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Visceral leishmaniasis: historical series of hospitalized patients and correlation with climate in an endemic area in Minas Gerais, Brazil

Leishmaniose visceral: série histórica de pacientes hospitalizados e correlação com o clima em área endêmica de Minas Gerais, Brasil

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ABSTRACT

Introduction: Visceral leishmaniasis (VL) is an infectious disease caused by the protozoa of the genus *Leishmania*; it is predominant in tropical, subtropical, and temperate regions. **Objective:** To characterize a series of cases of VL in patients treated at a referral hospital in the north of Minas Gerais over 18 years, as well as to describe the occurrence of cases, according to the climatic characterization, and correlate the distribution of the cases with rainfall and environmental temperature. **Methods:** The study design was a series of cases compiled between 1999 and 2016. The data were extracted from medical records selected chronologically. Climate information was collected at the Center for semi-arid study at the Federal University of Montes Claros (Unimontes). **Results:** There was a slight predominance of males (54.4%) and aged between one and four years (42.9%). The evolution time for clinical manifestations up to the time of admission ranged from five to 120 days, with the most frequent length of stay between 16 and 30 days (34.4%). Hepatomegaly, splenomegaly, skin pallor, and fever were manifestations present in more than 90% of patients at admission. The diagnosis was performed by serological methods in most cases (85.9%). The largest portion of admissions lasted between 16 and 30 days (44%), and hospital discharge with guidance for outpatient control was the most frequent outcome of admissions. The percentage of deaths was 2%. **Conclusion:** The predominant characteristics of VL are male children aged 1 to 4 years who sought the health service with the classic triad of the disease: hepatosplenomegaly, skin pallor, and prolonged fever. In this study, there was no statistically significant association between temperature, rainfall, and the number of cases, however, there are nuances in the environmental factors that influence the dynamics of VL transmission, which vary from region to region.

Key words: visceral leishmaniasis; temporal distribution; epidemiology.

RESUMO

Introdução: *A leishmaniose visceral (LV) é uma doença infecciosa causada por protozoários do gênero* Leishmania*; é predominante em áreas tropicais, subtropicais e regiões temperadas.* ***Objetivo:*** *Caracterizar uma série de casos de LV em pacientes atendidos em um hospital de referência no norte de Minas Gerais ao longo de 18 anos, bem como descrever a ocorrência dos casos, segundo a caracterização climatológica, e correlacionar a distribuição dos casos com pluviosidade e temperatura ambiente.* ***Métodos:*** *O delineamento do estudo foi uma série de casos compilados entre 1999 e 2016. Os dados foram extraídos a partir de prontuários médicos selecionados cronologicamente. Informações sobre o clima foram coletadas no Centro de Estudos do Semiárido da Universidade Estadual de Montes Claros (Unimontes).* ***Resultados:*** *Discreto predomínio do sexo masculino (54,4%) e da faixa etária de 1 a 4 anos (42,9%) foi observado. O tempo de evolução das manifestações clínicas até o momento da internação variou de cinco a 120 dias, sendo mais frequente a duração entre 16 e 30 dias (34,4%). Hepatomegalia, esplenomegalia, palidez cutânea e febre foram manifestações presentes em mais de 90% dos pacientes no momento da internação. O diagnóstico foi realizado por métodos sorológicos na maioria dos casos (85,9%). A maior parcela das internações durou entre 16 e 30 dias (44%), e a alta*

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hospitalar com orientação para controle ambulatorial foi o desfecho mais frequente das internações. O percentual de óbitos foi de 2%. ***Conclusão:*** *As características predominantes são crianças do sexo masculino de 1 a 4 anos que buscaram o serviço de saúde com a tríade clássica da LV: hepatoesplenomegalia, palidez cutânea e febre prolongada. Neste estudo, não houve associação estatisticamente significativa entre temperatura, precipitação e número de casos; contudo, há nuances nos fatores ambientais que influenciam a dinâmica de transmissão da LV, variando de região para região.*

Unitermos: *leishmaniose visceral; distribuição temporal; epidemiologia.*

RESUMEN

Introducción: *La leishmaniasis visceral (LV) es una enfermedad infecciosa causada por protozoos del género* Leishmania*; predomina en las regiones tropicales, subtropicales y templadas.* ***Objetivo:*** *Caracterizar una serie de casos de LV en pacientes mayores de 18 años atendidos en un hospital de referencia del norte de Minas Gerais, así como describir la ocurrencia de casos, según la caracterización climatológica, y correlacionar la distribución de los casos con la lluvia y la temperatura ambiente.* ***Métodos:*** *El diseño del estudio fue una serie de casos recopilados entre 1999 y 2016. Los datos se extrajeron de historias clínicas seleccionadas cronológicamente. La información climática se recopiló en el Centro de estudios del Semiárido de la Universidad Federal de Montes Claros (Unimontes).* ***Resultados:*** *Hubo un ligero predominio del sexo masculino (54,4%) y de edades comprendidas entre uno y cuatro años (42,9%). El tiempo de evolución de las manifestaciones clínicas hasta el momento de la hospitalización osciló entre cinco y 120 días, siendo la duración más frecuente entre 16 y 30 días (34,4%). Hepatomegalia, esplenomegalia, palidez cutánea y fiebre fueron manifestaciones presentes en más del 90% de los pacientes al ingreso. El diagnóstico se realizó por métodos serológicos en la mayoría de los casos (85,9%). La mayor parte de los ingresos duró entre 16 y 30 días (44%) y el alta hospitalaria con orientación para el control ambulatorio fue el resultado más frecuente de los ingresos. El porcentaje de muertes fue del 2%.* ***Conclusión:*** *Las características predominantes son niños varones de 1 a 4 años, que acudió al servicio de salud con la clásica tríada LV: hepatoesplenomegalia, palidez y fiebre prolongada. En este estudio no hubo asociación estadísticamente significativa entre temperatura, precipitación y número de casos, sin embargo, existen matices en los factores ambientales que influyen en la dinámica de transmisión de LV, los cuales varían de región a otra.*

Palabras clave: *leishmaniasis visceral; distribución temporal; epidemiología.*

INTRODUCTION

Visceral leishmaniasis (VL) is an infectious disease caused by the protozoa of the genus *Leishmania*; it is predominant in tropical, subtropical, and temperate regions, with an estimated worldwide incidence of 200 to 400,000 new cases each year[1]. It is a disease most commonly seen in children and is characterized by prolonged fever, hepatosplenomegaly, and pancytopenia; however, it has a wide clinical presentation, which ranges from asymptomatic to very severe cases[2,3]. In countries where VL is more prevalent, it mainly affects the socially less favored population, with a more notable incidence in rural and peri-urban areas[4,5]. The distribution on the planet concentrates 90% of cases in just six countries: Brazil, India, Bangladesh, Sudan, Ethiopia, and Nepal – regions known to have a tropical and subtropical climate. Mortality is around 50,000 individuals/year, as VL may be fatal if not diagnosed and treated promptly[1,6]. Some more recent studies highlight a change in the epidemiological picture of the disease, from the increase in cases among adults and the increase in the incidence of cases in peri-urban areas, possibly due to vector and natural reservoirs urbanization[7-9].

The north of Minas Gerais is one of the endemic regions of VL in Brazil[10]. It is an area of great territorial extension in the state, with approximately 130 thousand square kilometers (an area larger than that of many Brazilian states), comprising 89 municipalities, with a resident population of almost two million inhabitants. It is a transition region between the South/Southeast and the Northeast of the country, with a dry and hot climate and low rainfall. It also stands out for being one of the poorest regions in the country, with low human development indicators[11]. For the entire region, there is only one referral hospital for VL treatment, located in the city of Montes Claros, the region's hub: The University Hospital Clemente Faria (HUCF).

Considering that VL often leads to hospitalization, the survey of the profile of hospital admissions over time, as well as the climatic characterization of the same period, has the potential

to reveal important characteristics of the disease, enabling the development of preventive and control actions more effectively. The present study aimed to characterize the series of VL cases treated at a referral hospital in the north of Minas Gerais over 18 years, in addition to describing the occurrence of these cases, according to the climatic characterization, and correlating their distribution with rainfall and environmental temperature.

METHODS

Descriptive case series study, whose data were collected at the HUCF, State University of Montes Claros (Unimontes), the only referral institution for healthcare delivery to patients with VL in the region. Data were collected directly from the medical records of patients who had a diagnosis of VL on admission or during the hospital stay, from 1999 to 2016.

For data collection in the medical records, a specific form was used developed by the researchers, covering the patient's demographic, epidemiological and clinical characteristics, laboratory features, and clinical outcomes. A team of four specially trained medical students made a thorough reading of the medical records for data collection. Quality control was carried out through random access to the medical records of patients with VL to check the data collected in the forms.

The inclusion criteria were defined as all medical records that presented a diagnosis of VL defined by clinical, immunological, histological, or epidemiological parameters, or even the association between these criteria. Exclusion criteria were: illegible and inaccessible medical records (not found after an extensive search), and other types of leishmaniasis.

Information about the monthly average rainfall in cubic millimeters and the monthly average temperature in degrees Celsius were obtained from the Center for Coexistence with the Semiarid Studies [Centro de Estudos de Convivência com o Semiárido (CECS)], Unimontes' virtual platform. Spearman correlations were investigated between monthly rainfall average and monthly temperature average and the average of the numbers of hospitalized cases at a referral hospital over the years studied.

To characterize the case series, a descriptive analysis was performed, with the presentation of absolute and relative values, measures of central tendency, and amplitude. Spearman's correlation was verified between the average of monthly numbers of LV cases and the mean of average temperature, and also between the averages of monthly numbers of VL cases and the averages of local rainfall from 1999 to 2016. The collected data were processed using the Statistical Package for the Social Science – SPSS 20.0.

The research project was approved by the institution's administrative board and by the Research Ethics Committee, under opinion 1.471.595.

RESULTS

Over the period studied, 967 medical records were identified and located. The main characteristics of the patients are shown in **Table 1**. A slight predominance of males (54.4%) and in the age group from 1 to 4 years (42.9%) was verified. The evolution time

TABLE 1 – Demographic, clinical, and evolution data of hospitalized patients with a diagnosis of VL at the Hospital Universitário Clemente Faria, Montes Claros, Minas Gerais, Brazil, in the period 1999-2016

Variables	*n*	%
Sex		
Male	526	54.4
Female	441	45.6
Age		
< 1 year	82	8.5
1-4 years	415	42.9
5-9 years	128	13.2
10-19 years	117	12.1
20-59 years	198	20.5
≥ 60 years	27	2.8
Residence		
Urban	789	81.6
Rural	178	18.4
Time evolution		
≤ 7 days	79	8.2
8-15 days	261	27
16-30 days	333	34.4
31-89 days	186	19.2
≥ 90 days	63	6.5
No information	45	4.7
Clinical manifestations on admission		
Hepatomegaly	884	91.4
Splenomegaly	892	92.2
Pallor	910	94.1
Fever	949	98.1
Diagnostic definition		
Clinic	79	8.2
Serological	831	85.9
Biopsy/culture	42	4.3
No information	15	1.6
Length of stay		
≤ 7 days	36	3.7
8-15 days	423	43.7
16-30 days	425	44
31-59 days	75	7.8
≥ 60 days	8	0.8
Outcome		
Discharge/outpatient control	932	96.4
Transfer	16	1.7
Death	19	2

VL: visceral leishmaniasis.

of clinical manifestations until the time of admission ranged from five to 120 days, and the length between 16 and 30 days was more frequent (34.4%).

Hepatomegaly, splenomegaly, skin pallor, and fever were manifestations present in more than 90% of patients at admission. The diagnosis was performed by serological methods in most cases (85.9%). The largest portion of admissions lasted between 16 and 30 days (44%), and hospital discharge with guidance for outpatient control was the most frequent outcome of admissions. The percentage of deaths was 2%.

The distribution of assisted cases, according to the origin of the patients, is shown in **Figure 1**.

The monthly distribution of cases is listed in **Figures 2** (1999 to 2007) and **3** (2008 to 2016), which include graphs that also show the monthly average of temperatures and rainfall.

Table 2 shows the results of Spearman's correlation between the average of monthly numbers of LV cases and the mean of average temperatures (p = 0.292), and between the average numbers of monthly VL cases and average local rainfall (p = 0.214), over the years 1999 to 2016.

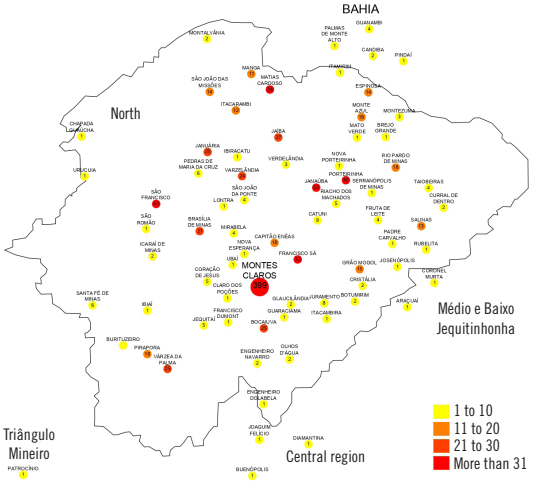

FIGURE 1 – *Distribution of VL cases admitted to a referral hospital in the north of Minas Gerais, according to place of origin (1999-2016)*
There was a record of a greater number of cases in the largest urban areas in the region in the region.

VL: visceral leishmaniasis.

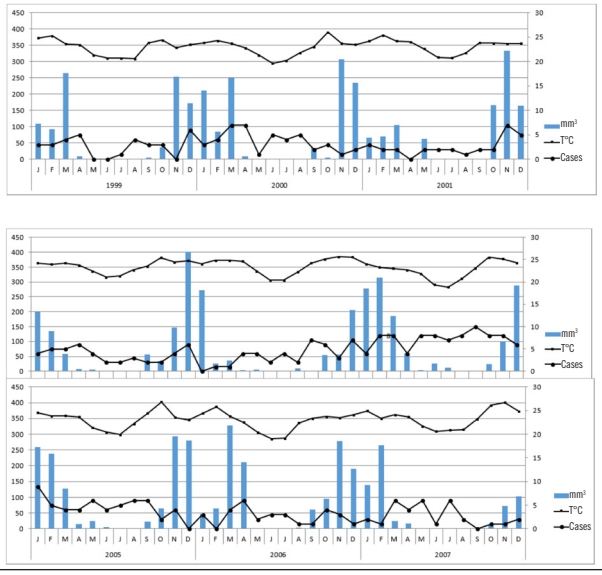

FIGURE 2 – *Monthly distribution of VL cases admitted to a referral hospital in the north of Minas Gerais, in addition to monthly averages of average temperature and monthly rainfall, 1999-2007*

VL: visceral leishmaniasis.

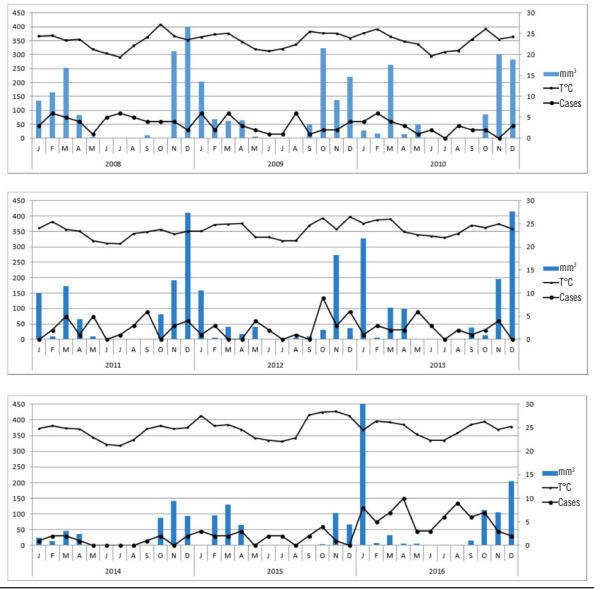

FIGURE 3 – *Monthly distribution of VL cases admitted to a referral hospital in the north of Minas Gerais, in addition to monthly averages of average temperature and monthly rainfall, 2007-2016*

VL: visceral leishmaniasis.

TABLE 2 – Spearman's correlation between monthly averages of number of VL cases, average temperature, and rainfall, between 1999 and 2016; HUCF, Montes Claros, Minas Gerais, Brazil

Months	Jan	Feb	Mar	Apr	Mai	Jun	Jul	Aug	Sept	Ocut	Nov	Dec		
Monthly average													Rh0*	*p* value
Number of VL cases	2.94	3.31	4.06	3.38	3.25	2.5	2.63	3.25	3	3.25	2.94	3.5	-	-
Rainfall	162.8	98	143.9	45.9	13.2	2.2	1	1.4	17.3	65.8	205.9	232.8	0.387	0.214
Average temperature	24.6	24.8	24.3	23.6	21.9	20.7	20.6	21.9	24.2	25.5	24.5	24.4	0.332	0.292

VL: visceral leishmaniasis; HUCF: Hospital Universitário Clemente Faria; Rh0: Spearman's correlation.

DISCUSSION

This study provided a detailed characterization of a series of VL cases treated at a reference hospital in an endemic area over 18 years, identifying that, in the aforementioned period, children were the main victims of the disease, with a predominance of cases in urban areas. The data reinforce the process of urbanization of the disease, as reported in other studies[12-16].

The clinical findings recorded over the study period confirm the predominance of cases in children, and the classic condition of hepatosplenomegaly, skin and mucous pallor, and fever. The triad of fever, increased abdominal volume, and skin pallor – the most prevalent findings reported on admission to the hospital –is still the main reason for patients to seek health care. Similar results have been presented in other studies[14, 15, 17, 18].

Observations regarding the time of evolution of VL, considering the appearance of signs and symptoms until hospital admission, revealed that most patients were admitted for hospital treatment within 30 days of manifestations of the disease. In another study[13], this interval ranged from 1 to 365 days, and the average reached 42.7 days, with 88.7% of cases manifesting symptoms for a period longer than 30 days. In another study[13], although the interval variation was the same as found by Queiroz *et al*. (2004)[13], the average reached 78.2 days, and 60% of cases evolved for more than 30 and less than 60 days. In the present study, as the municipality of Montes Claros is an endemic area with a referral hospital for leishmaniasis, this seems to justify the shorter time interval between the onset of symptoms and seeking medical care. However, there is still a considerable number of patients with disease evolution for more than 30 days, which suggests a late diagnosis and/or difficulties in accessing specialized health services[15].

The diagnostic confirmation, according to the analysis of the medical records, is mainly by serology, either by the indirect immunofluorescence method, immunoenzymatic test (Elisa), or rK39 antibody, or even the direct agglutination test. Although the gold standard is the identification of the protozoan in organic tissues, that is, the parasitological method, as observed in other studies[12-15], serological diagnosis and/or association with epidemiological and clinical issues have been widely used[19]. It is important to highlight the association of methods for the conclusion of the diagnosis and the timely implementation of therapy.

The length of stay is a significant variable, as the patient's long stay in the hospital can be a complication for hospital-acquired infections[20]. In individuals undergoing treatment for VL, this aspect takes on even greater importance, as concomitant infections represent a worse prognosis[21]. In this study, the average length of stay was 39.8 days and the longest time interval recorded was between 16 and 30 days. In the literature, the length of stay ranged from 11.2 to 46 days, with an average of 25.2 days[12-15].

In general, after the introduction of adequate treatment, the level of death significantly reduces. In this study, 19 cases (2%) evolved to death. Oliveira *et al*. (2010)[15] had 14.5% of death, while Xavier-Gomes *et al*. (2009)[17] and Diro *et al*. (2015)[19] reported less than 10%, a value closer to that found in our study. The Brazilian Ministry of Health evaluated the lethality caused by VL in the last two decades and observed an increase of more than 67%, that is, increased from 3.4% in 1994 to 5.7% in 2009[22]. This problem is due to drug resistance, the toxicity of first-line drugs, complications from the infection itself, and late diagnosis[22, 23].

In this study, there was no statistically significant association between environmental variables, temperature, and rainfall, and an increase in the number of cases over the period analyzed. Although the influence of the environment on the increase in the number of cases of certain diseases has been the object of study by several authors, physical factors are reported as intervening in the chain of transmission of zoonotic diseases. Rainfall, temperature variation, humidity, light intensity, presence of organic matter in household and peridomestic areas, altitude, among other factors, are highlighted within this perspective, since they can affect reproduction and nutrient availability for vectors and/or hosts, thus favoring disease transmissibility[16, 24].

A study on the distribution of VL in the city of Belo Horizonte, Minas Gerais, based on a spatial analysis, showed that the variable altitude was associated with an increase in the number of human and canine cases; 71.9% and 67.5%, respectively, were in a range between 780 and 880 meters above sea level. In this region, the highest vector density of the sandfly fauna was identified[25]. The municipality of Montes Claros, the highest number of cases (399) recorded in this study has an average altitude of 678 meters above sea level; the other municipalities that registered higher rates, according to data from the Brazilian Institute of Geography and Statistics [Instituto Brasileiro de Geografia e Estatística (IBGE)][11], were: Janaúba (53) with 510 m, Porteirinha (48) with 556 m, São Francisco (42) with 786 m, and Matias Cardoso (38) with 500 m. Although most of these cities are below the levels observed in the study mentioned above, it is important to highlight that there are other factors involved in the maintenance of the sandfly fauna, such as temperature, humidity, and the presence of organic matter.

This scenario greatly influences the available prophylactic measures, as well as their observance over time. The presence of the sandfly is inherent to the ecosystem of tropical and subtropical regions. The use of residual insecticide is a mandatory resource in maintaining low levels of sandfly population density, and its application is an elementary care before and after the period of greatest rainfall, although the abiotic factor of temperature is more correlated with the VL distribution in the environment. Considering the tropical bands with the highest solar incidence, it would be a difficult factor to control[25].

A statistically significant association was found between annual average temperature and the number of VL cases. In this study, the temperature varied between 25.3°C in the dry season and 26.3°C in the rainy season. Presumably, the temperature directly affects the VL incidence coefficient; therefore, milder temperatures can increase the number of cases of the disease[16].

Furthermore, other environmental aspects favor the proliferation of the vector and, consequently, the risk of contracting the disease, such as afforestation, accumulation of organic matter, and population displacement, which end up generating anthropic action on the environment[16]. A study carried out in Ethiopia on risk factors for VL discusses the concept of anthropic action by presenting variables with a strong statistical association, such as raising animals around the house, houses with cracks in the walls, larger families, and the number of days spent in the farm field[6]. These aspects have not yet been studied in Brazil.

In this study, the relationship between confirmed VL cases and accessibility/availability to health services was not evaluated. It is worth noting that the municipality of Montes Claros has 133 teams of the family health strategy (100% population coverage), a referral center for infectious parasitic diseases for the city and the entire northern region of Minas Gerais, and a hospital with a referral infectious parasitic disease outpatient clinic[26]. Moreover, the city is a university center in several areas of the health sciences, which, theoretically, combined with the epidemiological surveillance service, would make the organization of the service more sensitive to case detection.

Further works need to be developed in the region to verify other environmental aspects, such as those proposed in the studies selected for discussion. The altitude and the presence/quantity of organic matter in the peridomicile and the households, for example, would be elements to be included in understanding the dynamics of fluctuation in the number of cases throughout the year.

The results of the present study must be considered in light of some limitations. Secondary data from patient records were used. In similar situations, there is not always uniformity in recording information. Over the years considered in this study, the hospital's medical file service underwent important structural changes, especially in 2015, with the introduction of the electronic health record. The physical space of the service has also changed. These processes led to data loss, even respecting the 20-year interval for archiving the physical record, as provided by the Brazilian Federal Council of Medicine. Despite the limitations, the period and number of cases evaluated make the study relevant, which should support further research in the area.

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