Guidelines on Management of Visceral Leishmaniasis

Public Health Deputyship, Ministry of Health, Saudi Arabia

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Foreword

Leishmaniasis is still a major public health problem facing the global health community. However, in the kingdom of Saudi Arabia (KSA), with the great advocacy and through the strong support over last decades, major achievements have been reached in the field of leishmaniasis control. Cutaneous leishmaniasis (CL) cases have been reduced dramatically form thousands of cases during the 1980s and 1990s to 600 cases in 2021. For visceral leishmaniasis (VL), the last locally acquired cases were reported in 2018.

There is always a need to revise and update ongoing strategies and to strengthen the existing tools in order to win the battle against infectious diseases. Development of a national VL management policy, relying on the local literature and the gained knowledge, is one of the essential tools to combat this disease and to reach the planned objectives. These guidelines are going to provide the health professionals with the up to date recommendations for handling and providing care to cases of VL in KSA.

All health workers and professionals dealing with VL case management in Saudi Arabia should adhere to these guidelines to make the targeted goals of the ministry of health a reality in the near future.

Introduction

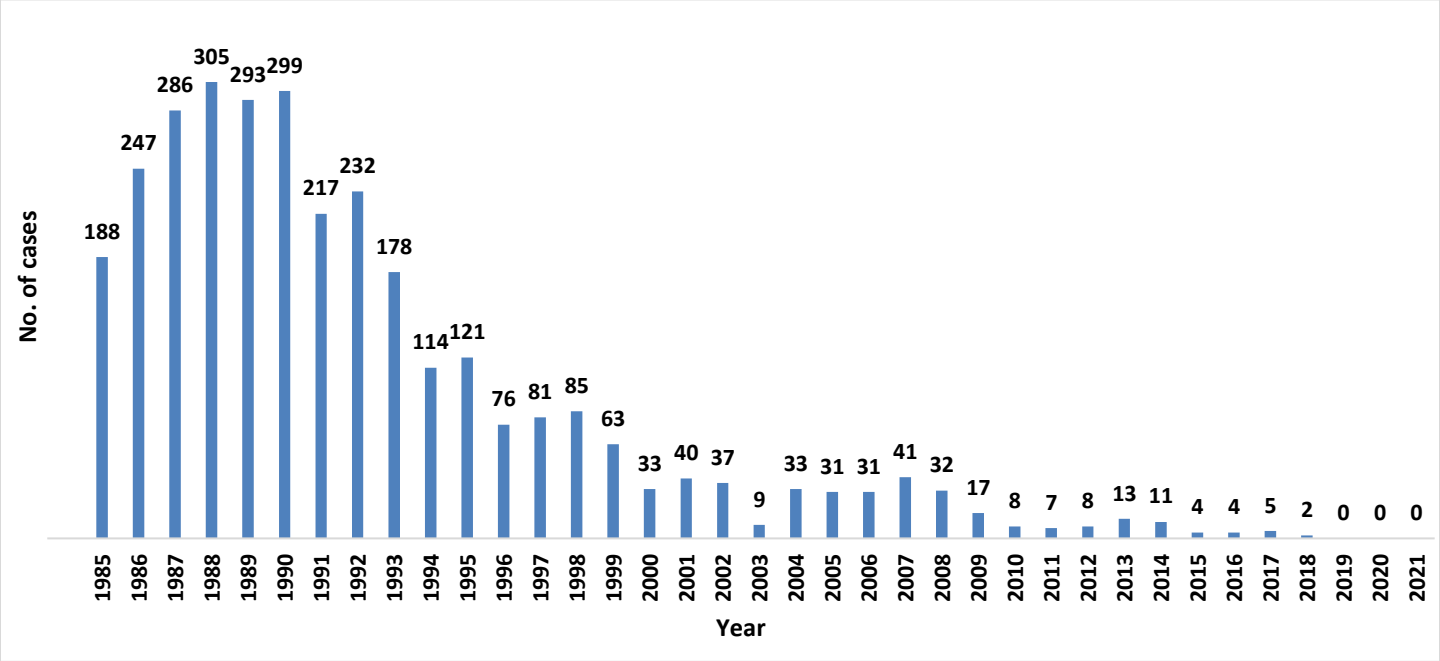
VL is a vector-borne parasitic disease caused by species of the genus *Leishmania*; *L. donovani* species are responsible for the disease in East Africa, Middle East and the Indian subcontinent, while *L. infantum* species are incriminated in Europe, North Africa and South and Central America. The disease is transmitted through the bite of infected female sandflies. Generally, sand fly species of the genus *phlebotomus* are responsible for disease transmission in the old world, while the genus *lutzomyia* is incriminated in the new world. According to mode of transmission, the disease is divided into two categories: anthroponotic transmission where the incriminated vector carries *L. donovani* species (anthroponotic species) from human to human, and zoonotic transmission where *L. infantum* species (zoonotic species) are transmitted by sandflies from animal reservoirs to humans. Dogs are described as the main animal reservoirs of the zoonotic type. VL is a fatal condition if left untreated.

It has been estimated that around 50,000- 90,000 new cases of VL cases occur worldwide annually. The majority of cases (more than 90% in 2020) are reported from Brazil, China, Ethiopia, Eritrea, India, Kenya, Somalia, South Sudan, Sudan and Yemen. KSA is known as one of the endemic countries for both CL & VL forms of leishmaniases. Previously, KSA was highly burden by VL (Fig. 1). Following the development of the Leishmaniasis Control Program (LCP) at the MOH, and the implementation of control measures, the country has achieved a great success in reducing the burden into very few cases in the last years, and reaching zero autochthonous case in the year 2019.

Epidemiology in KSA

The first VL case was diagnosed and treated in Dhahran Hospital, Northeast of Saudi Arabia, in 1953. Afterward, very few cases were reported from different regions, and it was unclear whether this due rarity of the disease or lack of awareness toward this disease. During the 1980s and 1990s, hundreds of cases have been reported (Fig. 1). In 1988, 305 cases were registered, which was the highest number of cases reported since the documentation of this disease. The increment in number of cases could be linked partially to the great urbanization seen all over the country, and the expansion of agriculture fields and irrigation schemes particularly in the southwestern parts. In the subsequent years, from 2000 afterward, the numbers of reported cases continued to drop steadily, and the last locally acquired cases were reported in 2018 (Fig. 2).

Fig. 1. Number of reported VL cases in Saudi Arabia (1985- 2021)



In 1980, a symposium about leishmaniasis was held in Dammam, east of Saudi Arabia, and thereafter, the disease started to gain more attention and advocacy. This was followed by the establishment of the National Leishmaniasis Research Program (NLRP), based at King Faisal University, Dammam in 1982. This growing interest was advocated and adopted by the LCP, which was established in 1978.

The endemicity of VL in Saudi Arabia has been confined mainly to the southwest regions, namely Jazan and Asir regions. In addition, solitary cases have been also reported from other regions. Since the beginning of the 21st century, all VL autochthonous cases were reported only from Jazan and Asir regions. However, Asir region has been considered free of VL since 2013 when the last confirmed cases were reported. Very few sporadic cases are also reported from other regions far from southwest, and all of them were imported from abroad, or residents with history of travel to Jazan, Asir or known endemic countries.

Aetiology

VL in Saudi Arabia is an anthroponotic disease caused by *L. donovani* species, and *P. orientalis* sandflies *are* the incriminated vector species. *L. infantum* species, the zoonotic species, have isolated only from dogs in southwest of the country.

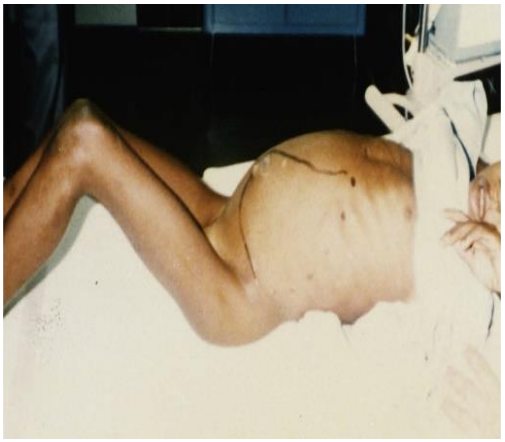
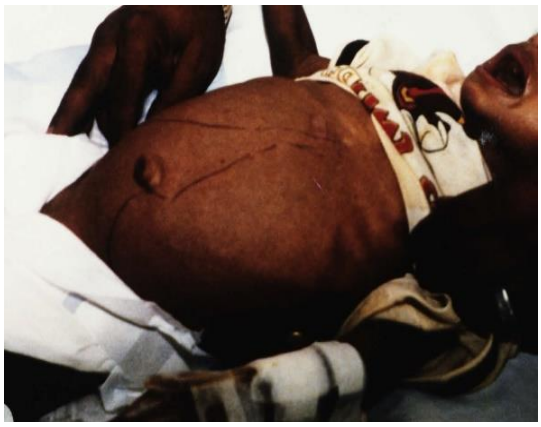
Clinical Features

The disease has a long incubation period that may extend to a year or even more. The majority of infected individuals develop no symptoms; this phenomenon is known as asymptomatic/ subclinical infection. In KSA, VL is mainly a disease of children; around 95% of reported cases were children under 15 years, with no great variation in sex distribution.

Common Clinical Features among Cases in Saudi Arabia

- Chronic fever,
- Abdominal distention (Fig. 2. A& b),
- Weight loss,
- Anemia (pale mucus membranes),
- Hepatosplenomegaly (non-tender) (Fig. 3. A& b).

Fig.2. Saudi VL cases with marked abdominal distention due to hepatosplenomegaly

(a)  (b) 

Many other symptoms may also exist e.g. malaise, shivering or chills, anorexia, vomiting, and discomfort in the left hypochondrium (due to huge splenomegaly). Lymphadenopathy is a rare finding in Saudi cases.

Diagnosis

Parasitology

Microscopic visualization of parasites remains the mainstay for diagnosis of VL. With varying sensitivities, specimens include lymph node aspiration, bone marrow aspiration (BMA), splenic puncture and blood sample. Culturing of these specimen increases the sensitivity of detecting the amastigote stage

of the parasites (diagnostic stage). PCR techniques are more sensitive than microscopy, but their usage is still limited to tertiary hospitals and research centers.

Serology

Several techniques are used to diagnose VL through the detection of antileishmanial antibodies, including the enzyme linked immunosorbent assay (ELISA), the indirect fluorescent antibody test (IFAT), the indirect hemagglutination assay (IHA), direct agglutination test (DAT), immunoblotting, rK39 antigen-based immunochromatographic test, and latex agglutination test. However, anti-leishmanial antibodies remains detectable for several years following successful treatment. Therefore, serological tests cannot be used to diagnose relapse cases. In addition, these tests cannot differentiate between past and current infection, as the sub-clinically infected individuals also show positive serological tests.

Other Common Laboratory Findings

Anemia, leukopenia, thrombocytopenia, hypoalbuminemia, hyperproteinemia and hypergammaglobulinemia, low serum iron, and abnormal liver enzymes (bad prognostic finding when heavily affected and associated with jaundice).

LCP Recommendations for Diagnosis

Suspected cases of VL in Saudi Arabia should be confirmed by parasitology and/or serological tests (ELISA and rk39 test). For serology, confirmation is based on positive tests following the presentation with compatible clinical and laboratory features of the disease, in the absence of history of VL. Rk39 rapid diagnostic tests are now available at all health facilities dedicated for diagnosis of VL in Saudi Arabia. Bone marrow (BMA) smears are highly recommended for parasitology, as lymph node enlargement is rare in Saudi patients, and splenic puncture require special skills and certain precautions.

Suspected Case

A person presented with chronic fever (two weeks or more), splenomegaly, and weight loss who lives in or returned from endemic area.

Confirmed Case

A person showing the clinical features with positive parasitology and/or serology.

Treatment

Several medicines have been approved by the World Health rganization (WHO) to treat VL cases. These drugs include pentavalent antimony (Sb^{5+}), amphotericin B deoxycholate, and lipid formulation of amphotericin B (e.g. liposomal amphotericin B), paromomycin and miltefosine. Pentavalent antimony has been used for several decades, and they are still effective against VL. Two Pentavalent antimonials are available: sodium stibogluconate (SSG) and meglumine antimoniate.

The available and registered drugs for treatment of VL cases in Saudi Arabia are pentavalent antimonials (sodium stibogluconate & meglumine antimoniate) and ambisome (liposomal amphotericin B).

Pentavalent antimonials

Presentation

- Sodium stibogluconate solution contains 10% Sb^{5+} (100 mg/ml)
- Meglumine antimoniate solution contains 8.1% Sb^{5+} (81 mg/ml)

Dosage

- 20 mg Sb^{5+} / kg/ day X 30 days
- The daily dosage amount should be calculated based on the antimony (Sb) contents.

Route of Administration

Antimonials are administered intramuscularly, or intravenously by infusion (over 5–10 min) or by slow injection through a fine needle.

Side Effects

Symptoms: anorexia, vomiting, nausea, abdominal pain, malaise, myalgia, arthralgia, headache, metallic taste and lethargy.

Laboratory: Elevated pancreatic enzymes (clinical pancreatitis is uncommon), Elevated liver enzymes, pancytopenia (, leukopenia, anaemia and thrombocytopenia), and Renal failure.

Electrocardiographic changes (Cardiotoxicity): the commonest being T- wave inversion, a prolonged Q–T interval and arrhythmia. Prolongation of a corrected Q–T interval (> 0.5 sec) signals the likely onset of serious and fatal cardiac arrhythmia. Cardiotoxicity and sudden death are serious but uncommon side effects.

Contraindications

- Elderly patient (> 50 years).
- Significant heart, liver, kidney disease.
- Pregnancy

General Considerations

- *Treatment with antileishmanials should be commenced only after confirmation of diagnosis.*
- *All cases should be treated as in-patients under the direct supervision of treating physicians.*
- *Before commencing treatment, contraindications should be ruled-out through investigations, which also can be used as a baseline data for follow-up.*
- *There is no upper limit of daily dosage. It has been shown that pentavalent antimony, without an upper limit on the daily dose, is more efficacious and is not substantially more toxic than regimens with lower daily doses.*
- *Supportive treatment is needed to treat the symptoms e.g. antipyretics, analgesics, and rehydration.*

- *Concomitant infections should be identified and treated.*
- *Monitoring of patients during treatment for the occurrence of side effects. It is highly recommended to perform investigations on weekly basis for monitoring of cure progress and adverse events.*
- *During treatment, if serious side effects arise, the drug should be stopped and alternative should be proposed.*

Ambisome (liposomal amphotericin B)

- This drug is similar to amphotericin B in efficacy, but it is significantly less toxic.
- Transient nephrotoxicity, thrombocytopenia and hypokalemia might occur, therefore, hydration and potassium supplement may be needed.
- It is given by intravenous infusion, and infusion reactions (fever, chills and rigor) might occur.
- It is given at a dose of 3mg/kg/ day for a total dose of 20-30mg.
- It is recommended to preserve this drug for resistant cases, or when pentavalent antimony's are contraindicated.

References

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