Canine and Human Leishmaniasis: Disease Progression to Brazilian Urbanized Areas

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Abstract

Leishmaniasis is a complex disease considered one of the most neglected tropical diseases of the world. The importance and role of domestic dogs and wild canids as a source of leishmaniasis infection is well recognized. The present mini-review discusses a series of epidemiological studies that reinforce the need to understand the role of reservoirs and vectors in the expansion of leishmaniasis to Brazilian urbanized areas, as Brazil is a country of continental dimensions and endemic for leishmaniasis. Emphasis is given on the diagnostic tools and treatment options that must be recognized as crucial options to prevent expansion of visceral leishmaniasis cases.

Keywords

Canids, Leishmaniasis, Urbanization

Introduction

Leishmania and leishmaniasis

Protozoan parasites belonging to the Leishmania genus (subgenera Leishmania, Viannia and Sauroleishmania, Trypanosomatidae, Trypanosomatida, Kinetoplastea, Euglenozoa) alternate their biological cycle between vertebrate and invertebrate hosts [1-4]. In terms of vertebrate hosts, not only humans can be accidentally affected but also dogs and cats. Besides, wild and domestic canids are well recognized as reservoirs of Leishmania in Brazil. It is estimated that more than 20 species of Leishmania cause leishmaniasis, being transmitted by phlebotomine vectors (Diptera, Psychodidae) [1,5]. Although occurring in warm areas, such as Central and South America, Southeast Europe, Asia, Africa and Australia, sandflies can also be found in latitudes greater than 50°N in South-West [6].

Basically, the parasite presents two distinct forms, depending on where they are found. When in the digestive tract of the phlebotomine vector, promastigotes present long flagellum and elongated cell body. When parasitizing the mammalian host, it presents round shape and internalized flagellum (amastigote stage) [7].

Leishmaniasis is widely distributed and classified as a prominent neglected disease as it causes up to 40,000 deaths per year, being the Indian sub-continent the region with the highest number of victims followed by Bangladesh, Sudan, South Sudan, Ethiopia, and Brazil. In Brazil, approximately 26,000 cases of cutaneous leishmaniasis (CL) were reported between 2003 and 2007, and approximately 3,500 cases of visceral leishmaniasis (VL) were reported for the same period [8,9]. In the New World, CL is mainly related to Leishmania (Viannia) braziliensis, Leishmania (Leishmania) amazonensis, L. (L.) mexicana, L. (L.) peruviana, L. (V.) panamensis, and L. (V.) guyanensis, differing from the Old World distribution, where L. (L.) major, L. (L.) tropica, and L. (L.) aethiopica are routinely identified mainly in the Mediterranean, Middle East and South Asia. L. (L.) donovani is the etiological agent of VL in the Old World while L. (L.) infantum causes VL in the New World and Old World [10-12]. VL, in its chronic and systemic form, is characterized by long-term fever, anemia, hepatosplenomegaly and hemorrhages.

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The urbanization of leishmaniasis: Decades of concern

The increase in the number of leishmaniasis cases is a growing problem of public health in Brazil and in other areas of the American continent. Of particular concern are the statistics that point to its reemergence and expansion of transmission areas, corroborating the recent urbanization of leishmaniasis, which until the mid-1980s affected mainly children in rural regions of Northeast Brazil [13]. In addition, a significant factor to be considered is the incidence of VL associated with immunosuppression, such as in patients with acquired immunodeficiency syndrome and transplanted patients [14-16]. Studies performed in Brazil reported an increase in the incidence of Leishmania/HIV co-infection in the Northeast and Central West regions, with VL being the first opportunistic infection in 60% of HIV-positive patients in the state of Mato Grosso do Sul [17]. The therapeutic approach in this case is extremely complex, since relapse rates after treatment can reach up to 100% of cases in the absence of effective antiretroviral therapy [18].

Jerônimo and collaborators [19] identified an urban distribution pattern of VL in Natal, capital of Rio Grande do Norte state, with increased case numbers of patients infected by _L. (L.) infantum_ in the early 1990s. In that case, the mortality rate was ~10% [19]. Outbreaks of VL in other urbanized areas of the Southeast and Central-West regions of the country have been reported. One of the most known examples has been described in the metropolitan area of Belo Horizonte, capital of the State of Minas Gerais, where it was observed the rapid dispersion of VL among the municipalities in the last 20 years. Between 1994 and 2005, approximately 750 cases were diagnosed and, despite some government surveillance measures for disease control, the number of cases continued to increase in the following years [20].

At the beginning of 2000, members of 46 families from the municipality of Três Lagoas (Mato Grosso do Sul State) were diagnosed with asymptomatic VL, accounting for approximately 36% of infection rate [21]. Barata, et al. [22] conducted a study in municipality of Governador Valadares urban area (Minas Gerais), which revealed VL mortality rates close to 16% for 86 human cases investigated between 2008 and 2011. Interestingly, the prevalence of VL in dogs in the same region ranged from 13.6 and 53.4% [23]. In fact, dogs are implicated as the main domestic reservoirs involved in the transmission of _L. (L.) infantum_ [23]. Oliveira, et al. aimed to clarify the role of cats as reservoirs of leishmaniasis, as is not fully understood in the epidemiological context of leishmaniasis [24]. In a review paper focused on the challenges related to control VL in Brazil, Oliveira, et al. [20] reported that VL outbreaks occur subsequently to the presence of infected dogs, such as the example of cases recorded in Araçatuba, an endemic area located in the Northwest of the state of São Paulo [25].

_Lutzomyia longipalpis_ females are the vectors responsible for the transmission of _L. (L.) infantum_ in Brazil and its first capture record in Araçatuba dated 1997 [26]. _Lu. longipalpis_ is highly adapted to the peri-urban and urban environment, thriving in peri-domestic areas [19,27]. There are numerous studies in the literature describing species and feeding habits of these insects increasingly adapted to the human dwellings and their surroundings, which has allowed the closest contact of this vector with humans and their domestic animals, especially dogs, a fact that emphasizes this relevant link in the VL epidemiological chain [28,29].

Canids and leishmaniasis

Dogs (_Canis familiaris_) are the most important urban reservoirs known for VL [30] and also present great susceptibility to _L. (L.) infantum_. They are hosts that show a wide range of clinical signs, such as dermatitis, alopecia, hyperkeratosis, lymphadenomegaly, ophthalmological diseases, splenomegaly, hepatomegaly, fever and onychogryphosis [31]. Biochemical tests alterations, such as uremia and hyper globulinemia [32] can be detected. It is important to highlight that the increase in parasitic load in tissues and organs (lymph nodes, bone marrow and spleen) is of great importance in these findings [33,34]. In addition to the domestic dog, different wild canids are important reservoirs of this parasite [35,36]. Abreu, et al. reported 6 cases of autochthonous canine leishmaniasis in the city of Pedregulho (São Paulo), an area considered non-endemic and free of sandflies; raising the assumption that there is a transit of the parasite independently of humans and domestic dogs in that region [37].

The difficulties of an accurate diagnosis facilitate this transit of reservoirs when it comes to domestic dogs. In 2017, Albuquerque, et al. showed that polymerase chain reaction (PCR) is a molecular tool that has broadened horizons regarding the detection of _Leishmania_ spp. in different tissue samples and different species, also allowing the identification of strains and genotypes of the parasites. Indeed, there are several protocols that are sensitive and specific, depending on different factors, such as DNA extraction method, primer sequences, reagents and reaction conditions [38]. In terms of the investigation of wild canids infections, research groups in several countries have applied different techniques. In Croatia, for example, the infection of a gray wolf (_Canis lupus_) by _L. (L.) infantum_ was confirmed by the isolation of parasite DNA from typical lesions of canine leishmaniasis [39]. Also, it has been shown that out of 67 red foxes (_Lupis lupis_) in Spain, 74% tested positive for the presence of _L. (L.) infantum_ [40] and in the Iberian peninsula, serological surveys of _Canis lupus_ populations kept in captivity showed that these animals produced antibodies against the parasite, even though in low titres, in addition to the presence of _Leishmania_ DNA [41]. Interestingly, Mol, et al. confirmed the trans-
mission capacity of *L. (L.) infantum* from maned wolves (*Chrysocyon brachyurus*) and vinegar dogs (*Speothos venaticus*) infected without symptoms to invertebrate hosts, probably sustaining the natural parasitic cycle [42]. In South America, especially in Brazil, the presence of *L. (L.) infantum* has been described in marsupials and rodents [43] and canids with a large territorial distribution, such as the crab-eating fox (*Cerdocyon thous*), hoary fox (*Lycalopex vetulus*), *Chrysocyon brachyurus* and *Speothos venaticus* [44,45]. Although these animals are not originally synanthropic, a fact that would place them as secondary reservoirs in the zoonotic VL transmission chain [23], it is possible that the role of these wild canids as potential reservoirs for *Leishmania* is still enlightened. This fact can be explained by the increasing interaction between humans and forest environments - both by expansion of urban and periurban areas with the population growth, as well as by the increase of ecotourism activities in forest areas - leading to the geographical overlap between wild species and humans (that in many cases, willbe accompanied by their pets).

In 2015, Casanova and colleagues [46] verified that cases of human leishmaniasis in the State of São Paulo occurred after the occurrence of canine leishmaniasis cases. An advance of the disease in the West-East direction of the state was also observed. In this sense, canine cases should serve as sentinels for human cases, preferably well monitored and diagnosed. Savani, et al. reported a case of VL in a dog of a family resident in a gated community in the region of Sousas/Joaquim Egídio districts (metropolitan region of the municipality of Campinas, São Paulo), located around 100 km from the State capital [47]. DNA obtained from liver and spleen samples implicated *L. (L.) infantum* as the etiological agent in that case.

Moreover, one study compiled epidemiological surveillance data in the same region carried out in 2009 by the Department of Health Surveillance of the Health Department of Campinas. At that time, blood samples from 198 dogs were examined and 4 cases of canine VL confirmed, indicating a prevalence of 2% of dogs infected with *L. (L.) infantum* [48]. Von Zuben and others carried out further entomological research and found *Lu. whitmani* (69.5%) and *Lu. longipalpis* (22.5%) as the predominant sandfly species [48]. Concerning the research of wild mammals that could be implicated in VL transmission, parasite DNA was not detected in any of the captured mammals, including rodent (*Nectomys squamipes*), primate (*Callithrix penicillata*) and marsupials (*Didelphis albiventris* and *Gracilinanus agilis*). The studies mentioned above that reported Leishmania-infected domestic dogs and the occurrence of competent vectors in the municipality of Campinas were crucial to add the region to the list of municipalities with established canine VL transmission in the state of São Paulo in 2010 [49].

Although the cases diagnosed were related only to dogs, one human CL outbreak has been documented in 1993 and 1994 in the districts of Sousas and Joaquim Egídio involving 25 cases of inhabitants of rural, peri-urban and urban areas. The authors described the mobility pattern of those cases, suggesting a rural-urban flow [50]. Unfortunately, no identification of *Leishmania* species has been performed. It is worth mentioning that in 2007, the first two cases of canine infection by *L. (L.) amazonensis* were described in the city of Araçatuba, considered an endemic area of VL in the state of São Paulo. The species identified in that case is typically associated with cases of CL in humans and has wild rodents as its main reservoirs [51].

**Challenges and perspectives**

Currently, the diagnosis of canine leishmaniasis is routinely performed in laboratories by direct parasitological examination and/or serological methods. More sensitive and specific methods such as molecular diagnostic tools are currently being applied to detect *Leishmania* infection, both in clinically suspect dogs and in asymptomatic dogs, which can serve as reservoirs as a possible source of infection for phlebotomine vectors. Recent clinical studies in Iran show that the majority of infected dogs do not show clinical signs [52]. The diagnosis of leishmaniasis in dogs can be considered complex for veterinarians due to:

i. The fact that clinical signs are highly variable in intensity and other pathologies may present similar signs, such as erliquiosis [53];

ii. Histopathological analyses are relatively invasive, costly and time-consuming;

iii. The lack of a highly sensitive and specific diagnostic method available on the market [54].

In this context, a symptom-based clinical score has been adopted to support diagnosis in endemic regions, as seen in Italy, where a severity score based on signs of the disease was proposed [33]. Once the clinical signs are identified, laboratory routine includes direct investigation of the parasite using for ex. puncture smear of lymph node, bone marrow or blood, and/or serological evaluation, by rapid immunochromatographic/ELISA tests. The lack of sensitivity should also be highlighted mainly in cases of subclinical carriers [55]. Polymerase chain reaction (PCR) is a sensitive and specific method, since it shows more reliable results even for healthy animals [56]. By using the PCR methodology, it is possible to amplify target sequences in the genome where the ribosomal DNA array (rDNA) allows the typing of *Leishmania* species [57].

In general, leishmaniasis chemotherapy is very complex not only for dogs, but also for humans [58]. Given the prohibition of treating dogs with the same drugs used to treat humans in Brazil for a long period, a great
controversy in veterinary medicine has raised. Recommendation of euthanasia of seropositive animals was supported despite low effectiveness in disease control. Recently, studies on drugs that act against leishmaniasis have evolved and the use of miltefosine (Milteforan®) has been approved by the Ministry of Agriculture in 2017. The release of the product mentioned has a strong relation with the exclusively zoonotic character of the disease in Brazil; unlike other countries (i.e., India) where the anthropoontic character is observed. The prophylaxis of leishmaniasis is closely related to the interruption of the transmission of the parasite between the links of the epidemiological chain. Until recently, euthanasia of animals with positive serology was recommended as a prophylactic measure, but this measure proved to be ineffective as there were wild reservoirs with close proximity to dogs and humans, for example, wild canids. Strategies for prophylactic performance in sand flies are those that have presented better results. The use of protective screens and collars repellents, as well as insecticides, plays an important role in controlling the transmission of VL. Unfortunately, it is not possible to rely solely on vaccines for prophylaxis, since the animal may show positive serology after immunization. In addition, the replacement of the animal owner associated with the lack of clinical history can lead to later diagnoses and more severe complications to the animals [59-61]. Unlike observed for humans, there are vaccines currently available for veterinarian use only.

Epidemiological surveys regarding the transmission dynamics and characterization of host-vector-parasite populations are key to achieve a better understanding of leishmaniasis in urbanized and non-urbanized areas. Through the combination of research on surveillance practices and modern parasitological studies, it will be possible to advance in the promotion of prophylactic strategies to restrict the progress of such devastating disease for humans and dogs.

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