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SHORT REPORT: DO INTESTINAL NEMATODES INCREASE THE RISK FOR MULTIBACILLARY LEPROSY?

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Abstract. Intestinal helminths are known to subvert the host's immune response towards a Th2 response, which in turn may lead to both eosinophilia and high immunoglobulin E titers often associated with these parasites. *Mycobacterium leprae* infection may lead to different clinical and pathological forms. Multibacillary forms are associated with Th2 cytokines, whereas paucibacillary forms are associated with Th1 cytokines. We report a significantly higher frequency of intestinal helminthic infections in patients with the lepromatous form, a multibacillary form of leprosy (odds ratio, 2.99; 95% confidence interval, 1.82–4.95; $P = 0.006$) when compared with patients with paucibacillary leprosy or to a control group without leprosy. A direct correlation was also found between mycobacterial index and the frequency of intestinal helminths. Our results suggest that the presence of intestinal helminths may facilitate the establishment of *M. leprae* infection or the progression to more severe forms of leprosy.

Intestinal helminthic infections are known to elicit an immune modulation in the host characterized by an upregulation of Th2 responses, such as peripheral blood and intestinal mucosa eosinophilia and high titers of circulating immunoglobulin E.[1] This Th2 upregulation was elegantly demonstrated in rodent experimental models and has been also reported in humans.[2–4] Experimental observations have shown that besides upregulating Th2 responses, helminthic antigens also downregulated Th1 responses, affecting the ability of the host's immune system to respond to other infections.[5–7] Bentwich and others[8] suggested that infection by intestinal helminths might affect disease severity on patients infected by either human immunodeficiency virus type 1 or *Mycobacterium tuberculosis.*

Prost and others,[9] investigating different regions with the same leprosy prevalence, reported that the frequency of lepromatous leprosy was significantly higher on areas where filariasis was hyperendemic than on those where it was either of low endemicity or absent. Also, a downregulation of the cellular immune response to *M. tuberculosis* antigens and an upregulation of Th2 cytokines were reported in children infected with *Onchocerca volvulus* in the Republic of Cameroon, suggesting that infection with helminths interfered with the normal immune response to mycobacterial infection.[10]

It is known that in leprosy, a Th1 response has been associated with resistance to *M. leprae,* or at least with the mild paucibacillary tuberculoid form, and that Th2 response has been associated with the severe multibacillary lepromatous form.[11] Therefore, it is possible that an upregulation of Th2 cytokines, elicited by an infection with intestinal helminths, may affect the immune response against *M. leprae,* favoring the establishment of multibacillary forms of leprosy.[11]

In an attempt to verify a relationship between intestinal nematodes and leprosy, we reviewed the records of 477 patients with leprosy attending to a Espírito Santo state health service (Centro de Saúde de Vitória) in Vitória, Espírito Santo, Brazil, from January 1992 to December 1999. As a control group, we randomly selected 470 patients without leprosy who were in the same unit during the same period. Records from either patients with leprosy or controls included results from at least one stool examination (performed by the Hoffman-Pons-Janer method at the same clinical laboratory).

Patients with leprosy were grouped according to their clinical form following the guidelines of the Brazilian Ministry of Health: 1) 115 (24.1%) patients were classified as having the indeterminate form; 2) 191 patients (40.0%) were classified as having the tuberculoid form; 3) 83 patients (17.4%) were classified as having the borderline form (including borderline-borderline, borderline tuberculoid, and borderline lepromatous); and 4) 88 patients (18.4%) were classified as having the lepromatous form.

Patients with leprosy were also grouped according to their mycobacterial index as either paucibacillary (negative baciloscopy, which includes indeterminate and tuberculoid patients) or multibacillary (positive baciloscopy, which includes borderline and lepromatous patients). The mycobacterial index ranged 0–6, according the number of bacilli by oil immersion field (oif): 0 = none/1,000 oif; 1+ = 1–10/100 oif; 2+ = 1–10/10 oif; 3+ = 1–10/oif; 4+ = 10–100/oif; 5+ = 100–1,000/oif; and 6+ ≥ 1,000/oif. Statistical analysis was performed by Epi Info version 6.0 (Centers for Disease Control and Prevention, Atlanta, GA).

The results are summarized on Tables 1 and 2. Frequency of stool samples positive for intestinal helminths was significantly higher among patients with leprosy, regardless of their clinical form (odds ratio [OR], 1.46; 95% confidence interval [CI], 1.08–1.97, $P = 0.01$). This difference disappears if these patients are grouped by sex (Table 2). However, when patients with leprosy were grouped according to their clinical form, the frequency of intestinal helminths was significantly higher among patients with lepromatous leprosy, regardless of their sex (OR, 2.99; 95% CI, 1.82–4.95, $P < 0.001$) (Table 2). The frequency of intestinal helminths was significantly higher among multibacillary patients (borderline and lepromatous) than in the paucibacillary group (indeterminate and tuberculoid): 38.3 and 24.6%, respectively (OR, 1.81; 95% CI, 1.17–2.79; $P = 0.006$). A direct correlation between the mycobacterial index and the frequency of intestinal helminths was also found (Pearson coefficient $R = 0.982$, $P = 0.01$).

TABLE 1
Gender and age of leprosy and control patients

Groups	N	Age			
		Mean	SD	Median	Range
Without leprosy	470	43.85	16.22	42.0	7–89
Male	135	45.24	17.73	44.0	7–81
Female	335	42.47	14.63	41.0	14–89
Leprosy (all forms)	477	41.60	17.72	41.0	5–86
Male	212	42.06	17.14	42.0	5–84
Female	265	40.71	18.04	40.0	6–86
Indeterminate	115				
Male	39	38.95	15.93	40.0	12–65
Female	76	35.54	16.01	33.0	10–77
Tuberculoid	191				
Male	77	39.64	16.59	41.0	5–79
Female	121	40.20	19.23	42.0	6–81
Borderline	69				
Male	36	44.61	20.33	45.5	9–84
Female	33	45.27	18.31	47.0	14–86
Lepromatous	88				
Male	60	45.05	16.61	44.0	16–75
Female	28	41.86	18.63	38.0	18–84

Although data for both patients in both the leprosy and control groups were collected at the same health center, our sampling method may be criticized because patients treated there came from different neighborhoods of metropolitan Vitória. Although members of both the leprosy and control groups were of similar socioeconomic status, hygiene and housing conditions may vary from region to region in Vitória's metropolitan area. In addition, leprosy is often a disease of families or people with close contact, and the ideal controls would be people in contact with patients with leprosy and people living in the same house or neighborhood.

Even with these caveats, the results presented here show a direct correlation between helminthic infections and multibacillary leprosy. The observed differences in frequencies of intestinal nematodes were significant when patients with multibacillary forms were compared with either patients with paucibacillary leprosy or with controls. Conversely, the frequency of other intestinal parasites, such as intestinal protozoans (*Giardia lamblia* and *Entamoeba* sp.) did not differ between leprosy and control groups. Considering that the transmission route is the same for both the most frequent helminths (*Ascaris lumbricoides* and *Trichuris trichiura*) and the most frequent protozoans (*Entamoeba* sp. and *Giargia lamblia*) identified in this study, we think that the risk of parasite contamination through the oral route was similar for members of both the leprosy and control groups.

Although the mycobacterial index is not a precise definition of disease spectrum, the high correlation coefficient between mycobacterial index and the frequency of nematode infections may provide another piece of evidence that associates these 2 infections.

Data presented here suggest that the presence of intestinal helminths may be associated with multibacillary leprosy (borderline and lepromatous forms). The immune modulation elicited by helminth antigens—upregulating Th2 responses and inhibiting Th1 immune responses and therefore favoring bacilli growth and dissemination—corroborate our observations. Considering that leprosy is a slowly progressing and chronic disease, it is difficult to determine whether or not the nematode infection preceded the *M. leprae* infection. However, we think that the immune modulation induced by nematode infection may disrupt the immune responses to leprosy, without regard to whether the helminth infection occurred before or after the *M. leprae* infection were established. The presence of intestinal worms before

TABLE 2
Frequency of intestinal parasites in leprosy and control patients

Groups	N	Nematode				Protozan			
		+	−	OR (95% CI)*	*P*	+	−	OR (95% CI)*	*P*
Control									
All cases	470	110	360			98	372		
Male	135	32	103			21	114		
Female	335	78	257	1.02 (0.60–1.68)	0.980	77	258	0.99 (0.72–1.38)	0.967
Leprosy									
All cases	477	147	330	**1.46 (1.08–1.97)**	0.010	99	378	0.62 (0.35–1.08)	0.095
Male	212	66	146	1.43 (0.87–2.45)	0.160	38	174	1.19 (0.64–2.21)	0.660
Female	265	81	184	1.49 (0.89–2.23)	0.055	61	204	1.00 (0.67–1.50)	0.929
Indeterminate									
All Patients	115	25	90	0.91 (0.54–1.5)	0.790	30	85	1.34 (0.81–2.20)	0.223
Male	39	9	30	0.97 (0.38–2.4)	0.677	8	31	1.40 (0.51–3.75)	0.455
Female	76	16	60	0.88 (0.46–1.67)	0.732	22	54	1.37 (0.75–2.46)	0.273
Tuberculoid									
All Patients	191	53	138	1.26 (0.84–1.8)	0.282	35	156	0.85 (0.54–1.33)	0.463
Male	77	21	56	1.21 (0.61–2.40)	0.186	11	66	0.90 (0.38–2.12)	0.804
Female	121	36	85	1.40 (0.85–2.20)	0.198	24	90	0.92 (0.54–1.56)	0.735
Borderline									
All Patients	69	18	51	1.16 (0.62–2.13)	0.820	17	52	1.24 (0.66–2.32)	0.473
Male	36	9	27	1.07 (0.42–2.79)	0.951	10	26	2.09 (0.80–5.36)	0.091
Female	33	9	24	1.24 (0.51–2.93)	0.764	7	26	0.90 (0.84–2.28)	0.354
Lepromatous									
All Patients	88	42	46	**2.99 (1.82–4.95)**	0.000	14	74	0.72 (0.37–1.37)	0.288
Male	60	26	33	**2.63 (1.32–5.28)**	0.004	9	51	0.96 (0.38–2.39)	0.921
Female	28	15	13	**3.80 (1.63–8.92)**	0.000	5	23	0.73 (0.23–2.11)	0.533

* Odds ratio (OR) compared to control group. Bold numbers indicate differences that are statistically significant ($P < 0.05$). CI = confidence interval.

the establishment of a *M. leprae* infection may shift the immune response toward a Th2 path, which in turn may favor the establishment of the mycobacterial infection. Similarly, if infection with helminths occurs after the establishment of a *M. leprae* infection, the strong Th2 modulation elicited by helminthic antigens may enhance mycobacterial dissemination and disease progression to the multibacillary forms of leprosy.

The hypothesis presented here is also supported by the observations of Prost and others,[9] who reported a higher frequency of lepromatous leprosy in patients with onchocerciasis when compared with patients without onchocerciasis living in the same endemic region. Also corroborating with our results are observations demonstrating that a constant immune challenge sustained by helminthic infections results in a wide immune dysregulation, with a predominance of Th2 cytokines and impairment of the ability of T cells to respond to stimuli.[12,13] Taken together, these findings suggest that chronic immune activation may lead to immune hyporesponsiveness and in some extreme cases to anergy, endangering the ability of patients harboring intestinal helminths to respond to other chronic infections, such as human immunodeficiency virus and tuberculosis.[8,12,14,15]

It has been reported that acute *Schistosoma mansoni,* intestinal nematodes, or *Toxocara canis* infections are risk factors for pyogenic liver abscess and for other staphylococcal infections on both children and adults.[16–18] Supporting this hypothesis are preliminary results from our laboratory, which indicate that the production of interleukin-4 and -10 by $CD3^+$ $CD4^+$ T cells is higher among patients with either lepromatous or tuberculoid leprosy coinfected with intestinal nematodes when compared with patients with leprosy without intestinal nematodes or compared with control individuals (data not shown).

Currently, a prospective case-control study is been carried on at our laboratory; we are attempting to further investigate the association of intestinal helminths and leprosy and to elucidate the immunological consequences of this association.

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