

An Update on the Imported Cutaneous Leishmaniasis in Europe

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The refugee crisis is one of the leading problems of the world today. Factors such as political unrest and wars, drought and famine associated with global warming, and overcrowded neighborhoods after the influx of refugees may seriously aggravate this problem (1, 2). According to the United Nations Refugee Committee, there are almost 27 million refugees in the world today; Syria, Venezuela, and Afghanistan are the leading countries of origin for refugees (3). The old, well-known Asian route of refugees starts in eastern India, passes through all of Afghanistan and Iran, and reaches western Anatolia, where they try to pass the border to reach western Europe illegally. Poor travel conditions of refugees and the poverty associated with the endemic infections may aggravate the transmission risk of many infectious diseases to Turkey and Europe, the primary and final destinations of refugees, consecutively. These infections include many life-threatening infectious diseases, such as tuberculosis, measles, malaria, various diarrheal diseases, scabies, and leishmaniasis. Among them, leishmaniasis has become one of the most prominent diseases as both its incidence and pathogenesis have been modified due to various factors, including the refugee crisis (1-3).

Leishmaniasis is a vector-borne, neglected parasitic disease caused by a group of flagellated protozoa, the *Leishmania* species, and transmitted by sandflies (*Phlebotomus* spp. or *Lutzomyia* spp.). Endemic in 102 countries today, leishmaniasis has an incidence of more than 1 million cases, and almost three-fourths of them are cutaneous leishmaniasis (CL), which involves only the skin of the patients and requires essential treatment for total recovery. It is endemic in many countries both in the Old and the New World; according to World Health Organization (WHO), almost 90% of all CL cases are reported in Afghanistan, Brazil, Iran, Peru, Saudi Arabia, and Syria, today (1, 4-7). In addition to geography, climate, and sandflies, individual genetic factors may also influence the risk of CL development among individuals (8).

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There has been a global rise in the incidence of CL in the last two decades; this is due to many factors associated with changes in nature, *Leishmania* species, and human activities (1, 4, 9, 10). Global warming, which is blamed for the documented increase in average temperatures in the world today, is one of the leading factors; such an increase in average temperatures may directly prolong the survival time of the vectors and exposure rates of humans to vector bites. Therefore, a longer exposure period will surely increase the incidence rate, not only for CL but also for other vector-borne infectious diseases, such as kala-azar (visceral leishmaniasis), malaria, West Nile virus infection, and Crimean-Congo hemorrhagic fever (1, 9, 10).

Another cause of the rise in CL incidence is the expansion of the habitats of *Phlebotomus* vectors in recent decades. This expansion has been clearly demonstrated in many field studies on the epidemiology of leishmaniasis and its vectors also in Anatolia and Eastern Europe. In addition, an increase in urban populations and, consequently, the expansion of human settlements toward rural regions have been observed in many countries. All these factors contribute to higher human-vector contact rates in daily life and more clinical cases of vector-borne diseases, including CL (1, 5, 10, 11).

Refugees are also associated with a rise in CL incidence in many countries today. Lebanon, Turkey, Pakistan, and (to an extent) Colombia are well-known examples of this phenomenon (1-3). Despite that “refugee problems” is a current hot topic, an initial major CL outbreak was reported in an Afghan refugee camp in Pakistan in 1997 (12). Nowadays, Venezuelans in Colombia and Syrians in neighboring countries constitute a major portion of the problem (3). It is reported that the influx of 1.5 million Syrian refugees in Lebanon has elevated the CL incidence significantly (13). For Turkey, in addition to the rise in CL incidence, especially in the early years of the influx of Syrian citizens due to civil war, a new *Leishmania* genotype (Syrian/Turkish *Leishmania tropica* population structure) with two sub-populations was just shown for the first time, by multilocus microsatellite typing studies on clinical isolates of *Leishmania* species within the country (14-16).

CL has been an old endemic infection in Turkey, especially in southeastern Anatolia (1). *L. tropica* and, less commonly, *Leishmania infantum* have been the primary causative agents of CL in Turkey, where the skin lesions may heal in time, even with a nasty scar in untreated individuals. There was a total of 46,002 documented CL patients in Turkey between 1990 and 2010, just before the onset of the political unrest in Syria, where CL incidence had always been much higher than in Turkey. However, according to the official records of the Ministry of Health, CL incidence tripled between 2012 and 2013 (n=2015 and n=5362, respectively) after the influx of hundred thousand refugees into Turkey, mostly from Syria (17). In addition to that, the identification of *Leishmania major*, *Leishmania donovani*, and *Leishmania aethiopica* in CL cases, as well as the hybrid *Leishmania* species and *Leishmania* RNA virus (LRV)-positive *L. major* isolates from clinical samples were all reported in Turkey, between 2012 and 2022 for the first time (1, 5-7, 18).

The emergence of hybrid *Leishmania* strains in nature has been described in many regions of the world. It is described as an adaptation mechanism to the changing environmental and host/vector factors, which enforce the *Leishmania* species exchange genetic material for survival. It is worrisome for many researchers that the hybrid *Leishmania* strains may cause altered pathophysiology in humans, and neither be detected nor treated effectively with the conventional methods and agents (1, 5). In addition to hybrids, in vivo models have shown that genomic/proteomic modification in *Leishmania* species may alter their clinical outcomes on in vivo models. Subcutaneous injection of the clinical isolates of *L. tropica* from Şanlıurfa and Hatay Provinces in southeastern Turkey – with the proximity of almost 350 km – to Balb/C mice has yielded the cutaneous infection in Şanlıurfa province; however, surprisingly, the visceral infection has been observed in mice in Hatay province. This may be due to the modifications in the proteome in Hatay isolates of *L. infantum*, shown by the proteomic analyses. Factors listed above that influence leishmaniasis in the world - global warming, deforestation, and the refugee crisis – may all contribute to the emergence of hybrid and clinically-modified *Leishmania* strains (5, 9-11, 15).

Another good example of how new *Leishmania* genotypes influence the local infection profiles is the identification of the rare MON-58 zymodeme in Crete (19). It was isolated from an Afghan refugee with CL in Crete in 2008 for the first time, followed by its identification in a local stray dog with visceral leishmaniasis symptoms and no history of going abroad. Involvement of local naïve individuals and animals, including the vectors and reservoirs of CL with the new *Leishmania* species brought in by the migrants (refugees), may contribute to the growing risks of the changes in *Leishmania* species.

In conclusion, CL has been on the rise in many regions worldwide, especially spreading with refugees

from highly endemic countries like Afghanistan and Syria. New case reports on CL in refugees identified in non-endemic, mostly European countries, have also been on the rise. Exposure of local people to *Leishmania* parasites in those new refugee destinations, especially where sandflies are already present, should be seen as a significant public health problem when considering the potential hazards of the “changing” parasites as well as the environmental conditions in today’s world. A multidisciplinary approach, together with international cooperation for this “hot topic” is obviously essential and urgent.

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