Visceral Leishmaniasis in Infancy and Childhood Epidemiology and Clinicopathological Study of 63 Cases in Al-Baha Province, Saudi Arabia

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Summary

The epidemiology, clinicopathological features, and response to therapy of 63 Saudi patients with visceral leishmaniasis are described. The clinical features in our cases were similar to those described from Asir province, India, and Ethiopia, except for the presence of lymphadenopathy. Fever, heparosplenomegaly, pancytopenia, and liver dysfunction were common findings. The unusual feature is the seasonal variation in the distribution of the disease. The response to sodium stibogluconate was excellent and the mortality rate was low (< 1 per cent).

Introduction

Although Phillips,[1] in 1903, first identified Leishman–Donovan (LD) bodies in the spleen of a man who lived for 15 years in Mecca, it was not until 1951 that Fawdry and Mazhar[2] reported the first two cases of clinical kala-azar in South Arabia. Following this, infantile kala-azar has been reported increasingly in the Kingdom, the majority of cases coming from the south-western provinces, namely Asir[3–7] and Gizan[3,8]. The cutaneous form has been extensively reported,[3] but reports of the visceral form are few.[1–21] Visceral leishmaniasis has, however, been more commonly reported from neighbouring countries such as Sudan,[11,12] and South and North Yemen.[11,13–15]

We report here the epidemiological and clinicopathological features of 63 cases of the visceral leishmaniasis in infants and children who were admitted to the pediatric medical ward of the King Fahad Hospital at Al Baha over an 8-year-period.

Materials and Methods

This retrospective study included all children under the age of 12 years, who were admitted to the pediatric medical ward at the King Fahad Hospital at Al Baha during the period June, 1982 to August 1990, with confirmed diagnosis of visceral leishmaniasis. The King Fahad Hospital at Al Baha is the only referral hospital in Al Baha province and also receives patients from some neighbouring regions.

The criteria for inclusion were (A) identification of LD bodies on bone marrow, liver biopsy, or splenic puncture; or (B) clinical features and laboratory findings compatible with the diagnosis in patients in whom LD bodies were not seen, but who had a significantly high indirect haemagglutination titre (IHAT) for leishmania, i.e. ≥ 1:64 (Haemagglutination titre—Behring Werke AG, West Germany) and who responded favourably to sodium stibogluconate (Pentostam).

The records of all patients were reviewed and data extracted for analysis included: age, sex, nationality, area of residence, month and year of admission, duration of illness, and presenting symptoms and physical signs on admission. Laboratory investigations included: complete blood count, peripheral smear, peripheral blood film for malaria, sedimentation rate, reticulocyte count, total serum protein, serum albumin, serum globulin, liver function tests, coagulation tests (PT, APTT), serology for brucella, enteric fever and indirect haemagglutination test for leishmania (IHAT), and stool analysis. Blood and other body fluid cultures, and chest X-ray were done when appropriate. Bone marrow aspiration was performed in all the patients, but splenic puncture and liver biopsy were done in only five and three patients, respectively.

Patients were treated with intravenous sodium stibogluconate (Pentostam, 10–15 mg/kg/day) and, depending upon the preference of the treating physician, the duration of therapy was 30 days (nine patients), 21 days (42 patients), and 14 days (four patients). In eight patients, treatment was continued only for 2–10 days due to either complications (four patients), patients discharged against medical advice

(three), or death (one). The duration to fever defervescence from the start of treatment, together with complications due to sodium stibogluconate were noted. Antibiotics and haematinics were prescribed if indicated. Blood transfusion, fresh frozen plasma, and platelets were given for severe anaemia and/or a bleeding tendencies.

Patient's response to therapy was monitored, and size's of the spleen and liver, complete blood count, peripheral smear, total protein, serum albumin, serum globulin, liver function test, and serology for leishmania (IHAT) were regularly checked during and at the end of therapy. Patients were considered cured when therapy resulted in improvement in clinical status and laboratory findings.

Results

There were a total of 12 727 admissions into the hospital during the period under review; 63 (0.5 per cent) of these were diagnosed as cases of visceral leishmaniasis. In 45 of the 63 patients LD bodies were seen in either bone marrow, spleen, or liver. In the remaining 18, the diagnosis was based on clinical and laboratory findings, and on favourable reponse to sodium stibogluconate therapy.

Epidemiology

Geographic distribution. Table 1 shows the distribution of patients according to geographic location. Fifty patients were from Al Baha province, of which 41 (82 per cent) were from the Tihama area.

TABLE 1
Distribution of patients according to geographical places

Place			
Province	District	No. (63)	%
Al Baha	Tihama	41	65.1
	—Qilwa	(23)	
	—Mikhawa	(18)	
	Akeek	5	7.9
	Dhafer	2	3.2
	Mandak	2	3.2
Others		13	20.6
Asir		(9)	
Mecca		(3)	
Yemen		(1)	

Temporal distribution of cases. Figure 1(a,b) show the monthly and yearly distribution of cases, respectively. Seventy-one per cent of cases occurred between January and June. The number of cases diagnosed has increased annually during the period.

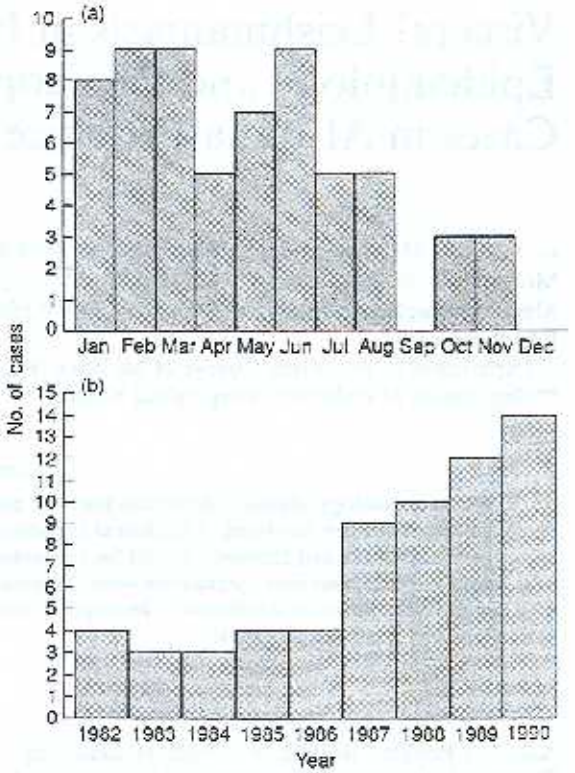

FIG. 1.

Sex and age distribution of patients. Thirty-seven patients were males and 26 females. Table 2 shows the age distribution of cases. Fifty-six (89 per cent) of patients were under the age of 4 years. The mean age was 2 years, (range 4 months–12 years).

TABLE 2
The age distribution of patients of visceral leishmaniasis

Age (months)	No. of case	%
<12	15	23.8
13–24	23	36.5
25–36	11	17.5
37–48	7	11.1
>49	7	11.1

Clinical features

Table 3 shows the clinical manifestation on admission. Fever, pallor, and hepatosplenogemaly were the most common. The average size of the spleen was 7.5 cm (range 1–18) and the liver was 3.2 cm (range 0–10) below the costal margin. Weight loss occurred in 26 (41

TABLE 3
Clinical manifestation on admission of 63 patients with visceral leishmaniasis

Symptoms/signs	No. of patients	%
Fever	59	93.60
Pallor	60	95.24
Abdominal distention	36	57.10
Weight loss	26	41.30
Vomiting ± diarrhoea	20	31.75
Jaundice	2	3.2
Splenomegaly	63	100
Hepatomegaly	59	93.6
Lymphadenopathy	14	22.20
Skin rash	2	3.20
Ascites	2	3.20
Oedema	5	7.9

per cent) patients and lymph node enlargement was found in only 14 (22 per cent) patients, the majority of which were small and involving the axillary, cervical, and inguinal regions. Symptoms had lasted from 2 weeks to 1 year (mean 10 weeks) before presenting in hospital.

Table 4 shows the infections associated with visceral leishmaniasis in 35 of the patients. Respiratory and gastro-intestinal infections were prominent. There were five cases with septicaemia, in three the isolated organism was *Klebsiella pneumoniae*, in one *Staphylococcus aureus*, and in the fifth *Acinebacter*. The

TABLE 4
Infection associated with visceral leishmaniasis in 35 patients

Infections	No.	%
Pneumonia	16	45.6
Otitis media/URTI*	6	17.2
Gastroenteritis	6	17.2
Urinary tract infection	5	14.3
Septicaemia	5	14.3
Hepatitis B	2	5.7
Abscesses	2	5.7
Schistosoma mansoni	1	2.9

* URTI, Upper Respiratory Tract Infection.

septicaemia was diagnosed on admission in three cases, and after 10 and 17 days of therapy, respectively, in the other two. All the five cases of septicaemia responded to antibiotics therapy. Subcutaneous abscesses were present in two patients, one at the time of presentation in the gluteal region and the other at the site of intravenous infusion.

Laboratory data

Table 5 shows the laboratory findings on admission. The haemoglobin concentration was low in all patients. The mean haemoglobin was 69 ± 17 g/l (range 27–102). The peripheral blood film showed anisopoikilocytosis in all, with preponderance of macrocytes in 15 (24 per cent) patients. Slight to moderate polychromasia was found in 48 (76 per cent) patients. The mean white blood count was $4.9 \pm 3 \times 10^9$/l (range, 1.5–11.1). Forty-eight (75 per cent) patients were neutropenic. The mean platelets count was $114 \pm 68.9 \times 10^9$/l (range 4–297). The total protein varied between 50 and 98 g/l with a mean of 73.4 ± 10.2. A striking feature was reversed albumin–globulin ratio, the mean serum albumin being 30.3 ± 6.6 g/l (range 14–48) and the mean serum globulin being 44.4 ± 12.5 g/l (range 26–67). Hepatic dysfunction was present in 39 (62 per cent) patients and in two of them hepatitis type B infection was proved serologically. Hepatic function improved in all the cases after therapy. Coagulation abnormalities, mainly prolonged PT and APTT, were noted in six (10 per cent) patients, and in three cases this was associated with disseminated intravascular coagulopathy (DIC).

Bone marrow aspiration was performed in all the patients for diagnostic purpose. Forty-one (65 per cent) were positive for LD bodies on microscopy; cultures were not performed. Increased cellularity of the bone marrow was found in 60 (95 per cent) patients. In three (5 per cent) patients with positive LD bodies the bone marrow was hypoplastic. Erythropoiesis was normoblastic in 55 (88 per cent) patients and megaloblastic in eight (13 per cent) patients. Variable degrees of erythrophagocytosis and leukophagocytosis were noted with preponderance of histiocytosis in 31 (49 per cent) patients and granulomatous formation in 14 (22 per cent).

Splenic puncture was positive for LD bodies in four out of five, liver biopsy was positive in two out of three.

An indirect haemagglutination (IHA) titre was performed on only 55 patients. Among these, four (7 per cent) had negative results, titre $< 1:64$, all of which had positive bone marrow biopsy. All the eighteen patients with negative bone marrow biopsies had positive titres with variable dilutions 1:64 (6), 1:128 (6), 1:256 (3), and $> 1:1024$ (3).

Treatment and clinical progress

All 55 patients who received full course of sodium stibogluconate responded well to treatment. Fever subsided in 2–18 days with a mean of 4.1 days. In two patients fever persisted for 15 and 18 days due to concurrent illnesses, which were viral hepatitis type B and bronchopneumonia, respectively. During the period of hospitalization, the patients gained weight, the spleen and liver size started to decrease; the most dramatic reduction occurred in the spleen, the mean splenic size becoming 2.8 cm (range 0–12) and the liver 2.6 cm (range 0–7) below costal margin. The haematological profile and liver functions improved, Table 5. Ten patients were, however, still neutropenic. Regarding the other eight patients one of them, a 7-month-old

TABLE 5
Laboratory changes in visceral leishmaniasis before and after treatment

Test	Before therapy			After therapy		
	Mean ± SD	Range	No. of cases	Mean ± SD	Range	No. of cases
Haematological						
Haemoglobin (g/l)	69 ± 17	27–102	63	111 ± 15	80–153	59
White blood cell (10^9/l)	4.9 ± 3	1.5–11.1	63	7.4 ± 2.8	2.7–17	59
Platelets (10^9/l)	114 ± 68.9	4–297	63	279 ± 100	66–469	56
Reticulocyte (%)	3.3 ± 2.1	0.4–8.1	41	—	—	—
Erythrocyte sedimentation rate (mm/hr)	52.7 ± 18	24–88	28	—	—	—
Biochemical						
Total protein (g/l)	73.4 ± 10.2	50–98	63	77.8 ± 17.6	55–100	41
Serum albumin (g/l)	30.3 ± 6.6	14–48	63	36.8 ± 7.4	22–54	41
Serum globulin (g/l)	44.4 ± 12.5	26–67	63	40 ± 13.4	24–60	41

child who was sick for 6 weeks prior to admission died on the third day of sodium stibogluconate therapy due to uncontrollable disseminated intravascular coagulation; three patients were discharged against medical advise, and in the other four, therapy had to be discontinued due to: severe neutropenia (one patient), haematuria (one patient), and disseminated intravascular coagulation in two patients. In one patient disseminated intravascular coagulation was associated with hepatitis-like-picture, but with negative viral studies. The four patients responded well to discontinuing therapy and supportive measures.

Discussion

Our observation on the occurrence of visceral leishmaniasis in Al Baha province indicates the lower endemicity of the disease, where children with visceral leishmaniasis compromised only about 0.5 per cent of all admissions for the study period. This figure is comparable to that reported from Asir, (1 per cent)[7] and far less than that reported from Kenya where about 20 per cent of the available beds are occupied by children over 2 years of age with leishmaniasis.[16] Although it is a disease, which is prevalent throughout the year, the majority of cases were reported between January and June, which might indicate the increased number of the sandflies after the September–December rainfall. This seasonal distribution is similar to what has been reported from India,[17] China,[18] Africa,[19] and Brazil,[20] in contrast to Asir experience.[7] The majority of our cases were reported from the coastal plain, i.e. Tihama area, which is quite warm and humid, and this is comparable to Asir.[7] The number of cases diagnosed increases annually and perhaps reflects the increasing awareness of kala-azar, coupled with the improvement in the health care system in the area.

The peak age incidence in our series is below 4 years (89 per cent), which compares well with figures reported previously from Asir,[7] Yemen,[14,15] Iran,[21] and Brazil,[20] but in contrast to the Sudanese[12] and Ethiopian[22] kala-azar which had no predilection for children.

The clinical features in this series are similar to those seen in Asir,[7] Ethiopia,[22] and India,[17,23] except for the presence of lymphadenopathy which was noted in 14 patients (22 per cent). Cases reported from Iran,[24] and Sudan[12] usually have significant lymphadenopathy. Fever, hepatosplenomegaly, and pallor were constant findings. Hepatic dysfunction and reverse albumin globulin ratio were common in our cases which is similar to the findings of Patil *et al.*[7] and Sabbah *et al.*[8] in Saudi Arabia, El-Hassan *et al.*[12] in Sudan, and Hashemi-Nasab *et al.*[21] in Iran. These abnormalities improved after sodium stibogluconate therapy.

The occurrence of other infectious diseases at the time of onset of symptoms or during therapy were common in our series (56 per cent), which is similar to the experience from Asir[7] and Iran,[21] but different from the findings of Badaro *et al.*[20] in Brazil. This susceptibility can be explained by the finding of neutropenia in 75 per cent of our patients, but impaired cell-mediated immunity could also be a major factor.[25]

The haematological findings consisted of pancytopenia in the majority of cases. Anaemia of varying degrees was present in all cases with a multifactorial aetiology of which nutritional factors have important bearings. This was obvious from depletion of bone marrow iron stores and peripheral smears findings of anisopoikilocytosis, macrocytosis, and polychromasia.[1] The pancytopenia is due to increased peripheral destruction rather than bone marrow failure of production as suggested by bone marrow hyperplasia, which is similar to the findings of El Hassan *et al.*[12] in Sudan and Li Volti *et al.*[26] in Italy.

Sodium stibogluconate is remarkably free from side

effects and well tolerated, with the exception of pain at the injection site.[23] Although in four of our patients therapy had to be discontinued due to various complications, i.e. neutropenia, haematuria, and disseminated intravascular coagulation, such complications can easily be contributed to the disease itself.[7,12,14,21,27] Sodium stibogluconate was effective in all our 59 treated patients, including four patients who received short courses of 6–10 days. No relapse has so far been reported. This is similar to Asir,[7] and Indian[23] experience, which indicates the necessity of less intensive therapy than the East African variety.[28] In our series, only one child died of disseminated intravascular coagulation, thus giving rise to a very low mortality rate (<1%). This is comparable to Asir,[7] Brazil,[20] and India,[23] but in contrast to findings in Yemen,[15] Salvador,[20] Ethiopia,[22] and Iran,[21] where the reported mortality rate was as high as 30 per cent. This might be contributed to early diagnosis, aggressive treatment of complication, and rapid response to antimony therapy.

A definitive diagnosis of visceral leishmaniasis can be made by identifying LD bodies on microscopic examination or following culture of bone marrow, liver, or spleen aspirates. However, the last procedures were considered invasive and carry hazardous complications,[7,8] Although, the sensitivity and specificity of the serological studies to identify leishmania antibodies is in question, in particular at low titres,[3,30] they also can be used as strong supportive evidence for diagnosis.

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