International Journal of Infectious Diseases 67 (2018) 118–121

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Clinical and epidemiological features of chronic *Trypanosoma cruzi* infection in patients with HIV/AIDS in Buenos Aires, Argentina

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ARTICLE INFO

Article history:
Received 13 September 2017
Received in revised form 21 November 2017
Accepted 23 November 2017
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
HIV/AIDS
Trypanosoma cruzi
Intravenous drug use
Chagas disease
Reactivation
Co-infection

ABSTRACT

Objectives: *Trypanosoma cruzi* reactivation in HIV patients is considered an opportunistic infection, usually with a fatal outcome. The aim of this study was to describe the epidemiological and clinical features of *T. cruzi* infection in HIV patients and to compare these findings between patients with and without Chagas disease reactivation.
Methods: The medical records of *T. cruzi*–HIV co-infected patients treated at the Muñiz Infectious Diseases Hospital from January 2005 to December 2014 were reviewed retrospectively. Epidemiological and clinical features were assessed and compared between patients with and without Chagas disease reactivation.
Results: The medical records of 80 *T. cruzi*–HIV co-infected patients were reviewed. The most likely route of *T. cruzi* infection was vector-borne (32/80 patients), followed by intravenous drug use (12/80). Nine of 80 patients had reactivation. Patients without reactivation had a significantly higher CD4 T-cell count at diagnosis of *T. cruzi* infection (144 cells/μl vs. 30 cells/μl, $p = 0.026$). Chagas disease serology was negative in two of nine patients with reactivation.
Conclusions: Serological assays for *T. cruzi* infection may be negative in severely immunocompromised patients. Direct parasitological techniques should be performed in the diagnosis of patients for whom there is a suspicion of *T. cruzi* reactivation. HIV patients with a lower CD4 count are at higher risk of reactivation.

Introduction

Chagas disease is a zoonotic disease caused by *Trypanosoma cruzi*, a flagellated protozoan. The acute phase of the infection is typically asymptomatic or associated with mild symptoms such as fever, malaise, swelling at the site of inoculation, and lymphadenopathy. Although it usually resolves spontaneously within 2–4 months, severe myocarditis or meningoencephalitis can be seen. Following this phase, a chronic phase is established that lasts years or throughout life. Approximately one-third of chronically infected patients develop cardiomyopathy and/or megaesophagus/megacolon after years or decades of infection (Cordova et al., 2008; Lattes and Lasala, 2014).

Reactivation of Chagas disease, defined as a high level of parasitemia in a patient with chronic Chagas disease, was initially described in immunocompromised patients secondary to organ transplantation or a hematological malignancy (Cantarovich et al., 1992; Kohl et al., 1982). The first case recorded in an HIV-infected patient was described in 1990 (Del Castillo et al., 1990). Since then, *T. cruzi*–HIV co-infection has been documented in countries where Chagas disease is endemic, as well as in non-endemic countries as a result of the migration flow from Latin America to the rest of the world (Almeida et al., 2011; Salvador et al., 2014, 2015). The rate of *T. cruzi*–HIV co-infection ranges from an estimated 1.3% in Brazil, to 5% in endemic areas of Brazil and 7.1% in intravenous drug users in Argentina (Dolcini et al., 2008; Stauffert et al., 2017). Chagas disease reactivation most frequently involves the central nervous

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https://doi.org/10.1016/j.ijid.2017.11.027

system (CNS) (74.2%), followed by myocardial involvement (16.7%) (Almeida et al., 2011). Although many case reports and case series of Chagas disease reactivation in HIV-infected patients have been published, few articles have described *T. cruzi*–HIV co-infection in patients without reactivation (Almeida et al., 2010, 2011; Sartori et al., 1998, 2007).

The aim of this study was to describe the epidemiological and clinical features of *T. cruzi* infection in HIV-infected patients and to compare these findings between patients with and without Chagas disease reactivation.

Patients and methods

The medical records of *T. cruzi*–HIV co-infected patients, who were treated at the Francisco J. Muñiz Infectious Diseases Hospital from January 2005 to December 2014, were reviewed retrospectively.

HIV infection was diagnosed by ELISA (VIDAS HIV; bioMérieux, France) and confirmed by Western blot tests (Bioblot HIV-1 plus; Biokit, Spain). Chagas disease was diagnosed when the following serological assays were positive: ELISA (ELISA Chagas III; Grupo BiosChile Ingenierìa Genética, Chile) and indirect hemagglutination (HAI; Chagas Polychaco S.A.I.C, Argentina). If results were discordant, a third assay was performed: indirect immunofluorescence assay with antigens provided by the National Parasitology Institute "Dr. Fatala Chaben", ARCHITECT Chagas (Abbott Laboratories), or the detection of trypomastigotes in fluids and/or amastigote nests in tissue samples.

The following data were assessed: sex, nationality, age at HIV diagnosis and at Chagas disease diagnosis, possible source of acquisition of HIV and *T. cruzi* infection, time between HIV and Chagas disease diagnosis, follow-up since Chagas disease diagnosis, minimum CD4 T-cell count and CD4 T-cell count at Chagas disease diagnosis, opportunistic infections prior to or at the time of Chagas disease diagnosis, results of direct microscopic examination for *T. cruzi* in blood, fluids, or tissue, Chagas disease treatment, use of highly active antiretroviral therapy (HAART) at the time of Chagas disease diagnosis and at the last follow-up evaluation, and finally the mortality rate in patients with *T. cruzi* reactivation.

The clinical form of chronic Chagas disease was classified as indeterminate, cardiac, and/or digestive chronic disease, according to clinical, radiological, and electrocardiographic findings (Dias et al., 2016). At least a chest X-ray and electrocardiogram were used for classification; echocardiography and digestive tube radiography (barium enema and/or series) were assessed when done (Guías para la atención al paciente infectado con *Trypanosoma cruzi*, 2012).

Chagas disease reactivation was defined when clinical manifestations of the disease, not observed in chronically infected immunocompetent individuals, were seen, and when *T. cruzi* was detected by direct microscopic examination in biological samples of peripheral blood or other fluids (cerebrospinal fluid (CSF), pericardial effusion, peritoneal effusion, etc.), or in those patients with high burdens of *T. cruzi* amastigote nests revealed by histopathological studies (biopsy or autopsy) (Almeida et al., 2010). The following data were also assessed in patients with *T. cruzi* reactivation: organ involvement, time to the diagnosis of reactivation, treatment received, and outcome.

This study was approved by the Ethics Committee of the Francisco J. Muñiz Infectious Diseases Hospital.

Continuous variables were compared between groups using the *t*-test or the Mann–Whitney *U*-test when appropriate. Multivariate analyses could not be done due to the small sizes of the groups. Categorical variables were compared between groups using the Pearson Chi-square test or Fisher's exact test when the Chi-square test assumptions were not fulfilled. Significance was set at $p < 0.05$. Data were entered into and analyzed using IBM SPSS Statistics software, version 23 (IBM Corp, Armonk, NY, USA).

Results

The medical records of 80 *T. cruzi*–HIV co-infected patients were reviewed. Sixty-three patients were male. The median age of the patients at Chagas disease diagnosis was 40.5 years (interquartile range (IQR) 13 years) and at HIV diagnosis was 34.5 years (IQR 20.5 years). The most likely route of *T. cruzi* infection acquisition was vector-borne transmission (32/80 patients), followed by intravenous drug use (IDU). All patients were considered in the chronic phase of Chagas disease, as they were adults living in a metropolitan area without vector-borne transmission and were not active IDUs. Only 25 of the 80 patients were on HAART at the time of Chagas disease diagnosis. Patients with and without

Table 1
Epidemiological characteristics of *Trypanosoma cruzi*–HIV co-infected patients.

	With reactivation ($n = 9$)	Without reactivation ($n = 71$)	Total ($n = 80$)
Sex, male (%)	8 (88.9)	55 (77.5)	63 (78.8)
Age at Chagas disease diagnosis, years, median (IQR)	39 (18)	42 (13)	40.5 (13)
Age at HIV diagnosis, years, median (IQR)	33 (24)	35 (21)	34.5 (20.5)
Nationality, *n* (%)			
Argentinean	7 (77.8)	50 (70.4)	57 (71.4)
Bolivian	0	8 (11.3)	8 (10)
Chilean	0	1 (1.4)	1 (1.2)
Paraguayan	0	1 (1.4)	1 (1.2)
Peruvian	1 (11.1)	0	1 (1.2)
Unknown	1 (11.1)	11 (15.5)	12 (15)
Risk factor for HIV, *n* (%)			
Unprotected heterosexual contact	4 (44.5)	46 (64.8)	50 (62.5)
MSM	1 (11.1)	3 (4.2)	4 (5)
IDU	2 (22.2)	18 (25.4)	20 (25)
Congenital	1 (11.1)	0	1(1.2)
Unknown	1 (11.1)	4 (5.6)	5 (6.3)
T. cruzi infection probable acquisition route, *n* (%)			
Vector-borne	5 (55.6)	27 (38)	32 (40)
IDU	2 (22.2)	10 (14)	12 (15)
Vector-borne and IDU	0	8 (11.3)	8 (10)
Unknown	2 (22.2)	26 (36.7)	28 (35)

IQR, interquartile range; MSM, men who have sex with men; IDU, intravenous drug user.

Table 2
Clinical characteristics of *Trypanosoma cruzi*–HIV co-infected patients.

	Total ($n = 80$)	Reactivation ($n = 9$)	No reactivation ($n = 71$)	p-Value
Minimum CD4 T-cell count, cells/μl, median (IQR)	80 (180.1)	30 (80.0)	94 (204.0)	0.032[a]
CD4 T-cell count at Chagas disease diagnosis, cells/μl, median (IQR)	103 (255.8)	30 (127.0)	144 (253.0)	0.026[a]
Patients with opportunistic infections prior/concomitant, *n* (%)	57 (71.3)	9 (100)	48 (68.6)	0.053
Patients on HAART at Chagas disease diagnosis, *n* (%)	25 (31.3%)	3 (33.3)	22 (31.0)	1.000

IQR, interquartile range; HAART, highly active antiretroviral therapy.
[a] Significant, $p < 0.05$.

Table 3
Clinical and parasitological information for patients with Chagas disease reactivation.

Patient number	Tissue involvement	Parasite in blood	Parasite in CNS fluid	Serology	Treatment	Outcome
23	CNS/myocardium	Pos	Pos	Neg	BZD/NFT	Relapse (died following second episode)
39	CNS	Neg	Pos	Pos	BZD	Died
54	CNS	ND	Pos	Pos	BZD	Disease resolution
65	CNS	Neg	Pos	Pos	BZD	Died
70	CNS	Neg	Pos	Pos	BZD	Died
73	CNS	Neg	Pos	Pos	None	Died
78	CNS	Neg	Pos	Neg	BZD	Disease resolution
79	CNS	Neg	Pos	Pos	BZD	Disease resolution
80	CNS/myocardium	ND	Pos	Pos	BZD	Died

CNS, central nervous system; Neg, negative; Pos, positive; ND, not done; BZD, benznidazole; NFT, nifurtimox.

reactivation were found to share epidemiological features (Table 1). Nine patients had confirmed reactivation of Chagas, with one of these patients experiencing two episodes of reactivation. Clinical data related to Chagas disease in the 71 patients without reactivation were complete in only 35 cases. In these 35 cases, the clinical form was indeterminate for 28 and cardiac for seven; no digestive form of infection was observed.

Patients without reactivation had a significantly higher CD4 T-cell count at diagnosis of *T. cruzi* infection (144 cells/μl vs. 30 cells/μl, Mann–Whitney *U*-test $p = 0.026$) and higher minimum CD4 T-cell count (94 cells/μl vs. 30 cells/μl, Mann–Whitney *U*-test $p = 0.032$) than patients with reactivation. Furthermore, fewer patients without reactivation had opportunistic diseases prior to or at the time of Chagas disease diagnosis than patients with reactivation, although the difference was not significant (68.6% vs. 100%, Fisher's exact test $p = 0.053$) (Table 2).

Chagas disease reactivation involved the CNS alone in seven patients, while CNS and the heart were affected simultaneously in two patients. Trypomastigotes were observed in the CSF samples of all patients ($n = 9$), while parasitemia was studied in seven patients and was positive in only one of them. Trypomastigotes were also isolated from the pericardial effusion of one patient. Chagas disease serology was negative by multiple techniques on numerous samples from two of the nine patients with reactivation. With the exception of the one patient who died before starting treatment, all patients received benznidazole; one patient was switched to nifurtimox due to toxicity. *T. cruzi* reactivation was considered the cause of death for six of the nine patients with reactivation (Table 3).

Discussion

The present study appears to represent the largest case series of HIV and *T. cruzi* co-infection published to date. Although the vector-borne route of infection was the most frequent, a significant number of these patients could have been infected with *T. cruzi* through IDU, as has been described previously (Dolcini et al., 2008; Scapellato et al., 2006). Chagas disease should be assessed in HIV-positive patients who have been engaged in IDU, regardless of their or their mothers' birthplace or place of residence.

Current HIV guidelines from the Argentinean Ministry of Health recommend assessing Chagas disease serology in all HIV-positive patients and performing a cardiac examination annually if *T. cruzi* infection is confirmed (Benetucci et al., 2013; Guías para la atención al paciente infectado con *Trypanosoma cruzi*, 2012). It is noteworthy that the median time from HIV diagnosis to the diagnosis of *T. cruzi* infection was prolonged (median 5.5 years, IQR 11.74 years).

Serological testing for Chagas disease was negative in two patients (2.5%), both with reactivation, who were diagnosed by the detection of *T. cruzi* in CSF samples. Non-reactive serological tests for *T. cruzi* infection in severely immunocompromised HIV-positive patients have been described previously (Cordova et al., 2008; Almeida et al., 2011). Therefore, the diagnosis of *T. cruzi* infection should not be rejected in immunocompromised patients with risk factors for Chagas disease, especially when there is a high suspicion that reactivation might have occurred.

There were nine patients with reactivation in this series (11.25%). When compared to patients without reactivation, they appeared more severely immunocompromised. Lower CD4 T-cell counts have already been described in HIV patients with *T. cruzi* reactivation (Almeida et al., 2011). No differences with previous reports were observed regarding the clinical presentation of *T. cruzi* reactivation (Almeida et al., 2010, 2011; Cordova et al., 2008; Simioli et al., 2017). CNS involvement was the most frequent clinical form of reactivation, presenting as meningoencephalitis, with (seven patients) or without (two patients) cerebral mass lesions seen on neuroimaging by computed tomography scan or magnetic resonance imaging, followed by cardiac involvement in two of the nine patients (these two patients also had CNS involvement). Although all patients were treated in an infectious diseases hospital with expertise in the management of HIV and Chagas disease, *T. cruzi* reactivation had a high mortality rate of 66.7%.

As a result of the retrospective design of this study, certain data were incomplete, such as family history of Chagas disease and myocardial involvement.

In conclusion, Chagas disease reactivation is an AIDS-defining illness with a high mortality rate. HIV-infected people should be studied routinely for Chagas disease. Serological assay results may

be negative in severely immunocompromised patients. Therefore, direct parasitological techniques should be performed in all patients for whom there is a clinical suspicion of *T. cruzi* reactivation, especially if they have a significant epidemiological background or IDU history. HIV-infected patients with lower CD4 counts are at higher risk of reactivation. HAART is mandatory for co-infected *T. cruzi* and HIV patients.

Funding

This work was supported by grants from the University of Buenos Aires (UBACyT ME043 to LMP).

Conflict of interest

None.

Acknowledgements

The authors would like to thank the staff at the parasitology laboratory and at the medical records depository of the Francisco J. Muñiz Infectious Diseases Hospital for the help provided. Andrés Benchetrit is the recipient of a Peruilh scholarship.

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