Systematic Review

Leishmaniasis in Saudi Arabia: Current situation and future perspectives

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ABSTRACT
Background and Objective: Leishmaniasis is endemic in Saudi Arabia with cases reported in many regions. This review refers to publications on leishmaniasis in Saudi Arabia and discusses issues related to parasite species, clinical manifestation and diagnosis.

Methods: This research was done at Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia by systematic literature search on PubMed and Google Scholar databases from 1989 to 2018. Selection criteria included original articles reporting on visceral leishmaniasis (VL) or cutaneous leishmaniasis (CL) in Saudi Arabia.

Results: The search identified 16 eligible articles, six for VL and 10 for CL. VL was reported in areas known to be non-endemic. Leishmania donovani was the main cause for human VL while Leishmania infantum seemed to cause the disease in animals. Dogs were considered the main reservoir hosts and black rats (Rattus rattus) were potential hosts. VL mainly affected infants and young children. It is important to note that VL diagnosis was based on either invasive parasite detection procedures or serologically using indirect hemagglutination test. CL represented the most frequent clinical form with the main endemic foci reported in the South-West and Eastern regions. CL appeared to have no demographic or socioeconomic restriction; it affected both rural and urban citizens, with the majority occurring among farmers. Travelling was recognized as an important risk factor. Leishmania tropica and Leishmania major were recognized as the main causes for CL.

Conclusion: This report summarizes the potential risks for VL and CL in Saudi Arabia in areas known to be non-endemic. There are substantial gaps in knowledge and practices in regard to leishmaniasis in Saudi Arabia, highlighting the need for more research and medical surveillance targeting the disease in humans and animals.

KEYWORDS: Epidemiology, Leishmaniasis, Saudi Arabia.

INTRODUCTION

Leishmaniasis is a vector-borne disease caused by different species belonging to the genus Leishmania. These species cause various clinical manifestations ranging in severity from self-limited cutaneous lesions to life-threatening visceral disease, including cutaneous leishmaniasis (CL), visceral leishmaniasis (VL), mucocutaneous leishmaniasis (MCL), and post kala-azar dermal leishmaniasis, PKDL. The disease is categorized...
into two types: zoonotic leishmaniasis (where wild and domestic animals are considered main reservoir hosts) and anthroponotic leishmaniasis (where humans are the source of the infection). Several domestic and wild mammalian hosts are involved in the transmission cycle of the disease, including certain rodents and dogs.\textsuperscript{1,2}

VL is the most severe form of the disease. It is caused by various species of \textit{Leishmania} in different endemic regions; \textit{L. donovani} in Asia and East Africa and \textit{L. infantum} in the Mediterranean area, Middle East, central Asia and America. It is the most severe form of the disease and still associated with high mortality.\textsuperscript{3} Laboratory findings include anemia, leukopenia, thrombocytopenia, hypoalbuminemia, and hypergammaglobulinemia. Kidney damage in VL is well-known and can appear as glomerulonephritis, acute or chronic renal disease.\textsuperscript{3,4}

The VL suspicion is present if fever persists more than two weeks in the presence of splenomegaly in individuals living in or having visited known VL-endemic areas. Clinical diagnosis is confirmed by various laboratory methods. These methods are based on detection of the parasite in aspirates collected from spleen, liver, bone marrow or lymph nodes. Sensitivity of these methods depends on the type of sample, being less sensitive for lymph nodes while more sensitive for spleen samples.\textsuperscript{2,5}

Due to the invasive nature of sample collection and low sensitivity, new methodologies based on detection of specific \textit{Leishmania} antibody are currently used. The direct agglutination test (DAT) using intact promastigote antigen and enzyme-linked immunosorbent assay (ELISA) using refined recombinant proteins of \textit{Leishmania} are most common methods. These methods are used for detection of VL in humans and animal hosts with variable diagnostic accuracy in the various endemic regions.\textsuperscript{6}

Worldwide, CL is the most common form of leishmaniasis, causing the greatest disease burden. It occurs across the Indian subcontinent, through the Mediterranean region and from Africa to America.
Most of the cases occur in six countries including Afghanistan, Brazil, Colombia, Iran, Algeria and Syria. CL is a self-limiting skin disease, causing skin ulcers on the uncovered body parts at the place of the infected sand fly vector bite. The appearance of characteristic lesions in areas with high endemicity of CL is enough to establish the clinical diagnosis. However, laboratory tests are required to distinguish leishmaniasis from several other skin diseases. The diagnosis is classically based on direct detection of Leishmania in lesion smears stained by Giemsa-stain or by culture. PCR techniques are highly sensitive and help to determine the parasite species, but it requires painful and invasive procedures for sample collection. Serological diagnosis is frequently used in epidemiological studies of leishmaniasis. It is an easy and quick approach, but its sensitivity is low due to limited circulating antibodies and potential antigen diversity of parasites that cause the disease.

METHODS

Literature Search Strategy: This systematic literature search was done at Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia. It was conducted by a literature search identifying epidemiological studies reporting leishmaniasis in Saudi Arabia. The search was performed on electronic databases using the PubMed and Google Scholar. The search was performed from 1989-2018. Keywords that were used included: epidemiology, leishmaniasis and Saudi Arabia. Only original research articles written in English language were selected. Furthermore, a Google search was used as an additional source of data. These articles were also included in the data analysis.

RESULTS

Sixteen eligible articles were identified (Fig.1), six studies reported VL and 10 articles reported CL. Results showed an uneven distribution of both diseases in the Kingdom. It was not possible to count the total number of individuals infected by the disease. In most of the published studies, only selected cases were involved (Table-I and II). None of these studies reported outbreaks or co-infections with other diseases. There were no reports on parasite characterization and genetic heterogeneity. The role of black rats in epidemiology of the disease was not confirmed. Also, there were no reports in regard to usage of new laboratory tests for the disease confirmation. The published studies also lack information on the use of new leishmaniasis drugs/regimens.

Visceral leishmaniasis: Epidemiological Characteristics: The major endemic areas that reported VL in Saudi Arabia were in the South and South-West. Sporadic cases were also reported in the city of Al-Madinah. Endemic areas included Gizan, Najran and Asser. In these areas, VL was characterized by seasonal variation with emergence of many cases in late spring and summer and few cases were observed in the winter. In Gizan, VL was confirmed in both humans and animals. L. donovani LON42 was associated with human infections while both L. donovani LON42 and L. infantum LON 49 were isolated from black rats (Rattus rattus). L. infantum LON49 was isolated only from dogs. In Najran, other animals might act as reservoirs for the parasite, such as goats and sheeps.

Most of the published articles reported VL among infant and adolescence in Gizan, Aseer and Al-Madinah. There was no gender restriction; both male and females were equally affected. In a study carried out in Najran involving 384 human samples,
anti-

Leishmania antibodies were significantly higher among old individuals.

Clinical Features: The common clinical features of VL among pediatric patients included fever (100%), pallor (>95%), hepatosplenomegaly (>90%) and lymphadenopathy (>90%). Other clinical presentations included abdominal distention, anorexia, and weight loss. However, none of the patients showed skin lesions (PKDL) while lymphadenopathy was a less common clinical finding. VL patients showed also abnormal laboratory results including anemia, leukopenia, thrombocytopenia, hypoalbuminemia and hypergammaglobulinemia. Abnormalities in liver functions were also observed.

Diagnostic Features: In endemic areas, primary VL suspected cases and diagnosis was based on clinical signs and symptoms. Laboratory diagnosis was based on either direct detection of Leishmania in bone marrow aspirates or serologically using indirect hemagglutination test (IHAT) kit (Siemens Healthcare Diagnostic, Marburg, Germany). IHAT detects anti-Leishmania antibodies in patients’ sera with hemagglutination cutoff titers of 1: 32-1: 64. This test performed very well with high sensitivity and specificity. Sensitivity of bone marrow aspiration for detection of Leishmania was also high (92.7%). None of the studies detected Leishmania in lymph node aspirates. Some studies used splenic and liver aspirates and isolation of the parasite in diphasic media for confirmation of the disease.

Cutaneous leishmaniasis:

Epidemiological Characteristics: CL was endemic in various parts of Saudi Arabia, with most of the cases reported in East, West, South-West, North-West and the Southern regions. Endemic areas included Al-Hassa, Aseer, Al-Baha, Al-Madinah, Al-Taif and Hail. Several cases were also reported in areas known to be non-endemic such as Al-Khobar and Riyadh province. CL was more prevalent among male than female. Infection included all ages with infant and young adults being the majority affected. There was no socioeconomic restriction for the disease. The affected populations included both rural and urban citizens, mainly among farmers. Temperature was recognized as an important factor associated with CL transmission in Aseer. Travelling was also recognized as a risk factor. Studies confirmed L. tropica and L. major as the causative agents for the disease in Saudi Arabia. Various zymodemes of L. tropica were identified in the South-West region, including LON-71, LON-72, LON-73, LON-10 and LON-63. L. major zymodeme LON-1 and LON-4 were also reported in the region.

Clinical Features: CL manifested as skin lesions on the face and exposed parts of the body. The number of skin lesions found in each patient differs, with the majority developing 2–3 lesions. In many cases the lesions were excoriated and were observed as insect bites. Ulcerative lesions varied in size (from 2-10 cm in diameter), with moderately rolled edges and granulomatous bases. The lesions were painful

Table-II: Included Studies of CL in Saudi Arabia.

<table>
<thead>
<tr>
<th>Author, Year [Reference]</th>
<th>Study Year</th>
<th>Study area</th>
<th>Total Identified	Cases</th>
<th>Diagnosis Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawash et al. (2018)21</td>
<td>2016-2017</td>
<td>Al-Taif, West</td>
<td>90</td>
<td>Parasite detection in skin smears, OligoC- PCR, and kDNA PCR</td>
</tr>
<tr>
<td>Alahmad et al. (2018)22</td>
<td>2009-2010</td>
<td>Al-Hassa, East</td>
<td>901</td>
<td>Parasite detection in skin smears</td>
</tr>
<tr>
<td>Haouas et al. (2017)23</td>
<td>2015-2017</td>
<td>Hail, North West</td>
<td>37</td>
<td>Parasite detection in skin smears and SSU-rDNA- PCR</td>
</tr>
<tr>
<td>Barradah (2017)24</td>
<td>2007-2016</td>
<td>Majmaah, Riyadh Province</td>
<td>87</td>
<td>Parasite detection in skin smears</td>
</tr>
<tr>
<td>Alanazi et al. (2016)25</td>
<td>2009-2013</td>
<td>Riyadh Province</td>
<td>370</td>
<td>Parasite detection in skin smears</td>
</tr>
<tr>
<td>El-Beshbishy et al. (2013)27</td>
<td>2010-2012</td>
<td>Al-Madinah, West</td>
<td>34</td>
<td>kDNA PCR</td>
</tr>
<tr>
<td>Uthman et al. (2005)28</td>
<td>1997-1999</td>
<td>Al-Khobar, East</td>
<td>120</td>
<td>Parasite detection in skin smears</td>
</tr>
<tr>
<td>Al-zahrani et al. (1989)29</td>
<td>1987</td>
<td>Al-Baha, Aseer, West</td>
<td>2302</td>
<td>Parasite detection in skin smears</td>
</tr>
</tbody>
</table>

kDNA PCR: kinetoplast DNA polymerase chain reaction, SSU-rDNA PCR: small subunit ribosomal DNA PCR.
* The number included cases with active lesions (117) and leishmanial scars (n=167).
This study reports epidemiological data on the carrier individuals possess decreased antibody titers as compared to clinical VL cases. Indeed, seropositive individuals have increased chance to progress to symptomatic VL cases. However, substantial numbers of VL seropositive patients will never develop a clinical disease. In reality, it is hard to judge whether an apparently healthy seropositive individual is truly infected or not.

In recent years, important changes in epidemiology of leishmaniasis have been noticed. In addition to rural areas, leishmaniasis has become common in urban settings. Classically, VL affects adults that are more exposed to sand fly vectors. This classical picture has changed; the disease became more prevalent among infants and young children. This seems to be the case in Saudi Arabia, where VL has been reported in younger age groups. Indeed, exposure to *Leishmania* may lead to development of protective immunity. This could be the reason of the high prevalence of VL among infant and young children. It has been shown that, VL is more common among men than women due to the nature of their work. In Saudi Arabia, women have a special situation. They often stay indoors or cover their body when outdoor, leading to less exposure and thus less susceptibility to *Leishmania*.

Diagnosis of VL can be challenging due to the overlap of VL and other disease areas such as malaria, typhoid, tuberculosis, and HIV. These diseases can coincide with VL. Population movement and increased travelling have led to appearance of VL in areas that were previously free of the disease. In such cases, the patients may develop atypical clinical presentation and may remain undetected. Recently, Alwazzeh and Alhashimalsayed have reported a case of a 42-years old patient in Al-Khobar (Eastern province), a known non-endemic VL area. This patient was originally from Gizan, but VL was not considered at first check-up due to atypical clinical presentation. After three months’ delay, VL was diagnosed serologically at the Mayo Clinic Labs. This case could have been diagnosed earlier if serological tests were available.

CL has a wide distribution across the world, reaching from Asia, through Middle East and North Africa, to North and South America. Saudi Arabia has the fourth highest prevalence rate of zoonotic CL after Afghanistan, Iran and Pakistan. It has been shown that factors such as poor access to health facilities along with the moderate nature of the disease (self-healing ulcers) have contributed to the poor passive reporting of the cases. Therefore, the actual prevalence and incidence of the disease would be higher than...
reported previously. Also, accurate diagnostic test systems would help identification of these cases. Molecular tools have identified *L. major* and *L. tropica* as causative agents of CL in Saudi Arabia, with the majority of the cases caused by *L. major*. *L. tropica* seems to be less prevalent occurring within small foci in the west and southwest regions.23,27 Despite the high prevalence of the disease in the country, few studies have been focused on identification of *Leishmania* species and little is known about molecular and isoenzyme characterization of the parasites species. This review identified poor application of control tools, including unavailability of modern diagnostics and treatment regimens. In most of the previous studies, diagnosis was based on clinical examination and passive detection of the parasite in skin biopsies. Indeed, many skin conditions may display similar clinical features resembling CL, thus laboratory diagnosis is essential. Additionally, considering the high toxicity and treatment cost, it is unacceptable to treat unconfirmed cases i.e., expose them to the medication.

**CONCLUSION**

This report highlights potential risks for VL and CL in Saudi Arabia in areas known to be non-endemic. There are also crucial gaps about diversity of the reservoir host and their role in the transmission cycle of *Leishmania*. We recommend active case detection using new test systems to identify the real number of undetected cases and to evaluate the magnitude of the problem.

**REFERENCES**


Authors’ Contribution:
EA, conceptualization, design, interpretation of data, project administration, supervision, writing and editing.
ZA, methodology, writing manuscript draft.
LYZ, checked validity of data, revise and editing of manuscript.

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