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Maria-Jesus Pinazo,
Jaime Saravia,
Ingrid Gainsborg,
Helmut-Ramon Magne,
Miriam
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Characterization of digestive disorders of patients with chronic Chagas disease in Cochabamba, Bolivia

Jimy-Jose Pinto^a, Maria-Jesus Pinazo^{b,*}, Jaime Saravia^d, Ingrid Gainsborg^d,
Helmut-Ramon Magne^a, Miriam Cuatrecasas^c, Núria Cortes-Serra^b,
Daniel-Franz Lozano^a, Joaquim Gascon^b, Faustino Torrico^a

^a *Fundación CEADES, Cochabamba, Bolivia*

^b *Instituto de Salud Global de Barcelona (ISGlobal), Hospital Clínic i Provincial/IDIBAPS, Universitat de Barcelona, Barcelona 08036, Spain*

^c *Pathology Department, Hospital Clínic of Barcelona, University of Barcelona/Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD)/Tumor Bank-Biobank Hospital Clínic-IDIBAPS, Barcelona, Spain*

^d *Bolivian Institute Japanese Gastroenterological Sucre, Bolivia*

* Corresponding author.

E-mail address: mariajesus.pinazo@isglobal.org (M.-J. Pinazo).

Abstract

Background: Chagas disease (CD) is endemic in Latin America and particularly common in Bolivia, but there is little information on the characteristics of chronic digestive involvement.

Objectives: To determine the prevalence and characterize digestive manifestations in chronic CD patients in Cochabamba, Bolivia.

Methods: Eighty-five *T. cruzi*-seropositive individuals with or without digestive symptoms (G1 group), and fifteen *T. cruzi*-seronegative patients with similar digestive symptoms to those seen in CD (G2 group) were included in the study. All patients underwent a detailed history including past medical history, epidemiological information, hygiene and dietary habits, a complete physical

examination, two serological tests for *T. cruzi*, video endoscopy, barium swallow, and barium enema.

Findings: We observed digestive manifestations in *T. cruzi* seropositive and seronegative patients. Colonic manifestations were detected in both groups, highlighting the relevance of other confounder factors in the region. Constipation was present in 52.9% of G1 patients, 62.4% presented two or more upper digestive tract symptoms, and 5.9% of them presented esophageal manifestations. *Helicobacter pylori* infection was detected in 58.8% of G1 patients, and all patients presented gastritis on endoscopy.

Conclusions: Prevalence of digestive involvement in CD patients is higher than expected. However, digestive symptoms are not always caused by *T. cruzi* infection and require differential diagnoses.

Keyword: Infectious disease

1. Introduction

Chagas disease (CD), caused by the parasite *Trypanosoma cruzi*, is the main infectious cause of heart disease in Latin America, where the disease is endemic [1]. It is estimated that 20% of Bolivians have CD and the vector that transmits *T. cruzi* infection is endemic in 60% of the country [2]. The epidemiology of the disease has changed due to migratory movements and *T. cruzi* infection is now considered a global problem [3].

CD is primarily transmitted by a blood-sucking insect known as the kissing bug, which is a member of the triatomine family. *Triatoma infestans* is the main vector in Bolivia [3]. Other modes of transmission, less common but also important from a public health perspective, are transmission by blood transfusion, organ transplant from infected donors, and congenital from mother to infant, which can cause disease spread in both endemic and traditionally non-endemic areas where triatomine bugs do not exist [4]. There have also been reports of oral transmission in Amazon regions [5] and urban environments [6].

Manifestations of chronic CD include heart damage (which affects 5%–30% of patients), digestive disorders (10%–20% of patients), and mixed and neurological alterations, which affect a smaller proportion of patients [7, 8, 9].

Gastrointestinal manifestations, which are the second most common cause of organ complications in CD, are associated with high morbidity and can seriously affect patient's quality of life. Although *T. cruzi* infection can affect all parts of the digestive tract, the esophagus and the colon are most commonly involved.

Little is known about the characteristics of digestive damage in chronic CD patients in Bolivia, its association with specific genotypes of *T. cruzi*, and the

possible relation between the degree of affectation and the symptomatology presented by patients. The aim of this study was to determine the prevalence of digestive manifestations and to characterize these in patients with CD in Cochabamba, Bolivia.

2. Materials and methods

A cross-sectional study was designed in which patients attending the Platform for the Integral Care of Patients With CD over a 2-year period (December 2009–December 2011) were prospectively included. Patients were recruited in the department of Cochabamba, whose capital lies at a height of 2558 meters above sea level (m.a.s.l.). Participation was voluntary and individual written informed consent was obtained from all study participants.

A total of 100 patients were included in the study, divided into two groups. Group 1 (G1) included 85 patients with positive serology for *T. cruzi* infection with or without digestive symptoms, and group 2 (G2) included 15 patients with negative serology for *T. cruzi* infection but with similar digestive symptoms to those seen in CD (11 patients had constipation, 2 had dysphagia, and 2 presented altered bowel habit).

All patients underwent a full physical examination and a thorough history that included past medical history, epidemiological information (place of origin, residence, contact with the insect vector that transmits *T. cruzi* infection), and hygiene and dietary habits. *T. cruzi* infection was diagnosed following detection of antibodies to *T. cruzi* using two commercial serological tests: Weiner Lab ELISA Chagatest Lisado and Weiner Lab ELISA Chagatest Recombinante (Rosario Argentina). Patients with conflicting results underwent a third test with a serology kit with high sensitivity and specificity (BioELISA Chagas, Biokit S.A., Lliçà d'Amunt, Barcelona, Spain). All patients were referred for barium swallow and barium enema using the Rezende et al. and Ximenes et al. techniques [10, 11].

Esophageal disease severity was classified using the criteria established by Ximenes et al., which proposes a four group classification based on the results of the radiological study [11]. The following colonic measurements—defined as normal—were used to distinguish between normal and abnormal colon findings: rectosigmoid colon of 6.5 cm (width) and 11–35 cm (length), 8 cm (width) and 25 cm (length) for the ascending colon, and 12 cm (width) for the cecum [12, 13, 14, 15, 16].

All patients were referred for video endoscopy to check for the presence of gastric disorders due to *Helicobacter pylori* infection or other causes. *H. pylori* infection was diagnosed by histological examination of gastric biopsy specimens. G1 patients

underwent an electrocardiogram and routine laboratory tests defined in the protocol for managing patients with *T. cruzi* infection at the Platform for the Integral Care of Patients With CD. All patients who met the criteria for specific treatment were offered benznidazole 5 mg/kg for 60 days.

Patients were also classified according to the altitude of their place of residence (above or below 3000 m.a.s.l.) to control a confounding effect of megacolon at high altitude [13, 15].

We analyzed means and standard deviations, ranges, and frequencies using SPSS (SPSS Statistics 17.0.1- December 2008).

The study was reviewed and approved by a local ethics committee (CEADES Salud y Medioambiente) and the ethics committee at Hospital Clínic in Barcelona, Spain.

3. Results

A total of 100 patients were analyzed: 85 from G1 group and 15 from group G2. Seventy-nine (93%) of the patients in G1 were women. The mean age of the patients was 46 years-old (range, 20–64 years) and 21 (24.7%) lived above 3000 m.a.s.l. In G2, there were 11 women (73%). The mean age of the group was 35 years-old (range, 18–55 years) and 3 patients (20%) lived above 3000 m.a.s.l.

The analysis performed showed digestive involvement in 71.8% of G1 and 53.3% of G2 patients. Colonic affectionation was observed in 67% of all patients included in the study, 6% presented esophageal manifestations, 100% presented some degree of gastritis and 58.2% were positive for *H. pylori* infection. Results are summarized in Table 1.

Colonic manifestations were detected in both groups. Barium enema results, taking as main characteristic symptom constipation based on Roma III criteria ref, are shown in Table 2. *T. cruzi* seropositive patients presented constipation in 52.9% (45/85) of cases, and 41.2% (35/85) of them had abnormal barium enema findings.

Table 1. Results of complementary studies performed in G1 and G2 patients.

	G1		G2	
	Altered	Not altered	Altered	Not altered
Digestive involvement with similar characteristics that digestive Chagas Disease radiological findings				
Barium enema	60		25	7
Barium swallow	5		80	1
Digestive involvement (other than megaesophagus and megacolon)				
Video endoscopy	84		0	14
Biopsy to determine <i>H. pylori</i> infection	50		34	7

Table 2. Findings in patients presenting constipation and not presenting constipation in barium enema.

	G1		G2	
	Presenting constipation	Not presenting constipation	Presenting constipation	Not presenting constipation
Normal	10	9	6	1
Dolichocolon	6	3	0	1
Dolichomegacolon	22	21	2	0
Megacolon	7	7	3	2
Total	45	40	11	4

According to the Ximenes and Rezende criteria [10], 67.1% (57/85) of patients in G1 presented criteria of colonic involvement due to Chagas disease (dolichomegacolon and megacolon), and only 50.9% (29/57) of them presented constipation.

Fifty-four (63.5%) of the 85 patients in G1 had radiological findings consistent with those caused by CD: dolichomegacolon (n = 27) and megacolon (n = 27). Of the 54 patients with manifestations consistent with those seen in CD, 13 (24.1%) lived above 3000 m.a.s.l. In G2, 2/15 patients (13.3%) had findings consistent with CD: megacolon (n = 1) and dolichomegacolon (n = 1). Neither of these patients lived above 3000 m.a.s.l. Results are summarized in Table 3.

Symptoms associated with esophageal manifestations detected by barium swallowing were dysphagia, regurgitation, retrosternal pain, heartburn, and abdominal distension. 15% of all patients included in the study were asymptomatic and 56% presented two or more symptoms. Similarly, 5 patients from group G1 presented abnormal barium swallowing results, and 4 of them presented at least one symptom. Results are shown in Table 4.

The most common manifestations in *T. cruzi* seropositive patients were heartburn (57.6%), abdominal distension (38.8%), retrosternal pain (27.1%), dysphagia

Table 3. Colonic manifestations in barium enema study by altitude of residence.

	G1		G2	
	>3000 m.a.s.l.	<3000 m.a.s.l.	>3000 m.a.s.l.	<3000 m.a.s.l.
Normal findings	6 (7.1%)	14 (16.5%)	2 (13.3%)	9 (60%)
Megacolon	6 (7.1%)	21 (24.7%)	0 (0%)	1 (6.6%)
Dolichomegacolon	7 (8.2%)	20 (23.5%)	0 (0%)	1 (6.6%)
Dolichocolon	2 (2.3%)	9 (10.6%)	1 (6.6%)	1 (6.6%)
Total	21 (24.7%)	64 (75.3%)	3 (20%)	12 (80%)

Table 4. Esophageal involvement based on barium swallow study.

	Asymptomatic	One symptom	Two symptoms	Three or more symptoms
G1				
Normal findings	9	21	31	19
Grade I esophagopathy	1	1	1	0
Grade II esophagopathy	0	0	0	0
Grade III esophagopathy	0	0	1	0
Grade IV esophagopathy	0	0	0	1
G2				
Normal findings	5	7	1	1
Grade I esophagopathy	0	0	1	0
Total	15	29	35	21

(14.1%), regurgitation (7.1%) and odynophagia (2.4%). Results are summarized in Table 5.

Four patients in G1 presented both esophageal and colonic manifestations: two had megacolon and grade I and grade IV esophagopathy, and two had dolichomegacolon and grade I and grade III esophagopathy. Out of total patients in G1 group, 71.8% presented digestive manifestations, consistent with Ximenes and Rezende criteria (56/85 colonic, 4/85 esophageal and colonic, and 1/85 esophageal).

4. Discussion

Digestive disorders in CD patients in Cochabamba are more common than expected based on prevalence rates reported for other countries (10–20% vs 68.2% in our series) [9, 15]. We also detected a high prevalence of digestive disorders in patients without *T. cruzi* infection, although it should be noticed that these patients were

Table 5. Esophageal manifestations presented by *T. cruzi* infected and non-infected patients.

	G1		G2	
	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic
Dysphagia	12	73	2	13
Regurgitation	6	79	0	15
Odynophagia	2	83	0	15
Retrosternal pain	23	62	2	13
Heartburn	49	36	5	10
Abdominal distension	33	52	7	8

selected because they had digestive symptoms, and therefore this observation cannot be extrapolated to the general population. Nevertheless, the fact that patients without CD presented similar esophageal and colonic manifestations to those seen in patients with the disease, suggests that there might be other region-specific factors or disorders at play. Previous studies have shown that, among other factors, prolonged stays at high altitudes or chewing coca leaves for long periods of time can cause dolichomegacolon or megacolon [13, 17]. Cochabamba is a medium-high altitude city, on the foothills of the Andes. However, internal migratory movements due to work are frequent in Bolivia, and mobility of people between Cochabamba and other places at higher altitude, as La Paz, Sucre or Potosi, are usual [18].

Based on the findings of our study, a large percentage of patients with CD in Cochabamba have colon-related symptoms (67.06%) while esophageal manifestations are lower (5.88%). Esophageal involvement is more common than colon involvement in patients with *T. cruzi* infection in other countries in the Latin American region, such as Argentina and Brazil [16]. In Bolivia, megaesophagus is more common in the plains and foothills, while megacolon is more common in the plateaus and mountainous regions. The above data, however, may be affected by confounders, such as exposure to high altitudes, a high-fiber diet, or long-term chewing of coca leaves in plateau areas of Bolivia, Chile, and Peru [17].

Altitude of place of residence is an important factor to consider. In our study, of the total patients who lived at an altitude over 3000 m.a.s.l., 13 (61.9%) in G1 and 0 (0%) in G2 presented colonic manifestations. Despite the small number of patients in this study, particularly in G2, we detected colon disorders in both groups of patients, showing that colon disorders are not necessarily associated with *T. cruzi* infection.

The main abnormality detected in patients with high-altitude hypoxia is dolichomegacolon, which is diagnosed when the transverse rectosigmoid diameter is greater than 6.5 cm. The presence of megacolon could be explained by Boyle's Law, which states that volume is inversely proportional to pressure [17, 19, 20, 21, 22]. Results of an unpublished study conducted by Saravia and colleagues at the Bolivian Japanese Gastroenterology Institute in Cochabamba show that intestinal volvulus is the most common complication of megacolon in patients living at a mean altitude of 2560 m.a.s.l., where the average atmospheric pressure is 560 mbar (sea level pressure of 760 mbar), the concentration of oxygen is 21%, and the partial pressure of oxygen in arterial blood is 60–70 mmHg (90–100 mmHg at sea level). In our series, dolichomegacolon was more common in patients living at an altitude of over 3000 m.a.s.l. (7/24 patients).

Another important confounder in this population is the long-term consumption of coca leaves. Coca leaf chewing is a popular endemic activity throughout Bolivian

communities. Coca leaf are a mild stimulant, used for centuries due their characteristics to alleviate altitude sickness and as an appetite suppressant [23]. Chewing coca leaves can produce megacolon through the inactivation of adrenaline metabolism in nerve endings, leading to progressive bowel wall ischemia with secondary atrophy of the muscle layer, atony, gradual enlargement and extension of the intestine, and a consequent reduction in intestinal activity [24, 25]. One study of the histological features of the colon in patients with non-Chagasic megacolon and a history of long-term ingestion of coca leaves reported the presence of fat globules in large intestine muscle fibers in 80% of cases. The authors of this study calculated that regular chewers of coca leaves were three times more likely to develop fat globules in the intestinal track than other patients ($p < 0.05$) [26].

The most common complications of megacolon are fecaloma, sigmoid volvulus, and acute abdomen. In our series, in G1, one patient had a sigmoidectomy due to a volvulus and two patients underwent surgical correction of a volvulus by rectosigmoidoscopy.

We were unable to define the impact of confounding factors such as residence at high altitudes or long-term consumption of coca leaves on the presence of megacolon, due to the cross-sectional nature of our study. We were also unable to determine whether or not patients living below 3000 m.a.s.l. had at some time lived at a higher altitude.

All patients in G1 and G2 groups who underwent video endoscopy presented different degree of gastritis. Histological examination revealed a high prevalence of *H. pylori* infection in both groups: 58.8% (50 patients) in G1 and 50% (7 patients) in G2. According to data in the literature, *H. pylori* infection affects between 80% and 90% of people in developing countries and 50% of people worldwide [22, 27]. The estimated prevalence in Bolivia is 50%–60% [28, 29], which is consistent with our findings. *H. pylori* infection causes a range of non-specific symptoms that can be confused with those seen in *T. cruzi*-infected patients with upper digestive manifestations [27]. The non-specificity of *T. cruzi* infection symptoms poses a diagnostic challenge. In our study, several patients in G1 with symptoms of CD had normal findings in the additional tests performed, while in G2, several patients had symptoms suggestive of *T. cruzi* infection but were not infected.

5. Conclusions

Digestive disorders in patients with CD in Cochabamba, Bolivia, are more common than would be expected. In our series, the colon was the most frequently affected

segment of the digestive tract. The most common abnormalities detected in patients with *T. cruzi* infection were megacolon and dolichomegacolon. However, colonic manifestations were detected in both groups, suggesting that there might be other region-specific factors. Overall, our findings suggest that symptoms typically seen in patients with CD are not always caused by *T. cruzi* infection and require greater investigation of alternative causes, such as concomitant infection by intestinal parasites, long-term consumption of coca leaves, megacolon at high altitude, and *H. pylori* infection.

Declarations

Author contribution statement

Jimmy-Jose Pinto, Maria-Jesus Pinazo: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Jaime Saravia, Ingrid Gainsborg, Helmut-Ramon Magne: Performed the experiments; Analyzed and interpreted the data.

Miriam Cuatrecasas, Núria Cortes-Serra, Daniel-Franz Lozano: Analyzed and interpreted the data.

Joaquim Gascon: Conceived and designed the experiments; Performed the experiments.

Faustino Torrico: Conceived and designed the experiments.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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