

# The Potential Impact of Early Exposures to Geohelminth Infections on the Development of Atopy

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## Abstract

Microbial exposures in early life may provide important signals for immune maturation and the development of an antiinflammatory network thereby preventing the development of dysregulated immune responses such as that associated with allergic disease. The human immune system has evolved in the presence of intense helminth infections and has developed regulatory mechanisms to limit the harmful inflammation that can be caused by the potent allergens secreted by these chronic pathogens. Geohelminth infections are highly prevalent childhood infections, and there is strong evidence that chronic geohelminth infections provide protection against atopy in the rural tropics. Because the early environmental exposures that may lead to the development of atopy are likely to occur in the first few years of life, geohelminth infections may exert their protective effects at this time. Early exposures to geohelminth antigens could occur transplacentally, through breast milk, or through early infant exposures, and could induce tolerance to parasite antigens resulting in suppressed allergic responses to the parasite. Tolerization to parasite antigens could suppress allergic responses to inhalant allergens through bystander effects or through tolerization of crossreactive epitopes that are shared between geohelminth parasites and inhalant allergens. Tolerization to crossreactive allergens could occur by thymic deletion or through peripheral mechanisms such as regulatory T cells. Immunologic studies of the mechanisms by which early exposures to geohelminth infections affect immune polarization to inhalant allergens are likely to provide important insights into the early regulation of the immune response and may lead to the design of novel interventions for the prevention of allergic disease.

## Index Entries:

Geohelminths; atopy; intrauterine; infancy; immune regulation.

## Introduction

The hallmarks of allergic inflammation are mastocytosis, tissue eosinophilia, the production of allergen-specific IgE, and mucus secretion, and these hallmarks are orchestrated by Th2 cytokines produced by allergen-specific CD4<sup>+</sup> T lymphocytes (1). Allergen cross-linking of IgE on sensitized mast cells is considered to be the primary initiating event in the development of allergic inflammation. Such inflammation is characteristic of the human response to environmental allergens and also to helminth antigens. Helminth allergens are the most potent known inducers of IgE production, and, unlike environmental aeroallergens, are capable of inducing a significant IgE response in almost everyone who becomes exposed (2). Because the human immune system is likely to have evolved in the context of heavy helminth infestations and intense exposure to helminth allergens, allergic inflammation may have developed as being caused by an important host-protective mechanism for preventing the establishment of helminth infections and in controlling parasite numbers (3). For this reason, atopic or allergic disease (i.e., asthma, rhinitis, and eczema) could be regarded as an inappropriate immune response to innocuous environmental allergens (4) that may occur in the relative absence of exposure to potent helminth allergens. Epidemiological and immunological studies indicate complex interactions between allergy and helminth infections (5–10). This review will focus on the potential role of geohelminth (or intestinal helminth) infections, the most prevalent of human helminth infections, in the development of atopy. Because information available on geohelminth infections is limited, the review will also draw on findings from other human helminth infections and experimental animal models.

## Environmental Determinants of Atopy

Atopy is an immune phenomenon that may be defined as the presence of either positive

skin tests to extracts of inhalant allergens or the presence of allergen-specific IgE in serum (11). Atopy appears to be determined by a complex interaction between genetic and environmental factors and is strongly associated with the risk of asthma in industrialized countries (12,13).

Factors associated with an increased risk of atopy in industrialized countries include small family size and high birth order (14–19), high socioeconomic status (19), allergen exposure (20), and family history of atopic disease (21). The converse is protective against atopy. Other exposures that appear to be protective against atopy include attendance at day care (22) and growing up on a farm (23–25).

The few studies that have examined risk factors for atopy in nonindustrialized countries have shown low socioeconomic level (26,27) and childhood infections such as measles (28), malaria (29), and helminth infections (6,29–31) to be protective. Exposure to infectious diseases (32) and microbial products (23) during childhood may provide important protection against the development of allergic sensitization.

## Early Exposures to Infections and the Development of Atopy

The intra-uterine period, early infancy, and childhood is a critical time for the development and maturation of the immune response. The major environmental and lifestyle factors that may unmask the atopic phenotype probably exert much of their effect during this time. Microbes may provide the important signals for the maturation of the immune system in early childhood. It has been argued that the lack of exposure to these signals or failure to respond to them may result in the persistence and consolidation of a Th2 bias in atopic children (33,34). Exposure to microbes and microbial products in the gastrointestinal tract may have important immune regulatory or maturational effects: (1) attendance at day care, which is likely to be associated with increased expo-

sure to both respiratory and gastrointestinal pathogens, is protective against the development of atopy (22,35); (2) marked differences in gastrointestinal flora have been observed between allergic and nonallergic children in Europe (36–39), and differences in types of microflora and the rate of turnover of microflora may be important for the development of atopy (40); (3) a critical step in the postnatal regulation of the antigen-specific reactivity seen at birth may be the acquisition of the appropriate commensal gut flora; colonization by intestinal bacteria during the neonatal period in germ-free mice is essential for the development of oral and systemic tolerance to Th2-inducing antigenic challenge (41); and (4) the risk of atopy is increased if a child receives antibiotics in the first 2 yr of life (42,43). Murine models have shown that decontamination of the gut with antibiotics may lead to a failure in the development of normal immunity (44).

These observations point to an important role of adequate microbial stimulation of the gut for the development and maturation of the immune response.

## Geohelminth Infections and Host Immune Responses

Geohelminth infections are a major enteric pathogen of children in many regions of the world, and infection often occurs in infancy and may persist throughout childhood. The most prevalent geohelminth infections are *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm, that infect an estimated 2 billion humans (45). Early enteric exposures to geohelminth infections in infancy may provide important maturational and regulatory signals for the developing immune response that allow it to control allergic inflammation directed against both parasite and environmental aeroallergens.

Geohelminths are transmitted by close contact with a contaminated environment, and infections are long-lasting, with adult stages

surviving between 1 and 15 yr (46–48). Typically, geohelminth infections are chronic in endemic areas, and, as with other helminth parasites, it is likely that geohelminths have developed ways of modulating the host immune response to permit adult development and survival. Likewise, the human host may have developed mechanisms to limit the pathology associated with the long-term presence of these highly allergenic parasites.

There are distinct differences in the host clinical and immune response between acute infections with helminths and chronic established infections (49,50). These differences are most marked between adults who are exposed to infection briefly (i.e., expatriates) and adults who have lived their whole lives under conditions of constant exposure to infection in a helminth endemic area (49). The former (i.e., acute helminth infections) may develop strong allergic reactions to helminth parasites, particularly invasive larval stages, whereas the latter (i.e., chronic infections) rarely develop allergic phenomena despite the presence of circulating parasite antigen, high levels of parasite-specific IgE, and significant numbers of FcεRI-bearing mast cells and basophils both at the tissue sites of parasite residence and in the peripheral circulation (49). Acute infections tend to develop among individuals with only transient, short-term, or recent exposures (49,50). The lack of allergic reactivity among individuals with chronic helminth infections may be associated with the development of immune regulatory mechanisms by the host to limit allergic inflammation directed against the parasites, and also to antiinflammatory factors elaborated by the parasite (e.g., secreted antigens that modulate or subvert the antiparasite response). The suppression of allergic reactivity in such individuals is a dynamic but fragile peace between host and parasite; allergic non-responsiveness may break down to cause severe immunopathologic reactions when the balance is tipped, such as when large quantities of parasite antigens are released following che-

mother therapy in the case of tissue helminth infections (49,51).

Acute and chronic infection phenotypes are features of geohelminth infections, particularly ascariasis (52). Acute ascariasis causing Loeffler's syndrome (53), and eosinophilic pneumonitis (54) is rarely observed in areas of high endemicity (55). How a child responds to early infections may depend on the local micro-epidemiology of geohelminth infections.

### **Factors Influencing the Development of the Early Immune Response and the Expression of Allergic Inflammatory Responses Against Geohelminths**

Allergens cross the placenta from the maternal circulation and stimulate specific immune responses in the fetus (56,57), and fetal IgE production can be initiated from 11 wk of age (58). Although studies of Western populations have identified allergen-specific IgE in relatively few cord-blood samples (59,60), similar studies in the Tropics demonstrate high cord-blood IgE levels that are unrelated to a family history of allergy (61), but are associated with maternal helminth infection (62). Cord-blood lymphocytes from infants delivered to helminth-infected mothers in Kenya, but not mothers living in the United States, spontaneously produce polyclonal and parasite antigen-specific IgE (63), and parasite-specific IgE has been demonstrated in 58% of cord-blood samples from infants delivered in India (62). It is clear, therefore, that helminth antigens in the circulation of infected mothers may cross the placenta and prime infant immunity. Likewise, mothers infected with geohelminths have antigen in the peripheral circulation (64) that is likely to cross the placenta and generate specific immune responses in the fetus.

Differences in the frequency of detection of parasite antigen-specific cytokine and IgE responses have been reported between different regions (65,66) and may reflect differences

in helminth endemicity. In areas of high endemicity where a large proportion of pregnant mothers are infected, fetal exposure to helminth antigens will occur frequently, whereas in areas of low endemicity, fetal exposure to maternally derived parasite antigens will be less common. Fetal exposure to parasite antigens may result in three possible outcomes: (1) tolerization by negative selection of parasite antigen-reactive T cells; (2) tolerization through anergy (i.e., peripheral tolerance); and (3) sensitization with induction of potentially pro-allergic responses. All three outcomes have been reported among infants of helminth-infected mothers (62,67–73), and the nature of the fetal response to exposure is likely to depend on several factors including the intensity of fetal exposure and genetics.

Low-level exposure to allergen in utero has been shown to prime the infant for the production of allergen-specific IgE and is associated with risk of atopic disease in early childhood (74). The range of concentrations of parasite-derived allergens to which a fetus may be exposed to parasite antigen from helminth-infected mothers is likely to be several orders of magnitude greater than that may occur for inhalant allergens: fetal exposure to helminth antigens may range from tiny traces in lightly infected mothers to the passage of entire parasites across the placenta, resulting in infection of the fetus (75,76). Transplacental transfer of anti-idiotypic antibodies could sensitize a fetus in a similar way as parasite antigen (77). Exposure to parasite antigen may occur in utero (transplacentally), neonatally (through the presence of parasite antigen in breast milk [78]), and also during infancy (through early exposures to infection). Heavily exposed fetuses and neonates may be more likely to develop tolerance to parasite antigens. Exposure to parasite antigens at these stages of immune maturation may prime for tolerance, facilitate parasite persistence (79), and protect the child from developing acute and pathologic inflammation on early acquisition of infection.

Heavily infected mothers from highly endemic areas are likely to have heavily infected children. It would be advantageous for a child raised in a highly endemic area not to be continuously mounting damaging allergic responses to the presence of parasites that it cannot avoid. Few individuals born and raised in areas that are highly endemic for schistosomiasis develop acute and symptomatic disease upon early exposure to infection, and only 5–8% go on to develop severe morbidity (80), whereas morbidity in populations recently exposed to schistosomiasis is more prevalent and severe. Because the nature of the parasite-specific immune response induced in offspring is very similar to that observed in the mother (66,81,82), newborns of heavily infected mothers start life with a parasite-specific immune response that is typical of chronic infection. In contrast, children from uninfected or lightly infected mothers would be less likely to be heavily exposed in infancy and early childhood, and it may be more beneficial for these children to mount more vigorous immune responses to control parasite numbers or even prevent the establishment of infections.

The “maternal effect” on a child’s parasite-specific immune response is present for the first 5 or so years of life, and thereafter, environmental factors may be more important (83,84). However, offspring with heavy early exposures that resulted in thymic deletion of parasite-reactive T cells may maintain their immune hyporesponsiveness indefinitely (71), irrespective of changes in environmental circumstances. A chronic-infection phenotype may only be maintained in offspring in whom peripheral tolerance is the main mechanism of suppression of allergic inflammation, under circumstances of continued and heavy exposure to helminth transmission.

## Relationship Between Atopy and Geohelminth Infection

Numerous studies have examined the relationship between geohelminths and allergy. These studies have provided conflicting evidence showing either no relationship between geohelminth infection and allergic asthma (5) or a negative relationship between geohelminth infection and skin-test reactivity (6,7,30) and symptoms of wheeze (9,85). There is evidence also for an increased prevalence of allergic disease and atopy among some population groups exposed to geohelminths (7,10,86).

A clue to these differences may be provided by the same factors that shape parasite-specific immune responses in early life, particularly geohelminth endemicity (27,50). Findings from previous studies suggest that human helminth infections may influence the immune response to nonparasite antigens to resemble more closely the parasite-specific response (87,88). The nature of the effects of geohelminth infections on the inflammatory responses to environmental allergens would be predicted to depend on the stage of geohelminth infection (i.e., acute vs chronic). Populations living in areas of low-level transmission with geohelminth parasites (and low prevalence) may have a greater prevalence of skin-test reactivity to environmental allergens (7) and enhanced allergic reactivity (86,89–91), whereas populations living in areas of high-level transmission (and high prevalence) may have a reduced prevalence of allergen skin-test reactivity (6,30). This view, first proposed by Lynch (27), and more recently reiterated by others (50,92), is consistent with the acute/chronic paradigm of helminth infection in which acute infections have allergy-enhancing effects and chronic infections have allergy-suppressive effects. Of course, this requires a somewhat broader definition of “acute” to encompass discontinuous or intermittent exposures and infections that would be typical of areas of low geohelminth endemicity (and low prevalence).

## **Mechanisms of Helminth-Induced Suppression of Atopy**

Geohelminths could affect the development of atopy either through modulation of the priming of allergen-specific responses or by modulation of the effector stage of atopy. The mechanisms by which acute infections may modulate allergic reactivity have been discussed previously (50). Chronic infections may suppress aeroallergen-specific immune responses through several mechanisms:

### **Mast-Cell Saturation**

Helminth allergens are potent inducers of polyclonal IgE production that may modulate immediate hypersensitivity reactions by saturation of FcεRI receptors on mast cells and basophils (93,94). Several studies have shown conflicting evidence for a role of mast-cell saturation in the suppression of allergen skin-test reactivity in helminth-endemic populations (6,29,95). An inverse association between very high levels of total IgE and the prevalence of atopy has been observed in children living in a geohelminth-endemic area of Ecuador (31), although this could be explained by other factors associated with high total IgE levels and Th2 polarization.

### **Anti-IgE Autoantibodies**

Elevated levels of anti-IgE autoantibodies have been reported in geohelminth-endemic populations (96), although their physiologic function is uncertain. Nonanaphylactogenic anti-IgE antibodies could prevent IgE-mediated inflammation by formation of circulating complexes and reduction in free IgE, reduced expression of FcεRI receptors on effector cells, and reduced production of specific IgE (97). Humanized monoclonal anti-IgE antibodies, when administered therapeutically to allergic patients, can prevent IgE-mediated inflammation and have significant therapeutic benefits (97,98).

## **Blocking Antibodies**

Helminth-induced polyclonal production of blocking antibodies (generally of the IgG4 isotype) that share the same epitope specificities as IgE could prevent IgE-mediated inflammation by binding to the same allergenic epitopes (99,100).

## **Antiinflammatory Molecules Secreted by Geohelminths**

Geohelminth parasites actively excrete antiinflammatory molecules that may suppress the antiparasite responses and the level of inflammation in the tissues. For example, hookworm infection may suppress host antiparasite responses by secretion of a metalloproteinase that digests eotaxin (101), by induction of apoptosis of T lymphocytes (102), and by secretion of calreticulin, which inactivates C1q and subsequent inflammatory responses (103). Such antiinflammatory effects would be greater in chronic than acute infections because of greater exposure to migrating larvae and greater parasite burdens.

## **Tolerance**

Geohelminth infections could induce tolerance to parasite and inhalant allergens either through cross-reactivity between parasite antigen and allergenic epitopes of inhalant allergens or through bystander effects. The broad cross-reactivity of helminth antigens indicates antigenic conservation of potential tolerogenic epitopes, and antigens most exposed to immune recognition show extraordinarily little divergence or species specificity (104). Many of these antigens exhibit immunologic cross-reactivity with insect allergens (e.g., house dust mite, cockroach) (105,106). In the case of bystander effects, chronic infections with helminth parasites are associated with the production of significant amounts of the cytokines interleukin-10 (IL-10) and/or transforming growth factor-β (TGF-β) (107–109). Production of IL-10 by parasite antigen-stimulated

immune cells may cause bystander suppression of immune responses to inhalant allergens (8). IL-10 appears to have potent antiallergic effects that could affect allergen skin-test responses (110,111). Three different mechanisms could explain tolerance to inhalant allergens through immunological cross-reactivity with parasite antigenic epitopes:

1. Central tolerance. Exposure of fetuses (transplacentally) and infants (via the maternal milk) to large quantities of geohelminth antigen through heavily infected mothers could lead to thymic deletion of cross-reactive T cells.
2. Peripheral tolerance. Intrauterine or early postnatal exposures to geohelminth antigens could result in clonal anergy of cross-reactive T cells, as has been shown to occur for parasite antigen-specific T cells in adults with tissue helminth infections (112). Peripheral tolerance would also be predicted to develop in young children infected chronically after earlier "acute" exposures. Peripheral tolerance could be maintained by distinct T-cell subpopulations, such as the recently described regulatory T cells, and could occur through either soluble cytokine (i.e., IL-10 and TGF- $\beta$ ) -dependent or -independent mechanisms (113,114).
3. Oral tolerance. Specific immunological unresponsiveness to challenge with an antigen can be induced by its prior feeding, and oral tolerance to IgE responses can be induced by feeding of allergens (115). Oral tolerance to cross-reactive allergens could occur during chronic enteric infections with geohelminth parasites. Adult geohelminths are highly metabolically active enteric pathogens that excrete and secrete significant quantities of proteins and glycoproteins. Oral tolerance could develop under these circumstances and be mediated through cytokine- and contact-dependent mechanisms (116).

## Conclusion

Infectious challenges, particularly with enteric microorganisms, in early childhood may provide protection against the development of atopy and allergic disease. Geohelminth infections are the most prevalent and persistent of all enteric infections of childhood. Early intrauterine and postnatal exposures to geohelminth parasites may protect against the development of atopy by affecting the maturation of the immune response through the development of a robust antiinflammatory network. Early fetal and infantile exposures to geohelminth may determine how a child responds to early infections either with acute allergic reactions to geohelminth larvae or a more "chronic" suppressed immunity. Immune tolerance, either through thymic deletion or by the induction of anergy to reactive T-cells, may be an important mechanism by which infants brought up in highly endemic areas avoid early morbidity caused by allergic inflammation to the invading parasites. Infants of heavily infected mothers are more likely to be "tolerant" to geohelminth antigens, whereas unexposed or lightly exposed infants may develop stronger allergic response against parasite larvae. Suppression of allergic responses to environmental allergens may occur either as bystander effects of a potent antiinflammatory environment in the tissues or through tolerization of IgE epitopes that are immunologically crossreactive between parasite and inhalant allergen. Other immunologic mechanisms could also explain the suppression of IgE-mediated inflammation in heavily exposed children. These suppressive mechanisms are not mutually exclusive and the relative role of each in any individual may depend on genetics, fetal and early infant exposures to parasite antigen, and the intensity of infectious exposures during childhood. Further studies are required to examine the effects of geohelminth infection on the postnatal development of allergen-specific T-cell responses in the context

of varying intrauterine and postnatal exposures to geohelminth antigens.

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