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Short communication

Helminthic infection and the risk of neurologic disease progression in HTLV-1

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ABSTRACT

Background: Infection with the human T-cell lymphotropic virus, type 1 (HTLV-1) has been associated with an increased Th1 response. Interestingly, a higher prevalence of helminthic coinfection has been observed among infected individuals, and subsequent modulation of the immune response typically associated with helminths may influence clinical outcomes among HTLV-1 coinfected individuals.
Objective: This study was conducted to elucidate the association between helminthic coinfection and the development of clinically characterized neurologic disease that occurs in HTLV-1 infection.
Study design: In a cohort analysis, incidence of HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) was recorded. Incidence of clinical outcomes and disease-free survival of several neurologic outcomes associated with HTLV-1 were estimated using the Kaplan–Meier method with log-rank tests. The relationships between helminthic infection and risk of HTLV-1 neurologic outcomes were assessed by Cox proportional hazard modeling.
Results: Seventy-four coinfected and 79 non-coinfected patients were followed, with 92 helminthic infections observed in the coinfected group. One patient per group developed HAM/TSP and the risk of progression to neurologic disease outcomes did not differ among those with and without helminthic coinfection ($p > 0.45$). A significant difference was noted in the prevalence of neurologic disease outcomes among all patients at the conclusion of the study ($p < 0.01$).
Conclusions: These data suggest that treated helminthic infection does not affect risk of development of neurologic disease in HTLV-1 infection, and reinforce that treatment of helminths does not adversely affect patients with HTLV-1. Importantly, among all patients, an overall progression of neurologic disease was observed.

1. Background

The human T-cell lymophotropic virus, type 1 (HTLV-1) is the causal agent of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and other neurologic manifestations not meeting World Health Organization (WHO) criteria for HAM/TSP.[1–7] Infection with HTLV-1 has been associated with an increased Th1 immune response, which may be responsible for the neurologic manifestations.[8,9] Interestingly, a higher prevalence of helminthic coinfection has been observed among HTLV-1-positive individuals.[10–14] Previous studies have shown that helminthic infections may downregulate both Th1 and Th2 responses, attenuating chronic inflammatory diseases.[15–18] Because HTLV-1 infection is associated with a high Th1 response, it is thought that helminthic infection and subsequent modulation of the immune response may influence clinical outcomes among HTLV-1 coinfected individuals, as compared to HTLV-1 infection without helminthic coinfection.

2. Objectives

This study was conducted to elucidate the association between helminthic coinfection and the development of clinically characterized neurologic disease that occurs in HTLV-1 infection.

3. Study design

Participants were selected from an HTLV-1-infected cohort, followed for development of neurologic disease at the Hospital

Abbreviations: HTLV-1, human T-cell lymphotropic virus type 1; HAM/TSP, HTLV-associated myelopathy/tropical spastic paraparesis; WHO, World Health Organization; HUPES, Hospital Universitário Professor Edgard Santos; HIV, human immunodeficiency virus; HR, hazard ratio; CI, confidence interval; prev., prevalence.

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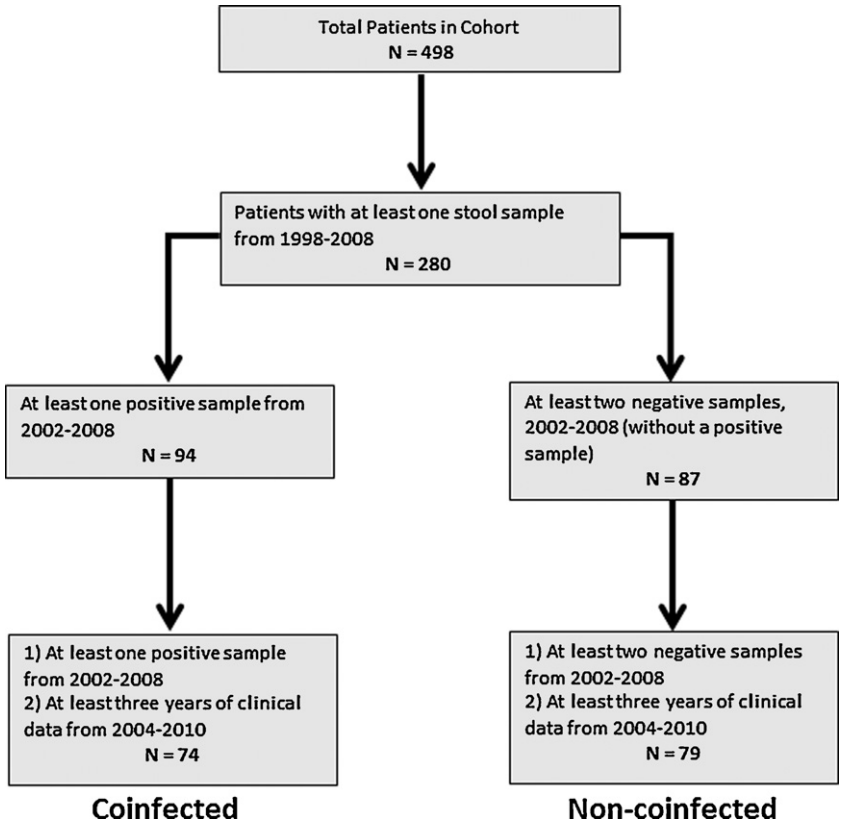

Fig. 1. Flowchart describing patient selection. From the neurologic disease cohort of 498 patients, 153 patients met criteria for designation as either coinfected or non-coinfected.

Universitário Professor Edgard Santos (HUPES) in Salvador, Brazil. The cohort totaled 498 patients in 2010 and has been followed since 1998, with clinical neurologic data collected from 2004 to 2010. HTLV-1 infection was confirmed by Western blot (HTLV blot 2.4, Genelab, Singapore) or proviral load. Exclusion criteria included ages outside 18–70 years and a positive HIV test.

Yearly stool samples were requested from all patients. Samples were assessed using Hoffman, Baermann, and Kato-Katz methods by one expert enteroparasitologist collaborator. Of the patients who provided samples, 153 met criteria set prior to analysis for designation into coinfected or non-coinfected groups. Designation as coinfected required ≥1 positive stool sample between the years 2002–2008, and three years of follow-up clinical neurologic data collection between 2004 and 2010 after establishment of helminthic infection. Designation as non-coinfected required ≥2 negative stool samples on separate years between 2002 and 2010, the absence of a positive stool sample since cohort establishment, and at least three years of clinical neurologic data collection between 2004 and 2010 (Fig. 1). Based on limited data concerning long-term effects of helminthic infection, the criteria allowed establishment of coinfection within two years of initiation of clinical neurologic data collection.[19] All coinfected patients were offered treatment with anti-parasitic medications, with follow-up and additional testing at the discretion of treating physicians.

Patients received yearly neurologic evaluations and replied to standardized questionnaires assessing socio-demographic characteristics. This study focused on the incidence of HAM/TSP and risk of developing overactive bladder, incontinence, dysuria, weakness in the arms or legs lasting ≥1 week, and difficulty walking or running. Patients presenting initially with an HTLV-1 neurologic outcome were not included in analyses for that outcome. Diagnosis

Table 1
Socioeconomic and environmental characteristics of HTLV-1 patients upon cohort enrollment.

Characteristic	Patients with helminths (n = 74)	Patients without helminths (n = 79)	p-Value
Male:female ratio	1:1.2	1:1.9	0.19[a]
Age, mean ± SD (years)	47.4 ± 10.4	47.6 ± 10.9	0.92[b]
Lifetime exposure to contaminated water			
Exposed	44 (59%)	59 (75%)	0.12[c]
Not exposed	24 (32%)	15 (19%)	
Unknown/no response	6 (8%)	5 (6%)	
Race/ethnicity			
White	17 (23%)	16 (20%)	0.70[c]
Multi-ethnic: white and black	27 (36%)	32 (41%)	
Black	27 (36%)	26 (33%)	
Other	1 (1%)	0 (0%)	
Unknown/no response	2 (3%)	5 (6%)	
Total family income (minimum Brazilian salaries)			
<1	6 (8%)	11 (14%)	0.40[c]
≥1 and ≤4	50 (68%)	52 (66%)	
>4 and ≤10	15 (20%)	13 (16%)	
>10	1 (1%)	3 (4%)	
Unknown/no response	2 (3%)	0 (0%)	
Past sexual activity			
Opposite sex relationships only	31 (42%)	33 (42%)	0.33[c]
Same sex relationships only	0 (00%)	0 (00%)	
Sexual relationships with both sexes	7 (09%)	3 (04%)	
Unknown/no response	36 (49%)	43 (54%)	
History of injection drug use	3 (4%)	0 (0%)	0.11[c]
Education, mean ± SD (years)	7.3 ± 4.2	7.3 ± 3.9	0.99[b]

[a] Pearson chi-squared test.
[b] Student's t test.
[c] Fisher's exact test.

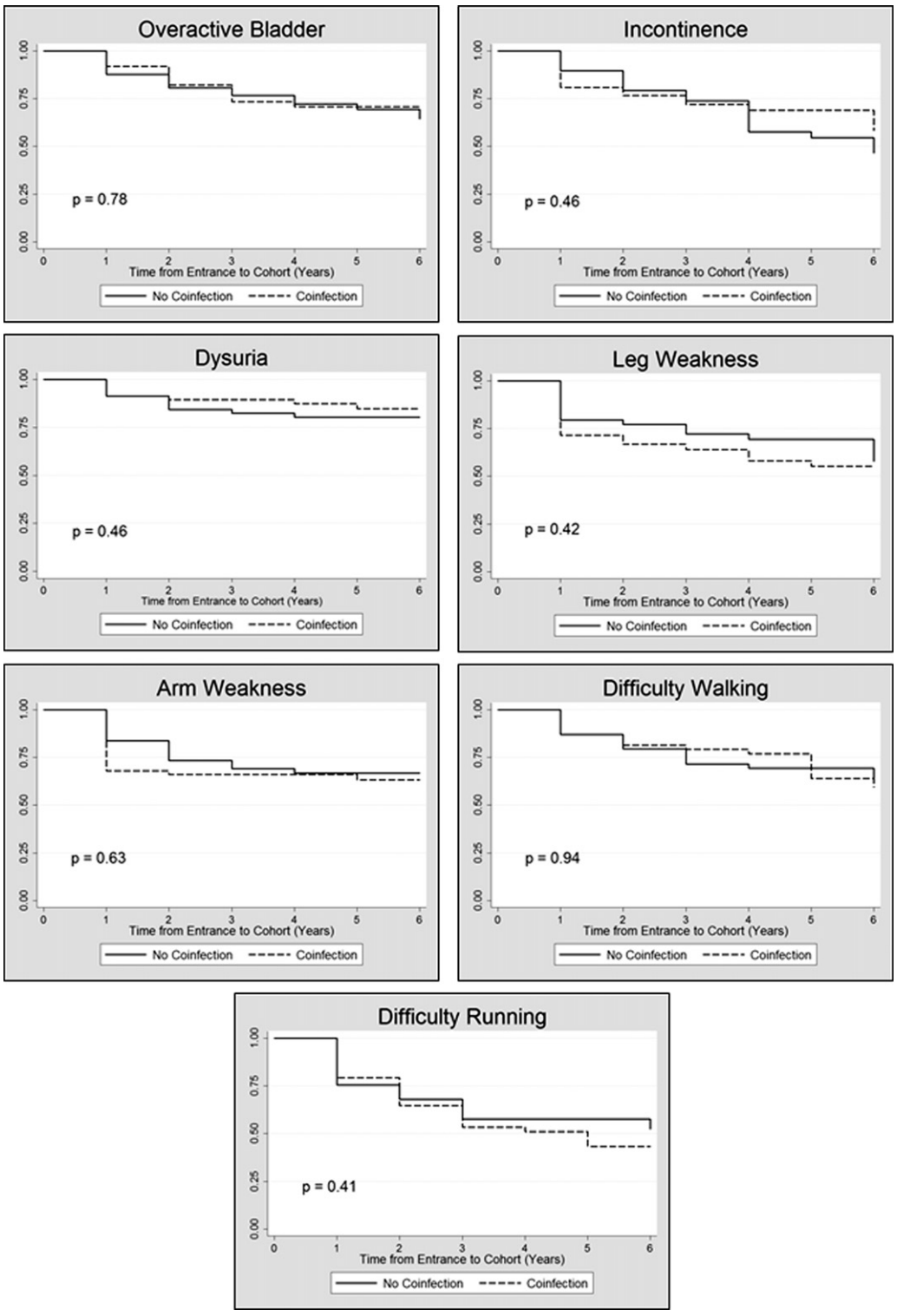

Fig. 2. Kaplan–Meier curves of development of clinical outcomes from time of patient entrance to the cohort. Log-rank test *p* values are included with each assessed outcome. Dashed line = coinfected group, solid line = non-coinfected group.

of HAM/TSP included the presence of WHO-defined characteristics and an Osame Motor Disability Score of ≥ 1. Patients who presented with or developed HAM/TSP were removed from analyses for other outcomes unless they first developed the outcome of interest. Overactive bladder was defined as urgency without infection or other clear cause.[20]

Analyses involved StataIC10 software (StataCorpLP, College Station, TX). Incidence of clinical outcomes and disease-free survival were estimated using the Kaplan–Meier method with log-rank tests. Cox proportional hazard models were used to assess the relationship between helminthic coinfection and neurologic disease progression.

Written informed consent was obtained from all participants. This study was approved by committees at HUPES, Weill Cornell Medical College, and Stanford University School of Medicine.

Table 2
Prevalence of clinical outcomes at initiation and conclusion of the cohort analyses.

Clinical outcome	(+) Helminths initial prev. ($n = 74$)	(−) Helminths initial prev. ($n = 79$)	p-Value	Overall prev. at cohort initiation ($n = 153$)	Overall prev. at cohort end ($n = 153$)	p-Value
OB	22 (30%)	17 (22%)	0.24[b]	39 (25%)	70 (46%)	<0.001[b]
Incontinence	25 (34%)	14 (18%)	0.02[b]	39 (25%)	79 (52%)	<0.001[b]
Dysuria	9 (12%)	11 (14%)	0.75[a]	20 (13%)	39 (25%)	<0.01[b]
Leg weakness	28 (38%)	34 (43%)	0.51[b]	62 (41%)	95 (62%)	<0.001[b]
Arm weakness	17 (23%)	22 (28%)	0.49[b]	39 (25%)	74 (48%)	<0.001[b]
Difficulty walking	19 (26%)	26 (32%)	0.33[b]	45 (29%)	80 (52%)	<0.001[b]
Difficulty running	25 (34%)	26 (33%)	0.91[b]	51 (33%)	100 (65%)	<0.001[b]

OB, overactive bladder; prev., prevalence.
[a] Fisher's exact test.
[b] Pearson chi-squared test.

4. Results

A total of 153 patients were included in the analyses. Seventy-four patients were classified as coinfected, and from these a total of 92 helminthic infections were observed: 34 *Strongyloides stercoralis* (37%), 24 *Ascaris lumbricoides* (26%), 20 *Schistosoma mansoni* (21%), six *Trichuris trichiura* (6%), five *Ancylostoma duodenale* (5%), and three *Enterobius vermicularis* (3%). Seventy-nine patients were classified as non-coinfected.

Socioeconomic data are included in Table 1, and prevalence of clinical outcomes in patients at the beginning and conclusion of the study period are included in Table 2. During the study period, one patient from both groups developed HAM/TSP. Thirty-one patients developed overactive bladder: 14 coinfected and 17 non-coinfected patients (hazard ratio [HR] 0.90; 95% confidence interval [CI] 0.45–1.84; $p = 0.79$). Forty patients developed incontinence: 16 coinfected and 24 non-coinfected patients (HR 0.79; 95% CI 0.42–1.51; $p = 0.49$). Nineteen patients developed dysuria: eight coinfected and 11 non-coinfected patients (HR 0.72; 95% CI 0.29–1.80; $p = 0.48$). Thirty-five patients developed arm weakness: 19 coinfected and 16 non-coinfected patients (HR 1.16; 95% CI 0.60–2.26; $p = 0.66$). Thirty-three patients developed leg weakness: 18 coinfected and 15 non-coinfected patients (HR 1.29; 95% CI 0.65–2.57; $p = 0.46$). Thirty-five patients developed difficulty walking: 18 coinfected and 17 non-coinfected patients (HR 1.02; 95% CI 0.53–1.99; $p = 0.94$). Forty-nine patients developed difficulty running: 26 coinfected and 23 non-coinfected patients (HR 1.24; 95% CI 0.71–2.17; $p = 0.46$). Kaplan–Meier curves with log-rank test results for each outcome are presented (Fig. 2).

5. Discussion

This study evaluated, for the first time, helminthic coinfection and the risk of neurologic disease development with HTLV-1. We found no difference in the risk of developing any assessed clinical outcomes among patients with or without treated helminthic infections. Likewise, incidence of HAM/TSP was low among both groups. There was, however, a significant change in clinical outcome prevalence among all analyzed patients from the beginning to the end of the study.

While past studies of helminthic coinfection in HTLV-1 point to possible immunomodulatory effects, no previous studies compared clinical progression of HTLV-1 disease with helminthic coinfection over time. A 2004 study in Brazil found that patients coinfected with *S. mansoni* and HTLV-1 had milder liver fibrosis than in those with schistosomiasis alone.[12] In a 2005 cross-sectional study by the same group, 23 percent of HTLV-1 asymptomatic carriers were coinfected with *S. mansoni* and/or *S. stercoralis*, while only three percent of patients with HAM/TSP had coinfection.[13] These results suggest a relationship between HTLV-1/helminthic coinfection and the pathogenic processes that cause disease progression. However, the 2005 study was a case-control study which did not establish causation. Likewise, while HTLV-1 may affect progression of schistosomiasis, the reverse may not be true.

Indeed, a variation in the clinical effects of helminths in many diseases, including tuberculosis, multiple sclerosis, Crohn's disease, celiac disease, and atopy have been observed.[21–27] Such inconsistencies may occur due to differences in type of helminthic infection, parasitic load, and treatment of infection.[28–30] This study evaluated all helminthic infections, which may have diminished the effects of a particular species, and data on parasite load were not available in most patients. Additionally, because of the known danger of disseminated strongyloidiasis in HTLV-1 patients, all helminthic coinfections were treated.[11,14,31] Therefore, it was not possible to evaluate untreated helminthic infections.

Despite finding a lack of association between coinfection and risk of neurologic disease progression in HTLV-1, these data remain valuable, as they are a first step in evaluating the clinical response to helminthic coinfections in patients with HTLV-1 and they reinforce that treatment of helminths does not adversely affect outcome. Furthermore, these data contribute information to the progression of neurologic disease in HTLV-1. HAM/TSP is a late complication, and, as expected, only two patients developed this condition during follow-up. However, the increase in prevalence and rapid progression of other clinical outcomes demonstrate that many patients go on to develop neurologic disease in some form.

Conflict of interest

Funding: none.
Competing interests: none.

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