

Chagas Disease: A Parasitic Infection with More than 100 Years of Discovery

María Elizabeth Márquez Contreras

Laboratory of Parasite Enzyme. Science Faculty. University of Los Andes. Mérida, Venezuela

Corresponding author: María Elizabeth Márquez Contreras, Laboratory of Parasite Enzyme, Science Faculty, University of Los Andes, Mérida, Venezuela, Email: emarquez@ula.ve

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Introduction

Chagas' disease (CD) is caused by the protozoan parasite *Trypanosoma cruzi*, and was discovered in 1909 by the Brazilian physician Chagas [1]. *T. cruzi* is transmitted when the infected feces of the triatomino vector are inoculated through a bite site or through an intact mucous membrane of the mammalian host. Vector transmission is the classical form of CD acquisition. This transmission route has the largest impact in Latin American countries and is also responsible for the maintenance of the disease [2]. *T. cruzi* can also be transmitted through blood transfusion, transplant organs, and congenitally [3]. In endemic countries, blood transfusion was considered the second most common way to acquire such parasitosis [4]. This infection has been recognized by WHO as one of the world's 13 most neglected tropical disease, because the people most affected are often poorest population, living in remote rural areas, urban slums or conflict zones. It is an important public health problem not only in Latin America where it is endemic in 21 countries but it is increasingly spreading in other areas such as Europe, North America, Japan and Australia, mainly due to migration [5,6]. Especially with respect to the quality control of serological screening for Chagas disease among blood donors, the occurrence of false positive results may lead to unnecessary disposal of blood units and consequently compromise the blood supply at blood centers [7]. Around 6 million people are affected worldwide and approximately 7000 deaths occur annually, making CD the major cause of death from a parasitic disease in Latin America and a significant contributor to the global burden of cardiovascular disease, with CD the main cause of infectious cardiomyopathy in the world [8]. The migratory trends of infected populations from rural areas to urban centres and/or to non-endemic regions along with changes in the eco-geographical distribution of vector populations have led to the gradual urbanization and globalization of Chagas disease, which is now recognized as an emerging worldwide threat to public health [9]. Latin America has made substantial progress toward the control of Chagas' disease. The estimated global prevalence of *T. cruzi* infection declined from 18 million in 1991, when the first regional control initiative began, to 5.7 million in 2010 [10]. The Pan American Health Organization has certified the interruption of transmission by domestic vectors in several countries in South America and in Central America [11]. The initial phase of Chagas disease is known as Acute Phase starts

when the parasite enters the body and extends for 40-60 days after initial infection. A local reaction known as a chagoma often develops at the point of entry, and a general malaise, with fever, lymphadenopathies, hepatomegaly and splenomegaly. There is sometimes a painless conjunctival reaction, with oedema of both eyelids on one side of the face (Romaña sign), and lymphadenitis of the pre-auricular ganglia. A few cases develop much more severe problems, of acute is occasionally myocarditis or meningo-encephalitis, are occasionally fatal [12]. Following an acute infection, all patients with Chagas disease will enter the chronic stage, for the most, part diagnosed by detecting IgG antibodies that react specifically with *T. cruzi* antigens. About 20% of patients with chronic Chagas disease develop chronic cardiomyopathy many years later. Clinically, Chagas cardiomyopathy manifests by sudden cardiac death (SCD), thromboembolism, precordial chest pain, arrhythmias and conduction defects, and chronic heart failure (CHF). Chagas disease is the most important cause of CHF in areas where the disease is endemic, mainly in patients with the advanced forms of the disease [13]. Diagnostic methods for *T. cruzi* can be included in three main groups: parasitological, serological and molecular. The parasitological diagnosis is to determine the presence of *T. cruzi* in the patient's blood, by smearing, or by culturing (Blood culture) or using non-infected, fed with the patient's blood to look for the parasite in the insect feces (xenodiagnosis). In the chronic phase of infection, the sensitivity of these methods is noticeably reduced due to the low parasitemia. The methods of serological diagnosis can determine the presence of antibodies against *T. cruzi*. The most employed are the enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence, haemagglutination indirect and Western blot. In all of them, the patient's serum is tested against *T. cruzi* (in solution or the intact parasite), considering that if the sample has anti-*T. cruzi* antibodies. The first ELISA evaluated were originally developed using total parasite homogenates or semi-purified antigenic fractions from *T. cruzi* epimastigote (the non-infective forms of the parasite). Diagnostic tests employing epimastigote antigenic extract have a limited specificity, associated to the fact of they do not possess highly reactive epitopes for IgG/IgM antibodies present in patients with acute or congenital Chagas disease [14]. Considerable variation in the reproducibility and reliability of these tests have been reported by different laboratories, mainly these fractions are complex mixtures of molecules that favors the appearance of cross-

reactivity (false positives) with sera from people with other diseases and cross-reactivity with sera from patients bearing other parasites, especially *Leishmania* spp. and *Trypanosoma rangeli* [15]. In addition, this antigenic heterogeneity does not allow the differential diagnosis between the acute and chronic phases and also among the clinical manifestations. Indeed, discrepancies or inconclusive results, such as false-positive reactions caused by cross-reactivity with antibodies induced by other pathogens (mainly *Leishmania*) and false-negatives, may occur [16]. The World Health Organization recommends using at least two of those serologic tests in parallel [17]. The use of well-characterized antigens and their preparation under quality-control conditions have introduced source variability in the final agent, and controversial results have been obtained with the reagents from whole or semi-purified extracts of *T. cruzi* [18]. In view of the problems caused by the use of complete extracts it has been decided to use parasite antigenic fractions purified by technical biochemical. The reported sensitivity and specificity of most of these assays is half. Nonetheless, their actual performance has been found to be somewhat lower [19] and no gold-standard has been identified for an accurate and reliable diagnostic of *T. cruzi* infection. As a consequence, the World Health Organization and most National guidelines in Latin American countries still recommend the use of two tests based on different principles and antigens, and in case of discordance, a third test can provide a final diagnostic [20]. In view of the need to develop quality antigens, be more specific and sensitive and produce more accurate results, in recent years the recombinant DNA technology has been developed. The recombinant DNA technology allowed the generation of parasite DNA or cDNA expression libraries, which were then coupled to high throughput screenings using serum samples from Chagasic patients or experiments infected animals. The molecular diagnostic through PCR is a very important tool to detect the presence of *T. cruzi*, which relies on amplification of DNA of *T. cruzi* DNA sequences in patient's blood samples. The molecular diagnostic provides high sensitivity and specificity. Márquez et al. [21] reported two main target regions of *T. cruzi* DNA amplification: kDNA also called the mini circle, or a nuclear mini-satellite region designated TCZ. Both of these targets are present multiple copies in the parasite genome, which increases the sensitivity of detection. PCR targeted against repetitive *T. cruzi* sequences (330 bp mini circle variable regions on the kinetoplastid genome, K-DNA and intergenic spacer of the spliced leader genes, SLDNA) as a sensitive laboratory test for diagnosis in clinical practice, as has been reported by Diez et al. [22]. Major challenges for the clinical implementation of PCR-based techniques derive from a number of technical factors such as source (i.e., cord blood, umbilical tissue, placental, tissue), volume, conservation and transportation of the samples, and underlying molecular biology protocols (i.e., DNA isolation, purification, pre-treatment, thermo-cycling conditions, etc.) [23]. In addition, the reproducibility and overall performance of PCR-based methods is significantly affected by the fluctuations in parasitemia that characterize the chronic phase of Chagas disease and by inter-DTU variations in dosage and/or sequence of the targets of amplification [24]. Chagas disease remains a major threat in several Latin American countries and an emerging global health problem, despite having more than 100

years of discovery and the enormous medical, economic and social problems it generates. Great efforts have been made in Latin America and other developed countries to halt the transmission of *T. cruzi*. However, one of the key points in the control of Chagas disease remains the diagnosis. Accessible and effective diagnostic tools and methods are needed so that infected persons can be identified in a timely manner and subsequently treated. As discussed here, current diagnostic methods are very accurate in the detection of *T. cruzi* infections in humans. However, there are still some clinical situations in which the diagnostic results are not efficient. Emerging diagnostic tests that integrate new, health-adapted tools will have a significant impact on the effectiveness of current intervention schemes and improve the clinical management of chagasic patients by providing the treating physician with an accurate and effective diagnosis.

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