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Mini Review

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Visceral leishmaniasis: situation diagnosis from the perspective of disease control in Brazil

Abstract

Leishmaniasis is a group of neglected diseases that are highly prevalent worldwide, mainly in the developing world, and can take on severe forms. They are transmitted to the man by the bite of phlebotomines, existing a range of animal reservoirs, among which the dog is considered the main urban host. In this context, leishmaniasis, mainly the visceral form, has been urbanized in Brazil, reaching large urban centers throughout the country. In addition, recently, new areas previously unaffected started to present autochthonous cases of human visceral leishmaniasis. The expansion of the disease to new areas has demonstrated the failure of the measures recommended by national health agencies and calls for a new control model in which popular awareness and environmental management are priority actions.

Keywords: visceral leishmaniasis, control, canine infection, health, population, Brazil

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Leishmaniasis is a spectrum of chronic-infectious diseases caused by intracellular protozoa of the genus *Leishmania* (Kinetoplastida, Trypanosomatidae). In the New World, the eco-epidemiology of the disease is closely related to animal reservoirs as the main source of parasites, being an anthropozoonosis of great importance in public health in Brazil.[1,2] Visceral Leishmaniasis (VL) is considered the most severe form of the disease, and potentially fatal if untreated. In the country, the etiological agent of this clinical manifestation is *Leishmania (Leishmania) infantum* and the main vector is *Lutzomyia longipalpis*.[3]

The *Leishmania sp.* life cycle is complex and involves both vertebrate and invertebrate hosts. There are two developmental stages of the parasite: one is found in the midgut of a variety of sandfly species (female only) - the proliferative forms named promastigotes; while another (amastigotes) are able to live in mammalian host cells. In general terms, the cycle begins when a female sandfly bites an infected host (i.e. humans, dogs) and is infected by the amastigote form present in the host macrophages. The amastigotes then transform into procyclic promastigotes that multiplies into the sandlfy midgut, migrating to the stomodeal valve. After several cell divisions, procyclic promastigotes transforms into metacyclic promastigotes, which is released by sandfly via regurgitation during the next the blood meal. Some known risk factors for visceral leishmaniasis are humidity and accumulated organic matter, absence of basic sanitation and garbage collection, proximity to green areas, domestic or farmed animals near houses (chickens, birds), low education.[4–8]

The first case of the disease in Brazil was identified by Penna in the state of Bahia, Northeast region, in 1934, by viscerotomy for the diagnosis of yellow fever.[9–11] Later, successive records were made to the same place and other states of the Northeastern Brazil, a region considered endemic for VL until nowadays.[10–12] The first reports on the disease, still in the 1930s, pointed to the strictly wild profile of the disease cycle, in which the characteristics of soil, vegetation, climate and landform seemed to favor the occurrence of both sand flies and reservoir animals.[12] In fact, leishmaniasis remained among wild and domestic animals, as well as sand flies in the tropical areas where the primary hosts were rodents, marsupials, edentates, procionids, ungulates, and primates.[13] Man was accidentally involved in the transmission cycle when invading the forest environment or colonizing areas near to wild foci, which associated the VL to work factors (e.g. agriculture, livestock, hunting), a profile still observed in the present day.[3,14] However, at that time, human settlements and the presence of domestic animals were not considered important factors for the spread and risk of the disease, a fact that proved relevant to the epidemiology of VL in Brazil in urban and peri-urban areas from 1980, when it expanded to several regions of the country.[15]

Currently, the disease can be found in all regions of Brazil, including two southern states that, until recently, had never presented autochthonous cases - Santa Catarina in 2017 and Rio Grande do Sul in 2009.[16,17] The emergence of cases in areas that previously did not register the occurrence of the disease in humans, along with the difficulty in effectively reduce the incidence of VL in the country, has raised questions about the effectiveness of the control measures recommended by the Ministry of Health.[18,19] These are mainly based on the early diagnosis and treatment of human cases, the reduction of the population of sand flies – *Lu. longipalpis* is the most important vector in the country – and the culling of infected reservoirs, namely domestic dogs, which are considered the main urban reservoir.[20,21] However, in view of the difficulty in containing the new cases of VL, the Ministry of Health also adopted environmental management strategies (i.e. cleaning of yards and public public) to control the immature forms of the vector and the treatment of canine positive cases with the Milteforan®, a drug recently released in Brazil by the Technical Note nº11/2016.[21,22]

Until the publication of this technical note, canine treatment in

Brazil was prohibited when it was based on drugs that were also used for human treatment or that were not released by the Ministry of Agriculture, a measure aimed at preventing the emergence of *Leishmania* strains resistant to the available medicines.[23] In the meantime, several treatment protocols were developed in an attempt to avoid canine sacrifice, either by drug association or by individual use - meglumine antimoniate, miltefosine, allopurinol, amphotericin b.[24–27]

However the controversy of "treatment x euthanasia" remains in Brazil. On the one hand, the scientific literature has supported the ineffectiveness of euthanasia in seropositive dogs and pointed out to more successful actions in VL control, whose focus is the combined use of strategies - popular awareness, risk control actions, prophylactic measures such as use of collars and repellents directed to dogs.[28–30] On the other hand, the technical note regarding the Milteforan® liberation stresses that the choice for treatment is an exclusive option of the owner of the animal, and that this attitude does not constitute a public health measure to control the disease.

Among the factors that have contributed to both the expansion of the VL as to reduce the effectiveness of control measures can be listed

i) The environmental changes of the last decades, mainly characterized by increased deforestation (hydroelectric, mining, urbanization).

ii) The uncontrolled growth of cities.

iii) The migration of people and animals from the endemic regions to the unaffected areas.

iv) The economic exploitation of forested areas, which favored the movement of sand flies and reservoirs to areas close to urban areas.

v) The adaptation of *Lu. longipalpis* to new niches and food sources (i.e. domestic and synanthropic animals).

vi) Reduction of investments in health and education accompanied by discontinuation of control actions.[31–36]

Another important factor is the adaptability of parasites and vectors to new ecological niches. Studies show, for example, areas of the state of Rio de Janeiro where there are autochthonous cases of VL, but in which the occurrence of the main vector - *Lu. longipalpis* - is not frequent or is even absent, directing suspicions to other recurrent species in the region, such as *Migonemyia migonei*.[37,38] In the state of Mato Grosso, central part of the country, the vector incriminated has been *Lutzomyia cruzi*, since no human and canine cases occur; *Lu. longipalpis* is absent, and *Lu. cruzi* has already been found naturally infected by *Le. (L.) infantum*.[39]

In this scenario, health education emerges as a key piece to adjust control and prevention practices to the reality of population and territories.[40] Studies have shown that having some knowledge about leishmaniasis can minimize the risk of its occurrence, and factors such as education are associated with the risk of VL involvement, especially in endemic areas.[8,41,42] However, studies in the country show that the affected populations are unaware of important concepts about the disease, such as transmission, treatment and prevention; and that education and health professionals, whose work is the connection between information and preventive practices, have incipient and fragmented knowledge on VL.[42–46] Therefore, it is envisaged as a concrete and necessary possibility the aggregation of scientific community, health professionals, and civil society to subsidize and act effectively in the VL Control Program in Brazil. To this end, supporting the implementation of appropriate actions needs a set of vital information that will enable constructing a clear diagnosis of the current situation (what are the reservoirs? what are the vectors? what do the population know?). Addressing this issue in the field of health, with all its nuances and complexities, involves having to understand the epidemiological and cultural peculiarities that surround the disease in each territory, thus contributing to define the most appropriate techniques that will support the analysis and/or the control of the situation (i.e. educational campaigns, prophylaxis of residences, investment in research).[30] This allows the information to be collected and organized in a correct way by which the resulting diagnosis makes sense, serving as the basis for implementing consistent and effective actions aimed at improving the health of the population. In this new scenario, there is a need to strengthen the links between science, politics and society, together with the support and engagement of health managers, to disseminate knowledge and promote the health of the population.

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Conflict of interest

The authors declare no conflict of interest.

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