CLINICAL PROFILE OF CHILDREN WITH VISCERAL LEISHMANIASIS IN TWO REGIONS IN YEMEN

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ABSTRACT

Objective: To identify and compare the demographic features and the clinical presentations of children with Visceral Leishmaniasis (VL) attend tertiary hospitals in two different geographical regions in Yemen.

Method: The study is a prospective study. Follow up done on children <15 years old presenting with fever > 2 weeks and wasting, hepatosplenomegaly or lymphadenopathey attending two tertiary hospitals in Sadah and Sana'a where they investigated to diagnose visceral elishmeniasis during the period from 2006 – 2011.

Results: One hundred and ninety five (195) children were confirmed as visceral elishmeniasis, 134 from Sadah and 61 from Sana'a. The comparison of the demographic, clinical and laboratory presentation of the patients from the two areas showed that those who enrolled from Sadah have poorer presentation as weight loss (93%), malaise (86%), pallor (86%) chest infection (6%), liver disease (5%) sickle cell anemiaand had more mortality rate.

Conclusion: VL is a common health problem and need to be addressed in Yemen. The most common presenting symptoms were fever, malaise and wasting and the most common signs were splenomegaly and anaemia. The high proportion of mortality and poor presentation in Sadah could be due to the endimecity of the disease in the area and the political and security instability in the region.

Keywords: Visceral leishmaniasis, children, clinical presentation, Sana'a, Sadah, Yemen.

INTRODUCTION

There are at least half a million new cases of Visceral Leishmaniasis (VL) each year. Although 90% of these are reported from India, Bangladesh, Brazil, Nepal and Sudan, numbers from other regions are underestimated because of poor surveillance systems in areas considered to have lower prevalence. Although new diagnosis and control strategies developed in the last decades have resulted in an attempt to eliminate the disease from the Indian Sub-continent; the disease is still spreading to new

areas due to environmental changes, human displacement associated with labour and refugees' movement due to social upheaval (Postigo, 2010).

VL is a major public health problem in the Eastern Mediterranean Region (WHO, 2002) affecting 14 of its 22 countries and outbreaks occur with 10-year intervals. In Yemen, the disease is endemic and the number of cases has increased in recent years. Although cases were initially confined to Sadah, Hajah and Amran Governorates, cases are spreading due to the civil war disrupting services and causing mass population movement. Sadah, in the North mountain region near the Saudi border, reported increasing numbers of cases linked to population movement as a result of military and civilian strife and army staff and multi-national contractors are reported to be at high risk of infection. Hospital services in Sana'a, located in a non endemic mountainous area, also treat many cases of VL, but these patients are often individuals who travel from remote endemic areas outside the capital.

Although VL has been reported from many decades, there are only two small case-series describing the clinical presentation of VL in children in the last 2 decades and the disease is poorly characterized (Daud & Rageh 1986; Haidar et al, 2001). A recent review of the clinical presentation of cases in Brazil, East Africa, Nepal, and India reported that there is substantial heterogeneity among the patients seeking care for VL and highlighted that drug development, procurement, and treatment protocols may require distinct strategies in these settings (Harhay et al, 2011)

This study therefore aims to describe the clinical spectrum and patients characteristics of Yemeni children with VL and compare the patient profile of patients attending Sana'a and Sadah to explore if the clinical presentation of VL varies in a settings with and without political conflict.

PATIENTS AND METHODS

This is prospective follow up study describes the characteristics, clinical presentation and the laboratory findings of children with VL attending the reference hospitals of Sana'a and Sadah governorates in Yemen during the period from 2006 – 2011. All children <15 years old admitted to Sadah hospital (SH) or to Al-Jamhori Teaching hospital (JTH) in Sana'a from 2006-2011 with a clinical diagnosis suggestive of VL were enrolled.

Inclusion criteria:

All children with fever > 2 weeks duration with signs of wasting and splenomegaly or lymphadenopathy were included in our study.

Exclusion criteria:

1- Malaria excluded by a blood smear examination.

2- Patients with previously confirmed VL episodes and those who had received VL treatment.

Method:

All patients underwent a Formol Gel Test. The diagnosis was considered to be parasitologicaly confirmed by the microscopic demonstration of *Leishmania donovani* bodies in Giemsa stained tissue aspirates of spleen or bone marrow.

Information from children with confirmed VL was extracted using standardised questionnaires and included demographic characteristics, clinical presentation, laboratory results, concomitant infections, diagnosis, treatment and outcome. Anaemia was defined as haemoglobin of <13 g/dl in males and <12 g/dl in females (WHO, 2008). A white cell count of <4500/dl and platelet count of <150 000/dl were used to define leucopenia and thrombocytopenia, respectively (Hurissa et al, 2010). Concomitant infections were identified based on the clinical presentation supported with laboratory examinations of clinical specimens whenever possible

Double data entry was performed and 20% of the records were randomly selected for further data entry checking. Continuous variables were analysed using unpaired Student's T-tests in normally distributed variables and Wilcoxon tests in variables with skewed distributions. Chi-square was used to compare categorical variables. Odds ratios (OR) were presented with 95% confidence intervals (95% CI). EPI Info was used for data management and statistical procedures. Ethical approval was obtained from the JTH and SH Research Ethics Committees and children were enrolled after obtaining parental informed verbal consent.

RESULTS

A total of 610 children were investigated during the study period (2006-2011). Of these, 195 (39%) were confirmed to have VL by parasitological diagnosis by biopsy of spleen or bone marrow aspirate. One hundred thirty four (134) confirmed VL children were enrolled in Sadah and 61 in Sana'a. Although children originated from 13 of the 21 gover-

norates, the majority originated from Amran (32%), Sadah (22%), Sana'a (13%) and Hajah (9%) (Fig.1). Patients who attended Sadah hospital were nearly exclusively from the North and resident in Sadah, Haja, Amran, Aljof and Mareb governorates. Patients attending Al-Jamhori Teaching hospital resident in the middle, West and South Governorates (Sana'a, Almahweet, Dhamar, Ebb, Taiz, Lahaj A, Albeda and Alhodedah), with the sole exception of patients from Amran governorate, who attended both hospitals.

The mean age ± SD of the children was 57 ± 38 months with a range of 7 to 156 months and 138 (71%) were male. The mean duration ± SD of symptoms before consultation was 16 ± 20weeks, ranging from 2 to 84 weeks. All children had a history of fever and the most common complaints were weight loss 181 (93%), malaise 167 (86%) and pallor 179 (92%), with less frequent signs listed as shown in (table -1) On examination, 190 (97%) had splenomegaly, 93 (48%) hepatomegaly and (149) 76% wasting. Only one child had lymphadenopathy (table-1).

Seventy four 74 (38%) children had other co-morbidities, including 46 (24%) with chest infections, 11 (6%) liver disease, 10 (5%) malaria, 10 (5%) otitis media, 4 (2%) sickle cell anaemia and 2 (1%) pulmonary tuberculosis (table- 1)

The most common abnormal laboratory tests were anaemia 194 (99.5%), thrombocytopenia 172 (88%) and leucopenia 145 (74%). 4 (2%) had a positive sickling test and 30 (15%) abnormal chest X rays. VL parasitological confirmation was obtained by bone marrow aspiration in 162 (83%) and splenic aspiration in 35 (18%) children. The Formal Gel test was positive in 88 (45%) children (table 4-b).

All confirmed VL cases received pentavalent antimonials. Of these, 180 (92%) improved and were discharged and 15 (8%) died (table 1).

There were no statistically significant difference regarding age and gender between Sadah and Sana'a. However children in Sadah had a lower WAZ ± SD -2.9 ± 1.2compared to -2.6 ± 1.2 for Sana'a, p = 0.02 (table 2) and were more likely to complain of malaise (94% vs. 65%; OR (95%CI) 0.1 (0.04-0.3) p <0.0001), and wasting (81% vs. 67%; OR (95%CI) 0.5 (0.2-0.9), p <0.02).

Children in Sana'a were more likely to have sweating (74%

vs.11%, p <0.0001); weight loss (100% vs. 89%, p 0.004), anorexia (38% vs. 20%, p 0.005), and headache (10% vs. O.7%, p 0.004), and complaining of abdominal distension (66% vs. 17%, p <0.0001), vomiting (39% vs. 6%, p 0.0001) and diarrhoea (8% vs. 0%, p 0.002) and to have hepatomegaly (100% vs. 24%, p <0.0001) (table 1).

Children from Sadah had a lower mean haemoglobulin concentration (mg/dl) 6.1 vs. 6.9 (p 0.01) (table 4-a) and were more likely to complain of oedema (11% vs. 0%, p=0.002), while more children in Sana'a had cough (30% vs.16%, p0.02), dyspnoea (23% vs.7%, p 0.001), chest pain (3% vs. 0%, 0.04) and abnormal chest examinations (23% vs. 8%, p 0.003).

Eleven (8%) children from Sadah and none in Sana'a had liver disease (p 0.003).

The method to confirm the disease also varied according to the sites and was achieved by bone marrow aspiration in the 61 children in Sana'a and in a 101 (75%) children in Sadah with significant difference (p<0.0001). All 33 children confirmed by splenic aspiration were admitted in Sadah (table)

Table (1): Demographic Charactristics of Studied Patients.

Clinical characterstics	**All**	**Sadah Total No 134 No (%)**	**Sana'a Total No 61 No (%)**	**OR (95% CI)**	**P value**
Age:(Mo) Mean ±2SD Range Median	57±(38) 7-156 48	58± (37) 9-140 48	59± (45) 7-180 48		0.8
Sex: Male (%)	139 (71%)	69 (72%)	43(71%)		0.4
Weight: (Kg) Mean ±2SD Range	12± (5.4) [5.5-31]	11.9± (5) [5.5 -31]	12.9± (6) [5.5 -29]		0.2
Height/Length:(Cm) Mean ± 2SD Range	92± (17) [60-155]	91 ± (15) [60-155]	94 ± (10) [60-135]		0.2
Duration of the disease before consultation: (Wks) Mean ±2SD Range	16± (19) [2-84]	11.5 ± (15) [2-72]	27 ± (24) [2-84]		**<0.0001**

Table (2): Clinical Criteria of Studied Patients.

Clinical Criteria	All	Sadah Total No 134 No (%)	Sana'a Total No 61 No (%)	OR (95% CI)	P value
History of blood transfusion	122 (63%)	85 (63%)	**37 (60%)**	0.9 (0.5-1.7)	0.4
Constitutional symptoms:					
Fever	195 (100%)	134(100%)	61 (100%)	-	-
Malaise	167 (86%)	127 (94%)	40 (65%)	0.1 (0.04-0.3)	<0.0001
Wasting	149 (76%)	108 (81%)	41(67%)	0.5 (0.2-0.9)	0.02
Rigor	42 (22%)	33 (25%)	9 (15%)	0.5 (0.2-1.2)	0.06
Sweating	60 (31%)	15 (11%)	45 (74%)	21.8 (10-49)	<0.0001
Headache	7 (4%)	1 (0.7%)	6 (10%)	14.3 (2.1-338)	0.004
Anorexia	50 (26%)	27 (20%)	23 (38%)	2.4 (1.2-4.7)	0.005
Signs:					
GIT Signs:					
Splenomegaly	190(97%)	129 (96%)	61(100%)	Undefined (0.5 undefined)	0.1
hepatomegaly	93 (48%)	32 (24%)	61 (100%)	Undefined (58-undefined)	<0.0001
Abdominal distension	63 (32%)	23 (17%)	40 (66%)	9.05 (4.5-18.5)	<0.0001
Vomiting	32 (16%)	8 (6%)	24 (39%)	10.1 (4.3-25.7)	0.0001
Jaundice	30 (15%)	18 (13%)	12 (20%)	1.6 (0.7-1.7)	0.1
Abdominal Pain	11 (6%)	10 (8%)	1 (2%)	0.2 (0.01-1.3)	0.09
Ascitis	3 ((2%)	1 (0.7%)	1 (2%)	2.2 (0.1-87)	0.5
Lymph node enlargement	1 (0.5%)	0 (0)	1 (2%)	Undefined (0.1-undefined)	0.3
Haematology signs:					
Pallor	179 (92%)	126 (94%)	53 (87%)	0.4 (0.1-1.2)	0.05
Epistaxis	10 (5%)	5 (4%)	5 (8%)	2.3 (0.6-8.8)	0.1
Renal signs:					
Oedema	15 (8%)	15 (11%)	0 (0)	0 (0-0.4)	0.002
Respiratory signs:					
Cough	40 (21%)	22 (16%)	18 (30%)	2.1 (1-4.4)	0.02
Abnormal chest examination	25 (13%)	11 (8%)	14 (23%)	3.3 (1.4-8.0)	0.003
Dyspnoea	23 (12%)	9 (7%)	14 (23%)	4.1 (1.6-10.5)	0.001
Sputum	17 (9%)	9 (7%)	8 (13%)	2.08 (0.7 -5.8)	0.08

Table (3): Co morbidities and Outcome of Studied Patients.

	All	Sadah Total No 134 No (%)	Sana'a Total No 61 No (%)	OR (95% CI)	P value
Associated conditions		49 (37%)	25 (41%)	1.2 (0.6-2.2)	0.2
Chest infection	46 (24%)	30 (22%)	16 (26%)	1.23 (0.6-2.5)	0.3
Otitis media	10 (5%)	9 (7%)	1 (2%)	0.23 (0.01-1.5)	0.1
SCA	4 (2%)	3 (2%)	1 (2%)	0.7 (0.02-6.9)	0.4
Liver disease	11 (6%)	11 (8%)	0 (0)	0 (0-0.6)	0.01
Outcome					
Died	15 (8%)	**13 (10%)**	2 (3%)	0.3 (0.04-0.7)	0.06

Table (4a): Haematological Findings of Studied Patients.

Haematological findings	All	Sadah Total No 134 No (%)	Sana'a Total No 61 No (%)	P value
HGB :(mg/dl) Mean ±2SD Range	6.3± (1.9) [1.2-13)	6.1± (1.9) [1.2 -11.7]	6.9± (1.8) [3.3 – 13]	0.01
WBC (10^3/dl) Mean ±2SD Range]	3.6± (2.2) [0.7-17]	3.4 ± (2.4) [0.7-17.3]	3.9 ± (1.9) [1.1 -11]	0.1
Platelets (10^3/dl) Mean ±2SD Range	88 ± (63) [4-446]	92.08± (67.9) [10-446]	79.4± (49.5) [4-328]	0.5

Table (4b): Laboratory findings of studied patients.

Laboratory findings	All	Sadah Total No 134 No (%)	Sana'a Total No 61 No (%)	OR (95% CI)	P value
Anaemia	194 (99.5%)	134 (100%)	60 (98.4%)	Undefined (0.1–Undefined)	0.3
Thrombocytopenia	172 (88%)	116 (86%)	56 (92%)	0.6 (0.18-1.5)	0.1
Leucopenia	145 (74%)	99 (74%)	46 (75%)	0.9 (0.4-1.8)	0.4
Positive Malaria smear	10 (5%)	8 (6%)	2 (3%)	0.5 (0.1-2.4)	0.3
Sickling test(out of 134)	4 (2%)	4 (3%)	0 (0)		
Abnormal chest x-ray	30 (15%)	14 (10%)	16 (26%)	3.02 (1.4-6.8)	**0.003**
Confirmation of the disease:					
Confirmed by Bone marrow	162 (83%)	101 (75%)	61 (100%)	Undefined (6 Undefined)	**<0.0001**
Confirmed by spleen aspiration	35 (18%)	33 (26%)	0 (0%)	0 (0-0.15)	**<0.0001**

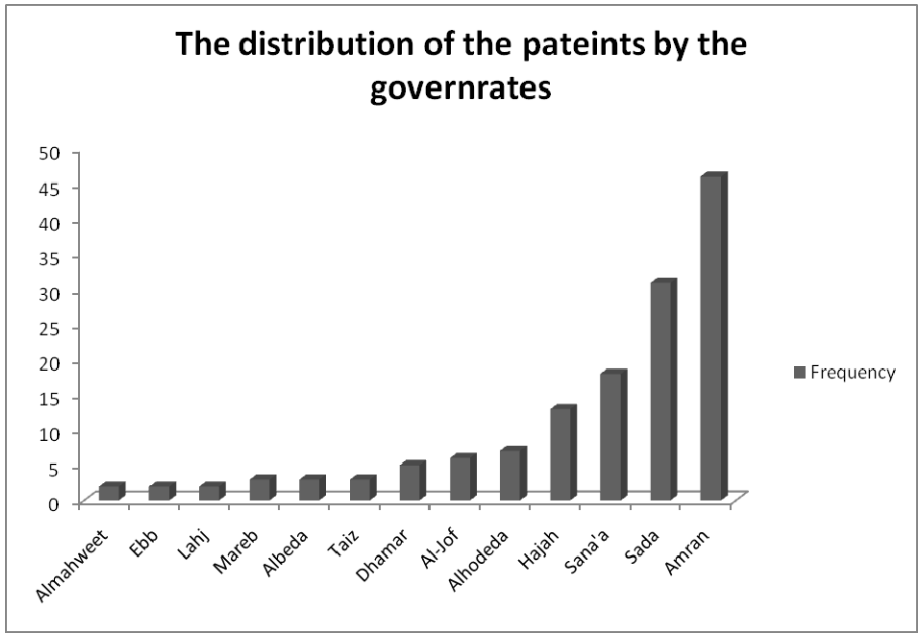

Figure (1): The distribution of the patients by the governorates.

DISCUSSION

VL is a major public health problem leading to severe morbidity and mortality if untreated, mainly affecting children (Tanoli et al 2005) and causing approximately 51,000 yearly deaths (Stark, 2008).

This study describes demographic, clinical and laboratory characteristics of VL in two different regions in Yemen. VL patients were more likely to be older than five year of age, which is consistent with the literature (Al-Orainey et al, 1994; Singh et al 1999; Haidar et al, 2001). There was no significant difference in the mean age of children who enrolled from Sadah or Sana'a, despite previous studies from the South of Yemen having reported that most cases occurred in younger children, with a mean age of 2.6 years (Hamid et al, 2004). Similarly there was no significant difference by gender or age, as reported elsewhere (Haidar et al 2001 and Hamid et al 2004).

Despite these similarities, patients in Sadah (compared to Sana'a) had longer disease duration, complained more frequently from malaise and wasting. On the other hand patients in Sana'a complained more frequently from sweating, headache, anorexia and vomiting and on examination they had

hepatomegaly and abdominal distension significantly more than patients who recruited in Sadah. However, odema was found in 15 cases, all were from Sadah; this oedma is a result of malnutrition, whereas none of the children who enrolled from Sana'a had oedema. Abdominal distension although was not striking criteria in the total study population but it is significantly prominent in children enrolled in Sana'a in comparison to those in Sadah (66% vs. 17%, P <0.0001). This finding may be due to hepatomegaly which is significantly more frequent in Sana'a; however this finding was in agreement with a study in Aden, south the country where abdominal distension was seen in (67.2%) (Hamid et al,2004), in Bangladesh(67%) (ICDDR, 2003) and Saudi Arabia (76.8%)(Al-Orainey,1994).

Lymphadenopathy, present in only one case from Sana'a was comparable to other studies reporting minimal involvement of lymph nodes (Ashkan et al, 2008; Tanoli et al, 2005; Al-Orainey et al, 1994); however other studies from South Yemen and Pakistan had reported Lymph node enlargement in 17.2% (Hamid et al 2004) and 40 % of cases; 83% of whom had localized to cervical region lymphadenopathy (Rai et al, 2008). This could be associated to co-morbidities or differences in the parasite strains. More children were died in Sadah than Sana'a (10% vs. 3%) with a total mortality rate of 8%.

Pancytopenia is the most consistent haematological finding in patients with visceral leishmaniasis (Mathur et al, 2005). The likely reason for the higher frequency of pancytopenia is the long duration of symptoms and splenomegaly before presentation to the hospital. Blood counts in this study are comparable to studies by Altaf et al (2005) and Tanoli et al. (2005). Hematological parameters are characteristic for VL. More children in Sadah had low haemoglobin level than those from Sana'a. Anaemia of varying degrees was present in all cases; nutritional factors and chronicity of the disease have an important bearing.

In this study, leucopenia occurred in 74% similar to another study that reported leucopenia in 67% of the cases (Hamid et al, 2004). Helmi et al. [1993] in Iraq and Rahim et al. [1998] in Pakistan found thrombocytopenia in 80-90% of the patients, similar to our results and study by Hamid et al (2004).

Several advanced, sophisticated and costly serodiagnostic tests are available to diagnose visceral leishmaniasis which are beyond the reach of a standard/field clinical diagnostic laboratory especially in underdeveloped countries like ours where diagnosis is established by demonstrating the parasite (LD bodies) in stained smears of bone marrow (Kaur & Kaur, 2013)

Leishmaniasis is endemic in many countries. The existence of different species combined with host factors may affect clinical presentation, and disease outcome. In an endemic country, a predominance of certain species and presentations may be expec-ted, whereas from the perspective of a tropical medicine referral unit a wider variety of cases from diverse geographical areas may be observed (Pérez-Ayala et al, 2009).

The difference in the clinical presentations in between these two regions could be as a result of many factors or reasons e.g. the geographical factors: Sadah located in the north with warm desert like environment while Sana'a located in the middle mountainous area with cold weather. This may lead to some differences in the strains of the parasite that may cause different clinical presentations. It was known that Kala-azar or VL is a disease of low altitude (approximately 500 meters mean sea level). In India, however cases have been reported from sub-Himalayan region (350-960 meters MSL) of Kumaon region of Uttaranchal (Mahajan et al, 2004). Also a study from India presented two patients of VL, natives of tribal district of Kinnnaur (2000-3000 meters MSL), Himachal Pradesh, who had never visited known endemic area for Leishmaniasis. These are probably first indigenous cases of VL being reported from an area situated at an altitude of 3000 meters and 2300 meters MSL (Mahajan et al., 2004).

Sadah is less urbanised area, and it is an area of political and security instability in the last few years and had low economic growth. These reflected on the low health care status and the lower health awareness and education of the population in this governorate. With the lack of roads and the insecure political situation in the area all these factors lead to reducing the accessibility to health facilities leading longer duration of the disease and the arrival of the cases at the end stages of the disease all these results in higher mortality and morbidity among

patients of Sadah. As a result of the low economic growth, malnutrition is prevalent more in Sadah than in Sana'a also as a result of the delay in the diagnosis the chronic illness leads to wasting and malnutrition. In a previous study in Sadah during 2001 fever, fatigability and abdominal distension were the most common symptoms (Haider et al 2001). Malnutrition was not prominent clinical presentation during that period suggesting that the change in the security and economic status of the northern country had major effect in the change of the clinical presentation of VL in Sadah.

Immunocompromised patients with VL due to malnutrition may present atypically, e.g. without fever or splenomegaly (Rosenthal et al. 2000; Russo et al. 2003). This may explain why fewer patients with splenomegaly in Sadah compared to Sana'a that has less prevalence of malnutrition. However, most cases included in this study had a classical VL presentation(Lopez-Velez et al. 1998; Pintado et al. 2001; Lyons et al. 2003), probably reflecting that this study targeted patients fulfilling the inclusion criteria of typical or classical VL cases, patients with atypical presentations may have beenmissed.

Regarding the co-morbidities; respiratory infections were significantly found more in Sana'a this explained by the significantly more numbers of patients in Sana'a complained from cough, dyspnoea and chest pain and had abnormal chest x ray. This may be due to the lower temperature and oxygen saturation in Sana'a that located at very high altitude 2200 m above the sea level. On the other hand there were grossly deranged liver function tests and liver disease was found predominantly in Sadah and these are considered bad prognostic signs (Ashkan & Rahim, 2008).

Yemen was an endemic area and although cases were initially confined to Sadah, Haja and Amran Governorates, cases are spreading due to the civil war disrupting services and causing mass population movement.

In conclusion, the most common presentation was fever followed by malaise and wasting, and the most common sign was splenomegaly followed by pallor and hepatomegaly. Pancytopenia was the most frequent hematological abnormality in VL patients.

The clinical presentation of VL in Yemen is similar to the presentations of countries of the Mediterranean regions. There

were no significant differences in the frequencies of the clinical symptoms and signs between the two governorates. However the laboratory data and nutritional parameters were significantly worse in Sadah group while Sana'a group characterised by significantly more constitutional symptoms such as sweating, headache and anorexia.

VL represents a severe public health problem in Yemen. Any patient from these areas with fever, anaemia with hepatosplenomegaly and pancytopenia associated with normal or high reticulocyte count must be subjected to bone marrow examination to rule out possibility of leishmania infection.

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