Special Article

Parasitic Infections and Allergy - A Review

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Parasitic infections have been one of the major health problems in Thailand for decades.However, the prevalence of parasitic infections has decreased considerably in recent years due to an increase in personal hygiene and public sanitation. In contrast, allergic diseases, their morbidity, and mortality appear to be on the rise. An immunological explanation and epidemiologic relationship between parasitic infections and allergies has been espoused since the late 1980s. The hygiene hypothesis has been the internationally recognized theory to explain the findings. IgE blocking hypothesis and the modified Th2 responses have also been purposed to describe the effect of preventing allergic diseases by parasitic infections and by IgG4 inducing tolerance, respectively. Several lines of evidence have suggested an inverse association between parasitic infections and the presence of allergic symptoms. Moreover, data have demonstrated interleukin-10 presenting the suppressive effect of parasitic infection to allergic responses. Nevertheless, a causal relationship between parasitic infections and allergies remains to be proven. Future prospective and intervention studies are required to determine the role of parasitic infection with allergic responses to host exposures.

Keywords: *Parasite, Parasitic infection, Allergy, Hygiene hypothesis, IgE, Cross-reactivity, IL-10*

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Parasitism is one of the major groups of enteric pathogens of children in many regions of the world[1]. It has been estimated that over a billion people worldwide are infected with helminthes such as *Ascaris lumbricoides*, *Trichuris trichiura*, and *Necator americanus*[2]. Recently, a cross-sectional study in the Karen hill-tribe of Thailand also showed that the most common parasitic infections are enterobiasis, followed by ascariasis and trichuriasis and hookworm[3]. Normally, the infections occur in early childhood and may persist into adulthood through repeated infectious exposures[4]. However, it seems that the prevalence of parasitic infection has declined in industrialized countries or in westernized countries[5].

On the other hand, allergic diseases have substantially increased in prevalence all over the world especially in industrialized countries[6]. These are generally manifested as, but not limited to, asthma, allergic rhinoconjunctivitis (rhinitis), atopic dermatitis/eczema, and food allergies[7]. Concomitantly, the mortality and morbidity of these diseases have significantly increased[8]. Based on previous studies, there are distinguishing differences in the prevalence of allergies between urban and rural areas in the tropics[9-13], with asthma occurring more frequently in urban than in rural areas[9-12].

Although there are marked differences between allergies and parasitic infections, there are certain parallels. For instance, with regard to environmental and helminth allergens, the immune response is similarly affected. Both are associated with elevated levels of IgE, tissue eosinophillia, mastocytosis, mucus hypersecretion and CD4+ T cells responses that preferentially secrete Th2 cytokines, IL-4, IL-5 and IL-13[14]. Consequently, some experts have suggested a cause-effect relationship between helminth infections and allergies. Intestinal worms may provide a protective mechanism against the development of allergic diseases[15,16].

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Hygiene hypothesis

The "Hygiene Hypothesis" was first postulated in the late 1980s[17] to explain the high prevalence of atopic disorders in developed countries. It linked atopic disorders with a lack of early life infections. David Strachan first observed a higher prevalence of atopic allergic diseases in first born children compared to their younger siblings. On the basis of this and other studies, the term, "hygiene hypothesis"[18] was introduced. It was suggested that improved hygiene, increased vaccinations and antibiotic use altered the human immune system in such a manner that it responded inappropriately to antigenic environmental substances. In other words, there was an imbalance of the immune responses between Th1 (bacterial, viral infections and autoimmune diseases) and Th2 (helminth infections and allergic diseases). For instance, if there was a lack of bacterial or viral infections in early life (a decreased Th1 response), there might be an elevated Th2 response which could be manifested as an increase in susceptibility to helminth infections and allergic disorders.

Several findings support the allergic type of immune responsiveness accounting for the Th1-Th2 imbalance. Matricardi et al showed that exposure to food or orofecal pathogens such as Hepatitis A, *Toxoplasma gondii* and *Helicobacter pylori* reduced the risk of atopy by more than sixty per cent[19]. Two years later, it was found that the prevalence of hay fever and asthma had also decreased in Hepatitis A, *Toxoplasma gondii* and the *Herpes simplex* type 1 exposure-group[20]. In addition, skin sensitization to peanuts and airborne allergens, with the exception of cockroaches, diminished among the Hepatitis A exposure-group[20].

Studies of intestinal microflora of Estonian and Swedish infants indicated differences in the rate of microbial colonization[21] and specific bacterial types[22] presented in children with or without allergies. The allergic infants had a smaller amount of lactobacilli and bifidobacteria when compared with the non-allergic subjects[20,23]. Moreover, if *Bifidobacterium* flora was found in allergic infants, it was of the adult-form[24]. Additionally, specific *Bifidobacterium* species seems to have an immunoregulatory effect against allergies[25]. Nevertheless, Murray, et al have recently found no differences in fecal microbial composition between sensitized wheezing and non-sensitized, non- wheezing children, notwithstanding the observation that some differences exist in those allergic children with eczema[26]. Heat-killed *Mycobacterium vaccae*, a potent down-regulator of Th2 and stimulator of Th1, prevented allergic manifestations and suppressed asthmatic features during an allergen challenge in mouse models[27]. Recently, an infection of *Mycoplasma tuberculosis* reduced the prevalence of atopic rhinitis and significantly decreased skin prick test reactivity in children with allergic rhinitis who also had a high incidence of tuberculosis[28].

In contrast, there are numerous studies presenting evidence against the hygiene hypothesis. First, the frequency of allergic reactions did not increase in patients who had defects in the IL-12 dependent IFN-gamma pathway, the Th1 immune response[29,30]. Second, there was a simultaneous rise in the incidence of Th1-mediated autoimmune diseases and Th2-mediated allergic diseases in the same population[31]. Data showed dissociation between an increasing prevalence of asthma and diabetes mellitus type1, which is a Th1-mediated disease[31]. Third, allergen-specific Th1 cells did not counterbalance Th2-mediated allergic asthma in a mouse model; quite the contrary, it caused airway hyperreactivity and severe airway inflammation which was reversed by transforming growth factor-beta (TGF-) to produce Th3 cells[32,33]. Fourth, helminth infection and allergic diseases did not overlap; although, both are expressed by Th2 responses[6]. Consequently, it is still controversial whether an intestinal helminth infection can reduce the risk of or exhibit a protective effect on asthma and allergy.

Helminth infection and allergy association

Several cross-sectional surveys and case-control studies have investigated the relationship between helminthes and the presence of allergies[10,34-39]. Most of them determined helminth infection by the presence of ova or larvae in stools while allergic responses were determined by several means, such as a history of allergic manifestations, skin prick tests and total and allergen-specific IgE serum levels. However, these studies presented conflicting data suggesting either no relationship or a protective effect of helminth infection to allergy. Nevertheless, there are a number of studies indicating an inverse association between helminth prevalence and allergic immune responses[10,35,37,39].

Atopy

Various studies have shown a negative correlation between helminth infection and allergen skin sensitization with a reduced risk of atopy for greater helminth infection such as *Schistosoma haematobium*[40], *Schistosoma mansoni*[16,41], *Ascaris lumbricoides*[35, 37] and *Necator americanus*[34,42]. Additionally, the percentage of *Plasmodium falciparum* re-infection also demonstrated an inverse relationship with the

presence of skin sensitization in atopic patients[43]. *Giardia lamblia* that was found in feces was significantly associated with chronic urticaria and pruritus of unknown origin[44]. Moreover, *Ascaris lumbricoides* or *Ancylostoma duodenale* infection, measured by high IgE or anti-*A. lumbricoides* IgG4 that is a marker for chronic infection, was independently associated with and offered significant protection against allergen skin reactivity[37]. As a result, active helminth infection and serological markers of chronic infection seem to independently offer a protective function against allergen skin-test sensitization. However, there was a high proportion of helminth infected patients exhibiting remarkable allergen-specific IgE level in the absence of skin-test reactivity[43,45]. In other words, allergen-specific IgE and allergen skin reactivity may or may not be associated with individual helminth infection.

To summarize, several lines of evidence suggest an inverse association between helminth infection and allergen skin sensitization. Nevertheless, the symptoms of the skin sensitization patients may be less than the actual number since some individual helminth infections do not express allergen skin reactivity but present allergen-specific IgE.

Asthma/Wheezing

Schistosoma mansoni infection was associated with a reduced course of asthma as well as less positive skin test sensitization in rural areas[46]. In addition, *Strongyloides stercoralis*, a nematode, depressed allergic reactions to airway inflammation[47]. Nested case control studies in Ethiopia indicated wheezing was more common in urban than in rural areas especially in an *Ascaris* infected group[34]. In addition, another cross-sectional survey in Ethiopia showed that there was a negative association between *Ascaris* infection and wheezing but no significant relation or any association between wheezing and hookworm or the whipworm, *Trichuris*[39]. Consequently, only *Ascaris* infection could protect against wheezing. In rural areas, as in Ecuador, there is evidence that the presence of geohelminth infections was protective against only exercise-induced wheezing symptoms, not against other types of wheezing[38].

Not all studies have shown an inverse association. A study in China has suggested that an *Ascaris lumbricoides* infection is associated with an increased risk of wheezing, asthma and inhaled aeroallergen sensitization[36]. Due to the fact that *Ascaris lumbricoides* infection is associated with pulmonary infiltrates with eosinophilia, elevations in IgE, and episodic airflow obstruction, immune responses to parasitization and the predisposition to wheezing may share common mechanisms and genetic determinants. Ascariasis may act to potentiate the Th2 immune response characteristic of childhood asthma. Recently, wheezing was found weakly associated with *Dermatophagoides pteronyssinus* and cockroach sensitization. There was no significant protective effect of overall helminth infections against wheezing or asthma[10].

Food allergy

There is a paucity of research dealing with the relationship between food allergies and helminth infection. Bashir et al showed that the nematode, *Heligmosomoides polygyrus*, offered dependent protection against an allergic reaction to the peanut extract antigen. The immunoregulatory mechanism might be from blocking the production of allergen-specific IgE[48].

Anaphylaxis

In a mice model, infection by helminthes induced the release of the cytokine, IL-10, which exerted an anti-inflammatory action, thereby diminishing anaphylactic symptoms as measured by histamine levels[48,49]. Moreover, helminth infection also suppressed the development of allergen-induced airway inflammation, which was induced by the release of eosinophils. This effect may be mediated by the transmission of IL-10[50]. Thus, helminthes may have a role in anaphylactic treatment or prevention.

However, this has the potential of being a two-edged sword in so far as infections by helminthes are strongly associated with not only the production of IgE antibodies but also with a large number of eosinophils in blood and tissues. Helminth destruction is directly caused by degranulated eosinophils adhering to the Fc epsilon receptor I, Fc RI in the presence of plentiful IgE antibodies. Further immunoregulatory research is still required in this area before treatment may even be considered.

Helminth intensity, chronicity and allergic response

The burden and chronicity of helminth infections either pose a risk or engender a protective factor against allergic diseases. Mild helminth infections seem to amplify allergen-specific IgE responses and high skin sensitization; whereas, severe infections appear to protect against atopic skin reactivity[51]. After treatment with an antihelminthic drug, allergic symptoms were improved in the milder infection but asthmatic symptoms were exacerbated in more severe infection[16].

An antihelminthic treatment trial in Gabonese school children has revealed that a reduction in *Ascaris* and *Trichuris* worm burdens resulted in a significant increase in the rate of developing skin reactivity to house dust mite[52]. Among asthmatic patients living in the parasite-endemic area, the number of asthmatic attacks and the need for maintenance therapy decreased in patients who had taken regular antihelminthic treatment with albendazole for one year. These effects had not occurred only in the period of antihelminthic administration, but also for the following year after cessation of the treatment[42]. In summary, mild and sporadic infections might potentiate Th2 responses, the release of IL-4, IL-13 and IgE from storage sites, but with severe and chronic infections, there was a diminution of allergen-induced hypersensitivity reactions in atopic individuals.

IgE blocking hypothesis and polyclonal IgE

Generally, clinical allergy is presented by efficient cross-linking of two high-affinity IgE receptors (Fc RI) on mast cells, basophils or activated eosinophils. A single antigen/allergen is captured by at least two Fc RI-bound IgE molecules to induce mediator release from the mast cells, basophils or the eosinophils and may lead to the development of a type I hypersensitivity reaction[53]. It was proposed that helminth infection produced large amounts of polyclonal IgE, which completely saturated the IgE receptor, Fc RI, on mast cells and blocked the binding of specific IgE. This was known as the "IgE blocking hypothesis". As a result, mast cell degranulation was inhibited and immediate hypersensitivity responses to specific allergens could not occur. Therefore, one of the theoretical approaches to prevent or treat allergic diseases would be to deliberately induce high IgE responsiveness, such as by artificial infection with parasites[54]. In several studies, the protective effect of helminth infection against allergic diseases was associated with highly polyclonal IgE release from plasma cells[16,55].

Nevertheless, numerous arguments have been proposed against the IgE blocking hypothesis. The major argument was that those studies seemingly in favor of the hypothesis did not control the confounding effects of age, sex and socioeconomic status. When these extraneous variables were controlled, rigorous statistical analyses revealed an insignificant effect of total IgE on parasite-mediated suppression of atopy[35,42]. Recently, Edward Mitre et al suggested that there was no association between the ratios of polyclonal IgE to *Brugia malayi* antigen (BmAg)-specific IgE and basophil responses to BmAg, which ranged from 14:1 to 388:1, in term of histamine released by general filarial infection[56]. By sensitizing normal donor basophils with increasing concentrations of polyclonal IgE to antigen-specific IgE in vitro, suppressive antigen-specific histamine responses occurred when cells were sensitized with ratios of greater than 500:1. These responses were completely blocked when the polyclonal IgE to antigen-specific IgE ratios were greater than 1,000:1. However, it was observed that polyclonal IgE to antigen-specific IgE ratios in filarial infected patients rarely reached the levels necessary to inhibit allergen-specific IgE- Fc RI binding[56].

Allergen-specific IgE: cross-reactivity

Allergen-specific IgE detection may elicit a false positive reading insofar it may be cross-reactive to antigens from helminthes as well as invertebrates and certain inhalant allergens as those attributable to dust mites or cockroaches. Consequently, it may contribute to a high prevalence of sensitization to these less potent allergens without exhibiting overt clinical symptoms. For example, mite allergic/immunotherapeutic patients were found to be cross-reactive to antigens found in food after ingesting shrimp and snails[57]. Another study involved a sample of mite- and cockroach-allergic Orthodox Jews who, while observing Kosher dietary laws prohibiting the consumption of shellfish, nevertheless exhibited an IgE antibody reactivity to the Pen a 1 (tropomyosin) allergen found in shrimp[58]. Tropomyosin has been identified as the major shrimp allergen since most shrimp-allergic patients react to it. This protein binds to approximately 85% of shrimp-specific IgE from shrimp-allergic patients. In addition, it has been shown that tropomyosin is an important allergen in other crustaceans such as mollusks, as well as in house dust mites[59], in the major cockroach allergen from *Periplaneta americana* (Per a 7)[60] and in *Ascaris lumbricoides*[15]. Recently, Arruda, et al determined the complete sequence of the Ascaris tropomyosin[15]. Not only is it an IgE binding protein, there is also a high degree of identity with tropomyosins from mites, cockroaches, shrimp and other parasites such as *Anisakis simplex* and *Onchocerca volvulus*[15]. It is speculated that an initial Ascaris infection could develop cross-reactive IgE antibodies upon exposure to mites and cockroaches, and could lead to airway inflammation and asthma-like symptoms. Therefore, infection with Ascaris could have an adjuvant effect on asthma development provided immunogens to mites/cockroaches are already present[61].

Modified Th2 responses

It is known that asymptomatic or chronic helminth infections are correlated with high levels of IgG4, one of the Th2-dependent isotypes. In addition, helminth-specific IgG4 antibodies can inhibit IgE-mediated degranulation of effector cells[62]. In the 1930s and 1940s, the concept of blocking antibodies, "Modified Th2 Responses" was initially proposed as a possible mechanism of allergen immunotherapy[63]. However, there had not been much evidence supporting this postulation until 2001 when Platts-Mills et al demonstrated that a high exposure to cat allergens resulted in a high IgG4 antibody response without sensitization or increased risk of asthma. Therefore, the modified Th2 response could be regarded as a form of tolerance and the concurrent production of the IgG4 antibodies, a desired objective of immunotherapy. The result would be a down-regulation of allergic responses[64]. Furthermore, case-control and population-based studies from many countries indicated that increased exposure to cat allergens did not lead to a higher prevalence of allergic responses[65,66]. A recent study found that the presence of a cat in the house did not decrease the IgE antibody response to dust mites, indicating that tolerance to cats can be cat-specific[67].

Likewise, there are several conditions associated with high IgG4 resulting from the immunosuppressory cytokine, IL-10[68], high levels of IL-10 in chronic helminth infection[69] and patients receiving allergen immunotherapy[70].

Role of IL-10

Chronic helminth infections in humans are associated with T cell hypo-responsiveness and reduced cytokine production. Nevertheless, the down-regulatory molecules such as IL-10, TGF- , and the immunomodulatory cytokines are also produced in chronic helminth infections, because of the activation of generations of regulatory T cells.

Several studies have demonstrated the suppressive effect of helminth infection, such as an *Ascaris suum* extract in a murine model of asthma[71] and in mice infected with *Strongyloides stercoralis*[47]. The data from both studies indicated a marked reduction of IL-4 and IL-5 levels that contributed to a profound inhibitory effect on lung inflammation and hyperresponsiveness.

Numerous studies point to the anti-inflammatory properties of IL-10, which can inhibit the release of histamine by human mast cells[72]. In a mouse model, the presence of an enteric helminth infection producing IL-10 could protect against an allergic response to a dietary antigen[48] as well as an allergic hypersensitivity response such as anaphylaxis[49]. The administration of killed *Mycobacterium vaccae*, induced allergen-specific regulatory T cells to release IL-10 and TGF- that could suppress experimental allergic airway inflammation[73]. Moreover, a helminth-induced activation of IL-10 significantly reduced (by 47%) the risk of skin reactivity to mites[35], to atopy[40] and the course of asthma[74]. Furthermore, it has been found that sharp increases in IL-10 production resulted in successful immunotherapy[69].

Implication and future research

The similarities between parasitic infections and immunotherapy strongly suggest that strategies for successful prophylaxis should be focused on the induction of anti-inflammatory responses, particularly IL-10, rather than on active induction of the allergen-specific Th1 response[53] since the transfer of Th1 cells could exacerbate rather than suppress airway inflammation[75]. IL-10 therapy is considered a promising effective treatment to control allergic diseases. Currently, it is well established that the regulatory T cells delivering IL-10 precisely to the site of inflammation in order to suppress the development of harmful responses to specific antigens. As a result, studies of suppressive cytokines derived from regulatory T cells and their interactions in various aspects such as chronicity, intensity, genetic predisposition and specific allergen reactions are needed.

In conclusion, a causal association between parasitic infections and allergy remains unclear; even though, there are evidences in support of helminth infection protecting or improving allergic symptoms. On the other hand, early exposure to helminthes may actually exacerbate immuno-inflammatory pathways involved in allergic responses. Therefore, it is important to determine several factors involved such as endotoxin exposure in early life, bacterial and viral infections in childhood, antibiotics use, vaccinations, housing conditions, lifestyle and diet. All of these may contribute to the development of allergic disorders[15]. Thus, further researches are required to determine the exact role of helminth infection with relevant host exposures, genetic influences and other important factors on allergic responses.

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การติดเชื้อปรสิตกับโรคภูมิแพ้

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โรคติดเชื้อทางปรสิตเป็นปัญหาสำคัญประการหนึ่งของไทยมาเป็นระยะเวลานาน อย่างไรก็ตามอุบัติการณ์โรคติดเชื้อทางปรสิตมีแนวโน้มลดลง เนื่องจากสุขอนามัยส่วนบุคคลและระบบสุขาภิบาลสาธารณสุขที่ดีขึ้น ในทางตรงข้ามอุบัติการณ์โรคภูมิแพ้มีแนวโน้มเพิ่มมากขึ้น นำมาซึ่งความสูญเสียทางสังคมและเศรษฐกิจอย่างมาก มีหลักฐานทางอิมมูโนวิทยาและระบาดวิทยาแสดงถึงความสัมพันธ์ระหว่างการติดเชื้อทางปรสิตและการเกิดโรคภูมิแพ้มากว่า 20 ปี จากการศึกษาสมมติฐานเรื่องสุขอนามัย สมมติฐานการปิดกั้น IgE และการตอบสนองผ่านทาง Th2 ซึ่งสนับสนุนความสัมพันธ์ในทางผกผันโดยผ่านทางการตอบสนองทางอิมมูโนวิทยา อย่างไรก็ตามยังเป็นที่ถกเถียงกันอยู่ถึงบทบาทที่ชัดเจนของการติดเชื้อปรสิตต่อโรคภูมิแพ้ ซึ่งต้องการการศึกษาวิจัยเพิ่มเติมต่อไป