

EDITORIAL

Clinical and Experimental Allergy

Toxocara canis infection: an important and neglected environmental risk factor for asthma?

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The prevalence of asthma has increased in industrialized countries over recent decades [1]. Large international studies such as the International Study of Asthma and Allergies in Childhood (ISAAC) have provided evidence for large international differences in the prevalence of asthma symptoms with trends of lower prevalence in non-industrialized countries compared with industrialized countries [2, 3]. This pattern does not appear to hold true for some urban centres in non-industrialized countries, particularly in Latin America, that appear to have a very high prevalence of wheeze within the previous 12 months [2, 3]. In contrast, the limited data from rural areas indicate a low prevalence of wheeze [3, 4], raising the possibility that environmental changes associated with the process of urbanization may be important determinants of asthma risk [5]. Considerable attention is now being paid to identifying environmental factors that may contribute to the international differences in asthma prevalence.

Among environmental exposures associated with asthma risk, there has been considerable interest in helminth infections, particularly geohelminth (e.g. *Ascaris lumbricoides* and hookworm) and schistosome infections [6, 7]. Geohelminth infections are highly prevalent infections and are estimated to infect in excess of 2 billion individual worldwide [8], and affect principally poor populations living in the rural Tropics. Observational studies of the association between geohelminths and asthma have provided conflicting evidence, with some showing a positive [9] or no association [4, 10], while others have shown an inverse association [11].

Although it is possible that helminth infections are not causally associated with asthma, the conflicting findings of epidemiological studies have also been interpreted in terms of different effects on the allergic process caused by

geohelminth parasites according to the stage of infection (i.e. acute vs. chronic). Acute infections that may predominate in populations with a low prevalence of infection may enhance allergic respiratory symptoms, and chronic infections that predominate in populations with a high prevalence of infection may suppress symptoms [6, 12]. It has been suggested that strong host allergic inflammatory or immune modulatory responses in acute and chronic infections, respectively, could affect host inflammatory responses to aeroallergens through bystander or allergen-specific effects [6, 7]. The acute/chronic phenotypes broadly reflect the immune response mounted by the host against the parasite – allergic phenomena appear to be rare during chronic helminth infections while individuals with 'acute' infections frequently present with allergic symptoms [13]. The findings of experimental murine models broadly support this scheme [14, 15].

Assuming a causal association, four factors may determine the effect of helminths on asthma: (1) *Timing* – the time of first infection and the duration of infection are likely to be important. Early and/or long-lasting (chronic) infections may be more likely to induce immune modulatory effects that suppress allergic inflammation caused by parasite and non-parasite allergens while later and/or periodic infections may enhance allergy [16]; (2) *Intensity of infection* – heavy parasite burdens may induce immune downmodulation while light infections may be more likely to have the opposite effect [6]; (3) *Host genetics* – the ability to induce specific host immune regulatory mechanisms may be partly determined by host genetics. Individuals who are genetically susceptible to atopic disease may be more likely to develop allergic responses to helminth and non-parasite allergens and may be more resistant to infection [17]; (4) *The parasite* – different helminth parasites may have different effects on the risk of asthma. A recent meta-analysis of observational studies provided some evidence that *A. lumbricoides* is associated with an increased risk of asthma, that hookworm infection is associated with a decreased risk of asthma, and that

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Trichuris trichiura infection is not associated with asthma risk [18].

Within the context of this debate, the paper in the current issue by Pinelli et al. [19] is a timely contribution to our knowledge of allergic inflammation in the lungs caused by a different helminth parasite. *Toxocara* infection of humans is caused primarily by *Toxocara canis* (a natural and universal infection of dogs), but may also be caused by *T. cati* (a natural infection of cats). The study investigated the effect of *T. canis* infection on airway inflammation in a well-defined experimental murine allergy model and showed that previous infection with *T. canis* exacerbates ovalbumin(OVA)-induced allergic airway inflammation. Like humans, mice are not permissive hosts for *Toxocara* infection. *Toxocara* larvae are unable to develop to adults and migrate through different organs, causing allergic inflammation in the tissues including the lungs. The study showed that pre-infection with *T. canis*, followed by OVA sensitization and challenge resulted in more severe pulmonary inflammation than that caused by *T. canis* infection or OVA alone. IgE levels and eosinophil counts in bronchoalveolar lavage fluid, and expression of IL-4 mRNA in lung tissue were elevated in pre-infected mice. Interestingly, the timing of infection was important; infection 3 days before OVA sensitization resulted in significantly greater airways reactivity than infection or OVA alone while infection 17 days before OVA sensitization did not appear to affect airways, reactivity. The presence of *T. canis* larvae in the lungs at the time of OVA sensitization may, therefore, be important for the development of severe inflammation – most larvae are present in the lungs 3 days after infection and disappear from the lungs by 20 days post-infection. This experimental model may contribute to our understanding of the pulmonary effects of human infection with this parasite.

Humans may become infected with *T. canis* by ingestion of infective eggs wherever dogs defecate, such as public play areas for children. The presence of infection (or past infections) is determined by measurement in serum of IgG antibodies to antigens of *T. canis*. Seroprevalence surveys suggest that prevalence is highly variable worldwide. Prevalences of 10% or more are not unusual in Europe [20] or the United States [21] and may be higher in many non-industrialized countries. In humans, the eggs hatch in the intestine from where the larvae penetrate the intestinal wall and migrate to different organs. *Toxocara* larvae release excretory/secretory antigens during migration that cause allergic inflammatory reactions in the tissues [22]. Although most infected individuals are asymptomatic, a few develop a severe illness called visceral larva migrans (VLM). VLM occurs most frequently in young children and a significant proportion (32–44%) of affected children have respiratory symptoms that may include an asthma-like illness with cough and wheeze [21]. There has been interest in the potential asthma-

inducing effects of *Toxocara* infection at a population level but epidemiological studies have provided inconsistent findings, with some studies showing no effect [23] and others showing a positive association between asthma and *Toxocara* seropositivity [24, 25]. To my knowledge, no epidemiological study has shown a significant inverse association between *Toxocara* seropositivity and asthma symptoms.

Whether *T. canis* is an important risk factor for asthma in human populations remains to be determined. Given the high prevalence of infection even in industrialized countries, it is a relatively neglected infection and one of the reasons for this is that active infection is difficult to diagnose. Current serologic assays, although reasonably specific and sensitive, cannot distinguish between current infections and past exposure and specificity may be poor at low antibody titre, particularly in areas where other helminth infections such as the roundworm *A. lumbricoides* are endemic. A definitive diagnosis of VLM requires the identification of the parasite in the tissues and tissue biopsies carry a significant risk to the individual.

The secular trends or international differences in asthma prevalence are unlikely to be explained by any helminth infection including toxocariasis. However, *T. canis* infection may contribute to asthma symptoms in a sub-population of young children exposed to high infectious doses or repeated infections in areas where the infection is present, and may be an important risk factor for asthma in some populations [25]. Because *T. canis* is not a natural infection of humans, the host (or parasite) may not be able to down modulate the allergic response as may occur during chronic infections with natural helminth infections of humans (e.g. geohelminths) that have co-evolved with their human hosts over thousands of years.

A limitation of the experimental model used by Pinelli et al. [19] is that infection is assumed to occur before allergen sensitization. The reverse may actually occur in human populations with *T. canis* infections being acquired in the second year of life while exposure to and sensitization to aeroallergens is likely to occur earlier. An infective dose of 500 eggs, used in the study by Pinelli et al. [19], is a large infective dose for a small mammal and comparable doses in humans may be unusual. These facts emphasize the important limitations of experimental animal models in inferring about complex disease processes in humans. Such models can rarely represent the sequence of environmental events that lead to the development of asthma symptoms, although they can provide useful insights into immunological mechanisms.

In this context, the study by Pinelli et al. [19] provides a useful experimental model with which to investigate the immunologic mechanisms by which a non-natural infection of mice, *T. canis*, may cause allergic inflammation in the lungs and airways reactivity. The study is also a reminder to investigators of the environmental

determinants of asthma in human populations that helminth infections, such as *T. canis* which are highly prevalent worldwide, should be considered as potential environmental risk factors for asthma.

Acknowledgements

This editorial discusses the findings of the paper in this issue by Pinelli et al. (2008). P. J. C. is supported by Wellcome Trust grant 074679/Z/04/Z.

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