

The role of helminth infections in protection from atopic disorders

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Purpose of review

The observation that allergies are less prevalent in developing countries, especially in rural areas, has stimulated considerable research to identify environmental factors associated with protection against allergic disorders. Here, we review recent studies conducted in developing countries.

Recent findings

Epidemiological studies conducted in South America, Asia and Africa have attempted to identify factors associated with differences in prevalence of atopy, asthma and atopic dermatitis. Particular attention is given to the complex relationship between helminth infections and allergies. In answer to the question of whether helminth infections are associated with protection against allergic disorders, conflicting data have been generated. In addition to epidemiological studies, animal models have been utilized to gain insight into the immunological mechanisms involved in the interaction between helminth infections and allergies. These animal studies are discussed. The possible explanations for discrepancies found within both human and murine studies have been considered, highlighting the need for further research.

Summary

An in-depth understanding of the relevant protective mechanisms against allergic disorders will open the possibility of developing novel therapeutics to prevent the allergic march worldwide.

Keywords

allergy, developing countries, helminths, immune suppression, infection intensity

Introduction

The reports [1] that atopic disorders are considerably less prevalent in developing than in industrialized countries have generated considerable interest worldwide. A full understanding of the factors that lead to the lower prevalences of allergies in some geographical areas will help us design strategies that hopefully will prevent the global allergic march. Such studies are, however, complex, not only due to the endless number of variables in terms of genetic and environmental factors, but also due to social and cultural differences that may complicate acquisition of accurate data via questionnaires [2]. Perception of wheeze is highly variable and dependent on, among other things, the phrase and language used [3]. Moreover, the question of how we should define 'asthma' in epidemiological studies is still awaiting a unified answer [4]. Questions asking for 'ever wheeze' or 'wheeze in the past 12 months' or 'doctor diagnosed asthma', as well as bronchial hyper-reactivity after exercise-induced bronchoconstriction have yielded different levels of asthma prevalence in school children in Indonesia (Wahyuni, unpublished data). Despite these obstacles, several studies have been initiated in the developing world, where lifestyle is starting to change and the situation represents the point at which the rise in allergies started in the Western world. These studies aim to describe genetic, immunologic and environmental factors associated with different prevalences of allergies. This might speed up the identification of specific risk or protective factors/mechanisms operative in allergic disorders.

Several hypotheses have been put forward to explain the rise in prevalence of allergies in the last few decades. Changes in level of pollution, exposure to allergens, dietary habits, sedentary lifestyle and exposure to infections have all been considered. All these changes take place when societies move from traditional to modern lifestyles, both in the industrialized world and within developing countries. In Africa [5–7], South America [8,9] and Asia [10–12], the prevalence of allergies is higher in urban centres, in those with high socio-economic status which have taken up a modern lifestyle, than in areas and populations that adhere to traditional ways of life. Although urban centres of the developing world are often highly polluted, the hypothesis that pollution can explain the increasing prevalence of allergic disorders has not been supported by studies carried out in East and West Germany. Prevalence of allergies in East

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Abbreviations

BHR bronchial hyper-responsiveness
HDM house dust mite
IgE immunoglobulin E

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Germany with a greater degree of pollution was considerably lower than in West Germany [13]. Although there is considerable evidence [14,15] that exposure to respirable suspended particles is involved in exacerbation of diseases such as asthma, it does not seem to be the only factor that has caused the recent rise in allergic diseases.

Differences in dietary intake and allergic disorders

Another important factor that influences allergic disorders is food intake. For example, it is thought that breast-feeding [16], intake of 3-omega fatty acids [17] as well as intake of farm milk can influence expression of allergic disorders [18]. Food allergies are becoming a serious problem in the West, with peanut allergy one of the most important ones [19]. In several African and Asian countries, however, peanut is a staple food and very few cases, if any, of peanut allergies have been reported from these areas. Food preparation and matrixes used in the food industry in the West are bound to have an important impact on the possible differences in peanut allergies seen in, for example, the United Kingdom and Ghana. Indeed, one expects to find large differences in the dietary intake of urban compared with rural residents within developing countries; however, there are, as yet, no large-scale studies of food consumption patterns that link detailed dietary intake to the prevalence of allergic disorders in, for example, Africa. In China, a recent study examined factors associated with prevalence of asthma in more than 10 000 children living in three different regions; frequent intake of raw vegetables was shown to be associated with reduced risk of wheezing [20]. The identification of molecular components in raw vegetables that drive the protective mechanisms will be of great interest.

Exposure to allergens is not the whole story

It is clear that allergen exposure and increased immunoglobulin E (IgE) production is needed for the development of allergic disorders. The multi-centre study in three regions of China [20] reported the use of foam pillows as a risk factor of current wheeze, supporting the notion that synthetic bedding might increase the extent of exposure to house dust mite (HDM) and therefore lead to increased airway inflammation. Although data were available for skin reactivity to HDM, the authors did not show the data for association between foam pillow usage and atopy. The question remains whether the so-called allergic march can be explained solely by increasing exposure to allergens. Studies conducted in the 1980s in Papua New Guinea [21] suggested that introduction of blankets in some highland communities resulted in high exposure to HDM and high prevalences of asthma; however, higher prevalences of asthma were only seen in adults and not in children. The children, who presumably were also exposed to HDM in the same house-

holds, seemed to be protected from developing asthma by environmental factors; it is these factors that we are now seeking to identify by studying allergic disorders in developing countries. In more recent studies [18], in which lower prevalences of allergies were reported in traditional farming families or in rural areas of developing countries [22,23], exposure to allergens did not seem to explain the differences recorded in allergic disorders: in homes of traditional farmers, high concentrations of HDM were found with low sensitization rates [24]; in rural and urban areas of Ethiopia, differences in exposure to Derp 1 could not explain skin prick test positivity to HDM [25]. Thus, although use of carpets and mattresses is associated with increasing prevalence of allergies to house dust mite [26], sensitization to HDM can be prevented by unknown environmental factors [18]. Moreover, when we consider outdoor allergens, which would not be expected to change with lifestyle, increasing sensitization to birch and grass was reported over the last 11-year period in Greenlanders [27]. This indicates that the immune system of Inuits is now reacting differently when it encounters an allergen than a decade ago. Taken together, there is much evidence that would argue against the theory that increasing exposure to allergens is the only factor that would explain differences in prevalence of allergic disorders or the rise in allergies worldwide.

Infections/microbial exposure in population studies

One of the major factors that might explain the geographical variations in prevalence of allergies is the extent of exposure to viruses, bacteria and parasites. Indeed, advances in indoor plumbing, less crowded living conditions, infrequent contact with livestock and mud, and an increase in antibiotic use might have decreased our contact with microbes and pathogens in the twentieth century. Altogether, these observations have led to the conclusion of an inverse relationship between exposure to microbes/pathogens and the development of allergies, and the promulgation of the hygiene hypothesis to explain the increase in atopic diseases. Substantiating this hypothesis, however, has proven difficult [28].

Recent epidemiological studies [29], which are questionnaire-based, have reported high prevalences of allergic disorders from Brazil, where about 20% of the population was reported to have asthma. A more extended ISAAC questionnaire used in Latin America [30] showed the prevalence of 'asthma ever', to range from 5.5 to 28%. The authors concluded that in areas in which infections are rampant, there does not seem to be any protection from allergies. A number of issues need to be resolved before it is concluded that these studies dismiss the hypothesis of a negative association between microbial exposure and allergies. First, the study [30] was questionnaire-based and

therefore highly culture sensitive. Secondly, there is often no indication on whether the study was conducted in urban or rural areas. Thirdly, no measurements of exposure to infections or presence of infections were reported. It is therefore too early to conclude that there are no negative associations between infections and allergies from such ecological studies. In the same continent, researchers who have measured the actual presence of infections in the communities studied have reported [31] that *Ascaris lumbricoides* and hookworm infections protect against atopy and exercise-induced wheeze. Another study from South America [32] reported that asthma is less severe in children infected with *Schistosoma mansoni*. Recently, the same group has studied the immunological reactions of patients with mild asthma, infected with *Schistosoma mansoni*, with reactions of patients with more severe asthma and free of helminth infections. They found that helminth-infected mild asthmatics produce higher interleukin 10 (IL-10) in response to *D. pteronyssinus* antigen alongside lower Th2 responses than severe uninfected asthmatics [33[•]]. Unfortunately, the uninfected asthmatics originated from a different area; although a serious confounder, this problem is understandable when prevalence of infections in the study area is high, making it impossible to find uninfected subjects.

There have also been recent studies in Asia that have examined the relationship between parasitic infections and allergies. A large study [34] conducted in the rural area of Anqing province in China documented an increased risk of asthma as well as skin prick test positivity to allergens in children with *Ascaris lumbricoides* infections. In this area, the prevalence of ascaris infections (history of or current stool positivity) was only 24.6%, which is considerably lower than has been reported in areas where a negative association was found between this infection and allergic disorders: 63.4% in Ecuador [35] or 74% in Gabon [36]. It is also important to note that the history of ascaris infection used in the Chinese study [34] has a high likelihood of generating inaccurate results. To ask the study subjects the question of whether they have had helminth infections in the past is likely to result in many misclassified individuals into ascaris-positive or negative individuals. It is important to try and obtain data on the actual presence of the worms and intensity of infections by parasitological examination of stool samples.

In a study completed in Indonesia, children from a school where high intensity of intestinal helminths was found in 92% of the pupils were compared with children from another school where light infections were detected in 23% of the pupils. The prevalence of skin prick test positivity to environmental allergens was 5.7 and 16.4%, respectively, and the presence of helminth infection was

not protective against atopy in the school with light infections (Wahyuni, unpublished data). These findings suggest that intensity of helminth infections might be an important factor in whether allergic disorders are suppressed by helminths or not.

Finally, recent publications from Africa report somewhat inconsistent findings. In a case-control study carried out in Ethiopia [37], the association between parasitic infections and atopic dermatitis was investigated and it was reported that intestinal helminth infections, in particular *Trichuris*, increased the risk of atopic dermatitis. In addition, the history of malaria infection was a significant risk factor for development of atopic dermatitis. The case definition determined by the ISAAC questionnaire, however, might have been problematic, as acknowledged by the authors. More than 60% of atopic dermatitis cases were not atopic to the allergens tested. Further studies are needed to firmly establish the association between atopic dermatitis and parasitic infections.

A relatively small-scale randomized placebo-controlled anti-helminth treatment trial in Gabonese school children [38] has shown that a reduction in *Ascaris* and *Trichuris* worm burdens results in a significant increase in the rate of developing skin reactivity to house dust mite. This study is in agreement with the findings by Lynch and co-workers [39], suggesting that helminth infections contribute to the lower prevalence of atopy in tropical populations. It would be preferable to use parasitological measurements of infection.

With respect to airway allergies, studies in South Africa [7] have indicated that there has been a dramatic increase in bronchial hyper-responsiveness (BHR) over the last two decades, with no current association between atopy and BHR. In this study, the authors concluded that *Ascaris* infection had no modifying effect on BHR; however, they had only measured serological responsiveness to *Ascaris*, which has a relatively poor specificity and specificity as a marker of infection.

In a large cross-sectional study conducted in the rural area of Butajira in Ethiopia by Britton and co-workers [40[•]], no evidence of a protective effect of intestinal helminth infections against wheeze or asthma was found – a finding that seems to contradict their previous data obtained in Jimma, another rural area in Ethiopia [41]. It was noted that, in Butajira, the prevalence and intensity of helminth infections were lower (33.8%) than the prevalences found in Jimma (77.3%). So, again in Butajira [40[•]], lower prevalences of *Ascaris* infections, which would predict light infections, did not protect against allergies, emphasizing the possible importance of intensity of helminth infections in modulating allergic responses [42]. Indeed, it has been argued that high

intensity of helminth infections might be associated with protection, whereas light helminth infections might exacerbate allergic disorders [43]. The mechanisms behind this are purely speculative; with light infections, helminth-associated molecules that drive Th2 responses might potentiate IL-4, IL-13 and IgE, whereas only with heavy infections, molecules that lead to regulatory immune responses might reach a sufficient level to modulate the immune system and downregulate Th2 responses [44].

Studies in Europe [45] have reported that *Toxocara* seropositivity is a risk factor for allergic asthma, as is exposure to the fish nematode, *Anisakis simplex* [46]. Both *Toxocara* and *Anisakis* are accidental infections and occur infrequently; thus, it is possible that the immune system would be exposed to readily available Th2-inducing molecules of these helminths but not to the immunomodulatory molecules that would be released upon frequent and chronic parasitism [42].

A group of investigators in the United Kingdom [47] intends to start a clinical trial to treat rhinitis patients with hookworm larvae. The results of this trial are eagerly awaited and hopefully will teach us whether light hookworm infections have a beneficial effect on allergic parameters.

Altogether, reports where association between helminth infections and allergic disorders are studied, present conflicting results. Trials that use helminths to prevent inflammatory disorders or prospective studies with anti-helminth treatment will give us the definitive answer to the question of whether helminths protect against inflammatory disorders such as allergies.

Infections/microbial exposure in animal models

The epidemiological studies have triggered much interest among immunologists working on animal models of allergy. Several studies in animal models have also supported the notion that helminth infections can suppress allergic reactions. Bashir and colleagues [48] have demonstrated that both allergen-specific IgE and IL-13 production to peanut is downmodulated by infection with the nematode *Heligmosomoides polygyrus*, which is a natural helminth infection in the mouse. When animals were treated with anti-IL-10, allergen-specific Th2 responses were no longer suppressed. Another set of studies with the same parasite but in an allergic airway inflammation model [49] have indicated that this helminth infection results in a strong reduction in OVA-driven eosinophilic airway inflammation. Several other helminth infections have been shown to inhibit airway inflammation. Mice infected with *Schistosoma*

mansoni show a clear infection intensity-dependent decrease in eosinophilic inflammation (Smits, unpublished results). *Nippostrongylus Brasiliensis* is also able to inhibit lung inflammation [50[•]] – a finding that was also reported with *Ascaris suum* extract implants, which inhibited lung inflammation and airway hyper-responsiveness [51]. Although in the *N. brasiliensis* study [50[•]], infection in IL-10-deficient mice significantly increased allergen-induced airway eosinophilia and other inflammatory parameters compared with control mice, in the *H. polygyrus* model [48], it was clear that suppressive activity of helminth infections on airway inflammation was not mediated by IL-10. Thus, the regulatory mechanisms whereby helminths suppress allergic disorders might be diverse and need further detailed characterization.

In a slightly different model of allergic reactivity [52^{••}] – systemic anaphylaxis to penicillin V – infection with *Schistosoma mansoni* was shown to protect mice from this extreme allergic response. The protection was not mediated by CD25⁺ T-cells or F4/80+ macrophages that have often been considered as the regulatory cells suppressing disease in various models [53,54]. In this anaphylactic model [52^{••}], it was the IL-10-producing B-cells that prevented fatal anaphylaxis, indicating that schistosome infections induce regulatory B-cells that can suppress allergic hypersensitivity reactions.

It has to be noted that there are also a number of studies in animal models [55,56] which show no/slight effect of helminth infections on T-cell cytokine responses or on eosinophilic airway inflammation, and variable outcomes with airway hyper-responsiveness allergen-specific IgE production, but no decrease in the ultimate eosinophilic airway inflammation. Again, this could reflect the difference between the acute and the chronic phase of infection, the species studied and dose. Well controlled, possibly multi-laboratory, studies may be able to resolve these inconsistencies.

Conclusion

Taken together, it is clear that the interplay between helminth infections and allergies is complex; however, as already commented by John Britton [57], it is important not to 'miss seeing the wood for the trees'. Future studies need to concentrate on determining the protective thresholds for helminth infections and the immunological mechanisms behind such threshold effects. Also, it is important to conduct such studies specifically for different species of helminths, as these multi-cellular and elaborate organisms may show distinct interactions with the immune system. Needless to say, the ultimate answer will only come from prospective intervention studies in endemic areas.

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