parasites is often patchy even in highly endemic countries [33], and is further complicated by high levels of inequality, and variable access to health care facilities, sanitation and potable water [33]. Improvements in sanitation and clean water and hygiene education are highly cost-effective public health interventions [34] against infections transmitted through the oral-fecal route [35].

From the 1990s, several federal programs in Brazil were adopted to increase access to sanitation including the Modernization of the Sanitation Sector Program (*Programa de Modernização do Setor de Saneamento* - PMSS) of 1995. As a consequence of these programs, the supply of piped water to households increased from 32.8% to 76.6% while household access to adequate sewage disposal increased from 13.1% to 46.5% (Figure 1A). Such strategies may explain the reductions in reported cases of STH infections (*Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm) and *Schistosoma mansoni* at a national level in Brazil (Figure 1B).

In the city of Salvador, capital of Bahia State in Northeast Brazil, a citywide sanitation program, initiated in 1997, increased access to a municipal piped sewer system. Studies from our research group have demonstrated the impact of this intervention on diarrheal incidence and prevalence of STH in children [33, 36, 37]. After implementation of the program, diarrheal prevalence fell by 21% overall and by 42% in the most marginalized neighborhoods. Similarly, prevalence rates of STH infections in children of school age declined by 25%, 33% and 82%, for each of *Ascaris lumbricoides, Trichuris trichiura* and hookworm, respectively. Further, the prevalence of enteric parasitic infections in children aged 0–36 months declined from 24.4% to 12.0% for *A. lumbricoides*, from 18.0% to 5.0% for *T. trichiura,* and from 14.1% to 5.3% for *Giardia intestinalis* [37]. These reductions were explained largely by the increased coverage of piped sewage disposal.

To understand better how poor hygiene exposures might mediate their effects on allergy risk through modification of the human cytokine response, we studied the effects of environmental exposures associated with poor hygiene, on cytokine profiles produced by peripheral blood leukocytes (PBLs) either spontaneously or

upon mitogen stimulation *in vitro* [38]. The study provided evidence of higher spontaneous IL-10 production by PBLs from children aged up to 8 years in the city of Salvador and living in unfavorable environmental conditions in early life (i.e. no sewage system, potable tap water or garbage collection). This effect was explained by a higher prevalence of STH infections among children living in these unfavorable conditions associated with an allergy-modulating immune regulatory network during childhood [38]. Further analysis within this population showed that chronic STH infections were associated with a generalized suppression of mitogen-induced type 1 and type 2 cytokines, probably explained by enhanced production of spontaneous IL-10 [29, 39]. Thus, changes in immune regulation within populations that are related to improvements in sanitary conditions may contribute to an increased prevalence of allergic diseases observed over recent decades in low and middle-income countries such as Brazil [40–42].

An inverse correlation between the prevalence of helminth parasitic infections and asthma can be seen regionally within Brazil between areas with different sanitary and socio-economic conditions: Northern and Northeastern regions with the highest prevalence rates of STH infections also have the lowest prevalence of asthma among adolescents while the converse is seen for the relatively more developed Southern and Central regions (Figure 2)[43, 44]. Differences in per capita income have been related also to asthma prevalence in Brazil. The cities of the Northeast of Brazil such as Maranhão (US$177), Alagoas (US$204) and Bahia (US$239) have lower average monthly incomes than those further South such as Rio Grande do Sul (US$480) [45].

While epidemiological data have shown temporal trends of a reduced prevalence of helminth parasitic infections and increased allergic disease prevalence, and there are ecologic data to suggest that regions of Brazil with poorer living conditions and a higher prevalence of STH infections have a lower prevalence of asthma, what is the evidence that helminth-associated immune modulation actually affects the prevalence of allergic diseases in Brazil?

Helminths and allergy in Brazil

Epidemiological evidence from the published literature for an effect of helminths on allergy is contradictory; while some studies have indicated a positive association with allergy [46, 47], others have not [49, 50]. The actual effects of helminths and allergies in a particular population may be affected by a number of factors including the age of first infection, duration and chronicity of infections, parasite burden, the parasite species present and the host genetic background of that population [51]. How may these factors explain the contrasting findings described between different studies in the literature? In this section, we will be discuss, where data are available, how these helminth parasite–related factors may affect allergy in Brazil.

The SCAALA (Social Changes, Asthma and Allergy in Latin America) initiative was set up to understand better the determinants of allergy and allergic diseases in Latin America. Within SCAALA, we have tried to evaluate the relevance of the hygiene hypothesis as an explanation for the epidemiology of allergic diseases in a Brazilian setting in the city of Salvador. An initial observation showed that a high parasite burden with *T. trichiura* infection in early childhood appeared to protect against allergen skin prick test (SPT) reactivity in later childhood, irrespective of whether the child was still infected. Repeated infections (documented on two occasions, in early and later childhood) were associated with the lowest prevalence of SPT in later childhood [28]. In contrast, infections with *T. trichiura* and allergic sensitization to *Ascaris* (i.e. having specific anti-*Ascaris* IgE antibodies) were associated with an increased risk of atopic wheezing [52].

Human infections with *A. lumbricoides* are considered to induce immune modulation and increased IgE production, the latter occurring through IL-4-mediated polyclonal activation of plasma cells producing IgE against parasite and non-parasite allergens [53–55]. Parasite-targeted IgE antibodies produced during infections with *A. lumbricoides* have been shown to cross-react with self or environmental allergens [56] such as tropomyosin [55, 57–60]. False-positive tests for IgE against environmental aeroallergens is a concern among parasite-exposed populations and might explain the reported association between anti-*Ascaris* IgE and atopic wheeze [52], although it does not explain the oberved association with wheeze, independent

of atopy, defined here by the presence of serum IgE antibodies against at least one allergen. The association between anti-Ascaris IgE and wheeze, which was not seen for the presence of *A. lumbricoides* eggs in stool samples [52], could be related to allergic inflammatory responses against *Ascaris* larvae migrating through the lungs, known as Loeffler's Syndrome [61].

We also observed, in the same study population in Salvador, a marked dissociation between levels of allergen-specific IgE and SPT to the same allergen such that many more children had detectable levels of specific IgE compared to SPT [62]. There are several explanations for this dissociation such as competition between polyclonal and specific IgE for binding to high-affinity receptors on mast cells [63, 64] and host genetic factors [62], among others. Additional studies are required to identify the mechanisms underlying this association [55, 57].

A previous meta-analysis of cross-sectional studies of the associations between STH infections and asthma, reported a positive association between the microscopic detection of *A. lumbricoides* infection in fecal samples and prevalence of asthma symptoms, while hookworm infection was associated with a reduced asthma prevalence [65]. Similarly a meta-analysis of cross-sectional studies showed an inverse association between STH infections and the prevalence of atopy defined by SPT positivity [66]. These meta-analyses included studies from Brazil, among which was one from southern Brazil showing that children with a higher parasite burden with *A. lumbricoides* (defined as ≥100 eggs/gram of feces) had a higher risk of bronchial hyperresponsiveness (BHR) compared to uninfected children and those with lower parasite burdens [67] This association may reflect airways inflammation and BHR secondary to Loeffler's Syndrome. Taken together, these results suggest that STH parasites may have contrasting effects on wheezing and atopy depending on parasite species, timing or duration of infection and parasite burden. Further studies are required to identify the mechanisms by which such effects occur.

Chronic infections and co-infections are thought to be more strongly associated with the presence of parasite-specific IgG4 antibodies. Children with chronic STH infections have elevated levels of anti-*A. lumbricoides* IgG4 and also greater ratios of parasite-specific IgG4 to IgE antibodies than do those with infections detected at only a single time point. Elevated levels of parasite-specific IgG4 may be explained

by increased production of IL-10 during chronic STH infections that enhances subclass switching to IgG4 compared to IgE [29, 39]. An analysis of effects of pathogen burden on allergy markers, showed that children infected with a larger number of chronic pathogen infections including STH, bacteria and viruses had a reduced risk of having SPT and allergen-specific IgE but not asthma compared to those with fewer infections [42] Moreover, using an unbiased cluster analysis approach called latent class analysis, it was observed that children living in better environmental conditions, having better educated mothers and a lower burden of childhood infections, were more likely to have a 'immune responsive' phenotype and a greater risk of atopy, measured by specific IgE and SPT positivity to aeroallergens [41]. Similarly, children infected with a greater number of helminth species were more likely to have evidence of stronger immune regulation (i.e increased IL-10 production by PBLs) and reduced risk of atopy defined, in this case, as the presence of aeroallergen-specific IgE irrespective of SPT results [68]. These observations are consistent with the hypothesis that the induction of 'appropriate' immune regulation by chronic pathogens may protect against atopy [27]. Host genetic background may also contribute to immune regulation; we have described polymorphisms in the IL-10 gene that are associated with reduced IL-10 production by PBLs stimulated with *A. lumbricoides* antigens and that in turn are associated with protection against helminth infections and a greater risk of atopic wheeze and markers of allergy (i.e SPT response and allergen-specific IgE level) [69]. Further, individuals with certain TGF-β polymorphisms appear to have an increased susceptibility to *T. trichiura* and *A. lumbricoides* infections and a lower risk of developing allergy [70].

As for STH infections, human infections with the cosmopolitan helminth parasitic infection, *Toxocara,* has been associated with allergy in humans [71–75]. *Toxocara* is a zoonotic infection that is unable to develop to adulthood in the human host. The infection is caused by contact with an environment contaminated with feces from dogs infected with *Toxocara canis* and cats with *Toxocara cati* [72]. Human infections with the larval stages of *Toxocara* spp. may last for years and have been associated with significant morbidity related to allergic inflammatory responses directed against larvae in tissues [51].

Several studies in Brazil have investigated the effects of human infections with *Toxocara* on allergy and allergic diseases. In the Amazon region in Northern Brazil, Ferreira and collaborators, observed a positive association between *Toxocara spp.* infection and wheezing in a sample of children aged 6-59 months [76]. We have reported in the SCAALA cohort, an association between the presence of anti-*Toxocara* spp IgG and eosinophilia, elevated levels of total IgE and anti-aeroallergen-IgE [32] but an inverse association with SPT and no association with asthma symptoms. Similarly, in a different population of 6-11 year olds near Salvador in the State of Bahia with a *Toxocara* seropositivity rate of 65%, positive associations were observed between seropositivity and eosinophilia and anti-aeroallergen-IgE, but no association with asthma [77]. In the SCAALA study population *Toxocara* seropositivity appeared to be a strong effect modifier of the association between anti-aeroallergen-IgE and that may, in part, explain the dissociation between the two markers of atopy (SPT and IgE). [32]. Similar effect modification has been observed for infections with *A. lumbricoides* and *T. trichiura* in the same population [62]. A possible explanation for such effect modification by helminth infections might be the presence of low-affinity antibodies to helminths that cross-react with arthropod allergens [58, 59]. Such low affinity IgE might have limited biological activity (i.e. for the activation of mast cells).

Immune regulation induced in host by helminth infections appears to modulate type 1 in addition to type 2 responses. A potent down-modulation of both type 1 and type 2 responses has been observed in individuals infected with *Schistosoma mansoni (S. mansoni),* a water-borne parasite of humans, which causes chronic infections [78]. A characteristic feature of chronic infections with *S. mansoni* is the activation of IL-10 producing regulatory T and B cells [79–81]. A study in the state of Bahia, showed that peripheral blood mononuclear cells (PBMCs) from *S. mansoni*-infected asthmatics produced lower levels of IL-5 and IL-4 but higher levels of IL-10 in response to *D. pteronyssinus* antigen compared to those of uninfected asthmatics before anthelmintic treatment [81]. Following treatment, half the infected asthmatics suffered a deterioration of asthma symptoms that was accompanied by a decline in PBMC IL-10 production [81].

A relatively high production of IL-10 by PBMCs from asthmatics infected with *S. mansoni* has been documented in other studies from Brazil [82] in which alternatively IL-10 producing activated monocytes/macrophages and CD4+CD25+ T cells appear to be involved in the downmodulation of inflammatory responses in asthmatics [83].

Asthmatics infected with *S. mansoni* appear to have a lower frequency of SPT and a more benign form of the disease compared to uninfected asthmatics also living in rural areas [84]. Even in a setting of low endemicity in Brazil, it appears that *S. mansoni* infection may reduce the risk of SPT positivity to one or more antigens [85]. In a study of the role of host genetics in determining susceptibility to schistosomiasis, significant heritability was observed both for total serum IgE levels (60%) and host egg count with *S. mansoni* (31%), although the specific genetic markers associated with these effects were not identified [86]. This study demonstrated that, in the context of a population where the primary environmental stimulus for type 2 immune pathways (measured indirectly by total IgE) was helminth infection, the regulation of host immunity was also likely to be due to host genetic factors. A study of subjects co-infected with hookworm and *S. mansoni* have shown an increase in levels of anti-Der p 1 IgE levels following chemotherapy, an effect that was independent of parasite burden [87].

Human lymphatic filariasis, still present in parts of northern Brazil, causes chronic infections in humans that may persist for many years, and is associated with a profound modulation of host anti-parasite immune responses [88, 89]. A study of individuals with lymphatic filariasis with and without antigenemia showed higher frequencies of IFN-γ- and IL-4-producing CD4+ T cells among patients without evidence of circulating microfilariae in the blood, consistent with a down-regulation of immune responses among patients with patent infections [90] observed previously in non-Brazilian populations [91, 92]. Despite such immune modulation in patent lymphatic filariasis, a recent study in Brazilian adolescents with combinations of *Wuchereria bancrofti* infection and allergic disease, was unable to identify evidence of an effect of infection on SPT positivity or Th2 cytokine responses to Der p 1 [93].

Another aspect of interest relating to helminth-allergy interactions is the potential effects of treatments for allergic diseases on parasite infections, such as the well-known but rare cases of *Strongyloides* hyperinfection syndrome developing in infected individuals taking oral corticosteroids as a consequence of uncontrolled replication of *Strongyloides stercoralis* larvae within the human host [26]. Immune mechanisms related to type 2 immune responses are considered to play a key role in protective immunity against helminth parasite infections [94]. Among such mediators of type-2 associated inflammatory responses, IgE is considered to have an important role [95]. The use of humanized monoclonal antibodies directed against IgE (anti-IgE, Omalizumab – Xolair,^{TM}) to treat allergic disease has raised the concern that such treatment might increase susceptibility to infection or increased parasite burdens. However, a randomized controlled trial to study the possibility of increased susceptibility to STH parasites among allergic patients receiving anti-IgE treatment, was unable to identify evidence of increased susceptibility to STH infections among patients receiving anti-IgE. [96]. The same concerns, however, are relevant for the use of new biological drugs (e.g. anti-IL-5) targeting different components of type-2 inflammatory pathways [26].

In summary, data from Brazilian studies have contributed important data that have informed our understanding of parasite-allergy interactions, although further studies are required to understand better the mechanisms by which helminths may modulate allergic responses. The epidemiologic data show that helminth parasites in the context of other childhood infectious diseases do appear to modulate atopy although the effects on allergic diseases are less clear. A better understanding of these mechanisms will help define the potential role of helminth-product derived therapies in the treatment of inflammatory conditions.

Protozoa and allergy in Brazil

The prevalence of intestinal protozoa infections is greater than that of helminth infections in Brazil [97–102]. These parasites are unicellular organism that during acute infections, induce a type 1 immune response, that is essential to control parasite replication [103–105].

Giardia lamblia elicits both a cellular and humoral immune response, inducing cytokines such as tumor necrosis factor (TNF) [106], interferon (IFN)-y [107, 108] and interleukin (IL)-17 [109], as well as, nitric oxide (NO) [110], production of anti-giardial IgA antibodies [111, 112] and intestinal mastocytosis [113, 114]. The relationship between giardiasis and allergy has been considered in the context of food allergy and allergic skin diseases [107, 115–117]. Studies in Brazil have addressed associations between giardiasis, total IgE and respiratory allergic symptoms [118, 119]. A cross-sectional study of children in Recife in Northern Brazil showed no association between *G. lamblia* and respiratory allergies [118].

Another protozoan parasite, *T. gondii,* has been extensively studied with respect to allergic sensitization in both murine models and humans [42, 103, 120–124]. Inverse associations have been observed in Brazilian populations between seropositivity for *T. gondii* and atopy (measured as both SPT and serum IgE to aeroallergens) [42, 123]. Although the mechanism whereby this modulation occurs is not well understood, data from murine models have shown that allergic inflammation can be suppressed by treating animals with *Toxoplasma* extract or derived proteins [125–127].

Concluding remarks

Many host and parasite factors are likely to play a role in determining the effects of parasites in the modulation of allergic inflammation. Urbanization and improvements in sanitation have been associated with temporal and geographical trends of increasing allergic disease prevalence in Brazil even though a large proportion of the population continues to live in conditions of poverty. Latin American countries, including Brazil, are currently experiencing a shift to non-communicable conditions, such as allergies and asthma, termed the epidemiological transition. Findings on the parasite-allergy interaction from human populations in Brazil remain contradictory and there is a need for more studies using standardized definitions for allergy outcomes and new approaches such as studies of epigenetic mechanisms related to parasite exposure.

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Figure legends

Figure 1. (A) Demographic census data from the Brazilian Institute of Geography and Statistics (IBGE)[45] between 1991 and 2010 showing improvements in sanitary conditions such as supply of piped water, sewage collection network and garbage collection. (B) Data from the Department of Informatics of the Unified Health System (DATASUS)[43] from Brazil for the Control Program of Schistosomiasis (PCE). Data is shown for reported infections with *Schistosoma* sp. and the soil-transmitted helminthes, *Ascaris lumbricoides, Trichuris trichiura*, and hookworm between 2002 and 2016. Both surveys were conducted in the north, northeast, southeast, south and central-west regions of Brazil.

Figure 2. Map of Brazil showing the five principal geographic regions. Circles represent the positivity rate in 2011 for *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm infections, from the Department of Informatics of the Unified Health System (DATASUS). Different shades of green shown for each region represent the estimated prevalence of current asthma among adolescents (12 to 17 years) observed in the ERICA study [44].

A

Households (x1000)

70.000
60.000
50.000
40.000
30.000
20.000
10.000
0

1991   2000   2010

Minimal sanitary condition*

B

Nº of cases

400.000
350.000
300.000
250.000
200.000
150.000
100.000
50.000
0

2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016

Ascaris lumbricoides   Hookworm
Trichuris Trichiura   Schistosomiasis

T. trichiura
A. lumbricoides
hookworm

7,40%

8,99%

3,00%

8,01%

7,23%

3,77%

0,18%

0,50%

0,35%

2,00%

0,89%

1,38%

2,2 2%

2,0 4%

0,0 9%

Prevalence of active asthma

☐ < 10%

☐ 10% - 12%

☐ 12% -14%

■ >14%