Major Article

Revista da Sociedade Brasileira de Medicina Tropical 47(1):38-46, Jan-Feb, 2014
http://dx.doi.org/10.1590/0037-8682-0180-2013

HIV/AIDS-related visceral leishmaniasis: a clinical and epidemiological description of visceral leishmaniasis in northern Brazil

Leonardo Cordenonzi Pedroso de Albuquerque[1], *Iatan Rezende Mendonça*[1], *Polyana Nascimento Cardoso*[1], *Leonardo Rodrigo Baldaçara*[1], *Myrlena Regina Machado Mescouto Borges*[1], *Joelma da Costa Borges*[1] *and Maria Cristina da Silva Pranchevicius*[1]

[1]. Curso de Medicina, Universidade Federal do Tocantins, Palmas, TO.

ABSTRACT

Introduction: This study aimed to describe the main features of visceral leishmaniasis (VL), both related to and independent of human immunodeficiency virus (HIV) infection, in patients who were registered in Tocantins, Brazil. **Methods:** Data from 1,779 new patients with VL, 33 of whom were also infected with HIV, were reviewed. **Results:** The incidence of VL/HIV coinfection increased from 0.32/100,000 inhabitants in 2007 to 1.08/100,000 inhabitants in 2010. VL occurred predominantly in children aged 10 years or younger, while VL/HIV was more common in patients aged between 18 and 50 years. There were more male patients in the VL/HIV group than in the VL group. Relapse rates were also considerably higher in the VL/HIV (9.1%) group than in the VL group (1.5%). Despite a similar clinical presentation, VL/HIV patients exhibited a higher proportion (24.2%) of concomitant infectious diseases and jaundice. Pentavalent antimonials were used for the initial treatment of VL and VL/HIV infections. However, amphotericin B deoxycholate and liposomal amphotericin B were also widely used in the treatment of VL/HIV coinfection. The mortality rate was higher in the VL/HIV coinfection group (19.4%) than in the VL group (5.4%). Furthermore, the mortality rate due to other causes was significantly higher in the VL/HIV group (12.9%) than in the VL group (0.7%). **Conclusions:** The study showed that the incidence, clinical characteristics and outcomes among the VL and VL/HIV patients in this state are similar to those from other endemic regions, indicating that both infections are emerging with increasing frequency in Brazil.

Keywords: Visceral leishmaniasis. Epidemiology. Public health. HIV-related visceral leishmaniasis. Urbanization.

INTRODUCTION

Visceral leishmaniasis (VL) is a vector-borne parasitic disease caused by several Leishmania spp., and if untreated, death occurs in 90% of cases[1]. VL is endemic to 70 countries[2], and approximately 90% of the VL cases documented on the American continent occur in Brazil[3]. It is considered an underreported disease, and some studies have demonstrated a high frequency of relapses during follow-up. VL symptoms include fever, weight loss, hepatosplenomegaly, lymphadenopathy, pancytopenia and hypergammaglobulinemia[4]. Some cases of VL present atypically, as they involve the lungs, pleura, oral mucosa, larynx, esophagus, stomach, small intestine, skin and bone marrow[5]. There is regional variation in the response to antileishmanial drugs, and recommendations for treatments vary by region[6] as a result.

Since 1980, more than 608,230 cases of AIDS have been registered in Brazil, with an incidence of 17.9/100,000 inhabitants in 2010[7], and unlike VL, the propagation of HIV transmission to regions with lower urbanization rates and to small and medium-sized cities has been observed[2]. HIV infections increase the risk of developing VL by 100- to 2,320-fold in endemic areas, reduce the likelihood of a therapeutic response and greatly increase the probability of relapse[2]. However, VL promotes the clinical progression of HIV and the development of AIDS-defining conditions[8].

In general, patients with coinfections show very similar clinical features to classical VL[9], although the usual clinical features associated with VL (prolonged fever, spleen and liver enlargement, wasting and pancytopenia) are not always present, and atypical presentations occur more often in immunocompromised patients. Furthermore, a clinical diagnosis can also be more difficult to establish due to other concomitant opportunistic diseases[10].

Considering that the endemicity of VL in many Brazilian regions is high and that some reports have addressed the clinical features, drug response and outcomes of HIV-related VL[9,11-13],

***Address to*:** Dr. Leonardo Cordenonzi Pedroso de Albuquerque. Av. NS 15 s/n (109 Norte), 77001-090 Palmas, TO, Brasil.
Phone: 55 63 3232-8158; 55 63 8404-1513
e-mail: leonardo.cordenonzi@gmail.com
Received 8 September 2013
Accepted 23 January 2014

in this study, we aimed to report the results of a comparative study (based on data from the Information System for Notifiable Diseases) on the epidemiology, clinical presentation, drugs used and outcome of both VL and VL/HIV patients in Tocantins, the newest Brazilian state, between 2007 and 2010.

METHODS

Study design and data collection

A descriptive study of confirmed cases with VL and VL/HIV infections was conducted between 2007 and 2010 in Tocantins, Brazil. Tocantins is the newest state of the country (created in 1988) and is located in the central part of Northern Brazil. The 2010 census estimated that the state had a population of 1,383,445 inhabitants, distributed over 277,720.520km^2, and a population density of 4.98 inhabitants per square kilometer; moreover, it comprises 139 municipalities.

The study was based on the data from the Information System for Notifiable Diseases *(Sistema de Informação de Agravos de Notificação* – SINAN). The patients were divided into two groups: the VL group, consisting of patients without HIV infection, and the VL/HIV coinfection group, consisting of patients with VL and HIV (with and without AIDS). An epidemiological description was produced from both groups. However, reports in which the "HIV coinfection", "drug initially administered" and "developments in the case" fields were left blank or incomplete were excluded from both groups. In this database, the diagnosis of VL was made by the presence of symptoms, a blood test for confirmation (immunological methods) and a parasitological diagnosis.

Inclusion and exclusion criteria

The study included patients diagnosed with VL due to the presence of amastigotes in bone marrow smears or indirect immunofluorescence, which were considered positive with results higher than 1:80, and clinical manifestations that included hepatomegaly or splenomegaly, anemia and thrombocytopenia. The study excluded patients undergoing prior treatment with antileishmanial drugs.

The "LV Investigation Form" included an "HIV coinfection" field. Cases were selected for the study using this information. Patients with a confirmed diagnosis of VL and positive HIV serum tests were included, while those who left the "HIV coinfection" field blank or marked it as negative were excluded. Co-infected patients were diagnosed with HIV by ELISA, and the result was confirmed by either indirect immunofluorescence (IIF) or western blot analysis.

Associated causes were considered for patients who, regardless of the efficacy of the treatment, eventually died from cytopenia or thrombocytopenia, and data were discarded in cases where the patient underwent an inadequate treatment course (e.g., someone who should have been treated with amphotericin B because they had cardiovascular involvement but was treated with Glucantime instead), suffered adverse reactions to the medication, such as renal or hepatic insufficiency, or developed associated infections such as pneumonia or severe sepsis**.**

Subjects from 0-65 years of age of either sex were included in the study. Females who were pregnant or lactating were not excluded. Exclusion criteria included forms with insufficient information regarding the initial drug used in the treatment, HIV coinfection status and the progression of the case.

Data analysis

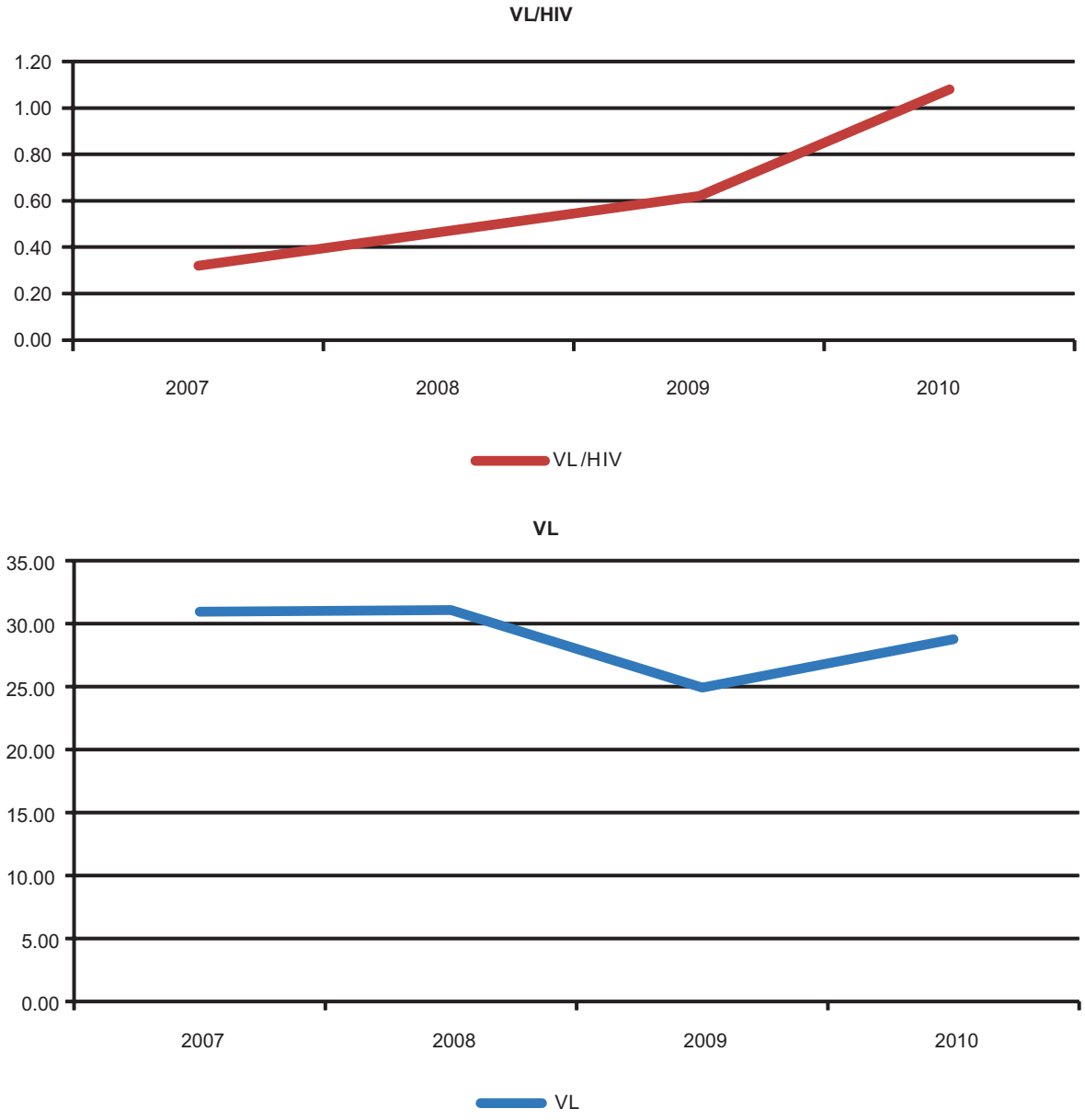
Data were codified and analyzed using the Statistical Package for the Social Sciences (SPSS for Windows, version 17.0). The variables used for comparative analyses were gender, age, scholarship, clinical manifestations, initial drug use and development of the disease. All variables are presented as numbers and proportions, and age and scholarship are also presented as means and standard deviations (SDs). The indicators were considered to be the following: the lethality of the VL and VL/HIV infections; the mortality rate directly related to VL and linked to other causes in both groups; the relapse rate in each group; and the annual rate of VL/HIV coinfection. Only new cases were used for the analysis, except for the analysis of relapses. The chi-squared test was used to calculate the difference in the nominal variables between the two groups. The differences in the means between the two groups due to age and scholarship were calculated using Student's t-test. A significance level (α) of 0.05 was considered statistically relevant. The variables with significant results were inserted in the stepwise multivariate model to determine the odds ratios (ORs) with 95% confidence intervals (CIs) for the association between the HIV/VL coinfection. We used HIV positivity as a dependent variable, each factor as an independent variable and age, gender and scholarship as covariates. Alpha was set at $p < 0.05$.

Ethical considerations

The study was approved by the Committee of Ethics in Human Research (Comitê de Ética em Pesquisas com Seres Humanos) of the Federal University of Tocantins (Universidade Federal do Tocantins – UFT) (number 030/2009) and was conducted in accordance with the ethical guidelines of the Declaration of Helsinki (created in 1964 and revised in 2002). Permission to conduct the study was obtained from the Health Department of the State of Tocantins (Secretaria da Saúde do Estado do Tocantins – SESAU).

RESULTS

According to SINAN, 1,779 VL patients were registered in Tocantins between 2007 and 2010. Of those, 33 (2.1%) were coinfected with HIV. There were no data for VL/HIV coinfection status, the initial drug used or developments in the case in 210 reports; thus, these patients were excluded from the comparative analysis. During the same period, there were 23 relapses in the VL group and 3 relapses in the VL/HIV group. Among these 26 cases, five were excluded due to the lack of data regarding the initial drug used for treatment and developments in the case. **Figure 1** depicts the incidence rate per year for LV/HIV and LV-only cases. The incidence of LV/HIV coinfections rose from 0.32/100,000 inhabitants in 2007, to 0.47/100,000



		VL/HIV		VL	
Year	Population	N	Incidence*	N	Incidence*
2007	1,243,627	4	0.32	385	30.96
2008	1,280,509	5	0.47	398	31.08
2009	1,292,051	7	0.62	322	24.92
2010	1,383,453	14	1.08	398	28.88

Year	VL/HIV	VL
2007	0.32	30.96
2008	0.47	31.08
2009	0.62	24.92
2010	1.08	28.77

FIGURE 1 – Incidence of VL/HIV-confirmed cases per 100,000 habitants per year in Tocantins, Brazil, from 2007 to 2010. VL/HIV: visceral leishmaniasis and human immunodeficiency virus coinfection group; VL: visceral leishmaniasis single infection group; *Incidence: number of new cases per 100,000 habitants per year.

inhabitants in 2008, to 0.62/100,000 inhabitants in 2009 and, finally, to 1.08/100,000 inhabitants in 2010. The incidence of LV alone decreased from 30.96/100,000 inhabitants in 2007, to 31.08/100,000 inhabitants in 2008, to 24.92/100,000 inhabitants in 2009 and, finally, to 28.88/100,000 inhabitants in 2010.

Details regarding the demographic characteristics of the VL and VL/HIV groups are provided in **Table 1.** The mean age of the VL/HIV group (27.9±15.1) was higher than that of the VL group (18.0±14.9); t=4.134, p<0.01. The more frequent age range for VL/HIV patients was 18-50 years, which is considered the economically active population in Brazil. In the VL group, there were more patients aged 10 years and younger (χ^2=35.873, p<0.01). The mean scholarship was higher in the VL group (6.9±3.7) than in the VL/HIV group (5.2±3.4), but the proportion between study stages was not significant (χ^2=10.461, p=0.06). The proportion of male patients was higher in the LV/HIV group (78.8%) than in the VL group (57.5%); χ^2=5.878, p=0.01. The relapse rate was also considerably higher in the VL/HIV group (9.1%) than in the VL group (1.5%); χ^2=11.328, p=0.01.

Despite the similar clinical presentation among the VL patients with or without HIV coinfection **(Table 2**), a higher proportion (24.2%) of patients in the VL/HIV group had concomitant infectious diseases (χ^2=6.023, p=0.02) and jaundice (χ^2=4.599, p=0.04).

The drugs most frequently used in the treatment of patients in both groups are shown in **Table 3**. The drug of choice for the initial treatment of VL (84.2%) and VL/HIV coinfection (62.5%) was pentavalent antimonials (χ^2=19.935; p<0.01). However, amphotericin B deoxycholate and liposomal amphotericin B were also widely used for the treatment of VL/HIV.

The mortality rate **(Table 3)** was higher in the VL/HIV coinfection group (19.4%) than in the VL group (5.4%). The VL-related mortality rate was 4.7%, and the VL/HIV-related mortality rate was 6.5%. Furthermore, the mortality attributed to other causes was significantly higher in the VL/HIV group (12.9%) than in the VL group (0.7%); χ^2=47.973, p<0.01.

For the multiple logistic regression analysis, we selected HIV positivity as a dependent variable and the following factors as independent variables: gender, age, scholarship, concomitant infections, jaundice, drugs, outcome and the occurrence of relapse. Gender, scholarship and age were selected as covariates. It was observed that being HIV positive was a risk factor for concomitant infections (OR=0.35, CI=1.14-0.85, p=0.02) and relapse (OR=0.23, CI=0.05-1.05, p=0.05). For more details, see **Table 4**.

TABLE 1 - Demographic characteristics of patients with visceral leishmaniasis and visceral leishmaniasis associated with HIV in Tocantins, Brazil, from 2007 to 2010.

Demographic characteristics	VL/HIV patients		VL patients		χ^2/t	p
Age in years (Mean, SD)[a]	27.9±15.1		18.0±14.9		1.456	<0.01
0-10	8	24.2	900	58.6	35.873	<0.01
11-17	0	0.0	136	8.9		
18-50	24	72.7	402	26.2		
>50	1	3.0	98	6.4		
Years of scholarship (Mean, SD)[b]	5.2±33.4	6.9±3.7	4,736	0.02		
none	1	3.0	24	1.6	10.461	0.06
primary school	12	36.4	418	27.2		
secondary school	7	21.2	189	12.3		
university	0	0.0	16	1.0		
unknown	13	39.4	902	57.5		
Gender[c]						
male	26	78.8	887	57.7	5.878	0.01
female	7	21.2	649	42.3		
Case type						
new case	30	90.9	1,503	98.5	11.328	0.01
relapse	3	9.1	23	1.5		

VL/HIV: visceral leishmaniasis and human immunodeficiency virus coinfection group; VL: visceral leishmaniasis single infection group. χ^2: chi-square. t: T-student test. [a]Age is presented as the mean and standard deviation (SD) in the first line and divided into groups by number and proportion below. [b]Scholarship is presented as the mean and SD in the first line and divided into groups by number and proportion below. [c]Gender is presented as a number and proportion.

TABLE 2 - Clinical characteristics of visceral leishmaniasis patients with or without HIV coinfection.

Characteristics	VL/HIV patients		VL patients		χ^2	p
Fever	31	93.9	1,488	96.9	0.902	0.34
Weakness	28	84.8	1,354	88.2	0.336	0.357
Weight loss	25	75.8	1,119	72.9	0.138	0.44
Mucocutaneous pallor	22	66.7	1,117	72.7	0.636	0.27
Splenomegaly	20	60.6	1,082	70.4	0.227	0.38
Hepatomegaly	17	51.5	969	63.1	0.952	0.21
Cough	17	51.5	830	54.0	0.085	0.45
Concomitant infectious diseases	8	24.2	175	11.4	6.023	0.02
Edema	5	15.2	214	13.9	0.072	0.47
Jaundice	9	27.3	215	14.0	4.599	0.04
Hemorrhage	0	0.0	50	3.3	1.079	0.35

VL/HIV: visceral leishmaniasis and human immunodeficiency virus coinfection group; VL: visceral leishmaniasis single infection group; χ^2: chi-square.

TABLE 3 - Drugs used in the treatment of patients with visceral leishmaniasis and patients with visceral leishmaniasis associated with HIV and their clinical outcomes in Tocantins, Brazil from 2007 to 2010.

Characteristics	VL/HIV patients		VL patients		χ^2	p
Drugs						
pentavalent antimony	20	62.5	1,272	84.2	19.935	<0.01
amphotericin B deoxycholate	7	21.9	154	10.2		
pentamidine	0	0.0	4	0.3		
liposomal amphotericin B	3	9.4	22	1.5		
other	0	0.0	18	1.2		
not used	2	6.2	40	2.6		
Outcome						
cured	25	80.0	1,349	89.8	47.973	<0.01
abandoned	0	0.0	7	0.5		
deaths from VL	2	6.5	71	4.7		
deaths from other causes	4	12.9	11	0.7		
transferred to another state	0	0.0	65	4.2		

VL/HIV: visceral leishmaniasis and HIV coinfection group; VL: visceral leishmaniasis single infection group. χ^2: chi-square.

TABLE 4 – Results from the multiple logistic regression analysis.

	Uncontrolled			Controlled		
Variable	OR	CI (95%)	p	OR	CI (95%)	p
Gender Male[a]	0.37	0.16 – 0.85	0.02	0.44	0.19 – 1.02	0.06
Age[b]						
0-10	1.14	0.14 – 0.92	0.90	0.70	0.08 – 6.00	0.25
11-17	-	-	-	-	-	-
18-50	0.17	0.02 – 1.28	0.08	5.66	0.76 – 42.50	0.09
>50	-	-	-	-	-	-
Scholarship[c]						
none	1.41	0.14 – 14.30	0.77	2.14	0.20 – 22.56	0.53
primary school	2.05	0.56 – 7.50	0.28	2.10	0.55 – 0.77	0.28
secondary school	1.59	0.40 – 6.36	0.51	1.43	0.35 – 5.83	0.62
university	-	-	-	-	-	-
unknown	4.92	1.32 – 18.50	0.02	2.15	0.47 – 9.31	0.31
Infectious[d]	0.37	0.16 – 0.84	0.02	0.35	0.14-0.85	0.02
Jaundice[d]	0.44	0.20 – 0.95	0.04	0.53	0.24 – 1.16	0.11
Drugs[e]						
pentavalent antimony	3.18	0.72 – 14.07	0.13	2.58	0.56 – 11.80	0.22
amphotericin B deoxycholate	1.10	0.22 – 5.50	0.91	0.79	0.15 – 4.10	0.78
pentamidine	-	-	-	-	-	-
liposomal amphotericin B	0.38	0.06 – 2.36	0.29	0.37	0.05 – 2.52	0.31
other	-	-	-	-	-	-
not used	-	-	-	-	-	-
Outcome[e]						
cured	3.48	-	0.99	-	-	-
abandoned	-	-	0.99	1.36	1.36 – 1.40	0.99
deaths from VL	2.29	-	0.98	-	-	0.99
deaths from other causes	1.77	-	0.99	-	-	0.96
transferred to another state	-	-	0.97	-	-	-
recidive[d]	6.53	1.86 – 22.95	<0.01	0.231	0.050-1.060	0.05

OR: odds ratio; CI: confidence interval. [a]Controlled by age and scholarship; [b]Controlled by gender and scholarship; [c]Controlled by gender and age; [d]Controlled by gender, age and scholarship; [e]Controlled by gender, age, scholarship and case type; -: Parameter set to zero or there were not enough parameters to be calculated. Result close to zero.

DISCUSSION

The transmission of VL has gradually spread to various Brazilian regions. It is believed that rural-urban migration, agroindustrial and man-made projects such as dams, irrigation systems and wells as well as deforestation contribute to the dissemination of this disease[14]. In Tocantins, located in northern Brazil, new urban VL cases have been reported since 2000[11]. This suggests that environmental changes such as the destruction of the cerrado vegetation, the construction of new cities and the rapid and intense migration of rural populations to urban peripheries could have played a role in the transmission of VL. HIV/AIDS is also endemic in Brazil[15], and an increase in the number of cases of VL/HIV coinfections has been observed since the early 1990s. The number of cases is projected to increase due to the geographical overlap of the two infections as a result of the urbanization of leishmaniasis and the

internalization of HIV infection. In VL-endemic regions, HIV infection increases the risk of developing clinically evident leishmaniasis. Leishmaniasis is endemic to Tocantins and is in the process of expanding both geographically and in magnitude. However, information on coinfection by VL and HIV in the northern region of Brazil is still scarce. Thus, our objective was to describe the main epidemiological and clinical features of VL/HIV-infected and VL-infected patients in Tocantins.

During the four years of this study (2007-2010), the significant number of VL cases when compared to the number of VL/HIV cases could have been overestimated because no HIV test was performed preceding the completion of the "LV Investigation Form", which resulted in only 33 patients completing the "HIV infection" field.

Additionally, of the total number of reports for VL infection, 210 records had incomplete "HIV infection" fields. This reinforces the importance of filling out the form in full, as the information contained in it is extremely important for the planning and execution of surveillance and disease control.

The highest prevalence rate (47.7%) of VL infection in children ≤ 5 years old was reported in other region of Brazil[16,17], with similarly high prevalence rates reported in other countries[18-20], and it could reflect increased exposure to sandflies[20]. In our study, there were two cases of VL in pregnant patients who transmitted the disease congenitally to their infants[21]. The diagnosis of VL among pregnant women was parasitological due to the presence of *Leishmania* in the bone marrow aspirate. PCR amplification of parasite kDNA from newborn bone marrow samples suggested that the leishmaniasis was transmitted vertically because the newborns developed signs of the disease shortly after birth[21].

VL/HIV coinfections were most commonly observed in the age range of 18-50 years (72.7%), and the proportion of male patients was higher in the LV/HIV group (78.8%) than in the VL group (57.5%). The same scenario was found in the central-west region of Brazil between 2000 and 2006[12], the southeast region between 2000 and 2005[8] and the northeast region between 2001 and 2005[22]. This shows that cases of coinfection have spread throughout Brazil.

Although it has been proposed that VL/HIV coinfections show different clinical manifestations – a lack of visceromegaly or fever, for instance[23, 24] – our study is in accordance with other reports[25, 7] that show that the initial clinical presentation of VL/HIV patients is similar to that of HIV-negative individuals, with fever, splenomegaly and hepatomegaly associated with weakness, weight loss, mucocutaneous pallor, airway infections and/or diarrhea, edema and jaundice. The only difference in symptoms between the two groups was an increased prevalence of infection in HIV-infected patients (25.9% versus 10.7%). However, our study confirms the findings of previous reports showing that HIV-induced immunosuppression impairs the body's protective mechanisms against intracellular parasites, such as *Leishmania* species. Additionally, VL could induce intracellular HIV replication, thus speeding up the clinical course of the HIV infection[26-28]. Consequently, it also demonstrates that VL has emerged as a serious opportunistic infection in HIV-infected patients[29].

The treatment for VL in HIV-infected patients is limited to pentavalent antimonials (sodium stibogluconate (SSG) and meglumine antimoniate) and amphotericin B (AmB, typically in the liposomal formulation AmBisome, Gilead Sciences Inc., Astellas Pharma, North Deerfield, IL)[25]. Although the use of pentavalent antimonials is no longer recommended in HIV-infected patients by most experts in the field, due to their unacceptable toxicity and high rates of treatment failure and mortality[30], we used pentavalent antimonials as the first choice of treatment for VL and VL/HIV infections in our study. In 2005, the World Health Organization stressed the need for multicenter trials of first-line treatment and secondary prophylaxis for patients with VL infected with HIV and the need to include treatment regimens with liposomal amphotericin B[31]. Nevertheless, the number of patients who received amphotericin B deoxycholate and liposomal amphotericin B was much higher in the VL/HIV group (31.3%) than in the VL group (11.7%). This indicates that the WHO recommendations for liposomal AmB as the best treatment choice for coinfected patients because of its success rate in the HIV-positive population[2] were followed.

In 2011, the Brazilian Health Ministry (Ministério da Saúde do Brasil) published a new guideline[32] recommending the use of AmB deoxycholate as the first-choice drug in the treatment of VL/HIV coinfection. However, some studies have demonstrated a high frequency of relapses during follow-up[2,33], further supporting the need for combined therapies.

Furthermore, a VL/HIV-coinfected patient's severely immunocompromised state could hinder the destruction of the parasite and contribute to an increased predisposition to frequent relapses[34]. This tendency toward relapses was observed in our studies (data not shown).

The immune deficiency caused by HIV facilitates the multiplication of the *Leishmania* parasite and further reduces the rates of cure through conventional treatments[2,7,35,36]. The lethality among the VL/HIV patients in this study was substantially higher than that in the VL patients (data not shown). Generally, infectious complications and bleeding are the main risk factors for death in children with LV. Furthermore, the involvement of the liver in children, which is generally not pronounced and is reversible after treatment, could be quite severe, causing a fatal outcome[37]. Lethality in the VL/HIV group prevailed in individuals older than 40 years, confirming the observation that adults older than 45 years have a higher risk of dying, possibly due to immune decline at this age. The progression of the disease symptoms with a consequent delay in diagnosis and treatment of patients with VL or VL/HIV has been identified as a risk factor for death[38]. Adverse reactions, including renal and liver failure, cardiac abnormalities and pancreatitis, and hepatitis drugs were also death-precipitating factors. The efficacy of the therapeutic approach could not be ascertained, and our results are in accordance with other reports[7,34,37]. Considering that other opportunistic diseases frequently develop during VL episodes in VL/HIV patients[33], there was a highly accentuated death rate due to other causes in the VL/HIV group (12.9%) in comparison to the VL group (0.7%). It has been suggested that knowledge

regarding the laboratory and clinical profiles of patients and their association with death from VL could assist in clinical management and reduce lethality[39-41]. Therefore, since 2011, the Brazilian Health Ministry (*Ministério da Saúde do Brasil*) has recommended the differential diagnosis of opportunistic infections and the use of serological tests for HIV in patients with VL in VL-endemic regions such as Tocantins.

There are some limitations to our study. Although the sample size was large, the number of HIV patients was small, which restricted our multivariate analysis. Because it was only possible to analyze the variables that were included on the notification form (data from the Information System for Notifiable Diseases), other associations could not be ascertained. However, this is the first comparative study on the epidemiologic and clinical features of confirmed cases of VL and VL/HIV infections in Tocantins, Brazil. Thus, our results contribute to increasing our knowledge of VL and VL/HIV infections, which can be used to implement strategies for the prevention and control of these diseases.

In conclusion, the VL and VL/HIV infections that occur in northern Brazil are comparable to those reported by other studies performed in other endemic areas throughout the world, attesting the fact that VL and VL/HIV infections have been emerging with increased frequency in Brazil. Therefore, there is a distinct need to develop and implement methods to identify new forms of treatment and to improve the diagnostic accuracy and therapeutic management of health services that function to control these diseases.

ACKNOWLEDGMENTS

The authors wish to thank the *Secretaria de Sáude do Estado do Tocantins* (Health Department of the State of Tocantins), SESAU–TO, for facilitating access to the data and for the valuable assistance provided in verifying the consistency of the SINAN databases.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

1. Maia-Elkhoury ANS, Alves WA, Sousa-Gomes ML, Sena JM, Luna EA. Visceral leishmaniasis in Brazil: Trends and Challenges. Cad Saude Publica 2008; 24:2941-2947.
2. Alvar J, Aparicio P, Aseffa A, DenBoer M, Cañavate C, Dedet JP, et al. The relationship between leishmaniasis and AIDS: the second 10 years. Clin Micro Biol Rev 2008; 21:334-359.
3. Harhay MO, Olliaro PL, Costa DC, Costa CHN. Urban parasitology: visceral leishmaniasis in Brazil. Trends Parasitol 2011; 27:403-409.
4. Mandell GL, Bennett JE, Dolin R. Mandell, Douglas and Bennett's principles and practice of infectious diseases, 6th Ed. Philadelphia (PA): Elsevier Churchill Livingstone; 2005 p. 2428-2442.
5. Sundar S, Chakravarty J. Liposomal amphotericin B and leishmaniasis: dose and response. J Glob Infect Dis 2010; 2:159-166.
6. Ministério da Saúde (MS). Secretaria de Vigilância em Saúde, Departamento de DST, AIDS e hepatites virais. Boletim Epidemiológico - AIDS e DST. Brasília: MS; 2012.
7. Cota GF, Sousa MR, Rabello A. Predictors of visceral leishmaniasis relapse in HIV infected patients: a systematic review. PLoS One 2011; e1153.
8. Hurissa Z, Gebre-Silassie S, Hailu W, Tefera T, Lalloo DG, Cuevas LE, et al. Clinical characteristics and treatment outcome of patients with visceral leishmaniasis and HIV coinfection in northwest Ethiopia. Trop Med Int Health 2010; 15:848-855.
9. Souza GF, Biscione F, Greco DB, Rabello A. Slow clinical improvement after treatment initiation in leishmania/HIV coinfected patients. Rev Soc Bras Med Trop 2012; 45:147-150.
10. Orsini M, Canela JR, Disch J, Maciel F, Greco D, Toledo Jr A, et al. High frequency of asymptomatic Leishmania spp. infection among HIV-infected patients living in endemic areas for visceral leishmaniasis in Brazil. Trans R Soc Trop Med Hyg 2012; 106:283-288.
11. Sousa-Gomes ML, Maia-Elkhoury ANS, Pelissari DM, Lima Jr FEF, Sena JM, Cechinel MP. Coinfecção Leishmania-HIV no Brasil: aspectos epidemiológicos, clínicos e laboratoriais. Epidemiol Serv Saude 2011; 20:519-526.
12. Nascimento ET, Moura MLN, Queiroz JW, Barroso AW, Araujo AF, Rego EF, et al. The Emergence of concurrent HIV-1/AIDS and visceral leishmaniasis in Northeast Brazil. Trans R Soc Trop Med Hyg 2011; 105:298-300.
13. Alexandrino-de-Oliveira P, Santos-Oliveira JR, Dorval MEC, Costa FCB, Pereira GROL, Cunha RV, et al. HIV/AIDS-associated visceral leishmaniasis in patients from an endemic area in Central-West Brazil. Mem Inst Oswaldo Cruz 2010; 105:692-697.
14. World Health Organization (WHO). The Leishmaniasis and leishmania/HIV Coinfection. WHO: 2000; [Cited 2013 September 03] Available at: apps.who.int/inf-fs/en/fact116.html/.
15. Daher EF, Fonseca PP, Gerhard ES, Leitão TM, Silva Júnior GB. Clinical and epidemiological features of visceral leishmaniasis and HIV Coinfection in fifteen patients from Brazil. J Parasitol 2009; 95:652-655.
16. Goés MAO, Melo CM, Jeraldo VLS. Série Temporal da leishmaniose visceral em Aracaju, Estado de Sergipe, Brasil (1999 a 2008): aspectos humanos e caninos. Rev Bras Epidemiol 2012; 15:298-307.
17. Botelho ACA, Natal D. Primeira descrição epidemiológica da leishmaniose visceral em Campo Grande, Estado do Mato Grosso do Sul. Rev Soc Bras Med Trop 2009; 42:503-508.
18. Sarkari B, Hatam G, Ghatee MA. Epidemiological features of visceral leishmaniasis in Fars Province, Southern Iran. Iranian J Publ Health 2012; 41:94-99.
19. Deribe K, Meribo K, Gebre T, Hailu A, Ali A, AseffaA, et al. The Burden of Neglected Tropical Diseases in Ethiopia, and opportunities for integrated control and elimination. Parasit Vectors 2012; 5:240.
20. Piscopo TV, Azzopardi CM. Leishmaniasis. Postgrad Med J 2007; 82: 649-657.
21. Mescouto-Borges MRM, Maués E, Costa DL, Pranchevicius MC, Romero GS. Congenitally transmitted visceral leishmaniasis: report of two Brazilian human cases. Braz J Infect Dis 2013; 17:263-266.
22. Maia-Elkhoury ANS, Lucena F, Sousa-Gomes ML, Alves WA, Paz L. Co-infecção da leishmaniose visceral e AIDS no Brasil. Rev Soc Bras Med Trop 2007; 40 (suppl I):124.
23. Fernandez Guerrero ML, Aguado JM, Buzon L, Barros C, Montalban C, Martin T, et al. Visceral leishmaniasis in immunocompromised Hosts. Am J Med 1987; 83:1098-1102.
24. Badaro R, Carvalho EM, Rocha H, Queiroz AC, Jones TC. Leishmania donovani: An opportunistic microbe associated with progressive disease in three immunocompromised patients. Lancet 1986; 1:647-648.
25. Jarvis JN, Lockwood DN. Clinical Aspects of Visceral Leishmaniasis in HIV infection. Curr Opin Infect Dis 2013; 26:1-9.
26. La Rosa R, Pineda JA, Delgado J, Macías J, Morillas F, Mira JA, et al. Incidence of and risk factors for symptomatic visceral leishmaniasis among human immunodeficiency virus type 1-infected patients from

Spain in the era of highly active antiretroviral therapy. J Clin Micro Biol 2002; 40:762-767.

27. Berhe N, Wolday D, Hailu A, Abraham Y, Ali A, Gebre-Michael T, et al. HIV viral load and response to antileishmanial chemotherapy in co-infected patients. AIDS 1999; 13:1921-1925.
28. Alvar J, Cañavate C, Gutiérrez-Solar B, Jiménez M, Laguna F, López-Vélez R, et al. *Leishmania* and human immunodeficiency virus coinfection: The first 10 years. Clin Micro Biol Rev 1997; 10:298-319.
29. Grabmeier-Pfistershammer K, Poeppl W, Brunner PM, Rappersberger K, Rieger A. Clinical challenges in the management of *Leishmania*/HIV coinfection in a non-endemic area: a case report. Case Rep Infect Dis 2012; 2012:787305.
30. World Health Organization (WHO). Control of the leishmaniasis: report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 22-26 March 2010. [Cited 2013 September 09] Available at: whqlibdoc.who.int/trs/WHO_TRS_949_eng.pdf. 2010/.
31. World Health Organization (WHO). Report of a WHO informal consultation on liposomal amphotericin B in the treatment of visceral leishmaniasis. WHO: 2005. [Cited 2013 September 09] Available at: http://www.who.int/neglected_diseases/resources/AmBisomeReport.pdf. 2005
32. Ministério da Saúde (MS). Secretaria de Vigilância em Saúde, Departamento de Vigilância Epidemiológica. Manual de recomendações para diagnóstico, tratamento e acompanhamento de pacientes com a coinfecção *Leishmania*-HIV. Brasília: MS; 2011.
33. Russo R, Laguna F, Lopez-Velez R, Medrano FJ, Rosenthal E, Cacopardo B, et al. Visceral leishmaniasis in those infected with HIV: clinical aspects and other opportunistic infections. An Trop Med Parasitol 2003; 97 (Suppl I):99-105.
34. Horst R, Collin SM, Ritmeijer K, Bogale A, Davidson RN. Concordant HIV infection and visceral leishmaniasis in Ethiopia: the influence of antiretroviral treatment and other factors on outcome. Clin Infect Dis 2008; 46:1702-1709.
35. Bentwich Z. Concurrent Infections that rise the HIV viral load. J HIV Ther 2003; 8:72-75.
36. Cacopardo B, Nigro L, Preiser, Famá A, Satariano MI, Braner J, et al. Prolonged Th2 cell activation and increased viral replication in HIV-*Leishmania* coinfected patients despite treatment. Transactions Trans R Soc Trop Med Hyg 1996; 90:434-435.
37. Bourgeois N, Lachaud L, Reynes J, Rouanet I, Mahamat A, Bastien P. Long-term monitoring of visceral leishmaniasis in patients with AIDS: relapse risk factors, value of polymerase chain reaction and potential impact on secondary prophylaxis. J Acquir Immune Defic Syndr 2008; 48:13-19.
38. Collin SM, Coleman PG, Ritmeijer K, Davidson RN. Unseen Kala-azar deaths in south Sudan (1999-2002). Trop Med Int Health 2006; 11: 509-512.
39. Oliveira JM, Fernandes AC, Dorval ME, Alves TP, Fernandes TD, Oshiro ET, et al. Mortality due to visceral leishmaniasis: Clinical and laboratory characteristics. Rev Soc Bras Med Trop 2010; 43:188-193.
40. Costa CH, Werneck GL, Costa DL, Holanda TA, Aguiar GB, Carvalho AS, et al. Is severe visceral leishmaniasis a systemic inflammatory response syndrome? a case control study. Rev Soc Bras Med Trop 2010; 43:386-392.
41. Sampaio MJAQ, Cavalcanti NV, Alves JGB, Fernandes Filho MJC, Correia JB. Risk factors for death in children with visceral leishmaniasis. PLoS Negl Trop Dis 2010; 4:e877.