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Review

Chagas disease in Bolivia: a brief review of the urban phenomena

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ABSTRACT

Chagas disease is a major public health problem in Latin America. At present, Bolivia has the highest rate of vector and congenital transmission, and the old rural profile of the disease is changing rapidly into urban. Recent epidemiologic data indicates that all the capital cities of the 9 Bolivian departments still have new cases of Chagas disease in children under fifteen years. However, good news came from Bolivia: the Chagas control program has reduced importantly the rate of infection. We present a brief review on the Chagas disease literature concerning Bolivia and discuss the present problems and challenges in epidemiology, vector distribution, clinical management, congenital transmission and drug treatment.

Key words: Chagas Disease, Bolivia, Urban

RESUMEN

Enfermedad de Chagas en Bolivia: Revisión sobre el fenómeno urbano

La enfermedad de Chagas es un problema grave de salud pública en América Latina. Actualmente, Bolivia presenta la tasa más alta de transmisión vectorial y congénita; el perfil rural antiguo de la enfermedad está cambiando rápidamente a la urbanización. Datos epidemiológicos recientes indican que todas las capitales de los nueve departamentos bolivianos arrojan todavía casos nuevos de la enfermedad de Chagas en niños menores de 15 años. Sin embargo, el programa de control de Chagas en Bolivia ha reducido la tasa de infección de manera significativa. Presentamos aquí una revisión de la literatura sobre la enfermedad de Chagas en Bolivia; discutimos también los problemas y los desafíos actuales en epidemiología, distribución de vectores, manejo clínico, transmisión congénita y tratamiento farmacológico.

Palabras clave: Enfermedad de Chagas, Bolivia, Urbanización

1. The dimension of Chagas disease problem in Bolivia

Chagas disease, caused by infection with the flagellate protozoa *Trypanosoma cruzi*, represents a major public health problem in Latin America (1). Due to the important international initiatives for controlling vector infestation and blood quality, in the last twenty years the prevalence of *T. cruzi* infection has decreased. In 2005 Bolivia accounted for 620,000 infected cases (1), half of the estimated numbers in 1985 (1,134,000). Previous to the start of the national vector and transfusion control program in 2000, infection rates in Bolivia varied

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from 26 to 71% in children between 1 to 6 years old, and from 32 to 93.5% in adults, depending on the endemic area (2, 3). 80% of the national territory in Bolivia (~600 km^2) is endemic for Chagas disease (1), with approximately 1,800 million people at risk of infection. Data from 2005 still indicates that more than 10,000 new cases/ year in Bolivia (1).

The infection occurs in many different geographic areas and affects primarily the lowest socioeconomic population. Seven out of the nine Bolivian departments are endemic for Chagas disease, regardless of their altitude (4). In blood banks, up to 63% of potential donors were determined to be seropositive for *T. cruzi* antigens (5) and the percentages of positivity in these 7 departments have an average of 28% and are distributed as follows: Sta. Cruz 51%, Tarija 45%, Cochabamba 28%, Sucre 39%, La Paz 4.9%, Oruro 6% and Potosi 24%(5). From the 1.3 million infected people estimated in 1982, 26% showed electrocardiograph alterations. The house infestation rate for the whole country was 41.2% in that year and the infection rate in the vectors was 30% (1). Data on serological prevalence show a rate of 28.8% in the general population; in the 0-4 years age group, seroprevalence is 22% in Cochabamba, but 0% in Potosi, where there is an active vector control program. The house infestation rate for the whole country was 41.2% in that year and the infection rate in the vectors was 30% (1). A low rate of 0.8% of house infestation was obtained in Tupiza, another department where there is an active control program (6). In highly endemic communities, such as the departments of Cochabamba, Chuquisaca, Tarija, and Santa Cruz, seroprevalence rates can reach 100% in older individuals (7). In the endemic areas, children are exposed to *T. cruzi* vectors at an early age, and high prevalence rates are reported in individuals less than 10 years old (8). In the village of Tabacal, 40% of infected children fall within this age group (9), and in the village of Mizque, a study reported 11.8% and 44.1% prevalence rates for children aged from one to five and six to 10 years old, respectively (10). *Triatoma infestans* is the main vector in Bolivia.

Despite the fact that Chagas disease is classically considered to be a rural illness, it is now known also as an urban disease. Briceño-Leon (11) pointed out that "the historical processes involved in Chagas disease transmission relate to the patterns and conditions of human settlements, especially in rural areas, due to proximity to forest areas, where both vectors and *T. cruzi* can occur, combined with precarious housing conditions and underlying poverty. However, seasonal and permanent rural-urban migration has played a major role in re-mobilizing vectors, *T. cruzi*, and Chagas-infected individuals"(11). In Bolivia, this phenomenon is clearly observed and we and others have reported active vector and congenital transmission of Chagas disease in poor urban areas (8, 12), as also described in other countries like Peru (13) and Chile (14). From 1995 to 1999, we confirmed urban transmission and distribution of Chagas disease in children from 5 to 13 years old in the city of Cochabamba (8), finding 25% of seropositivity in the South and 19% in the North zone districts, which differ in social, environmental, and agricultural conditions. Prevalence is proportionally related to age and in Carapari, southern Bolivia, an age-adjusted prevalence of 51.2% was found (15). Among women of procreation age, the prevalence was 63.9%. In children younger than 11 years, the prevalence was 21.5%, which confirmed the importance of residual vector transmission despite several years of vector control. In this study it was also observed a cline from the south to the north of the locality, where the prevalence ranged from 40 to 80%. Finally, international migration also plays a role in Chagas disease epidemiology and Bolivian people accounts for more than 50% of the estimated *T. cruzi* seropositive legal immigrants in Spain (16), with more than 3.6 thousand infected persons.

Bolivia is currently undergoing a vigorous urbanization process, and the rural population has

decreased from 58.5% in 1976 to approximately 42% in 1992 (17). Peripheral districts or "popular zones" are home to 58% of the city's population (18). Forty percent of people living in these districts originally from rural villages and may act as transport of triatomine vectors from rural to urban areas. Immigrants account for 30% of the total Cochabamba population (17, 19, 20), and this is most likely secondary to political, economic, and social causes (18). Individuals immigrated to the urban zone in pursuit of a better quality of life and improved conditions for their families (21).

Screening and diagnosis of the target population is mandatory to epidemiological studies and control programs. According to World Health Organization (WHO) recommendations, diagnosis of Chagas disease is confirmed using two different tests (22). In case of doubtful or discordant results, a third test must be used. Following national and regional recommendations, different tests are used. Conventional and recombinant ELISA, indirect hemagglutination inhibition (HAI) and indirect immune-fluorescence (IFI) tests are more commonly used. A new rapid diagnostic test using whole blood was introduced and successfully tested in Bolivia (23).

A recent study showed the feasibility and safety, but not a high effectiveness of etiological treatment programs for Chagas disease in Bolivia (24). In collaboration with National Health Ministry, the international medical humanitarian organization Médecins Sans Frontières/Doctors Without Borders (MSF) started its first program for the diagnosis and treatment of Chagas disease for affected populations in Latin America. In Bolivia, MSF implemented Chagas disease diagnosis and treatment programs, in the rural district of Entre Ríos, O'Connor Province, Tarija and in one peri-urban setting in Sucre. This study attained respectively 7,613 and 19,400 persons, mostly children and adolescents, and diagnosed as seropositive 1,475 (19.4%) and 1,145 (5.9%) patients from 2002 to 2008. All the patients were treated with benznidazol and contrasted to results obtained in previous findings of seroconversion between Bolivian people and patients from Honduras and Guatemala. In Sucre no seroconversion was observed after 18 months and only 5.4% of patients seroconverted after 60 months in Entre Ríos. These results highlighted the feasibility of implementing Chagas disease diagnosis and treatment programs in resource-limited settings, including remote rural areas, but also stressed the limitations in apparent treatment effectiveness, that may reflect differences in patient and parasite populations, and illustrates the limitations of current treatments and efficacy measures.

2. Congenital Chagas disease in Bolivia: an important route of transmission

Besides the important fact that many urban settings in Bolivia have active vector transmission of Chagas disease, a second important route of *T. cruzi* infection is the vertical transmission from infected mothers to their children. A seminal study was performed by Azogue (25) in a total of 910 mothers attending the Percy Boland Maternity Institute in Santa Cruz. She recorded a transmission rate of 9.5% transmitted Chagas disease the children, and a strong influence of certain socio-cultural factors related to the mother, such as increased fertility, early age of motherhood and blood transfusions, and also by the migration displacement from other endemic regions of Bolivia and from rural areas in the same department. It was postulated that the persistence of the disease in the urban setting was due to a second-generation transmission cycle. Azogue argues that regions where Chagas disease is endemic become risk areas for women migrating from non-endemic regions.

In Caraparí, a village of 9000 inhabitants in southern Bolivian Chaco (15), 63.9% of the women of procreation age were seropositive, resulting in a high risk of congenital transmission. For better diagnosis and management of *T. cruzi*-infected women, the rapid and low-cost (<2 US$ each test) Stat-Pak test (23) was applied to

459 pregnant women of a rural area and to 1030 urban women giving birth from the east of Bolivia. Nevertheless, the specificity differed significantly between rural pregnant and urban birthing women, a result which could be attributed either to differences of parasite strain or to Chagas prevalence in both areas. The authors recommend its use due to simplicity, reliability and low-cost, defending that its performance is compatible with a field use for large-scale screenings.

The same group carried out a study of a population of pregnant women delivering at Bermejo hospital, South Bolivia (26). This is an area where vector transmission of *T. cruzi* is negligible and women infect themselves during displacements in close endemic areas. The prevalence of *T. cruzi* in 508 pregnant women, diagnosed by several serological tests, was 33.9%. In 8 infants, they observed *T. cruzi* in the umbilical cord (congenital transmission rate of 5.2%). This is very similar to the 5-6% of materno-fetal transmission rate found in studies conducted by Torrico and colleagues (27), in 2 different periods (1992-1994 and 1999-2001) in the same maternity clinic in Cochabamba. Neonatal mortality related to congenital Chagas disease also decreased from 13% in 1994 to 2% in 2001, suggesting that the decrease in poverty that has occurred in Bolivia between both surveys might have contributed to reduce the morbidity and mortality, but not the transmission rate of *T. cruzi* congenital infection, which remains a serious public health problem in Bolivia. A difference in vector density in maternal residence area also contribute as a cause to this significant decrease in the proportions of severe and mortal forms of congenital Chagas disease in the two surveys (28). This conclusion was based on the comparison of hematological and parasitological results obtained from mothers infected with *T. cruzi*, and of clinical and biological data obtained from their infected and uninfected newborns, stratified according to vector density in the area of maternal residence: hematocrit blood rates or hemoglobin amounts were within the normal ranges and similar in all the maternal groups, but mothers living in areas with high vector density displayed a higher frequency of hemocultures positive for *T. cruzi*. Also, newborns congenitally infected with *T. cruzi*, but not uninfected babies born from infected mothers, displayed higher frequencies of very low Apgar scores, low birth weights, prematurity, respiratory distress syndrome or anasarca, as well as higher mortality rates when their mothers lived in areas of high vector density. The authors concluded that frequent bites of triatomine bugs during pregnancy do not induce maternal anaemia, but increase maternal parasitemia and worsen congenital Chagas disease, likely through multiple maternal re-infections with *T. cruzi*. The study at Bermejo (26) could confirm a less severity of the congenital disease of Chagas in the absence of re-infestation of the mother during pregnancy, since the means of birth weights, lengths and hemoglobin rates were similar in the children from both seronegative and seropositive women, and in children infected or not by *T. cruzi*. Maternal dwelling in areas of high vector density is associated with a serious increased risk of severe and mortal congenital Chagas disease. Therefore, these studies indicate that in the endemic regions of Bolivia the infection of the feminine population in fertile age by *T. cruzi* is frequent (20 to 50 % of the women in fertile age) and that a great percentage of infected women (95%) do not transmit the infection to the fetus.

The important series of studies performed by Torrico (27-34) showed that maternal chronic *T. cruzi* infection had no effect on pregnancy outcome and health of newborns when there was no materno-fetal transmission of parasites (27), and that the chronic maternal infection by *T. cruzi* seems to have no clinical influence, neither on the course of the pregnancy nor during birth, if a group of *T. cruzi* infected mothers is compared to a non infected group giving birth to a newborn of Chagas infected women who did not transmit the infection to the fetus (29). They also showed that parasitemia in mothers (> 90%)

are very low (<10 parasites/mL) as compared to those of their newborns (76%), that were more than 1,000 fold higher (30), as measured by quantitative real-time PCR. Besides, *T. cruzi* TcII sublineages infecting mothers and newborns were identical, without evidence of mixed infection in mothers or neonates. A positive association exists between a high number of parasites in blood and the morbi-mortality of the newly born children with congenital Chagas (31). The congenital transmission is associated with an immunological imbalance and a high parasitic load in infected mothers that had infected babies (32) since they produced less IFN-gamma and more IL-10 than those who gave birth to non infected newborns, and they are not able to produce IL-2. The group argues for an integral treatment of congenital Chagas disease (33, 34) and for detection and treatment of all cases, that would lead to an investment of US$ 1.2 per new-born in Bolivia. They defend that in addition to suffering relieve and improving of life quality indirect benefits related with Chagas vector control program increase "the demand thanks to increasing risk awareness and also induce demand testing all pregnant women in endemic areas. So the conclusion is that such investment is profitable".

3. Clinical forms, treatment and patient management

With such a huge health and social problem that drains around 200,000 persons to cardiology and gastrointestinal care by the national health system (~30% of the 620,000 infected cases estimated for 2005), Chagas disease in Bolivia needs more than prevention. Most of the seropositive people at the chronic phase will stay in relatively good health and asymptomatic all life long, just as the first girl (Berenice) that was identified as infected by T. cruzi by Carlos Chagas in 1909. She was refound at the age of 55 and 71 years old, with bloodstream circulating parasites, asymptomatic, in the so-called "indeterminate form" (35). It is estimated that about 1-2% of the cases in the undetermined form evolves each year to the other two chronic clinical forms: cardiac and gastro-intestinal. Management of patients in these different clinical forms is also different, since most of them - those in the indeterminate form- would need regular care in the primary health system units, according to the natural evolution of the disease (36). Just as has occurred with diabetes mellitus, hypertension, and AIDS, diseases that were initially treated by a specialist and later incorporated into primary health care services, these services can potentially focus on prevention (primary prevention of the infection and secondary for disease development), and adapt medical care for Chagas disease to local specificities, using different approaches based on geographic, social, cultural or other specific characteristics (36).

The indeterminate form of Chagas disease is diagnosed in asymptomatic subjects with a positive blood test for Chagas disease, normal resting electrocardiogram, chest X-ray, barium esophageal and large bowel radiological studies (36). Patients should be followed up annually and submitted to electrocardiogram. They have a benign course, are able to work and to a sexual healthy life. Under suspicion of disease evolution, they should be indicated to a Chagas disease reference service for adequate care.

The two less prevalent clinical forms, cardiac and digestive are well defined and managed also in primary but extended to secondary and tertiary care services, especially in urban areas. Many recent reviews cover the different clinical and progressive aspects of chronic Chagas disease in these forms (37-39).

One of the main concerns for health services is etiologic treatment with benznidazole (Bz) or Nifurtimox (Nif), the two drugs trypanocide available in Latin America (40,41). Treatment of acute cases, of children and of young patients (less than 18 years) is mandatory but due to a lack of international consensus about diagnostic and parasitological cure criteria, as well as to undesirable side effects and poor indices of

apparent cure, the trypanocide approach at the chronic phase is a matter of study and debate (42). Thus, unfortunately, integrated/all around care and management of the chronic patients in urban localities is not well established and programmed -and it should be- as it is for other infectious diseases like tuberculosis, hanseniasis, hepatitis or AIDS (43). Both at urban and at rural localities, Chagas disease program need to integrate 5 components, as proposed and implemented by MSF (24): 1. *Information, education, and communication* (IEC), to different target audiences such as community authorities, health staff, key community figures (*e.g.*, teachers, religious leaders, etc.), and patient families-this component is essential both for control and research programs, as we showed previously (8); 2. *Vector control*, since no success in treatment and monitoring could be sustainable without permanent vector control activities that lower infestation rates of the given community to less than 3%; 3. *Training of multidisciplinary health staff*, to orient for specific diagnosis and treatment skills, as well as to communicate and work with patient families to help ensure adherence and follow-up, including detection of adverse event detection and rapid intervention after benznidazole treatment; 4. *Active screening and diagnosis*, to detect infection and decide on management, and allow access to treatment; 5. *Treatment*, including family-based strategies.

4. The "vinchucas" as a great challenge: urban and climate changes and perspectives for Chagas disease in Bolivia

The globalization process is one of the most important elements influencing the outcome of Chagas diseases in Latin America countries, both in urban and in rural localities. More than 130 triatomine species have been found to be potential *T. cruzi* vectors and more than 100 wild reservoirs have been described (43). *Triatoma infestans* still remains the most important and widespread vector of Chagas disease in South America, and particularly in Bolivia, supporting the rational for the control programs as part of the Southern Cone Initiative (43) that aimed to eliminate domestic vectors by large scale use of pyrethroid Insecticides. Wild populations of *T. infestans* had been detected in the highland valley of Cochabamba, in Central Bolivia (44), but it has recently found to be much more widespread. Then the putative process of recolonisation of insecticide-treated villages is a real risk, since sylvatic foci have been demonstrated in peri-urban environments (44). However, current evidence does not support a flow of *T. infestans* between sylvatic and domestic areas in Bolivia, probably due to climatic factors that may hamper the process of domestic intrusion by wild bugs. However, for *Rhodnius prolixus*, a continued flow between palm trees and houses has been revealed (45). A delicate equilibrium between deforestation of trees that offer stable refuges for the vectors, environmental damage caused by human activities and climate changes due to global warming would certainly play a role in future ecological interplay between *T. cruzi*, its vectors, reservoirs and human populations.

The consequences of global climate changes with respect to interactions of the pathogen with triatomines remain a matter of debate (46,47). As any zoonotic and emergent disease, Chagas disease will vary as a result of anthropogenic changes of the biosphere and globalization. Global warming unrestricted exploitation of natural resources such as forests and fisheries, urbanization, human migration, and industrialization of animal husbandry cause environmental destruction and fragmentation (47). Any degradation of wild-life biotopes, affecting their diversity, contributes to the dissemination of zoonoses such as Chagas disease, Leishmanioses, Hantavirus and others, with increase interaction of the parasites with domestic animals and human populations. A recent study indicated that there is a potential for Chagas disease to emerge in the United States, when risk was determined by the simultaneous analysis of climate changes that would make the

triatomine vector effective and increase in the risk for transmission (48). Similar studies are still absent in Latin America countries.

5. Concluding remarks

To honor Carlos Chagas legacy is to active engage science for a better health for people affected by Chagas disease in Latin America. In this year when we commemorate the important and unique discovery of Carlos Chagas, this brief review of Chagas disease in Bolivia, especially in urban areas, stress remaining challenges:

(i) to develop strategies for maintaining sustainable and integrated surveillance in areas that display diverse epidemiological patterns, allowing the identification of priority areas for intervention

(ii) to guarantee patients adequate global care and access to available therapies

(iii) to improve the diagnostic tools for early (parasitological, serological) diagnosis of the infection

(iv) to identify and validate prognostic markers for disease progress to support rational interventions

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