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Spatial, clinical-epidemiological and laboratory analysis of children admitted with visceral leishmaniasis in Pará/Brazilian Amazon

Análisis espacial, clínico-epidemiológico y de laboratorio de niños admitidos con leishmaniasis visceral en Pará/Amazonia Brasileña

Análise espacial, clínico-epidemiológica e laboratorial de crianças internadas com leishmaniose visceral no Pará/Amazônia Brasileira

ABSTRACT
Visceral Leishmaniasis (VL) is a systemic infection that affects people worldwide. It is endemic in Pará. Objective: To analyze the spatial, clinical-epidemiological, laboratory, treatment and lethality characteristics of children with VL in a reference hospital in Pará. Method: Retrospective-analytical, cross-sectional study, with a quantitative approach to medical records of children with VL hospitalized between 2012 and 2016. Result: Cases predominated in rural areas (77.1%) and primary infection (86.5%). Children under 6 years old and males were the most affected. The spatial distribution of cases was heterogeneous, with a predominance of Northeast Pará (80.2%). Laboratory confirmation was the most used (86.5%). N-methyl glucamine was the therapy of choice (89.3% of cases). Conclusion: There was a cure in more than 90% of cases. Mortality was associated with bleeding, thrombocytopenia, initial treatment failure, treatment time and higher life risk assessment system (SARV) score.
DESCRIPTORS: Visceral Leishmaniasis; Children; Epidemiology; Lethality.

RESUMEN
La leishmaniasis visceral (LV) es una infección sistémica que afecta a personas en todo el mundo. Es endémica en Pará.Objetivo: Analizar las características espaciales, clínico-epidemiológicas, de laboratorio, de tratamiento y letalidad de niños con LV en un hospital de referencia en Pará.Método: Estudio retrospectivo-analítico, transversal, con enfoque cuantitativo historias clínicas de niños con LV hospitalizados entre 2012 y 2016. Resultado: Predominaron los casos en el área rural (77,1%) y la infección primaria (86,5%). Los niños menores de 6 años y los varones fueron los más afectados. La distribución espacial de los casos fue heterogénea, con predominio del Noreste de Pará (80,2%). La confirmación de laboratorio fue la más utilizada (86,5%). La N-metil glucamina fue la terapia de elección (89,3% de los casos). Conclusión: hubo cura en más del 90% de los casos. La mortalidad se asoció con hemorragia, trombocitopenia, fracaso del tratamiento inicial, tiempo de tratamiento y mayor puntuación del sistema de evaluación de riesgos de vida (SARV).
DESCRIPTORES: Leishmaniasis Visceral; Niños; Epidemiología; Letalidad.

RESUMO
A Leishmaniose Visceral (LV), é uma infecção sistêmica que afeta pessoas no mundo todo. É endêmica no Pará. Objetivo: Analisar as características espaciais, clínico-epidemiológicas, laboratoriais, tratamento e letalidade de crianças com LV em hospital de referência do Pará. Método: Estudo retrospectivo-analítico, transversal, com abordagem quantitativa dos prontuários de crianças com LV internados entre 2012 e 2016. Resultado: Os casos predominaram na zona rural (77,1%) e infecção primária (86,5%). Os menores de 6 anos e do sexo masculino foram os mais acometidos. A distribuição espacial dos casos foi heterogênea, predominando o Nordeste Paraense (80,2%). A confirmação laboratorial foi a mais utilizada (86,5%). N-metil glucamina foi a terapêutica de eleição (89,3% dos casos). Conclusão: Houve cura em mais de 90% dos casos. A letalidade associou-se à sangramentos, à plaquetopenia, à falha no tratamento inicial, ao tempo de tratamento e ao maior escore sistema de avaliação de risco de vida (SARV).
DESCRITORES: Leishmaniose Visceral; Crianças; Epidemiologia; Letalidade.

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INTRODUCTION

Visceral Leishmaniasis (VL), also known as Calazar or American Leishmaniasis, is a serious systemic infection caused by a protozoan of the genus Leishmania that affects two million people a year. Currently, the World Health Organization (WHO) considers VL one of the seven global endemics of absolute priority among the Neglected Tropical Diseases (NTDs). It is a major public health problem due to its endemic character in various regions of the world and its high potential for lethality. Among the 7 most affected countries are Bangladesh, Brazil, India, Ethiopia, Kenya, Nepal and Sudan, which together represent approximately 90% of cases. [1]

Worldwide, its incidence is estimated at 500.000 new cases and 50.000 deaths each year. In the Americas, Brazil is the most endemic country, covering approximately 97% of all cases on the continent. [2]

In Brazil, the main vector of VL is the Lutzomya longipalpis known as the straw mosquito or birigui, which transmits the species Leishmaniasis chagasi to vertebrates. The domestic dog is the main reservoir of leishmania in urban areas, which is an aggravating factor when taking into account the direct relationship between humans (final host) and dogs. [3]

In Brazil, the importance of VL lies in its high incidence (3.829 cases in 2015) and its wide distribution with a record of the disease in the Northeast (1.806 cases); Southeast (538 cases); North (469 cases); Midwest (157 cases); and South (5 cases). [4]

In Brazil, VL had its origins in rural areas, but due to the lack of basic sanitation and poor housing conditions linked to the country's disorderly urbanization process, the disease has spread to the suburbs of large Brazilian cities, in the last 40 years, as attest clinical reports or serological surveys, similar to what occurs in other countries. [5,6]

Due to its occurrence in rural areas and on the outskirts of large cities, VL usually affects individuals with low purchasing power. This social particularity can interfere with the population's health status due to the precarious sanitary conditions in which they live, in which infections and malnutrition aggravated by the disease are factors of poor prognosis. [6]

In 2014, in Brazil, of the approximately 1.980 cases of VL notified per year, a little more than half (54,4%) affected children under 10 years of age and, of these, 41% belonged to the under-five age group. In addition to being more susceptible, children are more exposed to the vector around the home, in addition to being more prone to malnutrition, a condition that worsens the clinical picture of leishmaniasis or is aggravated by it. [7]

Pará is one of the states in the country that contributes significantly to the spread of the disease, with 1.266 cases reported between 2010 and 2013. [8]

Among the factors that contribute to the expansion of VL in the country, there are the deficiency or absence of health services in the locations of the index cases, inadequate training of health professionals regarding diagnostic suspicion and ineffective control of the management of resources for diagnosis and treatment . This panorama predisposes the referral of sick individuals for hospital treatment. [8]

In this context, the objective of this work is to analyze the spatial, clinical-epidemiological, laboratory, treatment and lethality characteristics of children with VL in a reference hospital in the State of Pará.

METHODS

This is a documentary, retrospective-analytical, cross-sectional study with a quantitative approach carried out at the João de Barros Barreto University Hospital (HUJBB), a care, teaching and research unit, integrated to the Hospital Complex of the Federal University

of Pará (UFPA) , a reference in Pará, located in the state capital, Belém, in the Brazilian Amazon region, which is characterized by offering the population a public service (Unified Health System - SUS) of prompt care, diagnostic support, medical clinic, pediatrics, infectology, service reference to people with HIV and treatment for tuberculosis and leishmaniasis.

Data collection was carried out in the Division of Medical and Statistical Archives (DAME) from May to July 2019. Data were obtained by analyzing medical records, followed by filling out an individual assessment form with identification, origin, duration of illness, clinical and laboratory data, associated pathologies, use of medication, form of diagnosis, laboratory tests, type and period of treatment and clinical outcome. Children with VL at risk of evolving to serious situations and death were also identified, according to the official recommendation of the SARV, in a form adapted from the Health Surveillance Guide (BRASIL, 2017a).

The inclusion criteria were children and adolescents aged 0 to 12 years admitted to the HUJBB with a clinically and/or laboratory confirmed diagnosis of VL from January 1st, 2012 to December 31st, 2016. patients with VL who had insufficient information to complete the protocol prepared by the researcher or ineligible or insufficient information to complete.

In the construction of the cartographic base, there was collaboration of the LABGEO (Geostatistics Laboratory) of the State University of Pará (UEPA) to generate thematic maps in order to express the spatial and temporal relations of VL cases, in addition to the use of secondary sources, of public domain, for the creation of cartographic maps: the SIRGAS 2000 projection and the 2010 Census database (population data), both made available by the Brazilian Institute of Geography and Statistics (IBGE). The classification of the mesoregions of Pará followed the IBGE definitions.

Data debugging was performed using the Tabwin® Program (DATASUS/MS, available at: http://datasus.saude.gov.br to remove possible factors causing biases, such as incompleteness, redundancies and inconsistencies in the analyzed data. Following the debugging process, geographic coordinates were implemented, which were indexed to the database of reported cases in the study area and period.

Data were obtained by analyzing medical records, followed by filling out an individual assessment form with identification, origin, duration of illness, clinical and laboratory data, associated pathologies, use of medication, form of diagnosis, laboratory tests, type and period of treatment and clinical outcome.

An electronic spreadsheet was created to store the data in the Microsoft Excel® 2010 software. For descriptive representation of the data, tables (Microsoft Word® Software) were used in which the numerical variables were represented by means, standard deviation or by median, 1st quartile, 3rd quartile and minimum and maximum values of these variables. Categorical variables were described in absolute and relative frequencies.

Data analysis was processed using the Epi Info 7.2 program and the Jamovi version 0.9.5.15 program to compare the means in the death and survivors groups. The Student t-test (variables with normal distribution) or the Mann-Whitney test (variables with non-parametric distribution) were used. To identify the dependence between clinical variables (independent) and death (dependent) from leishmaniasis, Fisher's exact test was used. A significance level of 5% (p value ≤ 0,05) was adopted for all statistical tests.

Geoprocessing techniques in ArcGis 10.5 and TerraView 4.0 environments were used to analyze the spatial distribution of VL cases identified at the HUJBB, according to the infection site: Flow technique (for patient access to the service), Kernel geostatistical technique (identification of locations with the highest concentrations of cases) and map algebra (visual expression of the interrelationship of georeferenced databases of clinical, epidemiological, and public policy data).

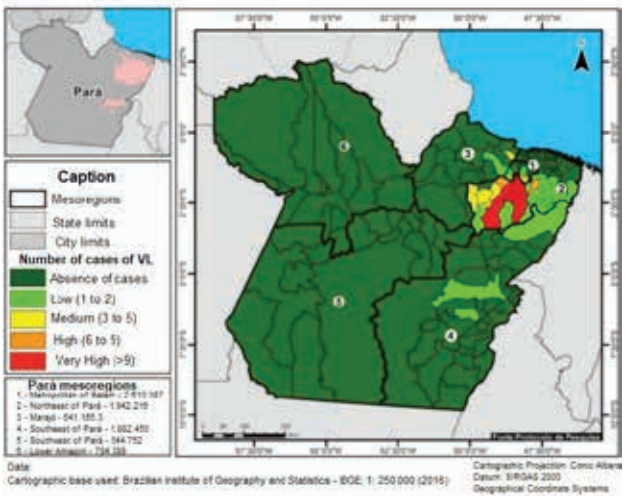
This study was approved by the Research Ethics Committee (CEP) of Instituto Evandro Chagas (IEC) on March 21st, 2019 (opinion no. 3.213.985, CAAE 08390919.5.0000.0019).

Table 1 – Sociodemographic data of children with VL admitted to the HUJBB from 2012 to 2016, Belém, Pará

VARIABLES	N	(%)
ZONE	22	22,9%
Urban	74	77,1%
Rural	96	100%
Total	22	22,9%
ENTRY TYPE		
New Case	77	86,5%
Relapse	12	13,5%
Total	89	100%
SEX		
Male	59	61,5%
Female	37	38,5%
Total	96	100%
AUTOCHTONE		
Yes	60	62,5%
No	36	37,5%
Total	96	100%
AGE		
0 to 6 years	80	83,3%
7 to 9 years	14	14,6%
≥ 10 years	2	2,1%
Total	96	100%

Source: Research data.

Figure 1 – Spatial distribution of VL cases in the state of Pará, treated by the reference Hospital, from January 2012 to December 2016. Belém, Pará.



Source: Research Protocol.

RESULTS

127 cases with VL were identified during the study period, with an analysis of 109 medical records (18 records were damaged and/or lost due to structural problems in the building, after heavy rains). Of the total available (109), 13 met the exclusion criteria, remaining 96 eligible records.

Mean time of illness was 71,5 days. Table 1 shows the socio-demographic data of the research, with most cases coming from the rural area (77,1%), the predominance of primary infections (86,5%), 61,5% were male; 62,5% were autochthonous. The greatest involvement (83,3%) occurred in children under 6 years old, followed by 14,6% between 7 and 9 years old and 2,1% in those over 10 years old.

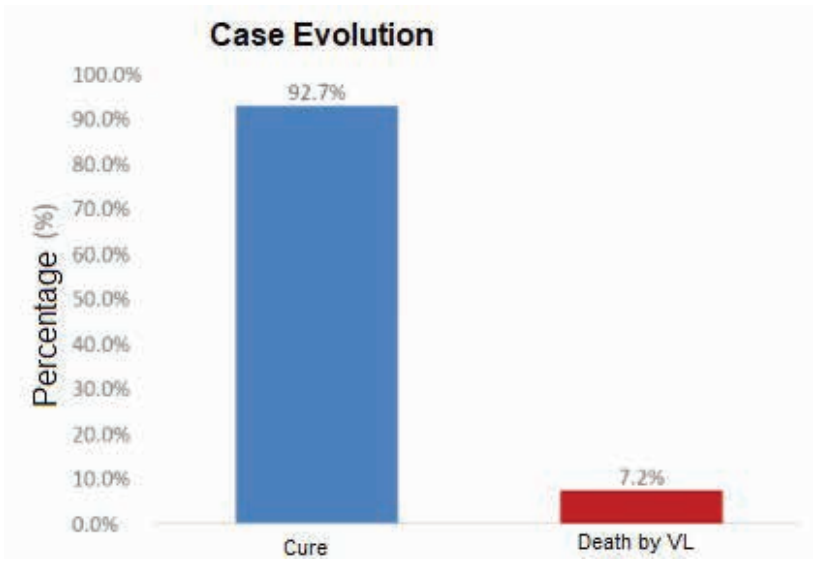
The spatial distribution was heterogeneous in the mesoregions of the state of Pará (Figure 1): the Northeast of Pará had the highest number of occurrences, with 80,2% coming from different municipalities, mainly distributed in Acará, Moju and Tome-Açu (10,4%), with 10 cases each, São Domingos do Capim (9,4%) with 9 cases and Abaetetuba (7,3%) with 7 cases.

The main clinical manifestations presented were: fever (97,8%), asthenia (78,8%), pallor (90,6%), splenomegaly (95,5%), hepatomegaly (94,4%). The laboratory criterion was the most used to confirm the disease (86,5%), with emphasis on indirect immunofluorescence (IFI) (91,1%). Treatment with N-dimethyl glucamine was performed in 89,3% of the children, with evolution to cure in almost all (92,7%), (Graph 1).

Table 2 shows that bleeding [the bleeding site(s) not being specified in most medical records] was the only clinical manifestation that had a significant influence on death (p=0,05; OR=10, 1; 95% CI: 1,3 - 79,4).

Table 3 shows the laboratory parameters between children and adolescents who progressed to cure and those who died, in which it is observed that only the

Graph 1 – Evolution of cases of children with VL admitted to the HUJBB from 2012 to 2016, Belém, Pará.



Source: Research data.

Table 2 – Clinical manifestations vs death of children and adolescents with VL admitted to the HUJBB from 2012 to 2016, Belém, Pará.

VARIABLES	DEATH (%)	OR (CI 95%)	P-VALUE
FEVER			
Yes	7,9%	-	0,99*
No	0%		
WEAKNESS			
Yes	7,4%	1,3 (0,14 – 12,5)	0,99*
No	5,5%		
PALLOR			
Yes	7,8%	0,6 (0,06 – 5,6)	0,51*
No	12,5%		
EDEMA			
Sim	15,6%	7,5 (0,84 – 68,6)	0,07*
Não	2,4%		
EMAGRECIMENTO			
Yes	6%	0,6 (0,1 – 3,1)	0,67*
No	9,9%		
ICTERUS			
Yes	5,2%	0,7 (0,07 – 6,8)	0,99*
No	7,1%		
SPLENOMEGALY			
Yes	8,2%	-	0,99*

hematocrit (p=0,05) and platelet count (p=0,03) were significantly lower in the group that progressed to death.

Children who received treatment for VL with amphotericin B had significant lethality compared to those who received N-methyl glucamine as the first therapeutic option (p<0,00; OR=40,5; 95% CI: 62-263), a fact not observed among those with or without treatment failure (Table 4).

The mean life risk assessment system (SARV) score was 1,6±1,5, close to the highest risk score 2 as determined by the Health Surveillance Guide. [9]

In this HUJBB series, children and adolescents who progressed to death had a significantly higher mean of the SARV score than those who progressed to cure (3,5 vs 1,4; p=0,00).

DISCUSSION

Leishmaniasis is a Neglected Tropical Disease (NTD) that constitutes a worldwide public health problem, considered by the WHO as one of the five most relevant endemic infectious and parasitic diseases, present in approximately 98 countries. [9,10] Brazil has 95% of registered VL cases in Latin America, growing rapidly, both in magnitude and in geographic expansion, with registration in all states, Pará being one of those with the highest incidence of the disease. [11,12] In this sense, the results obtained in this study provide important support for the development of strategic measures to combat the disease.

In the present study, there was a predominance of hospitalizations for VL from rural areas (75,2%), in contrast to the study by Silva et al. (2017)[13] who identified in the city of Palmas, Tocantins, a higher concentration of cases from the urban area with 98,2%.

For the majority (86,5%) of children and adolescents with VL it was a primary infection (new cases), a percentage lower than the 91,8% of new cases observed by Silva and Gaioso (2013)[14], when conducting research on VL in Pará, from 2007

No	0%	-	0,99*
HEPATOMEGALY			
Yes	8,3%	-	0,99*
No	0%		
BLEEDING			
Yes	33,3%	10,1 (1,3 – 79,4)	0,05*
No	4,7%		

OR = Odds Ratio, 95% CI = Confidence Interval (95%), * Fisher's exact test. Source: Research data.

to 2011. The cases of recurrence in this study were 13,5%, a percentage higher than the 2,5% (43/1.738 cases) observed in the study by the aforementioned authors.

All cases of VL seen at the HUJBB occurred in the pediatric age group, which characterizes the vulnerability of this group to the condition. In the study on VL in the State of Pará, between 2007 and 2011, children constituted the particularly susceptible population, with progression of the morbid state due to the immaturity of the immune system. [14]

The cases of VL in 83,3% were in children under 6 years and 14,6% between 7 and 9 years, similar to what was observed by Muller et al. (2008)[15] and less than about 60% in children under four years old in a survey of the number of VL cases in Brazil, from 2009 to 2013. [16]

The predominance of males (61,5%) corroborates other studies. [17,18] According to the aforementioned authors, hormonal factors and the tendency of this gender to carry out activities outside the home would contribute to a greater chance of exposure to the phlebotomine vectors of the disease.

The autochthonous cases in this research represented 62,5%, less than the 86% evidenced by Silva and Gaioso (2013) 14, in a study carried out in Pará with information regarding epidemiological data of VL cases notified in the state between January 2007 and December 2011, which also affected the pediatric population more.

Most cases of VL admitted to the HUJBB in the period of this study came

Table 3 – Lethality related to laboratory data of children and adolescents with VL admitted to the HUJBB from 2012 to 2016, Belém, Pará.

VARIABLE	NO DEATH		DEATH		P-VALUE
	MEAN ±SD *	MEDIAN (Q3 – Q1)**	MEAN ±SD*	MEDIAN (Q3 – Q1)**	
Hb	8,1 ±1,6	7,9 (9,1 – 6,8)	6,9 (±2)	7,5 (8,7 – 5,8)	0,09****
Ht	25% ±5%	24% (28% – 21%)	21% (±6%)	23% (27% – 16%)	0,05****
Leukocytes	4161,3 ±2721,8	3420 (5000 – 2430)	3021,5 (±1713,9)	2820 (3880 – 1720)	0,31***
Platelets (mil/mm3)	124,6 ±122,9	80,3 (125 – 50)	53,9 (±54,9)	27 (98,4 – 17,3)	0,03***

*SD = Standard deviation, **Q1= first quartile, Q3= third quartile, ***Mann-Whitney test, **** Student t test. Source: Research data.

Table 4 – Type, failure and duration of treatment vs death in children and adolescents with VL admitted to the HUJBB from 2012 to 2016, Belém, Pará.

VARIABLES	DEATH (%)	OR (CI 95%)	P-VALUE
INITIAL TREATMENT			
N-methyl glucamine	2,4%	40,5 (62 – 263)	0,00*
Amphotericin B	50%		
INITIAL TREATMENT FAILURE			
Yes	4,7%	0,6 (0,06 – 6,3)	0,99*
No	7%		

OR = Odds Ratio, 95% CI = Confidence Interval (95%), * Fisher's exact test. Source: Research data.

Table 5 – Risk Assessment System (RAS) vs Lethality in children and adolescents with VL admitted to the HUJBB from 2012 to 2016, Belém, Pará.

VARIABLE	N	NOT DEATH		DEATH		P-VALUE
		MEAN ±SD	MEDIAN (Q3 – Q1)	MEAN ±SD	MEDIAN (Q3 – Q1)	
Life risk assessment system	96	1,4 ±1,4	1 (2 – 0)	3,5 ±1,7	4 (5 – 2)	0,00**

SD = Standard deviation, Q1= first quartile, Q3= third quartile, **Mann-Whitney test. Source: Research data.

from the Mesoregion of Northeastern Pará, with emphasis on the municipalities of Acará, Moju and Tomé-açu, unlike the capital of Pará, which had few cases. Inadequate sanitary conditions regarding the supply and treatment of water and waste are a reality in these municipalities, which attract stray dogs that are the main reservoir of the disease. [19,20]. Another aggravating factor is the difficulty in accessing medical and hospital services due to limitations or deficiencies in the public transport system for a large portion of the population living in these areas, which would contribute to aggravate the disease with consequent hospitalization. [21]

The georeferenced data from VL cases in children and hospitalized at the HUJBB demonstrate the presence of the disease in the State of Pará and the need for its control, which includes overcoming the climatic and physical-geographic difficulties of the Amazon itself, improving management and the budget of resources destined for this purpose, and greater investment in the qualification of professionals for the analysis and dissemination of data related to Leishmaniasis. In this way, there will be more efficiency and agility in the demarcation of risk areas, with the transfer of this information to the competent authorities and health professionals. [18,22]

Fever (97,8%) was the main clinical manifestation in patients with VL admitted to the HUJBB. Kumar et al. (2018) [23] and Cunha et al. (2019) [24] they also highlighted prolonged fever, asthenia, weight loss and hepatosplenomegaly as the most common signs and symptoms. Enlarged liver and spleen (94,4% and 95,5%, respectively) followed more frequently after fever. Splenomegaly is a relevant data for clinical suspicion of the disease, [25] which is often absent in immunocompromised. [26]

Laboratory diagnosis (serological and parasitological) is sufficient to confirm VL,27 having predominated in this study (86,5%) similar (88,8%) to another research carried out in Pará between 2007 and 2011, whose cases also had laboratory diagnosis. [14]

Among the laboratory tests, the main form of diagnosis of VL was by IFI. Currently, this is the test made available by SUS [28] and it remains one of the most used in the main public reference laboratories in Brazil, despite the advent of new, more sensitive methods for identifying the disease. [29] The IFI evidences the presence of anti-leishmania IgG antibodies, however, it does not guarantee the active presence of the parasite and thus, in the presence of a reactive result, it is necessary to associate clinical and epidemiological information with other tests to confirm the diagnosis of the disease. [18]

Enlarged liver and spleen (94,4% and 95,5%, respectively) followed more frequently after fever. Splenomegaly is a relevant data for clinical suspicion of the disease, which is often absent in immunocompromised.

The main form of treatment was with N-methylglucamine antimoniate, as it has been used in the country since the 50s as an initial treatment, 30 similar (64,3%) to that prescribed to patients with VL in Governador Valadares, Minas Gerais, Brazil. [31]

N-methyl glucamine is especially effective in the treatment of visceral leishmaniasis (and in the cutaneous and cutaneous mucosal forms) with regression of the clinical and hematological manifestations of the disease. However, it is a drug that has cardiotoxicity and hepatotoxicity, which implies monitoring the cardiovascular and hepatic system during its use, especially in the presence of comorbidities, due to the higher risk of death from VL in these patients. [32]

Liposomal amphotericin B was not used in children with VL admitted to the HUJBB, despite reports of lower lethality rates in its use, especially in children under one year of age, where the disease has a worse prognosis. [33,34,35,36,37]

Cure occurred in 92,7% of the population studied, with a death rate of 7,3%, respectively higher than the 54,5% and 1,2% in patients with VL in Pará. [14] This higher percentage of cure may be related to the fact that HUJBB is a reference hospital for infectious and parasitic diseases, with good quality of services provided.

National studies in Bauru, SP and Campo Grande, MS reported mortality rates of 8,1% and 18,4%, however, they have limitations for comparison with children hospitalized with VL at the HUJBB, as the sample also included adults and with comorbidities (among which HIV/AIDS), which were associated with death, different from the cases treated at the HUJBB composed of children without comorbidities. [38,39]

Bleeding was significantly associated with death. According to the literature, depending on the degree of thrombocytopenia (in general, platelet counts below 50.000/mm3), bleeding can occur in the form of epistaxis, bruises, petechiae, di-

gestive bleeding, gingivorrhagia, traumatic bleeding or associated with medical-surgical procedures. [33,40,41]

Costa (2009) [41] observed a directly proportional relationship between the number of sites with bleeding and VL lethality, which occurs in all age groups, but more frequently in children under 2 years of age. This risk of death decreased to 50% in those aged between one and five years. In children hospitalized at the HUJBB, it was not possible to quantify the bleeding sites, thus making this comparison impossible.

Children who received initial treatment with amphotericin B progressed significantly more to death than children who started treatment with N-methyl glucamine without information on the criteria for therapeutic choice, another limitation of this study that did not allow for the analysis of the epidemiological criteria (age), clinical and laboratory severity, adverse events, among others that guide the indication of amphotericin B as a second-choice drug for the treatment of VL. [42,43]

In this sample, the population studied had a mean risk of 1,6, therefore, below the score defined by the SARV for risk estimation. However, comparing children who died with those who survived.

It was observed that children with higher SARV scores evolved significantly to death compared to those with lower scores (3,5 versus 1,4), thus demonstrating the importance of carrying out the epidemiological, clinical and laboratory evaluation of each child with VL to establish this prognostic value score. [41]

CONCLUSION

VL cases predominated in rural areas, mostly autochthonous and primary infection. Children under 6 years old and male were the most affected. The spatial distribution of VL cases was heterogeneous, with the highest number of occurrences in the Northeast of Pará, an endemic region for VL in the state of Pará. The laboratory criterion was the most used to confirm the diagnosis, mainly by indirect immunofluorescence. Treatment with N-methyl glucamine was the most used therapy of choice, with cure in more than 90% of cases. Children with the highest SARV score significantly progressed to death. Mortality was associated with the presence of bleeding, thrombocytopenia, initial treatment failure, treatment time and SARV score. ■

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