



Imported strongyloidiasis in Spain



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SUMMARY

Objectives: The objective of this study was to assess the epidemiological, laboratory, and clinical features of imported strongyloidiasis in a tropical medicine referral unit in Madrid, Spain.

Methods: This was a retrospective study based on a review of medical records. A patient was diagnosed with strongyloidiasis when the infection could be detected by conventional stool analysis and/or serology against *Strongyloides stercoralis*, regardless of the presence of symptoms.

Results: One hundred and seventy-eight cases of strongyloidiasis were included in the study. Stool tests were performed in all patients, and serology in 160 patients (89.9%). The diagnosis of strongyloidiasis was based on serology only in four patients; 21 patients only had positive stool tests. A third of the total strongyloidiasis cases in this study were travel-related, mainly associated with short trips (<2 months). Only 47.8% of total cases were symptomatic. We found no differences in clinical presentation between immigrants and travelers with strongyloidiasis.

Conclusions: Not only should strongyloidiasis be suspected in symptomatic travelers and immigrants, but it should also be ruled out when elevated IgE levels or eosinophilia are present. Strongyloidiasis can be asymptomatic in HIV patients, but it should be diagnosed and treated before a possible hyperinfection develops.

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1. Introduction

Strongyloidiasis is caused by *Strongyloides stercoralis*, an intestinal nematode. It is usually acquired by walking barefoot on infested soil, and is an endemic infection in the tropics and subtropics. The worldwide prevalence is estimated at between 3 million and 100 million.¹ Autochthonous cases have been reported in Spain, mainly in the Mediterranean area,^{2–4} but data from cases in immigrants and travelers are scarce.^{5–7} Other foci in Europe have also been reported.^{8–10}

Strongyloidiasis is one of the most difficult parasitic diseases to diagnose, because there is no gold standard for this purpose. It can

be suspected in symptomatic patients with digestive, respiratory, or cutaneous complaints; however asymptomatic eosinophilia and even 'silent' infections have also been described. Traditional diagnostic methods are based on the visualization of *S. stercoralis* in stools and the demonstration of antibodies by serology, but the sensitivity and specificity can vary in different groups of patients.

Hyperinfection and disseminated infections can be fatal in immunosuppressed patients (transplant recipients and those on corticosteroid treatment). Focusing on HIV infection, the prevalence of this co-infection is variable;^{11–13} the most frequently manifested symptoms are chronic diarrhea, fever, cough, and unintentional weight loss. *S. stercoralis* in persons infected with human T-cell lymphotropic virus type 1 (HTLV-1) is highly associated with parasite dissemination and the development of severe strongyloidiasis. These co-infected patients have a modified immunological responses against parasite antigens.^{14,15}

Several questions remain to be answered related to imported strongyloidiasis. How common is strongyloidiasis linked to travel? What countries are the main sources of infection? Should travelers and immigrants be tested routinely for strongyloidiasis? The main

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objective of this study was to assess the epidemiological, laboratory, and clinical features of imported strongyloidiasis in a tropical medicine referral unit in Madrid. Other goals were to describe the diagnosis method and to evaluate the differences between two groups: immunocompetent and immunosuppressed patients.

2. Methods

Hospital Carlos III is a referral unit for tropical diseases in Madrid, Spain. Most patients come by themselves to the emergency unit or are referred from primary care or general hospitals in Madrid. A very small proportion of patients come from other regions.

A retrospective study based on a review of the medical records of adults who attended Hospital Carlos III between January 1, 2007 and December 31, 2011 was performed. Patients with positive parasite samples for *S. stercoralis* or positive serology against this parasite were identified through the databases of the Microbiology Department and the Tropical Diseases Unit.

Exclusion criteria were: (1) unspecified diagnosis methods, and (2) medical records with a lack of data (>25% items): epidemiological data (>5 items), clinical data (>5 items), and analytical data (>7 items).

A patient was diagnosed with strongyloidiasis when the infection could be detected by conventional stool analysis and/or serology against *S. stercoralis*, regardless of the presence of symptoms. Countries considered endemic for Strongyloides were those on the map published by Stanford University.¹⁶

Cases of strongyloidiasis were defined as: (1) autochthonous, when diagnosed in a person who had never travelled to a country endemic for Strongyloides; (2) traveler, when a person was diagnosed after travelling to a country endemic for Strongyloides; (3) native, when a person was born in a country endemic for Strongyloides.

For each case, demographic, clinical, and laboratory data were documented (see Table 1).

Countries were classified as follows: Africa includes the World Health Organization (WHO) African Region, Egypt, Libya, Morocco, Somalia, Sudan, and Tunisia. Asia includes the WHO South-East Asia Region, Western Pacific Region (excluding Australia), Afghanistan, and Pakistan. Central and South America includes the WHO Region of the Americas, excluding the British Virgin Islands, Canada, and the USA.

Serum samples were tested for the qualitative screening of IgG antibodies to *S. stercoralis* using an ELISA technique (DRG Strongyloides IgG ELISA). The microtest wells were coated with Strongyloides antigen. One hundred microliters of diluted serum (1/64) was dispensed into the wells and incubated for 10 min at room temperature. Next the wells were washed three times with the washing buffer provided, 100 μ l of protein A-peroxidase conjugate was added, and the mixture was incubated for 5 min at room temperature. After washing and removing excess moisture, 100 μ l of tetramethylbenzidine was then dispensed into each well.

After incubation at room temperature, the reaction was stopped by the addition of 100 μ l of 1 M phosphoric acid. A negative control and a positive control provided by the manufacturer were included in each assay. The reading of the plates was carried out at 450 nm/620 nm, subtracting the blank from all wells. In this study we used a cut-off value of 0.200. A test was considered positive if the index (ratio of the OD measure of the sample and OD measure of the cut-off) was >1.1.

Stool samples were tested by microscopic examination of the stool issued on three consecutive days and by blood-agar culture. Microscopic diagnosis was based on the observation of larvae in stool samples (samples were treated in a Mini Parasep SF Faecal Parasite Concentrator). For the blood-agar culture method, stool samples were placed on a blood-agar plate and incubated for 7 days. As the larvae crawl over the agar, they carry bacteria with them, creating visible tracks.

Data were analyzed using SPSS for Windows v. 17.0 (SPSS Inc., Chicago, IL, USA). For the univariate analysis of categorical variables, Pearson's Chi-square test was used (Fisher's test when needed). The Mann-Whitney *U*-test was used for quantitative variables. A *p*-value of <0.05 was considered significant.

3. Results

3.1. General features

One hundred and seventy-eight cases of strongyloidiasis were included in the study. Fifty-eight cases (32.6%) were classified as travelers and 120 (67.4%) as natives. There were no autochthonous cases. The main features of all the strongyloidiasis cases are shown in Table 2. Equatorial Guinea was the main country where the infection was acquired in natives (40.8%), followed by Bolivia (24.2%) and Ecuador (11.7%). The countries visited by the travelers group were very heterogeneous (Table 2). Reported countries visited in Africa were Algeria, Angola, Benin, Burkina Faso, Burundi, Cameroon, Chad, Central African Republic, Congo, DR Congo, Côte D'Ivoire, Equatorial Guinea, Gabon, Kenya, Malawi, Mali, Morocco, Mauritania, Namibia, Nigeria, Rwanda, Senegal, Tanzania, Togo, and Zimbabwe. Countries visited in Asia were Afghanistan, Bangladesh, Cambodia, Malaysia, Nepal, Thailand, and Vietnam. Countries visited in America were Argentina, Bolivia, Colombia, Cuba, Costa Rica, Dominican Republic, Ecuador, Guatemala, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Peru, and Venezuela.

3.2. Symptoms, laboratory abnormalities, and comorbidities

Clinical features of strongyloidiasis are shown in Table 3, and laboratory abnormalities can be seen in Table 4 and Figure 1. An asymptomatic infection with eosinophilia >700 $\times 10^6$ cells/l was present in 28% of cases. Eosinophilia was higher (45.2%) in asymptomatic patients when the cut-off was lower (e.g. >500 $\times 10^6$ cells/l). An asymptomatic infection with normal IgE levels and with normal eosinophil counts was described in 27 cases (15.2%). An asymptomatic infection with normal IgE levels and

Table 1
Data collected^a

Demographic data	Age; sex; place of birth; place of residence; last endemic zone for Strongyloides visited; dates of travel (traveler); date of arrival to non-endemic zone for Strongyloides (native)
Clinical data	Presence of symptoms (yes/no); date of onset of symptoms; presence of urticaria, larva currens, purpura, nausea, vomiting, reflux, dyspepsia, abdominal pain, constipation, diarrhea, cough, sputum, wheezing, comorbidity
Laboratory data	Hemoglobin (g/dl); white blood cells ($\times 10^9/l$); total eosinophil count ($\times 10^6/l$); percentage of eosinophils (%); platelet count ($\times 10^9/l$); serum level of immunoglobulin E (IU/ml); HIV, HBV, HCV, and HTLV ^b antibody testing

HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HTLV, human T-cell lymphotropic virus.

^a Clinical definitions: anemia: hemoglobin <13 g/dl (12 g/dl in females); leukopenia: white blood cells <4 $\times 10^9/l$; thrombocytopenia: platelets <150 $\times 10^9/l$; absolute eosinophilia: >700 $\times 10^6$ eosinophils/l; relative eosinophilia: >7% eosinophils.

^b HTLV antibody testing is not routinely performed in clinical practice.

Table 2
Epidemiological features of the patients

Age, years, median (IQR)	37.5 (29–46)
Male, n (%)	76 (42.7%)
Time from arrival to diagnosis, days, median (IQR)	402 (43–2145) ^e
Autochthonous, n (%)	0 (0)
Travelers, ^a n (%)	58 (32.6)
Natives, n (%)	120 (67.4)
Travelers: visited region, ^b n (%)	
Africa	19 (32.8)
Asia	5 (8.6)
Central and South America	12 (20.7)
Africa and Asia	5 (8.6)
Africa, Central and South America	9 (15.5)
Asia, Central and South America	4 (6.9)
Africa, Asia, and Central and South America	4 (6.9)
Duration of the travel (travelers), days, median (IQR)	38 (15–182) ^f
Natives: region of origin, n (%)	
Sub-Saharan Africa ^c	60 (50)
Central and South America, including Caribbean ^d	60 (50)
Time of residence in Spain (natives), years, median (IQR)	3 (0–7) ^g
HBV infection, n (%)	3 (1.7)
HCV infection, n (%)	6 (3.4)
HIV infection, n (%)	9 (5.1)
HTLV infection, n (%)	0 (0)
Immunosuppression treatment	0 (0)

IQR, interquartile range; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTLV, human T-cell lymphotropic virus.

^a Fifty-seven patients from Spain; one patient from France.

^b See text for more information about countries visited (one or more countries in the same trip).

^c Natives from Angola, Cameroon, Equatorial Guinea, Mali, Mozambique, Nigeria, Senegal, and Tanzania.

^d Natives from Bolivia, Brazil, Colombia, Ecuador, Honduras, Nicaragua, Paraguay, Peru, Dominican Republic, and Venezuela.

^e From 161 patients.

^f From 46 patients.

^g From 109 patients.

eosinophilia (absolute or relative) was found in 21 cases (11.8%). An asymptomatic infection with increased IgE levels and without eosinophilia (any type) was present in 18 cases (10.1%). There were no cases of hyperinfection or disseminated infection.

A comorbidity was described in 72 cases (40.4%), mainly other infectious diseases. There were 22 cases of Chagas disease (12.4%), nine of filariasis (5.1%), seven intestinal helminthic infections (other than strongyloidiasis; 3.9%), and five cases of malaria (2.8%). Also described were co-infections with hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV (Table 2). No cases of HTLV infection were present. The main non-infectious disease reported was hypertension (10 cases). The median (range) Charlson index was 0 (0–7).

3.3. Analysis by groups

There were nine patients considered as immunosuppressed, all of them HIV-1-infected. The HIV subtypes were the following: B (three cases), A1, C, CRF02_AF, CRF02_AG, and CRF11; the subtype of one case was missing. The median (range) total CD4 lymphocyte count was 313.5 (32–877) cells/mm³; the median (range) viral load was 1.97 log (1.56–5.23) copies/ml. Only four patients were on highly active antiretroviral therapy (HAART), three of them with an undetectable viral load. Another patient was an elite controller. No cases of co-infection with HBV or HCV were reported.

There were no differences in clinical features in the two groups, as can be seen in Table 5. In immunosuppressed patients, cutaneous and respiratory symptoms were only described when the total CD4 lymphocyte count was <200 cells/mm³, and digestive symptoms were reported only in patients with >200 cells/mm³. No differences were found in the percentages of patients with increased IgE levels (63% in immunocompetent vs. 66.7% in immunosuppressed patients; $p > 0.999$, Fisher's exact

Table 3
Clinical characteristics of cases of strongyloidiasis (total and by group)

	Total (n = 178) (100%), n (%)	Travelers (n = 58) (32.6%), n (%)	Natives (n = 120) (67.4%), n (%)	p-Value ^a
Symptomatic, n (%)	85 (47.8)	33 (56.9)	52 (43.3)	0.09
Gastrointestinal symptoms, n (%)	54 (30.3)	22 (37.9)	32 (26.7)	0.12
Nausea	4 (2.2)	1 (1.7)	3 (2.5)	>0.99 ^b
Vomiting	4 (2.2)	2 (3.4)	2 (1.7)	0.59 ^b
Reflux	6 (3.4)	1 (1.7)	5 (4.2)	0.66 ^b
Dyspepsia	13 (7.3)	2 (3.4)	11 (9.2)	0.23 ^b
Abdominal pain	20 (11.2)	7 (12.1)	13 (10.8)	0.81
Constipation	8 (4.5)	2 (3.4)	6 (5)	>0.99 ^b
Diarrhea	22 (12.4)	18 (31)	4 (3.3)	<0.001
Pulmonary symptoms, n (%)	6 (3.4)	1 (1.7)	5 (4.2)	0.66 ^b
Cough	4 (2.2)	1 (1.7)	3 (2.5)	>0.99 ^b
Sputum	0 (0)	0 (0)	0 (0)	NA
Wheezing	1 (0.6)	0 (0)	1 (0.8)	>0.99 ^b
Cutaneous symptoms, n (%)	38 (21.3)	11 (19)	27 (22.5)	0.59
Urticaria	32 (18)	9 (15.5)	23 (19.2)	0.55
Larva currens	5 (2.8)	1 (1.7)	4 (3.3)	>0.99 ^b
Purpura	2 (1.1)	0 (0)	2 (1.7)	>0.99 ^b
Comorbidity, n (%)	72 (40.4)	13 (22.8)	59 (49.2)	0.001

NA, not applicable.

^a Comparison between travelers and natives.

^b Fisher's exact test.

Table 4
Abnormal laboratory data (total and by group)

	Total	Travelers	Natives	p-Value ^a
Total eosinophil count ($\times 10^6$ cells/l), median (IQR)	450 (200–900)	200 (150–400)	600 (300–1050)	<0.001
Percentage of eosinophils, median (IQR)	7.1 (3.4–14.9)	3.4 (2.45–5.45)	10.7 (5.6–16.9)	<0.001
Serum IgE levels (IU/ml), median (IQR)	326.5 (59–1014.2)	58 (23.15–147.5)	642 (191–1279)	<0.001

IQR, interquartile range.

^a Comparison between travelers and natives; Mann–Whitney U-test.

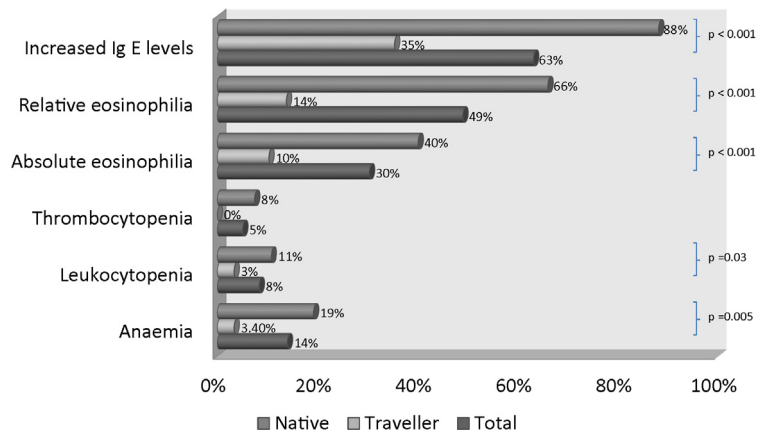


Figure 1. Laboratory abnormalities: serum IgE levels from 162 cases.

Table 5
Clinical features of strongyloidiasis in immunocompetent and immunosuppressed patients^a

	Immunocompetent (n = 165)	Immunosuppressed (n = 9)	p-Value ^b
Symptomatic, n (%)	78 (47.3)	4 (44.4)	>0.999
Gastrointestinal symptoms, n (%)	50 (30.3)	2 (22.2)	0.726
Pulmonary symptoms, n (%)	5 (3)	1 (11.1)	0.276
Cutaneous symptoms, n (%)	35 (21.2)	2 (22.2)	>0.999

^a Data from 174 patients.

^b Fisher's exact test.

test). However, absolute eosinophilia was less frequent in immunocompetent patients than in immunosuppressed patients (27.3% vs. 77.8%; $p = 0.003$, Fisher's exact test). Relative eosinophilia was also less frequent in immunocompetent patients (46.7% vs. 88.9%; $p = 0.016$, Fisher's exact test).

3.4. Diagnosis methods

Stool tests were performed in all patients, and serology in 160 patients (89.9%). The diagnosis of strongyloidiasis was based on serology only in four patients (two travelers and two natives); 21 patients (six travelers and 15 natives) had only stool tests positive. Three cases of strongyloidiasis (all in travelers) were positive by stool tests but negative by serology. In HIV patients with strongyloidiasis, stool tests were positive for all patients; serology was also positive for all patients tested (77.8%).

Abnormal laboratory findings depending on the method of diagnosis are shown in Figure 2.

4. Discussion

To our knowledge, this is the largest reported series of imported strongyloidiasis in Europe. Most reported cases of imported strongyloidiasis have been related to immigrants from endemic zones. In this study, travel-related strongyloidiasis constituted a third of the total (similar to the findings of Nuesch et al.¹⁷), and the origin of acquisition in this group was very heterogeneous. More than half of the strongyloidiasis cases in travelers were acquired in trips of less than 2-month duration, suggesting that some of the recommendations regarding screening tests in travelers may be debated.^{18,19} Only two thirds of cases of strongyloidiasis in our study were in natives, with a ratio of origin Africa to Central and South America of 1; no cases were from Asia. In this group of patients, some of the diagnoses had been delayed for a long time. Similar to González et al.,⁵ we found no differences in clinical presentation between natives and travelers. However, eosinophilia (absolute and relative) and levels of serum IgE were higher in natives. Comorbidities were present in nearly half of the cases, but

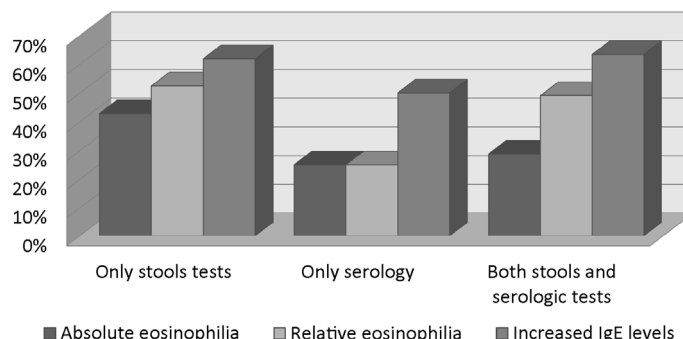


Figure 2. Percentage of abnormal laboratory tests regarding positive tests for strongyloidiasis.

without an impact on the prognosis (evaluated with the Charlson index). We found no cases of hyperinfection or disseminated infection. This could be explained by the following: (1) corticosteroid therapy is the most frequent associated condition, and we had no patients on this therapy;²⁰ (2) other risk factors such as malignancy, organ transplantation, HTLV-1 infection, and diabetes were not found in our series; (3) very few cases of hyperinfection and disseminated strongyloidiasis in HIV-infected individuals have been reported in the medical literature; and (4) although the median time to diagnosis was delayed up to 1 year, perhaps it was made early enough to prevent the development of a hyperinfection/disseminated infection.

A secondary purpose of this retrospective study was to describe the major clinical features of immunosuppressed patients. We were only able to find HIV-infected patients in this series. When AIDS was initially described, an outbreak of disseminated strongyloidiasis was predicted; however the relative paucity of cases led the US Centers for Disease Control and Prevention (CDC) and the WHO to remove disseminated strongyloidiasis from the list of signature infections. However, strongyloidiasis is more prevalent in HIV patients in endemic zones.^{11,12} It has been reported that the rate of parasitic infection increases with decreasing CD4 T-cell counts among HIV-infected individuals.¹² In our study, a significant finding in HIV patients was the difference in clinical presentation depending on the total CD4 lymphocyte count. Of note, even in HIV patients on HAART with good CD4 counts, stool tests were positive. General conclusions cannot be drawn from this finding, because a limitation of this study was the small number of HIV patients included; but this should be investigated further. Unlike other studies,²¹ we found that eosinophilia was less frequent in immunocompetent patients than in HIV patients.

The sensitivity of the classic stool microscopy examination (parasitic ova and larvae) varies between 75.9% and 92%, depending on the number of samples analyzed.²² Of note, a negative result does not necessarily indicate the absence of the infection.²³ ELISA serologic assays measure IgG responses to a crude extract of the filariform larvae of *Strongyloides sp.* ELISA tests for antibodies in serum have a high sensitivity (83–93%) and specificity (95–98%).²⁴ It takes 4–6 weeks for these tests to become positive, and they may remain positive after treatment for extended periods of time. In acute infections this can lead to false-negative results, and cross-reactivity with other helminthic infections has been described.²⁵ There is difficulty in calculating diagnostic efficiency parameters for ELISA techniques because of the absence of a definitive gold standard for diagnosing *S. stercoralis* infection. Specifically, the test used in our study has been used by other authors for the diagnosis of both cutaneous and intestinal strongyloidiasis, with a sensitivity of 89% and a specificity of 97.2%, although filariasis patients were not included in the calculation of sensitivity and specificity with this test.²⁶ Bon et al.²⁷ described an increased sensitivity of 91.2%, with a specificity of 93.3%, using a large panel of serum samples collected from patients, including some with a definitive diagnosis of strongyloidiasis, some with other helminthic infections, and some with eosinophilia without a parasitic infection diagnosis. Experts of the British Infection Society have suggested performing concentrated stool microscopy and *Strongyloides* serology in all cases of subjects with a consistent travel history, symptoms, and/or eosinophilia.⁷ In our daily clinical practice, stool tests are performed for all travelers and immigrants; serology for *Strongyloides* is usually solicited when abnormal laboratory results or symptoms are present. We can suggest from our results that elevated serum IgE levels are the most sensitive clue for suspecting strongyloidiasis, followed by relative eosinophilia. The percentage of patients with

eosinophilia or elevated serum IgE levels is greater when *Strongyloides* can be detected in stools. This probably reflects a longer period of immunological stimulation until the biological cycle is completed and the parasite is excreted in the stools. The fact that more than 50% of the strongyloidiasis in this series was detected in asymptomatic patients, points to the respective risk of missing the diagnosis.

Azole drugs (thiabendazole, mebendazole, albendazole) and ivermectin have been used for the treatment of strongyloidiasis. Currently, ivermectin is the best therapeutic option for strongyloidiasis. The most recent trials comparing ivermectin and azole drugs have shown the superiority and better tolerance of the former.^{28–30} Most patients in the study were treated with ivermectin, customized to the different status of immunity.

In conclusion, not only must strongyloidiasis be suspected in symptomatic travelers and immigrants, but it should also be ruled out when elevated IgE levels or eosinophilia are present. Strongyloidiasis can be asymptomatic in HIV patients, but it should be diagnosed and treated before a possible hyperinfection develops.

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Conflict of interest: The authors declare that they have no competing interests.

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