General Overview about Bronchial Asthma in Children and the Relation to Helminths Infection

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Abstract

Background: Bronchial asthma is a chronic inflammatory condition that affects the airways, its diagnosis is usually made based on pattern of symptoms and / or response to therapy over time. The prevalence of asthma has increased significantly since the 1970s. As of 2010, 300 million people were affected worldwide. In 2009 asthma caused 250,000 deaths globally. Despite this, with proper control of asthma with step down therapy, prognosis is generally good. In the United States of America (USA), asthma prevalence estimates have been obtained through several nationwide surveys. The most recent asthma data comes from the Centers for Disease Control and Prevention (CDC). In 2017, the overall prevalence of asthma in the USA is 7.9%. Asthma prevalence also varies by several variables, including sex, race and ethnicity, poverty status, region of the country, and Metropolitan Statistical Area (an index of urbanization of an area) Among the environmental factors that may trigger allergic disease, infections are the studied. Surprisingly, helminthic infection, the most common helminth infections are caused by geohelminths parasites include: Ascaris, Trichuris trichiura, Lumbricoides and hookworm

Keywords: Bronchial Asthma, Helminths Infection.

Bronchial Asthma

Epidemiology:
In the United States of America (USA), asthma prevalence estimates have been obtained through several nationwide surveys. The most recent asthma data comes from the Centers for Disease Control and Prevention (CDC). In 2017, the overall prevalence of asthma in the USA is 7.9% (1). Asthma prevalence also varies by several variables, including sex, race and ethnicity, poverty status, region of the country, and Metropolitan Statistical Area (an index of urbanization of an area).

Figure (1): Current asthma prevalence in the USA, stratified by age group, sex, race, ethnicity, poverty status, geographic region, and place of residence, (1).
There are many studies that was done in Egypt among school children showing that the prevalence of bronchial asthma among school children ranged from 6.2% in Upper Egypt, up to 46.1% in Cairo (2).

**Burden of asthma:**
The asthma in childhood affects rate of school absence as it was the top reason in the USA in 2013, accounting for 13.8 million missed school days, and from 2014 to 2017, half of all children with asthma were reported as having one or more asthma attacks in the past year. Furthermore, children with asthma leave school earlier, have lower school achievement, and may they need special educational requirements for mental health problems (3).

Asthma has important economic burden for children, including direct cost to children and their families. As asthma control is the main goal of treatment which need many drugs therapy, prevention of exacerbation and recurrent follow up visits all may become costly if there is no insurance. Also, there is burden over health care centers with emergency care and hospitalization, also indirect costs through loss of productivity (4).

**Etiology and risk factors of asthma:**
As considering increase asthma prevalence in past few years and associated burden also asthma therapy which depends mainly on asthma controlling rather than changing nature of disease. This is important to understanding disease mechanism (5).

Asthma is considered multifactorial disease as it has polygenetic nature with multiple environmental and risk factors that play role in triggering of the disease (5).

**Genetics:**
Twin and family studies showing that asthma has genetic back ground that control development of asthma as asthma is heritable disease about 119 asthma associated genetic variants were identified that has multiple relations with asthma. Most of people with asthma have a family history of atopy (6).

Numerous gene associations for asthma have been identified, including single-nucleotide polymorphisms (SNPs) found on long arm on chromosome 2, chromosome 6, chromosome 9, chromosome 15 and chromosome 22. Also, there is several SNPs on chromosome 17q21 show different associations between childhood onset asthma and adult-onset asthma (7).

**Maternal smoking:**
The meta-analysis and systemic review that was done over prenatal active smoking mothers showing odds of developing childhood asthma is more than double (8).

**Antibiotic use:**
There is longitudinal cohort study showing that 64% of pregnant woman received antibiotic. The study showing that increasing risk of childhood wheezy chest and asthma is dose dependent and more with broad spectrum antibiotic (9).

**Maternal nutrition:**
There is studies showing that vit.D sufficiency throughout pregnancy has protective role against early childhood asthma or recurrent wheezy chest up to 3 years old (10).

**Epidural anesthesia:**
The cohort study was done showing more exposure dose and duration to neuraxial anesthesia reduce risk to early asthma (11).
Stress:
The relation between prenatal stressful condition and developing of early childhood asthma and wheezy chest. The risk may increase through multiple mechanisms including altered Th1/Th2 cytokines with persistent Th2 in early life. Changes in DNA methylation and gene expression with abnormal regulation of neurotransmitter receptors interaction. Altered glucocorticoid receptors in the fetus or in hypothalamic-pituitary-adrenal axis in post-natal life (12).

Childhood risk factors:
Breast feeding:
There is multiple studies showed that exclusive breast feeding with increasing duration without eczema in first year of life leading to decrease odds of developing childhood asthma in first six years of life (13).

Gender and sex:
Asthma is more common in boys in childhood period, while adult asthma is more common in women, which suggests sex hormones may play a role in the etiology of some forms of asthma (14).

Obesity:
Obesity can increase the chances of developing asthma or worsening asthma symptoms. This may be because obesity can change the immune system (15).

Smoking:
The American Lung Association also states that secondhand smoke is particularly dangerous for children. An estimated 400,000 to 1 million children with asthma have their condition worsened by secondhand smoke (16).

Other risk factors and triggering:
There is multiple studies and survey showing that there is risk factors and triggering of pre sensitized airway and genetic inheritance as, low birth weight, parent smoking, temperature or weather changes, exercise, emotion as stress, allergen exposures as (pollen, tics, air pollution, fumes and furred pets at home), rhinovirus and respiratory syncytial virus with some drugs as NSAIDS (17).

Pathophysiology and pathogenesis of asthma:
The patho-physiological basis of asthma is considered a complex interaction at all levels and scales of disease from genetics to cellular, tissue and organs with involvement of risk factors and triggering. The pathogenesis of asthma including air way inflammation (T2high and T2 low), air way hyper responsiveness and air way remodeling. The interaction between these abnormalities leading to development of manifestations of asthma as wheezing, dyspnea and cough (18).
**Figure 2:** scales of disease of asthma with examples of disease heterogeneity at all levels from gene through to patient (7).

**Airway inflammation:**

1- **T2-high:**

T2HIGH-mediated eosinophilic disease, as result of T-cell polarization by the transcription factor GATA3, it is dominant inflammatory cell of asthma. T2HIGH eosinophilic inflammation is mostly come with atopy, and allergic asthma accounts for most cases in children and approximately half of cases in adults. Sputum eosinophilia is appeared in up to 80% of asthmatic patients without corticosteroid treatment, and 50% of corticosteroid treated asthmatics patients in addition to the eosinophilia, also mostly there is high levels of cytokines such as interleukins IL-4, IL-5 and IL-13 which are important in regulation of eosinophilic function (19).

There are some studies showing that almost all asthmatics have T2HIGH disease, even in the absence of measured eosinophilia. May due to reduction of T2-inflammation which suppressed by corticosteroids so appear as non-eosinophilic asthmatics. Secondly, eosinophils are cleared from the lung by macrophages, and the rate of clearance can be determined by measurement of the amount of eosinophil proteins in airway macrophages. In apparently non-eosinophilic patients, examination of eosinophil proteins in airway macrophages confirms the presence of eosinophil clearance processes, suggesting some eosinophilic inflammation that is being controlled by therapy. In other side, there is some patients have high sputum eosinophil counts but low levels of airway macrophage eosinophil clearance, suggesting treatment resistance due to either macrophage dysfunction or inadequate quantities of steroid reaching the airways (20). Those severe asthmatics with persistent T2HIGH inflammation and a significant sputum eosinophilia are more likely to suffer from uncontrolled asthma, and have a high risk of asthma exacerbation (21).
2-T2-low: T2LOW inflammation is non-eosinophilic and mediated by T1 and T17 pathway with or without neutrophilic inflammation and oxidative stress (22). Some asthmatic patients switch T2 with T17 inflammatory profile, so some neutrophilic asthmatic inflammation occur iatrogenic through corticosteroid suppression of T2 and up-regulating of T17 (23). Patients with isolated T2LOW neutrophilic airway inflammation (and absence of T2 cytokines) are mostly have non-atopic late-onset asthma with low response to inhaled corticosteroid treatment. Some studies suggested that the mechanism for neutrophilic airway inflammation is bacterial colonization and the presence of bronchiectasis, so, corticosteroid non responsiveness in neutrophilic asthmatic inflammation the CT must done to exclude bronchiectasis and may use antibacterial to decrease chronic bacterial colonization (24).

![Figure 3](image_url): Inflammation of the bronchial tubes could lead to permanent narrowing of the airways (25).

Airway hyper responsiveness: (AHR)
AHR meaning that increased or dysfunctional airway smooth muscle (ASM) contraction through direct or indirect stimuli. AHR is augmented by T2HIGH and T2LOW inflammation. Asthmatic patients who do not obviously provide in sputum profile either T2HIGH or T2LOW inflammatory profiles usually have less severe asthma and less frequent exacerbations. However, this group mostly having asthma by AHR, and they may have significant bronchoconstriction symptoms, even without detection airways inflammation (26).

Airway remodeling:
Airway remodeling may define as multiple structural changes in airway with change in a composition, contents and organization of cellular and molecular components in airway (27). These changes in form of epithelial damage, mucus gland hyperplasia, sub epithelial excessive collagen deposition, sub mucosal matrix deposition with hypertrophy and hyperplasia of ASM (28).
The mechanism of these remodeling through chronic interaction between different inflammatory cells as eosinophils and mast cells with epithelial cells and ASM and release of various cytokines and growth factors (27).

![Image: Comparison of normal and inflamed airways]

**Figure 4:** Airway narrowing in an asthma attack (29).

**Diagnosis of asthma:**
Making diagnosis of asthma is based mainly on identification of both characteristic pattern of respiratory symptoms and variable expiratory airflow limitation. The pattern of respiratory symptoms and evidence supporting diagnosis, asthma should be diagnosed when the patient first presented, as it is usually difficult to confirm diagnosis of asthma once the controller has been started (30).

**History:**
- **Family history:** presence of maternal and paternal history of asthma or atopic diseases strongly support diagnosis of asthma mostly maternal history (31).
- **Medical history:** presence of "atopic march " which is the pattern of clinically described atopic diseases. This atopic march firstly presented with eczema or allergic rhinitis in infancy then developing of asthma in childhood period (32). Also, early sensitization by allergens as house dust mites have been associated with increased risk of developing asthma (33).
- **Presentation of asthma symptoms:** presentation at early childhood till age of six years usually nonspecific and variable making diagnosis of asthma difficult. The symptoms including cough both dry and productive, wheezy and shortness of breath most commonly at night. The history of bronchodilators improving of manifestations in this age group is important for diagnosis of asthma. These symptoms usually intermittent and triggering mainly viral infection more than allergens (34). While presentation in late childhood commonly are wheezy chest associated with chest tightness and non-localized chest pain which usually intermittent and related mainly to allergen and exercise induced symptoms this leading to decrease activity and refusal of performance of any exercise but severe attacks are more common with exposure to triggering. Children diagnosed with asthma
may find that their asthma symptoms almost completely disappear or are less severe during puberty, but they may recur later in life (34).

**Physical examinations:**
The signs of asthma itself is variable and usually the patients come in between attacks with only history of asthma symptoms. The manifestations of acute attacks mostly by auscultation diffuse wheezy chest with prolonged expiration. Also, there is may variable degree of respiratory distress in form of tachypnea, retraction, grunting or even cyanosis which may need respiratory support (35).

**Investigations:**
Asthma is mainly clinically diagnosed, if asthma is suspected the pulmonary function test must be done. Several algorisms were done to connect between clinical history and manifestations with specific tests to decrease over-diagnosis or under-diagnosis. These tests including:

1- **pulmonary function tests:**
   **Spirometry:** which involves breathing in and out through a tube connected to a computer. This measures how much and how fast the air moves when breathing in and out with maximum effort. The elements measured in spirometry are forced vital capacity (FVC), forced expiratory volume in first second (FEV1) and or peak expiratory flow (PEF) (36). **FEV1 and FEV1 /FVC ratio** in children measuring of FEV1 alone may miss diagnosis of airway obstruction so using ratio of FEV1 to FVC which reduced is better. But once diagnosis of obstructions was done, FEV1 percentage give an idea about risk of exacerbation and control level with responsiveness of treatment (30).

   **Spirometry with bronchodilator tests:** to measure how much and how fast air moves in and out both before and after taking an inhaled medicine to relax the muscles in the airway. (Graham et al., 2019). Spirometry with bronchodilator response is considered positive if there is improvement >12 % and > 200 ml in FEV1. (30)

   **Bronchoprovocation tests:** to measure how airways react to specific exposures. During this test, inhalation of different concentrations of allergens or medicines was done. Spirometry is done before and after the test (37). This challenging test used in documenting bronchial hyper sensitivity. The test is sensitive has better negative than positive predictive value (37).

   **Peak expiratory flow (PEF) tests:** to measure how fast blowing air out using maximum effort. This an easy and not expensive test but less sensitive can be used to asses response to treatment (38).

2- **Tests to detect eosinophilic airway inflammations:**
   **Fractional exhaled nitric oxide (FeNO) tests:** to measure levels of nitric oxide in breath. High levels of nitric oxide may mean that the lungs are inflamed. As NO considered signaling molecules which produced by respiratory epithelium from L-arginine by NO synthase enzyme. This test is done in adults and children age 5 and older (39).

   **Sputum examination and Exhaled breath condensate:**
The sputum examination done to detect inflammatory cells, such as eosinophils and neutrophils.

2- **Tests for atopic status :**
   **Complete blood cell count :**
Presence of eosinophilia in CBC suggest asthma, allergy or both. The level of eosinophil more than threshold of $> 0.30 \times 10^9$ or $0.40 \times 10^9$ / L. This level may persist until two weeks of starting treatment if no improvement it is called persistent eosinophilia. Although the peripheral eosinophilia can be presented with other conditions in children as parasitic infections or malignancy but asthma and allergy are most likely causes (39).

**Serum IgE :**

IgE is secreted by B cell which undergo class-switching by effect of antigen-dependent receptor-ligand binding interaction with an activated T2 cell. This usually occurs within secondary lymphoid tissues while these lymphoid tissues immature in infancy therefore IgE level in infancy till age of 6 months if $>100\text{KU} / \text{L}$ determine presence of food allergy while in children level $> 200 \text{KU/L}$ (39).

**Allergy testing:**

Measurements of allergic sensitization in atopic children is important for proper care of these children, these tests including skin prick tests and measurement of specific IgE level. Skin prick test with common allergen is simple and rapid with high sensitivity. While measuring of specific IgE is more expensive but it can be used in non-cooperative patients, those with widely spread skin diseases or with risk of anaphylaxis (30).

**3- Investigations to exclude other diagnosis and detection of complications:**

**Chest Radiograph:**

Chest radiography usually is not necessary during initial routine investigations of asthma. The cost-effective approach would be delayed CXR and only performed in suspected complications or if etiology is uncertain (40).

**Diagnosing asthma in children younger than 6:**

It can be hard to tell whether a child under age 6 has asthma or another respiratory condition, because young children often cannot perform a pulmonary function test such as spirometry. After checking a child’s history and symptoms, try asthma medicines for a few months to see how well a child responds. About 40% of children who wheeze when they get colds or respiratory infections are eventually diagnosed with asthma (40).

**Impact of Helminthic Infections on Childhood Asthma and Its Relation to Disease Severity**

Asthma is common in urban centers in Latin America, but atopic asthma may not be the main phenotype among children. Helminth infections are highly prevalent in poor populations, and it was hypothesized that they attenuate allergic asthma. In contrast, other factors are related to the expression of a non-atopic wheeze/asthma phenotype (41). Helminth infections were inversely associated with positive SPT results. Before the age of 2 yrs., bronchiolitis was the major independent risk factor for asthma at age 10 yrs; high-load *Ascaris* infection, a family history of asthma, and positive SPT results were also asthma risk factors. Most asthma and wheeze are of the non-atopic phenotype, suggesting that some helminths may exert an attenuating effect on the expression of the atopic portion of the disease. In contrast, viral bronchiolitis predisposes more specifically to recurrent airway symptoms (42).

The increased burden and prevalence of wheeze and asthma since the 1960s are well documented, especially among children living in rich societies. Asthma in school-age children from developed countries is commonly associated with an atopic phenotype, including bronchial hyperresponsiveness, peripheral blood eosinophilia, increased allergen specific immunoglobulin (Ig) E levels and positive allergen skin-prick test (SPT) results.
The International Study of Asthma and Allergies in Childhood (ISAAC) has demonstrated that asthma and asthma-related symptoms are highly prevalent among many less-privileged communities in Latin America. These data are seemingly at odds with the so-called hygiene hypothesis. They suggest that the relationship between asthma and the atopic phenotype is less evident in children from developing countries. Data from Africa show that asthma with atopy is more potent in children living in urban rather than rural settings (43). Parasitic infections are common among disadvantaged populations in Africa and Latin America. Recent data from these areas have shown an inverse association between helminth infections and allergy (defined by SPT), causing attenuated asthma-related symptoms. A series of studies in rural Ecuador have shown that asthma is not common in a highly parasitized population and that helminth infections are inversely related to allergen skin test reactivity. This raises the question of which environmental factors might be responsible for the high prevalence of asthma and asthma-related symptoms in poor populations in Latin America (44).

Despite the inverse association of helminth infections and positive SPT results to aeroallergens, it was found that a higher load of Ascaris was a risk factor for asthma and asthma-related symptoms at the age of 10 yrs, independent of other common risk factors. This was particularly true when considering non-atopic children in isolation. A similar association has been observed in a large rural population in China. The respiratory effects of Ascaris on the airways may be related to its passage through the lungs during part of its life cycle and its high allergenicity. The clinical symptoms may be associated with Loffler-like syndrome through either local effect of larval tissue migration, airway reactivity or bronchospasm, infectious bacterial complications of parasitic migration and aspiration, or, even more rarely, chronic eosinophilic pneumonia. Helminths may suppress atopic inflammation in the airways while, at the same time, increasing the risk of non-atopic wheeze, possibly via the mechanism outlined above. (45).

Asthma and Ascaris lumbricoides infection are common health issues affecting 250 and 700 million people worldwide, respectively. The relationship between ascariasis and asthma is a matter of substantial interest and research. It is essential to take into account the fact that high-Ascaris or high-helminth loads were arbitrarily defined as being values in the upper tertile of the distribution. This corresponded to an infective load of ≥100 eggs, which suggests a significant but far from heavy infection. Other studies, mainly from rural environments, report a much higher burden of infection than found in the present, rather urbanised, community of Southern Brazil. Thus, a protective effect of helminth infection on asthma and allergies may be related to either infective load or frequency of infection rather than simply to the presence of helminths. In many African studies, a protective effect has been shown with hookworm, whereas, in areas in which Ascaris is the most prevalent species, a protective effect may not be found. However, longitudinal studies are needed to adequately investigate whether these apparent helminth-related differences are real and why they occur (46).

The relation between infection with helminths such as A. lumbricoides and atopy or asthma is controversial. Helminthiasis has been associated with a reduced risk of atopy and/or asthma symptoms in areas with a high prevalence of parasitic infections but with increased risks of atopy and asthma in areas with a low prevalence of parasitic infections. These findings suggest that the relation among helminthiasis, atopy, and asthma is complex and
influenced by host factors, timing and intensity of disease, and concurrent environmental exposures (47).

Studies of children not selected based on asthma in Brazil, Germany, and South Africa have reported that sensitization to Ascaris is associated with wheeze, increased total serum IgE levels, higher prevalence of asthma and hay fever (by parental report), atopic asthma, atopic airway responsiveness, and increased odds of sensitization to 1 aeroallergen. Those studies were limited by small sample size, limited information on socio-economic status, lack of data on the prevalence of helminthiasis in the source population, non-examination of stool specimens for helminths, and absent or limited assessment of lung function or airway responsiveness. Among children with asthma in an area with high prevalence of helminthiasis, unblinded anthelminthic treatment for 1 year resulted in a 2-year reduction in asthma attacks and medication use but no significant change in pulmonary function or frequency of sensitization to Ascaris (48).

Nematode helminth infections have a worldwide distribution, and their related disorders are associated with suppression of allergic effectors in hosts, a potential mechanism for parasite killing. These inhibitory effects on allergic inflammation and inverse geographical distribution with asthma suggested that helminthic infections may have an inhibitory effect on asthma and other allergic diseases. In contrast to other STH, toxocariasis could trigger the inception of allergic diseases such as asthma (49).

There are conflicting data in the literature regarding the relationship between Toxocara infection and childhood asthma (50).

It was found that there is strong evidence that Toxocara infection is a significant risk factor for childhood asthma. In the last two decades, there has been considerable interest in exposure to helminth infections, including toxocariasis, as an environmental risk factor for allergic asthma. However, some of these studies showed a protective effect by helminths. A previous study reported a slight, non-significant increase in asthma risk for individuals infected with any helminths parasites. Furthermore, the findings demonstrated that infection with Ascaris lumbricoides was significantly related to increased risk of asthma, while hookworm infection was associated with a significantly reduced risk of asthma (51).

An experimental study demonstrated that AIP-2 secreted by hookworms effectively suppresses airway inflammation in a mouse model of asthma. Several factors, including helminths species, acute or chronic infection, the intensity of infection, and host genetics, may influence the association between helminth infections and allergic manifestations. It is assumed that current helminth infection may be more involved in the induction of allergic asthma. The exact mechanisms for Toxocara infection to induce of asthma and other allergic disorder remains unclear (52).

Although experimental studies have clarified that infections with nematodes whose life cycle includes migration across pulmonary tissues to the development of larval stages (e.g., Toxocara spp. and Ascaris suum), are associated with diminished lung function, especially in accidental hosts like human. Toxocara larvae can’t mature further in the human body (accidental hosts) and migrate through different organs. Larval migration is associated with intensive immunological responses, resulting in allergic inflammation in involved tissues, including the lung. Pulmonary inflammation usually occurs within 48 hours post-infection and can be continued for up to two or three months. A previous study utilizing an animal
model, have shown that previous infection with *T. canis* intensifies ovalbumin (OVA)-induced allergic airway inflammation in mice. Moreover, they reported elevated levels of IgE antibody and eosinophil counts in bronchoalveolar lavage fluid and also the expression of IL-4 mRNA in lung tissue of pre-infected mice (52).

Human immunological responses to *Toxocara* infection seem to be the main effectors to the development of allergic disorders. A wide range of molecules in *Toxocara* spp. have a potential role in host-parasite interaction, including adhesion molecules, lectins, peptidases, and SCP/TAPS proteins. Immune responses against *Toxocara* infection are mediated by CD4+ T-helper type-2 cells (Th2) through the induction of cytokines such as IL-4, IL-5, IL-10, and IL-13, which can lead to an increase in the level of specific antibodies and eosinophilia, causing effective immune responses to parasite killing. It seems that *Toxocara* excretory-secretory (TES) antigens are vigorous stimulators that induce Th2-associated immune responses and therefore contribute to airway hypersensitivity and inflammation, associating chronic *T. canis* infection with allergic disorder like asthma, allergic rhinitis, atopy, and urticarial (53).

Progression of infectious diseases, including parasitic infections, often depends on which cytokine profile, type 1 or type 2, is preferentially induced. In the majority of cases, the immune responses of the hosts to helminthic infection are remarkably similar, being Th2-like with the production of significant quantities of IL-4, IL-5, IL-9, IL-10, and IL-13 and consequently the development of strong immunoglobulin E (IgE), eosinophil, and mast cell responses. Accordingly, polarization of the immune response to Th2 also down-regulates the Th1 cell subset (54).

Despite the vast amount of research investigating how the mammalian host recognizes helminth antigen (Ag) and reacts with a Th2 response, this issue remains unresolved. There are multiple suggested pathways for initiating the Th2 response in which IL-4 produced early in the reaction, plays an important role in the consolidation and amplification of the Th2 pathway. Sources of IL-4 include atypical subsets of T cells not restricted by class II major histocompatibility complex, including NK1+ CD4+ T cells, conventional CD4+ naïve and memory T cells, eosinophils, cells of the mast cell/basophil lineage, antigen-presenting cells, and dendritic cells (54).

Detection of *A. lumbricoides* infection was performed by microscopic examination of fecal samples. These methods have a high degree of specificity, but their sensitivity is low, especially in communities with low-level infections. Serological methods to detect *A. lumbricoides*-specific antibodies, indicating active or prior infection, could be helpful to understand better the association between *A. lumbricoides* and allergic disorders such as atopy and asthma. It has been shown that anti-Ascaris IgE and IgG are valuable markers for exposure to *A. lumbricoides*, especially in areas of low prevalence. Several epidemiological investigations have explored the association between anti-Ascaris IgE and asthma symptoms. Most of these investigations demonstrated a significant positive association; no studies have looked at an association between anti-Ascaris IgG and asthma. The goal of this study was to evaluate the association between *A. lumbricoides* infection and childhood asthma. It was found that potential risk factors associated with *A. lumbricoides* disease among children in the Mazandaran province of Northern Iran (55).

Communities in rural Africa typically have a very low prevalence of asthma and low rates of skin test reactivity to inhalant allergens. In addition, skin test positivity does not show a significant association with asthma, as demonstrated in developed countries. Mechanisms
associated with this inverse association are not entirely understood. It has been proposed that high levels of IL-10 and transforming growth factor-b (TGF-b) produced during chronic infections with helminth parasites, as a result of the generation of regulatory T cells, might downregulate allergic responses. Several lines of evidence point to the anti-inflammatory properties of IL-10, particularly inhibiting skin test responses and mast cell degranulation. Another hypothesis is that high levels of IgG4 produced during parasitic infections could act as blocking antibodies or be part of a modified Th2 response since IgG4 is a Th2-dependent isotype not associated with clinical allergy (56).

Studies performed in Brazil and those carried out in rural communities in Ecuador also point to a protective role of parasites in decreasing skin test reactivity and attenuating asthma symptoms, particularly of infections with Schistosoma. In addition, intervention studies have provided support for a causal association between helminth infection and atopy. For example, results of an open-label placebo-controlled randomized trial in Gabon revealed that children treated with anthelmintics (praziquantel and albendazole) every three months for over 30 months presented an increase in the rate of developing skin test reactivity compared with children who received placebo. This effect was shown to be partially mediated by reductions in helminth infections (57).

The epidemiologic observation that asthma is prevalent and helminthic infection relatively uncommon in developed countries and that the converse is true in many developing countries has led to speculation that the two phenomena may be inversely associated. However, the relationship between asthma and helminthic infection remains uncertain. Previous studies in endemically parasitized non-Chinese populations have variously argued that helminthiasis causes asthma, inhibits asthma, or is unrelated to asthma (57).

References


