Risk factors for acquiring *Strongyloides stercoralis* infection among patients attending a tertiary hospital in south India

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Abstract

**Purpose:** *Strongyloides stercoralis* causes persistent and fatal disseminated infections in immunocompromised hosts. In this study, we aimed to determine the risk factors for acquiring strongyloidiasis and the associated morbidity in south India. **Materials and Methods:** The study was carried out in two parts. This included a 6-month chart review of cases with strongyloidiasis and randomly selected controls conducted to determine the association with immunocompromised states. Secondly, a cross-sectional study was conducted to investigate hyperinfection in human immunodeficiency virus (HIV)-infected adults where the stool and sputum samples were examined by microscopy for *Strongyloides* larvae. **Results:** In the chart review, 118 cases were compared with 240 controls. A higher proportion of patients on corticosteroids [8 (53.3%)] and with HIV infection [3 (60%)] had the risk of acquiring strongyloidiasis than not, although the difference was not statistically significant in this population. In the cross-sectional study, 14/239 HIV-positive individuals had *Strongyloides* larvae in the stool samples but none had *Strongyloides* detectable in their sputum samples. The CD4 cell counts were significantly lower in cases with *Strongyloides* compared with HIV-infected individuals with no parasites in their stool samples (*P* < 0.001). **Conclusions:** In this setting, strongyloidiasis was seen more often in patients on corticosteroid therapy and with HIV infection. In HIV, an association with lower CD4 counts indicates the need for inclusion of *Strongyloides* as an opportunistic parasite. Gram negative sepsis was an important complication of strongyloidiasis hyperinfection in both HIV and steroid therapy. Further prospective studies on the risk of developing complicated *Strongyloides* infection are required.

**Key words:** Disseminated strongyloidiasis, Gram negative sepsis, human immunodeficiency virus, hyperinfection, immunosuppression, *Strongyloides stercoralis*
prevalence and complications of *Strongyloides* in HIV-infected subjects in India.

**Materials and Methods**

The study was conducted in a 2,200-bed, tertiary care hospital in southern India and comprised of two parts – a chart review and a cross-sectional study. The study was funded by a small institutional grant and was IRB approved.

**Chart review**

A 6-month chart review of cases with strongyloidiasis and controls without strongyloidiasis was carried out to determine the association with different immunocompromised states, including HIV infection among Indian patients. Cases identified as positive for *Strongyloides* larvae by wet mount microscopy were enrolled using the laboratory database. The control group comprised of the first two stool samples received each day that were negative for *Strongyloides* larvae during the same time period. Risk factors associated with strongyloidiasis reviewed included (i) HIV infection, (ii) use of corticosteroid therapy, (iii) malignancy, (iv) solid organ and haematological stem cell transplants, (v) diabetes mellitus, (vi) chronic obstructive pulmonary disease (COPD), (vi) tuberculosis, (vii) leprosy, (viii) hypochlohydria and (ix) chronic renal failure and other chronic diseases, which included hepatitis, chronic heart disease, chronic pancreatitis and mucormycosis. The presence of concomitant infections, including sepsis, was also recorded in the cases and controls. As none of the subjects was tested for HTLV-1 infection, it was not included in the risk factor analysis. Alcohol was also not included as a risk factor as history for alcohol intake was not well elucidated in the patient charts.

**Cross-sectional study**

To determine the prevalence of hyperinfection and dissemination syndrome and its association with Gram negative sepsis in HIV-positive individuals, a cross-sectional study was conducted on HIV-positive cases attending the inpatient and outpatient services. All subjects once enrolled provided a stool sample and blood for CD4 counts. If the stool sample was positive for *Strongyloides* larvae, a sputum sample was also collected. To determine the outcome, subjects were followed-up for a 6-month period after the diagnosis of strongyloidiasis by a review of medical charts.

**Laboratory methods**

Stool samples collected were screened for the presence of *Strongyloides* larvae using wet mount microscopy. Larvae were identified as *Strongyloides* rhabditiform (~300 μm in length, short buccal cavity with a prominent genital primordium) or filariform (~500 μm in length, long oesophagus and a notched tail) stages in order to differentiate them from hookworm larvae.\(^{[9]}\) Gram staining was carried out to identify the filariform stages in the sputum samples collected. Blood samples were examined for CD4 counts using the FACScount analyzer (Becton Dickinson, Franklin Lakes, NJ, USA).

**Statistical analysis**

Continuous variables were described using mean ± standard deviation and variables that are skewed were presented using median and range. Chi-square test was used to assess the associations between categorical variables and t-test was used to compare the continuous variables between the two groups. Mann-Whitney test was used for comparison of continuous variables that were skewed. All statistical analyses were performed using SPSS 11.0 for windows. A *P*-value <0.05 was considered statistically significant.

**Results**

**Chart review**

In the 6-month chart review conducted from January to June 2006, 118 cases found to have stool samples positive for *Strongyloides* were compared with 240 controls whose stools were negative for *Strongyloides* during the same period. The age of the cases was (mean ± SD) 44.1 ± 13.2 years while that of the controls was 41.5 ± 15.6 years, indicating that age did not predispose to the development of *S. stercoralis* infection (*P* = 1.20). Male gender was, however, significantly associated with strongyloidiasis (*P* = 0.003). There was also a strong positive correlation between hookworm and Strongyloides infections (*P* < 0.001). For 82 of the 118 cases and 169 of the 240 controls, eosinophil counts on peripheral smears were available and, when compared, there was a significant difference between the cases (median, IQR\(^{[25–75%]}\), 7, 10.5) and the controls (3, 4) (*P* < 0.001) as expected to occur during an invasive parasitic infection. Table 1 shows the proportion of cases and controls with one or more than one risk factor and Table 2 shows the results of comparison of risk factors occurring in cases and controls. The prevalence of various risk factors considered to predispose to strongyloidiasis showed no statistically significant difference between the cases and controls. However, a higher proportion of patients on corticosteroids for rheumatic disease/inflammatory bowel disease (*n* = 8, 148)

| Table 1: Proportion of cases and controls with predisposing factors to strongyloidiasis in the chart review |
|--------------------------------------------------|------------------|------------------|
| Number of predisposing factors per subject      | Cases number (%) | Control number (%) |
| None                                             | 44 (31.4)        | 96 (68.6)        |
| One                                              | 71 (60.2)        | 129 (53.3)       |
| Two or more                                      | 3 (2.5)          | 15 (6.3)         |
and those with HIV infection (n = 3, 60%) had strongyloidiasis than not (n = 7, 46.7% and n = 2, 40%, respectively).

Of the 118 cases, one subject was found to have *Strongyloides* hyperinfection complicated with Gram negative sepsis. She was a 16-year-old woman with previously diagnosed systemic lupus erythematosus (SLE) on oral daily dose of prednisone. Prior to starting corticosteroids, an initial stool examination was not conducted. She developed three episodes of *Strongyloides* hyperinfection syndrome, diagnosed by the presence of multiple filariform larvae in her stool and sputum samples, the last one being complicated by *E. coli* septicemia and causing subsequent death. The first two episodes were treated with albendazole. Ivermectin was administered when she presented for the third time with hyperinfection.

### Cross-sectional Study on HIV-Infected Adults

In the cross-sectional study, conducted from July 2006 to March 2008, 239 HIV-positive individuals were enrolled. Stool parasites were detected in 43 of the 239 HIV patients, 14 (5.86%) of whom had *Strongyloides* larvae. The other parasites seen were *Cryptosporidium* spp. (4.18%), *Isospora belli* (3.35%), hookworm (3.35%), *Giardia lamblia* (2.5%), *Ascaris lumbricoides* (1.25%), *Hymenolepis nana* (0.4%), *Enterobius vermicularis* (0.4%) and *Trichuris trichiura* (0.4%). None of the *Strongyloides* cases had sputum smears that were positive for larvae. All the 14 subjects infected with strongyloidiasis were male, and the mean age ± SD of the cases was 35.14 ± 4.79, which was similar to HIV-positive individuals with no parasites or other parasites in their stool samples (P = 0.379). CD4 cell counts were available for 162/239 HIV patients [Figure 1], and were found to be significantly lower in HIV-infected individuals with strongyloidiasis (median, IQR 25–75%, 80.5 cells/μl, 69) as compared with HIV-infected individuals with no parasites in their stool samples (301 cells/μl, 334) (P < 0.001). The CD4 counts of HIV patients infected with opportunistic coccidian parasites, including *Cryptosporidium* (63 cells/μl, 140) and *Isospora* (109 cells/μl, 180), were comparable to that of patients with strongyloidiasis. In addition, 10 of these 14 cases were diagnosed with HIV at the time of or within a month of detection of *Strongyloides* larvae.

Six months after the initial visit, eight of the 14 patients were available for follow-up and six of those lost to follow-up did not return to the hospital. One of the eight cases that were followed-up developed Gram negative infection on follow-up. He was a 35-year-old male who presented with a 2-week history of low-grade intermittent fever, cough with expectoration, loss of appetite and loss of weight and was diagnosed to have disseminated tuberculosis. His CD4
cell count was 56 cells/μl and he was not on antiretroviral therapy. He developed sudden-onset high-grade fever and his blood culture grew E. coli, but no focus of infection was found. Stool wet mount microscopy was performed, which showed multiple S. stercoralis larvae. However, his sputum on Gram staining was negative for S. stercoralis larvae. He was treated with amikacin and ivermectin and was stable on discharge. Due to the acute exacerbation of fever, E. coli septicaemia and presence of multiple larvae in his stool, he was diagnosed to have hyperinfection syndrome. This patient along with four others was started on antiretroviral therapy and all these have had no major illness since then. No major morbidity or mortality was reported in the remaining three cases not on antiretroviral therapy on follow-up.

Discussion

The purpose of this study was to identify the predisposing risk factors for acquiring Strongyloides infection and to determine the incidence of hyper- and disseminated infections along with associated complications in HIV patients in an Indian setting. Previous reports from India have shown that prevalence of strongyloidiasis in HIV-infected patients ranged from 0 to 5.3%, although one study conducted in northeastern India showed a high prevalence of 27.3%.[9-11] We found that patients on corticosteroid therapy or with HIV infection had strongyloidiasis more often. In this study, CD4 cell counts of HIV-positive patients with strongyloidiasis were significantly decreased compared with HIV-positive patients with no parasites, and was similar to the CD4 cell counts of patients with opportunistic protozoan infections, including Cryptosporidium and Isospora. A study from Thailand also reports an increased prevalence of Strongyloides in HIV-positive cases with CD4 counts less than 100 cells/μl.[12] These data along with the finding that in a majority of the cases Strongyloides larvae was identified at or around the time of detection of HIV suggest that although strongyloidiasis is not listed as an opportunistic infection in HIV,[13] there may be a need to re-explore whether this exclusion is justified in endemic regions. The TH2 response, promoted by helminth infections including Strongyloides spp., with suppression of TH1 function and decrease in CD4 cell counts may be an alternative cause for the low CD4 cell counts in HIV patients with strongyloidiasis in this study.[14] Such an interaction between Strongyloides and HTLV-1 infection has been well documented.[15]

Our study and those of others have found that Gram negative sepsis was an important complication attributable to Strongyloides in individuals on steroid treatment.[6] and with HIV.[16] Although there have been fewer than 30 reports of complicated Strongyloides cases in HIV-infected patients,[1] hyper- and disseminated infection in HIV does exist.[17] Complicated strongyloidiasis following initiation of antiretroviral therapy as part of immune reconstitution syndrome has also been found to occur.[18] Our findings highlight the need to conduct regular stool examinations for Strongyloides larvae prior to initiation of corticosteroid therapy and in those with a high risk like HIV infection. Ivermectin has been most successful in the treatment of complicated strongyloidiasis in patients with predisposing syndromes like AIDS.[19] Other findings of the study were that male gender was strongly associated with strongyloidiasis, which, according to Concha et al., is possibly due to an increased risk of acquiring infection outdoors.[20] However, unlike other studies, older age group did not seem to predispose to strongyloidiasis.[21] In India, although there have been no detailed studies that showed a male preponderance, a literature review of around 30 case reports and case series over the last 20 years reveals that a majority were in males (34/38 cases). There was also a significant association between hookworm and Strongyloides infection, and this may be explained by the similar route of infection of the larval stage.

Some of the limitations of the study were that the chart review had only a small number of cases and controls with risk factors, and a higher proportion were apparently healthy individuals possibly due to the endemicity in the region. In the cross-sectional study, HIV-infected patients provided only a single stool or sputum sample and no quantitative analysis was conducted. As the sample size of HIV patients with strongyloidiasis was small, and Strongyloides-negative HIV-positive patients were not examined in detail, the association of Strongyloides infection with concurrent conditions predisposing to infection were not examined.[1] In addition, sputum examination was carried out as a marker of hyperinfection only in cases that were positive for Strongyloides. On retrospection, we may have missed a few cases that were sputum-positive but stool-negative.

Although there is literature from India on complicated Strongyloides infection in the form of case reports and case series,[6,7] this is the first study that has attempted to determine the association of Strongyloides with predisposing factors, including HIV, and prospectively tried to identify the development of hyper- and disseminated infection. In conclusion, the study indicates that, in an Indian setting, strongyloidiasis is common in HIV-positive patients with low CD4 counts and may lead to the development of fatal complicated infection. This study also provides clinical data that could help physicians in the early diagnosis and treatment of strongyloidiasis and prevention of fatal disseminated Strongyloides infection and Gram negative sepsis.

Acknowledgement

The work was supported by the Fluid Research grant from Christian Medical College, Vellore, India. The funding agency had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.
We thank Mr Charles Livingston who helped in recruitment of patients and Mr M Thyagarajan and Dr Greeshma Chandran who helped in follow-up of the cases.

References


Source of Support: Fluid Research grant from Christian Medical College, Vellore, India, Conflict of Interest: None declared.