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Review

American trypanosomiasis and Chagas disease: Sexual transmission

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ABSTRACT

Objective: To contribute to the discussion on the research findings indicating the sexual transmission of American trypanosomiasis and Chagas disease in humans.
Methods: A review of the literature was performed to investigate the routes of transmission of *Trypanosoma cruzi* parasites and to evaluate the distribution of Chagas disease, which is now found across five continents.
Results: The epidemiological profile of American trypanosomiasis, which is still considered a neglected disease of the poor people of Latin America, has changed over time. A family-based study demonstrated that the blood protozoan *T. cruzi* can be transmitted sexually from infected males and females to naïve mates.
Conclusions: Evidence that Chagas disease can be transmitted sexually, coupled with the migration of individuals with Chagas disease to previously non-endemic countries and increased travel to endemic countries, has implications for public health. Improved screening of blood supplies and prenatal care are required to prevent congenital spread.

Contents

American trypanosomiasis, also known as Chagas disease, is endemic to people in rural areas of South America, where the *Trypanosoma cruzi* parasites are sympatric to the hematophagous triatomine insect vectors (Prata, 2001; Coura and Viñas, 2010; Teixeira et al., 2018). The migration of *T. cruzi*-infected people to the Northern Hemisphere and of travelers to endemic countries have likely made American trypanosomiasis a global challenge, since these infections can be transmitted from mother to offspring (Murcia et al., 2013), by blood transfusion and donated organs, and by contamination of hospital and laboratory workers (Teixeira et al., 2011a). Chagas disease is a social and economic burden, and specialized clinical centers in various countries have employed skilled personnel for the provision of health care to patients and their families (Repetto et al., 2015; Grigorenko et al., 2014; El Ghouzzi et al., 2010). The expertise stemming from these national centers is deemed important, because the problems associated with the emergence of Chagas disease can no longer be underestimated (Hotez et al., 2012; Teixeira et al., 2011a, 2009; Schmunis and Yadon, 2010).

Acute *T. cruzi* infections are usually asymptomatic and unrecognized, although approximately 5% of infected children may show fever, headache, drowsiness, tachycardia, edema, and shortness of breath (Pérez-Molina and Molina, 2018; Teixeira et al., 2011a, 2006). Morbidity and mortality in the acute phase of the infection are low, since an average of four deaths due to the acute disease have been recorded each year over the past three

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decades (Andrade et al. 2014). The chronic intermediate phase of lifelong *T. cruzi* infection ensues in the absence of clinical manifestations. However, approximately 30% of chronically infected people develop Chagas disease. Chronic Chagas disease kills people due to megaviscera and heart failure (Coura and Viñas, 2010; Prata, 2001); polyneuropathy and neuroendocrine syndromes are more rarely seen (Pérez-Molina and Molina, 2018; Teixeira et al., 2011a).

Several studies have shown the course of *T. cruzi* infections and the pathological consequences upon inoculation of a few parasites into dogs (Marsden and Hagstrom, 1968; Lana et al., 1988), primates (Falasca et al., 1990), and rabbits (Lauria-Pires, 1995). In addition, a family-based study was performed to identify chronically infected individuals with low parasite loads (Araujo et al., 2017). Nuclear DNA PCR (nDNA-PCR), Southern hybridization, cloning, and sequencing of a specific 188-nucleotide (nt) telomere repeat was used to validate the diagnosis of all *T. cruzi* infections. The use of these techniques assures high sensitivity and specificity for the diagnosis of Chagas parasites (Almeida et al., 2018). The in-house nDNA-PCR technology was able to detect as few as 1/10 of the total (270 fg) DNA of a single diploid *T. cruzi* only (Araujo, 2013; Hecht et al., 2010; Castro, 2009). In the family-based study, the diagnosis of sexually transmitted Chagas disease was confirmed by nDNA-PCR detecting the *T. cruzi* 188-nt telomere sequence in blood samples obtained on three different occasions 1 year apart (Araujo et al., 2017).

In a research protocol approved by the Faculty of Medicine Ethics Committee for Human and Laboratory Animal Research, semen samples were obtained from nDNA-PCR-positive male volunteers with the 188-nt telomere sequence present in their ejaculate. The instillation of aliquots of this semen from Chagas-positive donors into the vaginas of female mice and into the peritoneal cavity of male mice resulted in *T. cruzi* infections. Pathological examinations revealed parasite amastigote nests in the heart, skeletal muscle, vas deferens, and uterine tube (Figure 1).

A word of caution is required, because ELISA and indirect immunofluorescence (IIF) assays fail to detect *T. cruzi* antibodies in a majority of chagasic subjects (Almeida et al., 2018). In the absence of specific antibody, the immune tolerance present in a majority of the study family subjects was a consequence of the sexual transmission of *T. cruzi* infection to the early embryo before development of the immune system. In this regard, the diagnosis of a majority of the progeny from Chagas parents could not be accomplished with the immunoassays. In contrast, the presence of *T. cruzi* antibody in a minority of chagasic individuals indicates that *T. cruzi* parasites reached the fetus with a mature immune system (Almeida et al., 2018; Araujo et al., 2017; Guimaro et al., 2014; Teixeira et al., 2011b). Therefore, employment of immunoassays

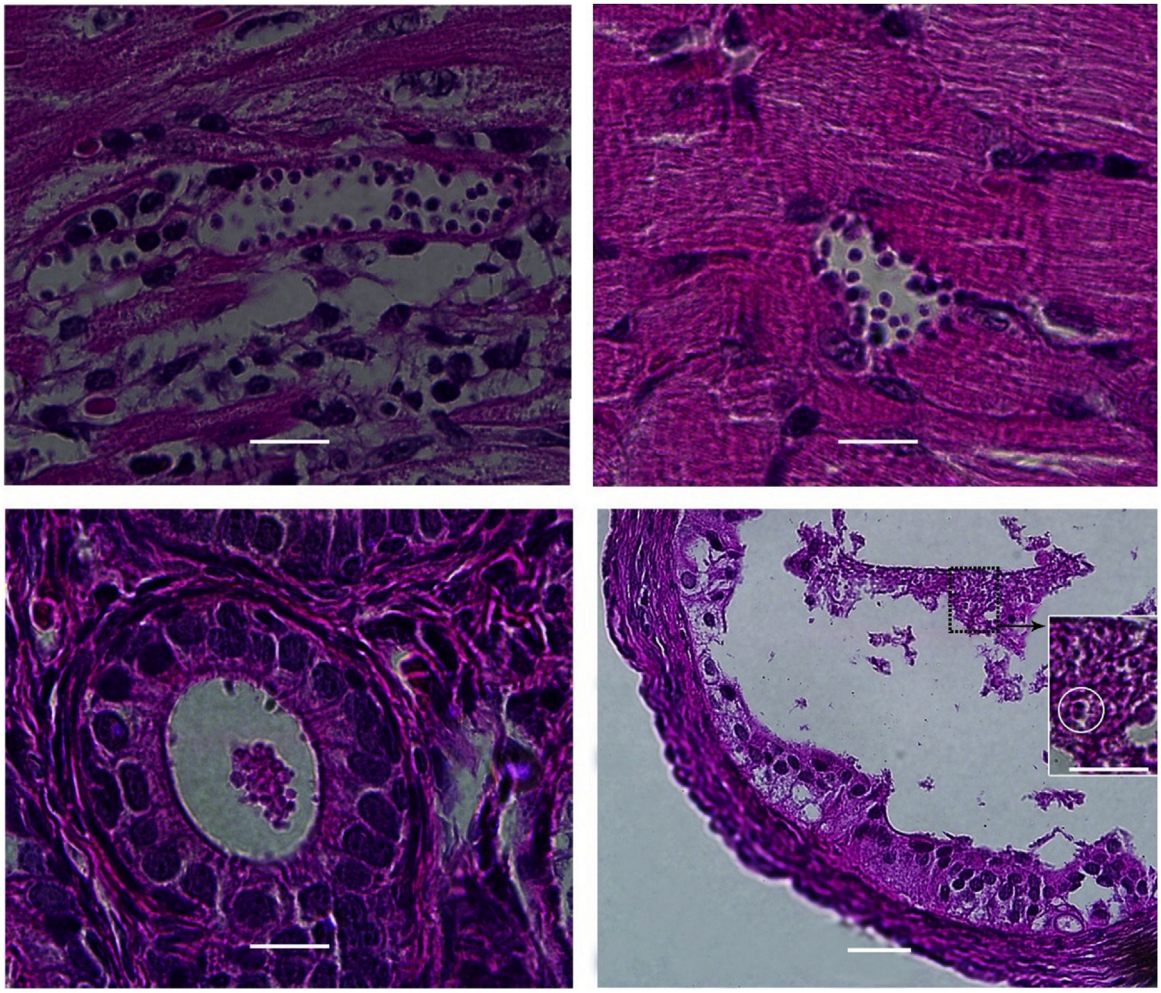

Figure 1. The infectivity of Chagas patient ejaculate shown upon instillation of nDNA-PCR-positive semen aliquots into the vagina of naïve female mice and peritoneal cavity of naïve male mice. Notice the clumps of *Trypanosoma cruzi* amastigotes (arrows) in the heart (top left), skeletal muscle (top right), lumen of the vas deferens (bottom left), and in the epithelial cells of the uterine tube (bottom right). The circle shows a dividing amastigote. Bars, 10 μm. Reprinted with permission from the author and the publisher (Araujo et al., Memorias do Instituto Oswaldo Cruz, 2017).

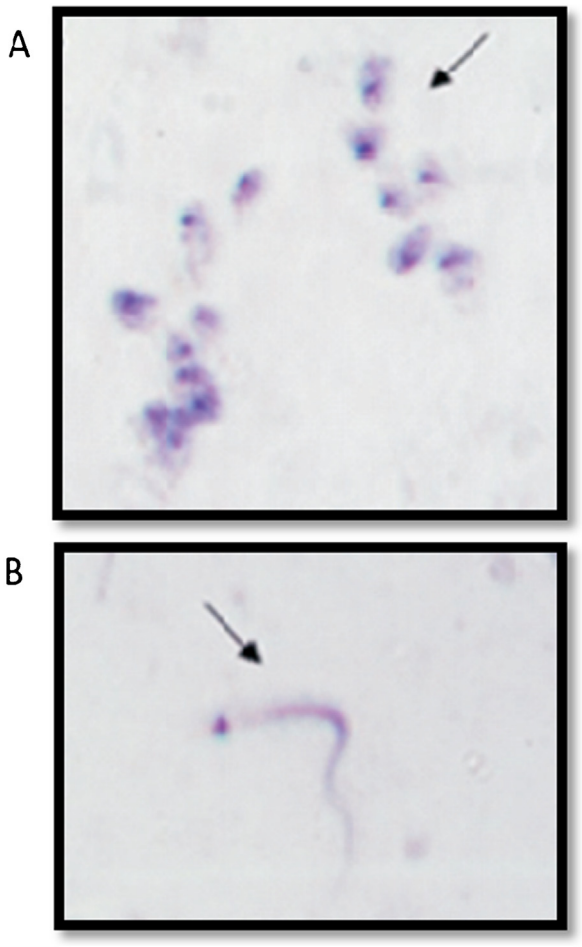

Figure 2. *Trypanosoma cruzi* in semen ejaculate from a chagasic male mouse. The arrows show: (A) amastigotes; (B) trypomastigote. The figure, with modification, is reprinted with permission from the author and the publisher (Alarcon et al., Boletín de Malariología y Salud Ambiental, 2011).

alone could underdiagnose congenital cases of Chagas disease. In consideration of this and for the safety of health facilities, nucleic acid techniques should be employed to discard blood contaminated with the *T. cruzi* 188-nt telomere sequence and from patients with Chagas disease.

The investigations in the mouse model showed *T. cruzi* forms expelled through semen ejaculates (Figure 2), and a further experimental study suggested that males and females could transmit the Chagas parasites present either in semen ejaculate or in vaginal fluid (Araujo et al., 2017; Teixeira et al., 1970).

Moreover, *T. cruzi*-infected male and female mice sexually transmitted *Trypanosoma* parasites to naïve mouse mates in three series of independent experiments (Araujo et al., 2017; Rios et al., 2018): chagasic male and female mice bred naïve female and male founders (F0) that generated F1 progeny, and further breeding generated F2 progeny with nDNA-PCR positive for the 188-nt telomere repeat sequence, thus showing vertically acquired *T. cruzi* infections. The breeding experiments confirmed the absence of *T. cruzi* antibody in 78% of F1 and F2 progeny mice, and pathology revealed *T. cruzi* amastigote nests in the reproductive system (Araujo et al., 2017; Almeida et al., 2018). Several studies have corroborated the sexual transmission of *T. cruzi* infections from male and female mice to naïve mouse mates (Rios et al., 2018; Ribeiro et al., 2016; Martin et al., 2015; Araujo, 2013).

In conclusion, (1) the sexual transmission of *T. cruzi* infections is a potential threat to public health worldwide; (2) specialized clinical centers are needed, because the emergence of Chagas disease can no longer be underestimated; (3) nDNA-PCR confirmed by Southern hybridization, cloning, and sequencing should be used to establish the diagnosis of all *T. cruzi* infections; (4) a high throughput digital platform is needed for the diagnosis of Chagas disease, epidemiological investigations, and to prevent blood contamination; (5) a robust education, information, and communication program should be implemented to prevent sexually transmitted *T. cruzi* infections and Chagas disease; (6) the perspective is that the control of Chagas disease requires international solidarity.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare that no conflict of interest exists.

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