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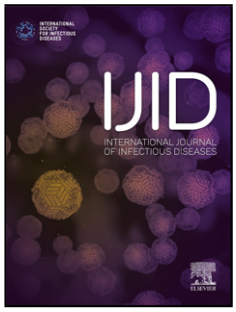

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Mycobacterium leprae-Helminth Co-Infections and Vitamin D Deficiency as Potential Risk Factors for Leprosy: A Case-Control Study in Southeastern Brazil

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Highlights:

- Schistosomiasis is more common in individuals with leprosy than their household contacts in a leprosy hyperendemic area
- Vitamin D deficiency is also common in individuals with leprosy, and statistically more common when compared to non-household controls
- Children with leprosy in the study had the highest burden of concommitent schistosomiasis
- These associations may affect the transmission of leprosy by predisposing individuals to disease and therefore contributing to the ongoing reservoir of infection

Abstract

Background: Evidence suggests that biological mechanisms involved in helminth infections and vitamin deficiencies increase susceptibility to other infections. Our aim was to investigate the associations of helminth co-infection and select micronutrient deficiencies with leprosy through a case-control study design.

Methods: From 2016-2018, individuals ages 3 years and older were recruited at clinics in and around Governador Valadares, Minas Gerais, Brazil in 3 groups: cases of leprosy, household contacts and community-matched controls. Helminths were diagnosed through stool Kato Katz exams and serum reactivity to anti-SWAP IgG4. Serum ferritin, 25-OH vitamin D, and retinol concentrations were measured. Multivariate logistic regression was conducted to identify associations with active leprosy.

Results: We recruited 79 cases of leprosy, 96 household contacts, and 81 non-contact controls; 48.1% male with a median age of 40 years old. Helminths were found in 7.1% of participants by Kato Katz with all but one *S. mansoni*, and 32.3% were positive for *S. mansoni* serology. In multivariate analysis, cases were more likely be infected with helminths (diagnosed by stool) compared to contacts (aOR: 8.69 95% CI 1.50, 50.51). Vitamin D deficiency was common and associated with leprosy when compared to non-contact controls (aOR = 4.66, 95% CI 1.42, 15.33). Iron deficiency was not associated with leprosy and we did not detect vitamin A deficiency.

Conclusion: These associations suggest that the immune consequences of schistosomiasis and vitamin D deficiency may increase the risk of active leprosy disease. Co-morbid conditions of poverty deserve further study as addressing co-infections and nutritional deficiencies could be incorporated into programs to improve leprosy control.

Keywords: leprosy, schistosomiasis, Hansen's disease, helminth, co-infection, micronutrient, Vitamin D

1. Introduction

Many obstacles remain in the control of leprosy, a neglected tropical disease (NTD) caused by *Mycobacterium leprae.* More than 200,000 new cases are detected annually with India and Brazil reporting the most cases[1]. Brazil has "hyperendemic" pockets throughout the country with > 40 new cases/100,000 persons per year, including eastern Minas Gerais in the southeast of the country[2]. Leprosy is associated with poverty, suggesting comorbidities of poverty may drive leprosy transmission[3,4]. Given their effects on the immune system, two factors could be helminth co-infections and micronutrient deficiencies[5-8].

Manifestations and symptoms of leprosy are highly driven by the host immune response[9]. Tuberculoid (TB) leprosy is characterized by a strong cell-mediated response and thus thought to be much less infectious, while at the other end of the spectrum, multibacillary (MB) leprosy, in particular lepromatous (LL) disease, is characterized by an ineffective cell-mediated immune response, and thus responsible for the majority of transmission[10]. Helminth infections typically illicit a strong T-helper 2 (Th2) immune response and have been noted to have bystander effects on other infections[11], meaning that the immune response directed to the helminth may also influence the control of the second disease, in this case, leprosy. Studies have shown this type of immune dysregulation in tuberculosis-helminth co-infection, as well as in leprosy–helminth co-infection, with soil-transmitted helminth infection more common in leprosy cases than

contacts[5,11]. Also significant was a shift to a more prominent Th2 cytokine response in co-infections and more MB cases in co-infected cases[5]. This suggests that helminth infection may facilitate *M. leprae* infection and the progression to its more infectious forms. Additionally, a study in 2017 found a spatial and temporal overlap of co-endemic schistosomiasis and leprosy in Minas Gerais, Brazil[12].

Nutritional deficiencies may also affect leprosy; however, the literature is sparse. Lower vitamin A levels were found in individuals with LL compared to controls , presumably from a suppression of the T-helper 1 (Th1) immune response as a result of low vitamin A levels[6]. Additionally, vitamin D has been shown to be influential in both the innate and adaptive immune responses in humans[13]. Macrophages of the innate immune system utilize vitamin D dependent antimicrobial responses to kill intracellular microbes suggesting that vitamin D levels in patients with leprosy could determine the antimicrobial response to infection with *M. leprae* bacteria [7]. Lastly, food shortage and food insecurity have both been linked to leprosy[4,14].

Eastern Minas Gerais is highly endemic for both schistosomiasis and leprosy and has significant rural and urban poverty[15]. In a pilot cross-sectional study of patients with MB leprosy, we found high proportions of patients with both vitamin D deficiency (52%) and serologic evidence of schistosomiasis (15%)[16]. We, therefore, have built on these preliminary findings to investigate potential associations between leprosy, helminth infections and micronutrients. Determining if helminth infections and / or micronutrient deficiencies are more common in those with leprosy than those without can increase our understanding of comorbidities that may affect susceptibility to, and thus, transmission of leprosy.

2. **Methods**

2.1 Study population and design

A case control study took place in the municipalities of Governador Valadares and Mantena in eastern Minas Gerais, Brazil between June 2016-December 2018. Individuals ages 3 years of age and older were recruited. Newly diagnosed, untreated cases of leprosy were enrolled either at a leprosy specialty clinic in Governador Valadares or through contact tracing of previously known leprosy cases in rural communities outside of the city. Cases were confirmed by dermatologists with expertise in leprosy; skin slit smears for bacillary index were done on all cases. Cases were classified as indeterminate, tuberculoid, borderline, or lepromatous based on the Madrid Classification[17]. Close contacts of cases were enrolled as one of the two control groups and were defined as family members who had lived with the index case or who lived nearby and had regular weekly contact with the case for at least the past year. The second control group included those with no known prior contact with someone with leprosy and were matched by sex, age (within 5 years older or younger) and community of residence. All controls were clinically evaluated to ensure they had no signs or symptoms of leprosy.. Pregnant women were excluded from this study.

2.2. Sample size calculation:

For this sample size calculation, we used a baseline, conservative estimate helminth prevalence of 15% for controls given the known *S. mansoni* data in this region[15]. The Diniz study of helminth-*M. leprae* co-infection found an odds ratio of 4.0 for leprosy cases being infected with helminths as opposed to healthy controls[5]. Using a more conservative estimate for the odds ratio (3.5) and the baseline 10-15% prevalence of helminths, a power 80% and a two-sided confidence level of 95%, we would need 60-75 cases and 60-75 of each control group (to conduct separate

analyses with each control group)[18]. We used the more conservative estimate and aimed for enrolling 75 of each group.

2.2 Data collection

Demographic and clinical data were extracted from medical records and a clinical exam. A detailed questionnaire was administered on socioeconomic status, education, occupation, as well as nutritional habits. Serum samples were taken for micronutrient status, complete blood count, and IgG4 reactivity to *Schistosoma mansoni* soluble adult worm antigen (SWAP). Helminth infection was diagnosed by the presence of eggs on stool samples collected over a three-day home collection by Kata Katz and HPJ methods[19,20]. Standard accepted cutoffs were used to diagnose iron, vitamin D, and vitamin A deficiency using ferritin (<30 micrograms (μg) / L in those age 5 years and up and <15 μg/ L in those under 5), 25-OH vitamin D (<20 μg / L) and retinol (<20 μg / L) respectively[21]. Vitamin A insufficiency was defined as a retinol concentration < 30 μg / dL. The cutoff of 30 μg / L for ferritin was used to account for the presence of infection or inflammation.

2.3 Data Analysis

Since the two control groups were treated differently, with the non-contact controls also matched by sex and age range, two sets of analyses were done: cases vs. household contacts and cases vs. non-contact controls. Descriptive and univariate statistics were conducted through frequency and Chi-square testing. The presence of active helminth infection in newly diagnosed patients with leprosy was compared to the presence in controls using multivariate logistic regression, controlling for age, sex (for contacts only) and vitamin D status. Additional models used IgG4 reactivity to SWAP to compare prior infection of schistosomiasis among cases and controls and a last model compared MB versus PB leprosy. The Akaike information criterion

(AIC) was used to arrive at the best fitting logistic regression model after accounting for collinearity and interaction between the main exposure (helminth infection) and the covariates. The model was also assessed through the Hosmer and Lemeshow goodness-of-fit test. Sample size was calculated using published data which found an odds ratio of 4 for the association between leprosy cases and soil-transmitted helminths, ensuring 80% power and 0.05 significance[5]. All statistical analyses were performed in SAS version 9.4 (Carey, NC) and an alpha of 0.05 was used to determine statistical significance.

2.4 Ethical considerations

The study was approved by the institutional review boards of Emory University and Universidade Federal de Juiz de Fora. All participants or parents of participants gave written informed consent and children ages 6 and up gave written assent.

3. Results

The total study sample included 79 cases, 96 household contacts, and 81 non-contact controls. Demographic and clinical details are described in Table 1. Stool exams were positive for *Schistosoma mansoni* (n=16, 6.6%), and ascaris (n=1, 0.4%). Vitamin D deficiency was notably higher in the cases as compared to the two sets of controls, (20.6% in cases, 12% in contacts, and 7% in negative controls). Serologic reactivity to *S. mansoni* was common at 32.5 % (n=77) of all participants and did not differ across groups. There were no cases of vitamin A deficiency among cases or any controls, although vitamin A insufficiency was present in 18 (8.7%) of total participants and iron deficiency in 23 (10.7) (Table 1). Seven (19.4%) children under 15 were positive for Schistosoma eggs on stool exam compared to 9 (4.4%) participants who were 15 years of age or older (p = 0.001).

On multivariate analyses, helminth infection was strongly associated with leprosy, with higher odds of helminth infection (predominantly *S. mansoni)* in cases compared to household contacts (aOR = 8.69; 95% CI 1.50, 50.51). This association was not present when cases were compared to non-contact controls (aOR = 1.27; 95% CI 0.38, 4.26). When using serology to schistosomiasis as a marker of infection, there were no statistically significant associations when cases were compared to either set of controls (Table 2). Vitamin D deficiency was associated with leprosy when compared to non-contact controls (aOR= 4.66; 95% CI 1.42, 15.33), but not when compared to household contacts (aOR = 1.63; 95% CI 0.64, 4.14). Lastly MB cases were not more likely to have schistosomiasis or vitamin D deficiency when compared to PB cases and adjusted for age and sex (aOR= 1.02; 95% CI 0.13, 7.93).

4. Discussion

Our data showed a distinct association with active helminth infection (all schistosomiasis in the cases) and leprosy when compared to household contacts. These associations suggest that patients infected with *S. mansoni* may have an altered immune response, such as polarization of Th2 immune response and modulation of cell-mediated immunity, which may increase the susceptibility to leprosy. A potential pathway could involve transition from latent to clinically evident leprosy in the setting of a new active *Schistosoma* infection with the helminth infection suppressing Th1 responses as has been seen in co-infections of other pathogens[11,22]. The fact that we did not find associations with SWAP serology suggests that the intensity of *S. mansoni* infection (and consequent likelihood of findings eggs on stool exam) may be a factor in the host immune effects. Our findings are consistent with a study by Diniz et al., who found a statistically significant association between soil transmitted helminth (STH) infections and leprosy compared

to healthy household contacts[5]. Also found in that study was an association between LL cases and STH when compared to tuberculoid cases and higher Th2 cytokines and lower Th1 cytokines in co-infected individuals compared to those with only leprosy[5]. While our study did not show an association between MB leprosy and schistosomiasis, the prior results from Diniz et al. and Oktaria et al. support that helminths could shift an individual away from a strong cell-mediated response and thus to the more infectious MB disease[5,8]. Our study had an overall low proportion of PB cases and, within the MB category (clinically diagnosed), many were bacillary index negative. Both factors may have limited our detection of an effect of polarization by the schistosomiasis. Furthermore, schistosomiasis cases predominated in children, who are less likely to have LL leprosy (none in our study). However, combined with the other studies, our study supports that helminths may contribute to continued transmission of *M. leprae* infection by increasing the number of leprosy cases in the community. With the higher burden of schistosomiasis in children in our study, this makes this association even more concerning since it suggests that schistosomiasis may particularly affect the susceptibility of leprosy in children. The lack of association of helminths and leprosy when compared to non-contact controls suggest a potentially different set of risk factors at play, and perhaps that when faced with a similar *M. leprae* exposure in the household, those with a moderate to high intensity *S. mansoni* infection as measured by Kato Katz, are more likely to present with active leprosy.

Vitamin D deficiency was also shown to be significantly associated with leprosy infection, this time when compared to the non-contacts. When looking at the immunologic response to *M. leprae* infection, Kim at al. found that the presence of sufficient levels of vitamin D prior to infection reduced the viability of the pathogen in macrophages [7]. A main source of vitamin D comes from sunlight and in Brazil there is a high amount of this, suggesting that the

lack of sufficient amounts of vitamin D could be attributed to dietary and nutritional factors[4]. It is hard to determine whether or not vitamin D deficiency is the cause of increased transmission, making people more likely to get an infection, or if leprosy infection causes the immune system to use up more vitamin D. However, our results suggest a potential predisposition to leprosy in those with inadequate vitamin D concentrations. Continued research into food security and dietary behaviors among those with leprosy could add value to assessing vitamin D deficiency as a risk factor or a consequence of leprosy. Vitamin A and iron deficiencies were not associated with leprosy, although the low prevalence of these disorders may have limited detection of associations.

Limitations of this study include the overall small study sample and observational nature of the study. It was not powered to detect differences in select age groups and it may be thus hard to generalize these findings to all ages. Furthermore, the fact that each factor (helminth infection and Vitamin D deficiency) showed associations when compared to one control group, and not the other deserves further study. These two control groups were, by definition, different from each other, with one group sharing similar living conditions and genetic factors and the other not, and therefore may have other unmeasured confounders that could explain the differences. Even then, about half of the household contacts were consanguineous and just under half, while they had frequent contact with a case, did not live in the same house as per the definition. The overall sample size and small number of stool-positive helminth infections limited further stratification of these contacts.

However, some inherent differences between the control groups could explain the outcomes. For instance, the household contacts may have had similar vitamin D levels as cases due to similarities in diet and sun exposure. Helminth exposures, on the other hand, are often

directly related to individual behaviors, especially schistosomiasis which requires contact with a body of fresh water. The differences in active schistosomiasis between household contacts and cases reinforces the potential role of immunologic derangement by helminth infections, more than if the non-contact controls showed a difference. In the scenario where members of the household or close family members have all been exposed to *M. leprae* infection and are likely to have similar genetic susceptibility to leprosy (for blood relatives), it is notable that schistosomiasis differs between these two groups, suggesting, again, a role of helminth infection increasing the likelihood of transition from latent to active leprosy.

5. Conclusions

Even with its long history, there are still many unknowns about the transmission of leprosy. This bacterium continues to infect individuals of all ages and there is a need for increased awareness and research into transmission. This study adds to the current body of literature investigating potential risk factors for leprosy transmission and may explain, in part, some of the poverty-related associations. Furthermore, our findings strongly support integrated control programs for NTDs. Next steps include analyses of cytokine results in co- and mono- infected individuals to further support our associations as well as a longitudinal cohort to better define risk factors.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Conflicts of Interest:

All authors report NO conflicts.

Ethical Approvals:

The study was approved by the institutional review boards of Emory University and Universidade Federal de Juiz de Fora. All participants or parents of participants gave written informed consent and children ages 6 and up gave written assent.

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Table 1. Description and univariate analyses of demographic, clinical, and infection status variables in cases, household contacts (HHC) and non-contact controls (NCC), using chi-square or t-test where appropriate. Bolded results are significant at a p<0.05.

A. Variable	Total (n = 256)	Cases (n=79)	HHC (n=96)	P-value: Cases vs HHC	NCC (n=81)	P-Value: Cases vs NCC
Age, years, mean (sd)	40.0 (20.5)	43.8 (20.5)	35.0 (19.8)	**0.005**	42.3 (20.4)	0.65
Children (age < 15 years), n (%)	37 (14.6)	9 (11.4)	17 (17.7)	0.24	11 (13.8)	0.68
Sex, n (%)						
Male	123 (48.1)	44 (55.7)	38 (39.6)	**0.03**	41 (50.6)	0.52
Race/Ethnicity^, n (%)						
White	57 (24.1)	13 (19.4)	27 (30.3)	0.22	17 (21)	0.62
Black	40 (16.9)	14 (20.9)	13 (14.6)		13 (16.1)	
Asian	3 (1.3)	0	2 (2.2)		1 (1.2)	
Mixed race	136 (57.4)	39 (58.2)	47 (52.8)		50 (61.7)	
Indigenous	1 (0.4)	1 (1.5)	0		0	
Education, n(%)						
Primary or less	38 (23.9)	12 (15.2)	31 (32.6)	**0.01**	26 (32.5)	**0.01**
Family Income, n (%)						
<1 x minimum wage	55 (31.6)	30 (38.9)	25 (26)	0.28	25 (31.3)	0.62
1-3 x minimum wage	103 (59.2)	42 (53.9)	61 (63.5)		49 (61.3)	
3-5 x minimum wage	13 (7.5)	4 (5.1)	9 (9.4)		2 (2.5)	
>5 x minimum wage	1 (0.6)	1 (1.3)	0		3 (3.8)	

Unknown / refused	2 (1.2)	1 (0.6)	1 (0.6)		1 (1.3)	
Leprosy Classification, n (%)						
Multibacillary	---	53 (70.9)	N/A	N/A	N/A	N/A
Paucibacillary		23 (29.1)				
Type of Leprosy, n (%)						
Indeterminate	----	8 (10.1)	N/A	N/A	N/A	
Tuberculoid		15 (19.0)				N/A
Borderline		42 (53.2)				
Lepromatous		14 (17.7)				
Bacillary index positive, n (%)	----	21 (26.6)	N/A	N/A	N/A	N/A
Helminth infection by stool exam* (n=241)	17 (7.1)	8 (10.7)	2 (2.3)	**0.03**	7 (9.1)	0.73
***S. mansoni* infection, by stool exam (n=241)**	16 (6.6)	8 (10.7)	2 (2.3)	**0.03**	6 (7.7)	0.52
IgG4 reactivity to SWAP[a]	77 (32.2)	29 (38.2)	25 (28.4)	0.18	23 (30.7)	0.33
Vitamin D deficiency[b]	31 (13.1)	15 (20.6)	11 (12.0)	0.14	5 (7.0)	**0.02**
Iron deficiency[c]	23 (10.7)	10 (13.7)	10 (12.4)	0.80	3 (4.9)	0.08
Vitamin A insufficiency[d]	18 (8.7)	5 (7.3)	8 (10.3)	0.52	5 (8.2)	0.84

^19 missing; [a]17 missing; [b]21 missing; [c]42 missing; [d]48 missing; *Infection diagnosed by stool exam: Kato Katz or HPJ.

Table 2. Multivariate logistic regressions with variables remaining after model diagnostics comparing odds of stool helminth infection in cases versus controls (A) and comparing odds of serum reactivity to anti-SWAP antibody in cases versus controls (B). Controls are split with household contacts on top and non-contact controls below. Bolded results are significant at a $p<0.05$.

A. Cases vs Household Contacts	**aOR**	**95% CI**	**Cases vs Household Contacts**	**aOR**	**95% CI**
Helminth infection*	**8.69**	**1.50, 50.51**	Positive IgG4 to SWAP	1.26	0.59, 2.71
Male sex	1.61	0.80, 3.25	Male sex	1.36	0.67, 2.75
Vitamin D deficiency	1.63	0.64, 4.14	Vitamin D deficiency	1.89	0.77, 4.67
Age, years:			Age, years:		
less than 15	**0.18**	**0.05, 0.65**	less than 15	0.29	0.59, 2.71
15-49	**0.41**	**0.19, 0.88**	15-49	0.44	0.20, 0.95
≥50	1	---	≥50	1	----
B. Cases vs Non-contact Controls	**aOR**	**95% CI**	**Cases vs Non-contact Controls**	**aOR**	**95% CI**
Helminth infection*	1.27	0.38, 4.26	Positive IgG4 to SWAP	1.64	0.76, 3.53
Vitamin D deficiency	**4.66**	**1.42, 15.33**	Vitamin D deficiency	**4.76**	**1.47, 15.40**

Age, years:			Age, years:		
less than 15	0.50	0.15, 1.70	less than 15	0.68	0.20, 2.24
15-49	0.92	0.44, 1.94	15-49	0.94	0.43, 2.02
≥50	1	---	≥50	1	---

* Infection diagnosed by stool exam: Kato Katz or HPJ.