Leishmaniasis acquired by travellers to endemic regions in Europe: A EuroTravNet multi-centre study

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Introduction

Leishmaniasis is a disease caused by protozoan parasites which belong to the genus Leishmania. Currently, leishmaniasis occurs in all continents with the exception of Antarctica and is considered to be endemic in 88 countries. In Europe, leishmaniasis is endemic to the Mediterranean basin including countries like Macedonia, Croatia, Greece, Italy and Southern parts of France and the Iberian peninsula, where it is transmitted by sand flies of the genera Phlebotomus. Rodents and canines are important reservoirs. Leishmaniasis is characterised by a broad spectrum of clinical symptoms related to the two major manifestations of cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL) that occur with a latency anywhere from a week to years [1–7].

The majority of persons affected with leishmaniasis live in endemic areas but travellers to endemic regions are also at risk, notably to South America and Central America [8,9]. In Europe, leishmaniasis occurs as zoonotic cutaneous and visceral leishmaniasis caused by Leishmania infantum in the Mediterranean basin and as an anthroponotic cutaneous leishmaniasis caused by Leishmania tropica sporadically occurring in Greece [10]. It has been estimated that around 700 new cases of leishmaniasis occur in southern European countries [11]. In Spain, one third of patients hospitalised with leishmaniasis have been described to be co-infected with HIV [12]. Several case reports on leishmaniasis occurring in travellers to Mediterranean areas have been published [13–17]. However, no systematic analyses of leishmaniasis in travellers visiting endemic areas in Europe are available. This retrospective analysis characterises leishmaniasis in European travellers infected in Europe who presented to surveillance sites of the EuroTravNet network within the years 2000–2012.

Methods

This retrospective analysis was conducted within EuroTravNet (www.eurotravnet.eu), a sentinel surveillance network of currently 18 European travel/tropical medicine reference centres in 10 countries [18]. Travellers with CL and/or VL who acquired their infection in Europe between 2000 and 2012 were included into the analysis. Migrants from leishmaniasis-endemic areas outside Europe, persons with history of travel to endemic areas outside Europe as well as local persons living in endemic European countries were excluded. Seven centres located in Germany (Hamburg, Munich), the Netherlands (Rotterdam), Norway (Oslo), Switzerland (Zurich, Geneva) and Great Britain (Cambridge) had records on patients fulfilling the above listed case definition. Cases were identified from patient registries at participating centres. Data were extracted from patient files and entered into a central database after pseudonymisation.

CL was considered as probable if typical dermal lesions were identified by an experienced physician in patients with appropriate travel history. CL was defined as confirmed if in addition to typical clinical aspects Leishmania sp. were identified by microscopy, histology, culture and/or PCR from skin biopsy. Confirmed VL was defined as the presence of typical clinical symptoms (e.g. hepatomegaly, splenomegaly, fever, cytopenia) in combination with appropriate travel history as well as direct and/or indirect proof of Leishmania sp. infection from blood and/or bone marrow by microscopy, histology, PCR and/or serology. Country of residence (where most of the year was spent), country of origin (where the patient was born) and country of infection (European country where the infection was most likely acquired) were recorded after exploring the documented travel history in order to be able to link the infection to a specific European region and to exclude those that may have obtained their infection outside of Europe. The following classification for travel reasons was defined: tourism, business, students, visiting friends & relative or army/military. The time of the last possible exposure until the date of diagnosis was used to estimate the incubation period. In addition, antiparasitic treatment as well as outcome of CL and VL were evaluated.

Summary

Background: Leishmaniasis is a disease caused by protozoan parasites of the genus Leishmania. Clinical manifestations of leishmaniasis include cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL). About 90% of cases occur in the tropics or subtropics but the disease is also endemic in the Mediterranean area. No systematic analysis on leishmaniasis in travellers visiting endemic areas in Europe is available.

Methods: Within the European travel medicine network EuroTravNet, we performed a retrospective analysis in travellers who acquired leishmaniasis within Europe diagnosed between 2000 and 2012.

Results: Forty cases of leishmaniasis (30 CL and 10 VL) were identified; the majority were acquired in Spain (n = 20, 50%), Malta and Italy (each n = 7, 18%). Median age was 48 years (range 1–79). Three of eight (37.5%) of the VL patients were on immunosuppressive therapy. The most frequent reason for travel was tourism (83%). Median duration of travel for patients with CL and VL was 2 weeks with ranges of 1–21 weeks in CL and 1–67 weeks in VL, respectively (P = 0.03).

Conclusions: Health professionals should include leishmaniasis in the differential diagnosis in patients returning from southern Europe — including short-term travellers — with typical skin lesions or systemic alterations like fever, hepatosplenomegaly and pancytopenia.
Student’s $t$ test or chi-squared test was used to compare continuous or numeric variables between groups of CL and VL. Statistical significance was defined as $P < 0.05$.

Results

A total of 40 cases of leishmaniasis acquired by travellers within Europe were identified, including 30 patients with CL (27 confirmed and 3 probable) and 10 patients with VL. All patients were of Caucasian origin, born in Europe and their countries of residence were Germany ($n = 28$), Switzerland ($n = 3$), Norway ($n = 4$), The Netherlands ($n = 2$) and United Kingdom ($n = 3$). The median age of all patients was 48 years (range 1–79 years), 19 patients (48%) were female. Only one third (32%) was infected during the typical summer holiday period (defined as most of the travel time was spent between June 1st and September 15th). In the majority of cases the travel reason was tourism. Likely places of infection included popular tourist destinations such as Balearic Islands ($n = 10$) with Mallorca ($n = 7$), Ibiza ($n = 2$) and Menorca ($n = 1$) as well as Peloponess (n = 1). Demographic data as well as information on travel and disease history are summarized in Table 1.

Of the 30 travellers with CL, 16 (53%) were infected in Spain, 7 (23%) in Italy, 6 (20%) in Malta and 1 (3%) in Greece (Fig. 1); 53% of the patients with CL presented with a single lesion. One HIV-infected patient with CD4-lymphocyte counts at 54$/\mu l$ presented with a disseminated form of CL and more than 100 cutaneous lesions; interestingly this patient, who resided significant parts of the year on Ibiza, owned 3 dogs of which 2 were diagnosed with VL. The responsible species was Leishmania donovani complex in 18 cases (60%). In two cases, the causative parasite was further specified into L. infantum and L. tropica. In all other cases, the differentiation was either not possible or the data were not available. No medical therapy was administered in 16 cases of which 11 cases showed a spontaneous remission while the remaining 5 patients were lost to follow-up. Of the 12 patients receiving local or systemic anti-parasitic therapy, the drugs used were oral miltefosine ($n = 7$), intraslesional pentavalent antimonials ($n = 2$) and topical paromomycin ($n = 1$). The patient with HIV and disseminated CL was treated with parenteral liposomal amphotericin B, and on one patient, cryotherapy was applied. The outcome after the initial therapy as far as we know was favourable in most cases (67%). In three cases, sequelae remained requiring subsequent intraslesional pentavalent antimonials ($n = 1$) or a second administration of oral miltefosine ($n = 1$).

Of the 10 cases of VL, 3 (30%) were infected in Spain, 2 (20%) in Portugal and 1 (10%) each in Greece, Macedonia, Malta or during roundtrips through southern France/Spain and southern Europe, respectively. One patient with two cutaneous lesions was initially considered to have CL solely, but because of clinical signs of systemic involvement a bone marrow aspiration was performed and VL was confirmed by microscopy, serology and PCR. While presence of immunosuppression was not known in this case, a total of three cases with VL were on immunosuppressive drug therapy (1x prednisolone plus cyclosporine, 2x prednisolone plus methotrexate) compared to none in the CL-group ($P < 0.01$). Eight patients with VL had a positive PCR, three were positive by microscopy and seven by serology. In nine of the VL-cases the tissue used for confirmation was bone marrow, in three cases alternative biopsies were obtained (skin, liver and spleen). The species was identified as L. donovani complex ($n = 8$), in one case it was further specified to L. infantum while in the last case the species could not be differentiated. Compared to CL, the time between last exposure and diagnosis was significantly longer (CL, median 9 weeks, range 2–36; VL, median 28, range 1–108. $P < 0.01$). All but one of the patients with VL presented with splenomegaly and showed either leucopenia (mean 2950$/\mu l$, standard deviation, SD, ±1615) or thrombocytopenia (mean 89,200$/\mu l$, SD ± 62,514). Antiparasitic therapy consisted of liposomal amphotericin B ($n = 8$), amphotericin B deoxycholate ($n = 1$), and sodium stibogluconate ($n = 1$). Two of eight patients in whom the outcome was known suffered a relapse which was treated with liposomal amphotericin. Four of the patients with VL received immunosuppressive medication with steroids ($n = 4$) and additional methotrexate ($n = 2$), one of these patients received in addition to steroids also cyclosporine.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic data and information on travel and disease history.</th>
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<tbody>
<tr>
<td></td>
<td>All ($n = 40$)</td>
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<tr>
<td>Age, median (range)</td>
<td>48 (1–79)</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>19/40 (47.5)</td>
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<tr>
<td>Duration of travel in weeks, median (range)</td>
<td>2 (1–67)</td>
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<tr>
<td>Time exposure – diagnosis in months, median (range)</td>
<td>7 (1–108)</td>
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<tr>
<td>Immunosuppression (%)</td>
<td>4</td>
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<tr>
<td>- HIV$^a$ (%)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>- Drug-induced$^b$ (%)</td>
<td>3 (10.3)</td>
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</tbody>
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Bold values in Table 1 signifies that $P$-value was calculated for comparisons between CL and VL.

CL = cutaneous leishmaniasis; VL = visceral leishmaniasis.

$^a$ Data on HIV-infection available for 26 patients (CL: $n = 18$; VL: $n = 8$).

$^b$ Data on drug-induced immunosuppression were available for 29 patients (CL: $n = 21$; VL: $n = 8$).
A. In both of the two relapsing patients, a prior immunosuppression was known, one was treated with methotrexate and prednisolone, the other with prednisolone only. No case of VL was known or proven to be HIV-infected.

Discussion

The present analysis of 40 travellers with leishmaniasis is, to the best of our knowledge, the largest study on leishmaniasis in tourists who acquired their infection in Europe. The majority of CL cases occurred in typical short term travellers spending a 1–3 weeks vacation at common tourist destinations of southern Europe including the Balearic Islands as well as Sicily and Peloponnese. Two of five patients with VL, for whom data on the duration of travel were available, spent 20 and 67 weeks in endemic areas, respectively, leading to a significant longer duration of travel in those with VL versus CL. Age was almost normally distributed in patients with CL with several children and adolescents affected. In contrast, all patients in the VL group were older than 55 years except for two children 1 and 4 years of age. Despite low numbers in this subgroup, there might be a tendency indicating that VL occurs more often in the typical retiree spending part of the year in endemic southern European countries. The higher proportion of individuals taking immunosuppressive drugs among elderly versus younger age groups may also influence infection and clinical manifestation or both. Nevertheless, our data clearly show that both, CL and VL might affect all types of travellers. Therefore, cytopenia, fever and splenomegaly of unknown origin in infants should prompt the paediatrician to obtain precise travel history including for example short-term camping vacations in Greece to include VL in the differential diagnoses as highlighted by a recent case of a 2-year-old boy diagnosed in Hamburg [16]. An exposure time of as short as two days has been described in U.S. tourists with American CL [19].

While it is important to obtain data on the travel history in patients with cutaneous or visceral signs of leishmaniasis information on the travel season seem to be less relevant as infections occurred more or less around the entire year in our tourist patient population. In the Mediterranean area, the numbers of the vector Phlebotomus spp. sand flies show seasonal variation with highest activity in August–September [20]. While this variation did not correspond with a seasonality in the prevalence of canine *L. infantum* infection in Spain, zoonotic cutaneous leishmaniasis in northern Africa as well as human cutaneous leishmaniasis in Israel showed clear seasonal variation with highest incidence rates in December–January [21–23]. This delay between peak activity of the vector and peak incidence of canine/ human leishmaniasis is most likely due to the comparatively long incubation period. The median time from infection to diagnosis in the present patient group was longer than half a year. In VL, the time to diagnosis was significantly longer than in CL which could be due to the circumstance that prolonged and enlarging skin lesions may result in earlier medical consultation and/or diagnosis than comparatively less characteristic systemic conditions like fever, organomegaly and blood count alterations — at least in the non-endemic countries of origin where physicians might be less familiar with this zoonotic infectious disease.

More than half of the patients with CL and 20% of those with VL acquired their infection in Spain where leishmaniasis occurs comparatively frequently. This is most likely due to the fact that the majority of patients described here originated from Germany, where Spain has been the most popular foreign tourist destination in the past decades [24]. In a retrospective study on 2028 individuals with

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**Figure 1** Countries in which leishmaniasis was acquired, separated by cutaneous (CL) and visceral leishmaniasis (VL), and countries of origin of infected tourists.
Leishmaniasis hospitalised in Spain within 1997–2008, the majority was male (73%), on average 33.5 years of age, and one-third was HIV-positive [12]. In endemic areas, more frequent outdoor activities related to profession and/or leisure activities may explain the preponderance of younger male individuals among leishmaniasis patients. In contrast, all tourists irrespective of gender and age will most likely be exposed to the vector. It is worth to note that persons living in endemic areas may acquire partial leishmania immunity as it has been shown that T cell-mediated immunity against sand fly saliva proteins protects against clinical disease [25].

Only one of our patients described here had a known HIV-infection. Most cases of co-infection with leishmania/HIV worldwide have been reported from south-western Europe, an area with intense disease surveillance activities [26]. Leishmania/HIV co-infection increases the risk of developing VL but the clinical manifestations in HIV-positive patients are not much different from those of immunocompetent patients in the Mediterranean area [27]. Immunodeficiency related to immunosuppressive therapy with methotrexate and cortisone played a role in four out of ten cases with VL. Numerous case reports on visceral and cutaneous leishmaniasis in patients under immunosuppressive therapy including methotrexate as well as tumour necrosis factor-alpha antagonists exists likely indicating an increased risk for symptomatic disease. While reliable information on absolute and relative risks can only be obtained by large epidemiologic studies, an association of immunosuppressive therapies including monoclonal antibodies with leishmaniasis may be of increasing importance giving the growing population group treated with biologics and related drugs [28,29].

There is a potential risk of introducing leishmaniasis to previously non-endemic areas by travellers and migrants. For example, serologic markers indicate a spread of leishmaniasis to northern parts of Italy [30]. In addition, sand fly species of the genus Phlebotomus capable of transmitting leishmaniasis have been identified in association with an autochthonous case of canine leishmaniasis in southern parts of Germany [31]. Transmissions to humans outside known endemic areas have been attributed to infected sand flies transported by aircraft, blood transfusions or imported stray dogs [32–34]. Congenital transmission from asymptomatic mothers to children has also been discussed in a few cases of infants with VL in which no appropriate travel history to leishmaniasis-endemic areas was discernible [34,35]. In endemic areas, stray dogs remain a significant reservoir and transmission factor while prevalence of asymptomatic human infections may increase due to the wide use of highly active antiretroviral therapy in HIV-positives [36]. Noteworthy, the documented antiparasitic effects of several HIV-1 protease inhibitors on Leishmania parasites may show an effect on the disease spectrum and, possibly, epidemiology in southern Europe and - with the global scaling up of HIV treatment - also in other endemic areas in future [37,38].

Like all retrospective investigations, this study has several limitations. The total number of cases is too low for reliable subgroup analyses. We are unable to calculate the precise risk to travellers as denominator data are lacking. Furthermore, the number of leishmaniasis in travellers to Mediterranean areas may be underestimated: first, migrants as well as those travellers returning from southern Europe who had been in other leishmaniasis-endemic areas in the past were excluded from analysis but may have acquired their infection during their travel to southern Europe and secondly, travellers returning ill from Mediterranean areas may not have been seen at tropical/travel medicine clinics but rather sought medical care at their general practitioner or dermatologist first.

In conclusion, in light of the high numbers of tourists to leishmaniasis-endemic countries of southern Europe each year the risk for travellers of acquiring leishmaniasis in southern Europe appears to be comparatively low. In the present study, however, the risk of acquiring leishmaniasis has not been restricted to long-term travellers. Travellers visiting endemic areas should be advised about the risk of acquiring leishmania infection and measures for the prevention of sand fly bites should be recommended.

Conflict of interest

No conflict of interest to declare.

Acknowledgement

All authors have seen and approved the final manuscript. The authors declare no conflict of interests.

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References

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