Interactions between helminth parasites and allergy

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Purpose of review

To review the findings of recent human studies of the association between helminth parasite infections and allergy and discuss their potential relevance to public health.

Recent findings

Different helminth parasites may have different effects on allergy that may depend on the timing or intensity of the exposure or host genetic factors. Infections with *Trichuris trichiura* in early life are associated with a reduced prevalence of allergen skin test reactivity later in life and infants of helminth-infected mothers have been reported to have a reduced prevalence of eczema. Hookworm infection has been associated with a reduced prevalence of asthma in Ethiopia. Several studies have reported that anti-*Ascaris* IgE is an important risk factor for asthma, but this could be explained by an enhanced ability of atopics to produce IgE. *Toxocara* infections may be associated with an increased risk of wheeze in some populations that may be caused by the host response to the parasite or by parasite-enhanced Th2 responses to aeroallergens.

Summary

Although helminth infections can modulate the host inflammatory response directed against the parasite, a causal association between helminths and atopic diseases remains uncertain.

Keywords

allergy, asthma, geohelminths, helminths

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Introduction

There is a large and growing literature of the interaction between parasite infections and allergy derived from observations in humans and experimental animal models. This article will review the more recent findings from human studies of the possible relationship between parasite infections and allergy. The findings from experimental animal models have been reviewed extensively elsewhere [1•,2]. The review will focus on the findings of the interaction between helminth parasites and allergy and will not discuss studies of protozoal parasite infections such as malaria [3] and giardiasis [4] for which there are very limited data.

The allergy epidemic

The prevalence of asthma and allergic diseases has increased in high-income countries over recent decades and may have reached a peak [5]. Allergic diseases are becoming an important public health issue in many low-income and middle-income countries. Urban centres of Latin America appear to be most affected and have some of the highest reported prevalences of asthma worldwide [6,7]. The prevalence of asthma and allergic diseases appears to be low in many rural areas [8], an observation that has led to the suggestion that common environmental exposures present from an early age [9] in rural areas may be protective against allergy [10].

The hygiene hypothesis

A popular explanation for the increase in the prevalence of allergy is the hygiene hypothesis that attributes the allergy epidemic to a failure to develop appropriate immune regulation because of reduced exposures to microbes and their products in childhood [11]. There is considerable interest in the potential role of helminth infections in reducing allergy prevalence – certainly, helminth infections have strong regulatory effects, are highly prevalent, and first occur in early life in endemic areas.

Helminth parasites

The most common helminth infections are caused by geohelminth parasites (also known as intestinal and soil-transmitted helminths). Geohelminth parasites including *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm (*Ancylostoma duodenale* and *Necator americanus*), have a worldwide distribution, are estimated to infect a quarter

of the World's population [12], and are most prevalent among children living in areas of the rural Tropics with poor access to sanitation and clean water. Other important helminth infections including schistosomiasis and filariasis have a more focal distribution within endemic countries.

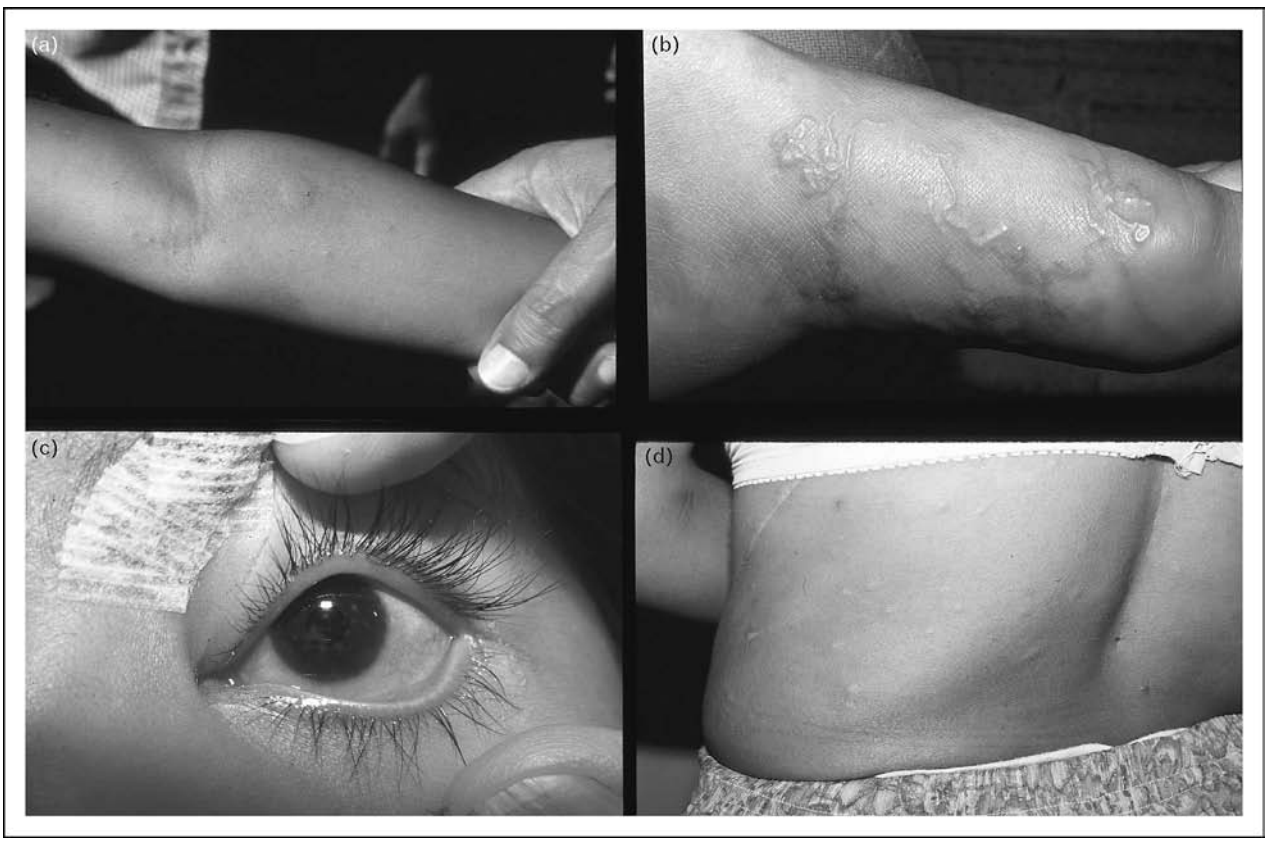
Allergic inflammation directed against helminths

The human immune response to helminth infections is associated with elevated levels of IgE, tissue eosinophilia, and mastocytosis, and the presence of CD4+ T cells that preferentially produce IL-4, IL-5, and IL-13 [1•]. Th2-associated mechanisms are considered to mediate protective immunity against these parasites [13]. Parasites in the tissues stimulate a strong localized Th2 response, characterized by an eosinophil-rich inflammatory infiltrate. A classic example is the Th2 granoluma that develops around schistosome eggs in the liver or wall of the intestine [14].

Individuals exposed to helminth infection may have allergic inflammatory responses to parasites and parasite antigens (Fig. 1). Individuals with limited exposures to helminths such as expatriates or recent migrants often develop allergic-type clinical manifestations (Table 1) [15], a probable host response to isolate and kill the parasites (Fig. 1b–d). A classic example is the asthma-like illness, Loeffler's syndrome, caused by the passage of *A. lumbricoides* larvae through the lungs. Helminth parasites in endemic areas tend to cause chronic infections – individual adult parasites may survive for many years in their human host – that are associated with few allergic-type reactions and a more tightly controlled Th2 response. Regulation of the Th2 response may be important for parasite survival and may allow the host to escape potentially damaging inflammation in the tissues.

For example, during infections with the tissue helminth, *Onchocerca volvulus*, the skin may be populated by millions of larval microfilariae and these appear to elicit little in the way of a host inflammatory response (Fig. 2a).

Figure 1 Examples of allergic-type reactions to helminth parasites



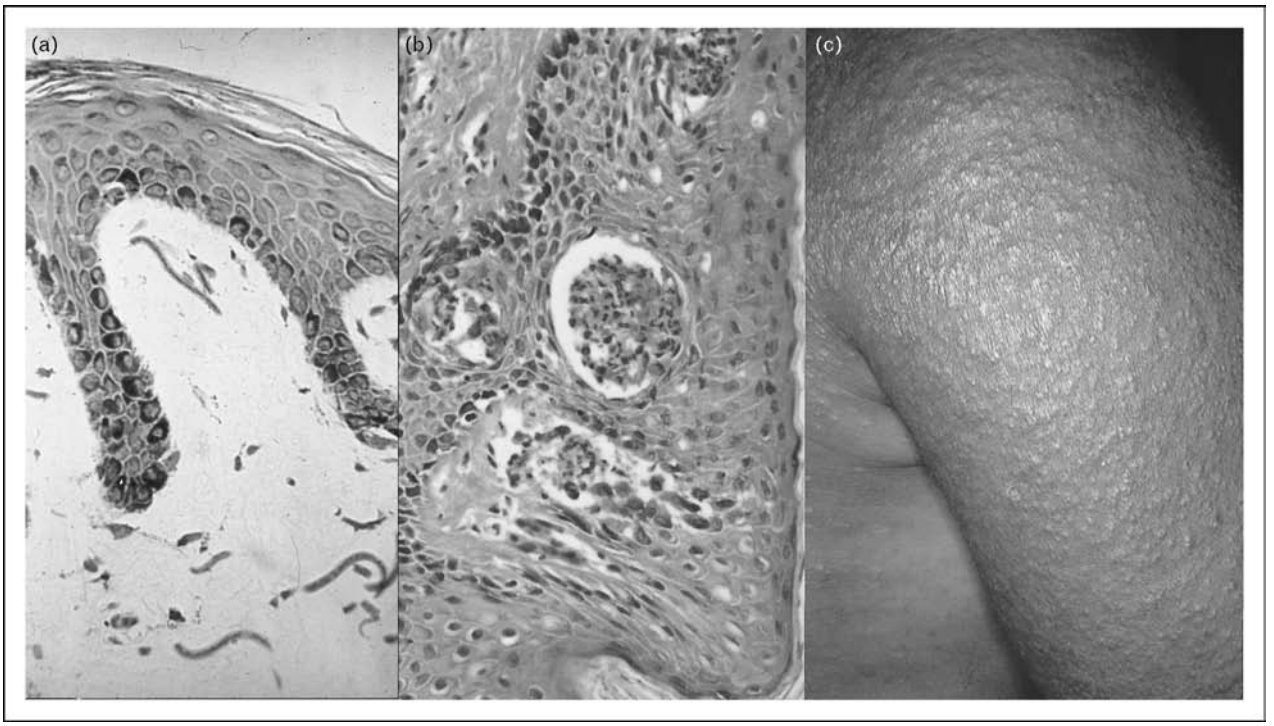
(a) Immediate hypersensitivity reaction to *Paragonimus mexicanus* antigen extract injected into the forearm of child. (b) Cutaneous larva migrans showing serpiginous track of dog hookworm larvae in foot. (c) Punctate keratitis in young child infected with *Onchocerca volvulus*. The punctate opacities are sites of microfilarial death in the cornea and are composed of eosinophil-rich inflammatory infiltrates. The photograph was taken after removal of an onchocercal nodule (surgical tape). (d) Acute papular onchodermatitis in woman infected with *O. volvulus*. Localized papular eruptions appear periodically in infected individuals representing the sites of 'spontaneous' microfilarial death.

Table 1 Allergic-type reactions associated with human helminth parasites and possible associations between helminth infections and atopic diseases

Helminth infection	Examples of allergic-type reactions and syndromes	Treatment reactions[a]	Atopic diseases
Intestinal helminths			
Ascaris lumbricoides	'Asthma-like' syndrome (Loeffler's)	No	Asthma
Trichiura trichiura	Tropical dysentery syndrome	No	No
Hookworm	Ground itch/allergic enteritis	No	Decreased asthma?
Strongyloides stercoralis	Larva currens/urticaria/'asthma-like' syndrome	No	No
Enterobius vermicularis	Itchy bum	No	Decreased allergic rhinitis?
Schistosomiasis			
S. mansoni	Cercarial dermatitis/acute schistosomiasis/	Yes[b]	Milder asthma?
S. haematobium	urticaria/'asthma-like' syndrome	Yes[b]	No
S. japonicum		Yes[b]	No
Filariasis			
Wuchereria bancrofti	Tropical pulmonary eosinophilia/acute lymphangitis	Yes	No
Onchocerca volvulus	Sowda/acute papular onchodernatitis/punctate keratitis	Yes	No
Loa loa	Calabar swellings	Yes	No
Others			
Toxocara spp.	Visceral larva migrans/'asthma-like' syndrome	No	Asthma
Anisakis spp.	'Gastroallergic'/asthma-like syndrome/urticara/anaphylaxis	No	Asthma
Paragonimus spp.	Asthma-like syndrome	No	No
Trchinella spiralis	Acute trichinosis	Yes	No
Echinococcus granulosus	Allergic reactions (e.g. urticaria) caused by cyst leakage, acute anaphylaxis associated with cyst rupture	No	No
Ancylostoma braziliense	Cutaneous larva migrans	No	No

[a] Treatment reactions are more commonly observed for tissue parasites associated with very high parasite burdens.
[b] Mild and infrequent.

Figure 2 Allergic-type inflammatory reactions to *Onchocerca volvulus* microfilariae in the skin



The figure shows effect of treatment with the microflaricidal drug diethylcarbamazine. Pretreatment skin biopsy (a) shows microfilariae in the dermis with few associated inflammatory cells. After treatment with a single dose 50 mg of diethylcarbamazine (DEC), the dead microfilariae become the focus of an intense inflammatory reaction composed of eosinophilic abscesses in the superficial dermis (b). Clinical appearance of the skin after DEC treatment (c).

This state of hyporesponsiveness may be reversed rapidly after the killing of microfilariae by chemotherapy. Treated individuals may develop allergic-type reactions (Fig. 2c) that are associated with the development of eosinophilic abscesses in the superficial dermis (Fig. 2b) within hours after treatment. The onset and severity of these reactions are associated with the release of allergic mediators such as tryptase and eosinophil degranulation products into the peripheral circulation [16]. The hyporesponsiveness associated with chronic helminth infections appears to be actively regulated and may require the presence of live parasites.

Geohelminth parasites that are confined to the intestinal lumen may be less likely to induce strong systemic immune regulation, although the tissue migratory life cycle stages of parasites such as *A. lumbricoides* may induce strong allergic reactions in infected individuals living in regions where transmission of infection is seasonal. The comparative rarity of such reactions in endemic populations with year-round transmission [17] may reflect difficulties in diagnosis or perhaps suppression of the inflammatory response.

Many zoonotic helminth infections cannot develop to maturity in the human host and the helminth larvae may migrate for prolonged periods in the tissues (Table 1). Examples are infections with *Toxocara* spp., *Ascaris suum*, and dog hookworms. Such infections cause allergic-type syndromes such as cutaneous (Fig. 1b) and visceral larva migrans [18–20]. Tissue damage is caused by allergic inflammation directed against the migrating larvae. During such infections there appears to be a failure of immune regulation probably because host and parasite have not co-evolved.

Factors determining the effects of helminths on allergy

Four factors may determine the effect of helminths on allergy: timing – the time of first infection and the duration of infection are likely to be important [21,22•]. Early and/or long-lasting (chronic) infections may be more likely to induce immune modulatory effects that suppress allergic inflammation caused by parasite and nonparasite allergens, whereas later and/or periodic infections may enhance allergy. The effect of geohelminths in suppressing atopy may be more important in the first years of life and the temporary elimination of infections later in childhood or adulthood may not affect a phenotype that is 'programmed' in infancy [21]. Intensity of infection – heavy parasite burdens may induce immune down modulation, whereas light infections may be more likely to have the opposite effect – the effects are likely to be stronger for tissue helminth infections than for geohelminth infections. Host genetics – the ability to induce specific host immune regulatory mechanisms– may be partly determined by host genetics. Individuals that are genetically susceptible to atopic disease may be more likely to develop allergic responses to helminth and nonparasite allergens and may be genetically more resistant to infection [23,24]. The parasite – different helminth parasites– may have different effects on the risk of atopy and allergic disease [25].

Association of helminths with allergic diseases

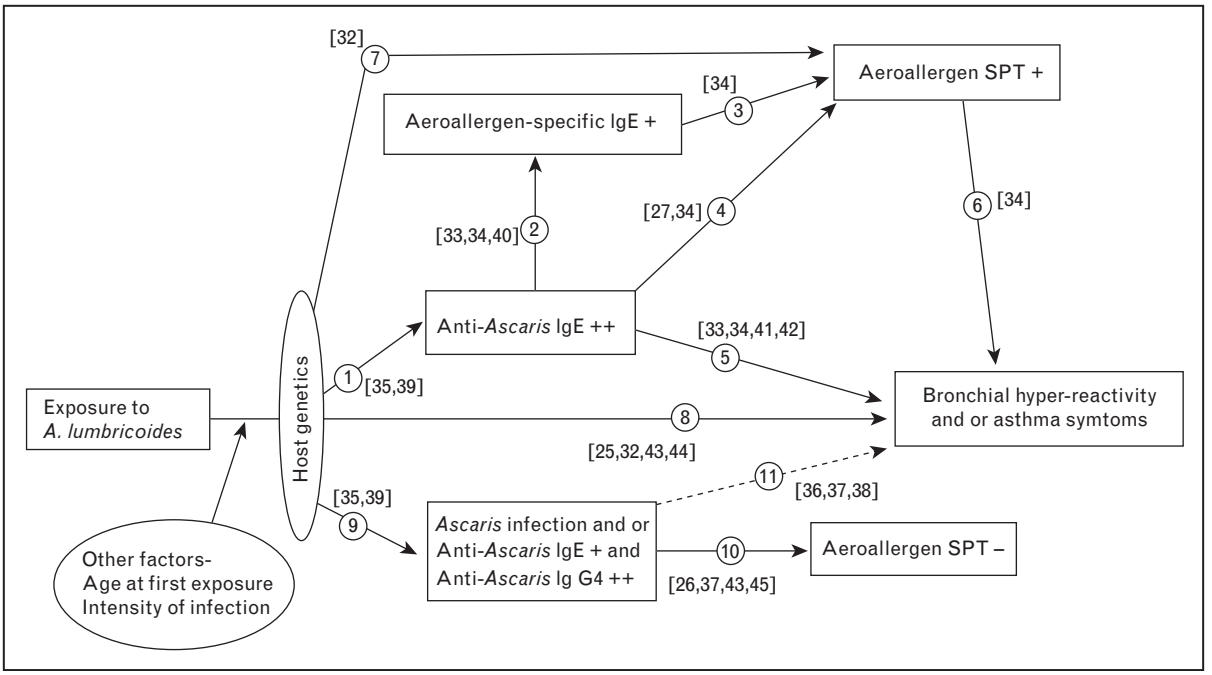
Helminth antigens stimulate allergic inflammatory responses directed against the parasite in the human host and this inflammation may be actively suppressed during chronic infection. A distinct question is whether helminth infections may also modulate allergic inflammatory responses directed against nonparasite allergens such as aeroallergens and affect allergic sensitization and the expression of allergic diseases.

Helminths and atopy

Epidemiological studies have shown inverse associations between allergen skin test reactivity and infections with *A. lumbricoides* [26,27] and *T. trichiura* [22•,26], hookworm [28], and schistosomaiasis [29,30]. Both active and past infections appear to mediate this effect. Infections with *T. trichiura* in the first years of life are associated with a reduced prevalence of allergen skin test reactivity later in childhood, independent of later infections [22•]. A study [31] of European farm children showed an inverse association between sensitization to ascariasis (measured by the presence of specific IgG antibodies) and the presence of aeroallergen-specific IgE. Not all studies, however, have shown an inverse association and some have provided evidence for positive associations between the presence of geohelminth infection [32] or *Ascaris*-specific IgE [27,33,34] and allergen skin test reactivity [27,32,34] or elevated allergen-specific IgE [33]. One study [27] showed that allergen skin test reactivity was positively associated with anti-*Ascaris* IgE and negatively associated with active *A. lumbricoides* infection. The possible relationship between atopy and *A. lumbricoides* infection is illustrated in Fig. 3 [25–27,33–45].

If helminth infections can actively suppress allergic inflammation, then anthelmintic treatment would be expected to reverse this effect. Several intervention studies have investigated this: a nonrandomized study [46] of 94 children in Venezuela provided evidence that monthly anthelmintic treatment of children for 18 months caused an increase in the prevalence of skin test reactivity to house dust mite. A randomized placebo-controlled study [47] of 165 children in Gabon showed that anthelmintic treatments every 3 months with treated the children with praziquantel and mebendazole every 3

Figure 3 Possible effects of *Ascaris lumbricoides* infection on atopy and asthma



The human response to exposure to *A. lumbricoides* is likely to be modified by host genetic factors and other factors including the intensity of infection and the age at which first infections occur. Exposure to *A. lumbricoides* could affect the development of allergen skin test reactivity in four ways (shown by paths 1–2–3, 7, 1–4, and 9–10). Pathway 9–10 represents the effect of chronic infections – a high IgG4/low IgE response to *A. lumbricoides* or modified Th2 response [1•] develops and may lead to the suppression of allergen skin test reactivity. The pathways leading from step 1 would be associated with a high IgE/low IgG4 response to *A. lumbricoides*. Pathway 7 represents the enhancement of allergen skin test reactivity by an unknown mechanism. Exposure to *A. lumbricoides* could cause or increase asthma symptoms and bronchial hyper-reactivity via enhanced allergen skin test reactivity (paths 7–6, 1–2–3–6 and 1–4–6) or be independent of allergen skin test reactivity but dependent on anti-Ascaris IgE (path 1–5), or independent of both anti-*Ascaris* IgE and allergen skin test reactivity (path 8). Suppression of asthma symptoms and or BHR could occur via path 9–11, although there is very limited evidence in support of this. Shown are published associations from cross-sectional studies and presumed causal directions (arrows). Reference numbers are shown in brackets. BHR, bronchial hyperresponsiveness. Continuous arrows show a positive effect and dotted arrows show a negative effect.

months for 30 months was associated with an increase in the incidence of skin reactivity to house dust mite. A cluster-randomized study [48] of 1632 children in Ecuador did not show an effect on allergen skin test reactivity of anthelmintic treatment given every 2 months for 12 months. The differences in the findings of these intervention studies may be explained by differences in the period of anthelmintic treatment, different parasites, parasite prevalence, and selection bias and uncontrolled confounding [21]. It would, however, appear unlikely that protection against allergen skin test reactivity is mediated by any single environmental exposure.

Helminths and asthma

A meta-analysis [25] of many of studies investigating the association between the presence of geohelminth eggs in stool samples and asthma provided some evidence for parasite-specific effects; *A. lumbricoides* was associated with an increased prevalence of asthma, *T. trichiura* with no effect, and hookworm with a reduced prevalence of asthma. All hookworm studies were conducted in Ethiopia and replication in other geographic regions is important.

Ascariasis may contribute to an increased risk of asthma either by causing directly inflammation in the airways (i.e. migrating larvae) or through increased atopy [34] and Th2 inflammatory responses in the airways. Studies investigating the association between the presence of anti-*Ascaris* IgE and asthma or bronchial hyperresponsiveness (BHR) have shown a strong positive association [34,41] that may be independent of endemicity and the presence of active infection (i.e. *A. lumbricoides* eggs in stool samples) [27,33,41]. Studies in urban Brazil have shown positive associations between *A. lumbricoides* infection and recent wheeze [43,49] and BHR [44]. The capacity to produce high levels of IgE on exposure to *A. lumbricoides* infection might simply be explained by a greater capacity to produce IgE on allergen exposure by (genetically susceptible) atopic children [50]. A study in Venezuela showed that the presence of atopy to *Ascaris* (elevated specific IgE and skin test reactivity) was an important risk factor for BHR in rural children but not in urban children in whom BHR was associated with atopy to house dust mite [42]. This could reflect a shift in the dominant allergen exposures to which children with atopic asthma are exposed [42]. The presence of anti-*Ascaris* IgE in asthmatics in Costa Rica has

been associated with asthma severity and morbidity [34]. Monthly treatments of children with anthelmintic drugs in Venezuela may reduce BHR [46], symptoms of wheeze and the need for asthma medications [51]. The possible relationship between exposures to *A. lumbricoides* and asthma and BHR is illustrated in Fig. 3.

An alternative explanation for the association between elevated *Ascaris*-specific IgE and asthma is infections with other common ascarid worms such as toxocariasis – antigen preparations from both worms show a high degree of immunological cross-reactivity. Toxocariasis is associated with asthma-like symptoms in children with visceral larva migrans [18] and there is some evidence that *Toxocar*a may be an important risk factor for asthma in some populations [52,53]. Whether such asthma symptoms are caused directly by the parasite or by Th2 adjuvant effects of parasite antigens on responses to aeroallergens is not clear.

Other zoonotic infections associated with asthma and that may be an important risk factor in some populations or high-risk groups is *Anisakis simplex*. Anisakiasis is caused by the ingestion of live L3 larvae in inadequately cooked seafood or perhaps exposure to *Anisakis* proteins [54], and is considered to be an important cause of food allergy and BHR in Spain and Japan [55].

Helminths and eczema

Recent studies have shown both positive [56] and negative [45,57] associations between geohelminth infection and the prevalence of eczema [45,57]. A small intervention study in Uganda showed that infants of mothers with helminth infection at the time of delivery had a reduced risk of eczema compared with those born of uninfected mothers, and also a nonsignificant trend of a reduced risk of subsequent atopic dermatitis in the offspring of the mothers given anthelmintic treatment during pregnancy [58].

Immunological mechanisms of helminth-mediated modulation of allergy

Helminth parasites could affect allergic inflammation in three ways:

(1) By enhancing or suppressing allergic inflammation directed against the parasite.
Chronic helminth infections of humans suppress antiparasite immune responses through regulatory immune cells such as regulatory T cells and alternatively activated macrophages and mechanisms that include the production of immune modulatory cytokines such as IL-10 and TGF-β [59].
(2) Through immunological cross-reactivity between helminth allergens and aeroallergens.
Important allergens such as tropomyosin of helminth parasites and invertebrates demonstrate immunological cross-reactivity [60]. A recent study [61•] of patients infected with *A. lumbricoides* and asthmatics sensitized to American cockroach showed that although IgE antibodies from both groups were cross-reactive for American cockroach and *A. lumbricoides* tropomyosin, the cross-reactive IgE did not appear to be clinically relevant – none of the patients with ascariasis had a positive skin test for American cockroach and none of the cockroach-sensitized asthmatic patient had ascariasis.
(3) By affecting allergic inflammation directed against aeroallergens through bystander effects in the same tissues such as the lungs.

Helminth infections may contribute to 'immune homeostasis'. Early-life exposures in particular could have important long-term effects [21]. Immune homeostatic mechanisms affected might include the production of baseline levels of regulatory cytokines (e.g. IL-10) by immune cells in the tissues that could raise the thresholds for the induction of effector cell responses to aeroallergens. A study of children infected in Cameroon provided some evidence for elevated production of IL-10 and TGF-β1 by unstimulated peripheral blood leukocytes (PBLs) that was associated positively with geohelminth parasite burden and inversely with immune reactivity [62•]. Regulatory homeostasis may be expected to be insensitive to short-term fluctuations in parasite burdens (e.g. single-dose anthelmintic treatment) but could be 'reset' by long-term changes in parasite levels (e.g. increases in parasite burdens or repeated anthelmintic treatments). Single anthelmintic treatments for geohelminth infections do not affect cytokine responses to parasite antigen [63,64], but repeated doses over prolonged periods caused an increase in Th2 cytokine responses of PBLs from Ecuadorian children [65]. Long-term anthelmintic treatment did not affect cytokine responses to aeroallergens indicating that the suppressive effect was specific for antiparasite responses [65].

Bystander suppression may be also a more active process that requires the continued presence of the parasite. Active immune regulation may be mediated through mechanisms such as the direct suppressive effects of parasite secretions and parasite-specific regulatory immune cells in the tissues. Such suppression may be reversed rapidly after anthelmintic treatment or parasite death and appears to be an important survival mechanism for tissue helminth parasites. Such suppression may also affect immunity to aeroallergens and could explain the observation of an inverse association between the production of parasite–antigen-induced IL-10 by PBLs and skin test reactivity to house dust mite among children from Gabon living an endemic area for *S. mansoni* [30].

Further, a study [66] in Brazil that compared asthmatics infected with *S. mansoni* and those not infected (albeit from a different population) showed that *D. pteronyssinus*-stimulated PBLs from infected asthmatics produced fewer Th2 cytokines and more IL-10 compared with controls. However, studies conducted in areas where *A. lumbricoides* is the predominant helminth have not provided evidence for either enhanced IL-10 responses to aeroallergens [67,68] or an increase in the frequency of regulatory T cell populations induced by aeroallergen stimulation of PBLs [68].

Public health importance of parasite–allergy interactions

Helminth infections cause significant morbidity in endemic countries and treatment programmes for a number of these diseases are being implemented as a public health priority. Helminth parasites are presumed to be protective against allergic diseases [1•,21] and there is some concern that treatment programmes, by controlling helminth parasites [48], may increase the prevalence of allergy among rural populations in which atopic diseases are considered to be relatively rare [8]. However, there is no compelling evidence that helminths protect against atopic diseases or that the treatment of endemic populations increases the prevalence of these [21,46,48]. Anthelmintic treatment may increase the prevalence of allergen skin test reactivity in some studies [46,47], but the public health relevance of this is not clear – only a small proportion (~11%) of asthma may be attributable to allergen skin test reactivity in some areas of Latin America [7,69•]. Further, ascariasis and toxocariasis may be important risk factors for asthma in some populations [34,41,43,44,46,52,53], and therefore, anthelmintic treatment programmes may have beneficial effects. Early exposures to parasites such as geohelminth infections may contribute to programming of immune homeostasis and the long-term effects of anthelmintic treatment programmes in endemic populations on public health (i.e. inflammatory diseases) remains to be established. There is some evidence that hookworm infection may protect against asthma in Ethiopia [25] and clinical studies of experimental infections with hookworm in individuals with atopic diseases are in progress [70]. Helminth infections produce powerful modulators of the host inflammatory response that protect them against killing or expulsion by the host. The identification of these factors and an understanding of the mechanisms by which they work may lead to the development of novel anti-inflammatory treatments.

Conclusion

Helminth infections have strong modulatory effects on antiparasite inflammatory responses in the human host but it is not clear if helminths can affect allergic inflammatory responses to aeroallergens. Helminth infections have been associated with both a reduced prevalence and increased prevalence of atopy and atopic disease in different populations. The immune regulatory effects of tissue helminths are likely to be stronger than those of geohelminths. Further research in prospective observational and intervention studies is required to address the question of causality. An understanding of the mechanisms by which helminth parasites modulate the host allergic inflammatory response may lead to the development of novel anti-inflammatory interventions. The demonstration of a causal association between some helminth parasites (particularly geohelminths and toxocariasis that have a worldwide distribution) and an increased risk of asthma could lead to anthelmintic treatment programmes in populations considered to be at high risk.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 82).

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