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Original Article

Soil-transmitted helminth infection and skin prick test reactivity in children

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Abstract

Background Allergic diseases cause an increasingly large burden in developed countries and in urban areas of middle-income countries. Parasitic infections may induce allergic responses in humans, particularly soil-transmitted helminth (STH) infections that are prevalent in childhood in developing countries. Although soil-transmitted helminth infections have been associated with lower prevalence of allergen skin test reactivity, study outcomes remain inconclusive.

Objective To analyze for an association between STH infections and skin prick test reactivity in children.

Methods We conducted a cross-sectional study in August 2009 among primary school students aged 7-12 years, at Secanggang Subdistrict, Langkat District, North Sumatera Province. Sixty eight children were recruited in this study consisted of 34 children with STH infections and the other 34 children without any STH infection. Soil-transmitted helminth infections were determined by Kato-Katz stool examinations. All subjects underwent skin prick tests for seven allergens. Results were considered to be positive if wheal diameters ≥ 3 mm and negative when wheal diameters < 3 mm. Data was analysed by Chi-square test.

Results Stool examinations revealed that the most common infection was *T. trichiura* (18/34 subjects), followed by mixed infections (*T. trichiura* and *A. lumbricoides*; 12/34 subjects), and *A. lumbricoides* (4/34 subjects). There was a significant association between STH infections and negative skin prick test (P=0.002). In addition, there were significant associations with negative skin prick tests for each helminth type: *A. lumbricoides* (P=0.001), *T. trichiura* (P=0.01) and mixed infection (P=0.006). Severe infection intensity was also significantly associated with negative skin prick tests (P=0.031).

Conclusion Children with STH infections tend to have negative skin prick test results. **[Paediatr Indones. 2014;54:52-6.]**.

Keywords: *soil-transmitted helminth, skin prick test*

More than two billion people worldwide are chronically infected with soil-transmitted helminths (STHs) including *Ascaris lumbricoides*, *Trichuris trichiura* and hookworms *Ancylostoma duodenale* and *Necator americanus*.[1] The International Study of Asthma and Allergy in Childhood (ISAAC) reported large differences in the prevalence of self-reported symptoms of allergic disease. For asthma symptoms, the highest prevalences were from centers in the United Kingdom, Australia, New Zealand, and Ireland, while the lowest prevalences were from centers in China, Indonesia, India, and Ethiopia.[2,3] In addition, a Makassar, Indonesia study in 2008 reported a 60% prevalence in moderate-severe allergic rhinitis.[5]

Soil-transmitted helminth infections may induce strong allergic responses in humans. There are close similarities in allergic inflammation caused by host immune responses to environmental allergens and to parasite antigens.[6] Nonetheless,

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several epidemiological studies suggested an inverse relationship between STH infections and allergies. A cross-sectional study pointed out the possible inverse association between sensitization to *A. lumbricoides* and asthma severity among children with asthma in Costa Rica, a country with a low prevalence of ascariasis (estimated to be 2% in adults and children), but high prevalence of asthma (23.7% among adolescents).[6] Furthermore, a Salvador, Brazil study found that early infection of *T.trichiura* may protect against the development of allergen skin test reactivity in later childhood.[7]

Even today skin testing remains the main test for confirming an allergic response. New primary care guidelines for the management of asthma, rhinitis and eczema now recommend allergy testing as part of an atopic child workup.[8] With the right technique and interpretation, as well as good allergen quality, this test has higher sensitivity and specificity. In addition, it is easy, quick, less expensive, and painless.[9] Our study was designed to investigate the relationship between STH infections and skin prick test results in children.

Methods

This cross-sectional study was conducted in August 2009 in children from 2 primary schools, SDN 050706 Karang Gading and SDN 056007 Rintis, in Secanggang Subdistrict, Langkat District, North Sumatra Province. We included children aged 7 to 12 years whose parents were willing to fill out questionnaires. Children using medications such as antihistamines within 3 days prior to enrollment, antihelmintics within 2 months prior to enrollment, currently using corticosteroids at the time of enrollment, or with a history of dermatographism were excluded. Subjects were consisted of two groups, with and without STH infection. We calculated the minimum required number of subjects to be 34 for each group. Informed consent was provided by subjects' parents or guardians.

Stool specimens were analyzed by *Kato-Katz* method for the presence and severity of infection. Appropriate treatment was given to all children with STH infections after stool analysis. Severity of infection was classified as mild, moderate, or severe, based on the number of eggs per gram (EPG) on stool microscopic examinations. The World Health Organization Expert Committee 1987 criteria were used to sub-classify the STH groups: *A .lumbricoides*, mild (1-4,999 EPG), moderate (5,000-49,999 EPG), or severe infection ($\geq$50,000 EPG), and *T. trichiura* mild (1-999 EPG), moderate (1,000-9,999 EPG), or severe ($\geq$10,000 EPG).[10]

Subjects underwent skin prick tests (SPT) of seven allergens including house dust mites, house dust, cotton, feathers, cat dander, cockroach, and fungi. Allergens were produced by the Department of Pharmacy, Dr. Soetomo Hospital, Surabaya. Positive and negative controls were 1% histamine and 0.9% NaCl, respectively. The SPTs were performed on the volar forearm area with a blood lancet at a 45^0 angle to the forearm. Sensitization was assessed 15-20 minutes after skin puncture and considered to be positive in the case of a red wheal $\geq$3 mm in diameter, or negative in the case of a red wheal <3 mm in diameter. Overall SPT results were considered to be positive if at least one allergen was positive. This study was approved by the Ethics Committee of the University of North Sumatra Medical School.

The data collected was processed, analyzed, and presented using SPSS version 15.0. To assess the association between STH infections and skin prick test results in children, we used Chi-square test with a significance level of $P<0.05$.

Results

During the study period, 94 children underwent stool examination screening, 68 out of them were consecutively selected, consisted of 34 children with STH infections and 34 children without STH infection. Subjects' characteristics are shown in **Table 1**.

Comparing the two groups, there was a significant relationship between STH infection and skin prick test ($P=0.002$). Skin prick test was negative on 31/34 subjects in STH infection group and 20/34 subjects in non STH infection group. Positive skin prick test results were observed in 3 subjects in STH infection group and 14 subjects in non STH infection group **(Table 2)**.

Negative skin prick test was significantly associated with all three infection types, *A. lumbricoides*

(P=0.001), *T. trichiura* (P=0.01) and mixed infection (P=0.006). Furthermore, severe infection intensity was significantly associated with negative SPT (P=0.031), but mild and moderate infections were not (**Table 3**).

Table 1. Characteristics of subjects

Characteristics	STH infection group (n=34)	Non STH infection group (n=34)
Gender, n		
Males	19	18
Females	15	16
Mean age (SD), years	10.7 (1.05)	10.2 (1.01)
Mean weight (SD), kg	20.1 (5.79)	18.4 (2.05)
Mean height (SD), cm	128.5 (6.42)	123.9 (5.95)
History of atopy, n		
Positive	12	10
Negative	22	24

Table 2. Association between STH infection and skin prick test result

Variables	STH infection group (n=34)	Non STH infection group (n=34)	P value
SPT positive, n	3	14	0.002
SPT negative, n	31	20	

SPT: skin prick test

Table 3. Relationship of SPT to type and severity of infection

Variables	SPT positive n=3	SPT negative n=31	P value
Type of infection			
A.lumbricoides	2	2	0.001
T.trichiura	1	17	0.01
A.lumbricoides + T.trichiura	0	12	0.006
Intensity of infection			
Mild	3	12	0.35
Moderate	0	8	0.186
Severe	0	11	0.031

SPT: skin prick test

be approximately 1.5 billion people.[13] A Nottingham 2008 study reported that more than 2 billion people are chronically infected with STH.[1] We found that the prevalences of *A. lumbricoides, T. trichiura,* and mixed infections were 11.8%, 52.9%, and 35.3%, respectively. The average age of our subjects was 10-11 years. A 2002 Kenyan study also found the mean age of infected children to be about 11 years,[14] while in Ecuador the peak prevalence and intensity of infection was 5 to 15 years of age.[15]

Discussion

Soil-transmitted helminth is a common affliction in the tropics causing serious public health problems in developing countries.[11] The 2004 data from North Sumatera reported the percentages for *A. lumbricoides, T. trichiura* and mixed infections to be 6.7%, 7.5%, and 55.8%, respectively.[12] In China, the ascariasis global infection burden was estimated to

Epidemiological studies in London reported that children with allergies and severe worm infection at an early age have significantly reduced skin prick test reactivity.[7] Furthermore, active worm infection, the most common chronic infection, provided protection against the effects of allergen skin prick test reactivity.[16] Similarly, we found a significant relationship between STH infection and negative skin prick test results (P=0.002).

Two mechanisms modulate allergic inflammatory reactions. Firstly, acute infection with invasive parasitic worm larvae occurs in the lungs, the primary target of a parasite-specific immune response. In early infection, larvae secrete large amounts of allergenic substances that are likely to be the primary stimulus for immunoglobulin-E (IgE) production in infected individuals. These larvae antigens induce helper T-2 (Th2) cells and the release of mediators, such as interleukin (IL)-4, IL-5, IL-10 and IL-13, leading to mucus production and smooth muscle cell contraction which promote airway allergies.[7,15,17] Secondly, during chronic infection, helminth parasites may suppress parasite-specific and aeroallergen-specific immune responses. The principal mechanism appears to be the increased production of anti-inflammatory cytokines, such as IL-10 and transforming growth factor-β (TGF-β). The production of large amounts of anti-inflammatory cytokines may suppress immune responses to environmental allergens and directly downregulate allergic responses to inhibit the activation of allergies.[15,17,18]

We also found a significant relationship between the helminth type and skin prick test results. *A. lumbricoides*, *T. trichiura* and mixed infections were associated with decreased incidence of allergies, as diagnosed by the skin prick test. A London study stated that a large immune response to *A. lumbricoides* was protective against allergy inflammation.[19] The intensity of helminth infection also affects the immune response. Severe trichiuris, ascariasis, and mixed worm infections appeared to suppress immune system regulation. Epidemiological studies in the United States reported that the intensity of severe and multiple infections promotes stronger influence on immune system regulation. Hyperendemic exposure to the nematodes *A. lumbricoides* and *T. trichiura* induces the secretion of anti-inflammatory cytokines which suppress allergies.[20] We found a significant relationship between severe infection and negative skin prick test results in children (P=0.031).

We excluded children who had used anthelmintics within the 2 months prior to enrollment to avoid affecting the the skin prick test results. The administration of antihelmintics, such as mebendazole and praziquantel every 3 months for 30 months, in chronically infected children had been found to increase atopic reactivity.[21] Another study found that oxantel-pyrantel therapy for 22 months on a regular basis increased total serum IgE levels significantly.[22]

In conclusion, there is a significant relationship between STH infections and negative skin prick test results in primary school children. Positive skin prick test results in children with STH infections are lower than in uninfected children.

References

1. Flohr C, Quinnell RJ, Britton J. Do helminth parasites protect against atopy and allergic disease? Clin Exp Allergy. 2009;39:20-32.
2. Cooper JP, Chico ME, Bland M, Griffin GE, Nutman TB. Allergic symptoms, atopy, and geohelminth infections in a rural area of Ecuador. Am J Resp Crit Care Med. 2003;168:313-7.
3. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet. 1998;351:1225-32.
4. Hunninghake GM, Soto-Quiros ME, Avila L, Ly NP, Liang C, Sylvia JS, *et al*. Sensitization to *Ascaris lumbricoides* and severity of childhood asthma in Costa Rica. J Allergy Clin Immunol. 2007;119:654-61.
5. Rahmawati, Punagi AQ, Savitri E. Relationship between rhinitis severity, skin prick test reactivity and mite-specific immunoglobulin E in allergic rhinitis patients in Makassar. Med J Indonesia. 2008;1:1-9.
6. Cooper PJ, Barreto ML, Rodrigues LC. Human allergy and geohelminth infections: a review of the literature and proposed conceptual model to guide the investigation of possible causal associations. Br Med Bull. 2006;79-80:203-8.
7. Rodrigues LC, Newcombe PJ, Cunha SS, Alcantara-Neves NM, Genser B, Cruz AA, *et al*. Early infection with *Trichuris trichura* and allergen skin test reactivity in later childhood. Clin Exp Allergy. 2008;38:1769-77.
8. Morris A. Atopy, anamnesis and allergy testing. InnovAiT. 2009;2:158-65.
9. Munasir Z. Pemeriksaan penunjang klinis: uji kulit terhadap

alergen. In: Akib AAP, Munasir Z, Kurniati N, editors. Buku ajar alergi imunologi anak. 2nd ed. Jakarta: Ikatan Dokter Anak Indonesia; 2007. p. 445-7.
10. Montresor A, Crompton DWT, Hall A, Bundy DAP, Savioli L. In: Guidelines for the evaluation of soil-transmitted helminthiasis and schistosomiasis of community level. Geneva: World Health Organization; 1998. p. 3-49.
11. Firmansyah I, Ginting SA, Lubis M, Lubis IZ, Pasaribu S, Lubis CP. Factors associated with the transmission of soil-transmitted helminthiasis among schoolchildren. Pediatr Indones. 2004;43:127-32.
12. Dalimunthe W, Siregar C, Lubis M, Pasaribu S, Lubis CP. Treatment of intestinal helminthiasis: mebendazole only or mebendazole-pyrantel pamoate? Paediatr Indones. 2007;47:216-20.
13. Palmer LJ, Celedon JC, Weiss ST, Wang B, Fang Z, Xu X. *Ascaris lumbricoides* infection is associated with increased risk of childhood asthma and atopy in rural China. Am J Resp Crit Care Med. 2002;165:1489-93.
14. Perzanowski MS, Ng'ang'a LW, Carter MC, Odhiambo J, Ngari P, Vaughan JW, *et al*. Atopy, asthma, and antibodies to *Ascaris* among rural and urban children in Kenya. J Pediatr. 2002;140:582-8.
15. Cooper PJ. Can intestinal helminth infections (geohelminths) affect the development and expression of asthma and allergic disease? Clin Exp Immunol. 2002;128:398-404.
16. Cooper PJ, Chico ME, Rodrigues LC, Ordonez M, Strachan D, Griffin GE, *et al*. Reduced risk of atopy among school-age children infected with geohelminth parasites in a rural area of the tropics. J Allergy Clin Immunol. 2003;111:995-1000.
17. Wordemann M, Diaz RJ, Heredia LM, Collado Madurga AM, Ruiz Espinosa A, Prado RC, *et al*. Association of atopy, asthma, allergic rhinoconjunctivitis, atopic dermatitis and intestinal helminth infections in Cuban children. Trop Med Int Health. 2008;13:180-6.
18. Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites and the hygiene hypothesis. Science. 2002;296:490-4.
19. Cooper PJ, Chico ME, Sandoval C, Nutman TB. Atopic phenotype is an important determinant of immunoglobulin E-mediated inflammation and expression of T helper cell type 2 cytokines to ascaris antigens in children exposed to ascariasis. J Infect Dis. 2004;190:1338-46.
20. Turner JD, Jackson JA, Faulkner H, Behnke J, Else KJ, Kamngo J, *et al*. Intensity of intestinal infection with multiple worm species is related to regulatory cytokine output and immune hyporesponsiveness. J Infect Dis. 2008;197:1204-12.
21. Van den Biggelaar A, Rodrigues LC, van Ree R, van der Zee JS, Hoeksma-Kruize YC, Souverijn JH, *et al*. Long-term treatment of intestinal helminths increases mite skin-test reactivity in Gabonese schoolchildren. J Infect Dis. 2004;189:892-900.
22. Lynch NR, Hagel I, Perez M, Di Prisco MC, Lopez R, Alvarez N. Effect of anthelmintic treatment on the allergic reactivity of children in a tropical slum. J Allergy Clin Immunol. 1993;92:404-11.