

Chagasic Cardiomyopathy

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Abstract

Chagasic cardiomyopathy (CC) is a result of low intensity, but incessant, focal fibrosing myocarditis caused by persistent *T. cruzi* infection, associated with inflammation mediated by adverse immune mechanisms. About 30% of those infected develop chronic Chagas disease with multiple clinical manifestations, including sudden death, signs and symptoms of congestive heart failure, cardioembolic events, arrhythmias, and angina. Sudden death and progression of heart failure (HF) are the most common death mechanisms in this condition. The most relevant prognostic aspects are symptoms of advanced HF (NYHA CF III/IV), cardiomegaly, left ventricular systolic dysfunction and unsustained ventricular tachycardia. The prevention of cardioembolic events is an important aspect in the management of patients with CC.

Oral anticoagulant agents should be indicated for patients at high risk, according to the presence of a group of risk factors: Presence of apical aneurysm, HF, cardiac arrhythmia and female. The treatment of HF in chagasic cardiomyopathy follows the same principles applied to HF secondary to dilated cardiomyopathy of other etiologies.

Keywords: Infectious disease; Cardiomyopathy; Neuropathy; Immune-inflammatory

Introduction

Chagas disease or American trypanosomiasis is an infectious disease described in 1907 by the Brazilian physician Carlos Chagas. It is an endemic disease in several regions of Latin America, from Argentina to Mexico, and is also seen in areas of the southern United States. It is estimated that there are around 20 million people infected by the causative parasite, with an annual incidence of 300 thousand cases of infection, and 50 thousand annual deaths due to this disease.

Chagasic myocarditis is the most common form of cardiomyopathy in Latin American countries. The losses that the disease generates annually are estimated in 750,000 years of productive life, constituting a serious public health problem for the endemic areas [1,2].

Etiology, physiopathology and pathogenesis

The disease is caused by the *Trypanosoma cruzi* (*T. cruzi*), in honor of the Brazilian sanitarian Osvaldo Cruz, a protozoan human parasite, of wild and domestic animals, found only in America.

T. cruzi has as vectors of transmission many species of the subfamily Triatominae (barbers), which are hematophagous reduviid insects of nocturnal habits that become infected when it chews and ingests the blood of animals or the man, contaminated with trypanosomes. The vectors are found in domestic and peridomestic environments, making their nests in wall crevices, common in taperas made of stick, typical in endemic places. The insects ingest the parasite in its first evolutionary form, named trypomastigote. In the intestinal lumen of the triatomid the transformation occurs in the second evolutionary form: the epimastigote, which will multiply, generating the third evolutionary form: the amastigotes. New infective trypomastigotes are formed,

which will be excreted in the feces of the "barber" during the bite, with penetration into the bloodstream of the host, through the solution of cutaneous continuity generated by the bite or through a mucous membrane. By penetrating the cells (preferably myocardial, smooth muscle and glial cells of the central nervous system - CNS), in the form of amastigotes, the protozoa multiplies, promoting cell injury and stimulating the immune-inflammatory reaction [3-5].

Transmission can also occur through transfusion of blood components, organ transplantation, intrauterine and through laboratory material accidents, as well as cases of ingestion of contaminated food, the main mode of transmission currently (for example, sugar cane and açai) [6-9].

As for cardiac involvement, its complete pathogenesis has not yet been fully elucidated, but it is postulated that during the indeterminate phase a silent myocarditis occurs, with slow, progressive and cumulative destruction of cardiac fibers and replacement by fibrous tissue. There is rarely sudden death due to ventricular arrhythmia at this stage. There are four proposed mechanisms for the evolution of cardiac damage [10-12].

Neurogenic mechanisms: There is worsening of the autonomic control and the function of central and peripheral chemoreceptors, and parasympathetic dysfunction. These neurogenic disorders are major contributors to the complications of the chronic phase by triggering malignant arrhythmias and sudden death, disorders in the control of coronary microcirculation and ventricular dyssynergy.

Parasite-dependent inflammation: Evidenced by the finding that the higher the parasite load, the greater the inflammatory lesion; with the reduction of the parasitic load with the treatment, we obtain reduction of the inflammatory process; in the seropositive autopsied patients who did not present cardiac lesion, the presence of *T. cruzi* genetic material was not observed; 86% of the patients with presence of circulating *T. cruzi* DNA had chronic cardiomyopathy.

Microvascular disorders: It is suggested that its association with the inflammatory process is synergistic for the perpetuation of myocardial cell damage. It is postulated that there is participation of these disorders in the genesis of ischemic symptoms, electrocardiographic alterations and perfusion defects observed in angiographically normal patients.

Immune-mediated cardiac damage: A self-antigen called Cha is responsible for the development of anti-Cha antibodies that, in studies in animal models, was responsible for cardiac damage. In addition, cytokines, chemokines and nitric oxide released by affected cardiomyocytes are responsible for the attraction of leukocytes to the inflammatory site, and their action may contribute to injury to cardiac myocytes. The exact mechanisms of autoimmune response are still uncertain.

Clinical Findings

The clinical picture of Chagas disease has three phases:

Acute phase: Diagnosis is performed in only 10% of cases, since there is a high non-specificity in the clinical findings, and the progression is benign in most cases (95%) after a few months, even without treatment. The acute phase is observed mainly in children, has an incubation period of 7 to 10 days, lasting from two to four months and results in death of up to 10% of cases. The initial finding is at the site of inoculation, both in the eye, with the sign of Romaña (unilateral palpebral edema, conjunctivitis and local lymphadenopathy), and in the skin, with chagoma of inoculation (lesion similar to the furuncle with local lymphadenopathy). The symptomatology resembles an influenza picture (fever, myalgias, prostration), accompanied by hepatomegaly, discrete splenomegaly and generalized lymphadenopathy. In 90% of cases, there is cardiac involvement, with acute myocarditis, with involvement extending from the endocardium (with thrombus formation) to the epicardium (with pericardial effusion), which can lead to death due to ventricular failure, being the rare occurrence of arrhythmias at this stage. The frequency and severity of myocarditis are inversely proportional to the age of occurrence. The four chambers are usually involved, in addition to the intracardiac conduction system. It is observed that most of the cell lesions are due to immunological lysis by antibodies released by infected cells. Acute phase meningoencephalitis is limited to young children, and is usually fatal.

Latent phase (or undetermined phase): It can extend for a period of 10-30 years, during which the patient remains asymptomatic, but the serological tests and sometimes the parasitological examination confirm the presence of infection. The chronification rate is 2% per year, but it is estimated that more than 50% of those infected remain in latent phase, asymptomatic throughout life. Chagas cardiomyopathy has been reported in 38.3% of seropositive individuals over 10 years.

Chronic phase: It is manifested generally by the occurrence of cardiac involvement and/or digestive involvement. The predominance of each will depend on the strain of the parasite and the susceptibility of the host.

Chagas' heart disease is the main cause of Chagas disease morbidity and mortality. It is manifested basically by three events:

Cardiac insufficiency (HF) due to dilated cardiomyopathy: There is biventricular involvement, but the right ventricle is often more compromised than the left ventricle, making the systemic congestion predominate (lower limbs edema, ascites, hepatomegaly, jugular

swelling). The most characteristic cardiac anatomical lesion is the apical ventricular aneurysm, present in 52% of a total of 1,078 autopsied chagasic patients in a published series. There is no valve lesion, although tricuspid regurgitation due to ventricular dilatation and valve annulus is common. There may be atypical chest pain as symptomatology arising from abnormalities of the microvasculature or coronary vasomotor abnormalities.

Cardiac arrhythmias and conduction disorders: The most common electrocardiographic finding is the association of right bundle branch block with left anteroseptal divisional block. Blockades at the level of the atrioventricular node (AV) should be observed for correct indication of definitive pacemaker implantation. All forms of ventricular arrhythmias may occur and, in patients of higher risk-history of complex ventricular arrhythmia, unexplained ventricular tachycardia, unexplained syncope, sudden aborted death and EF less than 35% - an electrophysiological study (ES) should be evaluated for implantation of cardioverter defibrillator.

Autonomic dysfunction also causes heart rate changes to different tests and maneuvers. Sudden arrhythmic death occurs in 55% - 65% of patients with Chagas cardiomyopathy, even though they are asymptomatic. Generally, sudden death is precipitated by exercise and occurs by ventricular arrhythmia or atrioventricular block.

Thromboembolic events: Pulmonary or systemic, due to propensity for the formation of mural thrombi. There are reports of findings of such events in 44% (14% in lung territory) of chagasic patients autopsied in a series. In one study, the presence of apical aneurysm, HF, cardiac arrhythmia and the female sex were defined as independent predictors of the occurrence of stroke in Chagas' cardiomyopathy.

Other findings that occur very rarely are bronchial or urinary tract involvement. We must also remember that there may be reactivation of Chagas in immunosuppressed patients (e.g., acquired immunodeficiency syndrome).

Methods

Main acute phase examinations

In the acute phase, examination findings may be nonspecific. The hemogram shows leukocytosis at the expense of lymphocytosis; the electrocardiogram (ECG) may show A-V conduction disorders and diffuse ST-T changes; and chest X-ray may show an increase of variable degree of cardiac area, either by ventricular overload or pericardial effusion. In this phase, the serological tests can be negative for a few weeks, so that the detection of circulating parasites is of great value for diagnostic confirmation, since its positivity occurs in around 50% of the cases. It is most commonly performed by xenodiagnosis, which consists of the suspicious patient's exposure to the bite of a triatomine created in the laboratory, with subsequent research of the parasite in the insect's intestine. In addition to xenodiagnosis, trypanosomes may be screened by examining fresh anticoagulated blood or the leukocyte potato for mobile forms, and by examining one of the following Giemsa-stained smear preparations: thick, fine droplet, leukocyte potato and examination of the pellet after centrifugation of the coagulated blood supernatant. Finally, the research can be done by inoculating the patient's blood into a susceptible laboratory animal (e.g., mouse) and observing the development of the disease.

Other tests

Serologies: Highly sensitive IgG (immunoglobulin G) tests (inhibition of hemagglutination, ELISA, immunofluorescence) are routinely used and have presumptive value when positive. However, in the case of positivity, it is necessary to perform two or three of these tests, since false-positive results are common, especially with some infections or autoimmune diseases.

PCR: Blood culture diagnosis and identification of specific *T. cruzi* DNA sequences can be done by means of PCR (polymerase chain reaction test). In the chronic phase, it has a complementary role in association with serological tests.

Resting electrocardiography (ECG): The most common alteration is the association of complete right bundle branch block with left anteroseptal divisional block and diffuse changes in ventricular repolarization. Several forms of ventricular arrhythmia and different degrees of atrioventricular block may occur. Even with normal ECG, cardiovascular death occurs in chagasic patients.

Chest X-ray: The most common radiological changes are varying degrees of cardiomegaly, but pulmonary vascular congestion, usually mild, may be seen.

Dynamic electrocardiography (Holter): Virtually all types of ventricular arrhythmia can be observed, as well as atrial arrhythmias and conduction system disorders.

Doppler echocardiography: Abnormalities of cardiac structure and function can be identified in symptomatic and asymptomatic patients. In the chronic phase, variation of systolic function can be found from the normal to the severe reduction, either the left ventricle or the right. Diastolic dysfunction is also common and usually early compared to systolic. Left ventricular apical aneurysm is found in up to 9% of asymptomatic patients and in 64% of those with advanced disease. The presence of aneurysm and moderate or severe systolic dysfunction confer poorer prognosis to patients. Dobutamine echocardiography may reveal reduced contractile reserve in the chagasic patient.

Ergometry: It has limited value in chagasic heart disease, considering the basal alterations that the ECG can already show.

Angiography with radionuclides: Useful in the quantification of biventricular function.

Myocardial scintigraphy: May have reversible or irreversible perfusion defects. They are usually of postero-inferior and apical location. Fixed perfusion defects are related to areas of myocardial fibrosis and are confirmed by altered motility of the affected wall.

Angiography: Useful to confirm or exclude presence of coronary artery disease in symptomatic patients with other completely non-elucidating examinations.

Cardiac magnetic resonance imaging (MRI): Allows the evaluation of cardiac chambers volume, biventricular systolic function and, with the late enhancement method, detect regions of necrosis or fibrosis.

Electrophysiological study (ES): Indicated for the study of sinus function, atrioventricular conduction and in cases of ventricular arrhythmia, either for prognostic determination or for indication of antiarrhythmic therapy. It does not show as much efficacy in cases of preserved ventricular function.

Treatment

It is indicated, whenever diagnosed, to treat the acute phase with anti-Chagas therapy. There are two drug options: nifurtimox and benznidazole. They are used for long periods and there is a risk of toxicity. In the acute phase, the cure rate is approximately 70%, which may reduce the duration and severity of the disease.

Benznidazole is used at a dose of 5 to 10 mg/kg/day for 60 days. Its side effects are granulocytopenia, rashes and peripheral neuropathy. Children tolerate it better, and larger doses may be used.

Nifurtimox should be given in daily doses of 8 to 10 mg/kg divided into four doses after meals for a period of 90 to 120 days. Common gastrointestinal complaints, weight loss, tremors and peripheral neuropathy are common side effects. Rarely, hallucinations, seizures, and pulmonary infiltrates are observed.

In the chronic phase, anti-Chagas therapy is controversial. Although parasitemia and xenodiagnosis may become negative in up to 70% of patients, treatment does not alter the serologic reaction, cardiac function or disease progression.

Amiodarone appears to be the most promising antiarrhythmic drug, although there is no evidence of an impact on survival. Surgical excision of fibrotic tissue or catheter ablation may be effective as well as aneurysmectomy for patients with refractory ventricular tachycardia (VT), especially if overall ventricular function is preserved. Patients at high risk of sudden death also benefit from ICD implantation.

The therapy for HF studied so far involves the same treatment models for other forms of HF, with the use of beta-blockers (carvedilol), ACE inhibitors and spironolactone. Its impact on morbidity was well defined, which did not occur with regard to mortality yet.

Socioeconomic factors should guide the use of anticoagulation, when it is indicated for the prevention of thromboembolism.

Prognosis

Generally, in infants and young children, the acute phase is fatal, especially if there is CNS involvement.

Adults with chronic heart disease usually die from HF and its final consequences.

The prognosis has independent factors linked to higher mortality, which are:

- High heart rate;
- Presence of pathological Q wave to ECG;
- Presence of left antero-superior divisional block isolated to the ECG;
- Elongation of the QT interval;
- Presence of ventricular extra-systolic;
- The final systolic dimension to the echocardiogram.

Recently, an outpatient risk score was validated to which points were attributed according to six variables:

- Class III/IV IC (5 points);
- cardiomegaly to chest X-ray (5 points);
- Left ventricular systolic dysfunction (3 points);
- Holter unsustained VT (3 points);

- ECG with low voltage complexes (2 points);
- Male (2 points).

Between 12 and 20 points, mortality ranged from 84% to 85%, between 7 and 11 points was 37% to 44%, and between 0 and 6 points was 9% to 10%.

Prevention

There is no vaccine available against the parasite and the disease, but vector control measures have been shown to reduce the incidence of new cases. Even so, many advances are still necessary to reduce the impact of the disease on public health in the most affected areas.

Discussion and Conclusion

Chagasic myocarditis is the most common form of cardiomyopathy in Latin American countries, consisting of a serious public health problem for endemic areas.

It is caused by *T. cruzi* and transmitted by the insect "barber", which is infected through the blood of animals or man contaminated with trypanosomes. Contamination for humans occurs through the feces of the infected "barber" at the moment of the bite.

The vectors are found in domestic and peridomestic environments, making their nests in wall crevices, common in taperas made of stick, typical in endemic places.

The pathogenesis of cardiac involvement has not yet been fully elucidated, involving neurogenic mechanisms, parasite-dependent inflammation, microvascular disorders and immune-mediated cardiac damage. These mechanisms lead to a silent myocarditis, with slow, progressive and cumulative destruction of cardiac fibers and replacement by fibrous tissue.

The clinical picture of Chagas disease has three phases. In the acute phase, the initial finding is at the site of inoculation in both the eye and the skin. The symptomatology resembles an influenza clinical condition (fever, myalgias, prostration), accompanied by hepatomegaly, mild splenomegaly and generalized lymphadenopathy, in addition to acute myocarditis in 90% of the cases. In the latent phase (or undetermined phase), the individual remains asymptomatic, a phase that can last for 10-30 years.

In the chronic phase there is cardiac and/or digestive involvement. The predominance of each will depend on the strain of the parasite and the susceptibility of the host.

In the acute phase, examination findings may be non-specific, and serology is often negative. In this phase, the detection of circulating

parasites is of great value for diagnostic confirmation, since its positivity occurs in about 50% of the cases.

In the latent or chronic phase, the main diagnostic test is the serology. Other exams of great value are mainly ECG, Holter, echocardiogram and electrophysiological study.

The acute phase should be treated whenever diagnosed, with options being nifurtimox and benznidazole.

Therapy for HF caused by Chagas' disease involves the same treatment models for other forms of HF, with the use of beta-blockers (carvedilol), ACE inhibitors and spironolactone.

The best way to prevent disease is by vector control.

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