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HUMAN VISCERAL LEISHMANIASIS: FROM DIAGNOSIS TO TREATMENT

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ABSTRACT

Leishmaniasis is a parasitic disease caused by the protozoan of the genus Leishmania, which affects millions of individuals, particularly in tropical and subtropical regions, and is therefore responsible for high mortality and morbidity. Due to the relevance of this pathology, the objective was to build a literature review with emphasis on its diagnosis and treatment, addressing its clinical-pathological characteristics. The bibliographic research was built based on the analysis of articles from the electronic databases SciELO (Scientific Library Eletronic) and PUBMED. In men, the disease is characterized clinically and laboratorially by fever, anemia, hepatosplenomegaly, pancytopenia and changes in the cellular immune response, affecting mainly children. The disease is usually fatal when left untreated, and death results from complications such as secondary bacterial infections and coagulation disorders. The diagnosis is routinely made based on clinical and epidemiological parameters, associated with parasitological, serological and immunological methods. As for treatment, antimonial compounds are still the drugs of choice for the treatment of the disease. Of all the great endemics, leishmaniasis are certainly the ones with the greatest number of knowledge gaps and for this reason many doubts still need to be clarified.

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INTRODUCTION

Visceral leishmaniasis (VL) is a disease caused by protozoa of the genus Leishmania (L. donovani, L. chagasi and L. infantum) that parasitize cells of the host's mononuclear phagocytic system. It is one of the most important infectious diseases worldwide, affecting approximately 200,000-400,000 people and causing about 20,000 to 40,000 deaths each year. VL is autochthonous in 65 countries, in which the majority of cases (90%) occur in five countries: Bangladesh, India, Nepal, Sudan and Brazil (ALVAR *et al*., 2012; DESJEUX, 2004).

It is a generalized, chronic infectious disease, characterized by fever, hepatosplenomegaly, lymphadenopathy, anemia with leukopenia, hypergammaglobulinemia, edema and a state of progressive weakness, leading the patient to death if he does not undergo specific treatment. In India, it is known as kala-azar (meaning deadly disease) or dum-dum fever; in the Mediterranean, as infantile or visceral leishmaniasis; and, in Brazil, as visceral leishmaniasis or kala azar (GENARO, 2005). Currently, it is among the six endemic diseases considered priority in the world (WHO, 2009). It is a pathology considered an important public health problem and

WHO has concentrated its efforts on research for new diagnostic tests, drugs for treatment and vaccines (DESJEUX, 2004). Although the confirmatory diagnosis can only be made through the presence of the parasite in the infected tissue, the suspected diagnosis of VL must be based on epidemiological data and on clinical and laboratory findings (Pastorino *et al*., 2002). Of all the major endemic diseases, leishmaniasis is certainly the one with the greatest number of knowledge gaps. In addition, specific areas such as therapy have performed modestly in recent decades (Carvalho, 2005). Given the above, the objective of this work is to conduct a literature review about the diagnosis and treatment of VL. Clinical aspects, physiological and histopathological changes of VL will be addressed, which are indispensable in the construction of the diagnostic hypothesis and in the conduct exercised in the treatment of this disease.

EPIDEMIOLOGY

In Brazil, from 1990 to 2008, 48,149 cases of VL were reported, 4,236 in the state of Minas Gerais. In the last 10 years, the annual average of cases of VL was 3,383 cases; and the incidence of 2.0 cases per 100 thousand inhabitants (MAIA-ELKHOURY *et al*., 2007). In Montes Claros, the first indigenous case was notified in 1975. Since then, an increasing number of cases have been diagnosed each year. The Regional Health Management (GRS) of Montes Claros / SES-MG has 53 municipalities and presented an important epidemic of VL in 2004, as observed in Minas Gerais (RESENDE *et al*., 2009).

CLINICAL CHARACTERISTICS OF THE PATHOLOGY

In general, the disease has a long evolution. The initial symptoms are insidious and nonspecific, with fever, diarrhea, adynamia, prostration, general malaise, dry cough, pallor, progressive weight loss and mild splenomegaly (DESJEUX, 1996). Malnutrition has been described as a risk factor for the acquisition of VL, especially in children from endemic areas (ANSTEAD *et al*., 2001; MACIEL *et al*., 2008). Some studies have shown that malnourished patients have a worse prognosis, that is, a higher lethality and high chances of complications (CAVALCANTE, 2007; COLLIN *et al*., 2004). Fever has no special characteristics, and it can be intermittent or continuous. Bleeding is uncommon at first, this phase lasts two to six weeks. The incubation period is inaccurate. Some studies suggest periods of three to eight months (PISCOPO; MALLIA AZZOPARDI, 2007). As the disease progresses, the symptoms become decisive, characterizing the period of infection status. At this stage, the clinical picture is fever, cough, diarrhea, nausea, vomiting, dyspnea on exertion, headache, tinnitus, myalgia, arthralgia, adynamia, pallor, increased abdominal volume, low back pain, progressive weight loss, hair loss, dry hair and matte. Hepatosplenomegaly is observed in practically all cases, with splenomegaly being more exuberant and significant than hepatomegaly (CARVALHO, 2005; CAVALCANTE, 2007). In the final period, the patients are seriously ill, with continuous fever, exacerbation of the alterations present in the state period and more intense impairment of the general condition. Critical levels of hemoglobin (5-6 g%) and congestive heart failure are very common. Peripheral pancytopenia with very high globulins is the rule in these patients who, in general, do not respond promptly to the usual treatment (DIETZE; CARVALHO, 2003).

LABORATORY DIAGNOSIS

Hematological and biochemical tests: Laboratory findings show many changes: the erythrocyte sedimentation rate (ESR) is high and hemoglobin is, in general, below 10g%. The leukogram shows leukopenia with neutropenia, absent eosinophils, monocytosis and relative lymphocytosis. Platelets are generally decreased (AL-JURAYYAN *et al*., 1995). Among biochemical tests, liver function tests are abnormal, transaminases are increased, bilirubins slightly elevated and prothrombin activity between 60 and 80% (BADARÓ; DUARTE, 2005).

Parasitological diagnosis

Visualization of the parasite in the LV by direct methods or isolation by culture can be done in peripheral blood, bone marrow smears and splenic aspirate. Parasites can also be detected in liver or lymph node biopsy material, but with less sensitivity (ZIJLSTRA *et al*., 1992). *Immunological tests:* they are indirect methods of detecting the parasite. In Brazil, the most used techniques are indirect immunofluorescence (RIFI) and enzyme-linked immunoabsorbent assay - ELISA, immunochromatography assays. RIFI has a sensitivity of 87 to 100% and specificity of 77 to 100% and, despite being less sensitive than ELISA, it is the most used method in Brazil because it is available free of charge in most endemic regions, through the Leishmaniasis Program from the Ministry of Health (WHO, 2009). Other immunological tests that can also be performed for the diagnosis of VL are: The direct agglutination test (DAT) with sensitivity and specificity between 70 and 100% (PEDRAS *et al*., 2008) being useful as a first diagnosis in an endemic area (BOELAERT *et al*., 2004), immunochromatographic tests (Kalazar detect) that are easy to perform and interpret, being promising in the rapid diagnosis in endemic areas, their sensitivity and specificity have been above 98% (BERN *et al*., 2000). Recently, recombinant 39-amino-acid-repeat recombinant antigen leishmain - (rK39) antigens, defined as species-specific for L. chagasi, have been used in rapid immunochromatographic tests (BOELAERT *et al*., 2007). Multicenter study with commercial test for detection of antibody against the L. chagasi rK39 antigen performed in Brazil found sensitivity of 93% and specificity of 97% (ASSIS *et al*., 2008), opening up the prospect for a quick, easy and interpretation. Another test involving the use of molecular biology has allowed the detection of deoxyribonucleic acid (DNA) of the parasite through the use of polymerase chain reaction (PCR) techniques in biopsy tissues or in peripheral blood leukocytes from patients infected with VL, showing high sensitivity (92.3%) and specificity (97.5%) (BRUSTOLONI *et al*., 2007). However, this technique remains complex and expensive (WHO, 2009).

LV TREATMENT

Pentavalent antimonial compounds were introduced in the treatment of leishmaniasis in the 1940s and, since then, have been considered the drug of choice (Carvalho, 2005). In Brazil, N-methyl glucamine antimoniate (the only formulation available in the country) is used, at a dose of 20 mg / kg / day, for 20 to 40 consecutive days, parenterally (intramuscular - IM

or intravenous - IV), with efficiency greater than 95%. Despite more than seven decades of use, its mechanism of action is not yet fully understood, but it is known that the drug acts in the amastigote forms of the parasite (BERMAN, 1988). Of all the drugs used to treat leishmaniasis, antimonials, are the ones whose side effects are best known. In the gastrointestinal tract, the most frequent side effects include nausea, anorexia and abdominal pain, in percentages ranging from 12 to 28%. Hepatoxicity occurs in up to 50% of treated patients (FRANKE *et al*., 1990). Abdominal manifestations are due, in part, to chemical pancreatitis, which occurs in almost all patients (GRASSER *et al*., 1994). Antimonials are eliminated mainly via the kidney and in high doses they can cause kidney failure, renal impairment can reach 72% of cases (SAMPAIO *et al*., 1997). Although the toxic effects of antimonials are almost always reversible, they can become serious and lead to death if they are not identified (OLIVEIRA *et al*., 2009).

The second drug of choice for the treatment of VL is amphotericin B. It is the most potent of antileishmania drugs available, with an effect demonstrated both in vitro and in vivo. Its mechanism of action is due to the change in the permeability of the pathogen's membrane, promoting loss of nutrients and cell lysis (CROFT, 2002). Due to the increase in resistance to antimonials in the last decade, amphotericin has been more widely used in India (OLLIARO *et al*. 2005). The main side effects attributed to amphotericin B include: fever, chills, headache, asthenia, muscle and joint pain, vomiting and hypotension, usually observed during the infusion of the drug (CHIA; POLLACK 1989). Renal damage can occur when the total dose reaches 30 and 75 mg / kg of weight. Hypokalemia, hypomagnesemia, neurotoxicity, renal tubular acidosis and cardiotoxicity can also happen (BURGESS; BIRCHALL, 1972).

The new lipid formulations of amphotericin B, which emerged in the early 90s, have the following advantages: effectiveness close to 100% and reduction of side effects and treatment time, which can vary from one to five days (MEYERHOFF, 1999). The cost, however, is high, which makes its use difficult. Therefore, its use is recommended in patients who have presented therapeutic failure or toxicity to amphotericin B deoxycholate, kidney transplant patients or patients with renal failure (BERMAN *et al*., 1998). Miltefosine is the first effective oral agent for VL (BERMAN, 2005). It was first registered in India, with studies in 2000 and 2002, but evaluated only in the private market (SUNDAR; MURRAY, 2005). Daily doses of 2.5 mg / kg of weight administered orally for 28 days showed cure rates close to 94% (SUNDAR *et al*., 2000). Miltefosine is still being evaluated in Brazil in a clinical trial for the treatment of visceral leishmaniasis caused by L. (L.) chagasi.

Final Considerations

LV in Brazil has behaved like a rural anthropozoonosis until recently, but in the last 20 years its expansion has also been observed in the peri-urban regions of large cities, causing the pathology to present, today, a new model of urbanized eco-epidemiological distribution , currently having great relevance in the epidemiological context of the main urban areas of Brazil and the world and being considered an important public health problem. However, the scientific knowledge developed so far on the subject does not match its real importance. There is also a huge gap in knowledge about VL. Many challenges must be overcome in the fight against this pathology, but the emphasis must be placed on scientific, technological development and innovation in health. It is necessary to concentrate efforts on research for new diagnostic tests, new drugs for treatment and vaccines, so that VL is no longer a public health problem.

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