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Short Communication

Prevalence of HIV and associated factors among visceral leishmaniasis cases in an endemic area of Northeast Brazil

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Abstract

Introduction: Cases of visceral leishmaniasis (VL) and HIV co-infection have increased worldwide. We investigated the prevalence of HIV and associated factors among VL patients in Sergipe state, Brazil. **Methods**: We conducted a population-based study of all cases of VL and HIV reported in Sergipe from 1999 to 2015. **Results**: We studied a total of 917 patients; 41 (4.5%) co-infection cases were detected. VL-HIV co-infected patients were more likely to have weight loss, cough, treatment failure or loss to follow-up and death. **Conclusions**: The prevalence of VL-HIV co-infection was high and co-infected patients were more likely to have adverse outcomes.

Keywords: Visceral leishmaniasis. HIV. Co-infection. Brazil.

The spread of the HIV pandemic to areas where visceral leishmaniasis (VL) is endemic has raised important public health concerns, with cases of VL-HIV co-infection reported in more than 35 countries[1,2]. Although there has been a drop in global AIDS rates, largely because of the use of highly active antiretroviral therapy (HAART), the prevalence of VL-HIV co-infection has increased, especially in tropical low- and middle-income countries[1]. However, the rate of VL-HIV co-infection varies widely across areas, with poorer areas having the highest co-infection rates[1,3]. In Brazil, the AIDS prevalence ranged from 19.9/100,000 population in 2006 to 18.5/100,000 population in 2016[4], while the VL-HIV co-infection rates ranged from 0.01 to 0.07 per 100,000 population from 2001 to 2010[2]. In addition, both HIV and VL disease have high detection rates in poor areas of the North and Northeast of Brazil[2]. The clinical course of VL infection shows a wide spectrum of severity including irregular fever, swelling of the spleen and liver, and anemia, with a high fatality rate among untreated patients or those with HIV co-infection[3]. In fact, VL accelerates HIV replication and disease progression, mainly by chronic immune stimulation. In addition, the risk of treatment failures, relapses and mortality is highest in patients having VL-HIV co-infection[5,6].

We investigated the prevalence of HIV and associated factors among VL infected patients in an endemic area of Northeast Brazil.

We conducted a population-based study of all cases of VL and HIV reported in Sergipe, Northeast Brazil, from 1999 to 2015. Sergipe is one of the nine states of northeastern Brazil, with a population of 2.2 million people, according to the 2010 census[7].

The information was retrieved from the National System of Notifiable Diseases (SINAN, in Portuguese). SINAN is the national information system for all notifiable diseases in the country (http://sinan.saude.gov.br/sinan). In addition, we consulted the Mortality System (SIM, in Portuguese) of the Brazilian Ministry of Health, which records all deaths and their causes, and linked it to SINAN using the RecLink III software to check which patients had died due to VL-HIV co-infection. We excluded patients whose information on HIV testing was unknown.

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The information retrieved included demographic characteristics, clinical presentation, laboratory results, concomitant infections/diagnosis and treatment outcome. Diagnosis of VL was conducted according to the guidelines for the diagnosis of leishmaniasis in Brazil[8].

Categorical variables were described using frequencies and percentages. We calculated the detection coefficient of VL for each year using the general population numbers and the prevalence of HIV among VL cases per year. Continuous variables were analyzed using unpaired Student's *t*-tests for normally distributed variables and Mann-Whitney *U* tests for variables with skewed distributions. Chi-square test or Fisher's exact test was used to compare categorical variables. An analysis of the factors associated with adverse outcomes and deaths was performed for VL patients with and without HIV co-infection. The level of significance was set as 0.05. Data were analyzed using SPSS version 20.0 (IBM Corporation, Armonk, NY).

A total of 1,516 cases with VL were detected from 1999 to 2015. However, 599 patients had no information on HIV serology and were excluded. We, therefore, used 917 cases in the analysis and 41 (4.5%) of them had VL-HIV co-infection.

Figure 1 shows the trend of the detection coefficient of leishmaniasis per 100,000 population and the proportion of cases of VL with HIV co-infection. The highest and lowest rates of VL were observed in 2000 and 2003, with 7.54 and 1.46 cases per 100,000 population, respectively. In 2011 and 2014, the highest proportions of cases of VL co-infected with HIV were recorded.

Patients with VL-HIV co-infection were older than patients without HIV [median (IQR); 36 (27–46) vs 14 (3–34); P< 0,001]. Most of the patients were men (590, 64.3%) and they were more likely to have VL-HIV co-infection than women (P=0.04). Most of the patients lived in urban areas (588, 64.1%), but the place of residence was not associated with HIV co-infection (10/41 vs 319/876; P=0.08). There was a predominance of patients with a low educational level (543, 59.2%) and there was no difference between the proportions of VL patients with and without HIV infection (24/41 vs 519/876; P=0.09). VL-HIV co-infected patients were more likely to have weight loss (34/41 vs 637/876; P=0.008) and cough (28/41 vs 478/876; P=0.006), but not fever (36/41 vs 777/876; P=0.24), weakness (32/41 vs 685/876; P=0.21), splenomegaly (27/41 vs 685/876; P=0.63) and hepatomegaly (28/41 vs 623/876; P=0.57) (**Table 1**). Concerning the VL laboratory confirmation, all co-infected cases were diagnosed by parasitological test, and most non-co-infected cases by immunofluorescence and/or parasitological tests. All laboratory tests were carried out at the Sergipe Public Health Laboratory (LACEN/SE, in Portuguese).

Patients having VL-HIV co-infection were more likely to have an adverse outcome, such as failure of treatment, abandonment of treatment or loss to follow-up (19/41 vs 198/876; P<0.001) and death (10/41 vs 32/875; P=0.009) than HIV uninfected VL patients.

In Sergipe, the proportion of VL-HIV co-infected patients increased from 2010 to 2014 and had similar trend than other locations of Northeast Brazil[2,9], but the prevalence of co-infected cases was lower than the Brazil average (around 8%)[10] and other countries[5,11]. VL-HIV co-infection is underestimated worldwide[1,2], and it is possible that this may be the case in

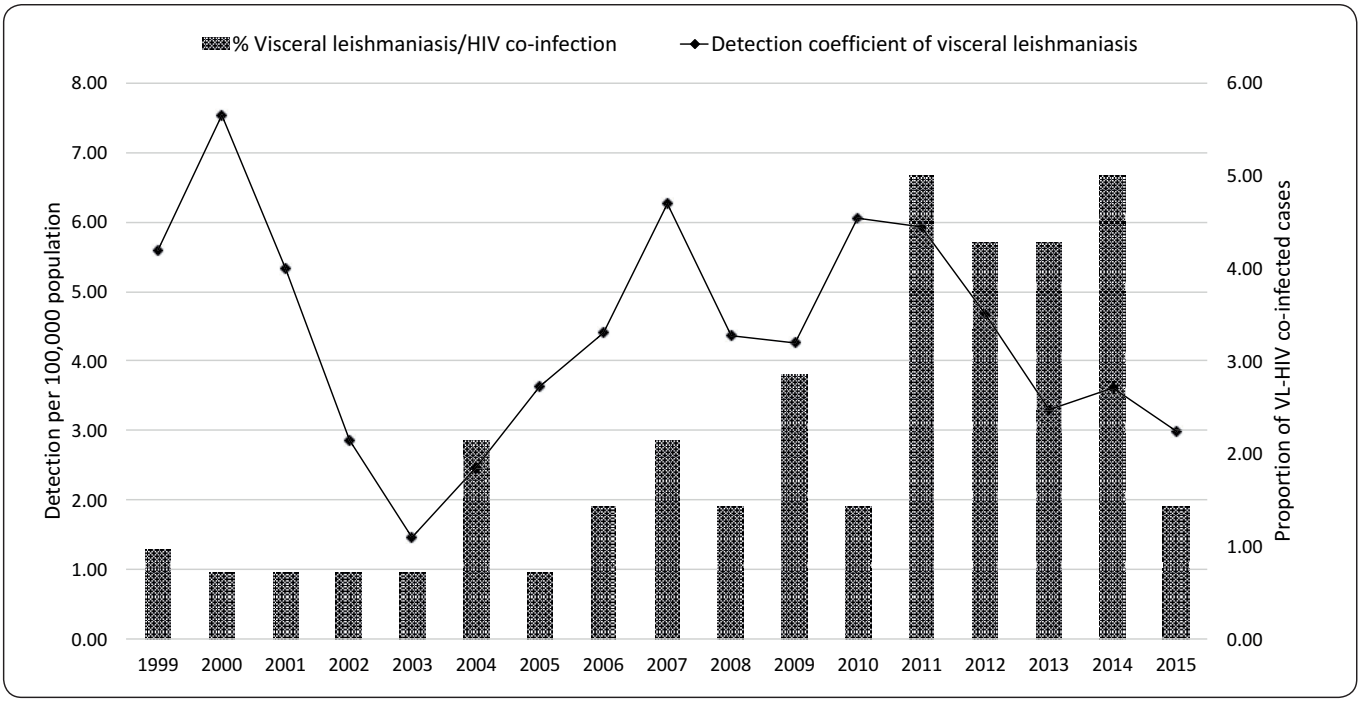

FIGURE 1: Detection coefficient of visceral leishmaniasis and proportion of HIV co-infected cases in Sergipe state, Brazil from 1999 to 2015.

TABLE 1: Demographic and clinical characteristics of patients with visceral leishmaniasis by HIV status. Sergipe State, Brazil, from 1999 to 2015

Variables	Total (N= 917) N (%)	HIV positive (n=41) n (%)	HIV negative (n=876) n (%)	P-value[a]
Age, median (IQR)	15 (3-35)	36 (27-46)	14 (3-34)	<0.001[b]
Sex				
Male	590 (64.3)	33 (78.0)	557 (63.7)	0.04
Female	327 (35.7)	8 (22.0)	319 (36.3)	
Rural area	329 (35.9)	10 (24.4)	319 (36.3)	0.08
Schooling				
0–4 years	543 (59.2)	24 (58.5)	519 (59.2)	0.09[c]
5–8 years	11 (1.2)	2 (4.8)	9 (1.0)	
Fever	813 (88.6)	36 (94.6)	777 (89.4)	0.24
Weakness	717 (78.2)	32 (75.6)	685 (78.3)	0.21
Weight loss	671 (67.3)	34 (80.5)	637 (72.8)	0.008
Cough	506 (55.2)	28 (65.9)	478 (54.7)	0.006
Splenomegaly	712 (77.6)	27 (65.9)	685 (78.2)	0.63
Hepatomegaly	651 (71.0)	28 (68.3)	623 (71.1)	0.57

[a]Chi-square test; [b]Mann-Whitney *U* test; [c]Fisher's exact test.

Sergipe, particularly since there were a high number of patients with unknown HIV serology.

The geographical overlap of leishmaniasis with major areas of HIV transmission, accentuated by the urbanization process, and the spread of HIV to rural areas has resulted in an increase in cases of VL-HIV infection[12]. This increase is epidemiologically significant because VL-HIV co-infection accelerates the clinical course of HIV infection. Thus, leishmaniasis has added importance as an opportunistic infection among patients with HIV infection who live or lived in areas considered endemic for these parasites.

The urbanization of leishmaniasis can also be explained by migration to urban centers, which can result in the construction of inadequate housing in peripheral areas near the forest where both the vector and the natural host of the disease are found. Often, this rural-to-urban migration process is carried out by people with no professional qualifications in search of better employment opportunities in urban centers, which may explain the greater occurrence of cases in people with low education level[12]. In fact, in low- and middle-income countries, poorer populations are continually exposed to a greater burden of disease, as well as to unemployment, a lack of information, malnutrition, and poor health services[9]. This makes them more susceptible to infectious diseases such as VL and HIV.

As in other studies[5,11,12,13], a higher proportion of VL-HIV co-infected men was identified in Sergipe, especially in the age group of the economically active population. This may be due to the migratory process, where men are generally those most involved in the migratory movement, particularly in seasonal migration in search of work and income[5,12]. In addition, men in this age group present the highest risk behaviors for HIV infection[5].

In this study, VL-HIV co-infected patients were more likely to have a cough. From this finding, some explanations may be offered. Cough is a symptom associated with the onset of leishmaniasis infection; however, it was not possible to establish it from the available information. Other possible explanations for the association between cough and VL-HIV co-infection would be the presence of an opportunistic lung infection, such as tuberculosis, mycosis and/or pneumonia due to *Pneumocystis jiroveci*[5,8]. Unfortunately, the lack of this information in the SINAN database made our ability to verify this relationship difficult.

In the present study, VL-HIV co-infected patients were less likely to present typical symptoms of VL, such as weakness, fever, splenomegaly and hepatomegaly than patients uninfected with HIV. This fact has also been demonstrated by other studies[3,5,14]. It is thought that the parasitic infection found concurrently with HIV induces chronic immune activation, and therefore an increased HIV load and accelerated progression towards AIDS. In addition, immunological disturbances caused by HIV are particularly favorable for the uncontrolled multiplication of the parasite. Due to this, in individuals with non-functional T-lymphocytes, such as in HIV-infected patients, leishmaniasis becomes increasingly problematic[6].

In this respect, the immunosuppression caused by HIV infection accelerates the course of VL disease, since the low immune-cellular response makes the patient susceptible to the process of infection by *Leishmania*[5,6]. This may result in the higher predisposition of these patients to adverse outcomes such as failure of treatment, abandonment of treatment, loss to follow-up and even death. In this study, VL-HIV co-infected patients were threefold more likely to exhibit adverse events or death. These data are consistent with those reported in other studies[5,11].

Because of the demographic expansion of VL, greater access to diagnostic techniques, as well as greater sensitivity of professionals in the identification of its signs and symptoms are required. In Brazil, the most common serological test for the diagnosis of VL is the indirect immunofluorescence reaction because of its availability in the public health care network, the Unified Health System (SUS, in Portuguese). On the other hand, the diagnosis of VL in HIV patients is a challenge, since

serological tests have a lower sensitivity and, although patients have a higher parasitic load, bone marrow aspirates can be paucicellular and have few parasites. These facts demand the development of diagnostic and therapeutic protocols more adequate to the management of this co-infection[15].

In the same way that VL has undergone the process of urbanization, HIV has spread from cities into rural areas and the interior of the country, making contact between these two diseases inevitable. As VL is an opportunistic infection, in endemic areas a differential diagnosis should be made of every individual with any immunosuppressed condition, not only HIV.

Our study has some limitations which mean its findings should be interpreted with a degree of caution. As the data were obtained from information systems, it represents information on patients who sought treatment, and consequently, there may be a number of cases in the community not recorded by the health services and it was not possible to describe details of how the laboratory tests were performed. In addition, there was a high proportion of VL patients with unknown serology for HIV, which may modify the real prevalence of co-infection. However, major efforts have been made to minimize any introduction of bias. To obtain the largest amount of information about each patient, including their HIV statuses and disease outcomes, record linkage was performed between the SINAN database (both HIV and VL) and mortality system. Furthermore, our findings and their interpretation are supported by 16-years of information on VL and HIV collected in Sergipe.

In conclusion, the results showed that there is a high proportion of cases of VL co-infection with HIV in Sergipe, an endemic area for both diseases. Although the profile of VL-HIV co-infected patients is not different from those with classic VL, the overlap of these infections impairs the clinical evolution of the patients. Therefore, we strongly recommend that HIV infected patients are screened for VL, and that VL patients are tested for HIV. This measure can help in the early diagnosis of this co-infection, the adequate management of the patients, and consequently reduce adverse outcomes, including death.

Ethical considerations

This study was approved by the Human Research Ethics Committee of the Federal University of Sergipe (CAAE: 46317115.0.0000.5546). The investigation was conducted according to the tenets of the Declaration of Helsinki and the Brazilian Ethics Declaration 466/2012.

Conflict of Interest: The authors declare that there is no conflict of interest.

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