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A Review on Biology, Epidemiology and Public Health Significance of Leishmaniasis

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Abstract

Leishmaniasis is a major vector-borne disease caused by obligate intramacrophage protozoa of the genus *Leishmania,* and transmitted by the bite of phlebotomine female sand flies of the genera *Phlebotomus* and *Lutzomyia*, in the old and new worlds, respectively. Among 20 well-recognized *Leishmania* species known to infect humans, 18 have zoonotic nature, which include agents of visceral, cutaneous, and mucocutaneous forms of the disease, in both the old and new worlds. Currently, leishmaniasis show a wider geographic distribution and increased global incidence. Environmental, demographic and human behaviors contribute to the changing landscape for zoonotic cutaneous and visceral leishmaniasis. The primary reservoir hosts of *Leishmania* are sylvatic mammals such as forest rodents, hyraxes and wild canids, and dogs are the most important species among domesticated animals in the epidemiology of this disease. These parasites have two basic life cycle stages: one extracellular stage within the invertebrate host (phlebotomine sand fly), and one intracellular stage within a vertebrate host. Co-infection with HIV intensifies the burden of visceral and cutaneous leishmaniasis by causing severe forms and more difficult to manage. The disease is endemic to Ethiopia, and the clinical signs are not pathognomic. The visceral form (Kala-azar) may be confused with other similar conditions such as malaria, tropical splenomegaly, schistosomiasis, milliary tuberculosis, and brucellosis. Similarly, cutaneous leishmaniasis should be differentiated from disease like tropical ulcers, impetigo and leprosy. There are several methods of laboratory diagnosis of leishmaniasis, including parasitological, immunological and molecular. Different forms of treatments are available including oral, parenteral, and topical medications such as pentavalent antimonials, liposomal amphotericin B, miltefosine and paromomycin. Methods of control are largely limited to destruction of animal reservoirs, treatment of infected humans, and management of sand fly populations. Development of an effective vaccine against leishmaniasis has been largely unsuccessful and hinders its prevention.

Keywords: Epidemiology; *Leishmania;* Public health significance; Reservoirs

Introduction

Leishmaniasis is a major vector-borne metazoonosis disease [1], caused by obligate intramacrophage protozoa of the genus *Leishmania* [2]. The parasite is of great medical and veterinary public health significance, for it infects numerous mammal species, including humans. Leishmaniasis has been known for many hundreds of years, with one of the first clinical descriptions made in 1756 by Alexander Russell, and called Aleppo boil. Many names correspond to this group of diseases such as Kala-azar, Dum-dum fever, white leprosy, espundia, and so on [3]. Leishmaniasis is transmitted by the bite of phlebotomine female sand flies of the genera *Phlebotomus* and *Lutzomyia*, in the old and new worlds, respectively [4]. The species are widespread on all continents except Antarctica [5]. Leishmaniasis is still one of the world's most neglected diseases, affecting largely the poorest of the poor, mainly in developing countries; 350 million people are considered at risk of contracting leishmaniasis, and some 2 million new cases occur yearly in 88 countries [6].

The primary reservoir hosts of *Leishmania* species are sylvatic mammals such as forest rodents, hyraxes and wild canids, and among domesticated animals; dogs are the most important species in the epidemiology of this disease. In addition to becoming ill, dogs are reservoir hosts for L. *infantum*, one of the two most important organisms in human visceral leishmaniasis [7-9]. Currently, leishmaniasis has a wider geographical distribution pattern than before, and it is considered to be a growing public health concern for several countries. The increase in leishmaniasis worldwide incidence is mainly attributed to the increase of several risk factors that are clearly manmade and include massive migration, deforestation, urbanization, immunosuppression, malnutrition and treatment failure [10]. Human made changes to the environment, as well as the population movements, may lead to alterations in the range and density of the vectors and reservoirs, and consequently, may increase human exposure to infected sand flies [2].

In Ethiopia, the disease affects people living in a significant portion of the country. Recurrent epidemics of visceral leishmaniasis have occurred in Metema and Humera. Following agricultural development in the region, a large number of labor migrants from the highlands were moved to the endemic areas in the late 1970 for crop harvesting. This led to out breaks of VL, which resulted in high morbidity and mortality [11]. A recent study investigating risk factors associated with the outbreak in Libo Kemkem identified dog ownership and habitual outdoor-sleeping to be risk factors for infection [12]. The cutaneous form was first described in Ethiopia in 1913, and is common in highland areas of altitude ranging from 1,700 to 2,700 meter above sea level. The majority of CL cases in Ethiopia are caused by *L. aethiopica* [13].

Leishmaniasis is one of the opportunistic infections that attack HIV-infected individuals. Most of the co-infection involves the

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visceral form. Recently, more notice has been taken of Leishmania/HIV co-infection. Visceral leishmaniasis has a mortality rate as high as 100%, if left untreated, and is spreading in several areas of the world due to increase number of AIDS victims [8]. *Leishmania* and HIV co-infections have been reported in 35 out of 88 countries, in which leishmaniasis are endemic [14,15]. In Africa, particularly Ethiopia and Sudan and Southern Europe, HIV *Leishmania* co-infection is regarded as emerging disease, and as many as 70% adults with VL also have HIV infection [10]. HIV/AIDS co-infection in the north-western VL focus in Ethiopia has the highest known VL/HIV co-infection rate in the world. Approximately, 30% of VL patients are estimated to have HIV [11,15]. Lack of a vaccine is one of the strongest drawbacks in controlling VL in endemic regions [3]. The objectives of this manuscript are to review the status of leishmaniasis, highlight its public health significance, and give an overview of the occurrence of leishmaniasis in Ethiopia.

Taxonomic Classification

Leishmania is an intracellular protozoan parasite, belonging to the family *Trypanosomatidae* (order Kinetoplastida), genus *Leishmania* shown in table 1 [3,16,17]. These organisms fall within two main groups; the old world species occurring in Europe, Africa and Asia, and the new world species occurring in America [18]. Approximately, 30 species have been described, and at least 20 of these organisms are pathogenic for mammals [19] (Table 1). The different species of zoonotic *Leishmania* are summarized in table 2.

Morphology

The amastigote are small, round to oval bodies, which measure about 3-5 µm, and found only in the macrophages of infected vertebrate hosts. They are colorless, have a homogenous cytoplasm, and are surrounded by a pellicle [20]. The promastigote forms are seen in the gut of the sand fly, that the parasite reaches the buccal cavity, which becomes the insect vector of the parasite. They are motile, slender organisms measuring 10-15 µm in length, with a single anterior flagellum [3]. Amastigotes lack the flagellum, but a short flagellum may be seen arising from the kinetosome [17,20].

Host affected

Man and among domesticated animals, dogs, are the most commonly affected species. Most cases of canine leishmaniasis are caused by L. *infantum*, but other species can also be found [21]. It is also seen occasionally in cats, horses, donkeys, and mules infected with various species of *Leishmania* [18]. Leishmaniasis is not a significant disease in livestock, other than equids, and a *Leishmania* infected pig was documented in South America. Clinical cases have been reported occasionally in rodents and wild animals or captive wild species, including non-human primates, bush dogs and wolves. Mountain hyraxes are the most reservoir host in Ethiopia for *L. aethiopica* [11,22].

Life cycle and mode of transmission

The life-cycle starts when a parasitized female sandfly takes a blood meal from a human. These parasites have two basic life cycle stages: one extracellular stage with in the invertebrate host (phlebotomine sand fly), and one intracellular stage within a vertebrate host. The parasites exist in two main morphological forms: the amastigotes and promastigotes, which are found in vertebrate and invertebrate hosts, respectively [23]. The promastigotes are then phagocytosed by the host's macrophages, and consequently, the parasite evolves into amastigote forms spherical, intracellular forms without flagellum, which they reproduce by binary fission. The multiplication of the parasites occurs inside the macrophages, which are their main targets. The macrophage lyses and the cycle continue when other hosts' phagocytes are being infected [5,24]. In cases of VL, all organs containing macrophages and phagocytes can be infected, especially the lymph nodes, spleen, liver, and bone marrow [3].

Kingdom	**Protozoa**
Subkingdom	*Protista*
Phylum	*Sarcomastigophora*
Sub-phylum	*Mastigophora*
Class	*Zoomastigophora*
Order	*Kinetoplastida*
Suborder	*Trypanosomatina*
Genus	*Leishmania*

Source: Arfan Ul and Simeen [17].

Table 1: Taxonomy of Leishmania parasites.

Leishmania species	Disease in humans	Geographical distribution	Main reservoir host
Leishmania (Leishmania) infantum	Visceral leishmaniasis; Localised cutaneous leishmaniasis	Mediterranean basin; Middle East and Central Asia to Pakistan; China; Central and South America	Dog
Leishmania (L) major	Localised cutaneous leishmaniasis	North Africa, Middle East and Central Asia, Sub-Saharan Africa and Sahel belt	Gerbillidae rodents
Leishmania (L) aethiopica	Localised cutaneous leishmaniasis, Diffuse cutaneous leishmaniasis	Ethiopia, Kenya	Rock hyraxes
Leishmania (L) mexicana	Localised cutaneous leishmaniasis	Central America	Various forest rodents
Leishmania (L) amazonensis	Localised cutaneous leishmaniasis	South America, north of the	
Amazon	forest rodents		
Leishmania (L) venezuelensis	Localised cutaneous leishmaniasis	Venezuela	unknown
Leishmania (Viannia) braziliensis	Localised cutaneous leishmaniasis; Mucocutaneous leishmaniasis	South America, Central America and Mexico	Numerous rain forest mammals (suspected)
Leishmania (V) peruviana	Localised cutaenous leishmaniasis	Peruvian Andes	Dog

Source: Gramiccia and Gradoni [19].

Table 2: Agents of zoonotic leishmaniases, their distribution and main reservoirs.

The disease is transmitted to vertebrate host by the female infected sand fly. The female needs a blood meal for egg production. Hence, like mosquitoes, only the female sand fly is haematophagous [23]. Species are usually transmitted indirectly between hosts by sandflies of the genera *Phlebotomus* and *Lutzomyia*, which are biological vectors [3]. Some ticks and canine fleas may also act as mechanical vectors [18]. These parasites have also been transmitted via blood transfusions in people and dogs [24], and by trans-placental transmission in dogs, mice and humans [11]. Rare cases of horizontal transmission have been reported between dogs in the same household or kennel. In canine leishmaniasis caused by L. *infantum*, the parasites can sometimes be found in saliva, urine, semen and conjunctival secretions, as well as in blood. Venereal transmission has been proven to occur in dogs, and other routes of spread might be possible [18].

Epidemiology

Human and animal leishmaniases show a wider geographic distribution than previously known. Leishmaniasis are widely distributed around the world. They range over inter tropical zones of America, Africa, and extend in to temperate regions of South America, southern Europe and Asia. Their extension limits are latitude 45° north

Locality	Sites	Tested	No pos.	Pos. in (%)
Melka Sedi	4th Camp	105	32	31
	Halaysumale	77	53	69
Melka Werer	Mahdol	66	37	56
	Woidolele	25	16	64
Amibara	Sheleko	84	46	55
	Hassoba	103	64	62
	Idolokore	118	47	40
Gewane	Old Gewane	69	16	23
	Medema	128	18	14
	Meteka	114	19	17
	Total	889	348	39

Source: Ali et al. [39].

Table 3: Leishmanin skin test positivity in the Middle Awash (two years report), Ethiopia.

and 32° south. Geographical distribution of the diseases depends on sand fly species acting as vectors, their ecology, and the conditions of internal development of the parasite [10]. The burden of VL remains unknown worldwide, since several cases are not diagnosed [25-27]. It has been estimated that there are approximately half a million new cases of VL annually worldwide, with more than 50,000 associated deaths. More than 90% of VL cases occur in just six countries, namely India, Nepal, Bangladesh, Sudan, Ethiopia, and Brazil [28]. *Leishmania infantum* and L. *chagasi* cause VL almost exclusively in infants, young children and immunosuppressed. In contrast, L. *donovani* infects both children and adults [29]. During the last two decades, emergence of resistance to pentavalent antimonial had a huge impact on the epidemiology of leishmaniasis [30-32].

New world cutaneous leishmaniasis: Epidemiology of new world cutaneous leishmaniasis is found in Mexico, Central America, and South America–from Northern Argentina to Southern Texas and southern Europe. Many such patients develop unusual cutaneous manifestations [33].

Old world cutaneous leishmaniasis: Old world cutaneous leishmaniasis occurs in Asia, Middle East and Africa. Zoonotic cutaneous leishmaniasis (rural, wet type) is caused by *L. major* in most part of the Central Asia, Middle East and North Africa, and transmission of infection is maintained in wild rodent/gerbil colonies. The estimated annual incidence is 1-1.5 million cases of cutaneous leishmaniasis in the old world, over 90% of annual cases occur in Afghanistan, Algeria, Iran, Iraq, Saudi Arabia, and Syria [2,25]. In the old world, *L. major* and *L. aethiopica* cause zoonotic cutaneous leishmaniasis. The risk of cutaneous leishmaniasis may be increased when agricultural projects are launched and irrigation systems extended. These man made ecological changes are accompanied by the intrusion of large numbers of non-immune immigrants into an existing sylvatic cycle of leishmaniasis [11,22]. Transmission to humans is favored by the practice of sleeping outside without a bed net during the hot season. In foci of cutaneous leishmaniasis caused by *L. aethiopica* in the highlands of Ethiopia and other places in East Africa, increased human fly contact occurs in villages built on rock hills or river banks, which are the natural habitat of hyraxes (reservoir hosts). Cases have also been reported in and near urban centers, including Addis Ababa [6].

Socio-economic factors: Poverty increases the risk for leishmaniasis in many ways. Poor housing and peridomestic sanitary conditions (e.g. lack of waste management, open sewerage) may increase sandfly breeding and resting sites, as well as their access to humans [34,35].

Malnutrition

Poor protein, energy, iron, vitamin A, and zinc nutritional status increase the risk that an infection will progress to clinically manifests visceral leishmaniasis. Recent experiments in protein, energy, zinc, and iron deficient mice suggest that this effect is mediated primarily through functional failure of the lymph node barrier and increased early visceralization of the parasite. Protein-energy malnutrition has also been associated with an increased risk for mucocutaneous leishmaniasis [22,28].

Population movements

Epidemics of both visceral and cutaneous leishmaniasis, in both the old and the new world, are often associated with migration and the introduction of non-immune people into areas with existing endemic or enzootic transmission cycles. Prediction of such outbreaks depends on the availability of ecological information, and on evaluation of development areas, before implementation of projects or population movements [11]. Seasonal labor movements may also spread the disease, with the return of migrants to non-endemic areas, as appears to have occurred in the highlands of Ethiopia in the 2000s. Behaviour, such as sleeping outside under acacia trees and living in houses constructed of grassy material, appears to increase risk for the disease [6].

Environmental changes

In most endemic regions, leishmaniasis is characterized by a patchy distribution, with discrete transmission foci. This focal distribution of leishmaniasis transmission sites is due to micro ecological conditions that affect the vector, the parasite, and the reservoir host [6]. Environmental changes that can affect the incidence of leishmaniasis include urbanization, domestication of the transmission cycle, and the incursion of agricultural farms and settlements into forested areas [6,34,35].

Climate change

Leishmaniasis is a climate-sensitive disease, occupying a characteristic climate space that is strongly affected by changes in rainfall, atmospheric temperature and humidity [22]. Global warming and land degradation together are expected to affect the epidemiology of leishmaniasis by a number of mechanisms. First, changes in temperature, rainfall and humidity can have strong effects on the ecology of vectors and reservoir hosts, by altering their distribution, and influencing their survival and population sizes [29]. Secondly, drought, famine and flood, resulting from changes in climate conditions, could lead to massive displacement and migration of people to areas, with transmission of leishmaniasis, and poor nutrition could compromise their immunity [6,10,28].

HIV co-infection

It is the fifth opportunistic disease. The Human Immunodeficiency Virus (HIV)/acquired immunodeficiency syndrome-pandemic had also an impact on the epidemiology of VL [15,36]. Due to deficient diagnostic capacities and surveillance, the burden of VL-HIV-co-infection in Africa remains grossly unknown; however, HIV-co-infection is emerging in this continent. In North West Ethiopia, up to 30% of VL cases are HIV/co-infected [29].

Vector distribution

The vector of *Leishmania* is transmitted by phlebotomine sandflies. These sandflies are widely distributed in the tropics and other warm mainland areas, and extend northwards to latitudes in the region of 50° N. Species in three genera, *Phlebotomus*, *Lutzomyia* and *Sergentomyia*, suck blood from vertebrates, only the former two transmit disease to man [25]. There are over 50 species of genus *Phlebotomus* in the old world, and genus *Lutzomyia* in the new world that transmit disease to man [17].

Disease Status in Ethiopia

Economic impact of the disease in Ethiopia is not only limited to high cost of treatment, but also time lost during hospitalization. The disease affects the rural poor community and usually outbreak occurs during harvesting seasons [12]. The MoH estimates the annual burden of VL to be between 4,500 and 5,000 cases. While there is currently no reliable estimate of the prevalence of CL, it has been estimated that the number of CL cases significantly exceeds that of VL [37]. Several studies have definitively demonstrated that VL occurs in north western Ethiopia (Humera and Metema), Segen and Woito valleys in Gemu Gofa. Sporadic cases of VL have been diagnosed from Wolkayit Tsegede, Gibdo, Raya, Kobo, Kijawa (Gambella) and Gelana (Sidamo) and Genale (Bale) river basins. Recently, a devastating epidemic occurred in Humera with an estimated annual incidence of 1,500-2,000 cases. Due to high mortality, occurrence of epidemics, and high incidence of the disease in 15-45 age group, leishmaniasis has become one of the leading health problems in Ethiopia [11,22].

The north-western VL focus in Ethiopia covers the Semi-arid Metema and Humera plains in Tigray and Amhara regional states bordering Sudan. A marked increase occurred during the 1970s, when migrants from the non-endemic highlands began to arrive in the area to harvest crops on the large-scale agricultural schemes introduced at the time. In 2005, an outbreak of VL in Libo Kemkem woreda, a highland area of Amhara regional state, was identified. By 2007, around 2,450 primary cases and 120 deaths had been reported, since the outbreak began in 2003 [12]. The north-western VL focus in Ethiopia has the highest known VL/HIV co-infection rate in the world. Approximately, 30% of VL patients are estimated to have HIV [15]. The south west foci include the Omo plains, Aba Roba plains and Weyto River Valley in Southern Nations and Nationalities People's Region–all areas of lowland savannah with low rainfall. The lower Omo plains are the oldest known VL focus in Ethiopia. The other main focus in the southwest occurs in the lower course of the Rift Valley, most notably, the Segen (Aba Roba focus) and Weyto valleys in the drainage basin of the Chew Bahir Lake, near Konso woreda. The Aba Roba focus has a particularly high VL endemicity and high population immunity, with 36.4% testing positive with the leishmanin skin test [22].

Cutaneous leishmaniasis occurs in highlands of Ethiopia. Transmission occurs in Cuttaber (Dessie), Aleku (Wellega), and Ochollo (Gemu Gofa). In Ochollo, the overall prevalence of localized CL was 3.6-4.0%, with a peak value of 8.55 in the 0-10 years old age group. Sporadic cases of CL have been diagnosed from many localities in the northern, central, and southern high lands of Ethiopia. CL transmission in Ethiopia is zoonotic, with the rock hyrax acting as the main reservoir [11]. Cutaneous form has been extensively studied in the western highlands and lake areas of the Rift Valley. The main areas of transmission include the Ochollo focus in the Rift Valley escarpment above Lake Abaya, the Kutaber area in the eastern Ethiopian plateau near Dessie, the Aleku area of Wollega zone, the south-west highlands of Bale and Sidamo, and the Sebeta area near Addis Ababa [38] (Table 3).

Clinical Signs in Humans and Animals

The incubation period is difficult to evaluate precisely. It is generally 2-6 months, but can range from 10 days to many years. The onset of disease may be sudden or gradual; the overall condition of the patient is usually good in the early stages [28]. The most common symptoms of visceral leishmaniasis are prolonged undulant fever, weight loss, decreased appetite, signs of anemia, and abdominal distension, with splenomegaly and hepatomegaly [2]. Other symptoms may include coughing, chronic diarrhea, darkening of the skin, lymphadenopathy, and in many cases, signs of chronic kidney disease. Post-Kalazar Dermal Leishmaniasis (PKDL) occurs after recovery, in some cases of visceral leishmaniasis [18].

Leishmaniasis are characterized by a spectrum of clinical manifestations: ulcerative skin lesions, which they develop at the site of the sand fly bite localized cutaneous leishmaniasis, diffuse cutaneous leishmaniasis, mucosal leishmaniasis, and disseminated visceral leishmaniasis [11,25]. The first sign of an infection is a small erythema. The erythema develops into a papule, then into a nodule, and the nodule ulcerates over a period of two weeks to six months, to become a lesion that is characteristic of the cutaneous leishmaniasis [18,40]. Mucocutaneous leishmaniasis tends to occur 1 to 5 years after cutaneous leishmaniasis caused by these organisms has healed, but it can also be seen while skin lesions are still present. The initial signs are erythema and ulcerations at the nares, followed by destructive inflammation that can spread to involve the nasal septum, and in some cases, the pharynx or larynx. Frequent nose bleeds can be an early sign. The inflammation may perforate the nasal septum, cause severe disfigurement of the face, and block the pharynx or larynx. In some cases, the genitalia may also be involved. Mucocutaneous leishmaniasis does not heal spontaneously [18].

Both visceral and cutaneous manifestations may be found simultaneously in dogs; unlike humans, separate cutaneous and visceral syndromes are not seen. In symptomatic cases, common visceral signs include lethargy, weight loss, a decreased appetite, anemia, splenomegaly, and local or generalized lymphadenopathy. Bleeding disorders, including epistaxis and hematuria can also be seen [41]. Chronic renal disease is common in dogs infected with L. *infantum* [42,43]. Clinical cases are uncommon in cats. Most reported cases have been characterized by cutaneous signs, without visceral lesions. Localized nodules, papules, and chronic crusted or ulcerated lesions are most often found on the nose, ears (pinnae), eyelids or lips. Systemic cases in cats have involved the liver, spleen, lymph nodes and kidney [18]. Horses, mules and donkeys may develop skin lesions, particularly on the head, ears, neck, legs and scrotum. The most common lesions are solitary or multiple papules or nodules, which are often ulcerated [41]. Skin lesions were the only clinical signs reported in a sheep, goat and calf in Africa. The goat also had enlarged lymph nodes. Captive wild species and wild animals: Infections seem to be inapparent in many infected wild animals. In rodents, may cause swellings with hair loss or ulcers. This animal later developed ascites and cervical edema, and eventually died [18].

Diagnostic and Differential Diagnosis

Conventional parasite detection techniques

The confirmatory diagnosis of leishmaniasis relies on either the microscopical demonstration of *Leishmania* amastigotes in the relevant tissues aspirates or biopsies, such as bone marrow, spleen, lymph nodes, liver and skin slit smears. The amastigotes are readily seen in smears or touch preparations of infected tissue stained with Giemsa's stain [20]. Animal inoculation and Culture: *Leishmania* spp. can also be cultured. However, each species will grow only in certain media, and some species can be difficult to isolate. Novy-MacNeil-Nicole medium, Grace's medium and Schneider's Drosophila medium might be used initially. Animal inoculation into hamsters may also be valuable, especially with contaminated material [42,43].

Immunological methods of diagnosis

The Indirect Fluorescent Antibody (IFA) test is one of the commonly used tests for anti leishmanial antibody detection using fixed promastigotes. The test is based on detecting antibodies, which are demonstrated in the very early stages of infection, and are undetectable six to nine months after cure. The lower sensitivity of the tests can be overcome by using *Leishmania* amastigotes as the antigen, instead of the promastigotes. The direct fluorescence test is more useful in the diagnosis of CL, MCL and PKDL [2,18,42,44,45].

Direct agglutination test: The Direct Agglutination Test (DAT) is a highly specific and sensitive test. It is cheap and simple to perform, making it ideal for both field and laboratory use. DAT in various studies has been found to be 91-100% sensitive and 72-100% specific [2,11,42,44-46]. Study was conducted in 2006-2007 in Humera investigating the accuracy of the rK39 rapid diagnostic test. Sensitivity of the rK39 RDT was found to be 84%, which was lower than that found for DAT (94%). However, specificity of the rK39 rapid diagnostic test was higher than that of DAT at 99%, compared to 92%, respectively. Sensitivity was also disaggregated by HIV-positive and HIV-negative patients [47]. Enzyme Linked Immuno Sorbent Assay (ELISA): ELISA is a valuable tool and one of the most sensitive tests for the serodiagnosis of visceral leishmaniasis. The test is useful for laboratory analysis or field applications, and to screen a large number of samples at a rapid pace. The sensitivity and specificity of ELISA is greatly influenced by the antigen used [44,45].

Leishmanin Skin Test (LST)

Delayed hypersensitivity is an important feature of cutaneous forms of human leishmaniasis, and can be measured by the leishmanin test, also known as the Montenegro reaction [20].

Molecular methods

Molecular biology is increasingly becoming relevant to the diagnosis and control of infectious diseases [46]. Polymerase Chain Reaction (PCR): Amongst the molecular methods used for clinical diagnosis, PCR has been proved to be most sensitive and specific technique. The specificity of the PCR can be adapted to specific needs by targeting conserved region of the gene. Gene amplification through the PCR has several advantages compared to traditional techniques, because of its extremely high sensitivity, rapidity and the ability to be performed with a broad range of clinical specimens [42,46]. Several studies have reported that PCR assay could detect parasitaemia a few weeks before the appearance of any clinical signs [20]. Also, a modified form of PCR such as nested PCR, has proved its predictive values in diagnosis of PKDL. In a study, nested PCR was positive in 27 of 29 (93%) samples, while only 20 of 29 (69%) samples were positive in the primary PCR assay [20,48]. The real-time PCR is used qualitatively and quantitatively, as the fluorescence is directly proportional to the number of amplicons, or in other words, the parasite load in the given specimen. The multiplex PCR can be used whenever, double or mixed infections are suspected as in AIDS patients [6,20].

Differential diagnosis

The differential diagnosis of visceral leishmaniasis includes other tropical and infectious diseases that cause fever or organomegaly (e.g. typhoid fever, miliary tuberculosis, brucellosis, histoplasmosis, malaria, tropical splenomegaly syndrome and schistosomiasis), as well as diseases such as leukemia and lymphoma. Post-kalaazar dermal leishmaniasis should be differentiated from syphilis and leprosy [6]. Cutaneous leishmaniasis is frequently confused with tropical, traumatic and venousstasis ulcers, foreign-body reactions, superinfected insect bites, myiasis, impetigo, fungal infections [45].

Treatment

In human: Patients should be referred to a specialist tropical disease unit for diagnosis and treatment of all forms of leishmaniasis, depending upon the form of the disease. There are several drug treatments available including oral, parenteral, and topical medications [45]. Pentavalent antimonials such as stibogluconate and meglumine antimoniate, have been the mainstay of treatment since the 1940's, but are complicated by adverse side effects, resistance and cost. Liposomal amphotericin B is more favourable in regions where resistance is common. Research into new antileishmanial drugs such as miltefosine, paromycin and sitamaquine may expand treatment options in the future [28]. Data on miltefosine use in East Africa are restricted to one study that was conducted in northern Ethiopia, in which it was found to be as safe and effective as sodium stibogluconate in HIV-negative patients and safer, but less effective in HIV co-infected patients [15,49]. Oral sitamaquine, an 8-aminoquinoline derivative, has been shown to have clinically significant antileishmanial activity. This effective oral anti leishmanial compound has been tested in Kenya, Brazil, and India [3]. Patients should be properly hydrated and given nutritional supplements. Severe anemia should be corrected with blood transfusions, and concomitant infections should be treated with appropriate anti-infective agents. Successful therapy improves the general condition, resolves fever, causes regression of splenomegaly, and recovery of blood counts towards normal [6].

In animals: Treatment can produce clinical improvement, although it may not eliminate the parasite. Pentavalent antimonials are often used for treatment, where they are available. Other drugs used, such allpurinol, amphotericin B, or second line drugs may also be employed, either alone or in combination. Allopurinol has been used as a maintenance drug to prevent relapses. The prognosis is poorer in dogs that are severely ill and animals with kidney disease [18].

Control Strategies and Prevention Measures

Since antileishmanial vaccines are still being developed, the current control strategies for leishmaniasis rely on case management (case detection and treatment), vector, and reservoir control. Attention has been mainly focused on prevention strategies of visceral leishmaniasis, the form with the highest fatality rate. Nevertheless, prevention strategies should be also considered for cutaneous leishmaniasis, which is also a major burden for certain areas, with serious psychosocial effects [23]. The integrated analysis of parasite genetics, parasite virulence factors, host immune responses, host genetics, as well as socioeconomic and environmental risk factors, will provide a better understanding of the interplay between these different factors and the risk of developing the disease [3].

Control of reservoir hosts

On the other hand, new tools have been developed for the surveillance and control of zoonotic VL, based on the control of the canine domestic reservoir. Culling of infected dogs is not considered an acceptable measure, both for ethical reasons and the low impact of this measure in situations of permanent transmission [2]. Active case detection, surveillance and effective treatment, accompanied by measures for preventing reinfection, depending on the coverage achieved, should reduce or eliminate the parasite load and reduce transmission. The use of insecticide-treated bed nets and other

materials by patients with kala-azar and PKDL, or with chronic L. *tropica* skin lesions may also decrease the likelihood that sandflies will feed on infected individuals [6]. The elimination of stray and feral dogs is justified for many reasons connected with health, the environment and conservation. Before control activities begin, the distribution and frequency of the infection in dogs should be determined. Mass screening of domestic dogs is usually done by serological examination (ELISA, IFAT). All symptomatic or seropositive dogs should be eliminated [6,50]. Control of hyraxes around villages may reduce the transmission of East African cutaneous leishmaniasis caused by *L. aethiopica*. Elimination of hyraxes within 1 km of settlements is thought to be effective in reducing transmission [24].

The aim of a vector control program is to reduce or interrupt transmission of disease. An effective strategy for reducing human leishmaniasis is to control sandfly vectors, especially in domestic and peridomestic transmission habitats. A number of control methods are available, including chemicals, environmental management and personal protection [6,24]. Health education is a core element in implementation of any disease prevention and control programme. Multidisciplinary working groups should be established [6,11].

Conclusion and Recommendations

Leishmaniasis is caused by a protozoan parasite. The parasite is transmitted from one host to another through the bites of female sandfly, and with some exceptions, the leishmaniases are zoonoses, and the human infection is incidental. The primary reservoir hosts of *Leishmania* are sylvatic mammals, such as forest rodents, hyraxes and wild canids, and among domesticated animals; dogs are the most important species in the epidemiology of this disease. Currently, leishmaniasis has a wider geographical distribution pattern than before, and it is considered to be a growing public health concern for several countries, including Ethiopia, and this is mainly due to risk factors such as environmental, demographic and human behavior contribute to the changing landscape of leishmaniasis for zoonotic cutaneous and visceral leishmaniasis. The disease is public health significance in Ethiopia, and both VL and CL are endemic. HIV/AIDS co-infection VL focus in Ethiopia has the highest known VL/HIV co-infection rate in the world. Taking into consideration the lack of a commercially available vaccine, the lack of access to efficient drug therapy, mainly in the developing countries, the limited local resources of the affected countries, it is concluded that elimination of the disease is still a challenge for the international health community. Priority should be given to the establishment of control programs, and government should take the lion share to empower and support concerned institutions to address control programs. Destroying the breeding and resting sites of the vector, control of hyraxes and rodents in the proximity of human dwellings, should also be implemented. Policy should be formulated to control leishmaniasis in the direction of to eliminate stray and feral dogs. Extensive research in epidemiology of leishmaniasis should also be conducted in non endemic areas, too.

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