Research Article

Study of visceral leishmaniasis (kala-azar) in children of Iraq

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Date Submitted:1.12.2011

Date Accepted:10.4.2012

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Abstract

Background: Leishmaniasis is a parasitic disease caused by a Leishmania species, transmitted to humans through bites of female sand fly and is endemic in Iraq.

Aims: To study the epidemiological, clinical, diagnostic and therapeutic aspects of visceral leishmaniasis in Iraqi children.

Patients and Methods: This was a retrospective study done on patients with Kala-azar admitted to Welfare Child Hospital-Medical City from October 2004 to September 2005. The diagnosis was based on serological test and/or bone marrow exam. For each patient the following data were reviewed: age, sex, time of admission, signs, symptoms, laboratory investigations and treatments.

Results: A total of 50 visceral leishmaniasis cases were included. All patients were in the age range 0-10 years. Most cases occur in winter 70%. Fever was recorded in 100%, splenomegaly in 92%, hepatomegaly in 80%, and pallor in 70% of cases. Concomitant conditions were frequent: 34% of cases had cough; jaundice was present in 26%; diarrhea in 18%; vomiting in 12% whereas lymphadenopathy was present only in 1% of cases. Sodium stibogluconate (pentostam) was most often prescribed medication (86% of cases) while miltefosine was less prescribed (14% of cases).

Conclusions: in Iraq, kala-azar should be suspected in any patient with prolonged fever and/or hepatosplenomegaly with pancytopenia whereas in case of presence of lymphadenopathy the kala-azar would be the last possible differential diagnosis. Also Pentostam remains the most common prescribed medication for kala-azar in our country.

Keywords: Leishmaniasis, Kala-azar, Hepatosplenomegaly

INTRODUCTION

Visceral leishmaniasis also known as kala azar, is a vector borne disease caused by a protozoan of leishmania donovani.[1] A phlebotomize sand fly transmits the parasite from person to other or via an animal reservoir. This disease is the second-largest parasitic killer in the world (after malaria), responsible for an estimated 500,000 cases each year worldwide.[2] The disease is endemic in tropical and subtropical regions except Australian and anctarctila.[3] In Iraq it represent one of the serious public health problems and it is more in south and middle and lowest in north, with highest frequency in winter followed by spring and more lower in summer and autumn.[4-6]

In endemic area incidence of clinical disease decrease with age indicating that immunity is acquired in population overtime.[7] This disease typically affects children less than five years of age in new word and Mediterranean region.[8]

Visceral leishmaniasis is characterized by intermittent fever, substantial weight loss, enlargement of the spleen and liver, and anemia (occasionally severe). Although anemia is a usual finding, autoimmune hemolytic anemia has rarely been reported in association with this disease.[9] Less frequently, other symptoms could be seen such as diarrhea vomiting, respiratory symptoms and lymphadenopathy.[1, 3] Appetite usually remains good.[3] Petechiae, echymoses and mild edema may appear, but jaundice and ascites are rare.[9] In the present study we describe the epidemiological, clinical, diagnostic and therapeutic aspects of visceral leishmaniasis in Iraqi children based on reported cases between 2004 and 2005.

PATIENTS AND METHODS

This retrospective study was performed to children with visceral leishmaniasis admitted to Welfare Child Hospital-Medical City from October 2004 to September 2005. Visceral leishmaniasis was defined as identification of the amastigote form of Leishmania in bone marrow smear, positive serological test (immunofluorescence antibody test), or both in a patient with manifestations compatible with visceral leishmaniasis i.e. fever, hepatosplenomegaly, anemia, leukopenia, and thrombocytopenia. Fever was defined as a temperature >38°C. Anemia was defined as a hemoglobin value of <9.0 g/dL while in severe anemia the value is <7 g/dL. Reticular production index was defined as low when its <2 and high when its >3.[10] Coombs-test had been done to patients with normal and high reticular production index. Leukopenia was defined as <4000 WBCs/mL of blood and thrombocytopenia as <150,000 platelets/mL. Patients were treated with Sodium stibogluconate (pentostam) or with miltefosine. Patients were considered to have achieved hematological restoration if we noted recovery of their WBC count (> 4000 neutrophils/mL), platelet count (> 150,000 cells/mL), and hemoglobin (>9.0 g/dL).

Clinical response was assessed at the completion of treatment and was defined as cure (defervescence, restoration of laboratory parameters, or significant reduction of spleen size) or failure (persistent or worsening clinical and laboratory findings). Relapse was defined as the reappearance of signs and symptoms of infection in association with identification of amastigote forms of Leishmania in bone marrow smear after initial successful treatment.[3] For each patient the following data were reviewed: age, sex, time of admission, signs, symptoms, laboratory investigations and treatments. The response to treatment was also noticed. All data were tabulated, diagrammatized and analyzed through descriptive statistics in a Microsoft Excel spreadsheet, release 2010.

RESULTS

During the period of study, 50 children were diagnosed with visceral leishmaniasis. The patients' median age was 1.7 years (range, 3 months–10 years); twenty patients (40%) were aged <12 months. Thirty patients (60%) were males. Most cases 43 (86%) presented in winter and spring while few cases 7 (l2%) were seen in summer and autumn (Table 1).

Most patients 39 (78%) needed less than four weeks for diagnosis and treatment to be established, 17 patients (34%) were diagnosed within two weeks of onset of symptoms whereas only 11 patients (22%) needed more than four weeks to be diagnosed (Table 2).

Table 1. Seasonal distribution visceral leishmaniasis**.**

Month of onset	No. of patients	Percentage
Jan.	17	34%
Feb.	5	10%
Mar.	3	6%
Apr.	2	4%
May	2	4%
June	1	2%
July	1	2%
Aug.	1	2%
Sep.	1	2%
Oct.	1	2%
Nov.	2	4%
Des.	14	28%
Total	15	100%

In our patients, the most frequent signs & symptom was fever which present in all patients 50 (100%), while the least frequent feature was lymphadenopathy which present in only 1 patient (2%) (Table 3).

Table 2. Delay in admission in cases of visceral leishmaniasis.

Time from onset (In wks.)	No. of patients	Percentage
< l	3	6%
1-2	14	28%
3-4	22	44%
5-6	2	4%
7-8	2	4%
<9	5	10%
>9	2	4%

Table 3. Frequency of clinical features in cases of visceral leishmaniasis.

Clinical Features	No. of Patients	Percentage
Fever	50	100%
Splenomegaly	46	92%
Hepatomegaly	40	80%
pallor	35	70%
cough	17	34%
jaundice	13	26%
Diarrhea	9	18%
vomiting	6	12%
Edema & ascites	5	10%
Bleeding tendency	2	4%
Lymphadenopathy	1	2%

Regarding hematological evaluation, the most frequently encountered finding in this study was anemia which was detected in in 46 patients (92%), of them 30 patients (60%) had severe anemia (Table 4).

Table 4. Range of anemia in cases of visceral leishmaniasis.

Hb g/dl	No. of Patients	Percentage
<7	30	60%
7-10	16	32%
>10	4	8%
Total	50	100%

In this study it has been found that reticulocyte production index was higher than normal in 7 patients (14%), normal in7 patients (14%) and low in 36 patients 72% (Table 5).

Regarding other hematological parameters, it has been found that leukopenia was present in 24 patients (48%), whereas thrombocytopenia in 16 patients (32%).

Diagnosis of visceral leishmaniasis was established by direct microscopy of bone marrow together with positive IFAT in 5 patients; by means of IFAT alone in 36 patients and by microscopy alone in 9 patients. Diagnosis was made at a median of 1 day (range, 0-10 days) after admission.

Table 5. Reticulocyte Production Index (RPI).

RPI	No. of Patients	Percentage
<2	36	72%
2.1-3	7	14%
>3	7	14%
Total	50	100%

Forty three of the patients (86%) were treated with Sodium stibogluconate (pentostam) while the rest 7 patients were treated by the new oral drug miltefocine. All patients treated with sodium stibogluconate recovered, and none relapsed whereas of the 7 patients treated with miltefocine, 1 was still febrile after 6 days, so treatment was switched to sodium stibogluconate. Overall, all 49 patients became afebrile a median of 3 days (range, 1-6 days) after treatment was initiated, whereas hematological restoration occurred a median of 15 days later (range, 7-28 days).

DISCUSSION

Leishmaniasis is recognized as an important public health problem in some countries including Iraq owing to its considerable impact on morbidity, which impose a heavy burden on national health.[1-3, 11] In the current study about 2/3 of patients were below 2 years of age and this result was compatible with other Iraqi studies [4-6] and with studies from Saudi Arabia and Yemen. [12, 13] this finding is different from what found in India and Africa, where the disease affect older children and adults.[14, 15] Hence, the disease in Iraq is similar to the Mediterranean variety; namely, zoonosis for which canines are the main reservoir. On the other hand, the youngest patient affected in this study was 3 months of age which might be attributed to the incubation period of the disease and also referred to the possibility of congenital transmission of the disease which should be confirmed by Montenegro skin test of the mother.[16]

This study showed obviously that visceral leishmaniasis is seen throughout the year, suggesting that the sand flies, which are the vectors of kala azar, are present throughout the year. The highest number of cases was recorded in winter and spring and less number of cases was in summer and autumn and this is agreement with other Iraqi studies.[4-6, 17] This differ from Saudi Arabia where

is the peak in late spring and summer, then declines in winter.[13, 18] This finding corresponds to the sand fly season in our country that last from April to November with maximum peak in September, taking the consideration of incubation period of the parasite.[17]

An interesting finding in the present study was the appearance of lymphadenopathy during the course of visceral leishmaniasis in 1 patient (2%). This is probably a quite common feature in African type of the disease. [15], but it is rarer in our region.[8, 12, 13] Moreover, in our experience, except for slightly enlarged posterior cervical lymph nodes, which is actually common but nonspecific finding among children 2–14 years of age, lymphadenopathy was not detected in any case. It would be very valuable to know if, in the more recently reported pediatric researches, the finding of enlarged lymph nodes was unquestionably correlated to visceral leishmaniasis or, it was an occasional finding related to concomitant conditions rather than the Kala-Azar itself.

Bronchopneumonia is a well-known complication in patient with Kala-Azar; it may mask the real cause of the disease and delay the diagnosis. In this study respiratory symptoms especially cough was presented in 17 patients (34%) which is lower than other Iraqi studies and higher than studies in Saudi Arabia and Yemen,[4-6, 12, 13] and this indicates that infected children should be carefully evaluated for respiratory complications like pneumonia.

All our patients presented with fever, and the majority with hepatosplenomegaly which is similar to other studies done in Iraq,[4-6] while it is lower than the incidence of organomegaly recorded in Saudi Arabia.[13] So this may indicate that parents of our patients may seek early medical advice and Iraqi medical staff are with high awareness to kala azar, hence earlier diagnosis, was noticed in Iraq.

The main hematological findings in this study were anemia, leukopenia, and thrombocytopenia. Its well-known that Anemia is one of the most striking features of visceral leishmaniasis.[1, 3, 9] Anemia probably is multifactorial and due to combination of iron deficiency, bone marrow invasion and suppression (anemia of chronic disease) and hemolysis.[9] In this study 46 patients (92%) had anemia (60%) with severe anemia and (32%) with mild anemia and this result is compatible with other studies done in Iraq[4-6] but it was less than the another study from Saudi Arabia where there was 98.3% of cases developed anemia[13] which indicates early medical presentation.

It's well-known that reticulocyte production index RPI should increase in response to any loss of red blood cells.[10] If reticulocyte production is not raised in response to anemia, then the anemia may be due to a defect with red blood cell production in the bone marrow. In the present study it has been found that RPI was low in more than two third of patients. So although the cause of anemia is multifactorial, This study pointed out that 36 patients (72%) had bone marrow suppression as a cause of anemia while the hemolysis considered as a cause of anemia in 7 patients (14%), and this due to sequestration and destruction of the RBCs in the enlarged spleen, immune mechanism, alteration in RBC membrane permeability and the presence of RBC associated IgG circulating immune complexes and rheumatoid factor in patients with untreated visceral leishmaniasis.[19]

A critical issue we would like to highlight in the present study is the presence of positive Coombs test in 1 patient out of 14 anemic patients with normal and high RPI whom subjected to Coombs test. Its well-known that although anemia is a usual finding in visceral leishmaniasis, Coombs' positive hemolytic anemia has rarely been reported in association with this disease.[9] The present study confirm this fact and compatible with other study.[20] So visceral leishmaniasis must not be excluded in patients with Coombs' positive autoimmune hemolytic anemia and living in endemic region for this disease.

Total WBC was reduced less than 4000 cell/mm in 24 patients (48%) and that correlate with other Iraqi studies.[4,6] also platelet count were reduced to less than 150000/cub.mm in 16 (32%) patient. That goes with other studies in Iraq and Saudi Arabia.[4, 6, 13] Neutropenia and thrombocytopenia are likely to be due to hypersplenism as they are absent in patients who have splenectomy.[21]

Definite diagnosis of visceral leishmaniasis depends on demonstration of amastigotesin the tissue or isolation of the organism in culture.[3, 8] Concerning diagnostic method used in this study, it has been found that IFAT and BM are the main reliable tools in confirmation the diagnosis of kala-azar in patient suspected to have visceral leishmaniasis whereas there was no patient had B.M. culture because of lack of culture facilities in our country at time of study. Our cases were diagnosed within relatively short time compared to longer duration of illness reported from other regions,[12,13] this may be explained by high awareness of the disease among our

doctors which led them to earlier referral of the cases to hospital for confirmation of the diagnosis and treatment.

As far as therapy of visceral leishmaniasis is concerned, the respond to sodium stibogluconate drug in present study was excellent. This is similar to another Iraqi experiences.[4, 6] The Indian variety of disease also respond well to therapy, while in Africa seems to be less responsive (Relapse rates after treatment in Kenya ranges for (5-36%) but these patient may respond to a second or even third course of therapy.[14, 15]

In conclusions visceral leishmaniasis in Iraqi differs from African type in some aspects of presentation and in response to treatment. Kala-azar should be suspected in any patient with prolonged fever, hepatosplenomegaly and pancytopenia. The presence of lymphadenopathy in patient with fever and hepatosplenomegaly makes the K.A. is the least possible diagnosis whereas visceral leishmaniasis must not be excluded in patients with Coombs' positive autoimmune hemolytic anemia and living in endemic region for this disease. Finally sodium stibogluconate (pentostam) remains the drug of choice in treatment visceral leishmaniasis.

Conflict of interest: none

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