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Visceral leishmaniasis: clinical and epidemiological features of children in an endemic area

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Abstract

Objective: To describe the clinical and epidemiological features of children with visceral leishmaniasis admitted to a pediatric referral hospital, and to describe treatment measures and the case fatality rate.

Methods: Retrospective analysis of biological, demographic, clinical and laboratory data from children with visceral leishmaniasis admitted to Instituto Materno Infantil de Pernambuco (Recife, state of Pernambuco, northeastern Brazil) between 1996 and 2001.

Results: 431 children were included in the study. Age ranged from 4 months to 13.7 years. 50.3% were female and 82.5% came from the interior of the state of Pernambuco. 70% of the patients lived in brick homes, and 70% were not served with piped water and sewage services. Average maternal schooling was 3 years. Clinical presentation included splenomegaly (97%), fever (95.6%) and malnourishment (44.5%). Associated infections were diagnosed in 10.9% of cases. The mean values for laboratory variables were: hemoglobin 6 g/dl, leukocyte count 3,516/mm³, and platelet count 118,641/mm³. The first line treatment used in 98% of the cases was glucantime. Amphotericin B was used in seven cases. The case fatality rate was 10.2%. The main immediate causes of death were associated infections, bleeding and liver failure.

Conclusions: Health care workers should be trained for the early recognition and appropriate management of visceral leishmaniasis and its complications.

J Pediatr (Rio J). 2004;80(2):141-6: Visceral leishmaniasis, kala-azar, childhood, diagnosis, treatment, case fatality rate.

Introduction

According to the World Health Organization (WHO), leishmaniasis affects around two million people a year, 500 thousand cases of which are of the visceral form. It is estimated that 350 million people are exposed to the risk of infection with a global prevalence of 12 million infected individuals.[1,2]

Visceral leishmaniasis is widespread in Brazil, with autochthonous cases being reported in at least 19 states of the Brazilian federation, and four of the five national regions (North, Northeast, Midwest and Southeast). Only the South remains unaffected.[3] Between 1984 and 2000 67,231 cases were reported.[4] More than 90% of these reports are concentrated in the Northeast region which reports cases within all of its federal units. In the state of Pernambuco,[5] 1,203 cases were reported during the period between 1990 and 1997. During recent decades there has been a strong tendency towards urban areas, with epidemic outbreaks taking place in a number of different state capitals[6] and constituting a serious public health which threatens the population and concerns health authorities.

Visceral leishmaniasis (VL) is a systemic infection caused by protozoa of the genus *Leishmania*. The primary vector in Brazil, is *Lutzomya longipalpis*, domestic dogs are the most significant reservoir and man is the final host.[3] The majority of infections are asymptomatic or develop moderate or transitory symptoms such as

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diarrhea, dry coughing, adynamia , light fever, diaphoresis and discrete hepatosplenomegaly,[7] which may or may not progress to the classic form of the disease. The classic presentation is of fever, hepatosplenomegaly, with voluminous splenomegaly, weight loss, coughing, diarrhea, pain and abdominal distension. Jaundice and renal involvement have also been described. During the last phase of the disease patients may develop edema and ascites.[1]

Diagnosis is based on identification of the parasite in bone marrow, liver, spleen or lymph node tissues.[7] A number of different serum-based tests have been developed for diagnosis (e.g. complement fixation test, indirect immunofluorescence, direct agglutination test, ELISA and Dot-ELISA), as have certain molecular biology techniques (polymerase chain reaction), although certain issues remain in relation to the sensitivity, specificity, and availability of these tests in clinical practice.[8] When laboratory-based diagnosis is not possible, initial treatment is based on clinical and epidemiological findings.[9]

Pentavalent antimonial compounds continue to be the first-choice drug and amphotericin B is the second line of attack in cases of resistance to antimoniate.[3] Recently, a new, orally administered, drug, miltefosine, has proven successful in India for VL treatment.[10] Infections, hemorrhages and severe anemia are responsible for the majority of deaths while late diagnosis, low age at onset and malnutrition are important contributing mortality factors.[3,7]

This paper describes epidemiological, clinical and laboratory data from leishmaniasis patients admitted to a pediatric hospital which is a center of excellence. Emphasis is given to the importance of early diagnosis and treatment to avoid elevated lethality.

Patients and methods

Four hundred and forty-five patients with VL, aged up to 14 years, were admitted to the Instituto Materno Infantil de Pernambuco (IMIP), one of the regional centers of excellence within the state of Pernambuco for the diagnosis and treatment of this disease, during the period between May 1996 and December 2001. Eight medical records were not located and other patients were excluded, despite a final diagnosis of leishmaniasis, because they did not fit the study's inclusion criteria. Data was obtained by retrospective analysis of the medical records of children admitted with VL and entered onto a standardized form. The form, developed by the research group, covered identification, origin, domestic characteristics, maternal education, primary complaints and their durations, previous treatment history, physical examination findings, laboratory test results and treatment received. Patients were included who had had a diagnosis confirmed by myelogram, direct agglutination test (DAT) $\geq$ 1/1,600 or indirect immunofluorescence (IIF) $\geq$ 1/40 as were probable cases in which myelogram results were negative but there was a clinical, epidemiological and laboratorial (pancytopenia) suspicion of leishmaniasis, ruling out other pathologies.

Nutritional status was assessed based on a weight for age scale, at the point of admission, taking the United States' *National Center of Health's Statistics* curves as a reference. Children with edema of at least the feet were considered severely malnourished (edematous malnutrition). Pancytopenia was diagnosed when leukopenia was present set at WBC $\leq$ 5.000/mm³. Anemia was defined as hemoglobin < 11 g/dl for patients between six months and five years old, < 11.5 g/dl for those between six and nine and < 12 g/dl for female adolescents and <12.5 g/dl for male adolescents. Thrombocytopenia was defined as a platelet count < 150.000/mm³.

Statistical analysis was performed using Epi-Info 6.0 4b, to produce distributions for frequency, mean average and standard deviation from the data returned when applicable.

Scientific and ethical aspects were approved by the Ethics Commission at the Hospital before data collection commenced.

Results

The distribution of cases over time is shown in Table 1. The greatest number of cases in any one year (180) occurred in 2000, although peak lethality observed in 1999 (14.8%).

Fifty point three percent of the children were female. The average age was 4.2 years (SD = ±3) and the youngest child was 4 months old. The worst affected age group was the under-fives (68.2% of cases) and 9% of the children were less than one year old. Of the 317 cases in which information was available on the mother's educational level, it was found that the average length of time spent at school was 3.1 years (SD = ±3)**.** Three hundred and fifty-eight medical records yielded information about sewerage and sanitation and of these around 70% of patients did not have access to these services at home.

Table 1 - Distribution of children admitted to IMIP with diagnosis of leishmaniasis from May 1996 to December 2001

Year	Cases	Deaths (n)	%
1996	25	–	–
1997	34	2	5.9
1998	26	2	7.2
1999	94	14	14.8
2000	180	18	10.0
2001	72	08	11.1
Total	431	44	10.2

Source: Pesquisa HGP/IMIP.

The majority were from Pernambuco State itself (99%), three were from Alagoas and one was from Paraíba. Eighty-two point five percent of the sample was from the interior of Pernambuco state while 14.8% were from the metropolitan region of the state capital Recife.

Nutritional evaluation revealed that 44.5% of the population under study was under-nourished, while 26.9% of the children were severely malnourished graves.

The patients had suffered from the disease before hospitalization for periods varying from 2 to 365 days, giving an average of 42.7 days (SD = ±45). Eighty-eight point seven percent of the patients had endured symptoms for less than 60 days before seeking treatment. The average hospital stay was 11.2 days (SD = ±5,7), varying from zero to 47 days. Among the symptoms referred to by family members, the following stand out as the most common: fever, increased abdominal volume, pallor, anorexia and coughing (Table 2). Approximately 50% of the patients' mothers had tried some type of medication, chiefly antibiotics. Fifteen parents reported having used leishmaniasis-specific treatments.

Table 2 also contains the findings of physical examinations at the point of admission, recording that splenomegaly, pallor and hepatomegaly were the most common abnormalities. Some type of infection was detected on admission in 47 (10.9%) of the children, of which the most common were: pneumonia in 66% of cases, otitis in 18.4% and sepsis in 8.2%.

Table 2 - Main symptoms and clinical findings of children admitted to IMIP with diagnosis of leishmaniasis from May 1996 to December 2001

Symptoms	**n**	**%**
Fever	412	95.6
Abdominal volume	277	64.3
Pallor	250	58.0
Anorexia	215	49.9
Coughing	181	42.0
Weight loss	163	37.8
Asthenia	163	37.8
Abdominal pain	73	16.9
Diarrhea	55	12.8
Edema	71	16.5
Infection	50	11.6
Clinical findings	**n**	**%**
Splenomegaly	418	97.0
Pallor	393	91.2
Hepatomegaly	376	87.2
Malnutritrion	191	44.5
Edema	69	16.0
Dyspnea	53	12.2
Infection	47	10.9
Hemorrhage	49	11.4
Jaundice	19	4.4

Source: Pesquisa HGP/IMIP.

Hematological data from the point of admission on red and white blood cell and platelet tests are listed in Table 3. The average hemoglobin level was 6 g/dl, and erythrocyte transfusions were necessary for 170 patients while interned. Average white blood cell count was 3,516/mm³ and was below 5,000/mm³ in 367 cases (85,3%). The average neutrophil level was 1,215/mm³ and values below 500/mm³ were found in 15.9% of the patients. Average platelet count was 118,641/mm³. Forty-three platelet transfusions were required and 68.4% of the patients had $\leq$ 150.000/mm³ platelets on admission.

Table 3 - Hematological data of children admitted to IMIP with diagnosis of leishmaniasis from May 1996 to December 2001

Parameters	**Mean±SD**	**Value Minimum**	**Maximum**
Red blood cells (g/dl)	6.1±1.7	1.8	11.2
White blood cells (mm³)	3,516±1,923	600	16,300
Neutrophils (mm³)	1,215±1,052	32	9,682
Platelets (mm³)	118,641±88,359	2,540	808,000

Source: Pesquisa HGP/IMIP.

It was possible to confirm diagnosis in 79.4% of cases. Four hundred and twelve patients were investigated for the parasite using myelograms, of whom 311 (75.5%) had positive results. DAT was positive in 28 cases and IIF in three. In the remaining cases, in which none of the above methods gave definitive proof, analysis of epidemiological, clinical and laboratory data was enough to justify treatment.

The treatment of choice for visceral leishmaniasis was glucantime (meglumine antimoniate) for 98% of the patients. Seven of these received glucantime in association with allopurinol. Seven patients continued to suffer symptoms after the first course of treatment and were given amphotericin B. The average time taken for fever to recede was 3 days (SD = ±2.7) and 50 patients did not exhibit fever while hospitalized. Seven patients died before receiving treatment specifically directed at the disease.

There were 44 deaths registered, among which the average length of hospital stay was 10 days (SD = ±9) and two patients died on the day of admission. Immediate causes of death included infection in 32 (72.7%) cases, hemorrhage in 26 (59.0%) and liver failure in 14 (31.8%). Seventy percent of the patients had more than one affliction in association (Table 4). The most common infections were pneumonia in 26 (66.7%) and sepsis in 15 (38.5%) patients. Convulsions and respiratory insufficiency were each observed in nine patients directly prior to death.

Table 4 - Main death causes in children admitted to IMIP with diagnosis of leishmaniasis from May 1996 to December 2001

Causes	Death	
	n	%
Associated infections	32	72.7
Hemorrhage	26	59.0
Hepatic insufficiency	14	31.8
Hemorrhage + infection	10	22.7
Hemorrhage + infection + hepatic insufficiency	10	22.7
Severe anemia	8	18.2
Infection + hepatic insufficiency	4	9.0

Source: Pesquisa HGP/IMIP.

Discussion

One important characteristic of visceral leishmaniasis is that the greater the incidence of the disease, the greater the risk to the youngest children. This fact has already been documented in Brazil, where the disease's preference for the infant population has remained constant over the years.[3,5,7,11] The characteristics of the current study are similar, with VL predominating among under-fives, in which age group 68.2% of the sufferers are to be found. Since lasting immunity develops with age 1 it is probable that the higher incidence of and death rate among the lower age group is due to increased susceptibility to infection and the reduced levels of immunity observed within this age group.

Extant literature suggests that the male sex is more prone to this disease.[3,5,12] In this series, children of both sexes were equally affected. We would point out that the issue of higher rates of prevalence among males has not yet been completely understood. It has been suggested that there may be a hormonal factor linked to gender or exposure.[13]

The distribution of the disease across Brazil reveals a cyclical tendency with a peak recorded in 2,000 also reflected in our sample. The increase in the number of cases during the study period is probably the result of endemic areas expanding which has led to the appearance of the disease in the outskirts of large cities, an occurrence hitherto unknown, which has made diagnosis more difficult and increased lethality rates. In fact, since the last few years of the eighties, leishmaniasis has been expanding into previously unaffected rural areas and into the peripheral regions of large urban centers.[3,14] In Pernambuco, VL was traditionally found on the coast and the high sierra; nowadays it affects almost the entire State,[15] including the metropolitan area of the State capital Recife,[16] which fact was highlighted in this study where almost 15% of the children came from the metropolitan area of Recife.

Unsatisfactory socio-economic living conditions are associated with increased incidence of a number of different infectious diseases including VL, as can be seen in this sample where, despite the majority of patient residences being brick-built, the availability of running water and sewerage is still at an unacceptably low level. It is rare for the classic form of the disease to affect middle-class people, even in endemic areas.[3] According to Bezzerra,[17] the level to which parents have been educated has a protective relationship with this infection, as can be corroborated by the results of our investigation, in which around 80% of the mothers had only received elementary education.

When confirmed cases were compared with probable cases it was found that there was no statistically significant difference between the two groups in terms of sex, age, origin or nutritional status. However, when the time during which the disease had been evolving before admission was evaluated we noted that the probable cases had been progressing for a significantly shorter period of time (30.4 days) than had the confirmed cases (459 days).

The great variation in disease duration before admission (2 days to one year), is in line with published data. Pastorino[11] reports an average period of 6 months, while Marzochi[18] describes a range of 1 to 5 months. Leishmaniasis is generally an insidious disease, with non-specific initial symptoms. This, in conjunction with potential bias due to faulty memory and the low educational level of the populations of endemic areas makes this variable particularly difficult to interpret. Furthermore, the high proportion of cases (at least 30%) in this series, in which medical attention had been sought previously and in which other medications, including antibiotics, had been used, suggests that opportunities for early diagnosis may have been lost. This must be a cause for concern in areas in which leismaniasis is endemic since late diagnosis is a risk factor for death.[19]

Nutritional evaluation revealed the disease's wide range of clinical variation, demonstrated by the presence of patients within the normal weight percentiles (55% of the children), while approximately 27% were severely malnourished. It should be noted that a majority of the children (83%) had suffered from the disease for less than 60 days; a period which may well not be sufficient for chronic nutritional problems to develop and which may explain the presence of well-nourished patients, as Pastorino[11] also observed. It is possible that under-nourishment may suppress the cell-mediated immunoresponse and thus be responsible for the development of progressive visceral leishmaniasis.

The clinical manifestations of leishmaniasis exhibited by the children in this sample were similar to those in published descriptions[1-3,5,7,11] both in terms of symptoms described by family members and physical findings. Fever, hepatosplenomegaly and wasting are the classic signs of the disease and were presented by almost all of the patients at the point of admission. This is because it is

precisely at this point in the clinical course that the majority of patients arrive at the clinic or hospital and it becomes possible to confirm diagnosis. The fact that many mothers describe previous attempts at medication is of no surprise as the initial symptoms are common to many childhood diseases leading to diagnostic confusion. Previous use of drugs specifically for the treatment of leishmaniasis by 3.5% of the sample should be taken as a warning of the possibility of resistance to therapy or of its failure. Cases refractory to treatment have been described before in Brazil by Badaró[20] and, in the majority of cases, are the result of inappropriate treatment.

Infection is one of the principal complications associated with VL and it has even been described in relation to subclinical forms of the disease. It affects people of all ages and in its classic form is associated with a fatal outcome in around 50% of cases.[11,21,22] In this investigation, infection was found to have been present in 10.9% of the patients at the time of admission, developed in 24.4% of cases during hospitalization and was associated with leishmaniasis in 72.7% of the patients who died. The most common infections were pneumonia, otitis, skin infections and sepsis. Reduced length hospital stays and the resulting reductions in exposure to nosocomial germs may have had an influence on the incidence of nosocomial infections; an aspect which should be better explored ion future studies. As has been explained by other authors,[20-22] in this sample, a number of different factors, in association or isolation, may have been associated with infection. Of these factors, average hemoglobin, leukocyte and neutrophil levels deserve special attention.

Descriptions of liver involvement contain percentages varying from 2 to 28% of patient samples,[23,24] with higher frequencies occurring when VL diagnosis is late and indicating a higher degree of severity. Liver problems are often resolved during the course of treatment. Moderate forms of hepatitis are the most frequent liver complaints and, in the majority of cases, are only diagnosed by means of laboratory test results.[23] In our study, 19 (4.4%) children were admitted with jaundice. There is a possibility that liver compromise has been underestimated since hepatic enzymes were not routinely measured and only the clinical criterion (jaundice) was used for diagnosis of liver involvement. The pentavalent antimony (glucantime), that was used to treat the disease, is known for its principle side effect of liver toxicity[7,21,25] and can contribute to liver failure. However, because jaundice was calculated only at the time of admission and as none of these patients had previously been given glucantime, liver involvement was probably the result of leishmania hepatitis, as Jerônimo observed in Natal.[25]

In the current study, hemorrhagic phenomena were observed in 12.3% of the patients at the time of admission and in around 60% of the patients who died. It is, therefore, an important warning sign as to the severity of the disease.

According to the WHO, anemia is recorded in 98% of cases diagnosed in Brazil and, when severe (< 5 g/dl), is an indication for hospitalization. An early study performed at the IMIP[7] found that 88% of the patients were anemic, while in the present sample this occurred in 99.5% and in 25% hemoglobin levels were < 5 g/dl. It is probable that the anemia has multiple origins and it could be the result of cessation of production by bone marrow, splenic sequestration, immune hemolysis, hemorrhage, intestinal parasites or iron deficiencies. We draw attention to the fact that severe anemia should be considered one of the most import factors in the management of and vigilance over these patients, and erythrocyte transfusions should be given whenever necessary. Leukopenia and neutropenia (< 1,500/mm³) are found with great frequency among LV patients,[2,11,26] in common with what we have found in our work, where 85% of the children progressed to leukopenia and 74% to neutropenia, probably because of hypersplenism with or without hypoplasia or marrow depression and hemophagocytosis. Thrombocytopenia is a common finding with VL patients and is exhibited by between 50 and 70% of patients.[11,26,27] Alves,[7] in an earlier study at the IMIP, found thrombocytopenia in 64.7% of the patients. This is similar to the results of the current study, in which 68.4% of the children had platelet counts below 150,000/mm³. Platelet counts can be a predictive factor for severe hemorrhage which was one of the causes of death, and so should be monitored carefully.

The present study's results reveal a lethality rate of 10.2% which was similar to rates found in three hospitals in Natal (9%) by Jerônimo,[25] in a São Paulo teaching hospital by Pastorino[11] (9.3%) and in an earlier study at the IMIP by Alves.[7] It can, however, still be considered elevated when compared with national lethality rates which have varied between 3.6% in 1997 and 6.3% in 1990, according to data published by the Brazilian Health Ministry.[14] The elevated lethality rates found in this and other studies performed in hospitals, may be due to the fact that centers of excellence and more complex hospitals may well attract the cases that are of a greater potential severity, thus selecting a clientele that is at greater risk of death. Furthermore, national statistics based on notification systems possibly underestimate the real number of deaths due to leishmaniasis nationally due to incomplete case follow-up.[5] Of the 44 deaths registered from among our sample, 38 were children under five years old and 47.7% were under-nourished, in common with published data.[7,19,24] The main immediate causes of death were similar to those described by other authors: infection, hemorrhage, anemia and liver failure.[5,9,11,22,23] Despite previous knowledge of the main immediate causes of death, they persist over the years even though there is evidence of a general decrease in lethality.[6] This being the case, there are both indications and space for vigorous activities with the objective of achieving significant reductions in lethality. To this end it is

necessary to empower health workers, nursing professionals and doctors to recognize and treat the disease as early as possible.

Further complicating the problem is the fact that a large proportion of the municipalities affected encounter operational difficulties due to deficiencies in the basic health system, still in the process of creation, in particular in terms of VL diagnosis, treatment and notification. All this is proof of the necessity of greater integration between the activities of disease control and health care.

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