



Identification of an area predominantly endemic for childhood and adolescent visceral leishmaniasis in central Sudan

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ABSTRACT

Although widely spread throughout Sudan, visceral leishmaniasis (VL) is predominantly endemic in the Gedaref, southern Blue-Nile, and Umrimita areas located in the eastern, southern, and central regions, respectively. Regardless of form (endemic or epidemic), VL occurrence follows similar patterns as all ages and both sexes are affected. From January 2005 to May 2016, we received a total of 563 patients with high suspicion for VL from various endemic areas; 159 were children and adolescents (0.5–18 years) from Umrimita (central Sudan). A significant observation during this 11-year period of uninterrupted monitoring using a standard liquid direct agglutination test (LQ-DAT) version was the exclusive VL occurrence (100%) in the child and adolescent populations of Umrimita when compared with other endemic areas (27.3%–48.0%). Among 12 child and adolescent suspects who initially tested marginal in the standard LQ-DAT, 6 scored unequivocally positive readings both in an improved LQ-DAT version (based on an autochthonous *Leishmania donovani* strain) and rK28 VL reference test. None of the 4 (2.5%) VL adult suspects (≥ 19 years) referred had positive outcomes in the improved LQ-DAT version or the VL reference freeze-dried direct agglutination and rK28 tests. Further incorporation of antigens derived from autochthonous *L. donovani* strains from Umrimita (central Sudan) or Gedaref (eastern Sudan) in LQ-DAT significantly increased the agglutination titer levels in the respective VL homologous sera ($p = 0.0263$ $T = 505$ and $p = 0.2814$ $T = 219$), suggesting possible antigenic variation within the predominant Sudanese *L. donovani* complex. Additional research is required to determine characteristics other than the serologically-based ones reported for the *L. donovani* strain involved.

1. Introduction

Sudan and the newly established Republic of South Sudan are among the 6 countries that contribute to > 90% of the worldwide annual incidence of visceral leishmaniasis (VL). The 3 major VL endemic areas in Sudan are in the eastern, central, and southern regions; several other areas of sporadic occurrence are scattered in Kordovan state and in the central and western parts of Darfur state. Following the devastating outbreak of 1989–1995 and the subsequent mass migration of the affected Neur tribe from the Bentiu area in the former state of Upper Nile to the capital Khartoum (± 900 km northwards) seeking treatment, the disease has spread along this migration route to areas previously unknown as VL endemic (de Beer et al., 1991). VL infections in

Sudan seem to have no demographic preference; both sexes and all age classes are affected. In comparison with adults, infected children were reported to have a higher grade fever and splenomegaly (Zijlstra and el-Hassan, 2001).

In 1988, a group of > 100 patients in different age classes from 4 villages on the west banks of the White-Nile state with high grade fever were reported to have died before cause of death was identified as being VL (Khalil et al., 2002; Ahmed et al., 1988). Eighteen years later, a group of 150 patients consisting of mostly children in the same area developed similar grade fevers that were unresponsive to anti-malarials or antibiotics; 100 were diagnosed as VL cases by either bone-marrow or lymph-node aspiration (Khalil et al., 2008). In addition to VL, this area is also known to be endemic for cutaneous leishmaniasis due to

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Leishmania major (el-Safi and Peters, 1991).

In January 2005, our Laboratory for Biomedical Research at Ahfad University for Women had started receiving patients with suspicion of VL from the various hospitals and health centers across Sudan. At the request of the physicians in charge, patients were tested for the presence of anti-*L. donovani* antibodies by a locally produced liquid version of the well-known direct agglutination test (LQ-DAT) (de Beer et al., 1991). Until May of last year, a total of 563 patients were seen of whom 387 were from the 3 major endemic areas namely Gedarif (Eastern state), Umrimita (White-Nile state), and the Southern part of the Blue-Nile state; 176 other cases were from areas of relatively lower endemicity scattered throughout the country.

A significant observation though during our 11-year monitoring period was the exclusive VL occurrence in Umrimita children and adolescents (0.5–18 years), as compared to that in the other endemic areas of Sudan (27.3%–48.0%). It is of relevance to mention that of the total VL suspects referred (163) from Umrimita during this period only 4 (2.5%) were adults with ages varying between 25 and 61 years.

In this phase of our study, we intended to investigate whether this selective VL occurrence in the children and adolescents of Umrimita (central Sudan) was associated with prevalence of an *L. donovani* strain that differs serologically from the one causing the disease in Gedaref (Eastern Sudan). This area is the most well-known and it's the one of stable endemicity in Sudan (Zijlstra and el-Hassan, 2001). Since the Umrimita area is also known to be endemic for cutaneous leishmaniasis due to *L. major*, the possibility of mixed infection with *L. donovani* and *L. major* was not excluded. Based on this information and the knowledge that *L. major* tends to visceralize under conditions of malnutrition or impaired immunity, sera from some of the VL affected children and adolescents were also assessed for the presence of agglutinating anti-*L. major* antibodies (Soliman, 2005; Babiker et al., 2014).

2. Material and methods

Since January 2005, the laboratory of Biomedical Research at Ahfad University for Women was recognized as the reference laboratory for VL (sero)-diagnosis in Sudan. Patients with suspicion for VL were referred for application of a locally produced liquid version (LQ-DAT) of the well-known direct agglutination test. Most of those patients were aware of the disease and the problems that it can cause if left untreated. Therefore, they do their utmost to meet the expenses related to traveling, diagnosis, and eventual treatment. Patients are advised to present themselves first at any polyclinic section in the various public or private hospitals in Khartoum, Khartoum-North, or Omdurman from where they will be referred to our laboratory. Almost all VL suspects < 19 years were referred from the Omdurman Emergency Hospital for Children. Of the 563 patients received, 333 were children and adolescents and 230 were adults of 0.5–18 and 19–61 years of age, respectively (Table 1). Almost half (47.7%) of the referred child and adolescent populations was from the Umrimita locality in the White-Nile state (central Sudan).

Table 1

Positive liquid direct agglutination test (LQ-DAT) readings in 563 patients with high suspicion for visceral leishmaniasis (VL) referred from various endemic areas in Sudan to Ahfad Laboratory for Biomedical Research during the period 2005–2015.

Endemic area/state	Number of suspects referred	LQ-DAT positives among suspects referred	LQ-DAT positives per age class (years)	
			0.5–18	19–61
Umrimita locality White-Nile state	163	70 (42.9%)	70 (100%)	0 (0%)
Gedaref locality Eastern state	133	49 (36.8%)	20 (40.8%)	29 (59.2%)
Blue-Nile state	91	33 (36.3%)	9 (27.3%)	24 (72.7%)
Other endemic states	176	25 (14.2%)	12 (48.0%)	13 (52.0%)
Total	563	177 (31.4%)	111(62.7%)	66 (37.3%)

2.1. Umrimita area

Umrimita is one of 8 localities in the White-Nile state, lies about 150 kilometers south-west of the capital Khartoum with 160,000 inhabitants. The habitats in this locality resemble those of areas generally known to be endemic for VL in Sudan characterized by presence of *acacia* and *balanites* trees favoring sand-fly breeding. In addition to VL, the area is also known to be endemic for cutaneous leishmaniasis, malaria, brucellosis, and tuberculosis. Most of the inhabitants in this area are well aware of VL signs and symptoms. Patients who are suspected to have the disease were advised to travel either to the nearby major state hospital in Aldweem or for the few who can afford it, to hospitals with better facilities in Omdurman, Khartoum, or Khartoum North.

2.2. Ethical approval

The study was approved by the ethical committees of Ahfad University for Women, Omdurman and the Federal Ministry of Health, Khartoum (Walieddeen et al., 2010). Since the study involved a retrospective analysis of routine data, informed patient's consent was not applicable. All collected blood and serum samples remained anonymous.

2.3. VL diagnosis

Almost all of the children and adolescents who presented with suspicion for VL at Omdurman Emergency Hospital for Children were referred to our laboratory for diagnosis of the disease. This was largely encouraged by the availability of a non-invasive diagnostic procedure such as LQ-DAT, the highly reputed efficiency of this procedure for VL diagnosis and the privilege of its free of charge application. The criteria for VL suspicion included residency or visit to this or similar other endemic areas, presentation of signs and symptoms indicative of VL, such as presence of fever for periods > 2 weeks, and exclusion of malaria and typhoid.

Prior to LQ-DAT application, a file was created for the registration of the relevant administrative and demographic information, history, nature, and type of complaints. A blood sample (2–5 ml) obtained by venous puncture were collected from adults (≥ 19 years) and older children (≥ 10 years) or by finger prick (1–2 spots) onto filter-paper (Whatman no 2 or 3) from younger children and severely anemic patients. The separated serum was either used immediately for LQ-DAT application or stored frozen at -20°C until needed. After thorough air-drying the blood samples on filter paper were handled in a similar way. Due to the instability of antibody content on the filter paper in comparison with serum under situations of frequent electric failure, filter-paper collected blood samples were considered invalid for LQ-DAT testing if the length of the storage period at -20°C exceeded 3 months.

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