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The Ethiopian SORT IT Course

Clinical features and treatment outcomes of visceral leishmaniasis patients admitted to three centers in Oromia, Ethiopia

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Abstract

Introduction: In three health care facilities in the Oromia region, the aim of this study is to report on 1) the number of VL cases registered over time (2013-2018) and 2) the clinical profile, type of treatment used and response to treatment.
Methodology: A retrospective cohort study was conducted among all VL cases admitted with a diagnosis of VL.
Results: A total of 434 VL cases were registered at the three health facilities, but patient files were available for only 188. Most (51.6%) were children and only three presented with VL relapse. 78 (41.5%) of the 188 patients presented within one month of symptom onset. Concurrent severe acute malnutrition (27.1%), tuberculosis (6.4%) and malaria (6.4%) were common. There were only two cases with HIV coinfection. Fourty-three percent were treated with antimonials, 34% with antimonials combined with paromomycin and 23% with AmBisome. Amongst the 188 patients with patient files there were no deaths and one treatment failure. Six months outcome data were however missing for all. Aggregated data from the 434 VL cases reported three deaths, two treatment failures and one relapse.
Conclusions: Children were most commonly affected, suggesting long-term endemicity. While short-term outcomes are encouraging, long-term follow-up data are required.

Key words: Visceral leishmaniasis; treatment; Ethiopia.

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Introduction

Visceral leishmaniasis (VL) is a life-threatening parasitic disease caused by the *Leishmania donovani* complex. It is a vector-borne disease, transmitted by sandflies. VL affects an estimated 50,000 – 90,000 people each year. More than 90% of all VL cases occur in only seven countries, namely India, Brazil, Sudan, South Sudan, Somalia, Kenya and Ethiopia [1,2]. The disease is characterized by persisting fever, hepatosplenomegaly and pancytopenia. Untreated, VL is usually fatal [1,2].

In Ethiopia, the disease is prevalent mostly in the lowlands, and the parasite involved is *L. donovani*. There are an estimated 2000 new VL cases every year, with a population at risk of more than 3.2 million [3-6]. VL is predominantly found and well-characterized in the North-West of the country, with VL treatment programs established in several sites [5]. However, VL

has also been documented since 2011 in the Oromia region, the largest region in the country, and located in the South of the country. Only in 2013, the Ministry of Health in collaboration with the World Health Organization (WHO) started offering VL diagnosis and treatment activities in three health care facilities in the region.

While the clinical features of VL are well-characterized in the North-West of the country, with a number of studies published [4-6], a PubMed search revealed not a single study from the Oromia region. However, it has been observed that striking differences in clinical presentation and treatment response exist within and between countries [5]. This could relate to differences in circulating parasite strains, human genetic background, or prevalence of concurrent conditions such as malnutrition. In areas such as Oromia where VL care is only recently introduced, outcomes could potentially be worse due to delayed health seeking behavior of the patients, or lack of experience of the health care staff. Regional information is thus required to optimize VL care provision and monitor progress in reducing the VL burden at the country level.

In Ethiopia, data on VL cases are recorded in registers and based on these, aggregated data are reported to the national program. However, this only provides crude information. Medical patient files would constitute a better source for individual and more refined analysis of the VL clinical profile in the region. Patient files could also be useful to validate reported treatment outcomes. In high-income countries, electronic medical record systems have been implemented to capture routinely collected clinical information and are a valuable source for research. In resource-constrained settings, paper-based systems are still predominantly used. To what extent such paper-based patient files are effectively stored and retrievable in these settings (including Ethiopia) and to what extent detailed information is noted is not known.

In three health care facilities in the Oromia district, the aim of this study is to report on 1) the number of VL cases registered over time (2013-2018), 2) the proportion with patient files available and 3) the clinical profile, the type of treatment used and the response to treatment.

Methodology

Study design

A descriptive, retrospective cohort study using routine data from medical files over a six-year period.

Study setting

Ethiopia is a country in the Horn of Africa, with a population of 110 million inhabitants and a surface of 1,104,300 km². There are numerous ethnicities in the country, predominantly the Oromo and Amhara. The Oromia region in the South of Ethiopia is one of the most populated regions in the country, with a population of over 37 million. The three VL treatment centers in Oromia are Negelle hospital, Yabello hospital and Ginnir hospital. In 2013, the Ministry of Health together with WHO started providing VL services in the area. VL endemic areas were mapped, VL diagnostic tests and treatment were provided, health care workers were trained and the three VL treatment centers become operational. The hospitals have basic laboratory machines: a hematology machine, a chemistry machine and a blood bank service. VL care capacity was further enhanced by support of various international partners, including the KalaCORE initiative (http://www.kalacore.org) with funding by UK-AID (DFID).

Visceral Leishmaniasis management in Ethiopia

According to the Ethiopian national guidelines, a VL suspect is: "a person who presents with fever for more than two weeks and an enlarged spleen (splenomegaly) and/or enlarged lymph nodes (lymphadenopathy), or either loss of weight, anemia or leucopenia while living in a known VL endemic area or having travelled to an endemic area" [7]. Diagnosis is confirmed mainly by the rK39 rapid diagnostic test (Kalazar Detect™ InBios, Seattle, USA). Patients are classified as primary VL (first episode of VL) or VL relapse (a new diagnosis of VL in a patient who was previously treated for VL – a history of VL).

Historically, first line VL treatment consisted of sodium stibogluconate (SSG) given at 20 mg/kg intramuscularly for 30 days. From June 2013, on, this was modified to SSG and paromomycin combination therapy for 17 days. Liposomal amphotericin B (AmBisome, San Dimas, California, USA), with a total dose of 30 mg/kg given intravenously, is reserved for patients with more severe manifestations of the disease, treatment failure, pregnant women, VL relapse and extremes of age category (< 2 and > 40 years of age) [8]. According to the national guidelines, all VL patients should be screened for HIV co-infection.

Before discharge, the patient is evaluated clinically to assess the treatment response. In case treatment failure is suspected, spleen or bone marrow aspiration is done to assess whether the parasites have been cleared or if microscopic examination remains positive

(parasitologically-confirmed failure). However, tissue aspiration cannot be done at the study sites, and failure is ascertained clinically. At the end of treatment, patients are classified as cured if they display improvement of signs and symptoms during treatment (fever resolution, hemoglobin increase, weight gain, reduction in spleen size). Those who fail to respond to a full course of VL treatment (no improvement of symptoms and signs) are defined as failure.

At discharge, patients are recommended to return to the health facility at three and sixth months after discharge to ascertain for cure, and anytime VL symptoms reappear. A new case of VL after a previous episode is defined as VL relapse. VL treatment is provided free of charge in Oromia region, as well as additional laboratory tests and treatment for concurrent conditions. Physicians can also refer patients to a higher level facility. This could be due to stock rupture but also for patients presenting with more complicated VL or with a poor response to treatment.

Assessment of nutritional status

The nutritional status of all patients is systematically assessed using the national guidelines [8].

Severe acute malnutrition (SAM) in children

Mid-upper arm circumference (MUAC) is the circumference, measured in mid-position, of the relaxed left upper arm, taken in children of 6 to 59 months (65 to 110 cm in height). MUAC measures the degree of muscle wasting. A MUAC of < 115 mm indicates SAM and significant mortality risk.

Weight for height (W/H) index assesses the degree of weight loss by comparing the weight of the SAM child with non-malnourished children of the same height. Severe malnutrition is defined as a W/H index of < – 3Z with reference to the new WHO child growth standards.

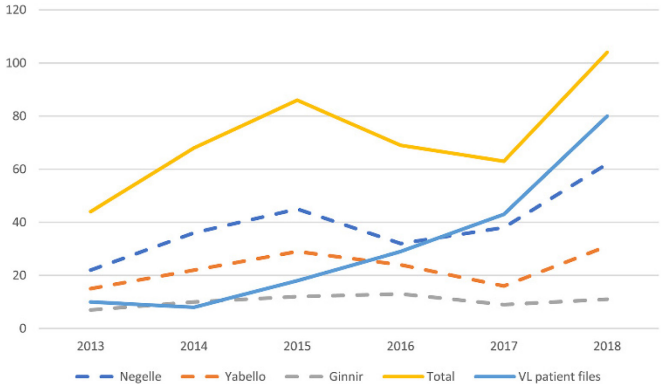
The presence of bilateral oedema of the lower limbs (when other causes of oedema have been ruled out) indicates SAM, regardless of the MUAC and W/H.

Severe acute malnutrition in adolescents and adults

Adolescents: W/H according to WHO criteria or bilateral lower limb oedema grade 3 or more, having excluded other causes of oedema).

Adults: MUAC < 160 mm or bilateral lower limb oedema or MUAC < 185 mm in poor general condition (for example, inability to stand, evident dehydration).

Figure 1. Number of cases of visceral leishmaniasis cases reported to the regional health bureau and the number with patient files available in three treatment centers, Oromia region, Ethiopia (2013-2018).



Study population and period

All VL cases diagnosed at the three treatment centers in the Oromia regional state from September 2013 to September 2018 were included.

Data collection and analysis

At the health care facilities, all VL cases are registered in a health management information system (HMIS) register. This book contains minimal patient information (only one line per patient), such as date of presentation, demographics, condition, treatment and discharge status. This register is used to make an aggregated data report to be sent to the regional level. Details of patient care are recorded in the medical files. These files contain observations of the treating physician, the presence of certain symptoms or clinical signs, and data on adverse events and technical procedures done. After discharge, these patient files are kept at the card room, where all patient files are stored. If a patient presents with a now medical condition later on, this individual patient file will be retrieved and additional relevant medical information added. For the study, the patient card number of VL cases diagnosed during the study period was retrieved from the register by three trained data collectors. With this number, the patient file was retrieved.

Data were extracted by trained data collectors using a standard data extraction tool and stored electronically. Variables collected included sociodemographic information, clinical presentation, type of diagnosis and treatment given, treatment outcome and reported side effects during treatment. Descriptive analysis entailed the calculation of medians (interquartile range (IQR)) and frequencies (%). Data storage and analysis was done using Epidata.

Ethics

Permission to conduct the study was secured from the Union Ethics Advisory Group, Paris, France/TDR and ethics approval was obtained from the Ethics Committee of the Oromia regional health bureau, Addis Ababa, Ethiopia.

Results

Between 2013 and 2018, a total of 434 VL cases were reported from the three district hospitals to the Ministry of Health. Most cases were from Negelle Borena hospital, followed by Yabello and Ginnir hospitals (Figure 1). The case load ranged from 44 cases in 2013 to 104 cases in 2018. Of the 434 registered cases, 188 patient files could be retrieved from the medical registration units. Almost all (178; 95%) came from the Oromia region, 10 (5%) from surrounding regions. As to the Oromia region, cases originated from 24 out of 377 districts. The median age was 14 years (IQR 6-23); 51% were children < 15 years old (Table 1). The vast majority (80%) were male. Out of 188, there were 185 (98%) cases with primary VL (first VL episode); only three presented with VL relapse. 41.5% of patients presented to the hospital within a month after symptom onset; ninety percent within three months. Concurrent conditions were present in 83 (44%), predominantly severe acute malnutrition (n = 51; 27.1%), tuberculosis (n = 12; 6.4%) and malaria (n = 12; 6.4%). There were two cases with HIV co-infection. The median hemoglobin at VL diagnosis was 7 g/dL.

Most patients received antimonials (sodium stibogluconate), either in monotherapy (n = 80; 43%) or combined with paromomycin (n = 64; 34%). Combination therapy was most common during more recent years (Table 2). Fourty-four (23%) cases were treated with liposomal amphotericin B. Of the 434 cases reported to the regional health bureau, 317 were reportedly cured, 2 had failed the initial treatment and 3 had died. One hundred and four (21%) of the 434 patients were referred to a nearby referral hospital (Table 3). Of the 188 patients initiated on treatment and with patient files available, 178 (94.7%) were discharged cured, three (1.6%) were referred, 2 (1%) defaulted and one (0.5%) had initial treatment failure. There were no deaths. Out of 188 patients, only 103 patients came for the third month follow-up and none of them came for the six months' follow-up visit. No relapse cases were seen during this follow-up period.

Table 1. Baseline demographic, clinical and laboratory characteristics of patients with visceral leishmaniasis (VL) diagnosed at the three treatment centers in Oromia, Ethiopia (2013 – 2018; n = 188).

Variables	N (%)
Age, years; median (IQR)	14.0 (6.2-23.0)
< 5	34 (18.1)
5 – 15	63 (33.5)
> 15	91 (48.4)
Gender	
Male	151 (80)
Female	37 (20)
Type of VL	
Primary	185 (98.4)
Relapse	3 (1.6)
rK39 rapid diagnostic test	
Positive	187 (99.5)
Not done	1 (1.5)
Months since onset of symptoms	
< 1	78 (41.5)
1 – 3	91 (48.4)
3 – 6	14 (7.5)
> 6	5 (2.6)
Presenting symptoms (at diagnosis)	
Fever (self-reported)	117 (62)
Splenomegaly	149 (79)
Hepatomegaly	86 (46)
Jaundice	4 (2)
Peripheral oedema or ascites	0 (0)
Comorbid condition	
None	105 (56)
Severe acute malnutrition (SAM)	51 (61)
Tuberculosis	12 (14)
Malaria	12 (14)
Hepatitis B	5 (6)
HIV and SAM	2 (2.4)
Tuberculosis and SAM	1 (1.2)
Pregnancy	1 (1.2)
Hemoglobin (g/dL); median (IQR)	7 (6-9)
White blood cells (cells/mm^3); median	2900 (1900-
Platelet count (count/µL); median	129500 (91750-

Table 2. Comparison of treatment types among VL cases between 2013-2015 and 2016-2018 in Oromia region, Ethiopia (n = 188).

Treatment type	2013- 2015	2016 - 2018	Total
	N	N	N (%)
SSG-PM	0	64	64 (34)
SSG alone	34	46	80 (43)
AmBisome	2	42	44 (23)
Total	36	152	188

SSG: Sodium stibogluconate; PM: Paromomycin.

Table 3. Treatment outcomes of visceral leishmaniasis patients diagnosed at patients with visceral leishmaniasis diagnosed at the three treatment centers in Oromia, Ethiopia (2013 – 2018).

Available patient files (n = 188)		**VL cases reported data to Oromia regional Health Bureau (n = 434)**	
Treatment outcome (end of treatment)	**N (%)**	**Treatment outcome (end of treatment)**	**N (%)**
Initial cure	178 (94.7)	Initial cure	317 (73.0)
Referred	3 (1.6)	Referred	104 (24.0)
Defaulted	2 (1.0)	Defaulted	7 (1.6)
Treatment failure	1 (0.5)	Treatment failure	2 (0.5)
Death	0 (0.0)	Death	3 (0.7)

Discussion

Over the six-year period, a total of 434 cases were registered. Patient files were however only available for 188 cases. All but three presented with primary VL, and half of the cases were seen in children. Concurrent conditions such as severe malnutrition were common. Treatment outcomes were favorable, with low treatment failure rates and the end of treatment and low case fatality rates. However, long-term follow up was limited.

The young age of many VL cases suggests VL to be endemic in the area. Indeed, two VL cases have been documented in the Oromia region already in 1984 [9], and VL has also been reported from other parts of Southern Ethiopia [5]. The young age is in contradiction with the findings from the north-west part of the country where most of the patients are adult migrant workers, with a high prevalence of VL/HIV-coinfection [5,10,11]. As in other studies from Ethiopia, malnutrition at VL diagnosis was common, reflecting weight loss due to VL in a country remaining with a high prevalence of malnutrition [4].

The number of cases gradually increased over time, and combination therapy – as recommended by the national guidelines - gradually increased. Contributing factors likely include the launch of the KalaCORE initiative in the region since the end of 2015. This capacity building project, a collaboration between the Ethiopian Ministry of Health and international R&D and academic partners, aims for increased community awareness on VL and better diagnostic and treatment services in affected areas.

Overall, the treatment outcomes in this study compare favorably to those from North-West Ethiopia, with clearly lower mortality and treatment failure rates. In part, this likely relates to the high prevalence of HIV coinfection in the North, with HIV having a pronounced impact on prognosis and treatment response [5]. On the other hand, cure rates have been found higher in the South compared to the North in trial settings for a number of treatments, including SSG/paromomycin combination therapy and liposomal amphotericin B [13],. It remains to be defined whether host or parasite factors contribute to this.

While the aggregated outcomes of the 434 reported cases generally look favorable - with only two cases of treatment failure and three deaths ascertained - a number of areas with uncertainty remain. First, we could not validate the reported outcomes of 246 patients due to missing files. As more recent files were more likely to be available, selection bias is a concern. Moreover, since the end of 2015 the KalaCORE initiative was implemented hence our data predominantly reveal patient outcomes during this period and much less so for 2013-2015. Second, tissue aspiration could not be done in the three hospitals, hence some failure cases might have been missed. Given the suboptimal sensitivity of the rK39 RDT used, some cases (and thus potentially unascertained deaths) might have been missed. Third, a substantial proportion of patients was referred to another health care facility, without information on their ultimate outcomes. While stock ruptures surely contributed to that, it is also not excluded that some of these were referred because of more complicated VL or a poor response to treatment. There could thus be unascertained deaths or treatment failures amongst the referred cases. Finally, definite treatment response should be ascertained by six months after treatment, and none of the 188 patients with files available had documented follow-up visits at this point in time. There could thus be unascertained relapses or deaths (early) after discharge. Overall, current data look reassuring but need to be confirmed in future studies.

While information recorded in medical files was generally good, a high number of patient files could not be retrieved. While this issue clearly improved over time, it nevertheless raises several concerns. First, as the fate of the patient files is currently unknown, there could be issues related to patient confidentiality. Second, having access to a detailed medical history is useful for improving quality of care, particularly for chronic medical conditions. As to VL care, lack of patient files could also lead to erroneously labeling a VL relapse case as a new (primary) VL cases, which

would not only lead to suboptimal treatment but also to underestimation of treatment efficacy. Finally, medical files can be useful to validate reported program data or for pharmacovigilance purposes. Further operational research is required to document potential reasons for patient files not being available, ranging from understaffed medical chart services to destruction of patient files by environmental hazards and transfer of patient files upon referral to another health care facility.

Conclusion

A total of 434 VL cases were registered over the six-year period. Most occurred in children, concurrent malnutrition was common. Initial treatment failure and mortality rates were low, but long-term follow-up information was missing. Patient files were often not available and the reasons behind remain to be determined.

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