Published in final edited form as:

Trans R Soc Trop Med Hyg. 2011 May ; 105(5): 298–300. doi:10.1016/j.trstmh.2011.01.006.

The emergence of concurrent HIV-1/AIDS and visceral leishmaniasis in Northeast Brazil

E.T. Nascimento^{a,b}, M.L.N. Moura^c, J.W. Queiroz^b, A.W. Barroso^c, A.F. Araujo^d, E.F. Rego^d, M.E. Wilson^e, R.D. Pearson^f, and S.M. Jeronimo^{b,c,g,*}

^aDepartment of Infectious Disease, Health Sciences Center, ...

^bHealth Post-Graduate Program, Health Sciences Center, ...

^cDepartment of Biochemistry, Biosciences Center, ...

^dUniversidade Federal do Rio Grande do Norte, Natal, RN, Brazil

^eHospital Giselda Trigueiro, Secretaria Estadual de Saúde, ...

^fDepartments of Internal Medicine, Microbiology and Epidemiology, University of Iowa and the VA Medical Center, Iowa City, IA, USA

^gDepartments of Medicine and Pathology, Division of Infectious Diseases and International Health, University of Virginia, Charlottesville, VA, USA

Abstract

HIV has become increasingly prevalent in the Northeast region of Brazil where *Leishmania infantum chagasi* is endemic, and concurrent AIDS and visceral leishmaniasis (VL) has emerged. In this study, persons with HIV/AIDS and VL ($n = 17$) had a mean age of 37.3 years (range 29–53 years) compared with 12.5 years (1–80 years) for persons with VL alone ($n = 2836$). Males accounted for 88% of cases versus 65%. The mean CD4 count and antileishmanial antibody titre were lower and recurrence of VL and death were more likely with co-infection. Considering the prevalences of *L.i. chagasi* and HIV in the region, this may herald the emergence of an important public health problem.

Keywords

Visceral leishmaniasis; HIV; AIDS; *Leishmania chagasi* infection; Brazil

© 2011 Royal Society of Tropical Medicine and Hygiene. Published by Elsevier Ltd. All rights reserved.

*Corresponding author. Present address: Department of Biochemistry, Biosciences Center, Universidade Federal do Rio Grande do Norte, CP 1624, Natal, RN, Brazil. Tel.: +55 84 3215 3428; fax: +55 84 3215 3428. smbj@cb.ufrn.br (S.M. Jeronimo).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Authors' contributions: ETN conducted the study of VL and AIDS patients and designed the study; MLNM conducted the study of VL and AIDS patients; JWQ performed the data analysis; AWB helped in patient enrolment; AFA helped in patient enrolment and the care of patients with AIDS; EFR helped in patient enrolment and the care of patients with AIDS; MEW reviewed the manuscript and helped design the study; RDP reviewed the manuscript and helped design the study; SMJ helped in VL enrolment, drafted the manuscript and helped design the study. Guarantor?

Conflicts of interest: None declared.

Ethical approval: The protocol was reviewed and approved by the Ethical Committee of Universidade Federal do Rio Grande do Norte (Natal, Brazil) (CEP-UFRN 19-01 and CEP-UFRN 172-06). All participants or their legal guardian read and signed the informed consent.

1. Introduction

Visceral leishmaniasis (VL) was first previously recognised as an opportunistic infection in individuals with HIV/AIDS in southern Europe.^{1,2} VL and HIV/AIDS are also endemic in Brazil, but to date a limited number of co-infections have been reported.³ Particularly in urban areas, HIV/AIDS is still predominantly a disease of men who have sex with men in Brazil, but women comprise an increasing risk group. Historically, VL caused by *Leishmania infantum chagasi* was primarily observed among children living in rural endemic areas of the northeastern states.⁴ However, over the past two decades VL has emerged as an epidemic disease in the outskirts of Brazilian cities such as Teresina⁵ and Natal.⁶ The outcome of *L.i. chagasi* infection varies from self-resolving asymptomatic infection to progressive life-threatening VL.⁷ Control of infection and resistance to re-infection requires a *Leishmania*-specific type 1 CD4+ T-cell response.⁸ It is therefore not surprising that T-cell abnormalities, such as those associated with HIV/AIDS or neoplasia, can result in progression of infection to clinically apparent VL. The goals of this study were to document and characterise VL and HIV co-infection in the state of Rio Grande do Norte, Northeast Brazil, and to determine whether it is similar to HIV/AIDS and *L. infantum* co-infection in southern Europe.

2. Materials and methods

Suspected cases of VL came from the state of Rio Grande do Norte where VL has been endemic.⁶ Diagnosis of HIV infection was based on detection of anti-HIV antibodies by ELISA with confirmation by Western blot, whereas diagnosis of AIDS was based on the modified CDC and Rio de Janeiro–Caracas criteria. The term ‘HIV/AIDS’ used in this manuscript refers to subjects who were HIV-positive and who met these criteria for AIDS. A total of 3157 cases of AIDS were reported in the state of Rio Grande do Norte between 1990 and 2009 (<http://www.saude.gov.br>). An age-matched group of individuals with VL, made up of subjects with VL and negative for HIV from the same population, was used for comparison ($n = 17$). Demographic data were compared with the overall VL case reports for the state of Rio Grande do Norte from 1990 to 2009 ($n = 2836$). Diagnosis of VL was based on identification of amastigotes in bone marrow aspirates and on serological studies. The presence of antileishmanial antibodies was determined in sera as previously described.⁹

Statistical analyses were performed using STATISTICA release 6.1 (StatSoft, USA).

The protocol was reviewed and approved by the Ethical Committee of the Universidade Federal do Rio Grande do Norte and by the National Committee of Ethical in Research (Comissão Nacional de Ética em Pesquisa, CONEP 4572 and CONEP 13745, CAAE 0139.0.051.069-06). All participants or their legal guardian read and signed the informed consent.

3. Results

Seventeen cases of concurrent HIV/AIDS and VL were documented in Rio Grande do Norte between 1990 and 2008. HIV infection was attributed to sexual transmission in all cases, but the illicit use of intravenous drugs could not be excluded. The diagnoses of HIV/AIDS and VL were made concurrently in seven cases, whereas the diagnosis of HIV preceded that of VL in seven cases and the diagnosis of VL preceded HIV in three cases. In persons who were diagnosed initially with VL, the recognition of HIV infection occurred within 1.6 ± 0.5 years (mean $\pm$ SD). Those with an initial diagnosis of HIV/AIDS developed VL within 3.4 ± 1.7 years. The mean age of patients with combined diseases was 37.3 ± 6.6 years and 15

(88%) of the 17 patients were males. This is in contrast to the lower mean age of 12 years in subjects with VL but without concurrent HIV infection. Patients with concurrent HIV/AIDS and VL had a mean CD4 count of 86 cells/mm³ (range 2–297 cells/mm³) compared with a mean of 1257 cells/mm³ in those with VL alone. Co-infected persons had lower antileishmanial antibody titres than those with VL alone, as measured by ELISA using the same soluble *Leishmania* antigen ($P < 0.01$) and rK39 ($P = 0.03$) (Table 1). Patients with HIV/AIDS–VL co-infection received monthly amphotericin B prophylaxis, but VL relapses occurred even in the setting of prophylactic therapy. The relapse rate was high in the HIV co-infected group; 6 of 17 patients relapsed after clinically successful treatment for VL. VL relapse occurred a mean of 1.42 ± 1.16 years (range 4 months to 5 years) after the last treatment for VL. All subjects with HIV/AIDS were discharged on highly active antiretroviral therapy, but compliance varied. The in-hospital mortality after re-admission of co-infected persons was 23.5% (4/17) compared with 6.9% in persons with VL alone. Physical findings associated with progression to death were jaundice (present in 50% of those who died versus 0% in those who lived; $P = 0.044$) and increased liver size (9.5 ± 2.5 cm below the right costal margin in those who died versus 4.5 ± 4.8 cm in subjects who lived; $P = 0.01$).

4. Discussion

HIV/AIDS and VL co-infection has emerged in Northeast Brazil. Co-infected persons were adults with an average age of 37.3 years, whereas VL typically occurs in children. Of note, 41% of co-infected persons had a previous history of clinically apparent VL, suggesting that their current VL may have been due to relapse in the setting of HIV/AIDS. Since the mid 1980s, VL has been recognised as a complication of HIV/AIDS in southern Europe. *Leishmania infantum* has been the aetiology and it was logical to hypothesise that HIV/AIDS would predispose persons infected with *L.i. chagasi* in Brazil to develop symptomatic VL.

The documentation of concurrent HIV/AIDS and VL in Rio Grande do Norte suggests that the epidemiology of Brazilian *L.i. chagasi* infection is once again evolving. Since the mid 1980s, a number of major periurban outbreaks have been reported.^{5,6} Concurrently, the highest incidence of HIV infection has typically been in urban centres, beginning in the south of Brazil and extending to the northeast.¹⁰ The two infections have come to overlap. Continued surveillance in Natal and elsewhere in Brazil will be important to assess the evolving impact of concurrent HIV/AIDS and VL as the number of people with asymptomatic infection residing in areas with HIV is substantial. Furthermore, there are increased numbers of subjects receiving therapy for autoimmune diseases, cancer or transplants that result in suppressed cellular immunity. We suggest that concurrent HIV/AIDS and VL is likely to emerge with increasing frequency in Brazil. A better strategy for management of patients co-infected with HIV and VL is needed to lower relapse rates and death.

Acknowledgments

The authors thank the staff of the Hospital Giselda Trigueiro for the availability and review of patients' diagnoses, and Mr Manoel Gomes Fernandes (Fundação Nacional de Saúde) for help with patient enrolment.

Funding: This work was funded in part by grants from the US National Institutes of Health (AI030639) to SMBJ and MEW, and by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

References

1. Montalban C, Martinez-Fernandez R, Calleja JL, Garcia-Diaz JD, Rubio R, Dronda F, et al. Visceral leishmaniasis (kala-azar) as an opportunistic infection in patients infected with the human immunodeficiency virus in Spain. *Rev Infect Dis.* 1989; 11:655–660. [PubMed: 2672242]
2. Desjeux P. Global control and *Leishmania* HIV co-infection. *Clin Dermatol.* 1999; 17:317–325. [PubMed: 10384871]
3. Daher EF, Fonseca PP, Gerhard ES, Leitão TM, Silva Júnior GB. Clinical and epidemiological features of visceral leishmaniasis and HIV co-infection in fifteen patients from Brazil. *J Parasitol.* 2009; 95:652–655. [PubMed: 19642802]
4. Badaró R, Jones TC, Lorenço R, Cerf BJ, Sampaio D, Carvalho EM, et al. A prospective study of visceral leishmaniasis in an endemic area of Brazil. *J Infect Dis.* 1986; 154:639–649. [PubMed: 3745974]
5. Costa CH, Pereira HF, Araújo MV. Visceral leishmaniasis epidemic in the State of Piauí, Brazil, 1980–1986 [in Portuguese]. *Rev Saude Publica.* 1990; 24:361–372. [PubMed: 2101528]
6. Jeronimo SM, Oliveira RM, Mackay S, Costa RM, Sweet J, Nascimento ET, et al. An urban outbreak of visceral leishmaniasis in Natal, Brazil. *Trans R Soc Trop Med Hyg.* 1994; 88:386–388. [PubMed: 7570812]
7. Badaro R, Jones TC, Carvalho EM, Sampaio D, Reed SG, Barral A, et al. New perspectives on a subclinical form of visceral leishmaniasis. *J Infect Dis.* 1986; 154:1003–1011. [PubMed: 3782864]
8. Carvalho EM, Barral A, Pedral-Sampaio D, Barral-Netto M, Badaró R, Rocha H, et al. Immunologic markers of clinical evolution in children recently infected with *Leishmania donovani chagasi*. *J Infect Dis.* 1992; 165:535–540. [PubMed: 1347057]
9. Braz RF, Nascimento ET, Martins DR, Wilson ME, Pearson RD, Reed SG, et al. The sensitivity and specificity of *Leishmania chagasi* recombinant K39 antigen in the diagnosis of American visceral leishmaniasis and in differentiating active from subclinical infection. *Am J Trop Med Hyg.* 2002; 67:344–348. [PubMed: 12452487]
10. Alexandrino-de-Oliveira P, Santos-Oliveira JR, Dorval ME, Da-Costa FC, Pereira GR, da 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. [PubMed: 20835619]

Table 1Characteristics of HIV-positive and -negative patients with visceral leishmaniasis (VL) matched by age^a

	HIV-positive (<i>n</i> = 17) [<i>n</i> (%)]	HIV-negative (<i>n</i> = 17) [<i>n</i> (%)]	<i>P</i> -value (M-L χ^2)
Age (mean $\pm$ SD)	37.3 $\pm$ 6.6	38.2 $\pm$ 16.5	0.8400
Gender			0.5419
Male	15 (88.2)	16 (94.1)	
Female	2 (11.8)	1 (5.9)	
Previous VL			0.0469
Yes	7 (41.2)	2 (11.8)	
No	10 (58.8)	15 (88.2)	
Bone marrow aspirate			0.0364
Positive	15 (88.2)	13 (76.5)	
Negative	2 (11.8)	4 (23.5)	
Anti-SLA			0.0019
Positive	11 (64.7)	17 (100)	
Negative	6 (35.3)	0 (0)	
Anti-rK39			0.0349
Positive	14 (82.4)	17 (100)	
Negative	3 (17.6)	0 (0)	
Death			0.0136
Yes	4 (23.5)	0 (0)	
No	13 (76.5)	17 (100)	
Relapse			0.0082
Yes	9 (52.9)	2 (11.8)	
No	8 (47.1)	15 (88.2)	

SLA: soluble *Leishmania* antigen.^aData are *n* (%) unless otherwise stated.