Leishmaniasis during the increased Syrian refugee traffic

Abstract

Especially in recent years, important population mobility occurs worldwide, including refugee crisis affecting especially Middle East and Europe. Consequently, like other infectious diseases have significance for public health, leishmaniasis is spreading globally. 350 million people in 88 countries, mostly in developing areas, are at risk of leishmaniasis. The diseases may be seen in three clinical forms as cutaneous, mucocutaneous, or visceral caused by about 20 different species of Leishmania parasite. The parasitological diagnosis is made by microscopic examination, cultivation, PCR and serological methods. There is currently no available vaccine for this infection. Pentavalent antimonials are the first line therapeutic choice, whereas amphoterin B, pentamide, miltefosine, and paromomycin are alternative drugs. Other side, increasing resistance and toxicity of the current therapeutics are significant problems. The combination therapy, immunotherapy, anti-leishmanial synthetic and natural products, and local hyperthermic applications are promising for future treatment of leishmaniasis. The preventive efforts have been applying based on individuals and community. In CHB patients, habits of drinking alcohol and cigarette smoking, elevated serum levels of TBil and serum AST/ALT ratio, increased duration of hepatitis B, a family of hepatitis B, male gender and older age can increase the risk of LC development.

Introduction

In last several years, an important population relocation occurs worldwide for various reasons, including immigrants, refugees, and international students [1,2]. In the US National Intelligence Council study (2000), it is reported that nearly two million people each day travel across borders, and it is estimated that ~2% of the world’s population resides in a nation different than the one in which they were born [3]. This movement of people led to the spread of global infectious disease [4].

During the on-going conflict in Syria, which is one of the southern border neighbor of Turkey, about 6.5 million people are displaced within the country, as well as more than 4.2 million Syrians have crossed borders. Turkey hosts more than 2.7 million, Lebanon 1 million, Jordan 630,000 and Iraq 235,000 refugees, and approximately 682,000 asylum applications happened to Europe countries [5–7]. Cutaneous leishmaniasis (CL) is highly endemic in Syria. In addition to other infectious diseases, the number of leishmaniasis, especially cutaneous form, cases increased in Turkey and the other countries depend on crowded and bad environments. The increased mobility due to the conflict can be considered an emerging new threat for unaffected regions [6]. Since these kinds of risk factors led to an increase in the variability of species and a rise in the frequency of infectious agents, it is required to reevaluate the treatment policy [8,9]. We focused on leishmaniasis rather than other diseases because CL is a major health problem in Turkey. Therefore, we aimed to summarize the current knowledge on leishmaniasis in this review.

Protozoan parasites of the genus Leishmania and the causative agent of leishmaniasis diseases, are spread via the bite of female sand flies belonging to either Phlebotomus spp (Old World) or Lutzomyia spp (New World). Also, the parasite has about 20 different species; and the disease caused by the parasite could emerge as cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL), or visceral leishmaniasis (VL) (Table 1) depending upon the infecting species and the host’s immune status [10]. The visceral form could be fatal, while the skin lesions in cutaneous form tend to heal spontaneously, or scarification affecting life quality [11,12].

| Leishmaniasis | Number of People | Region |
|---------------|------------------|-------|
| CL            | 4.2 million      | Turkey|
| MCL           | 2.7 million      | Turkey|
| VL            | > 2 million      | Europe|

Epidemiology and etiology

The leishmaniasis is widely seen across the tropical, subtropical, and temperate regions in 88 countries, mostly in developing areas. 350 million people are at risk of the diseases.
Over 12 million people currently suffer from leishmaniasis, with 500,000 new cases of VL per year and 1 to 1.5 million new cases of CL [13].

Cutaneous for of the disease is the most common in general. Different Leishmania species cause Old World (the Eastern Hemisphere) versus New World (American, the Western Hemisphere) CL [14]. In the Old World, the most common species that cause CL are L. tropica, L. aethiopica, and L. major; otherwise, in the New World, they are L. mexicana, L. amazonensis, L. braziliensis, L. panamensis, and L. guyanensis [12,15]. The causative agents of VL are commonly L. donovani in Indian subcontinent and Africa, L. infantum in Mediterranean, L. chagasi in Central and South America [13].

CL cases mostly occur in Afghanistan, Algeria, Brazil, Colombia, Iran, Pakistan, Peru, Saudi Arabia and Syria. The CL epidemiology in the Region of the Americas is complex depend on variation in transmission cycles, reservoir hosts, sandfly vectors [16].

The most endemic city in Turkey, which cutaneous form more common, is Sanliurfa with over 50% of 50381 cases between 1988-2010 years. Although Sanliurfa is in subtropical region of Turkey, some sporadic cases have been observed in the non–endemic west and north regions due to the population movements in recent years [1]. However Lebanon had no cases of CL before 2008, 96.6% of 1033 confirmed cases were among Syrian refugees by 2013, and some sporadic cases were seen in the following years [17]. Similarly, it was detected different Leishmania species between travelers, observed leishmaniasis cases, to the Mediterranean and New World regions. This implicates that the species distribution is related to exposure region [18]. The refugees take huge supports for health by the government in Turkey, maybe in some other countries. Even if so, some factors such as health accessibility, reservoir hosts, sandfly vectors become important issues for leishmaniasis cases in any big population movement.

Upon the sand-fly injecting the promastigote form (1.5 to 3.5 by 15 to 200 μm) into the skin of the host, the parasites are taken up by macrophages. Then the promastigote forms differentiate into amastigote forms (3 to 5 μm in length) (Figure 1). Interestingly, the parasites replicate in the immune defense cells following the differentiation [13].

Immunologic response in leishmaniasis

The host immunological response varies widely between species; especially Th1-type immune response has a crucial role in the infection control [13]. Parasitic clearance is happened by nitric oxide (NO) which is produced by macrophages. Some cytokines such as IFN-γ and TNF-α activate macrophages to produce nitric oxide, while cytokines like IL-4, IL-10, IL-13, and TGF-β dampen NO production, thereby decreasing the leishmanicidal ability of the cells [19,20]. Besides being an important effector cell, macrophage can serve as a host for the replication and spread of the parasite by in inhibition of phagosomal–endosome fusion, thereafter referring as Trojan horse [22]. In condition parasite–driven Th2 response, it is seen a progression of the disease mediated by the expression of non-protective Th2-related cytokines such as IL-4, IL-10 and IL-13 [20]. Like this, Th1 suppressing cytokines such as TGF-β and IL-10 increase susceptibility to VL [23].

Clinical Manifestations of Leishmaniasis Visceral leishmaniasis

Visceral form of the illness is a systemic infection, which affecting the liver, spleen, and bone marrow. The spectrum of VL varies from asymptomatic to life-threatening degree in severity. VL is caused by both New and Old World species [24,25].The incubation period ranges from as short as 10 days or longer than a year (usually 3–6 months) depending on the species of Leishmania, as well as the host’s immune status, age and the other factors [13].

The disease is known as kala-azar due to the characteristic darkening of the skin. The most common sign and symptoms are hepatosplenomegaly, hypergammaglobulinemia, pancytopenia, fever, and weight loss. The untreated VL may result in death frequently within two years because of hemorrhage, serious anemia, immunosuppression, and secondary infections. Sometimes, multiple, hypopigmented, erythematous macular lesions occur in skin following VL therapy. This is called as post–kala–azar dermal leishmaniasis (PKDL) [20]. Lesions in PKDL may resemble leprosy clinically and pathologically [13].

Cutaneous leishmaniasis (CL)

Depending on species of the parasite and host factors, CL represents a broad spectrum in clinical manifestation. The hallmark for CL is skin lesions. The lesions are usually painless and can spontaneously heal in 2–10 months [23]. The incubation period of CL typically ranges from 2 weeks to several months, and sometime years. There is no evident systemic symptom. A species-specific immunity occurs following recovery or successful treatment of CL. Generally, L. tropica tends to cause “dry,” crusted, slowly enlarging lesions, while the lesions in L. major and L. braziliensis infections tend to be “moist,” exudative lesions and larger (Figure 2) [13].

The classic form of Old World CL is also known as “oriental sore” by a variety of colorful local expressions. The clinical spectrum in CL may vary from single or multiple, localized,
cutaneous ulcers to diffuse cutaneous leishmaniasis (DCL) [13]. Both New World and Old World CL may represent localized cutaneous involvement. Old World CL usually presents multiple lesions, while New World CL is usually associated with a solitary nodule [24].

DCL is usually associated with a defect in the cell-mediated immune response and anergy to *Leishmania* antigen. The initial lesion does not ulcerate, and then satellite lesions develop around the initial papule, and organisms gradually spread in the skin, resulting in dissemination. DCL is an uncommon syndrome mainly associated with *L. aethiopica, L. mexicana,* and *L. amazonensis* infection [24,25].

Leishmaniasis recidivans (LR) is an infrequent syndrome that may be seen years after resolution of a localized cutaneous lesion caused by *L. tropica* [24]. LR lesion is generally seen on the face. LR may infer from reactivation of dormant parasites or new infection with a different species [24,25]. LR has been demonstrated in North Africa, the Middle East, Southwest Asia, as well as Turkey and Iran [13].

**Mucocutaneous leishmaniasis (ML)**

Mucocutaneous form of the disease, which has a significant rate of morbidity and mortality, is rarely seen in the Old World [26]. ML is mainly a problem of the New World. ML occurs in 2% to 5% of persons infected with *L. braziliensis,* and more rarely in persons infected with *L. panamensis,* *L. guyanensis,* or *L. amazonensis* [13]. ML is characterized by mucosal destruction and also known as “esundra” in South America. It usually develops by metastasis from disseminated protozoa rather than by local spread [23]. In ML, mucous membrane involvements usually occur in the nose, oral cavity, pharynx, or larynx months to years after their skin lesions recovered (Table 1) [13].

**Diagnosis**

The parasitological diagnosis of leishmaniasis is made by microscopic examination, cultivation, PCR and serological methods. The samples obtained by biopsy, scrapings, and/or needle aspirates in the CL, or the specimens from peripheral blood, bone marrow, liver, or splenic aspirates in the VL are examined for parasitological investigation. The smears stained by Leishman, Giemsa, or Wright stains are examined under oil immersion microscope [24]. Specimens are inoculated into one of several media (Schneider’s modified media, Novy-

| Clinical form               | Common causative species                      | Major clinical manifestations                        |
|----------------------------|-----------------------------------------------|------------------------------------------------------|
| Visceral leishmaniasis      | *L. donovani* in Indian subcontinent and Africa, *L. infantum* in Mediterranean, *L. chagasi* in Central and South America | Hepatosplenomegaly, hypergammaglobulinemia, pancytopenia, fever, and weight loss in visceral form. Hypopigmented, erythematous macular lesions in PKDL. |
| Cutaneous leishmaniasis     | In the Old World *L. tropica, L. aethiopica,* and *L. major* | Single or multiple and dry-crusted or moist-exudative lesions in localized type, satellite lesions around the initial papule in diffuse type. |
| Mucosal leishmaniasis       | *L. braziliensis,* is mostly a disease of the New World | Mucosal destructions following the skin lesions recovering. |

MacNeal–Nicolle [NNN] media, and others) for culture of the parasites. A definite diagnosis can be made by amplifying *Leishmania* specific DNA or RNA in a PCR assay. The serologic tests are usually used for VL. The serological methods using recombinant k39 (rK39) have revealed excellent sensitivity and specificity for the diagnosis [13].

**Treatment**

Currently, there is no available vaccine for the prevention leishmaniasis. Furthermore, the variability in species of the parasite affects standard treatment recommendations negatively [13]. The first line therapeutic choice is pentavalent antimonials, sodium stibogluconate (SSG) and methylglucamine antimoniate (MA), for all forms of leishmaniasis around the world. The drugs are given intramuscularly (IM), intravenously (IV), or intraleisional (IL). Recommended IM and IV regimen is 15–20 mg SbV/kg of body weight daily for 21–28 days [27]. Painful injection, high toxicity and resistance problems are significant disadvantages of the drugs [28,29].

Amphotericin B with different formulations, pentamidine, miltefosine, and paromomycin with intramuscular and topical formulations are commonly used as alternative drugs in the treatment of leishmaniasis [28,29].

**Prevention**

The preventive approaches to leishmaniasis are handled based on individuals and community. Unfortunately, there is no individual immunoprophylactic prevention (vaccine or immunoglobulin) method for travelers to endemic areas. Standard personal protective measures are recommended applying permethrin or other insecticides to clothing and insecticide-impregnated fine-mesh bed nets. In endemic areas, due to zoonotic features of the disease, the vector control and reservoir control applications are effective for community-based preventive efforts. Residual insecticides can be applied in houses and other buildings. The early diagnosis and complete treatment, integrated vector management and effective vector and disease surveillance establish basis of elimination of the infection [13].

Citation: Ardic N, Ardic AF, Gunel Z (2018) Leishmaniasis during the increased Syrian refugee traffic. Glob J Infect Dis Clin Res 4(1): 013-016.
DOI: http://doi.org/10.17352/2455-5363.000020
Conclusion

Although leishmaniasis is an old disease, it remains as a significant public health. The disease is spreading and globalizing due to the heavy population movement. To prevent and treat the disease effectively, an important task awaits the scientists of the future, including us.

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