

## OUTCOME OF HOSPITALIZED CHILDREN WITH VISCERAL LEISHMANIASIS IN BASRAH, SOUTHERN IRAQ

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## ABSTRACT

**Objectives:** A prospective study was carried out to study the outcome of patients with visceral leishmaniasis and to determine factors associated with poor outcome.

**Methods:** The study included 132 in-patient children who were admitted to Basrah Maternity and Children Hospital and Basrah General Hospital during one year (from the first of November 2004 till the end of October 2005), with visceral leishmaniasis confirmed by bone marrow examination and direct agglutination test.

Nutritional assessment was done for each patient. All patients with confirmed visceral leishmaniasis were sent for complete blood count. The final diagnosis and the outcome of the patients with visceral leishmaniasis were recorded also.

**Results:** Among 132 sero-positive cases, 78 (59.0%) cases were males, and 54 (40.9%) were females. The age of patients ranged between 2 months to 12 years.

Sixty five (49.2%) of the cases were improved, 31.8% were discharged on the family responsibility, and 15 cases died. The commonest cause of death was bleeding in 6 cases (40%), followed by hepatic failure in 4 (26.6%), other causes of death were bronchopneumonia, renal and heart failure.

Nutritional status and duration of illness were significant determinants of the outcome of visceral leishmaniasis patients. A significantly higher number of malnourished patients didn't improve compared to well nourished patients, and a significantly higher percent of patients who presented late have died compared to those who presented earlier especially in the first 2 weeks of illness,  $P < 0.05$ . By using multivariate regression analysis, six variables; low hemoglobin value, low platelet count, male sex, young age, high Direct Agglutination Test titer and malnutrition were found to be significant predictors of death and relapse.

**Conclusion:** Male sex, anemia, thrombocytopenia, high DAT titer and malnutrition are poor prognostic factors in addition late presentation.

## INTRODUCTION

Leishmaniasis have been included into the list of notifiable diseases in the majority of the countries with areas of local transmission. Passive case detection continues to be the main source of information and depends largely on the awareness of the population about the early symptoms of the disease and the recognition of the need to seek medical assistance.<sup>[1]</sup> During the last few years, there were increases in visceral leishmaniasis (VL) cases in following governorates of Iraq (Basrah, Missan, Thi-Qar, Al-Qadysia and Al-Muthanna), it was reported that (72.7%) and (69.5%) of all recorded cases all over the country during the years 1995 and 1996, respectively, were from these governorates. Maysan was found to be the main endemic governorate during this period, (31.9%) of total number recorded, while (10.2%) were from Basrah during the same period.<sup>[2]</sup> According to the data of CDC Surveillance Unit/ Primary Health Care Department/ Basrah, the number of cases that was reported during the years (2004-2005) was 608; about 210 (34.5%) of them were

from Al-Qurna district.<sup>[3]</sup> Visceral leishmaniasis is a highly morbid and incapacitating infection, which usually presents with prolonged fever, weight loss and hepato-splenomegaly. At the terminal stages of kala-azar the hepatosplenomegaly is massive, there is gross wasting, the pancytopenia is profound, and jaundice, edema, and ascites may be present. Anemia, bleeding episodes, especially epistaxis, are frequent. The late stage of the illness is often complicated by secondary bacterial infections, which frequently are a cause of death. Death occurs in  $> 90\%$  of patients without specific antileishmanial treatment.<sup>[4,5]</sup> VL symptoms often persist for several weeks to months before patients either seek medical care or die from bacterial co-infections, massive bleeding or severe anaemia.<sup>[6]</sup> Despite the availability of effective treatment, the disease have a high mortality even at referral centers.<sup>[4]</sup> The aim of this study was to assess the outcome of children with visceral leishmaniasis and to determine for factors associated with poor outcome.

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## PATIENTS & METHODS

### *Patients:*

This study is a prospective study that was carried out over 12 months (from the first of November 2004 till the end of October 2005), it involved 132 children with visceral leishmaniasis who were admitted to pediatric wards of Basrah Maternity and Children Hospital and Basrah General Hospital. The diagnosis was confirmed by Direct Agglutination Test (DAT), and bone marrow examination.

### *Data Collection*

The following clinical data were recorded from each patient; age, sex, residence, history of fever, pallor, jaundice, cough, vomiting, abdominal distention, loss of appetite, loss of body weight and diarrhea. Nutritional assessment was done for each patient. Weight was determined by an infant weighing scale and the child was freed from heavy clothing's before weighing, for children who could stand the weight measured by ordinary weighing balance. Recumbent height was measured for children who couldn't stand using rollameter, while the standing height was measured for children who could stand, with out shoes using stadiometer. Weight for height was assessed using the National Center for Health Statistics (NCHS) / WHO normalized reference values charts.<sup>[7]</sup>

1. Well nourished.
2. Mild malnutrition -1SD
3. Moderate malnutrition <-2 SD
4. Severe malnutrition <-3 SD

An informed consent from one of the parents was obtained before enrollment in the study. All patients with confirmed visceral leishmaniasis were sent for complete blood count (hemoglobin measurement, white blood cell count; total and differential, and platelet count), and blood film for red blood cell morphology. Sodium Stibogluconate (Pentostam) was given for all cases in a dose of 20 mg/kg for 28 days. These patients were followed for the development of any complication. The outcome of the patients with visceral leishmaniasis was recorded also. Complete blood pictures were done by using Coulter AC.T, from Beckman Coulter, USA. This apparatus gives all the blood picture measurements like Hb, WBC (total and differential), RBC, and Platelet. Blood film for morphology was done for all patients. The normal haemoglobin value (Hb) ranges between

(9.5-16gm/dL). Cases with Hb value (<6g/dl) were considered to have severe anemia, while those with Hb value (6-10g/dL) were considered to have mild to moderate anemia and the cases with Hb value (>10g/dL) were considered normal.<sup>[8,9]</sup> The normal value of white blood cell (WBC) count ranges between (4500-13000/mm<sup>3</sup>).<sup>[8,9]</sup> The normal value of platelet count ranges between (150000-400000/mm<sup>3</sup>).<sup>[8,9]</sup> The Direct Agglutination Test (by Koninklijk Institute Voor De Tropen-Royal Tropical Institute/Amsterdam) was carried out using *leishmania* freeze-dried antigen with a parasite density of ( $5 \times 10^7$  parasite per ml).

### **Statistical Analysis**

The chi-square ( $X^2$ ) test was used as a test of significance. Differences were recorded as significant whenever probability (p) was less than 0.05.

SPSS-version 10.0 windows computer program was applied for multivariate regression analysis model.

## **RESULTS**

The study included 132 patients with visceral leishmaniasis confirmed by direct agglutination test and bone marrow examination. Seventy eight out of 132(59.1%) cases were males, and 54(40.9%) were females. The age of patients ranged between 2 months and 12 years, mean age  $\pm$  SD was (5.89 $\pm$ 4.57) years. Most of the sero-positive cases were less than two years of age (74.3%). These cases were from southern governorates of Iraq, 89(67.4%) cases were from Basrah, 36 (27.3%) cases were from Missan, 6(4.5%) cases were from Thi-Qar, and one case (0.7%) was from Baghdad.

### ***Outcome of Sero-Positive Cases:***

About half of these cases 65(49.2%) were improved and discharged well from the hospitals, 42(31.8%) were discharged on the family responsibility with unknown outcome, while 15(11.4%) patients died during the period of hospitalization. Ten patients (7.6%) were admitted again after discharge from the hospital. In this study, death was recorded in 15 cases (11.3%). Reported causes of death were bleeding in 6 cases (40.0%), hepatic failure in 4 (26.6%) and severe bronchopneumonia in 3(20.0%). Two patients were died as a result of renal failure, and heart failure, **Table-1**

**Table 1. Causes of death among 15 cases with visceral leishmaniasis**

Causes	No.	%
Bleeding	6	40
Hepatic failure	4	26.6
Severe Pneumonia	3	20
Renal Failure	1	6.7
Heart failure	1	6.7
Total	15	100

**Outcome in Relation to the Age:**

The mortality rate was (14.8%) among infants. This rate was decreased as age increased (except for the age group 9-12 years; 1 patient improved

and the other died). The results of cases that remain in the hospital till they complete the treatment, show that the percentages of improved cases increased with age. Statistically there was no significant difference in the outcome of patients in relation to the age ( $P>0.05$ ), **Table-2**

**Outcome in Relation to the Sex:**

Out of 78 males with visceral leishmaniasis 35(44.8%) discharged with complete recovery and 10 (12.8%) died, compared to 30(55.5%) and 5(9.2%) of females respectively. Statistically the difference was not significant,  $P>0.05$ , **Table-2**.

**Table 2. Outcome of visceral leishmaniasis cases in relation to age and sex**

Variable	Total no. Examined	Improvement		Discharged on family responsibility		Death		Relapse	
		No.	(%)	No.	(%)	No.	(%)	No.	(%)
<b>Age (years)</b>									
< 1	54	21	(38.8)	20	(37)	8	(14.8)	5	(9.5)
1 -	44	25	(56.8)	14	(31.8)	5	(11.3)	0	(0)
2 -	13	8	(61.5)	3	(23)	1	(7.6)	1	(7.6)
3 -	5	3	(60)	1	(20)	0	(0)	1	(20)
4 -	2	2	(100)	0	(0)	0	(0)	0	(0)
5 -	4	2	(50)	1	(25)	0	(0)	1	(25)
6 -	5	2	(40)	3	(60)	0	(0)	0	(0)
7 -	1	0	(0)	0	(0)	0	(0)	1	(100)
8 -	2	1	(50)	0	(0)	0	(0)	1	(50)
9-12	2	1	(50)	0	(0)	1	(50)	0	(0)
Total	132	65	(49.2)	42	(31.8)	15	(11.3)	10	(7.5)
<b>Sex</b>									
Male	78	35	(44.8)	28	(35.8)	10	(12.8)	5	(6.4)
Female	54	30	(55.5)	14	(25.9)	5	(9.2)	5	(9.2)
Total	132	65	(49.2)	42	(31.8)	15	(11.3)	10	(7.5)

For age;  $X^2$  test was done between < 1 year and > 1 year  
 $X^2$  3.75 df 3 P value >0.05  
 For sex  $X^2$  2.1 df 3 P value >0.05

**Outcome in Relation to Nutritional Status:**

The outcome of the visceral leishmaniasis patients in relation to nutritional status was also studied. The rate of improvement was decreasing as the nutritional status deteriorates or decreases where (65.2%) cases with normal nutritional status improved, compared to only (18.1%) with weight for height < -4SD. But the

differences were statistically not significant, ( $p>0.05$ ). Also the percent of death was higher among children with malnutrition compared to well nourished children. However, the differences was statistically not significant, ( $P>0.05$ ), **Table-3**.

Table 3. Outcome of visceral leishmaniasis cases in relation to nutritional status

Nutritional status	Total No.		Improvement		Discharged on family responsibility		Death		Relapse	
	No.	%	No.	%	No.	%	No.	%	No.	%
Well nourished	46	34.8	30	65.2	10	21.7	3	6.5	3	6.5
- 1 SD	33	25	17	51.5	8	24.8	6	18.1	2	6.1
- 2 SD	27	20.5	11	40.7	12	44.4	2	7.4	2	7.4
- 3 SD	15	11.4	5	33.3	7	46.6	2	13.3	1	6.6
- 4 SD	11	8.3	2	18.1	5	45.4	2	18.1	2	18.1

X<sup>2</sup> 7.27 df 3 P value >0.05

**Outcome in Relation to the Hematological Values:**

The hematological values of the sero-positive cases in relation to the outcome are shown in **Table-4**. The distribution of cases according to the severity of anemia and the condition on discharge from the hospital showed that the mortality rate was (49.9%) in anemic patients compared to (16.6%) in cases with normal hemoglobin level. All cases who had improved had mild anemia or normal hemoglobin level (100%); none of the improved cases had severe anemia. The distribution of cases according to WBC count at presentation and the condition on discharge from the hospital showed that (13.0%) of cases with leucopenia died during

hospitalization compared to (9.6%) and (9.0%) of the cases with normal WBC count and leukocytosis, respectively. Statistically, there was no significant difference, P>0.05. The distribution of cases according to platelet count and the condition on discharge from the hospital showed that the mortality rate was (30%) in cases with severe thrombocytopenia, (11.7%) in cases with mild to moderate thrombocytopenia, and (9%) in cases with normal platelet count. Statistically, there was no significant difference at (P>0.05).

Table 4. Outcome of visceral leishmaniasis cases in relation to hematological values.

Variable	Range	Total no.	Improved		Discharged on family responsibility		Death		Relapse	
			(no. 65)		(no. 42)		( no.15)		(no. 10)	
			No.	(%)	No.	(%)	No.	(%)	No.	(%)
Hemoglobin Value(g/dl)	< 6	5	0		1	(20.0)	2	(40.0)	2	(40.0)
	6-10	121	63	(52.0)	40	(33.0)	12	(9.9)	6	(4.9)
	> 10	6	2	(33.3)	1	(16.6)	1	(16.6)	2	(33.3)
WBC count (cell/mm <sup>3</sup> )	<4000	69	30	(43.4)	25	(36.2)	9	(13.0)	5	(7.2)
	4000-13000	52	30	(57.6)	14	(26.9)	5	(9.6)	3	(5.7)
	>13000	11	5	(45.4)	3	(27.2)	1	(9.0)	2	(18.1)
Platelets (/mm <sup>3</sup> )	<50000	10	5	(50.0)	0	(0)	3	(30.0)	2	(20.0)
	50000-150000	34	18	(52.9)	10	(29.4)	4	(11.7)	2	(5.8)
	>150000	88	42	(47.7)	32	(36.3)	8	(9)	6	(6.8)

P value > 0.05 (for WBC and Platelets)

**Outcome in Relation to the Duration of Illness:**

Thirty patients (90.9%) that were presented early were improved and discharged well, compared to cases presented rather late (55.5%). In addition, 7 cases (38.8%) with prolonged duration of illness were died during

hospitalization compared to 4 (12.2%) who were admitted and received treatment in the first 2 weeks of the illness. These differences were statistically significant,(P<0.05), **Table-5**.

**Table 5. Outcome in relation to duration of illness**

Duration of illness (weeks)	Outcome				Total	
	Improved		Death		No.	%
	No.	%	No.	%		
1-2	30	90.9	4	12.2	33	41.2
3-4	25	86.2	4	13.7	29	36.2
> 4	10	55.5	7	38.8	18	22.5
<b>Total</b>	<b>65</b>	<b>81.8</b>	<b>15</b>	<b>18.7</b>	<b>80</b>	<b>100</b>

X<sup>2</sup> 8.5      df 2      P value <0.05

**Predictors of Poor Outcome:**

In order to identify the most significant predictors of the outcome of the disease, multivariate regression analysis was used. Six variables (younger child, male sex, low Hb value, low platelet count, malnutrition and high DAT titer) were found to be significant predictors of death and relapse (R<sup>2</sup>=0.82), **Table-6.**

**Table 6. Predictors of poor outcome**

Variable	Beta	T-test	P value
Nutritional status	0.613	5.37	< 0.001
Sex	- 0.623	- 3.73	< 0.001
DAT titer	0.818	5.29	< 0.001
Age	0.137	2.09	< 0.05
Hb. Level	- 0.598	- 2.06	<0.05
Platelet count	0.906	3.765	< 0.001

R<sup>2</sup> = 0.82

**DISCUSSION**

Visceral leishmaniasis is a potentially fatal disease caused by *Leishmania donovani* complex. It has a worldwide distribution and affects up to half million children and adults in both developing and developed world setting.<sup>[10]</sup> The disease is presented with fever, gradual weight loss, hepatosplenomegaly, hypergammaglobulinemia and pancytopenia. Thus, for successful control of the disease, efficient and reliable diagnosis and a successful treatment with anti-leishmanial therapy will lead to significant results in decreasing morbidity and even mortality.<sup>[11]</sup> Death during hospitalization was higher than that reported in other studies in Iraq (4% - 8.9%)<sup>[12-14]</sup>, and this can be explained by longer duration of illness and delay to seek medical advice and treatment. About one third were discharged on the family responsibility with unknown outcome and only (7.5%) were relapsed and returned to the hospital because of unresponsiveness to the

treatment. This rate of relapse is similar to that reported in Iran by Rahim et al<sup>[15]</sup> but lower than that reported in Missan Province(15%).<sup>[13]</sup> Bleeding tendency was the main cause of death; reported in cases who died. Many families of ill patients discharge their children (on their responsibility) when the condition of their children deteriorate and don't improve. This can explain the high percent of children discharged on their families responsibility. This finding is in agreement with that of Majeed in Najaf governorate.<sup>[12]</sup> In Iran, Barati et al reported that despite treatment of all the VL cases with meglumine antimoniate, four (7%) died in pediatric ward, all four having concurrent bacterial infections,<sup>[16]</sup> While in Saudi Arabia, jaundice and grossly deranged liver function tests were found to be bad prognostic signs.<sup>[17]</sup> No significant difference between the different age groups was found regarding the outcome on discharge from hospital. Rey et al in Brazil have reported that VL mortality was 8.7% in the study period. Mortality was 21.2% in children younger than one year and 7.6% in children older than one year (P<0.001).<sup>[18]</sup> The study has revealed a difference between both sexes in mortality rate. This difference was reported also by Alwan but in reversed results. He reported that the mortality rate in males was (7%) compared to (11%) in females, and he concluded that this difference in mortality rate could be attributed to social factors as parents react more toward affection of a male child than a female.<sup>[19]</sup> Multivariate regression analysis has revealed that male sex is a significant factor for poor outcome of the disease. However, Seaman et al in Sudan didn't report a significant difference in mortality between both sexes.<sup>[20]</sup> Malnutrition was not found to be significant risk factor for poor outcome in this study. However, Rey et al reported that moderate to severe malnutrition was related to a 13.2% mortality rate, compared to 7.0% in well nourished children.<sup>[18]</sup> In an epidemic VL in Southern Sudan, it was found that the approximate relative risk for death was 12.2 (confidence interval 95%) for those with a body mass index less than 12.2 kg/m<sup>2</sup>.<sup>[20]</sup> This study has reported that VL cases that had anemia, leucopenia, and thrombocytopenia on presentation had a worse prognosis than cases presented with normal hematological values. This probably because

such cases were more advanced with bleeding and depression of bone marrow function and complicated by secondary infections. So early detection of VL is important since early presented cases carry a better prognosis compared to late cases. Nearly all other studies show decreases in hemoglobin value, leukocytes and platelets.<sup>[12-14,21,22]</sup> Furthermore, this study has revealed that there is significant difference between the duration of illness and the outcome of the patients. Mortality rate was lower (12.2%) in children presented early, compared to that who had symptoms more than 4 weeks (38.8%). This can be explained by the delay in seeking for medical advice and treatment and development of complications because of long duration of illness which gives this bad prognostic result. This result was in agreement with other studies.<sup>[12,14]</sup> High DAT titer was found to be a significant factor for poor outcome of the disease. This result is in contrast with an earlier study which had mentioned that DAT may yield positive results for a long time after complete cure and thus has not proved to be of much prognostic value.<sup>[23]</sup> However, Mengistu et al have found that DAT assay used to monitor improvement of disease status following treatment of diffuse cutaneous leishmaniasis patients, correlates well with the changing clinical status of the patients.<sup>[24]</sup> Boelaert et al have concluded that in addition to confirmatory tests for diagnosis, a marker indicating the prognosis in treated patients, a test of cure after therapy, a marker of asymptomatic infection and assays that allow easier surveillance of parasite drug resistance are also needed.<sup>[25]</sup>

Thus it can be concluded that early medical consultation and treatment are important and significantly associated with better outcome and improvement. Effective control programs for VL should be implemented soon in all areas of Basrah and other governorates as well where the disease is endemic.

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