Allergic diseases and helminth infections

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The relationships between allergic diseases and helminth infections are inconsistent. Some studies have suggested that helminth infections induce or increase the severity of atopic diseases. Other studies report that children infected with some helminths have lower prevalence and milder atopic symptoms. Expanding our knowledge on the mechanism of immunological modification as a result of helminth infection, and understanding the interaction between helminth infections and allergic diseases will be useful for developing potentially new treatments using some helminths, and for evaluating the risks and benefits of eradicating helminth infections in endemic areas. This article reviews current knowledge on the mechanisms of allergic disease, the immunological modifications that result from helminth infections, and clinical evidence of the effects of these infections on allergic diseases.

Keywords: Helminth, Geohelminth, Allergy, Hygiene hypothesis

Introduction

The prevalence of allergic diseases is high in industrialized and developed countries.¹ It is also increasing in developing and urbanizing regions.^{2,3} Inversely, soil-transmitted helminths, or geohelminths, are frequently found in developing tropical countries, especially in tropical rural areas.⁴ This could be explained by the ‘hygiene hypothesis’, whereby people in developed countries have less exposure to microbial infections — bacteria, viruses, and helminths — causing abnormal natural immune development, and finally resulting in higher incidence of allergy compared to people in developing countries. In addition, some authors also point to the modification of the allergy pathway induced by helminth infections.^{5,6}

The relationship between helminths and allergic disease can be separated into two groups: reactions against helminths resembling allergy, and allergic diseases influenced by helminth infection. The reactions against helminths resembling allergy are reactions induced by human defense mechanisms directly against the antigens of helminths. For example, Loeffler’s syndrome is caused by *Ascaris* larvae moving through the lungs, leading to symptoms resembling asthma.⁷ The allergic diseases influenced by helminth infection are modifications of allergic diseases either changing in incidence or severity that are associated with helminth infection. Many studies have shown that the prevalence of these diseases, or

reactions to them, decrease in association with helminth infections.^{8–10}

Allergies and Allergic Reactions

An allergy is a hypersensitivity reaction to stimuli (allergens) which are normally not harmful to the body. Allergic reactions are complex interactions between genetic predisposition and environmental exposure causing inflammation. Common allergic diseases include allergic rhinitis or rhinoconjunctivitis, asthma, atopic dermatitis (AD), and food allergy.¹¹ The main mechanism of allergy is the abnormal development of T cells into T-helper2 cells (T_H2), which increases activation of IgE, mast cells, and eosinophils. The inflammatory process in allergic disease starts from mast-cell degranulation and release of mediators that activate inflammatory cells — eosinophils, monocytes, and neutrophils. These cells consequently release cytokines which then affect specific organs. One example is interleukin-13 (IL-13) in the bronchi of asthmatic patients; it stimulates goblet cells to produce tumor necrosis factor-alpha (TNF-alpha), which causes spasms of the bronchial smooth muscles.¹²

The prevalence of allergic disease is increasing, and it has become an important health problem in developed countries. One study in Scotland reported asthma prevalence rates of 10% in 1964, 20% in 1989, and 28% in 1999.¹ The prevalence of asthma is also increasing in developing countries. A study from Thailand in 1998 showed asthma, allergic rhinitis, and AD prevalence to be 12.7–18.3, 38.7–44.2, and 14.0–15.4%, respectively.² This study also compared the prevalence of atopic diseases with previous

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studies, and concluded that the prevalence of asthma and allergic rhinitis had increased, but the prevalence of AD was more or less the same. It is worth noting that the prevalence of allergic diseases in rural areas is still not very high, especially in developing countries.³

Helminth Infection and Immune Response

The most common helminth infections worldwide are soil-transmitted helminths, or geohelminths, like *Ascaris* spp., *Trichuris* spp., and hookworms, which are very prevalent among children in rural tropical regions — areas which often have poor sanitation.⁴ Some helminth infections are found only in particular regions of certain countries. For example, filaria (*Wuchereria bancrofti* and *Brugia malayi*) are found in Southeast Asia, and *Schistosoma* spp. (*S. haematobium*, *S. mansoni*, and *S. japonicum*) in sub-Saharan Africa/South America and East Asia.

Helminth infections stimulate an immune-system reaction via a T_H2 immune response, with an increase in IgE, eosinophils, and mast cells, as in an allergic reaction. But the T-cell response in helminth infections is a modified type 2 immune response, which induces T-cell hypo-responsiveness, such as T-cell anergy and an increase in regulatory T cells. This response leads to an increase in IL-10, and the production of transforming growth factor-beta and parasite-specific IgG and IgG4, which do not induce allergic inflammation like an atopic immune response⁵ (Table 1).

The innate immune system also affects T_H2 immune response against helminth infection. A study on innate immune cells revealed that intestinal epithelial cells, dendritic cells (DCs), and alternatively activated macrophages can regulate T_H2 immune response against helminths. Intestinal epithelial cells are major sources of IL-25 and IL-33 which promote T_H2 cytokine production and eradicate worms. DCs activate T_H2 differentiation and response. Alternatively activated macrophages are hallmarks of helminth-mediated inflammation and stimulate T_H2 cell function.¹³ One recent study demonstrated an epithelial cell-derived repair molecule named 'TFF2' (trefoil factor2) which influences T_H2 cytokine production and promotes IL-33, a T_H2 cytokine produced by lung

epithelia, alveolar macrophages, and DC after hookworm infection in mice.¹⁴

Reaction against Helminths Resembling Allergy

The reaction against helminths is mediated via increased IgE, tissue eosinophils, mastocytes, and $CD4^+$ T cells, which produce T_H2 cytokines (IL-4, IL-5, and IL-13). This reaction is the body's response to destroy helminths,⁵ especially tissue helminths that stimulate an excessive T_H2 response, e.g. T_H2 granuloma occurring around *Schistosoma* spp. eggs in the bowel wall.¹⁵ The migration of helminths from one organ to another induces a body reaction with clinical symptoms resembling allergic disease, such as Loeffler's syndrome, which occurs during the movement of *Ascaris lumbricoides* larvae through the lungs; this causes symptoms similar to asthma. Larvae of zoonotic helminths, such as *Toxocara* spp. and dog hookworm, cannot complete the mature stage in humans. However, they can remain in human tissues for a long time. Their tissue migration induces reactions along the movement track, in both the skin and internal organs.¹⁶ The diseases caused by these reactions are described in Table 2.⁷

Mechanisms of Helminth Infection that Influence Allergy

The rising prevalence of allergic diseases in developed countries can be explained by the 'hygiene hypothesis', which states that a lack of early childhood exposure to infectious agents, including parasitic infections, suppresses the natural development of the immune system in T_H1 polarization, increases T_H2 polarization, and results in an increased incidence of allergic diseases.^{5,17} This can also be explained by the cause and effect theory by Hill in 1965.¹⁸ In endemic areas, helminth infection in early childhood stimulates strong regulatory immunological effects. Allergen exposure among children not exposed to helminth infections in early life will induce allergic phenotypes. As a result, these children may develop allergic diseases, mediated by an increase in T_H2 and T_H2 cytokines, a decrease in T_H1 , and an excessive decrease in T-reg and other IL-10-producing cells. T_H2 cytokines induce production of allergen-specific IgE, eosinophils, mast cells, and basophils that

Table 1 Comparison between allergen T_H2 response and modified T_H2 response

Immune effects	T_H2 allergic response	Helminth infection (modified T_H2 response)
IL-10	↑	↑ ↑ ↑
IL-5	↑ ↑ ↑	↑
IL-4	↑ ↑ ↑	↑ ↑ ↑ ↑
IL-13	↑ ↑ ↑	↑ ↑ ↑ ↑
IgE	↑ ↑ ↑	↑ ↑ ↑ ↑
IgG ₄	↑	↑ ↑ ↑

Notes: T_H2 , T-helper2; IL, interleukin.
Adapted from Ref. 5.

Figure 1 Helminth infection and allergic response. Adapted from Ref. 5.

mediate the allergic inflammatory response. However, the development of allergic response in some children may not relate to helminth infection (Fig. 1).

On the other hand, it is worth considering the argument that an increase in the incidence of allergies is actually a result of increased exposure to poisonous substances and pollutants, not decreased exposure to microbial agents. Urban people living close to high traffic regions would expose to pollutant which precipitates type I hypersensitivity reaction, destroys T_H1 and T_H2 balance, and increases risk of allergic diseases especially asthma.¹⁹ The diesel vehicles increase diesel exhaust particle (DEP). A study revealed that DEP exposure in humans accelerated T_H2 cytokine production, reduced T_H1 cytokine production, and led to increased allergic reactivity.²⁰ Toxicants from traffic such as lead, mercury,

benzene, and DEP decrease glutathione storage and lead to increased T_H2 dominance. These chemical pollutants also accelerate allergic reaction after DEP exposure.¹⁹ Recent studies also suggest that helminth infections may be linked to rising and falling prevalence rates of allergic diseases.^{8–10}

Clinical Evidence of the Relationship between Helminth Infections and Allergies

Helminths that have been shown to have a significant relationship with allergic diseases include *Ascaris lumbricoides* (*A. lumbricoides*), hookworm (*Ancylostoma duodenale* and *Necator americanus*), and *Trichuris trichiura* (*T. trichiura*).

Ascaris lumbricoides (*A. lumbricoides*)

Some *Ascaris*-infected patients were found to have a decrease in skin-test reactivity to at least one allergen.

Table 2 Helminthic reactions resembling allergic diseases

Helminths	Reactions
1. Intestinal helminths	
<i>Ascaris lumbricoides</i>	Loeffler's syndrome
<i>Trichuris trichiura</i>	Tropical dysentery syndrome
Hookworm	Ground-itch/allergic enteritis
<i>Strongyloides stercoralis</i>	Larva currens/urticarial/'asthma-like' syndrome
<i>Enterobius vermicularis</i>	Itchy burn
2. Schistosomiasis	
<i>Schistosoma</i> spp.	Cercarial dermatitis/urticaria/'asthma-like' syndrome
3. Filariasis	
<i>Wuchereria bancrofti</i>	Tropical pulmonary eosinophilia
<i>Onchocerca volvulus</i>	Acute papular onchodermatitis
4. Other helminths	
<i>Toxocara</i> spp.	Viscera larva migrans/'asthma like' syndrome
<i>Anisakis</i> spp.	Gastroallergic/'asthma-like' syndrome urticaria/anaphylaxis
<i>Paragonimus</i> spp.	'Asthma-like' syndrome
<i>Echinococcus granulosus</i>	Urticaria/anaphylaxis
<i>Ancylostoma braziliense</i>	Cutaneous larva migrans

Note: Adapted from Ref. 7.

However, it was not statistically significant, especially with regard to skin-test reactivity to common allergens such as dust mites and cockroaches.^{8,21,22}

Hookworm (*Ancylostoma duodenale* and *Necator americanus*)

Hookworm infection was found to be linked to a decrease in skin-test reactivity to at least one common allergen, but this was not considered statistically significant. Studies of the relationship between hookworm infection and reduced skin-test reactivity to other allergens also showed no statistical significance.^{8,21,23} In addition, an experimental study determining effects of hookworm infection revealed that hookworm larvae in asthmatic patients did not result in significant improvement in bronchial hyperresponsiveness and asthma control.²⁴

***Trichuris trichiura* (*T. trichiura*)**

Trichuris trichiura infection is associated with a statistically significant decrease in skin-test reactivity to at least one allergen.^{8,21–23,25} Some studies, however, reported that *T. trichiura* infection actually increased skin-test reactivity to cockroaches²⁶ and dust mites^{26,27} and increased the prevalence of asthma. However, these were not statistically significant. A murine study revealed that *Trichuris* infection decreased severe allergic reaction and specific IgE against peanuts among mice fed with peanut extract plus mucosal adjuvant cholera toxin.²⁸

Other helminths

One study reported that *Schistosoma* infection significantly reduced allergic reaction, but the methodology of this study was not satisfactory.²⁹ A study on *Enterobius vermicularis* did not show any influence on allergic diseases.³⁰

Association between Allergic Diseases and Chronic Helminth Infection

Skin test

A. lumbricoides and *T. trichiura* infections since infancy have been found to be associated with a reduction in skin-test reactivity to aeroallergens in childhood.⁸ One study from children living in rural areas reported an inverse relationship between *Ascaris*-specific IgG antibodies and aeroallergen-specific IgE but no association between these specific IgG antibodies and prevalences of allergic diseases.³¹ A placebo-controlled trial in Vietnam showed that reduced helminth burden after anti-helminth therapy increased allergen skin-test sensitivity, but not allergic symptoms of wheezing, rhinitis, and eczema.³² Recently, a systematic review and meta-analysis by Feary *et al.* concluded that infection by geohelminths, especially *A. lumbricoides* and *T. trichiura*, was linked to decreased skin-test reactivity to at least one allergen.⁹

On the other hand, *Ascaris* infection diagnosed by positive stool examination or history of *Ascaris* infection was associated with increased allergic skin-test reactivity in one study.³³ Another study showed that children with *Ascaris* infection diagnosed by *Ascaris*-specific IgE increased allergic skin-test reactivity and aeroallergen-specific IgE together with significant higher prevalence of asthma and allergic rhinitis.³⁴

Asthma

A study of 7155 children on the relationship between parasitic infection and wheezing revealed that *Ascaris* infection associated with statistically significant decreased wheezing risk; hookworm infection also associated with decreased risk of wheezing but without statistical significance, and *Trichuris* infection had no relationship with wheezing.²⁶

On the other hand, some studies have reported that anti-helminthic drugs for *A. lumbricoides* decreased asthma symptoms and the medication required for it.^{35,36} A study administered albendazole 400 mg monthly for 1 year to the treatment group and found that asthma control was significantly better in treatment group than placebo group but asthma was deteriorated after 2 years of treatment.³⁶

One systematic review and meta-analysis reported that *A. lumbricoides* infection increased the prevalence of asthma; hookworm infection decreased it; and *T. trichiura* infection had no effect. Migration of *A. lumbricoides* larvae through the airway passage, and airway inflammation inducing T_H2-mediated immune response, was one proposed mechanism of increasing airway hyper-reactivity and the prevalence of asthma.³⁷

AD

Studies of soil-transmitted helminths have shown both positive³⁸ and negative¹⁰ associations with the prevalence of AD. A study in children with AD found no reduction in AD risk related to helminth infection; conversely, the AD prevalence was increased in trichuris-infected patients.³⁸ However, a survey study revealed that atopic eczema affected significantly less in children with history of helminth infection than children without any history.¹⁰ One particular study found reduced risk of AD among infants of mothers suffering perinatal helminth infection.³⁹

Role of Helminths in Allergy Treatment

Previous studies have reported that T_H2-mediated disease, such as ulcerative colitis, could be treated by eating *Trichuris suis* (*T. suis*) ova.⁴⁰ It was proposed that helminth infection induced the adaptive production of regulatory T cells and cytokines, such as IL-10 and transforming growth factor-beta.⁴¹ There was a placebo-controlled study treating grass pollen-induced allergic rhinitis with *T. suis* eggs. The result

showed no statistically significant difference in allergic rhinitis symptoms, but there was an increase in levels of IgG, IgG4, IgA, and eosinophils. Diarrhea due to helminth infection was an important side effect.⁴²

A phase I study of treatment for peanut anaphylaxis using *T. suis* ova was started following a successful study in mice;²⁸ this study is ongoing (<https://ClinicalTrials.gov>). There were also additional studies done in animals, revealing adaptation of immune regulation by way of increasing regulatory T cells in airway hyper-reactivity.^{6,43,44}

Conclusions

Even though a large number of previous studies have suggested that helminth infections may decrease allergic diseases, other studies have shown different results. Evidence from clinical trials is still not strong enough to recommend using helminths in the treatment of allergy. Further studies should be conducted, particularly on specific components of helminths that affect immune modification directly. It is still recommended that helminth infections should be controlled or treated, because they can impair health and cause serious complications.

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