

Review Article

Intestinal worms and human allergy

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SUMMARY

The immunoepidemiological interactions between intestinal worm (or geohelminth) infections and allergy are of great interest to parasitologists, immunologists, and allergists because of the close similarities between the human immune response to geohelminth parasites and environmental allergens. Allergic diseases appear to be most rare in populations living in the rural tropics with high rates of infection with geohelminth parasites, and this has led to suggestions that the relationship between geohelminth infections and allergy may be causal. Allergic sensitization and disease results from a complex interaction between environmental exposures and genetic background, and the numerous epidemiological studies that have investigated the relationship between allergy and geohelminth infections have provided conflicting findings. The strongest epidemiological evidence for a causal association is provided by intervention studies that demonstrate evidence for an effect of anthelmintic treatment on atopy or asthma risk. There is evidence also for an inverse relationship between geohelminth infection and either atopy or asthma symptoms from cross-sectional studies that have been conducted in areas of high infection prevalence. Chronic geohelminth infections could affect allergy risk by modulation of the immune response to environmental allergens, and an area of great research activity at present is the investigation of the role of regulatory T cells in modulating host inflammatory responses. However, a causal association between geohelminth infections and allergy remains to be proven, and prospective and intervention studies are required that investigate the development of allergy in early life at a time when humans are first exposed to geohelminth parasites and their antigens.

Keywords allergy, atopy, geohelminths, immune tolerance, intestinal helminths

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INTRODUCTION

Intestinal worm (or geohelminth) infections are a major enteric pathogen of children in many regions of the World, and first infections occur in infancy and may persist into adulthood through repeated infectious exposures to a faecally contaminated environment. The most prevalent of geohelminth infections are those caused by infections with *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm (*Ancylostoma duodenale* and *Necator americanus*), and infect an estimated 2 billion humans (1). Infection with pinworm, *Enterobius vermicularis*, remains a universal enteric helminth infection of childhood in non-industrialized countries and persists, although with a declining prevalence, as an infection of childhood in industrialized countries (2,3). The classic geohelminth parasites (*A. lumbricoides*, *T. trichiura*, hookworm, and *Strongyloides stercoralis*) cause chronic infections in regions where these infections are endemic.

In contrast to intestinal worm infection, allergic disease appears to be of low prevalence in many less-developed regions of the world but is the commonest cause of chronic disease of childhood in industrialized countries (4,5) – up to one-third of the UK population will develop allergy at some time in their lives (6). Allergic disease appears to be becoming an increasingly important cause of morbidity in rapidly developing and urbanizing populations in non-industrialized countries (7,8). The inverse association between parasitic infections including geohelminths and allergy has led to suggestions of a causal association – that intestinal worms and other parasitic infections may provide protection against the development of allergic disease. This has been the subject of numerous epidemiological studies that have shown contradictory findings (9–17).

The relationship between allergy and helminth infections is not only of interest to epidemiologists but has intrigued immunologists for many years, because of the close parallels between the allergic inflammation caused by the host immune responses to environmental allergens and that caused by parasite antigens: both are associated with high levels of

IgE, tissue eosinophilia and mastocytosis, mucus hypersecretion, and T cells that preferentially secrete Th2 cytokines (IL-4, IL-5, and IL-13) (18,19).

This review will focus on the epidemiological evidence for a causal association between intestinal helminth infections and human allergy, will attempt to put the potential role of geohelminth infections on allergy risk into context by discussion of other important factors that contribute to the development of allergy, and will discuss the role of tolerance in the modulation of allergic inflammation by geohelminth parasites.

WHAT IS ALLERGY?

In this review the word 'allergy' will be used to refer to an allergic predisposition (atopy) that may or may not coexist with allergic disease. Human allergic disease follows allergic inflammation that may affect different organs manifesting as asthma, allergic rhinoconjunctivitis (rhinitis), atopic dermatitis/eczema and food allergy. Allergic disease is strongly associated with atopy (20), although there is evidence for a disassociation between atopy and allergic disease in some regions of the tropics (17,21,22) and in rural agriculture-based populations in Europe (23).

Atopy has been defined by elevated levels of total IgE, the presence of IgE specific for common environmental allergens (generally defined with a cut-off of greater than 0.35 kU/L), or evidence of *in vivo* immediate hypersensitivity responses as determined by skin prick testing with the same allergens (a positive test is generally defined as a wheal of at least 3 mm in diameter) (24). In industrialized countries, a high proportion (25–30%) of individuals with atopy can be expected to develop clinically relevant allergic disease (25). The factors that lead to the translation of an atopic predisposition into allergic disease are not understood.

Prospective epidemiological studies conducted in industrialized countries have provided evidence that different atopic diseases may develop at different stages of growth in childhood in susceptible individuals, a phenomenon that has been referred to as the atopic march (26). Atopic dermatitis is generally the first manifestation of allergic disease and develops during the first 6 months of life in 45% and before 5 years of age in 85% of affected individuals (27). Food allergy – a clinical entity that is difficult to define – is common in early infancy and is associated with allergic reactions of the skin and intestinal tract to common dietary allergens such as cow's milk and hens' egg (28). Food allergy may develop concurrently with or independently of atopic dermatitis in infancy and, like atopic dermatitis, tends to be self-limiting with resolution occurring often by 5 years of age (28). Allergic rhinitis and asthma are difficult to diagnose in the early years because respiratory viral infections

confuse the diagnosis. However, both atopic asthma and allergic rhinitis tend to become important clinical conditions later in childhood and affect up to 37% and 40%, respectively, of 13–14 year old school children (29). A prospective study in the UK of children of atopic parents conducted from birth to 22 years of age illustrates the atopic march (31): the prevalence of atopic dermatitis peaked at 20% by 1 year of age and declined to 5% at the end of the study, while the prevalence of allergic rhinitis slowly increased over time to 15% by 22 years of age. The prevalence of wheeze increased from 5% in the first year of life to 40% at 22 years. Allergic diseases are strongly correlated at a population level (29) and individuals who develop early atopic dermatitis, particularly if severe, are at high risk of subsequently developing respiratory allergic disease (26).

The expression of allergic disease is a consequence of a complex interaction between genetic phenotype and environmental exposures (30). There is strong epidemiological evidence that the prevalence of allergic disease has increased in populations living in industrialized countries over the last 30–40 years (6,32), and because changes in the genetic make-up of these populations appear to be an unlikely explanation over so short a time period, it is probable that changes in environmental exposures are responsible.

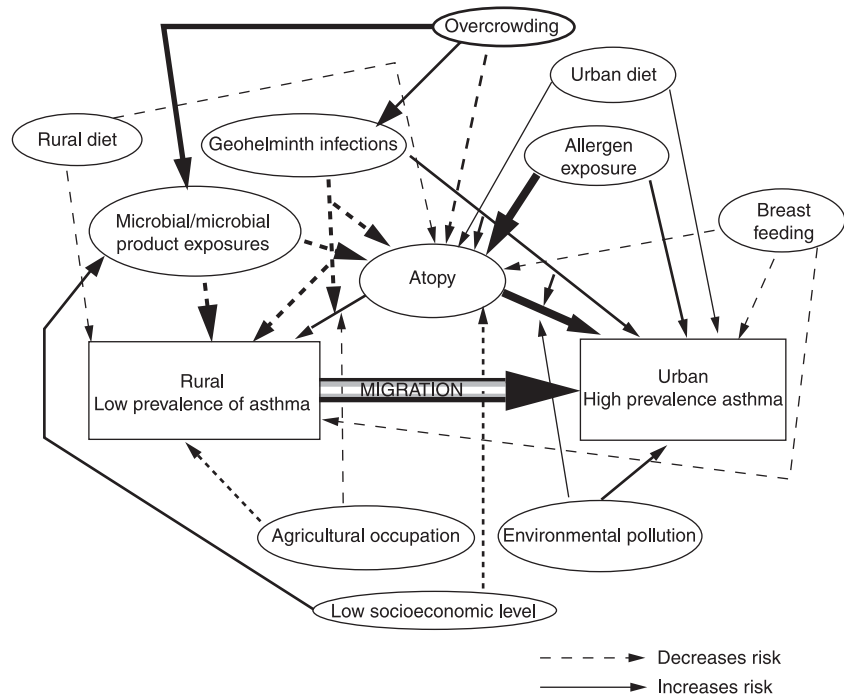
ENVIRONMENTAL DETERMINANTS OF ALLERGIC DISEASE

Large international differences in the prevalence of asthma, allergic rhinoconjunctivitis, and atopic eczema have emerged from the ISAAC (International Study of Asthma and Allergies in Childhood) studies (29,33,34). The ISAAC studies show a greater prevalence of allergic disease in industrialized countries compared to countries with more traditional agricultural economies (29,33,34). There are large differences in the prevalence of allergy between urban and rural areas in the tropics, with higher rates of allergic disease (8,35–39) in urban populations, although recent studies appear to demonstrate that urban and rural populations are or are becoming less different with respect to allergic disease prevalence (14,40,41).

Environmental exposures are important determinants of allergic sensitization to environmental allergens and the expression of allergic disease. Such environmental factors include high-level exposure to allergens (42), exposure to pets (43) and farm animals (44), socioeconomic level (45,46), nutritional status (47), number of siblings (45,48), day care attendance in infancy (49,50) and life style factors such as diet (51), breast-feeding practices (52), and maternal smoking (53).

The observations that children that are low in the birth order or that live in large families (45,46,48,54,55), that have

Figure 1 Hypothetical illustration of risk and protective factors for atopy in a migrant population in the tropics. Geohelminth infections are just one of many potential exposures that may alter the risk of allergy. Not shown is genetic phenotype that underlies risk of allergy and that interacts with different risk/protective exposures in determining allergy expression. Some exposures such as geohelminths may be protective in a rural area and risk factors in an urban area. The ‘balance’ of risk and protective exposures may determine risk of allergy. The size of the arrows denotes the magnitude of the risk and arrows on arrows represent potential interactions.



attended day care (49,50), or live in overcrowded households (56), have a reduced risk of atopy and/or allergic disease has led to the suggestion that multiple and continued exposures to childhood viral and bacterial infections may protect against the development of allergy (54,57,58) – the so-called hygiene hypothesis.

Several epidemiological studies have demonstrated a protective role for single or multiple infectious agents and or microbial products against the development of allergic sensitization and or allergic disease. These include measles (59), malaria (60,61) gastrointestinal infections such as hepatitis A virus and *Helicobacter pylori* (62,63), the normal gastrointestinal flora of the gut (64), environmental endotoxin and other microbial products in the environment (65,66) and helminth infections (10,12,14,16).

It is unlikely that any single environmental factor, infectious or non-infectious, can adequately explain either the time trends in allergy prevalence or urban–rural disparities. More important may be the pattern of environmental exposures (and balance between protective and risk exposures) at different stages of growth and development that interact with genetic phenotype to determine the development of allergic inflammation in tissues and the clinical expression of allergic disease. The pattern of these environmental exposures that may increase risk or provide protection against (or both under different circumstances) the development of allergy may determine the prevalence of allergic disease and atopy in a population. For example, a declining disparity in allergy prevalence between urban and

rural areas of Africa may be explained by an increasing uniformity of life style and living environment. The urban–rural balance of risk/protective factors is illustrated in Figure 1. Within this hypothetical illustration, the effect of a single environmental exposure on allergy risk will depend on interactions with other exposures and genetic predisposition. Further complexity would be expected according to the timing of the exposure relative to disease development (e.g. exposure within the first year of life is required for the protective effects against allergy of some exposures (67)) and the nature of the stimulus (e.g. dose and frequency). The model does not consider how environmental exposures translate into biological (immunological) mechanisms in causal pathways for allergy. What then is the evidence for geohelminth infections contributing to altered risk of allergy?

EPIDEMIOLOGICAL STUDIES OF WORMS AND ALLERGY

Numerous studies have examined the relationship between geohelminths and allergy. The evidence for an epidemiological association between geohelminth infection and different parameters of allergy is summarized below.

Atopy

The findings of studies that have examined the relationship between allergen skin test reactivity and faecal evidence of geohelminth infections are summarized in Table 1. Several

Table 1 Findings of studies that have examined the relationship between allergen skin prick test (SPT) reactivity and geohelminth infection (measured by stool examinations). Studies with information too incomplete to allow a comparison have not been included

Study	Country	Design	Population Urban/rural Sample size ^a Age range	Geohelminth prevalence	SPT	Risk OR (95% CI) ^b
Scrivener <i>et al.</i> , 2001 (13)	Ethiopia	Nested case control	Urban/rural 572 ≥ 16 years	<i>Ascaris</i> : 42% urban/47% rural <i>Trichuris</i> : 69% urban/59% rural Hookworm: 21% urban/50% rural	9% controls urban/ 25% controls rural	Positive association with <i>T. trichiura</i> , <i>A. lumbricoides</i> , and hookworm 0.30 (0.11–0.80)
Nyan <i>et al.</i> , 2001 (14)	Gambia	Cross-sectional survey	Urban/rural 429 15–34 years	Any: 8.2% rural/17% urban	22% rural vs. 35% urban	
Palmer <i>et al.</i> , 2002 (15)	China	Cross-sectional (asthmatic families)	Urban 2164 8–18 years	<i>Ascaris</i> : 12.2%	40.3%	Positive association
Cooper <i>et al.</i> , 2003 (16)	Ecuador	Cross-sectional	Rural 2865 5–19 years	Any: 68.6% <i>Ascaris</i> : 54.5% <i>Trichuris</i> : 46.4% Hookworm: 2.8%	21.9%	Any: 0.64 (0.52–0.78) <i>Ascaris</i> : 0.74 (0.60–0.91) <i>Trichuris</i> : 0.82 (0.67–1.01) Hookworm: 0.39 (0.18–0.85)
Dagoye <i>et al.</i> , 2003 (70)	Ethiopia	Cross-sectional survey	Urban/rural 563–856 ^c 1–4 years	Any: 69% <i>Ascaris</i> : 37.8% <i>Trichuris</i> : 53.5% Hookworm: 10.3%	HDM: 3.8% Cockr: 5.9%	HDM: <i>Ascaris</i> : 1.1 (0.7–1.7) HDM: <i>Trichuris</i> : 1.4 (0.9–2.2) HDM: Hookworm 1.2 (0.7–2.0) Cockr: <i>Ascaris</i> : 1.0 (0.7–1.4) Cockr: <i>Trichuris</i> : 1.7 (1.1–2.4) Cockr: Hookworm: 1.3 (0.8–2.2)

^aNumber with stool samples; ^bresults of adjusted multivariate analyses; ^csample size for analysis unclear. HDM – house dust mite extract; Cockr – cockroach extract; Any – any geohelminth infection.

studies have shown an inverse relationship between geohelminth infection and allergen skin test reactivity (14,16,61) with evidence of a reduced risk of atopy for greater geohelminth parasite burdens (16). There has been some concern that studies examining the relationship between geohelminths and allergy are likely to be confounded by other exposures that are correlated with geohelminth infections. A study of risk factors for atopy in a rural area of Ecuador showed that the inverse effects of geohelminth parasites (with atopy) were independent of other important risk factors such as overcrowding and socioeconomic level (56). The strongest evidence for a causal association between geohelminth infection and atopy is derived from intervention studies that have demonstrated that repeated anthelmintic treatments administered to geohelminth-infected children can cause either an increase in the prevalence (68) or the rate (69) of developing allergen skin test reactivity. It is important to point out that although the prevalence of atopy in individuals infected with geohelminths may be reduced, the overall atopy prevalence in these populations does not differ markedly from that observed in industrialized countries, at least when allergen skin test responses to a wide range of environmental allergens have been considered (14,23,56,68). Not all studies, however, have shown an inverse association and a study in China in an area low geohelminth prevalence, demonstrated a positive association between *Ascaris* infection and allergen skin test reactivity (15), and studies in Ethiopia in rural and urban areas of high geohelminth prevalence have shown also positive associations between geohelminth infection and skin test responses (13,70).

Atopy can be defined also by measurement of total and allergen-specific IgE, but because helminth parasites are potent inducers of IgE production (71), studies that have examined the relationship between levels of these parameters and atopy risk are difficult to interpret (12,16,60). For example, levels of allergen-specific IgE and allergen skin test results are disassociated in individuals infected with geohelminth parasites (22,60,84), and a high proportion of infected individuals have significant levels of allergen-specific IgE in the absence of skin test reactivity (22,60,84). In such individuals, detection of allergen-specific IgE may be caused by false positive reactions (22), by cross-reactivity between helminths and inhalant allergens (60), or by polyclonal stimulation of existing IgE-producing plasma cells (11,85).

Asthma

Numerous studies have investigated the relationship between wheeze symptoms and geohelminth infections, with conflicting results (9; Table 2). More recent studies have provided evidence for inverse associations between wheeze within the

previous 12 months and infections with either hookworm (13) or *Ascaris* (70) that are infection-intensity related, whereas other studies have shown no statistically significant relationship (17) or even a positive association between recent wheeze/asthma symptoms and the presence of *Ascaris* infections in stool samples (15) or the presence of IgE to *Ascaris* (22,72). The clinical course of asthma may be altered in individuals infected with helminth (schistosome) parasites causing a milder form of illness (73). In contrast, a study in Venezuela provided evidence that the treatment of geohelminth infections may ameliorate the symptoms of wheeze and reduce the requirement for asthma medications (74). Collaborations such as the Parasites in Asthma Collaboration based at the University of Nottingham that aim to review systematically and perform meta-analyses of data from different studies should provide a clearer idea of the relationship between asthma symptoms and geohelminth parasites (in general) and individual geohelminth parasites.

Atopic dermatitis

Few studies have examined the relationship between atopic dermatitis and intestinal worm infections (75). There is little epidemiological data on the prevalence of atopic dermatitis in rural areas of the tropics, although the condition appears to be rare (17,34). A cross-sectional study of school children in Ecuador provided no evidence for an association between geohelminth parasites (any geohelminth or different geohelminth parasites) and questionnaire-based evidence of flexural dermatitis (17). Future studies using standardized and validated epidemiological instruments that include clinical evaluations of flexural dermatitis (as opposed to purely questionnaire-based data) may provide a more definitive answer to the question. An example of such instruments is the 'Atopic Dermatitis Field Manual' (www.nottingham.ac.uk/dermatology/eczema/index.html).

Allergic rhinitis

Anecdotal observations have suggested that geohelminths may protect against allergic rhinitis (76,77). A cross-sectional study in Ecuador showed no relationship between reported symptoms of allergic rhinitis and geohelminth parasites (17). In another cross-sectional study conducted in urban Taiwan, the presence of enterobiasis appeared to be inversely associated with a previous diagnosis of allergic rhinitis in school children (78). However, questionnaire-based studies for identifying rhinitis symptoms in school-age children are likely to be subject to significant misclassification errors and bias, and newer epidemiological instruments are needed to provide more accurate identification of this condition.

Table 2 Findings of studies that have examined the relationship between wheeze symptoms within the previous 12 months (recent wheeze) and geohelminth infection (determined by stool examinations). The findings of studies conducted up to 1981 have been reviewed in (9)

Study	Country	Design	Population Urban/rural Sample size ^a Age range	Geohelminth prevalence	Recent wheeze	Risk OR (95% CI) ^b
Scrivener <i>et al.</i> , 2001 (13)	Ethiopia	Nested case control	Urban/rural 572 ≥ 16 years	<i>Ascaris</i> : 42% urban/47% rural <i>Trichuris</i> : 69% urban/59% rural Hookworm: 21% urban/50% rural	3.7% urban/1.2% rural ^c	Hookworm: 0.48 (0.29–0.82) No associations for other geohelminths
Nyan <i>et al.</i> , 2001 (14)	Gambia	Cross-sectional survey	Urban/rural 429 15–34 years	Any: 15% urban/8.2% rural	4.9% urban/3.8% rural	Any: No association
Palmer <i>et al.</i> , 2002 (15)	China	Cross-sectional (asthmatic families)	Urban 2164 8–18 years	<i>Ascaris</i> : 12.2%	10.1% ^d	<i>Ascaris</i> : 2.26 (1.58–3.23)
Cooper <i>et al.</i> , 2003 (17)	Ecuador	Cross-sectional	Rural 4035 5–18 years	Any: 63.4% <i>Ascaris</i> : 49.7% <i>Trichuris</i> : 43.8% Hookworm: 2.3%	2.1%	Any: 0.78 (0.49–1.26) <i>Ascaris</i> : 0.88 (0.58–1.34) <i>Trichuris</i> : 1.06 (0.70–1.61)
Dagoye <i>et al.</i> , 2003 (70)	Ethiopia	Cross-sectional survey	Urban/rural 617 1–4 years	Any: 69% <i>Ascaris</i> : 37.8% <i>Trichuris</i> : 53.5% Hookworm: 10.3%	3.8% urban/1.7% rural	<i>Ascaris</i> : 0.5 (0.3–0.9) <i>Trichuris</i> : 1.1 (0.6–1.8) Hookworm: 0.6 (0.2–1.8)

^aNumber with stool samples; ^bresults of adjusted multivariate analyses; ^cestimated – from cross-sectional study from which nested-case control study derived (25).

^dPhysician-diagnosed asthma, history of two or more respiratory symptoms or asthma attacks in previous 12 months, and airways responsiveness to methacholine. Any – any geohelminth infection.

Food allergy and the atopic march

There are no published data available on how maternal geohelminth infections and early infant infections may affect the occurrence of food allergy or the development and progression of the atopic march in infancy. Early exposure to geohelminth parasites could affect the early expression of allergic disease, prevent the development of atopic dermatitis in infancy or contribute to milder clinical forms of disease, and reduce the risk of severe asthma and allergic rhinitis or asthma symptoms in later life. These questions can be addressed only in large prospective observational or intervention studies.

Summary

In summary, the evidence for an epidemiological association between allergy and geohelminth infection is inconsistent, and different studies providing evidence for positive or inverse associations between geohelminth infections and either allergen skin test reactivity or asthma symptoms. The results of intervention studies do provide stronger support for an inverse association between geohelminth infection and atopy. There is very little evidence so far to support an association between geohelminth infection and other forms of allergic disease.

The conflicting findings of enhanced allergy vs. reduced allergy associated with geohelminth infection have been explained by differences in geohelminth endemicity (61,79,80), with populations living in areas of low prevalence of geohelminth parasites having a greater risk of allergic responses to environmental allergens, and populations living in areas of high prevalence having a reduced risk of allergy. This theory appears to explain better the findings of studies examining risk of wheeze symptoms (Table 2) than studies that have investigated allergen skin test reactivity (Table 1).

DOES ALLERGY PROTECT AGAINST INTESTINAL WORMS OR DO WORMS PROTECT AGAINST ALLERGY?

Because most studies investigating the relationship between geohelminth infection and allergy have been cross-sectional, it has been difficult to identify the temporal sequence between geohelminth infection and allergy – which is the exposure and which is the outcome? Do geohelminths protect against allergy or does allergic predisposition protect against geohelminth infection?

Evidence for geohelminth infections being the outcome

The human immune system has developed in the context of heavy exposures to geohelminth infections, and it has

been argued that allergic inflammation has developed as an important host protective mechanism against these parasites (81). Certainly, different arms of the allergic Th2 response (e.g. IgE, eosinophils, mucus, and mast cells) mediate protective immunity against different helminth infections in animal models (82). Human studies have provided evidence for reduced parasite burdens with geohelminths in atopic humans compared to non-atopics (11,16,83), and for enhanced Th2 cytokine expression and IgE-mediated inflammatory responses to parasite antigen (84) in atopics, indicating that children with evidence of allergen skin test reactivity are less likely to be infected with ascariasis and other geohelminth parasites, and that resistance to parasite infection is associated with enhanced allergic immune responses to parasite antigens. Previous studies have shown that resistance to infection with geohelminth parasites is associated with markers of an allergic response such as: high levels of anti-parasite IgE (85) or antigen-specific IgE antibodies (86), elevated levels of eosinophilic cationic protein and other acute inflammatory markers (86), and Th2 cytokine production (87).

Evidence for geohelminth infections being the exposure

The results of intervention studies using anthelmintics have provided evidence that geohelminth infection is the antecedent exposure (rather than the outcome): (a) a non-randomized intervention study in Venezuela that showed that monthly anthelmintic treatment (oxantel-pyrantel) over a period of 18 months resulted in an increase in the prevalence of atopy among children with a high prevalence of infection before treatment (68); (b) an open-label placebo-controlled randomized intervention study in Gabon that treated children with anthelmintics (praziquantel and albendazole) every 3 months and examined skin test reactivity to house dust mite at 6-monthly intervals over 30 months, provided evidence for an increase in the rate of developing skin test reactivity in the treatment group compared to the placebo group, an effect that appeared to be mediated partly by reductions in geohelminth infections (69); and (c) an open-label randomized intervention study in Venezuela showed that monthly anthelmintic treatments (albendazole) over the period of a year, reduced symptoms of wheeze and the need for asthma medications (74).

How can these different viewpoints be reconciled? In fact, both perspectives may be valid. The expression of atopy depends on interactions between an individual's genetic phenotype and environmental exposures (30). The expression of atopy varies over time in a single individual (69,88) and may depend on the balance of environmental exposures (protective vs. risk exposures). Individuals with strong genetic traits associated with atopy are more likely to have

positive skin tests to environmental allergens and may be more resistant to geohelminth infections but, given adequate exposures to geohelminths, particularly if these occur early in life, may develop chronic infections and develop immune regulatory mechanisms to limit allergic inflammation and its pathological effects (99), and lose allergen skin test reactivity. The treatment of geohelminth infections may unmask 'atopic' individuals through reductions in the magnitude of immunoregulatory mechanisms directed against helminth allergens.

MECHANISMS OF GEOHELMINTH-INDUCED SUPPRESSION OF ALLERGY

Assuming a causal association between geohelminth infection and allergy, geohelminths could affect the development of allergy either through modulation of the priming of allergen-specific responses or by modulation of the effector stage of allergy. The high rate of allergic sensitization but low prevalence of allergic disease reported among populations living in areas that are highly endemic for geohelminth parasites (14,17) would suggest that priming for allergic responses may even be enhanced (total IgE or allergen-specific IgE) and that chronic geohelminth infections may modulate allergic inflammation primarily by alteration of effector immune responses. This would explain, for example, the apparent dissociation between serum levels of allergen-specific IgE and skin test responses (22,56,60). The effector phase of allergic inflammation could be affected by alterations in the state of activation of mast cells bearing specific IgE either in general (i.e. allergen prick testing in the skin) or in specific tissues (e.g. in the lungs exposed to migratory geohelminth larvae), and by effects on dendritic cell and T cell activation, effector cell recruitment, and the accessory immune functions of tissue epithelium. The effects of helminth infections on immunity are highly complex and have been examined extensively in experimental animal models (reviewed in (89)).

Few published studies have examined the mechanisms underlying the immunomodulatory effects of geohelminth infections on heterologous antigen responses in humans (90,91), and there is very little information available on how geohelminth infections may modulate allergic reactivity. The discussion that follows will examine the potential role of tolerance to geohelminth antigens in the modulation of allergic inflammation by reference to the findings of human studies of tissue and other helminth infections. Because of the close similarities between the human immune response to tissue and intestinal helminths (19,61,84,87), it is reasonable to assume that the human host employs similar mechanisms for the modulation of immunity to chronic helminth infections irrespective of the tissue location. For example, both geohelminths and schistosome parasites can have a suppressive effect on atopy in the same population (12,61)

that may be reversed partially by treatment with broadly active anthelmintic drugs (69).

INTESTINAL WORMS AND THE EARLY DEVELOPMENT OF ALLERGY

If we are to understand how geohelminth infections may affect the development of allergy, we need to examine the factors that determine the development of allergy in early life and how these may be related to early exposures to geohelminth parasites. The first exposures to geohelminths and environmental allergens may occur *in utero*. Allergens can cross the placenta and stimulate specific immune responses in the foetus (92,93). Although IgE is detected rarely in cord blood samples from neonates in industrialized countries (94,95), IgE (both polyclonal and specific) is found frequently in the cord blood of neonates from tropical countries (96–98). Stimulation of IgE in such foetuses is associated with maternal helminth infection (99).

Low-level exposure to allergen *in utero* may cause the production of allergen-specific IgE that may be associated with the risk of atopic disease in early childhood (100). In contrast to the level of exposure that may be expected to environmental allergens, the range of concentrations of helminth antigens to which a foetus may be exposed is likely to be considerably greater, and may range from trace amounts in mothers with light infections to the passage of entire parasites across the placenta in the case of filarial infections (101). The level of exposure to parasite antigen that can be expected from exposure to parasites that are resident predominantly in the intestinal lumen (vs. the vascular system in the case of some filarial parasites) is unclear. However, a significant proportion of dietary proteins are absorbed antigenically intact across the intestinal epithelium (102), and the same is likely to be true of antigens that are excreted and secreted by intestinal lumen-dwelling helminths – geohelminth antigens can be detected in the peripheral circulation of infected individuals (103). Variations in the quantity of geohelminth antigens that cross the placenta from the maternal circulation could determine the infant response to subsequent infections. Alternatively, the passage of maternal IgG anti-idiotypic antibodies that are internal self-images of parasite antigens could prime modulatory anti-parasite immune responses in the developing foetus (104,105).

Foetal sensitization by an infected mother could cause either tolerance (106,107) or sensitization (108,109) with induction of inflammatory immune responses. Tolerance could occur under conditions of continuous exposure to maternal parasite antigens, through early postnatal exposures during breast-feeding (110) or through infectious exposures to geohelminths and their antigens *in utero*, in infancy, or in childhood (99).

TOLERANCE – AN IMPORTANT ANTI-ALLERGY MECHANISM?

Tolerance to parasite antigens through early exposures to geohelminths and their antigens may affect immunity to environmental allergens. Tolerance to environmental allergens caused by geohelminth exposures could be antigen-specific, occurring through antigenic cross-reactivity between parasite antigens and environmental allergens (111–113), or nonspecific, occurring through bystander effects via the secretion of the immunomodulatory cytokines, IL-10 and TGF- β , that are typical of chronic infections with helminth parasites (114–116). For example, schistosome antigens induce IL-10 production by immune cells, and levels of this cytokine have been associated with suppression of atopy to house dust mite in children infected with *Schistosomiasis mansoni* (12). IL-10 has powerful anti-allergic effects that may affect allergen skin test responses (117,118).

Tolerance to environmental allergens caused by immunological cross-reactivity with parasite antigens could be explained through: (a) central tolerance – exposure of foetuses (transplacentally) and infants (via the maternal milk) to geohelminth antigens in maternal infections could lead to thymic deletion of cross-reactive T cells; (b) peripheral tolerance – early intrauterine or postnatal exposures to geohelminth transmission could result in clonal anergy of cross-reactive T cells or the induction of regulatory T cell subsets that actively suppress immune responses; and (c) oral tolerance – adult parasites are highly metabolically active enteric pathogens that excrete and secrete significant quantities of proteins and glycoproteins, and systemic hyporesponsiveness induced to epitopes on helminth antigens could affect allergic inflammatory responses to cross-reactive epitopes on environmental allergens.

Immune tolerance induced to cross-reactive geohelminth and environmental allergen epitopes could have short-term or long-term effects on allergy. Children exposed to heavily infected mothers and intense infections in infancy that cause thymic deletion of parasite-reactive T cells, are likely to remain anergic indefinitely (106). Children in whom allergic inflammatory responses are controlled by peripheral tolerance to cross-reactive antigens may continue to suppress allergic inflammation under circumstances of continued exposure to geohelminth infection, but loss of exposure caused by migration or sustained anthelmintic treatment may cause peripheral tolerance to wane with activation of allergic responses (68,69). In contrast, children born to uninfected mothers and who live in circumstances of low-level transmission to geohelminth parasites may react with enhanced allergic responses to early geohelminth exposures (119), and suppression of these infections by anthelmintic treatment may, paradoxically, cause an improvement in allergic symptoms (74).

The role of regulatory T cells in the induction of tolerance and in controlling inflammatory responses is the focus of considerable research activity. There appear to be several subgroups of regulatory T cells that are defined by surface markers (e.g. CD4⁺CD25⁺) or immunoregulatory cytokine expression (e.g. IL-10 and TGF- β) (120). Two subgroups of regulatory T cells, Tr1 (116,122) and CD4⁺CD25⁺ cells (19,89), appear to be up-regulated during chronic helminth infections. Tr1 cells regulate immunity through IL-10-dependent mechanisms (116,122), while CD4⁺CD25⁺ T regulatory cells regulate immunity through both soluble cytokine-dependent and -independent mechanisms (124). CD4⁺CD25⁺ T regulatory cells have a role in modulating anti-parasite immunity in murine models of chronic parasite infection (121), and may be important also in chronic helminth infections (89,122,123) and allergic disease (124).

The early development and functional maturation of 'the immunoregulatory network' (19), in which regulatory T cells limit strong inflammatory responses generated in response to infectious exposures such as geohelminths, could be an important mechanism for the avoidance of potentially damaging allergic inflammatory responses to environmental allergens and parasite antigens. However, to date, there are no published data on the role of regulatory cells in the modulation of allergic inflammatory responses among individuals infected with geohelminth parasites.

IMPORTANT AND UNRESOLVED QUESTIONS

Future studies could address the following questions. (a) What are the effects of chronic geohelminth infections on the development of different forms of allergic disease (asthma vs. atopic eczema vs. allergic rhinoconjunctivitis) using standardized epidemiological instruments for the definition of allergic disease? (b) Do geohelminth infections induce tolerance to related inhalant allergens through antigenic cross-reactivity or non-antigen-specific mechanisms? (c) Can changes in risk of allergic disease in urbanizing populations be attributed to declines in the prevalence and intensity of geohelminth infections? (d) Do maternal infections and early infant exposures to geohelminth parasites affect the atopic march and the early development of atopy and allergic disease? (e) Has the prevalence of atopy/allergy increased in areas where sustained anthelmintic control programmes are in place?

CONCLUSIONS

The suppression of allergy by helminth infections is an area of great research activity by parasitologists, but the causal relationship or even the causal direction between geohelminth infections and allergy has not been established with certainty.

Arguments in favour of a causal association include temporal sequence (all published prospective and intervention studies favour geohelminths as the antecedent exposure), biological plausibility (there is growing evidence, at least from experimental animal models, for an allergy-modulating effect of geohelminth parasites), dose-response effect (a few studies have shown an inverse relationship between allergy risk and geohelminth parasite burden), and reversibility (intervention studies conducted in areas of high geohelminth endemicity have shown an increase in the prevalence or risk of allergy after anthelmintic treatment).

Arguments against a causal association include the inconsistent findings of many studies, and the relatively weak estimates of effect of geohelminth infections on allergy risk that could be explained by uncontrolled bias and confounding. Equally, changing geohelminth prevalence over the past 2–3 decades in industrialized countries appears to be a weak argument for the time trends in allergic disease, and an unlikely explanation for the very high rates of asthma reported from the poorest sector of the population in the inner cities of North America, where the control of geohelminths as a public health problem would be expected to have occurred much earlier than the start of recent trends, at the time of widespread provision of clean water and sanitation.

Perhaps more important to an understanding of the potential role of geohelminth infections in modulating allergic disease is to consider chronic geohelminth infections as one of the mechanisms, and particularly important in areas of high geohelminth prevalence, by which the maturing immune system is educated in early life to control polarized immune responses that cause inflammatory disease. It is probable that the immune maturational effects of geohelminth infections occur in the context of other chronic infections and exposures and can be substituted by these. The allergy-modulating effects of geohelminths may require complex interactions with other environmental exposures and host genetics.

The jury remains out on the causal association between geohelminth infections and allergy. To address this question adequately, future well-designed prospective studies will be required that take a far more sophisticated approach than previously and that consider the role of geohelminth infections in the context of a wide number of relevant environmental exposures and host genetics.

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