

Clinical conditions associated with intestinal strongyloidiasis in Rio de Janeiro, Brazil

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ABSTRACT

Introduction: *Strongyloides stercoralis* is a soil-transmitted helminth that produces an infection that can persist for decades. The relationships between certain clinical conditions and strongyloidiasis remains controversial. This study aims to identify the clinical conditions associated with intestinal strongyloidiasis at a reference center for infectious diseases in Rio de Janeiro, Brazil. **Methods:** The clinical conditions that were assessed included HIV/AIDS, HTLV infection, cardiovascular diseases, diabetes, obstructive respiratory diseases, viral hepatitis, tuberculosis, cancer, chronic renal disease, nutritional/metabolic disorders, psychiatric conditions, rheumatic diseases and dermatologic diseases. We compared 167 *S. stercoralis*-positive and 133 *S. stercoralis*-negative patients. **Results:** After controlling for sex (male/female OR = 2.29; 95% (CI): (1.42 - 3.70)), rheumatic diseases remained significantly associated with intestinal strongyloidiasis (OR: 4.96; 95% CI: 1.34-18.37) in a multiple logistic regression model. With respect to leukocyte counts, patients with strongyloidiasis presented with significantly higher relative eosinophil (10.32% ± 7.2 vs. 4.23% ± 2.92) and monocyte (8.49% ± 7.25 vs. 5.39% ± 4.31) counts and lower segmented neutrophil (52.85% ± 15.31 vs. 61.32% ± 11.4) and lymphocyte counts (28.11% ± 9.72 vs. 30.90% ± 9.51) than *S. stercoralis*-negative patients. **Conclusions:** Strongyloidiasis should be routinely investigated in hospitalized patients with complex conditions facilitate the treatment of patients who will undergo immunosuppressive therapy. Diagnoses should be determined through the use of appropriate parasitological methods, such as the Baermann-Moraes technique.

Keywords: *Strongyloides stercoralis*. Co-infection. Risk factors.

INTRODUCTION

Strongyloides stercoralis is a soil-transmitted helminth that produces an infection that can persist for decades. Infected patients may be asymptomatic or may present with clinical manifestations ranging from symptoms similar to peptic disease to a severe disseminated form of strongyloidiasis with a high fatality rate. Neumann et al. reported strongyloidiasis prevalence rates of up to 50% in Latin America and Africa⁽¹⁾. The prevalence rates of strongyloidiasis vary across different Brazilian regions; in particular, the Rio Doce basin is an endemic region⁽²⁾. In Amazonian Brazil, frequencies of *S. stercoralis* infection range from 4.2% to 5.6%⁽³⁾⁽⁴⁾.

Humans are the main reservoir and source of *S. stercoralis* infection. There are three forms of *S. stercoralis* transmission:

heteroinfection, external autoinfection and internal autoinfection. Internal autoinfection can lead to the development of severe cases of strongyloidiasis, hyperinfection and the spread of the parasite⁽⁵⁾⁽⁶⁾⁽⁷⁾. Importantly, disseminated strongyloidiasis, which produces a fatality rate of up to 87%, may result in sepsis caused by Gram-negative bacteria that cross the intestinal barrier during the course of the parasite's life cycle⁽⁸⁾.

Because most cases of severe disease are associated with the presence of other conditions that induce changes in the immune response, severe forms of strongyloidiasis may be linked to the dysregulation of cellular immunity. Researchers have observed that patients with severe strongyloidiasis have generally been subjected to corticotherapy. This treatment could cause changes in helminth biology and generate a stimulus for parasite reproduction, increasing a patient's parasite burden⁽⁸⁾.

Patients infected with human T-lymphotropic virus (HTLV) exhibit increased susceptibility to infection with *S. stercoralis* and progression to severe forms of strongyloidiasis. This phenomenon is likely to be associated with elevated interferon gamma (IFN- γ) levels caused by the deviation of the immune response towards a T-helper 1 (Th1) response instead of a T-helper 2 (Th2) response, which is associated with protection against helminths⁽⁸⁾. The high frequency of intestinal nematode

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infections in patients with pulmonary tuberculosis suggests that helminth-induced immunomodulation may facilitate *Mycobacterium tuberculosis* infection and disease progression. The association of parasitism by *S. stercoralis* with chronic alcoholism has been demonstrated by Zago-Gomes et al.⁽⁹⁾. No clear association between human immunodeficiency virus (HIV) infection and strongyloidiasis has been demonstrated.

The relationships between certain clinical conditions and strongyloidiasis remain controversial. A better understanding of these relationships could benefit patients with cellular immunodeficiency and patients who are undergoing treatment regimens that result in severe immunosuppression, particularly in regions where strongyloidiasis is endemic. This study, which was conducted at a reference center for infectious diseases in Rio de Janeiro, Brazil, aims to identify clinical conditions associated with intestinal strongyloidiasis.

METHODS

The study included patients at the Pedro Ernesto University Hospital of the State University of Rio de Janeiro (UERJ). The study site was the hospital's Infectious Diseases Unit. Cases of strongyloidiasis (n = 167) were identified through the examination of stool samples by the Baermann-Moraes technique. Briefly, fresh stool samples were initially processed in glass funnels containing 20ml of water that had been heated to 45°C. These funnels were connected to 15ml polypropylene tubes. Approximately 10 g of feces wrapped in gauze was placed in the heated water in each funnel. After 60 minutes, the water was collected, centrifuged (500 × g, 1 minute) and examined by light microscopy. Patients were regarded as positive for strongyloidiasis if rhabditoid and/or filarioid larvae morphologically consistent with *S. stercoralis* were detected by this examination.

Patients who were not infected with *S. stercoralis* (n = 133) were selected from the log book of the parasitology laboratory; in particular, the uninfected subjects assessed in this study consisted of *S. stercoralis*-negative patients who immediately followed an *S. stercoralis*-positive patient. Each *S. stercoralis*-negative patient was age-matched to a *S. stercoralis*-positive patient. The baseline clinical conditions of *S. stercoralis*-negative and *S. stercoralis*-positive patients were obtained from their medical records. The medians and interquartile ranges for the ages of *S. stercoralis*-positive and *S. stercoralis*-negative patients were 49.3 (38.5-60.4) years and 50.7 (37.8-66.4) years, respectively. Blood counts were performed with a Pentra DX 120/DF120 (Villanova, Philadelphia, USA).

Frequencies of co-infection with HTLV, HIV and tuberculosis were assessed in *S. stercoralis*-positive and *S. stercoralis*-negative patients. In addition, both groups were assessed for the presence of various clinical conditions, such as cardiovascular diseases, diabetes, obstructive respiratory diseases, viral hepatitis, neoplasms, chronic renal disease, nutritional/metabolic disorders, psychiatric conditions, rheumatic diseases and dermatologic diseases. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated.

Because only one specific clinical condition was present in each patient, we did not perform multivariate analysis with all of the explanatory variables. Thus, a multiple logistic regression model was applied that only controlled for sex. We also used Student's t test to compare the mean leukocyte counts in the two groups the statistical significance level was 5%.

RESULTS

Table 1 shows that univariate analysis indicated that rheumatic diseases were associated with intestinal strongyloidiasis (OR: 3.65; 95% CI: 1.02-13.11; p-value = 0.03). In the multiple logistic regression, which controlled for sex (male/female OR: 2.58; 95% CI: 1.57-4.24; p-value < 0.01), rheumatic diseases continued to be significantly associated with intestinal strongyloidiasis (OR: 4.96; 95% CI: 1.34-18.37; p-value = 0.02).

With respect to white blood cell counts, strongyloidiasis patients exhibited higher proportions of eosinophils (10.32% ± 7.2 vs. 4.23% ± 2.92; p-value < 0.01) and monocytes (8.49% ± 7.25 vs. 5.39% ± 4.31, p-value < 0.01) than *S. stercoralis*-negative patients. In addition, *S. stercoralis*-positive patients presented with fewer segmented neutrophils (52.85% ± 15.31 vs. 61.32% ± 11.4; p-value < 0.01) and lymphocytes (28.11% ± 9.72 versus 30.90% ± 9.51; p-value < 0.01) than *S. stercoralis*-negative patients (**Table 2**).

DISCUSSION

Severe outcomes due to hyperinfection with and the consequent dissemination of *S. stercoralis* have been associated with clinical conditions that require immunosuppressive therapy^{(10) (11) (12)}. In the present study, which did not include cases of disseminated strongyloidiasis, we compared the frequencies of *S. stercoralis* larvae elimination in patients with distinct clinical conditions. In this context, demonstrations of the presence of intestinal strongyloidiasis reinforce the need to perform parasitological examinations using appropriate techniques on patients who could potentially suffer from immunosuppressive conditions.

In this study, a significant relationship between intestinal strongyloidiasis and rheumatic diseases was observed. An association between disseminated strongyloidiasis and rheumatic diseases, including a description of fatal outcomes among strongyloidiasis patients with systemic lupus erythematosus, has previously been reported⁽¹³⁾. Our group of patients with rheumatic conditions was heterogeneous and included cases of systemic lupus erythematosus, rheumatoid arthritis, gout, scleroderma, Behcet disease, Sjogren syndrome, psoriasis, and eczema. In the absence of parasite dissemination, the use of immunosuppressive drugs likely contributes to the diagnosis of intestinal strongyloidiasis in this group of patients^{(14) (15) (16)}. Importantly, although immunosuppressive therapy with steroids is not associated with uncomplicated intestinal strongyloidiasis, this treatment can potentially increase parasite reproduction in the gut, enhancing the excretion of *S. stercoralis* larvae and improving

TABLE 1 - Medical conditions associated with intestinal strongyloidiasis in Rio de Janeiro, Brazil.

	<i>S. stercoralis</i> -positive (n=167)		<i>S. stercoralis</i> -negative (n=133)		OR (95% CI)	p-value	Sex-adjusted OR (95% CI)	p-value
	n	%	n	%				
Sex (male)	119	63.3	48	42.9	2.29 (1.42 - 3.70)	<0.01	-	-
HIV/AIDS	40	24	25	18.8	1.36 (0.77 - 2.38)	0.17	1.19 (0.67 - 2.13)	0.53
HTLV infection	14	8.4	12	9.0	0.92 (0.41 - 2.06)	0.50	0.92 (0.41 - 2.06)	0.84
Cardiovascular diseases ^a	27	16.2	46	34.6	0.36 (0.21 - 0.62)	<0.01	0.40 (0.23 - 0.70)	<0.01
Diabetes	8	4.8	4	3.0	1.62 (0.47 - 5.51)	0.31	1.74 (0.42 - 5.12)	0.54
Obstructive respiratory diseases ^b	11	6.6	8	6.0	1.10 (0.43 - 2.82)	0.52	1.10 (0.42 - 2.87)	0.84
Viral hepatitis ^c	11	6.6	3	2.3	3.05 (0.83 - 11.18)	0.06	3.36 (0.89-12.59)	0.07
Tuberculosis ^d	10	6.0	4	3.0	2.05 (0.62 - 6.70)	0.17	1.70 (0.51 - 5.65)	0.38
Cancer ^e	17	9.9	10	5.2	1.39 (0.61 - 3.15)	0.28	1.22 (0.53 - 2.81)	0.63
Chronic renal disease	5	3.0	0	0.0	-	NA	-	NA
Nutritional/metabolic disorders ^f	3	1.8	8	6.0	0.28 (0.07 - 1.09)	0.05	0.27 (0.06 - 1.06)	0.06
Psychiatric conditions ^g	3	1.8	6	4.5	0.38 (0.09 - 1.57)	0.15	0.52 (0.12 - 2.22)	0.38
Rheumatic diseases ^h	13	7.8	3	2.3	3.65 (1.02 - 13.11)	0.03	4.96 (1.34 - 18.37)	0.02
Dermatologic diseases ⁱ	5	3.0	4	3.0	0.99 (0.26 - 3.78)	0.62	0.96 (0.24 - 3.74)	0.95

S.: *Strongyloides*; **OR:** odds ratio; **95%CI:** 95% confidence interval; **HIV/AIDS:** human immunodeficiency virus/acquired immunodeficiency syndrome; **HTLV:** human T lymphotropic virus type; **NA:** not applicable. ^a61 patients with arterial hypertension, 7 patients with angina pectoris, 4 patients with congestive heart failure, and 1 patient with myocardial infarction; ^b8 patients with asthma and 11 patients with chronic obstructive pulmonary disease; ^c6 patients with hepatitis B and 8 patients with hepatitis C; ^d12 patients with pulmonary tuberculosis, 1 patient with bone tuberculosis, and 1 patient with lymph node tuberculosis; ^e5 patients with lymphoma, 1 patient with multiple myeloma, 1 patient with uterine cancer, 1 patient with colon cancer, 1 patient with esophageal cancer, 1 patient with stomach cancer, 2 patients with laryngeal cancer, 1 patient with pancreatic cancer, 3 patients with prostate cancer, and 11 patients with lung cancer; ^f5 patients with dyslipidemia, 3 patients with hypothyroidism, and 3 patients with obesity; ^g6 patients with depression, 2 patients with schizophrenia, and 1 patient with anxiety; ^h6 patients with systemic lupus erythematosus, 3 patients with rheumatoid arthritis, 3 patients with gout, 2 patients with scleroderma, 1 patient with Behcet disease, and 1 patient with Sjogren syndrome; ⁱ5 patients with psoriasis and 4 patients with eczema.

TABLE 2 - White blood cells counts in patients with and without intestinal strongyloidiasis in Rio de Janeiro, Brazil.

	<i>S. stercoralis</i> -positive (n=167)	<i>S. stercoralis</i> -negative (n=133)	p-value
White blood cells (x1,000), total	7.945 ± 2.980	8.052 ± 3.375	0.30
Nonsegmented neutrophils (%)	1.70 ± 3.33	1.19 ± 1.58	0.16
Segmented neutrophils (%)	52.85 ± 15.31	61.32 ± 11.4	<0.01
Eosinophils (%)	10.32 ± 7.2	4.23 ± 2.92	<0.01
Lymphocytes (%)	28.11 ± 9.72	30.90 ± 9.51	<0.01
Monocytes (%)	8.49 ± 7.25	5.39 ± 4.31	<0.01

S.: *Strongyloides*.

the sensitivity of the strongyloidiasis detection technique. This phenomenon demonstrates the need to diagnose intestinal strongyloidiasis prior to the start of immunosuppressive and/or corticoid therapy to avoid the dissemination of the parasite.

In this study, we observed no association between intestinal strongyloidiasis and HTLV 1-2 infection. This association has been reported in Brazil by Furtado et al.⁽¹⁷⁾. The synergistic effects of co-infection with HTLV and *S. stercoralis*, which have been

demonstrated, suggest that co-infected patients exhibit elevated parasite burdens and HTLV-1 proviral loads^{(18) (19) (20)}. With respect to the interaction between strongyloidiasis and acquired immunodeficiency syndrome (AIDS), our study indicated that the frequency of HIV infection tended to be higher among *S. stercoralis*-positive patients than among *S. stercoralis*-negative patients but that this difference was not statistically significant. A case-control study performed in Thailand found

that HIV is a predictor of strongyloidiasis⁽²¹⁾. *S. stercoralis* was the most frequently detected helminth among AIDS patients in Laos⁽²²⁾. In Brazil, a prior investigation found an elevated prevalence of strongyloidiasis during the pre- and post-highly active antiretroviral therapy eras and a greater frequency of strongyloidiasis among male patients than among female patients⁽²³⁾. Similarly, our study found that males were more frequently infected with *S. stercoralis* than females. More frequent exposure to infective forms of *S. stercoralis* in the environment has been postulated as the reason for the higher prevalence of strongyloidiasis among males than among females.

Although no association between infection by *S. stercoralis* and viral hepatitis has been detected, reports have indicated that antiviral therapy with ribavirin could trigger disseminated strongyloidiasis in parasitized patients⁽²⁴⁾. Our study found that the frequency of infection with hepatitis B and C viruses was slightly higher among patients with strongyloidiasis than in the *S. stercoralis*-negative group.

Strongyloides stercoralis infection is extremely significant in patients with neoplasms because immunosuppressive chemotherapy can lead to severe forms of this parasitosis⁽²⁵⁾. Strongyloidiasis in patients who are undergoing chemotherapy should be appropriately treated with effective drugs. In this study, distinct malignancies were present in almost 10% of patients with strongyloidiasis; this rate was 5.2% among *S. stercoralis*-negative patients. These data reinforce the need to conduct appropriate stool examinations to detect *S. stercoralis* larvae as part of the routine care of cancer patients. In patients with chronic renal disease, the presence of strongyloidiasis is important due to the possible initiation of immunosuppressive therapy after renal transplantation. Thus, transplant patients should also be evaluated for infection by *S. stercoralis*⁽²⁶⁾. Although patients with chronic respiratory diseases typically receive steroids, we observed no association between this group of diseases and strongyloidiasis. Importantly, strongyloidiasis itself can be a cause of obstructive pulmonary symptoms⁽²⁷⁾.

In this study, we observed that mean relative eosinophil counts were significantly higher in the group of strongyloidiasis patients than in the *S. stercoralis*-negative group. Given this finding and the presence of elevated monocyte counts in the strongyloidiasis group, it is unsurprising that lower relative neutrophil counts were detected in the strongyloidiasis group than in the *S. stercoralis*-negative group. The association between strongyloidiasis and eosinophilia has been well established, although the absence of this correlation has also been reported in the literature^{(28) (29)}.

We conclude that strongyloidiasis should be routinely investigated in patients hospitalized with complex conditions, irrespective of whether these patients require immunosuppressive therapy. This disease should be diagnosed using appropriate parasitological methods, such as the Baermann-Moraes technique.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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