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Chagas Disease, a Review of the Literature

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ABSTRACT

Chagas disease is a vector-borne (triatomine) infection caused by the protozoan parasite *Trypanosoma cruzi*. Synonyms for this disease are: American trypanosomiasis, Chagas disease and *T. cruzi* infection. [10, 5]

The most common form of transmission of Chagas disease is through hematophagous triatomine insects (triatominae), which develop in dwellings in precarious conditions, The disease can also be transmitted by blood transfusion, organ transplantation, oral and congenital routes, and even more rarely by exceptional routes such as sexual contact and non-Triatominae vectors. American Trypanosomiasis is endemic in much of Mexico, Central and South America [1,11]. it is estimated that ~6 million individuals are infected throughout Latin America, while ~300,000 are infected in the U.S.[1, 10, 11,16]

Chagas disease has two clearly differentiated phases. Initially, the acute phase lasts about two months after infection, they may have a skin lesion or a purplish swelling of an eyelid, they may have fever, headache, enlarged lymph nodes, pallor, muscle aches, shortness of breath, swelling, and abdominal or chest pain. During the chronic phase, the infection can cause sudden death due to cardiac arrhythmias or progressive heart failure due to destruction of the cardiac muscle and its innervations. [15]

Appropriate diagnostics for acute infection, nucleic acid amplification testing (NAAT) from blood is recommended; For chronic infection, serological testing is employed. Antitrypanosomal agents, benznidazole and nifurtimox, have shown efficacy in treating *T. cruzi* infection, The most serious complication is chronic chagasic heart disease, since it is the main cause of death in sick patients. [16]

Palabras clave: Chagas disease, American trypanosomiasis, triatomine, chagoma.

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INTRODUCTION

Chagas disease is a complex parasitic infection caused by the protozoan parasite *Trypanosoma cruzi*. The disease is designated one of six neglected parasitic infections in the United States by the Centers for Disease Control and Prevention (CDC) and one of sixteen neglected tropical diseases by the World Health Organization. [16]

Human infection is highest in some rural areas of continental Latin America, where the triatomine vector infests houses and peridomestic settings. [16]

Antitrypanosomal agents, benznidazole and nifurtimox, have shown efficacy in treating *T. cruzi* infection, but the courses are long (2 months), and side effects (dermatologic and gastrointestinal) are common. [16]

CHAGAS DISEASE

Chagas disease is a vector-borne (triatomine) infection caused by the protozoan parasite *Trypanosoma cruzi*. Synonyms for this disease are: American trypanosomiasis, Chagas disease and *T. cruzi* infection. [10, 5]

It was described in 1909 by Carlos Chagas in Minas Gerais, Brazil. Today it represents a serious health problem in Latin America and is an emerging disease in non-endemic countries.[10.]

ETIOLOGY

The most common form of transmission of Chagas disease is through hematophagous triatomine insects (triatominae), which develop in dwellings in precarious conditions, inhabiting mainly in cracks and roofs of houses built with mud and branches (in its domestic variety); and in the wild variety in tree hollows, rocks, burrows, palm trees, etc.

Therefore, people living in rural areas are more susceptible to infection. The disease can also be transmitted by hemotransfusion, organ transplantation, oral and congenital routes, and even more rarely by exceptional routes such as sexual contact and non-Triatominae vectors.[10,11]

In immunodeficient persons, such as those with acquired immunodeficiency syndrome (AIDS), the disease is particularly severe.[11]

EPIDEMIOLOGY

American Trypanosomiasis is endemic in much of Mexico, Central and South America and has also spread in recent decades to non-endemic regions, particularly to the European Union and the United States, through the migration of thousands of infected people, thus globalizing the disease.[4,11]

The infection is not endemic in any of the Caribbean islands. About 8 million people are chronically infected with *T. cruzi*, approximately 56,000 new infections occur each year, and about 12,000 people die of the disease each year. About 300,000 immigrants with Chagas disease currently live in the United States. it is estimated that ~6 million individuals are infected throughout Latin America, while ~300,000 are infected in the U.S.[4,16]

Since January 2007, donated blood in the United States of America has been screened for *T. cruzi.* The overall prevalence of *T. cruzi* infection among donors is one per 29,000 and 1,200 infected donors have been identified to date.[3, 4]

Epidemiology in Mexico.

Thirty-two species of transmitting triatomines have been identified in the Mexican Republic, 23 are exclusive to the country; currently, 13 species of epidemiological importance have been identified due to their vectorial capacity and distribution, among which Triatoma barberi, T. dimidiata and M. pallidipennis stand out. It is estimated that in Mexico two thirds of the territory have the conditions for vectorial transmission to take place.[12, 2]

The Pan American Health Organization (PAHO), in 2006, estimated that in Mexico there were approximately 1'100,000 infected individuals and 29'500,000 at risk of contracting the infection. In the period 1995-2013, 6,494 cases of Chagas disease were officially reported and 496 deaths from the disease were registered from 1982 to 2010. Most of the reported cases correspond to adults aged 25-44 years, followed by 45-64 years, showing a higher mortality in individuals older than 45 years. The states with the highest incidence were Veracruz, Morelos, Oaxaca, Yucatan, Chiapas, Guerrero and Jalisco with 729 new cases in 2014. [3, 14]

In 2015, 1,081 cases were reported in the republic according to the Epidemiological Bulletin of the Ministry of Health, and in 2016, 805 cases were reported, corresponding to 515 males and 290 females. [2, 3, 14]

Epidemiology in Jalisco.

In Jalisco, eight species of Triatoma were identified in 2008 in domestic environments. The main vectors are, in order of importance, T. longipennis, T. pallidipennis and T. barberi, while T. picturata, T. mazzottii and T. dimidiata are secondary species. One of the municipalities where more specimens have been identified is the Ameca Valley, with T. longipennis being the dominant species. [7]

In 2016, according to the Epidemiological Bulletin of the Ministry of Health, 83 cases were reported in Jalisco, of which 43 corresponded to men and 40 to women. [7]

LIFE CYCLE OF *TRYPANOSOMA CRUZI.*

The causative agent of American trypanosomiasis, as mentioned above, is *Trypanosoma cruzi*, transmitted by several species of blood-sucking triatomine bugs, kissing bugs or vinchucas. These insects become infected by sucking the blood of infected humans or other mammals, ingesting with the blood the circulating parasite in the form of trypomastigotes (infectious form of the parasite). [4, 3]

Ingested parasites multiply in the midgut of insects as epimastigotes (the form in which the parasite multiplies), which are flagellates of a different morphological type, and in the hindgut are transformed into infective metacyclic trypomastigotes which are released along with the feces when the triatomine subsequently ingests blood.[1,3]

Transmission to a second vertebrate host occurs when the triatomine bites the human (usually at night) and deposits feces with infective metacyclic trypomastigotes in the wound, mucous membranes or conjunctiva.[4]

The parasites then enter the various cell types of the host, transform into amastigotes and multiply by binary fission in the cytoplasm of these cells. When the multiplying amastigotes fill the host cell, they differentiate into trypomastigotes and the cell ruptures. [3]

Released parasites invade local tissues or spread hematogenously to distant sites, thus initiating further multiplication cycles, mainly in muscle cells (including cardiac muscle), lymphoid tissue and nerve cells.[3, 4]

PATHOPHYSIOLOGY

During the acute phase and as the first manifestation, in some cases an inflammatory lesion called chagoma appears, which corresponds to the site of entry of the parasites. [4, 5]

Histologically there is intracellular parasitism of the muscles and other subcutaneous tissues, lymphocytic infiltration, interstitial edema and hyperplasia of the lymph nodes draining the area. Muscles, including the myocardium, are the most parasitized tissues, but any tissue may be invaded. [4, 5]

Myocarditis may develop in association with focal areas of infected cardiomyocytes, inflammation and necrosis. Pseudocysts, which correspond to host cells filled with the parasite in the form of amastigotes, are characteristically found in infected tissues. In some patients *T. cruzi* can be found in the cerebrospinal fluid (CSF).[1, 5]

The heart is the most affected organ in chronic Chagas disease, bilateral ventricular dilatation may occur, more frequently on the right side of the heart, thinning of the ventricular walls, apical aneurysms and mural thrombi, generalized lymphocytic infiltration accompanied by diffuse interstitial fibrosis and myocardial cell atrophy. Chronic inflammation affects the conduction system and causes a variety of rhythm disturbances, including atrial bradyarrhythmias and fibrillation; premature ventricular contractions; bundle branch block, often of the right bundle branch; ventricular tachycardia; and third-degree atrioventricular block. [4, 5]

SYMPTOMATOLOGY

The incubation period is usually 5 to 14 days after exposure to triatomine feces, and 20 to 40 days if it was a blood transfusion infection. A large number of cases are reported to be asymptomatic until the chronic stage, which may occur 5 to 40 years after infection. [15]

Chagas disease has two clearly differentiated phases. Initially, the acute phase lasts about two months after infection. During this acute phase a large number of parasites circulate in the bloodstream. In most cases there are no symptoms or symptoms are mild and non-specific. [15]

In less than 50% of people bitten by a triatomine bug, a characteristic initial sign may be a skin lesion or a purplish swelling of an eyelid. In addition, they may have fever, headache, enlarged lymph nodes, pallor, muscle aches, shortness of breath, swelling, and abdominal or chest pain. [15]

During the chronic phase, the parasites remain hidden mainly in the heart and digestive muscle. Up to 30% of patients suffer cardiac disorders and up to 10% have digestive (typically enlargement of the esophagus or colon), neurological or mixed disorders. Over the years, the infection can cause sudden death due to cardiac arrhythmias or progressive heart failure due to destruction of the cardiac muscle and its innervations. [15]

Acute phase.

Generally this period is asymptomatic and more frequent in young people under 15 years of age. It begins at the time of inoculation of the parasite and the inflammatory reaction may lead to chagoma, which occurs during the first 15 days. If entry occurs through the ocular mucous membranes, painless edema of one or occasionally both eyes may occur, often accompanied by conjunctivitis and enlargement of local lymph nodes, known as Romaña's sign, although it is a characteristic sign, it is very rare.[13]

This stage is characterized by the fact that parasites can be easily found in the blood because of the high parasitemia and parenchymal tissue invasion that occurs at this stage. [13]

It can occur at any age, but is more frequent in children. Symptomatic patients present: fever, gateway clinical signs (chagoma/Romaña's sign), satellite lymphadenopathy (mainly pre auricular), cardiac involvement, hepatosplenomegaly. Fever is frequent and irregular, but can be continuous and high. It is accompanied by anorexia, asthenia, myalgias, headache and occasionally arthralgias. The febrile picture may persist for a period of 2 to 4 weeks.[13]

Acute Chagas disease is usually benign in immunocompetent patients. The case fatality rate is 2-7%. However, complications such as acute myocarditis or meningoencephalitis may occur, mainly in children, the elderly and immunocompromised subjects (in the latter, due to reactivation or acute infection).[13]

Chronic phase:

This phase begins when parasitemia drops to undetectable levels and general symptoms and any clinical manifestations of acute myocarditis or meningoencephalitis disappear. These parasitological and clinical changes usually occur 4 to 8 weeks after infection.[13]

A large portion of patients enter an asymptomatic phase, of variable duration (years), with no detectable parasitemia. About 20-30% of chronically ill patients will develop complications characterized mainly by irreversible visceral involvement, characterized by organ failure, usually of the heart or digestive system (megasyndromes).[13]

Heart disease is the most common chronic form of Chagas disease and can present as arrhythmias, conduction abnormalities, heart failure, apical aneurysms, embolisms leading to stroke and pulmonary accidents, and even sudden death.[13]

Abnormalities of the digestive system may cause: megaesophagus or megacolon, which may be a consequence of heart disease. Symptoms of megaesophagus may include: dysphagia (mainly with dry, solid and cold foods), excessive salivation, reflux and chest pain. In severe cases, there may be weight loss or cachexia, and esophageal rupture. Symptoms of megacolon include severe constipation, which may last for a few days or months, and abdominal pain that is often associated with episodes of constipation. In some cases, the abdomen may distend asymmetrically, and in these cases, complications such as intestinal obstruction, volvulus, fecalomas, ulcers or perforation with peritonitis may arise.[13]

- It is important to consider that women infected by this parasite may give birth to infected children. Congenital infections can occur during any of a woman's pregnancies, regardless of whether she is symptomatic or not. In general, most infected newborns are born asymptomatic (70-80%).[15]
- The most frequent symptoms in congenitally infected children are premature birth, hepatosplenomegaly, meningoencephalitis, retinal changes, acute myocarditis or heart failure. These transplacental infections are also associated with miscarriages.[15]
- AIDS patients present with a much more severe form of the disease, with a high percentage of neurological and cardiac signs. Many of these patients develop *T. cruzi* brain abscesses. Immunocompromised patients are at risk of reactivation of parasite replication.[15]

Inderteminate phase:

This phase represents 50 - 70% of all people with Chagas disease between 20 - 50 years of age. [13]

It is characterized by the absence of cardiac, digestive and other symptoms. However, they are infected (positive serological tests), although routine laboratory tests are normal. About 30% of these patients remain in this form throughout their lives. The remainder may progress to the chronic form within 10 to 30 years.[13]

DIAGNOSIS

Appropriate diagnostics for *T. cruzi* infection are dependent on the presentation, which can be broadly categorized as acute versus chronic. For acute infection, nucleic acid amplification testing (NAAT) from blood is recommended; it has largely replaced peripheral blood examination due to increased sensitivity. For chronic infection, serological testing is employed, given that the sensitivity of NAAT drops below 50% in most cases.[16]

Laboratory diagnosis of *T. cruzi* infection can be made by:

- Direct methods that test for the presence of the parasite in the sample.

a) Fresh microscopic observation (peripheral blood): identifies the presence of trypomastigotes.
b) Peripheral blood examination
c) Microstrout concentration method: it is the microscopic examination of the leukoplatelet fraction of whole blood from a microhematocrit capillary loaded with the patient's blood.Método de concentración
d) Xenodiagnosis: its objective is to detect trypomastigote forms in triatomine droppings after infected blood suction, using nymphs of insects free of infection.[8]

- Molecular methods in which the presence of genetic material of the parasite in the sample is tested.

a) Polymerase chain reaction. It is useful to be used in different types of samples and tissues in acute, chronic and indeterminate phase.
b) Indirect methods that detect the presence of specific antibodies against the parasite in the sample.
c) Indirect hemagglutination: this method is based on the reaction of red blood cells sensitized with *T. Cruzi* that come into contact with specific Ac of the parasite producing agglutination.
d) ELISA
e) Indirect immunofluorescence.
f) Western Blot (immunoelectrotransfer).[8]

There are optimal periods for sample collection according to the stage of evolution of the disease:

In the acute stage, direct methods should be performed early after the primary infection occurred, while indirect studies should be performed after 15 days.

In the chronic and indeterminate stage, indirect or serological methods can be performed at any time during the chronic stage. Direct and molecular tests can also be useful, although they have a reduced sensitivity due to fluctuations in parasite load.[13]

According to the Mexican Official Standard, in the chronic symptomatic phase, in addition to serological studies, parasitological diagnosis, indirect xenodiagnosis and blood culture should be considered.[9]

All patients with *T. cruzi* infection, regardless of age or the absence or presence of cardiovascular symptoms, should undergo a conventional 12-lead electrocardiogram (ECG), if possible, with long DII, chest teleradiography in posteroanterior projection (PA) and transthoracic echocardiography (ECHO).[12]

TRATAMIENTO

Early stage Chagas disease can be treated with antiparasitic drugs. Treatment for acute or congenital disease is recommended to prevent it from progressing to a chronic state. Antiparasitic drugs are ineffective for indeterminate or chronic disease and treatment recommendations may vary with the age of the patient and other factors. There are significant side effects with these drugs, which must be administered on a long-term basis. [15]

In the chronic stage, treatment of cardiomyopathy is mainly symptomatic and similar to the treatment of other causes of heart disease. Pacemakers may be necessary, and the need for heart transplantation may be considered. Surgery, balloon dilatation of the gastroesophageal junction or symptomatic relief may be used for megaesophagus or chagasic megacolon.[15]

Chemotherapeutic treatment suppresses parasitemia and may be curative in the acute phase of the disease:

- Nifurtimox in doses of 8 to 10 mg/kg/day for 30 to 120 days.
- Benzodinazole in doses of 5 to 7 mg/kg/day. [15]

Its most significant side effects are: gastric intolerance, peripheral neuritis, dermatosis and leukopenia. [2]

In Mexico, treatment is indicated in cases of acute infection, in children and young people with recent chronic infection, in young people and adults with positive serology up to the age of 60 years.[2]

In subjects over 70 years of age, treatment is not suggested due to the risk-benefit ratio at this age; in these cases, follow-up and etiological treatment are considered.[2]

COMPLICATIONS

The most serious complication is chronic chagasic heart disease, since it is the main cause of death in sick patients. The most frequent symptoms are palpitations and dyspnea on exertion. The evolution of the cardiopathy is heart failure. Arrhythmias are frequent and varied, representing signs of poor prognosis. The progression of Chagasic heart disease to heart failure is about 25%.[8]

PROGNOSIS

Morbidity and mortality rates vary according to the stage of the disease. Approximately 5% of infected persons develop acute symptoms.Estimates on the case fatality rate for acute Chagas disease vary from less than 5 - 8% in immunologically competent persons, with deaths occurring primarily in children with acute myocarditis or meningoencephalitis.[15]

CDC reports estimate that 20-30% of humans infected with this parasite develop the chronic form. The reason why the disease evolves in some patients and not in others is unknown. It is possible that this is related to genetic factors of each patient, the dose of the parasites, the number of inoculations, the strain, and immunological or nutritional factors. Heart disease is usually fatal. Occasionally, deaths can also be caused by volvulus from a dilated sigmoid megacolon.[6]

PREVENTION

According to the World Health Organization, there is no vaccine against Chagas disease. The most effective method of prevention in Latin America is vector control. Screening of donated blood is necessary to prevent infection through blood transfusions and organ donation. [13]

Originally (more than 9000 years ago), *T. cruzi* only affected wild animals; it was later that it spread to domestic animals and humans. Because of the large number of wild animals that serve as a reservoir for this parasite in the Americas, it cannot be eradicated. [13]

Instead, control objectives are to eliminate transmission and to ensure that infected and sick people have early access to health care.

T. cruzi can infect several species of triatomine bug, the vast majority of which live in the Americas. Depending on the geographical area, WHO recommends the following prevention and control methods: [13]

- Spraying of houses and their surroundings with insecticides.
- House improvement and cleaning to prevent vector infestation.
- Personal preventive measures, such as the use of mosquito nets;
- Good hygienic practices in food preparation, transportation, storage and consumption.
- Screening of donated blood.
- Screening tests on donated organs, tissues or cells and their recipients.
- Screening of newborns and other children of infected mothers for early diagnosis and treatment. [13]

DISCUSSION

Chagas disease, an infection by the causative agent *Trypanosoma cruzi*, is considered a neglected tropical disease worldwide, considered endemic in Latin America, estimating up to 6 million infected persons, and present but not endemic in the United States, estimating 300,000 infected migrants. [1, 11, 16]

Transmission has been reported through various routes: Inoculation by triatomines, being the most common; blood transfusion, organ transplantation, oral transmission, congenital, sexual transmission. [10,11]

In its most common route of transmission, it is vector-borne by a triatomine arthropod of the *Reduviidae* subfamily. The entry point of infection originates when the triatomine ingests blood and subsequently defecates on the wound; transmission is enhanced by the triatomine's salivary proteins. [16]

In Mexico, 32 species of transmitting triatomines have been identified, 23 are exclusive to the country; currently, 13 species of epidemiological importance have been identified due to their vectorial capacity and distribution, among which *Triatoma barberi, T. dimidiata and* M. *Pallidipennis* stand out.[2, 12]

The incubation period is 1 to 2 weeks, during this phase may manifest with unilateral periorbital swelling by conjunctival transmission, known as Romaña's sign, or as a subcutaneous nodule, known as a chagoma, if located elsewhere on the body. The acute phase lasts 4 to 8 weeks and is usually asymptomatic or has nonspecific symptoms such as fever, malaise, and hepatosplenomegaly. Chronic infection is lifelong if treatment is not established. Spontaneous clearance has been reported in rare cases. Chronic infection is asymptomatic and can only be detected by antibodies to *T. cruzi*. 20-30% of individuals develop chagasic cardiomyopathy and/or gastrointestinal motility disorders decades after infection. [16]

CONCLUSION

Chagas disease, also known as American Trypasonosomiasis, is a tropical disease endemic in Latin America and mostly transmitted by triatomine vectors, of which *Triatoma barberi*, *T. Dimidiata* and *M. Pallidipennis* stand out epidemiologically in Mexico. Currently, the disease has become globalized due to the migration of infected people to areas such as the United States of America and Europe.

Despite the existence of characteristic signs of the infection such as Chagoma and the Romaña´s sign, this disease can be asymptomatic in each of its phases, so that establishing a diagnosis can be a difficult task for a physician.

It is extremely important for health personnel to have a thorough knowledge of the clinical, epidemiological, diagnostic, and therapeutic characteristics of this disease, in addition to widely informing people living in endemic areas about the prevention methods that can be carried out. Establishing a timely diagnosis and treatment should be the main objective when dealing with this disease, in order to avoid highly lethal complications such as chronic Chagasic heart disease.

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