Hookworm-Related Cutaneous Larva Migrans in Northern Brazil: Resolution of Clinical Pathology After a Single Dose of Ivermectin

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To assess the effect of ivermectin on the morbidity caused by hookworm-related cutaneous larva migrans in patients in hyperendemic areas, we treated 92 patients (with 441 tracks in total) from Manaus, Brazil, with single-dose ivermectin (200 µg/kg). Four weeks later, patients had 60 tracks, and the associated morbidity improved significantly.

Keywords. HrCLM; ivermectin; clinical pathology; Brazil; endemic area.

Hookworm-related cutaneous larva migrans (HrCLM) is a zoonosis caused by larvae from animal hookworms (eg, Ancylostoma species or Uncinaria stenocephala). Once the larvae have penetrated the human skin, they are not capable of passing through the epidermal basal membrane and therefore migrate in the epidermis up to several months [1, 2]. HrCLM is present in many subtropical and tropical countries [3, 4], where its prevalence in resource-poor communities may be up to 4% in the general population [5] but may reach >50% in exceptional situations [6]. HrCLM is also observed in travelers returning from HrCLM-endemic destinations, in whom it is the most frequent dermatologic disorder [3, 4]. In endemic areas, HrCLM is often associated with considerable morbidity, for example through multiple infestations or bacterial superinfection of excoriated tracks [5], and significantly impairs the quality of life of affected individuals [7].

Ivermectin is effective against helminths and ectoparasites and has been used in travelers with cure rates of 77–100% [1, 8]. Travelers, however, often present a single larval infestation and milder clinical manifestations of HrCLM than do individuals from endemic areas [9, 10]. In the present study, we investigated the effects of a single dose of ivermectin on the dynamics of the HrCLM-associated morbidity (determined semiquantitatively) in patients living in a hyperendemic area. At the time the study was conducted, topical thiabendazole or household remedies were used as treatment for HrCLM in this population [11].

METHODS

Ethics Statement

The objectives and procedures of the study were explained verbally in simple and comprehensible Portuguese to each participant and, in the case of minors, to their legal guardian. The right to withdraw at any time was clarified. Each participant or his/her legal guardian signed the informed consent form. In case of illiteracy, consent was given via fingerprint in the presence of an independent witness.

HrCLM patients <5 years of age and girls or women who were pregnant were not included in the study and were treated with topical thiabendazole. Patients with skin diseases other than HrCLM were referred to the public health service where they received treatment free of charge. The study was approved by the ethical committee of the Foundation for Tropical Medicine in Amazonia, the public reference institution for tropical diseases of Amazonas State, Brazil.

Study Area and Design

The study was carried out in Manaus, North Brazil, from October 2008 to May 2009. The study area has been described in detail previously [7]. Patients were actively recruited in 7 resource-poor communities in Manaus via word-of-mouth advertising. Inclusion criteria were age ≥5 years and the presence of at least 1 active HrCLM track (ie, the characteristic elevated linear or serpiginous track was visible and the lesion had moved forward during the preceding days). Scabies and other dermatological disorders were excluded clinically. All clinical examinations have been described previously [7].

The severity of HrCLM was determined semiquantitatively by using a severity score of 1–10 points [7] that included the
following parameters: number of tracks (1–2 tracks, 1 point; 3–5 tracks, 2 points; 6–9 tracks, 3 points; 10 tracks, 4 points); presence/absence of bacterial superinfection (0/2 points); signs of local inflammation, pain, or nodules (0–3 points); and local lymphadenopathy (0/1 points). Severity was classified as light (1–3 points), moderate (4–6 points), or high (7–10 points).

All study participants were treated with a single dose of oral ivermectin (200 μg/kg; Reventina Solvay Farma Ltda, São Paulo, Brazil) and were reexamined 2 and 4 weeks after treatment. Ten patients were excluded from data analysis because of reinfection (ie, the presence of a new track at a new topographical site).

Statistical Analysis
The data were entered twice into a database using the Epi Info software package (version 3.4.3; Centers for Disease Control, Atlanta, Georgia) and were checked for errors. Statistical analysis was performed using SPSS software for Windows (version 16.0; SPSS Inc, Chicago, Illinois). The skewness was assessed to evaluate the normality of data distribution. Because data did not follow a normal distribution, the median and the interquartile range (IQR) or the total range were used. The Spearman rank correlation coefficient, χ² test, Mann-Whitney test, Wilcoxon matched-pairs signed-rank test, and Kruskal-Wallis test were used for statistical analysis as appropriate.

RESULTS
Ninety-two patients with a total number of 441 tracks were included; 64 (69.6%) patients were male and 28 (30.4%) female, and the median age was 9.5 years (range, 5–55 years). The median number of HrCLM tracks per person was 2, and the maximum was 51 tracks. Thirty-two (34.8%) patients had 1 track, 32 (34.8%) had 2–4 tracks, 14 (14.2%) had 5–9 tracks, and 14 (14.2%) had ≥10 tracks. The track length varied between 1 and 20 cm (median, 3 cm). Sixty-two percent of the tracks were accompanied by local erythema, 18.5% were swollen, and 6.8% were superinfected; 57.6% of the patients presented local lymphadenopathy. Pruritus, pruritus-associated insomnia, and pain were present in 92%, 70.5%, and 30.5% of the patients, respectively. The localization of the tracks is summarized in Figure 1A. The number and localization of tracks and the clinical pathology did not differ significantly regarding sex or age (data not shown).

HrCLM-associated morbidity was moderate (median, 4; range, 1–10). The severity of HrCLM correlated with the intensity of pruritus (ρ = 0.274; P = .010), the intensity of insomnia (ρ = 0.283; P = .008), and pain (ρ = 0.449; P < .001). Also, the intensity of insomnia correlated with the intensity of pruritus (ρ = 0.642; P < .001).

All individuals responded clinically to ivermectin treatment. Two weeks after treatment, the total number of tracks and also the numbers of complex, crusted, excoriated, or superinfected tracks were significantly reduced (all P < .001, Figure 1B). Four weeks after treatment, all complex, crusted, excoriated, or superinfected tracks had disappeared (all P < .001). The median length of the tracks had significantly shortened from 3 cm (IQR, 2–4 cm) at baseline to 2 cm (IQR, 0–3 cm 4 weeks after treatment (P < .001). Accordingly, the severity of HrCLM decreased from a median of 4 points (range, 0–6) at baseline to 1 point (range, 0–7) 2 and 4 weeks after treatment (P < .001). Fewer patients complained about pruritus (baseline, 92%; 2
weeks after treatment, 33%; 4 weeks after treatment, 3%), pruritus-associated insomnia (baseline, 70.5%; 2 weeks after treatment, 24%; 4 weeks after treatment, 0%), or pain (baseline, 33%; 2 weeks after treatment, 9.2%; 4 weeks after treatment, 0%) (all \( P < .001 \)).

**DISCUSSION**

In our patients, 68.5% of the tracks were complex. More than 50% of the patients presented HrCLM lesions associated with local lymphadenopathy as a sign of a strong local immune response against the pathogens. Correspondingly, 30% of the patients complained about pain at the site of the lesion. Notably, we observed fewer superinfected tracks than before in northeast Brazil (6.8% vs 24%) [5], and these data are comparable to those reported for HrCLM tracks in travelers (0%–8%) [8, 10]. The severity of HrCLM in our patients, however, was also reflected by the number of tracks per patient: two-thirds of our patients had >1 track and 30.4% even ≥5 tracks. This rate of multiple infestations observed by us was considerably higher than in our previous study in northeast Brazil (69.9% vs 17.7%) [5].

Expectedly, the severity of the infestation was significantly associated with the intensity of pruritus, insomnia, and pain. The high number of simultaneously present infestations might be explained by environmental and climatic characteristics of the study area. Stray dogs and cats were abundant and animal feces were present on roads, paths, and compounds [7]. Furthermore, in the tropical climate of Amazonia, hookworm larvae may survive for several months in the humid soil [2]. Additionally, many inhabitants walk barefoot or only wear flip-flops and play football on sandy ground. Together, these factors explain why in impoverished urban neighborhoods the risk of HrCLM is high and the infestation occurs year-round.

After ivermectin treatment, most tracks healed, and the number of crusted, excoriated, or superinfected tracks was reduced significantly. At the same time, the number of simple tracks had increased, suggesting the involution of complex tracks into simple tracks during the healing process. A single dose of ivermectin also resolved pruritus-associated insomnia and local pain in all patients and pruritus in most patients within 4 weeks. This rapid resolution of HrCLM-associated morbidity after treatment with ivermectin corresponds to previously published data from travelers [1, 8].

Notably, 10 HrCLM patients had to be excluded from the study because of reinfection. This indicates that the durability of the improvement of morbidity induced by a single dose of ivermectin may be limited in endemic areas. Future studies should focus on this aspect. This would help to determine the overall cost-effectiveness of this approach and to identify populations that might benefit most from this intervention.

In conclusion, a single dose of ivermectin effectively resolves clinical pathology and symptoms in HrCLM patients suffering from considerable morbidity. Ivermectin should be available in primary healthcare settings in HrCLM-endemic areas.

**Notes**

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