EPIDEMIOLOGICAL, CLINICAL AND THERAPEUTIC FEATURES OF PEDIATRIC KALA-AZAR

Kadivar Mohammad Rahim[1] and Moslehi Mohammad Ashkan[1]

[1]Department of Pediatrics, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

Abstract. Kala-azar (visceral leishmaniasis) is endemic in southern Iran. We retrospectively evaluated 367 infants and children with visceral leishmaniasis at hospitals affiliated to Shiraz University of Medical Sciences in Fars Province (located in the southwestern part of Iran). Seasonal variation was observed with more cases presenting in late winter, spring and a few in summer. The predominant clinical features in these patients were chronic fever, pallor, weight loss, abdominal distention, and hepatosplenomegaly. Lymphadenopathy was less common. Common laboratory abnormalities included anemia, leukopenia, thrombocytopenia, hypoalbuminemia and hypergammaglobulinemia. Liver function tests were deranged in two-thirds of patients. Immuno-fluorescence antibody (IFA) test was positive in all patients and all had positive bone marrow smears or cultures for *Leishmania donovani*. Patients responded well to Glucantim therapy with a cure rate of 96.7%. Relapse was observed in 8.2%(30) of patients. Mortality in this series was 7.3%. Twenty-three patients died during therapy. Jaundice and grossly deranged liver function tests were bad prognostic signs.

INTRODUCTION

Visceral leishmaniasis (VL) or kala-azar, is most commonly caused by *Leishmania donovani*, *L. infantum* and *L. chagasi*, but on occasion other *Leishmania* species, such as *L. amazonensis* are isolated from patients with typical VL (Jeromino *et al*, 2005). A viscerotropic syndrome caused by *L. tropica* was identified among a small number of American military personel who served in the Middle East (Magil *et al*, 1993). The first case of VL in Iran was reported from the northern part of the country in 1949. Increasing numbers of cases have been diagnosed from other parts of the country (Edrissian *et al*, 1998). Presently, the major foci of the disease are located in Meshkin-Shahr in the northwest and Farashband in the Fars Province. The Fars Province (site of study) is located in southwestern Iran and consists of two geographic regions (plain and mountainous). The epidemiological form of the disease in Iran is Mediterranean type, with a canine (dog, fox, jackal) reservoir, and the etiologic agent is *L. infantum,* which is transmitted by the bite of sandflies (Mohebali *et al*, 2001). We performed a retrospective study of epidemiological, clinical, therapeutic features and laboratory findings of VL in children.

Correspondence: Dr Moslehi Mohammad Ashkan, Department of Pediatrics, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran.
Tel: 98-711- 6262015; Fax: 98-711- 6261001
E-mail: moslehim@sums.ac.ir

MATERIALS AND METHODS

This study was conducted at hospitals affiliated with the Shiraz University of Medical Sciences in the southwestern part of Iran. Medical records of all children younger than 15 years with a final diagnosis of VL were reviewed from 1996 to 2006. Inclusion criteria were a positive serologic test result [indirect immunofluorescence antibody (IFA) test >1/128] and/or the presence of leishmania in the

bone marrow aspiration samples. Data recorded included age, sex, nationality, history of travel, fever, weight loss, anorexia, diarrhea, cough, abdominal distention, respiratory symptoms, and temperature at presentation, lymphadenopathy, hepatosplenomegaly, and skin changes. Laboratory records were reviewed for CBC, WBC with differential, ESR, reticulocytes, liver function tests, Widal test for typhoid and brucella, blood film for malaria, blood cultures for bacteria, urinalysis and urine culture, stool for ova and parasites, IFA and chest x-ray. Bone marrow aspirates were taken for *Leishmania donovani* bodies. Patients were treated with Glucantim 20 mg antimony/kg daily for 21 days. Response was assessed by defervescence, improvement in general condition, weight and anemia and regression of organomegaly. Drug side effects also were reviewed.

RESULTS

There were 62% males and 38% females. Their ages ranged from 3.5 months to 10 years. The disease was most common in those younger than 2 years of age (Table 1). The majority presented in late winter (March and April, 40.2%), followed by spring (23.5%) and a few were seen in the summer (11.3%) and autumn (18%) (Fig 1). About 80% of the children were from rural areas and nomads.

The majority of patients (98.4%) presented with a long history of fever (especially nocturnal type), usually for one month or more. Most patients were febrile on admission, a few (3.8%) were afebrile. Other symptoms included loss of appetite (64.3%), abdominal distention (50.1%), weight loss (40.6%), cough (38.7%), diarrhea (37.5%), abdominal pain (13.8%), jaundice (9.6%), and vomiting (5%). Joint pain, hemoptysis and hematemesis were less common (<0.5%). Ninety-six percent of patients had pallor on examination. Splenomegoly was found in the majority (91.2%),

Table 1
Age distribution of patients with visceral leishmaniasis.

Age (years)	No. of patients (%)
< 1	32 (8.9)
1.1 - 2	223 (61)
2.1 - 5	89 (24.5)
5.1 - 10	16 (4.4)
≥10.1	7 (1.2)

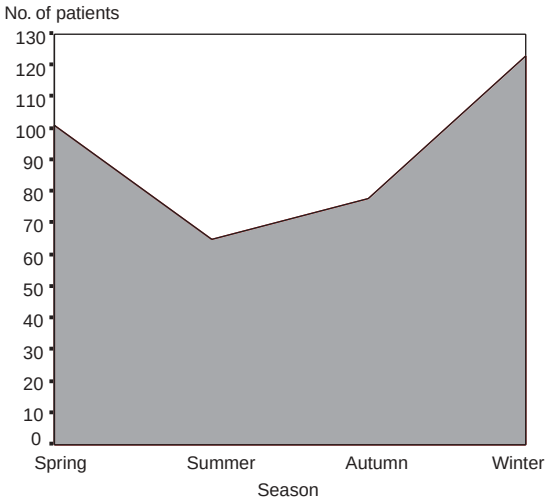

Fig 1–Seasonal variation of visceral leishmaniasis patients.

more than 6 cm below the costal margin in 78% of patients. Hepatomegaly was present in 86.6% of patients. Only 10.1% of patients had lymphadenopathy, mostly in the cervical area.

Table 2 shows the main clinical features. The majority of patients (95.3%) were anemic with a hemoglobin ≤ 9. The total WBC was less than 4,000/mm^3 in 59.1% of patients, while polymorphonuclear cells were less than 1,500/mm^3 in 72% of cases. The lymphocyte count was normal in the majority of patients, but 14% had an increased lymphocyte count (>4,000/mm^3). The platelets were less than

Table 2
Frequency of clinical features in patients with visceral leishmaniasis.

Symptoms/Signs	No. of patients (%)
Duration of illness	
<15 days	29 (8)
15 days-6 months	209 (57)
>6-12 months	102 (28)
>12-24 months	27 (7)
Symptoms	
Fever	121 (98.4)
Loss of appetite	236 (64.3)
Abdominal distention	184 (50.1)
Weight loss	149 (40.6)
Cough	142 (38.7)
Diarrhea	137 (37.5)
Abdominal pain	50 (13.8)
Jaundice	35 (9.6)
Vomiting	183 (5)
Joints pain, hemoptysis, hematemesis	<1%
Signs	
Pallor	355 (96.5)
Splenomegaly	334 (91.2)
Hepatomegaly	317 (86.6)
Lymphadenopathy	37 (10.1)

Table 3
Laboratory profile in patients with visceral leishmaniasis.

Parameters	Mean± SD	Range
WBC (/mm^3)	5,633.67±4,071.5	800-34,900
Hemoglobin (g/dl)	6.5±2.18	2-10.5
Platelets (10^3/mm^3)	65.3±28.6	7-365
Reticulocytes (%)	4.35±2.68	0.4-12
ESR (mm in 1 hour)	65.43±22.36	25-145

100 x 10^3/mm^3 in 91.6% of cases (Table 3). Liver function tests were abnormal in 83.5% of patients. The serum asparatate aminotransferase (AST) was increased in 78.5% of cases and alanine aminotransferase (ALT) in 69%.

Table 4
IFA titers in patients with visceral leishmaniasis.

Titer	No. of patients (%)
1:64	18 (4.9)
1:128	145 (39.7)
1:256	171 (43.1)
1:512	23 (8.6)
1:1,024	10 (3.7)

Gross derangement of liver enzymes was a bad prognostic sign. Albumin was less than 3 g/dl in about 80.1%, and globulin was more than 3.5 g/dl in 91.7% of patients. The IFA test was positive in all patients with titers ranging from 1:64 to 1:1,024 (Table 4). A bone marrow smear for *Leishmania donovani* bodies was positive in 175 patients. All the children were treated with Glucantim. The mean dose was 20 mg antimony /kg/day and the mean duration of treatment was 21 days. Response to Glucantim therapy was excellent with a cure rate of 96.7%.

Fever subsided within the first week and hepatosplenomegaly regressed gradually between the second and third weeks. Relapse was observed in 8.2% (30) of patients. These patients received a second course of Glucantim plus allapurinol or amphotericin B. The mortality rate in this series was 7.3%. Twenty-three patients died during therapy (after receiving 2 to 12 doses of Glucantim). They all had jaundice and markedly elevated liver enzymes (SGOT>1,000). The cause of death in these patients is likely to be secondary bacterial infection (9 cases) and severe bleeding (14 cases). Four patients had positive blood cultures and received appropriate antibiotics in addition to antileishmania therapy.

DISCUSSION

The results of the present study indicate

VL is a relatively common disease in southwestern Iran. Visceral leishmaniasis in southern Iran affects predominantly infants and young children (Soleimanizadeh *et al*, 1993). Several studies in countries where the infantile form of VL is common (Saudi Arabia, Yemen) show similar results (Rageh, 1990). In Africa and India, the disease affects older children and adults (Pearson and Sousa, 1990).

About 70% of patients were males. Most were from rural areas or were nomads. Because of the age distribution of the cases, the disease in Fars Province (site of study) was thought to be similar to the Mediterranean variety, a zoonosis for which canines are the main reservoir (Shamsizadeh *et al*, 2006).

A study by Al-Zahrani *et al* (1989) identified the causative organism isolated from patients in southern Saudi Arabia as *L. donovani* SL. zymodeme LON-42. This was isolated also in Yemen (Rageh, 1990) and eastern Ethiopia (Maru, 1979). The clinical manifestations of VL exhibited by the children in this sample were similar to those published previously (Elnour *et al*, 2001).

Seasonal variation was observed in this study. The disease peaked in late winter and spring, then declined sharply in summer. This is similar to that seen in the Mediterranean variety (Manson-Bahr and Apted, 1982).

The predominant clinical features seen in our patients were fever, weight loss, anorexia, abdominal distention and hepatosplenomegaly. This is similar to the Saudi Arabian (Al-juraygan *et al*, 1992) and Indian experiences (Thakur, 1984). Lymphadenopathy was less common. Lymphadenopathy is commonly seen in the African type of the disease (Maru, 1979).

The main hematological findings were anemia, leukopenia and thrombocytopenia. Anemia is probably due to a combination of iron deficiency, hemolysis and bone marrow suppression (anemia of chronic disease). Neutropenia and thrombocytopenia were likely due to hypersplenism since they were absent in patients who had splenectomy (Maru, 1979). Although the liver was enlarged in most patients, liver enzymes and bilirubin levels showed minimal derangement. Serum albumin was low in the majority, probably as a result of chronic infection and malnutrition. The IFA test was positive in all patients. Cross-reactions occur with leprosy, malaria, schistosomiasis and cutaneous leishmaniasis (Badaro *et al*, 1983).

Definite diagnosis of visceral leishmaniasis depends on demonstration of amastigotes in the tissue. These results are comparable to those reported in the literature (Ho *et al*, 1948). Glucantim is the first-choice treatment and the side effects are few. The response to Glucantim in our series was excellent. This is similar to another Iranian (Shamsizadeh *et al*, 2006) and Saudi Arabian experience (Al-juraygan *et al*, 1992). The Indian variety of the disease also responds well to therapy (Thakur, 1984). Visceral leishmaniasis in Africa seems to be less responsive (Maru, 1979). The relapse rate after treatment in this study was 8.2%, but in Kenya ranged from 5-36.7%. Patients who do not respond to the initial course of antimony may respond to a second course (Thakur, 1984). The mortality in this series was 7.3%. The mortality rate was similar to that in published literature. Jaundice and markedly deranged liver function were found to be bad prognostic indicators. As death occurred early in the course of therapy, it is unlikely to be related to Glucantim toxicity. In summary, visceral leishmaniasis in Fars Province, Iran bears many clinical similarities to the Indian and Mediterranean types of this disease. All are known to have a good response to therapy.

ACKNOWLEDGEMENTS

The authors would like to express their sincere appreciation to Ms Shadab Moslehi for

her grammatical support of this study. We would also like to thank Ms Maryam Seraj for helping to collect our data.

REFERENCES

Al-juraygan N, Al-Ayed I, Al-Nasser M, Al-Mugeiren M, Boohene A, Al-Herbish A. Visceral leishmaniasis in infancy and childhood, epidemiology and clinicopathological study of 63 cases in Al- Baha province, Saudi Arabia. *J Trop Pediatr* 1992; 38: 12-6.

Al-Zahrani M, Peters W, Evans D, *et al*. Leishmania infecting man and wild animals in Saudi Arabia. Diversity of parasites causing visceral leishmaniasis in man and dogs in the southwest. *Trans R Soc Trop Med Hyg* 1989; 83: 503-10.

Badaro R, Reed S, Carvalho E. Immunofluorescent antibody test in American visceral leishmaniasis: sensitivity and specificity of different morphological forms of two leishmania species. *Am J Trop Med Hyg* 1983; 32: 480-4.

Edrissian G, Nadim A, Alborzi A, Ardehali S.Visceral leishmaniasis ; the Iranian experience. *Arch Intern Med* 1998; 1: 22-6.

Elnour IB, Akinbami F, Shakeel A, Venugopalan P. Visceral leishmaniasis in Omani children: A review. *Ann Trop Paediatr* 2001; 21: 159-63.

Jeromino S, Sousa A, Pearson R. Leishmania species: Visceral (Kala-Azar), cutaneous and mucocutaneous leishmaniasis. Principles and practices of infectious diseases. 6th ed. Philadephia: Saunders, 2005: 3145-56.

Ho E, Soong T, Li Y. Comparative merits of sternum, spleen and liver punctures in the study of human visceral leishmaniasis. *Trans R Soc Trop Med Hyg* 1948; 41: 629-36.

Magil A, Grogl M, Gasser R, Sun W, Oster C. Visceral infection caused by *Leishmania tropica* in veterans of Operation Desert Storm. *N Engl J Med* 1993; 328: 1383-7.

Manson-Bahr P, Apted F. Manson's tropical diseases. 18th ed. London: Bailliere Tindall, 1982: 93-115.

Maru M. Clinical and laboratory features and treatment of visceral leishmaniasis in hospitalized patients in northwestern Ethiopia. *Am J Trop Med Hyg* 1979; 28: 15-8.

Mohebali M, Hamzavi Y, Edrissian G, Forouzani A. Seroepidemiological study of visceral leishmaniasis among human and animal reservoirs in Bushehr Province, Islamic Republic of Iran. *East Mediterr Health J* 2001; 7: 912-7.

Pearson D, Sousa A. Leishmania species: visceral, cutaneous and mucosal leishmaniasis. Mandel principles and practice of infectious diseases. 3rd ed. New York: Churchill Livingstone, 1990, 2066-77.

Rageh H. Visceral leishmaniasis in the Yemen - a report of 72 cases in Taiz. *Saudi Med J* 1990; 11: 105-7.

Shamsizadeh A, Nikfar R, Maraghi S, Zaker N. Pediatric visceral leishmanisis in the South West Part of Iran: A study of 215 cases. *Pak J Med Sci* 2006; 22: 461-4.

Soleimanizadeh G, Edrissiam G, Danesh A, Nadim A. Epidemiological aspects of kala-azar in Meshkin-shahr, Iran: human infection. *Bull World Health Organ* 1993; 71: 759-62.

Thakur C. Epidemiological, clinical and therapeutic features of Bihar kala-azar (including post kala-azar dermal leishmaniasis). *Trans R Soc Trop Med Hyg* 1984; 78: 391-8.