



Contents lists available at ScienceDirect



Effect of ivermectin on allergy-type manifestations in occult strongyloidiasis

Lahari Rampur, MBBS^{*}; Sunit P. Jariwala, MD[†]; Golda Hudes, MD[‡]; David L. Rosenstreich, MD^{*,†}; Gabriele de Vos, MD[‡]

^{*} Department of Allergy and Immunology, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, New York

[†] Department of Medicine (Allergy and Immunology), Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, New York

[‡] Department of Medicine (Allergy and Immunology), Albert Einstein College of Medicine/Jacobi Medical Center/Montefiore Medical Center, Bronx, New York

ARTICLE INFO

Article history:

Received for publication May 12, 2016.

Received in revised form June 8, 2016.

Accepted for publication July 15, 2016.

ABSTRACT

Background: The immunomodulatory effects of helminths have been well described. However, there is a relative lack of literature regarding the link between parasites and allergic diseases. A number of patients with allergic symptoms have positive serologic test results for *Strongyloides stercoralis*.

Objective: To identify patients with allergy-type symptoms and coexisting *Strongyloides* infection and to analyze the effect of *Strongyloides* eradication therapy with ivermectin on these symptoms.

Methods: The medical records of our allergy clinic sites were reviewed for *Strongyloides* test results between January 2011 and October 2014. Each allergy-type symptom was assessed separately with regard to improvement after ivermectin therapy.

Results: Among the 1,446 patients who had *Strongyloides* serologic tests ordered, 127 (8.8%) had positive test results. Eighty-four patients had follow-up data regarding allergy-type symptoms after ivermectin treatment. Among these, 52 patients (61.9%) reported skin-related problems (pruritus, urticaria, angioedema, and/or rash). Forty-nine patients (58.3%) had asthma, and 73.8% had allergic rhinoconjunctivitis. Although respiratory symptoms typically did not respond to ivermectin treatment, 24 of 48 patients (50%) with skin symptoms reported a significant subjective improvement of symptoms after ivermectin treatment. Peripheral eosinophil counts significantly decreased after ivermectin treatment from 450 to 200/ μ L ($P < .001$).

Conclusion: Serologic testing for strongyloides may be indicated for patients with allergy-type symptoms and a suggestive exposure history. Patients with strongyloidiasis and primarily cutaneous symptoms experienced significant symptomatic improvement after ivermectin therapy.

© 2016 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

The prevalence of allergic diseases has continued to increase in the industrialized world. Recent reports have suggested that helminth infections may manifest as allergic diseases, although the underlying mechanisms remain unclear.^{1,2} *Strongyloides stercoralis* is a soil-transmitted helminth infection that is endemic to tropical and subtropical regions, including Southeast Asia, sub-Saharan Africa, South America, the Caribbean, the Southeastern United States, and Southern Europe.¹ This infection, which affects an

estimated 30 million people worldwide, is relatively uncommon in developed societies.³ However, travel and immigration are contributing to the increasing incidence of strongyloidiasis in developed countries. Infected patients may be asymptomatic or may present with cutaneous or systemic manifestations.

During the past few years, we have treated a number of patients who presented with allergic symptoms and were subsequently found to have strongyloidiasis.¹ Most of these patients were from endemic areas, and some of them experienced a significant reduction in allergy-type symptoms after therapy with ivermectin. Given the marked improvement after ivermectin, we sought to further analyze the association between allergy-type symptoms and strongyloidiasis and symptomatic response to ivermectin therapy.¹ In this study, we describe the allergy type of manifestations of a large cohort of patients with previously unrecognized chronic strongyloidiasis and their clinical response to antiparasite therapy.

Reprints: Lahari Rampur, MBBS, Division of Allergy and Immunology, Albert Einstein College of Medicine/Montefiore Medical Center, 1295 Neill Ave, Floor 2, Bronx, NY 10461; E-mail: lahari.j@gmail.com.

Drs Rampur and Jariwala have equally contributed as authors and share first authorship.

Disclosures: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2016.07.021>

1081-1206/© 2016 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Methods

Study Design and Population

We conducted a retrospective medical record review of patients tested for *Strongyloides* infection at the allergy/immunology clinics at Montefiore Medical Center, Jacobi Medical Center, and North Central Bronx Hospital, serving primarily inner-city, low-income minority populations. *Strongyloides* testing was performed when the physician thought that the patient's immigration history, past travel, socioeconomic conditions, or eosinophilia suggested possible parasite infection or if symptoms had failed standard treatment and other differential diagnosis were being explored.

At Montefiore Medical Center, Bronx, NY, patients were searched through the Clinical Looking Glass software using the search criteria selecting all patients for whom *Strongyloides* IgG testing was ordered by all allergists between January 2011 and August 2014. At North Central Bronx and Jacobi hospitals, Bronx, NY, patients were searched by using the criteria selecting all patients for whom *Strongyloides* IgG testing was ordered in the allergy clinic by one allergist using the *International Classification of Diseases, Ninth Revision*, codes for asthma (code 493.00), angioedema (code 995.1), urticaria (code 708), food allergy (code 995.3), eosinophilia (code 288.3), pruritus (code 698.9), allergic rhinitis (code 477.9), or allergic conjunctivitis (code 372.14) between January 2011 and October 2014. A total of 1,446 tests had been ordered in our allergy division during this period, of which 127 had positive results. Two additional patients with serologic test results positive for *Strongyloides* before 2011 (1 in 2006 and 1 in 2010) were included in the ivermectin treatment outcomes analysis. The medical records of all *Strongyloides*-positive patients were reviewed in further detail as described below. Institutional board review approval was obtained from the Albert Einstein College of Medicine, New York.

Inclusion Criteria

To analyze the effects of ivermectin on allergy symptoms, only the medical records of *Strongyloides*-seropositive patients with at least 1 follow-up visit after ivermectin treatment were reviewed for the study.

Data Collection and Management

Patient medical records were analyzed for the following variables: age; sex; country of origin; race; duration of allergic symptoms; list of medications on presentation; concurrent treatment with any other medication for the allergic disease and/or immunotherapy; vitamin D supplementation at the time of ivermectin treatment; physical examination findings; percutaneous allergy skin testing results, including aeroallergens and food allergens; laboratory testing (complete blood cell count, serum chemical analyses, liver function tests, thyroid function testing, antinuclear antibody, antineutrophil cytoplasmic antibody, total serum IgE, specific serum IgE levels, and serum 25-hydroxyvitamin D levels); and the clinical response to antiparasite therapy (ie, 2-day course of ivermectin, 200 µg/kg daily).

Symptoms for up to 6 weeks were considered to be acute and for greater than 6 weeks were considered to be chronic. The time (in weeks) taken for improvement after ivermectin therapy was noted for all the patients, and time to symptom improvement was based on the report of patients at the subsequent 2 follow-up visits. At least 2 subsequent (ie, after ivermectin therapy) clinic notes were analyzed for the improvement in presenting symptoms. The follow-up duration was variable for each patient. Eosinophilia was defined as an absolute eosinophil count greater than 400/µL, and atopy was defined as at least 1 positive allergy skin test result or elevated (>0.35 kU/L) allergen-specific IgE result. Vitamin D deficiency was

defined as a serum 25-hydroxyvitamin D level less than 20 ng/mL (2 SDs below the population mean in our laboratories). *Strongyloides* infection was diagnosed by an enzyme-linked immunosorbent assay, a rapid and sensitive serodiagnostic assay for strongyloidiasis that uses a recombinant antigen from *Strongyloides stercoralis* and diffraction-based optical biosensor technology, at the Jacobi Medical Center.⁴

In determining whether ivermectin therapy was directly linked to the improvement of allergy symptoms, we considered allergy medications that might have been started or had a dose increase (ie, medications that were being used before ivermectin) within 1 week before or at the time when ivermectin therapy was started. These medications included oral and nasal antihistamines, oral corticosteroids, inhaled corticosteroids, nasal corticosteroids, montelukast, and allergen immunotherapy. We advised all patients regarding environmental control and allergen avoidance.

Statistical Analysis

All the baseline characteristics were tested for normal distribution. Mean values were determined for the normally distributed variables, and median values were calculated for the variables not distributed normally. Median pretreatment and posttreatment eosinophils and serum total IgE were computed, and changes between pretreatment and posttreatment levels were analyzed for significance using the Wilcoxon matched pairs signed-rank test. The pretreatment values are the values available closest to the date ivermectin therapy was started, and the posttreatment values are taken from the subsequent laboratory tests performed after the ivermectin treatment. $P \leq .05$ was considered statistically significant. Because we were unable to ascertain to what extent the patients implemented environmental or dietary control recommendations, we were unable to adjust for these factors during the statistical analysis. We used STATA statistical software, version 10.2 (StataCorp, College Station, Texas) for all statistical computation.

Results

Participants' Demographic and Clinical Characteristics at Baseline

A total of 1,446 patients were tested for the presence of *Strongyloides* serum IgG. Of the 1,446 tested patients, 127 (8.8%) were found to have a positive *Strongyloides* IgG test result. Eighty-four patients (25 men and 59 women) had follow-up visits after ivermectin treatment and were used for the study analysis. The mean (SD) age of these 84 patients was 53.5 (16.3) years (Table 1). Seventy-one patients had specific IgE testing or skin testing to a battery of aeroallergens, and 36 patients had food testing. Of these patients, 57 of 71 (80.3%) were allergic to aeroallergens. Ova and parasite stool testing was performed on 34 of 84 patients, and only 1 patient had a stool specimen that tested positive for *Strongyloides* (Table 1). Two other patients had positive stool samples for *Blas-tocystis hominis* (data not shown). Thirteen patients underwent additional serologic testing for specific parasites, and 3 tested positive for filaria, *Schistosoma*, or *Trypanosoma cruzi*, respectively. Seventy-six of 84 patients had pretreatment eosinophil counts available, and 30 of 76 (39.5%) had eosinophilia (eosinophil count ≥ 0.4 kU/µL at baseline). Median pretreatment serum total IgE level (available test results for 78 of 84 patients) was 726.8 kU/L (range, 9.2–7,359 kU/L). Among the 76 patients with available data, the regions of origin were Caribbean, Central, or South America ($n = 48$), Asia ($n = 15$), the United States ($n = 10$), Africa ($n = 2$), and Europe ($n = 1$) (Fig 1). All patients from the United States are from the New York City area. The distribution of serum IgE levels is shown in Figure 2. Fifty-nine of 78 patients (75.6%) had an IgE level of 100 IU/L or higher (Fig 2).

Table 1
Demographic and Clinical Characteristics of the Study Population

Characteristic	Finding ^a (N = 84)
Female	59 (70)
Age, mean (SD), y	53.5 (16.3)
Patients with environmental atopy ^b	57 (80)
Patients with food atopy ^b	17 (47)
Stool test positive for <i>Strongyloides</i> ^c	1 (3)
Stool test positive for other parasites	2 (6)
Serum/blood testing positive for other parasites ^d	3 (23)
Vitamin D level, median (range), ng/mL	21 (6.6–76)
Patients with vitamin D serum level <20 ng/mL ^e	27 (47)
Patients with eosinophilia (eosinophil count ≥ 0.4 kU/L) ^f	30 (39)
Blood eosinophil count, median (range), kU/ μ L	0.3 (0–13.2)
Total IgE level, mean (range), kU/L ^g	726.8 (9.2–7,359)

^aData are presented as number (percentage) unless otherwise indicated. The percentages were calculated based on nonmissing data for each variable.

^bAtopy evaluated by skin prick and specific IgE testing in 71 patients for environmental allergens and 36 patients for food allergens.

^cStool for ova and parasites tested in 34 patients.

^dSerum testing for selected other parasites was performed in 13 patients.

^eVitamin D levels available in 58 patients.

^fPretreatment eosinophil count available for 76 patients.

^gPretreatment IgE levels available for 78 patients.

Presenting Allergic Symptoms in Patients With Chronic Strongyloidiasis

Medical record review of the 84 patients indicated that most reported multiple allergic symptoms. Fifty-two of 84 patients (61.9%) reported skin symptoms, and 65 patients (77.4%) reported respiratory symptoms, with 35 patients (41.7%) reporting both skin and respiratory symptoms (Fig 3). Onset of skin symptoms was documented in 44 of these 52 patients, and 34 (77%) indicated that they had experienced skin symptoms for more than 6 weeks, with a duration of symptoms for more than 2 years in 16 patients (36%) (data not shown).

Respiratory symptoms included rhinitis, asthma and cough, alone or in combination (Fig 3). Onset of respiratory symptoms was documented in 62 patients, and 59 (95%) indicated that symptoms had lasted at least 2 years or more before ivermectin treatment.

Improvement in Allergic Symptoms After Ivermectin Therapy

All 84 patients were treated with ivermectin for 2 consecutive days, and none of the patients received a second course of treatment. Because patients receiving ivermectin therapy may have concurrently received allergy medications (eg, antihistamines) for

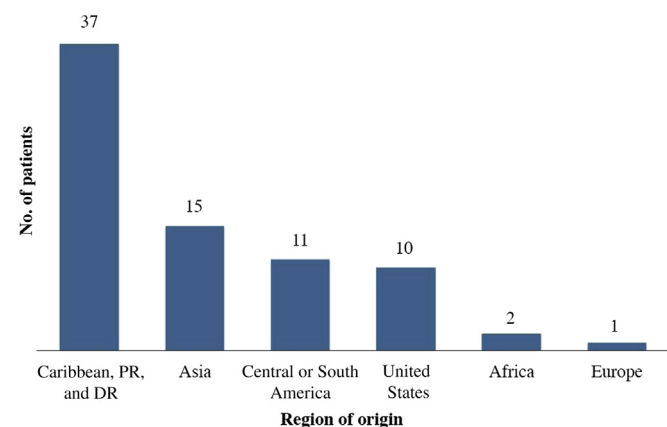


Figure 1. Number of study participants by region of origin (place of birth). Data were available for 76 of the 84 study patients. PR, Puerto Rico; DR, Dominican Republic.

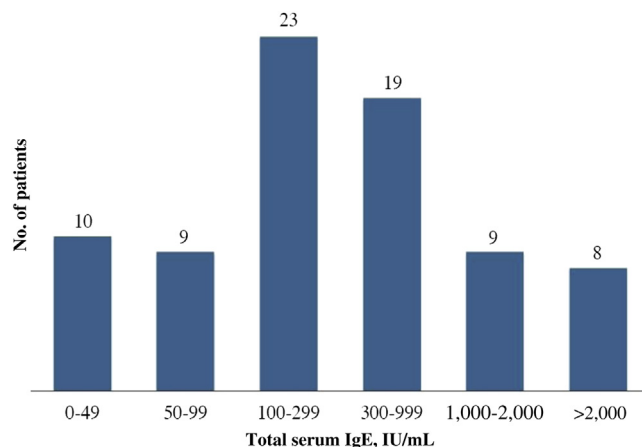


Figure 2. Baseline total serum IgE levels. Data were available for 78 of 84 patients.

symptomatic relief, we stratified the analysis by the use of other medications (ie, medication modifications) in evaluating the response to ivermectin therapy. Skin symptoms responded best to ivermectin treatment. Seventy-seven percent of patients with only pruritus (without rash) responded to ivermectin therapy with resolution of symptoms without other medication modifications (Table 2). In the entire skin symptom subgroup (urticaria, pruritus, angioedema, or undefined rash), 50% of patients reported a significant subjective improvement after ivermectin treatment without any other medication modifications (Table 2). Most patients reported improvement of skin symptoms within 6 weeks after ivermectin treatment (40% improved within 3 weeks, 43% within 6 weeks, and 18% within 16 weeks) (data not shown).

In contrast to skin symptoms, respiratory symptoms (asthma, rhinitis, and cough) did not respond as well to ivermectin treatment. Only 25% of patients with rhinitis and only 16.7% of patients with asthma or cough reported improvement in these symptoms after taking ivermectin alone (Table 2).

Improvement in Laboratory Parameters After Ivermectin Therapy

Pretreatment and posttreatment eosinophil counts were available for 36 patients. In this group, eosinophil counts decreased from a median of 400/ μ L (range, 0–13200/ μ L) before ivermectin treatment to 170/ μ L (range, 0–800/ μ L) after treatment ($P < .001$) (Fig 4). Pretreatment and posttreatment serum IgE levels were available for 15 patients. In this group, during the short period studied, there was a small decrease in median serum IgE levels, but the change

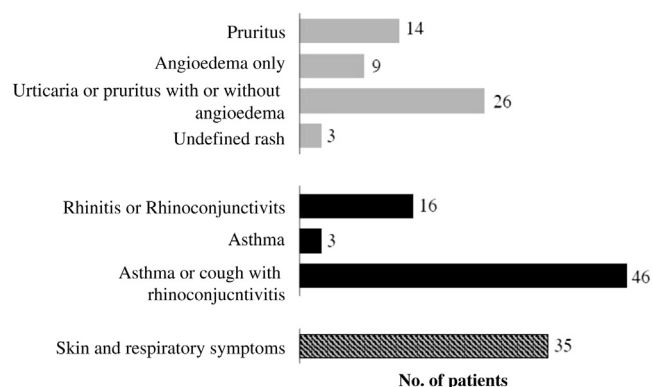


Figure 3. Symptom manifestations of study patients. A total of 52 patients (62%) had cutaneous symptoms, 65 (77%) had respiratory symptoms, and 35 (42%) had both cutaneous and respiratory symptoms.

Table 2
Improvement of Symptoms in Association With Ivermectin Treatment in 84 Patients

Symptom	No. of patients ^a	Improvement			No improvement
		Before ivermectin treatment	After ivermectin treatment, with other medication modifications ^b	After ivermectin treatment, no other medication modifications	
Skin					
Pruritus only	13	1	1	10	1
Angioedema only	7	4	1	2	0
Urticaria or pruritus with or without angioedema	26	7	3	11	5
Undefined rash without pruritus	2	NA	NA	1	1
Total	48	12	5	24	7
Respiratory					
Rhinitis only	12	2	2	3	5
Asthma only	3	1	0	0	2
Asthma or cough with rhinitis	34	7	7	5	15
Total	49	10	9	8	22

Abbreviation: NA, not applicable.

^aNumber of patients in whom follow-up data after ivermectin treatment were available.

^bAntihistamines, steroids, leukotriene receptor antagonists, and/or allergy immunotherapy for skin symptoms and nasal, oral, or inhaled steroids, nasal or oral antihistamines, leukotriene receptor antagonists, and/or allergy immunotherapy for respiratory symptoms.

was not statistically significant (pretreatment: 583 kU/L; range, 46.6–5,714 kU/L; posttreatment: 431 kU/L; range, 41.6–2,018 kU/L; $P = .12$) (data not shown).

Discussion

This study presents a large case series of patients presenting with allergy-type symptoms and concurrent, previously unrecognized strongyloidiasis. Most patients presented with multiple dermatologic or respiratory allergy-type symptoms, including pruritus, urticaria, rhinitis, and asthma/cough. Most patients presenting with pruritus responded to ivermectin therapy alone as did 50% of patients with any cutaneous symptoms (pruritus, urticaria, angioedema, or nonspecific rash). In contrast, 25% or fewer patients

with respiratory symptoms reported improvement in symptoms after ivermectin therapy by itself.

The early diagnosis and treatment of strongyloides infection are crucial, and this is especially true in the setting of allergic diseases because corticosteroid therapy, which is often used in the management of allergic diseases, may worsen parasitic infections with potentially life-threatening consequences, including hyperinfection syndrome.^{5,6} Therefore, a high level of suspicion is required to diagnose parasitic infections, especially in patients who may have emigrated from or traveled to endemic regions (eg, Southeast Asia, Latin America, sub-Saharan Africa, and Southeastern United States).¹ Ten patients in this study originated from the United States and were found to have strongyloidiasis. This finding can be explained by these patients having lived in endemic areas within the United States and/or traveling to endemic regions abroad, but it indicates that *Strongyloides* infection should be considered even in patients who have never left the United States.

Acute *Strongyloides* infections may present with multisystem (eg, cutaneous, respiratory, gastrointestinal) findings and may or may not be accompanied by eosinophilia and elevated serum total IgE.¹ They may also produce cutaneous reactions when larvae penetrate the skin, including petechiae, serpiginous or urticarial tracks, angioedema, and severe pruritus.^{7,8} According to a recent review, patients with strongyloidiasis were more often diagnosed as having urticaria when compared with healthy individuals without strongyloidiasis in endemic regions.⁹ Patients with chronic strongyloidiasis may also develop asthma that paradoxically worsens with corticosteroid use.^{10,11} In our study, patients most commonly had respiratory and cutaneous symptoms. Only 39% of our *Strongyloides*-seropositive patients had eosinophil counts of 400/ μ L or higher. Some studies have reported a prevalence of eosinophilia in 60% to 80% with high variability. This finding is likely attributable to variation in the baseline patient characteristics, variation in criteria for eosinophilia, underlying diseases, exposure to other parasites, stage of parasite infection, and the effect of medications.^{12–15} Because ivermectin can also be used to treat scabies, improving rash and itching in some of the study patients, possible scabies infection could also explain improvement with ivermectin.¹⁶ However, the strongest effect of ivermectin was found in patients presenting with pruritus without any visible rash, arguing against scabies as a potential confounder.

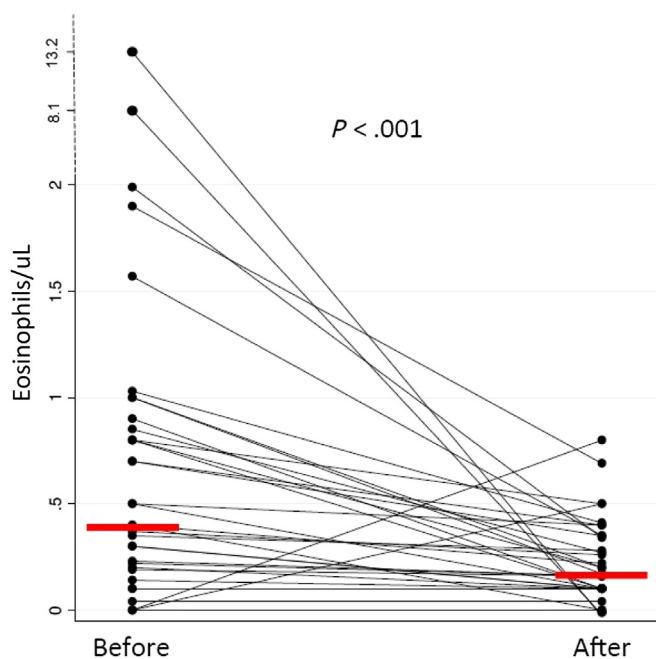


Figure 4. Pretreatment and posttreatment absolute eosinophil counts in peripheral blood. Red bars indicate median counts.

Strongyloides infections may be difficult to diagnose through available laboratory testing. Standard stool examinations are relatively insensitive (30% sensitivity for a single stool examination) for detecting *Strongyloides*.¹⁷ Additional stool testing improves sensitivity, which has been reported to reach 100% positivity after 7 serial stool examinations.^{1,17} Enzyme-linked immunosorbent assay test results may be positive even when the results of additional examinations of stool samples have been negative.^{18,19} *Strongyloides* serologic testing in our laboratory was 96.3% sensitive and 100% specific. Assay performance was tested using retrospectively collected serum samples from patients with parasitologically confirmed strongyloidiasis in the stool.⁴ *Strongyloides* IgG test result can be falsely positive in patients with other parasitic infections, such as filariasis, schistosomiasis, and *Ascaris lumbricoides*.^{1,20} Even though only 40% of our study patients were tested for the presence of parasites in stool and 15% for other parasitic infections in the blood, the low number of parasitic coinfections found in our study suggests that false-positive results for *Strongyloides* infection attributable to coinfection with other cross-reactive parasites were rather unlikely. In addition, the decrease of eosinophils after ivermectin treatment in most patients suggests that true ivermectin-responsive parasite infections were present in most seropositive patients.

In light of the observed coexistence between strongyloidiasis and presenting allergic symptoms among patients in this study, it is interesting to consider how helminths could pathophysiologically contribute to allergic diseases. Acute helminth infections can often act as masqueraders of allergic diseases.^{7,8} Geohelminth parasites (eg, *Strongyloides stercoralis*, *Ascaris lumbricoides*) with a pulmonary phase of larval migration may cause an asthmalike syndrome (Loeffler syndrome) characterized by cough, dyspnea, and eosinophilia.^{21,22} Ascariasis may present with allergic rashes and acute anaphylaxis.²³ Previous data suggest that antihelminthic treatment of patients with asthma living in endemic areas may result in an improvement in asthma symptoms and/or the reduction in skin test reactivity to environmental allergens or reduced eosinophilia.²⁴ The serpiginous rash seen during the migration of larva under the skin (larva currens) improves after *Strongyloides* treatment, but this type of rash was not present in any of our patients.

However, for the chronically *Strongyloides*-infected patients included in this study, it is more likely that the increase in allergy-type skin symptoms seen in our study cohort was most likely attributable to a general increase in allergic reactivity caused by the chronic *Strongyloides* infection. Recent data suggest that immune response to helminth infections is similar to allergy-type responses mediated by T_H2-mediated cytokines (interleukin [IL] 4, IL-5, IL-9, IL-13), which increase total and allergen specific IgE, eosinophil counts, mast cell and basophil numbers, and goblet cell hyperplasia.²⁵ Helminths may also induce the polyclonal stimulation of IgE.²⁶ Acute parasitic infections are known to cause T_H2-mediated responses, resulting in eosinophilia, increased serum total IgE level, and the production of IL-4 and IL-13.^{27,28} Consistent with this hypothesis are the findings of a recent study demonstrating that *Strongyloides* infected individuals had significantly higher serum levels of the cytokines IL-4, IL-5, IL-9, IL-10, IL-13, IL-27, IL-37, and transforming growth factor β .² In this latter study, there was a significant decrease in the serum levels of these cytokines after treatment of the *Strongyloides* infection. Because these cytokines play such a predominant pathogenic role in allergic diseases, it is likely that they are triggering or enhancing allergy-type symptoms in parasite infected patients, such as those in our study.²

On the other hand, there are also a number of studies that indicate that helminth infections are protective against the development of atopy and asthma. However, this effect seems to be mostly mediated by a high burden of parasitic infestation in

endemic areas. In contrast, low burden parasitic infections have been associated with an increase of allergies.^{29–33}

In summary, we found that among a large group of patients with both allergy-type skin or respiratory symptoms and a travel, immigration, or socioeconomic history consistent with a parasite infection, 8.8% of patients had positive *Strongyloides* serum IgG test results. Most seropositive patients with skin symptoms improved after ivermectin therapy. In contrast, 25% or less of respiratory symptoms improved after the ivermectin treatment. Eosinophilia (eosinophil count $\geq 400/\mu\text{L}$) was only present in approximately 39% of patients and was often mild, making it a poor predictive marker of *Strongyloides* infection. Nevertheless, eosinophilia also improved rapidly after ivermectin treatment in most patients. Although randomized clinical trials of ivermectin in *Strongyloides*-infected patients with allergic symptoms would raise ethical concerns, larger prospective studies may help to demonstrate a response to treatment in patients who have allergy-type symptoms and positive *Strongyloides* serologic test results.

References

- [1] Fodeman J, Jariwala S, Hudes G, et al. Scratching the surface. *Am J Med*. 2010; 123:22–26.
- [2] Anuradha R, Munisankar S, Bhootra Y, et al. Systemic cytokine profiles in *Strongyloides stercoralis* infection and alterations following treatment. *Infect Immun*. 2015;84:425–431.
- [3] Centers for Disease Control and Prevention. Epidemiology and Risk Factors. Parasites – *Strongyloides*. www.cdc.gov/parasites/strongyloides/epi.html. Accessed May 19, 2014.
- [4] Pak BJ, Vasquez-Camargo F, Kalinichenko E, et al. Development of a rapid serological assay for the diagnosis of strongyloidiasis using a novel diffraction-based biosensor technology. *PLoS Negl Trop Dis*. 2014;8: e3002.
- [5] Siddiqui AA, Berk SL. Diagnosis of *Strongyloides stercoralis* infection. *Clin Infect Dis*. 2001;33:1040–1047.
- [6] Link K, Orenstein R. Bacterial complications of strongyloidiasis: *Streptococcus bovis* meningitis. *South Med J*. 1999;92:728–731.
- [7] Van Dellen RG, Maddox DE, Dutta EJ. Masqueraders of angioedema and urticaria. *Ann Allergy Asthma Immunol*. 2002;88:10–14, quiz 15, 41.
- [8] Mehta RK, Shah N, Scott DG, Grattan CE, Barker TH. Case 4: chronic urticaria due to strongyloidiasis. *Clin Exp Dermatol*. 2002;27:84–85.
- [9] Kolkhir P, Balakirski G, Merk HF, Olisova O, Maurer M. Chronic spontaneous urticaria and internal parasites: a systematic review. *Allergy*. 2016;71: 308–322.
- [10] Sen P, Gil C, Estrellas B, Middleton JR. Corticosteroid-induced asthma: a manifestation of limited hyperinfection syndrome due to *Strongyloides stercoralis*. *South Med J*. 1995;88:923–927.
- [11] Wehner JH, Kirsch CM, Kagawa FT, Jensen WA, Campagna AC, Wilson M. The prevalence and response to therapy of *Strongyloides stercoralis* in patients with asthma from endemic areas. *Chest*. 1994;106:762–766.
- [12] Gonzalez A, Gallo M, Valls ME, et al. Clinical and epidemiological features of 33 imported *Strongyloides stercoralis* infections. *Trans R Soc Trop Med Hyg*. 2010;104:613–616.
- [13] Gill GV, Welch E, Bailey JW, Bell DR, Beeching NJ. Chronic *Strongyloides stercoralis* infection in former British Far East prisoners of war. *Q J Med*. 2004; 97:789–795.
- [14] Roman-Sanchez P, Pastor-Guzman A, Moreno-Guillen S, Igual-Adell R, Suner-Generoso S, Tornero-Estebanez C. High prevalence of *Strongyloides stercoralis* among farm workers on the Mediterranean coast of Spain: analysis of the predictive factors of infection in developed countries. *Am J Trop Med Hyg*. 2003;69:336–340.
- [15] Loutfy MR, Wilson M, Keystone JS, Kain KC. Serology and eosinophil count in the diagnosis and management of strongyloidiasis in a non-endemic area. *Am J Trop Med Hyg*. 2002;66:749–752.
- [16] Madan V, Jaskiran K, Gupta U, Gupta DK. Oral ivermectin in scabies patients: a comparison with 1% topical lindane lotion. *J Dermatol*. 2001;28:481–484.
- [17] Nielsen PB, Mojon M. Improved diagnosis of *Strongyloides stercoralis* by seven consecutive stool specimens. *Zentralbl Bakteriol Mikrobiol Hyg A*. 1987;263: 616–618.
- [18] van Doorn HR, Koelwijin R, Hofwegen H, et al. Use of enzyme-linked immunosorbent assay and dipstick assay for detection of *Strongyloides stercoralis* infection in humans. *J Clin Microbiol*. 2007;45:438–442.
- [19] Bisoffi Z, Buonfrate D, Sequi M, et al. Diagnostic accuracy of five serologic tests for *Strongyloides stercoralis* infection. *PLoS Negl Trop Dis*. 2014;8:e2640.
- [20] Fernandez Rodriguez C, Enriquez-Matas A, Sanchez Millan ML, et al. *Strongyloides stercoralis* infection: a series of cases diagnosed in an allergy department in Spain. *J Invest Allergol Clin Immunol*. 2012;22:455–457.
- [21] Bruno P, McAllister K, Matthews JI. Pulmonary strongyloidiasis. *South Med J*. 1982;75:363–365.

- [22] Patz IM. Acute eosinophilic pneumonia possibly due to infection with *Ascaris lumbricoides*. *Cent Afr J Med*. 1959;5:399–404.
- [23] Cooper PJ. Can intestinal helminth infections (geohelminths) affect the development and expression of asthma and allergic disease? *Clin Exp Immunol*. 2002;128:398–404.
- [24] Lynch NR, Palenque M, Hagel I, DiPrisco MC. Clinical improvement of asthma after anthelmintic treatment in a tropical situation. *Am J Respir Crit Care Med*. 1997;156:50–54.
- [25] Harris N, Gause WC. To B or not to B: B cells and the Th2-type immune response to helminths. *Trends Immunol*. 2011;32:80–88.
- [26] Lynch NR, Hagel IA, Palenque ME, et al. Relationship between helminthic infection and IgE response in atopic and nonatopic children in a tropical environment. *J Allergy Clin Immunol*. 1998;101:217–221.
- [27] Cooper PJ, Chico ME, Sandoval C, et al. Human infection with *Ascaris lumbricoides* is associated with a polarized cytokine response. *J Infect Dis*. 2000;182:1207–1213.
- [28] Holland MJ, Harcus YM, Riches PL, Maizels RM. Proteins secreted by the parasitic nematode *Nippostrongylus brasiliensis* act as adjuvants for Th2 responses. *Eur J Immunol*. 2000;30:1977–1987.
- [29] Scrivener S, Yemaneberhan H, Zebenigus M, et al. Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia: a nested case-control study. *Lancet*. 2001;358:1493–1499.
- [30] Smits HH, Everts B, Hartgers FC, Yazdanbakhsh M. Chronic helminth infections protect against allergic diseases by active regulatory processes. *Curr Allergy Asthma Rep*. 2010;10:3–12.
- [31] Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites, and the hygiene hypothesis. *Science*. 2002;296:490–494.
- [32] van den Biggelaar AH, van Ree R, Rodrigues LC, et al. Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. *Lancet*. 2000;356:1723–1727.
- [33] Nyan OA, Walraven GE, Banya WA, et al. Atopy, intestinal helminth infection and total serum IgE in rural and urban adult Gambian communities. *Clin Exp Allergy*. 2001;31:1672–1678.