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Strongyloides stercoralis: there but not seen

Martin Montes[1,2], **Charu Sawhney**[2,3], and **Nicolas Barros**[1]

[1]Instituto de Medicina Tropical `Alexander von Humboldt' Universidad Peruana Cayetano Heredia in Lima, Peru

[2]Department of Internal Medicine, Division of Infectious Diseases University of Texas Medical Branch at Galveston, Texas, USA

[3]Department of Preventive Medicine and Community Health. University of Texas Medical Branch at Galveston, Texas, USA

Abstract

Purpose of review—Diagnosis of *S. stercoralis* is often delayed due to patients presenting with non-specific gastrointestinal complaints, a low parasite load and irregular larval output. Although several diagnostic methods exist to detect the presence of *S. stercoralis* there is no gold standard. In immunocompromised hosts (patients with malignancy, organ transplantation or concurrent HTLV-1 infection or those on corticosteroid therapy), autoinfection can go unchecked where large numbers of invasive *Strongyloides* larvae disseminate widely and cause hyperinfection with dissemination, which can be fatal. This review will highlight current published research on improved diagnostic methods for *S. stercoralis* and the immune mechanisms thought to be responsible for hyperinfection syndrome.

Recent findings—Recent advances in diagnosis of *Strongyloides stercoralis* include a luciferase immunoprecipitation system that shows increased sensitivity and specificity to detect *S. stercoralis* specific antibodies and a real time quantitative PCR method to detect *S. stercoralis* in fecal samples. The severe clinical manifestations of *S. stercoralis* observed in HTLV-1 co-infected patients has been associated to an increased proportion of regulatory T cells that may be responsible for blunting otherwise effective granulocyte responses.

Summary—Strongyloidiasis is a major global health challenge that is underestimated in many countries. Novel diagnostic methods are expected to improve epidemiological studies and control efforts for prevention and treatment of strongyloidiasis. More studies are needed to unveil the mechanisms of severe clinical manifestations of human strongyloidiasis.

Keywords

Strongyloides stercoralis; strongyloidiasis; diagnosis; hyperinfection; immunology

Introduction

Strongyloides stercoralis is a nematode endemic in humid, tropical regions (1, 2) including Africa, Southeast Asia, and Latin America (3). It is also endemic in southeastern United

Corresponding author: Martin Montes, MD Instituto de Medina Tropical `Alexander von Humboldt' Universidad Peruana Cayetano Heredia Av Honorio Delgado 430 SMP Lima, Peru +51-1-4823910 montes@bcm.edu.

States and southern Europe, although most cases in the US occur in immigrants and military veterans who have lived in endemic regions (2). A second species of *Strongyloides, S. fuelleborni* can cause human strongyloidiasis but is less common and mainly found in Africa and Papua New Guinea (4). *S. stercoralis* is unique in its ability to replicate in the human host permitting ongoing cycles of autoinfection. Strongyloidiasis can consequently persist for decades without further exposure to exogenous infection (2, 4). The estimated prevalence of strongyloidiasis is between 50 to 100 million infections worldwide; however, the accuracy of these estimates is uncertain due to the poor sensitivity of screening methods (2, 5).

Chronic *S. stercoralis* infections can be asymptomatic or cause cutaneous, gastrointestinal and/or pulmonary symptoms (4). In patients with concurrent Human T-cell-lymphocytic virus 1 (HTLV-1) infection or those on corticosteroid therapy, autoinfection can go unchecked and large numbers of invasive *Strongyloides* larvae may disseminate widely and cause hyperinfection, which can be fatal (2, 6, 7). Other recognized predisposing conditions or risk factors for infection include living in an endemic region, chronic malnutrition, malignancies, organ transplantation, diabetes mellitus, chronic obstructive pulmonary disease (COPD), alcoholism, chronic renal failure and breast milk from an infected mother (7, 8).

Pathogenesis

Strongyloides has a complex biology with two separate life cycles, the free living cycle and the parasitic cycle (8, 9). Filariform larvae in the soil infect the human host by penetration of intact skin to begin the parasitic cycle. The larvae enter circulation, are transported to the lungs, penetrate alveolar spaces, ascend the bronchial tree, are swallowed and reach the small bowel (2, 4, 9). There the parthenogenetic females (i.e., capable of reproducing without males) embed in the duodenal mucosa and lay embryonated eggs that hatch in situ, releasing the rhabditiform larvae in the intestinal wall (4). The larvae migrate into the lumen and are either passed into feces or mature into filariform larvae, which can infect the intestinal mucosa or skin of the perianal region to restart the parasitic cycle (2, 4). Rhabditiform larvae passed into feces can become infectious filariform larvae directly or go through a free-living cycle of development in the soil. This adaptability allows for the parasite's survival in the absence of mammalian hosts (2, 8).

Animal studies have suggested a role for innate and adaptive immune mechanisms in the control of strongyloidiasis. The innate response requires eosinophils to kill *Strongyloides* larvae, which in turn need cytokine interleukin-5 (IL-5) for their development and activation. Eosinophils serve as antigen presenting cells and are required for an optimal antibody response. The adaptive response involves specific antibody production (IgG and IgE) and granulocytes, which are also needed to kill the larvae (8, 10). Helminth infections induce T helper 2 (T_H2) responses and may also stimulate regulatory T cells (T_{reg}). T_H2 cells secrete interleukin-4 (IL-4), IL-5 and other cytokines that promote antibody production by B cells; produce a high level of tissue eosinophilia, mucosal mastocytosis and IgE production; and control excessive inflammatory reactions such as that caused by unrestricted T helper 1 (T_H1) cell-mediated inflammation (8, 11). T_{reg} cells reduce injurious host inflammatory and immune responses through mechanisms of cell-to-cell contact, inhibitory cytokines and/or cytokine deprivation. This prevents an over exuberant immune response with bystander tissue damage during the host response to infections (10). However, T_{reg} cells may also blunt T_H2 responses such as IL-5-dependent eosinophil activation required to kill the parasite. The interplay and balance among host T_H1, T_H2 and T_{reg}-cell responses is crucial in the defense against a parasitic infection (11).

Clinical Manifestations

The spectrum of disease for strongyloidiasis includes acute infection with Loeffler's syndrome, chronic intestinal infection, asymptomatic autoinfection, symptomatic autoinfection, and hyperinfection syndrome with dissemination (7, 12). Immunocompetent patients usually develop an asymptomatic, chronic or mildly symptomatic infection (10). Chronic and symptomatic infections can present with abdominal complaints such as discomfort, bloating, nausea, vomiting, diarrhea and anorexia; respiratory complaints such as cough, shortness of breath and symptoms mimicking COPD or asthma; or a fleeting serpiginous, urticarial rash (larva currens) at the entry of *Strongyloides* larvae (4, 7, 10). Laboratory findings are usually nonspecific and may include intermittent eosinophilia (13).

Patients such as those on corticosteroid therapy or co-infected with HTLV-1 may develop hyperinfection syndrome with dissemination (10, 13). Hyperinfection syndrome is characterized by a spectrum of gastrointestinal complaints including abdominal pain, dyspepsia, diarrhea, constipation, ileus, obstruction, enteritis, and/or gastrointestinal bleeding. Many patients concurrently have worsening pulmonary function starting with wheezing and progressing to hemorrhagic pneumonitis and respiratory failure. During hyperinfection, invading filariform larvae transport luminal bacteria to the blood stream and central nervous system leading to bacteremia and meningitis (3, 7, 13). Although easy to diagnose due to high parasite load, hyperinfection syndrome can be difficult to treat with mortality rates ranging from 70 to 85 percent (6, 14). Of note, patients with hyperinfection syndrome do not typically have eosinophilia (12).

Hyperinfection syndrome with dissemination is associated with corticosteroid administration and HTLV-1 infection that disrupt granulocyte function, T_H2 humoral-mediated and mucosal immunity (12, 15). Immunosuppression induced by corticosteroids reduces the number of circulating eosinophils by inhibiting proliferation and promoting apoptosis of T_H2 cells. Corticosteroids also cause immature lymphocyte cell death and loss of jejunal mast cell response to *Strongyloides* antigenic stimulation following treatment with steroids. HTLV-1 appears to blunt the host's immunological response against the parasite. HTLV-1 infects T-cells and induces a strong T_H1 response and weakens the T_H2 response. This allows for secretion of high levels of type 1 cytokines (interferon-gamma) and activation of cytotoxic T cells and natural killer cells. At the same time there is a decrease in type 2 cytokines (IL-4, IL-5, IL-13 and IgE). The decrease in IL-4 and IgE may diminish mast cell function and reduced levels of IL-5 hinder eosinophil recruitment and parasite killing ability (7, 8). Our group demonstrated increased *Strongyloides* parasite among patients who have co-infection compared to patients who were infected with just *Strongyloides*. We also noted relatively decreased circulating eosinophil counts and reduced antigen driven IL-5 production in co-infected patients (10). The net effect of these interactions is an inadequate host response, which may predispose HTLV-1 patients to augmented parasite numbers, organ damage, bacteremia and death (7, 10, 12).

Other diseases associated with hyperinfection syndrome include malignancies and organ transplantation (7, 13). A study examining 77 patients with gastrointestinal and other types of cancers in Brazil found that patients with gastrointestinal cancer had a 6–7 fold greater chance of testing positive for *S. stercoralis*. This small study highlights the importance of diagnosing *Strongyloides* in patients with gastrointestinal cancer living in endemic regions (7, 16). Several case reports of hyperinfection syndrome have been published in kidney (17), heart, lung, intestine, pancreas (13), liver (18, 19) and peripheral blood hematopoietic stem cell (20) transplant recipients. In most cases, these patients were treated with corticosteroids with rates of strongyloidiasis decreasing in patients treated with lower doses of corticosteroids. The mortality rate of *Strongyloides* hyperinfection syndrome in post-

transplant patients is >50% indicating the need to educate physicians on current guidelines recommending serological screening or stool examination to detect chronic intestinal strongyloidiasis in patients from endemic areas, with gastrointestinal symptoms or those with eosinophilia before transplantation (13). Interestingly, while strongyloidiasis is common among AIDS patients in endemic areas, hyperinfection syndrome is rarely noted. Among AIDS patients, strongyloidiasis is more commonly associated with chronic diarrhea (4, 7, 8).

Diagnosis

There is no gold standard for diagnosing *S. stercoralis* and diagnosis is often delayed or overlooked due to patients presenting with non-specific gastrointestinal complaints (3). Patients with chronic strongyloidiasis usually have a low parasite load and irregular larval output making it exceedingly difficult to diagnose (4). Several diagnostic methods have been compared to detect the presence of *S. stercoralis* including stool examination, modified Baermann's technique, stool culture on a blood agar plate, enzyme-linked immunosorbent assay (ELISA), serum indirect fluorescent antibody test (IFAT), polymerase chain reaction (PCR) and gastrointestinal aspirate or biopsy. However, all of these techniques have problems with sensitivity, specificity or availability in endemic areas (1, 4, 7, 21).

Stool can be examined for presence of rhabditiform larvae in direct fecal smears or using formalin-ethyl acetate concentration techniques (4). Stool examination has poor sensitivity with a single sample being positive in only 30 to 50% of cases (7). Multiple repeated stool studies are needed to improve sensitivity (22). A modified formalin-ethyl acetate concentration method resulted in higher recovery rates of *S. stercoralis* larvae and presumably an improved diagnostic efficiency (23). The Baermann method also uses stool to detect parasite larvae. The Baermann method is more sensitive than stool smears but is cumbersome and rarely available in clinical parasitology laboratories. It also requires multiple samples to achieve adequate sensitivity (1, 4). In the agar culture method stool is placed on a nutrient agar plate, incubated for at least 2 days and evaluated for visible tracks created as larvae carry bacteria over the agar. Although the agar culture method has a higher sensitivity (96%) than direct fecal smears or the Baermann method, it is more laborious, time consuming and expensive (4).

ELISA tests for antibodies to a crude extract of the filariform larvae in serum and has a high sensitivity (83–93%) and specificity (95–98%) (4, 7, 22). Unfortunately, the presence of antibody does not distinguish between past and current infections (4). *Strongyloides* antibody assay can also cross react with other helminth infections (filariasis, *Ascaris lumbricoides* infection and schistosomiasis) limiting the predictive value in high-risk populations (3, 4). Conversely, for populations naive to parasitic infection ELISA is useful in the diagnosis of strongyloidiasis. ELISA requires a constant supply of *Strongyloides* filariform larvae making it an impractical diagnostic test with limited availability (4). Researchers in Egypt developed an antigen-capture ELISA that was successful in identifying *Strongyloides* antigen in fecal samples from infected patients(24). This fecal ELISA did not cross react with sera from patients with *Schistosoma mansoni, Fasciola gigantica* or *Capillaria philippenensis*. Fecal ELISA may improve the diagnosis of strongyloidiasis.

A recent study described using a luciferase immunoprecipitation system using a recombinant *S. Stercoralis* antigen to identify specific antibodies in serum. The assay had a better sensitivity (97%) and specificity (100%) than ELISA and did not cross react with serum samples of filarial-infected patients. It can be performed rapidly (< 2.5 hrs) and can detect changes in antibody response over time. An even faster version of this assay can be performed in less than 2 minutes and has the potential to be utilized as a rapid diagnostic

test. This may be especially useful in critically ill patients suspected of having hyperinfection syndrome (25).

Verweij and colleagues have developed a real-time PCR method to detect *S. stercoralis* DNA in fecal samples utilizing a primer and probe set from the 18s rRNA gene sequence. The assay was performed on 145 control samples, known positive fecal samples and fecal samples from a region in Ghana where *Strongyloides* is highly endemic with a high sensitivity and 100% specificity. The stool samples were collected in ethanol allowing for storage at room temperature and simplifying transportation to facilities with real-time PCR capabilities. Although appropriate facilities for PCR are difficult to maintain in endemic countries with scarce resources, real-time PCR has a promising role in industrialized countries for detection of *S. stercoralis* and post-treatment analysis (21).

Patients with hyperinfection syndrome with dissemination may present with severe GI complaints such as GI bleeding or ulcers and/or significant respiratory complaints that lead to the diagnosis of strongyloidiasis via endoscopy or bronchoscopy. While endoscopy and bronchoscopy are effective methods for diagnosis, they are invasive procedures and recommended only in patients suspected of having an overwhelming infection (4, 7, 26).

Treatment

All patients, regardless of the severity of symptoms, with strongyloidiasis have to be treated to prevent long-term complications. Treatment options include ivermectin, tiabendazole and albendazole. The drug of choice for strongyloidiasis is ivermectin, which kills the worms in the intestine at 200 μg/kg (7). Two doses are given 1–14 days apart, which has a cure rate of 94–100%. If possible serological studies can be done to assure clearance of infection at 6 and 12 months (22). Tiabendazole at a dose of 25 mg/kg orally twice a day for three days is an alternative for complicated infections. Albendazole at a dose of 10 mg/kg/d can be used as an alternative if nothing else is available as it has a lower efficacy (38–45%) (7, 27).

Patients who have hyperinfection syndrome may not tolerate oral therapy and can receive subcutaneous ivermectin (200 mg/kg) every 48 hours until they are able to tolerate medications by mouth. Patients require a longer course of ivermectin (up to 1 week) with multiple follow-up stool studies for two weeks thereafter. This is to assure clearance of larvae as the internal parasite development cycle takes almost two weeks (6, 7, 19). In immunocompromised patients to prevent recurrence of hyperinfection syndrome, achieve prophylaxis and cure, two doses of ivermectin can be given every two weeks for six weeks (7).

Conclusion

Strongyloidiasis is a major global health challenge that is underestimated in many countries. It remains an important helminth disease due to increases in travel, migration from non-endemic to endemic countries, autoinfection and risk of hyperinfection syndrome in immunocompromised patients. Novel diagnostic methods are expected to improve epidemiological studies and control efforts for prevention and treatment of strongyloidiasis. Meanwhile, clinicians need to recognize the risk factors associated with *Strongyloides* infection and screen patients from endemic areas with vague gastrointestinal or pulmonary symptoms prior to receiving corticosteroid therapy or organ transplantation. It is also essential to note that prevention efforts in endemic countries such as health education campaigns on the disease, proper sanitation through appropriate disposal of fecal material, regular de-worming and the use of protective footwear are achievable goals to reducing the prevalence of strongyloidiasis (8).

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