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Chagas Disease and Transfusion Transmission: A Review

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Abstract

Chagas Disease (CD), caused by *Trypanosoma cruzi*, is a medical and social problem of great importance in Brazil and a serious public health problem in Latin America. The World Health Organization estimates that the *T. cruzi* infection affects about 7 million of people in 15 countries, with an annual incidence of 200,000 cases. In this context, is worth mentioning the main forms of transmission of CD: contaminated excreta of vector (triatomine) at the moment of the blood repast and secondary transmission routes as: Oral intake of food contaminated with triatomine excreta infected, labs accident and blood transfusion. The last one, was a reason of disease transmission to many people until it was discovered that the parasite could be found in the bloodstream of the individual with the disease and during blood transfusion, these infecting forms would be transferred to the blood receiver of a contaminated individual that can be symptomatic or asymptomatic. Evaluating the methods available for the diagnosis of CD, serological tests are methods of choice in clinical laboratories and blood banks, because they have the highest sensitivity coefficients, which allow avoiding with greater reliability the transmission by blood transfusion. However, for the serological control of CD on blood banks, it is necessary to seek tests that show 100% of sensitivity and specificity to protect the blood transfusion receivers, furthermore to identifying a donor as a CD holder, ruling out cases of false positive. Nowadays, the serological diagnosis of Chagas' infection still presents some limitations such as the presence of inconclusive and false-positive results (due to cross-reactions with other parasitic diseases). This is a big concern of blood banks throughout the country, because the tests used today have a great sensitivity, however may erroneously exclude some blood donors able. After some years of discovery of this type of transmission, this subject is considered a public health problem nowadays due to the fact to cause great damage by the discard of supposedly contaminated blood bags; as well causing psychic problems for volunteers who believe have a serious and no cure illness.

Introduction

The Chagas Disease (CD), is an anthropozoonosis that has as etiologic agent the protozoan *Trypanosoma cruzi* (*T. cruzi*), which develops in hematophagous insects of the *Reduviidae* family, in small wildlife mammals and humans [1]. The distribution of the disease was more restrict to South of America, but nowadays it has reached several countries in Europe and even Australia [2].

CD is characterized by two distinct phases: acute, with approximately 60 days of continuance, and the chronic one that has an indeterminate duration. The acute phase can be asymptomatic or present specific symptomatology [3]. The evolution of disease can lead to the chronic phase, which may be asymptomatic or present specific symptoms that will determine the anatomical-clinical forms, among them: Cardiac, Digestive, Mixed (cardiac and digestive), Nervous and in the last decades, the reactivation of CD [4-8]. In the chronic phase, between 20% to 30% of infected patients develop the cardiac or digestive clinical form until 30 years of infection. Besides that, about 20-25% of those infected people present progressive cardiac damage resulting from massive destruction of cardiomyocytes and conducting system, culminating on chronic Chagas' cardiomyopathy [9].

The main transmission path of Chagas' disease is the vectorial, nevertheless recently has been reported an increase in the incidence of contamination by secondary routes, such as accidental transmission in laboratories, congenital, organ transplantation and blood transfusion [10-12]. The vector transmission is due to the presence of metacyclic trypomastigote forms of *T. cruzi* in *Triatoma spp*, being the most common vector found in the human infection *Triatoma infestans* [13]. Due to the fight against triatomines, the rural-urban migration in Latin America and also immigration of Latinos to other countries in America and Europe, the secondary mechanisms of CD transmission have been highlighted, among them the accidental transmission in laboratories, congenital, organ transplantation and blood transfusion and its products, which are responsible for the maintenance of the disease on the present day [14,15].

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In non-endemic regions, without vector, one of the potential means of CD transmission is through the transfusion of blood and its products, due most patients are asymptomatic, often unaware of their condition, and in the case of blood donors may pose a serious threat to the safety of blood supply [16]. Already in endemic regions in Latin America, have been reported transmission of CD by blood transfusion [17-20]. In the years 1991, 1993, 1997 and 2010, seroepidemiological surveys were carried out on workers in the Rio Negro micro-region of the state of Amazonas, and a were found a considerable number of people serologically positive for *T. cruzi* infection [21].

There are a large number of infected people coming from endemic regions migrating to non-endemic countries, increasing the risk of transmission through blood transfusion. Thus, it is necessary a more careful screening of blood donors so that there is no spread of the disease. In the United States, for example, it is estimated at least 300,000 new cases of CD have occurred among people from Latin American countries [22].

An effective strategy to prevent the transmission of CD by blood transfusion would be the leukoreduction, especially in endemic countries and non-endemic countries with high immigration rates from Latin America. Migration of populations from endemic countries to non-endemic countries causes the expansion of disease to regions where vector-borne infection would not occur. This is extremely relevant for CD transmission by blood transfusion [23]. Bolivia established a mandatory blood screening for *T. cruzi* between 1996 and 2002. In this period it was detected and discarded 11.489 units of *T. cruzi*-infected blood and prevented 2.879 potential of infections through blood transfusion [24]. A guideline that is currently followed specifies that all blood donors must go through a questionnaire where they must answer questions about the history of the risk of being contaminated with the CD [25].

In a study carried out with blood donors from 12 Latin American countries, from 1993 to 1994, it demonstrated a positivity rate of 14.8% of *T. cruzi* contamination in Bolivia [26]. Other studies performed in 2002 showed that there were still different contamination rates among donors of blood banks in different countries: about 4.47% in Argentina, 12.4% in Bolivia, 0.62% in Brazil, 0.9% in Chile, 2.81% in Paraguay and 0.47% in Uruguay [27].

An important fact to note is: In all the evaluated countries, except for Bolivia, the positive blood donors are screened for serology [28]. The coverage of the serological examination for *T. cruzi* in blood donors also varies depending on the country: Approximately 6% coverage in Costa Rica, 15% in Mexico, 20% in French Guiana, 28% in Panama, 74% in Nicaragua, 90% in Ecuador and up to 98% in Paraguay, Honduras and Colombia. Brazil has 100% coverage [29].

The transfusional risk for CD can vary, both among endemic and non-endemic countries. There are many differences about the procedures taken by the blood services and the rules that regulating this type of service. The risk is about 1: 46 in Bolivia, 1: 921 in Chile, 1: 4.923 in Ecuador, 1: 403 in Colombia, 1: 1.072 in Honduras, 1: 15.479 in Brazil and 1: 500.000 in the United States [30,31]. Some studies indicate that the risk of infectious diseases transmission through blood transfusion is extremely low in developed countries [32-34].

The rate of blood bags discard due to *T. cruzi* contamination also varies greatly from country to country: 4.4% in Argentina, 0.82% in Brazil, 0.67% in Colombia, 2.5% in El Salvador, 0.09% in Ecuador, 0% in Guyana, 1.53% in Honduras, 0.6% in Mexico, 0.33% in Nicaragua, 0.6% in Panama, 4.34% in Paraguay, 0.2% in Peru, 0.6% in Uruguay and 0.55% in Venezuela [35].

Etiologic Agent and Evolutionary Cycle and Forms of Transmission

T. cruzi is the etiologic agent of Chagas' disease, very common in the Americas, especially in Latin America. It is considered a public health problem because it is closely related to the poorest populations living in the most precarious conditions. The transmitter of this disease, had live restricted to wild ambient, and due to deforestation and the invasion of man in the rural environment, it was included in the epidemiological cycle of the disease. The adaptation of triatomines to human life (domiciliation and colonization) had proved efficient for many species and is considered a primary factor on occurrence and expansion of human Chagas' disease, so the vectorial transmission was established as the primary diffusion mechanism of CD [13,36].

The protozoan that causes the CD performs its biological cycle in vertebrate and invertebrate hosts through various evolutionary forms. On vertebrates, the metacyclic trypomastigotes are eliminated in the vector urine and excretion during or shortly after the blood repast, penetrate on the site of the insect bite and interact with the mucous membrane or macrophages of the skin, at this site occurs the differentiation of the trypomastigotes into amastigotes and the replication the protozoan by binary division simple. Then, the amastigote forms differ in trypomastigotes that are released by the host cell, at this point the parasite may have two major destinations: Either it fall into the bloodstream reaching other cells and organs, for the purpose of fulfilling a new cell cycle, or it is destroyed by immunological mechanisms of the host. The triatomine vectors become infected by ingesting the trypomastigote forms presents in the bloodstream of the vertebrate host during hematophagism. In the insect's stomach, trypomastigotes differentiate into rounded forms, called epimastigotes. In the midgut, the epimastigotes multiply, keeping the infection in the vector. In the rectum, epimastigotes differentiate into the metacyclic trypomastigote form, being eliminated in excretion or urine of the insects [37,38].

The primary mechanism of chagasic infection transmission occurs through triatomine vectors, by the contact of infected insects' excretion with the mucous membranes or skin. Besides this form of infection, there is several other forms of contagion like as blood transfusion, oral (contaminated food), transplacental or in the born canal, laboratory accidents, management of infected animals, organ transplantation, blood transfusion or it products and even by non-triatomid vectors, these are considered secondary mechanisms of infection. Within the secondary mechanisms of infection, the transfusional one stands out, because it presents a high incidence mainly in larger cities and places where the CD is not endemic [39,40].

Expansion of Secondary Transmission and its Relation to Immigration

The spatial distribution of the disease was limited to the American continent, however currently the disease has reached non-endemic countries due to the displacement of infected persons [41]. On this process of expansion, are also taken into account the secondary mechanisms of infection, which is result of the intense globalization

process [42-44]. According to the World Health Organization there are estimated 7 million people infected worldwide, the majority in Latin America [44].

Immigration is the major form to introducing Chagas disease from non-endemic countries as can be observed in some countries on the following data: In 2005 about 483.074 immigrants moved to 15 European countries, of which about 14.009 (2.9%) led the infection. On Australia in 2006, moved 80.522 immigrants, of these 3.059 (3.8%) may have led to infection and in Canada, of the 156.960 immigrants, 5.494 (3.5%) probably led the infection. The United States received 17 million of Latino American immigrants and it is estimated that 340.000 (2.0%) may be infected [13]. On the same year, 24 of 92 babies born in South America, which delivered for adoption on Spain, may have been infected congenitally by *T. cruzi* [45]. These epidemiological data are very important because they highlight a considerable possibility of transfusion transmission, through organ donation, or congenital pathway in non-endemic countries for Chagas disease [46,47].

He probability of CHD infection through transfusion of blood products depends on some factors at the moment of donor blood collection, such as the presence of circulating parasites on the bloodstream (hence the probability of contamination is greatest in the acute phase), volume of blood to be transfused containing the infecting forms, immune status of the receptor (people with decreased immunity have more susceptible), prevalence of *T. cruzi* infection on the region where blood donor candidates live and control measures of the blood to be transfused [48].

Epidemiology of Chagas Disease Cases by Transfusion Transmission

In fifties, when transfusion transmission of CD was confirmed, the mean prevalence estimated to *T. cruzi* reactive serology among blood donors was 8.3%. There was a significant reduction to 6.9% in the seventies, and in the early nineties it reached 3.2%. In 2006, for Brazil, this estimate was 0.21% [49-51]. WHO data, based on the year 2010, estimated the prevalence in the country at 0.18%. This significant decrease in the donors potentially infected by *T. cruzi* is also due to the obligatory clinical-epidemiological and serological screening in most of the endemic countries [51,52].

Brazil has advanced not only on the search for greater security in the transfusion system, but also in the process of haemovigilance, with the establishment of the national system of integration of hemocenters, epidemiological and sanitary surveillance. Thereby, there was an improvement on the investigation of the possible CD cases transmitted by the blood, which are associated with the residual risk of transfusion and transplants, possible failures during the process, candidates screening for donation of tissues or organs. Also in this point, it is worth mentioning that transfusion transmission is characterized in case the person received blood or some blood components untill120 days before the onset of symptoms [44].

This tendency to decrement the risk of transmission from blood transfusions has occurred in other endemic and non-endemic countries too, into a greater or lesser degree. Countries such as the United States, Canada, Spain, France, the United Kingdom, Switzerland and Australia, for example, have already introduced serological screening strategies (universal or selective) in the screening process for blood donors [16].

Pathophysiology of Classical CD

CD is initiated by an acute phase, most frequently asymptomatic, but in some cases it may be symptomatic, presenting specific symptomatology. The general manifestations are fever, localized and generalized edema, polyadenia, hepatosplenomegaly, splenomegaly, and more rarely, heart failure and neurological disorders [37,53].

The most important specific signal of vector infection in the acute phase is the parasite's input port signal, also known as the Romanã sign (when conjunctival) or chagoma of inoculation (when on the skin), evidenced in less than half the cases and within a maximum of ten days after the insect´s bite, regressing after one or two months. The Romanã signal is evidenced by a unilateral swelling of both eyelids, Conjunctival congestion, enlargement of the neighboring lymphnodes and fat tissue cellulite, where there is an abundant presence of intra and extra cellular parasites [37,53]. Exceptionally, some patients may present myocarditis and several changes in the electrocardiogram with diverse severity. Neurological disorders are rare and occur as a result of meningoencephalitis, being more frequent in immunosuppressed patients. In untreated patients, spontaneous recovery usually takes 6 to 8 weeks and may be prolonged for up to 4 months. Thereafter, the disease follows the natural course for the indeterminate or chronic phase (with changes mainly in the heart, esophagus and colon) [48].

After the acute phase, chagasic patient go through a long asymptomatic period, remaining on this situation for 10 to 30 years. This stage is denominated indeterminate phase of illness, which is characterized by positive serological and / or parasitological examinations, absence of signs and symptoms of the disease, the conventional electrocardiogram is normal and the heart, esophagus and colon are radiologically normal. On the anatomo-pathological point of view, there are sereval lesions identical those of the acute phase, but of greater intensity and immunologically there is presence of lithic antibodies [37,48].

After they remain asymptomatic for several years, most patients begin to have symptoms in the cadiocirculatory system (cardiac form), digestive (digestive form), or both (mixed or cardiac-digestive). The following is a brief look at the main forms of chronic chagasic disease.

The cardiac form of CD is the most important because of its high mortality in endemic areas. In chronic inflammation, myocytolysis and fibrosis of cardiac tissues occur progressively, leading to increased organ volume. The main myocardial lesions occur due the significant lesions in the autonomic nervous system (sympathetic and parasympathetic nervous system) and an intense fibrosis of cardiac tissues and exuberant inflammatory exudate in activity, these factors lead to Congestive Heart Failure (CHF) and arrhythmias. Chronic Chagasic cardiopathy has a progressive character and is aggravated by the sequential superposition of inflammation, cellular destruction and fibrosis, generating thromboembolic phenomena. Thrombi may also to form in the lower limbs, from where plunger erupts, be able to lead to the infarction on heart, lung, kidney, spleen and other organs, causing death [37]. When cardiac compensation mechanisms become unable to overcome their deficiencies caused by the disease, the Congestive Heart Failure appears which presents the clinical conditions of effort dyspnea, insomnia, visceral congestion and lower limb edema, evolving into continuous dyspnea and death. Patients with this condition have intense cardiomegaly [37,41].

The digestive manifestations are characterized by possible alterations in all digestive tract, that are generated by nerve plexus lesions and consequent sympathetic neuronal destruction, as result may be detected several alterations on motility and morphology on digestive tract, being the megaesophagus and megacolon the most common manifestations. The main signals and symptoms of megaesophagus are dysphagia, regurgitation, epigastralgia or retrosternal pain, odynophagia, hiccups, ptyalism, slimming, parotid hypertrophy. On megacolon, which often is associated with megaesophagus, there is other manifestations as meteorism and tympanism of the left hypochondrium; Palpable, voluminous and tumor-like sigmoid, due to fecalomas in the advanced stages [37,54].

Cardiac and/or digestive disorders are the most communs, but they are not the only found chagasic patients. A large number of minor disturbs can occur in CD, on liver occurs hepatomegaly and tendency to steatosis occur due to CCI. On biliary and extrahepatic biliary paths have been sporadically reported mega vesicle and mega bile duct, associated with autonomic denervation. On urinary tract was reported the presence of "megas" on the ureters and urinary bladder. On the autonomic nervous system, a number of cardiovascular and behavioral problems are also observed. At the level of the central nervous system there are disorders in nerve transmissions on the brainstem and optic nerve, as well some neuropsychological deficiencies, such as poorer cognitive performance than normal controls [5,37].

Moreover, on immunocompromised patients infected with *T. cruzi* may occur the reactivation of chronic or asymptomatic phase, which starts to assume more severe acute forms than usual, with evident parasitemia. In many cases of patients subjected to organ transplantation occur cases of severe encephalitis or myocarditis with high lethality; therefore those patients have to receive the immunossupressure therapy [37].

Pathophysiology of Transfusional CD

Acute CD is transmitted through blood transfusion, presenting milder signs and symptoms than vector transmission, and does not exhibit the characteristic enter portal signs. General symptoms begin after 20 days of contact with infected blood and can last for up to 140 days. At this time, the metacyclic trypomastigote form can be visualized in the drop thick examination or peripheral blood smear [55]. The disease course begins with high quantity of parasite and the mortality rate can reached between 10 to 15%, depending the parasite strain [56].

Fever is the most frequent symptom, affecting 80 to 100% of cases and is often the only symptom found [48,57,58], that usually does not respond to antibiotics and lasts for 6 to 8 weeks if no specific tripanomicide therapy is administered and is often confused with fever of bacterial origin, especially in surgical patients [59]. Lymphadenopathy and hepatosplenomegaly are also observed frequently in patients affected [48]. Cardiac disorders such as electrocardiographic abnormalities, tachycardia, or reduction of ejection fraction, with or without pericardial effusion or cardiac insufficiency, may be observed, in general more severe or fatal in immunosuppressed patients. The central nervous system can be affected, especially in immunologically debilitated patients, being somnolence, fatigue or tremors the most common symptoms. In immunosuppressed patients, the progression to tonic-chronic convulsions, due the meningoencephalitis, is associated with a worse prognosis. The involvement of the gastrointestinal system in the acute phase is extremely rare. Finally, in about 20% of the cases, no symptoms are observed (asymptomatic infections).

Immune Response of Chagas Disease

The host immunological response is essential for the evolution of CD, being important on the reduction of the parasitic load and contributing to the appearance of chronic manifestations [60]. In immunocompetent individuals, the immune response occurs in three steps: The first one develops during the first two weeks post-infection, before the increasing of parasitemia, and depends on the effector mechanisms of the innate immune response, such as the inflammatory response. The second stage develops on the intermediate and late stages of the acute phase of infection, while there is a decrease in parasitemia and depends on the cellular and humoral components of the acquired specific immune response. The third stage, also dependent on the specific immune response, is maintained throughout the chronic phase of the infection and is responsible for the maintenance of low parasitemia to long term, for strong positive serology and for immunological memory that guarantees resistance to reinfection in the immunocompetent host, but not in immunosuppressed. This latter phase does not occur if the infected individual is treated during the acute phase and is cured parasitologically [60].

The inflammatory response is the initial step of the innate immune response, and the first stage of this initial inflammatory process is the recruitment of macrophages and NK (Natural Killer) cells in the local of parasite inoculation. After passing through the skin, the parasite first activates the innate immune response, where the macrophages and dendritic cells phagocyte the parasite and stimulated by their multiplication, begin to produce cytokines IL-12 and IFN-γ [61,62]. Furthemore, macrophages also produce nitric oxide, generating macrophagic potentiation. The produced cytokines activate the NK cells, maintain the production of IFN-γ and also produce TNF-α, essential in the activation of the macrophage and destruction of the parasites [63].

Then, there is the presentation of antigens on the macrophage membrane, initially for TCD4+ lymphocytes, resulting from Th0 differentiation in Th1. TCD4+ lymphocytes also produce type I cytokines (IFN-γ and TGF-β) with the aim of eliminating the parasite and a cytotoxic TCD8+ response. Finally, activation of T lymphocytes occurs generating IgG antibodies [60,64].

In excess, high levels of TNF-α, NO and IFN-γ can be extremely detrimental to the host itself [65]. Thus, in the experimental situations of resolution of the acute phase, both the acquired immune response, specific anti *T. cruzi*, and the control of innate response activation play a decisive role. The cytokines responsible for this "deactivation" are IL-10 and TGF-β whose synthesis increases. IL-10 begins to be detected three weeks after infection in Balb/c, both with virulent and attenuated strain of *T. cruzi* [66] and presents higher serum levels, precisely in the more resistant model, without tissue injury. The production of IL-10 is required to control the lethal inflammatory effects of type 1 cytokines produced during infection [65] and resistant mice show higher IL-10 production when compared to susceptible [67].

Diagnosis of Chagas Disease

Serological tests, microscopy or PCR-based assays are used for diagnosis of *T. cruzi*, but these methods have sensitivity and specificity limitations. In this way, alternative assays have to be developed in order to increase the reliability of blood bank tests. *T. cruzi* Excreted Secreted Antigens (TESA), are released into the blood of an infected host, so can be used as biomarkers with high specificity [68].

Serological tests performed on blood banks with inconclusive results for CD have a significant impact on blood banks worldwide, where high numbers of blood bags are unnecessarily discarded or pockets of contaminated blood are transfused into patients who require blood. Thus, a promising prospect can be visualized with the possibility to use serum samples for molecular diagnosis, detection of parasite DNA and quantification of the parasitic load by qPCR, suggesting its use in reference laboratories for the diagnosis of patients with CD potentially donors of blood [69]. Blood donors infected with *T. cruzi* can donate contaminated blood without knowledge. Risk factors and presence of *T. cruzi* antibodies in Dutch blood donors have been studied to assess whether specific blood safety measures are warranted in the Netherlands [70].

The diagnosis of CD is made in two stages, observing the clinical manifestations as well as the laboratory abnormalities. The main clinical alterations found in the acute phase are: The presence of portal signal, Accompanied by irregular or absent fever, tachycardia, generalized edema of feet. Already, the chronic phase is characterized by cardiac alterations confirmed on electrocardiogram, and / or the digestive ones, as previously mentioned [37].

The laboratorial tests performed for diagnosis are specific to each stage of disease. In the acute phase, there is presence of high parasitemia, presence of non-specific antibodies and the onset of specific antibodies formation (IgM and IgG) that can reach high levels. Due to the high levels of parasites, parasitological research techniques are recommended, such as: (1) Examination of fresh blood or thick drop (preparation of blades for visualization of the parasite may or may not be stained with Giensa); (2) Blood culture or biopsy of specific material in appropriated mediums and (3) Xenodiagnosis. These parasitological research methods present high sensitivity and can reach 100%, but both blood culture and xenodiagnosis are not recommended since the results take long time to stay ready. The parasitological tests of fresh blood or thick drop are widely used, especially in cases of diagnosis of congenital or transfusional transmission. Even in the acute phase, the diagnosis can be made through of serological methods, such as precipitation reaction or precipitin (this methodology is the most indicated for the acute phase due to its high degree of sensitivity), indirect immunofluorescence reaction and ELISA (Enzyme-Linked Immunosorbent Assay), the last two techniques aim at the investigation of IgM antibodies. In the chronic phase the circulating parasitemia is very low, because the parasites are already allocated in some tissue and the levels of IgG antibodies are high. Thus, at this stage of disease it is recommended for diagnosis the serological tests , within this methodology are mentioned the techniques of reaction of the complement fixation (also called "ax warrior", nowadays it is not used anymore, due the techniques difficulties presented), ELISA, Indirect Hemagglutination (HAI) and Indirect Immunofluorescence (IFAT), showed sensitivity varying from 95% to 100% [50,71]. Parasitological methods such as hemoculture, presented in this phase low sensitivity, varying from 40% to 50% [72,73].

ELISA is an immunoenzymatic test based on the antigen-antibody interaction revealed through a chromogen activated by the specific reaction between enzyme and substrate. In this technique *T. cruzi* antigens are absorbed into microtiter plates wells and the diluted serum (sample) is added subsequently, then the plate is incubated. The antibodies present in the sample bind to the plaque antigens and are revealed by addition of anti-immunoglobulin antibodies conjugated to an enzyme that, in contact with its substrate, donates electrons making the chromogen added change the color. The performance of the different diagnostic kits for chagasic infection has shown a sensitivity of 97.7 to 100% and specificity of 93.3 to 100% [73-76]. Moreover, it has the characteristic of being easy to manipulation and requires a small amount of sample. The results read are made through spectrophotometry, which the intensity of staining is proportional to the amount of specific antibodies present in the sample [50,71,72]. The possibility of automation is one of its greatest technical advantages; therefore it is possible to test several samples at the same time in a 96-well plate, being the most used approach in blood banks.

Indirect Hemagglutination (HAI) is a technique that relies on the agglutination of mammalian or Human blood red cells previously sensitized with *T. cruzi* antigens on the presence of serum containing specific antibodies. This serological test is done on plastic microtiter plates, it is easy to read (Can be made with the naked eye) and has excellent stability even under adverse storage and temperature conditions. If the sample is positive anti-*T. cruzi* antibodies it bind to the red blood cells forming a homogeneous carpet-shaped network occupying an area greater than 50% of the bottom of the plaque. If the result is negative the blood red cells accumulate in the form of a button. Any different result than those cited is said to be indeterminate [71]. HAI is widespread methodology both for the acute phase and for the chronic phase due to its ease of execution, quickly read, no need for additional equipment, low cost and high sensitivity, but presents false positive results in cases of Leishimaniosis [37,71].

The RIFI method was used on the national serological survey because it has high sensitivity, but it presents cross-reactions with other diseases, especially with leishmaniosis. This test is based on interaction of *T. cruzi* epimastigote forms with specific anti-*T. cruzi* antibodies. Currently, this test is considered a reference for the serology of CD, so that methodology is widely used, especially in cases of acute phase diagnosis (natural, accidental or transfusional) and congenital transmission, through IgM screening [37,71].

The reaction is done as follows: In a glass slide, where epimastigote forms of *T. cruzi* are fixed, a diluted sample is added that may or not contain specific antibodies. Subsequently, the conjugate, composed of a human anti-immunoglobulin bound to fluorescein isothiocyanate, is added and will serve as a revealing of the antigen-antibody reaction. This reaction is evidenced by fluorescence of the antibodies, observed by a specific microscope for detection of fluorescence [37,71]. The standardization of the reagents allows a high reliability of the results.

Hemoculture is a parasitological technique used in specialized services to define anti-parasitic therapy it will be used, cure control and diagnostic confirmation. It consists in sow the patient blood with suspicion of CD, previously collected in tubes with anticoagulant and centrifuged, in specific *T. cruzi* culture medium (LIT medium). The

culture tubes are maintained at 26-28°C and homogenizing weekly. They are examined once a month, up to 90 days, investigating the presence of *T. cruzi* epimastigote and trypomastigote forms [74].

There are also other techniques for the detection of *T. cruzi*, such as the Polymerase Chain Reaction (PCR), which is a confirmatory method, and consists of the amplification of DNA fragments of the parasite, present in patient samples of blood, serum or tissues. This technique is highly sensitive because it is able to detect amounts of DNA from a single cell of the parasite. On this technique, from the patient material obtained, the DNA is extracted, and subjected to PCR using more three components: The primers (complementary to the parasite DNA sequence), the enzyme taq DNA polymerase and dNTPs. The amplification of the DNA segment occurs in the thermal cycler. DNA copies increase exponentially with each reaction cycle, and subsequently can be visualized in polyacrylamide or agarose electrophoresis gel [68,73,78,79].

Evaluating all the methods available nowadays for the CD diagnosis, serological tests are the most widely used method of choice, both in clinical laboratories and in blood banks, because they present the highest sensitivity coefficients, a higher technical accuracy and greater accessibility. However, with regard to the serological diagnosis of CD in the public blood banks, it is still necessary to search for tests that present 100% sensitivity and specificity, with the purpose of greater protection of both the recipient and the donor, reducing the chances of CD transfusional transmission and also to avoid misidentification of false positives in potential donors [80].

Because of the necessity of sensitivity and specificity improvement and better performance many antigens have been tested. Then, in 1980s, emerged the technique of purification of antigens, but the purification and production of these antigens is a difficult and expensive task. However, with the construction of parasites DNA genomic libraries, *T. cruzi* specific recombinant antigens have been tested through ELISA showing excellent performance [81-84]. Nevertheless, some of these antigens have been used with less frequency, for technical and economic reasons [84]. The use of only one recombinant antigen should no diagnosticate some individuals with chagasic infection, showing that the test with this conformation may have decreased sensitivity. Thus, the authors recommend the use of various recombinant antigens for plaque sensitization.

Some studies show improved of the sensitivity when recombinant antigens were associated [82,85]. Despite the existence of serological tests presenting desirable performance (high sensitivity and specificity), there is a necessity for confirmation of inconclusive results. Thus, Western blot is the technique of choice for this purpose, because PCR still requires standardized protocols and presents a sensitivity of only 80% [76,86]. TESA-blot employs excretory antigens that are secreted, originated from *T. cruzi* trypomastigotes of strain Y transferred to the nitrocellulose membrane, where antibodies (sample) can bind and be revealed by the addition of anti-IgG antibodies conjugated to enzyme. TESA-Blot was defined as a sensitive method in cases of acute and congenital CD presenting 100% sensitivity and 96% specificity [55].

Prevention of Transfusional Chagas Disease

The strategies used to prevent transfusional CD are mainly three [48]:

(1) The anamnesis and questionnaire to the donors (currently the donation is a voluntary act in Brazil), in endemic regions specific questionnaires should be applied so the first screening can be done, Removing from the donor list persons who have already been bitten by the barber, who live in houses that are infested by triatomine or that have previous positive serological tests.

(2) The second measure is the performance of the serological tests. Currently, there are several methodologies available for serological screening. Complement fixation was replaced by HA, IF or ELISA, although no method can be considered as 100% sensitive, the last one being more accurate and more efficacious. On the other hand, false-positive results are also reported, in the order of 0.1 to 4.0% for HA and ELISA and up to 30% for IF [48,85].

(3) Chemoprophylaxis: Among the several compounds that have already been tested, only Violet Crystal (Gentian Violet) is the only in vivo agent actually recognized as effective. Violet crystal eliminates totally the viability of *T. cruzi* in 24 hours of exposure at a concentration of 1: 4000 or 200 g/mL. It is potentiated by light and ascorbic acid, reducing both the exposure time (20 minutes) and the final concentration [68,69]. The main alteration of Violet Crystal occurs on platelets, perhaps by direct action on the metabolism of Calcium in mitochondria. However, its use is questioned because of the high toxicity to the host [48].

Final Considerations

The main route of transmission of CD is vectorial, however, there has been an increase on the incidence of contamination by secondary routes, such as accidental transmission in laboratories, congenital, organ transplantation and blood transfusion. Due to the combat against triatomines, rural-urban migration in Latin America as well as immigration of Latinos to other countries in America and even in Europe, the secondary mechanisms of transmission of CD have been highlighted, among them: Accidental transmission in laboratories, congenital, organ transplantation and via transfusion of blood and blood products, which are the pathways responsible for the maintenance of the disease in the present day.

In Brazil, the emergence of transfusion contamination was proved on fifties. At the beginning of the 1980s, there was an alarming increase in cases of transfusion contamination, followed by a significant decrease in the last decades, but it is still a matter of great concern in blood banks, because the serological diagnosis of chagasic infection still presents technical limitations regarding the presence of inconclusive and false-positive results (due to cross-reactions with other parasitoses). This is an important point for the country's blood banks because these tests are highly sensitive and may be excluding mistakenly suitable blood donors.

Although CD is considered controlled due to the strategies of vectorial and transfusion control, even today, acute cases are being reported, mainly by oral and congenital transmission, leading to concern for the resurgence of the disease. Thus, there is a necessity to the development of more effective serological diagnostic methods for the acute phase, especially rapid tests, that can be used in difficult to reach places, as well as the development of policies to prevent transfusion transmission.

A critical point in relation to the CD patients is the treatment. Currently, CD therapy is partially ineffective, due the differences

in susceptibility of *T. cruzi* to the available medications; therefore a continuous treatment regimen is necessary. Wherefore, the medicines used nowadays have many side effects and high toxicity to the host.

Other therapeutic methodologies have been continuously studied to assuage the toxicity and the undesirable effects of the drug and also to increase its effectiveness against the parasite. Therefore, in view of the high morbidity and mortality caused by CD, the toxicity and limited efficiency of the currently available treatment, it is extremely important to develop new, less harmful and more efficient methods and therapeutic regimens.

Another important point to be approached is the preventive measures regarding transfusional CD, a good patient history (excluding possibly infected patients) and serological screening, through more effective serological methods (such as indirect hemagglutination, ELISA and Immunofluorescence) are the best ways to conduct a safe donation process, avoiding discarding suitable donors and also minimizing the chances of the patient receiving the blood donation to be contaminated.

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