The Epidemiology, Clinical Manifestations, and Management of Chagas Heart Disease

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ABSTRACT

Chagas disease results from infection by the protozoan parasite *Trypanosoma cruzi* and is endemic in Latin America. *T cruzi* is most commonly transmitted through the feces of an infected triatomine, but can also be congenital, via contaminated blood transfusion or through direct oral contact. In the acute phase, the disease can cause cardiac derangements such as myocarditis, conduction system abnormalities, and/or pericarditis. If left untreated, the disease advances to the chronic phase. Up to one-half of these patients will develop a cardiomyopathy, which can lead to cardiac failure and/or ventricular arrhythmias, both of which are major causes of mortality. Diagnosis is confirmed by serologic testing for specific immunoglobulin G antibodies. Initial treatment consists of the antiparasitic agents benznidazole and nifurtimox. The treatment of Chagas cardiac disease comprises standard medical therapy for heart failure and amiodarone for ventricular arrhythmias, with consideration for implantable cardioverter-defibrillator. Chagas disease causes the highest infectious burden of any parasitic disease in the Western Hemisphere, and increased awareness of this disease is essential to improve diagnosis, enhance management, and reduce spread.

Introduction

Chagas disease (CD) was discovered in 1909 by Carlos Chagas and was thought to be limited to Latin America, where it is the leading cause of nonischemic cardiomyopathy.¹ With the migration of infected individuals from Latin America to the United States, the Centers for Disease Control and Prevention (CDC) estimates that more than 300,000 persons with *Trypanosoma cruzi* infection reside in this country, where it now poses a major public health concern because of its rising prevalence and limited awareness within the medical community. For this reason, the CDC has classified CD as 1 of the 5 neglected parasitic infections in the United States, a group of diseases that has been targeted for public health action.² The importance of CD in this country is illustrated by a recent study of immigrants in Los Angeles County. Of 135 persons from Central and South America with nonischemic cardiomyopathy of unknown etiology, 20% were found to have Chagas heart disease. Further, this report showed that individuals with Chagas cardiomyopathy died at a younger age and had fourfold higher all-cause mortality than patients with more conventional causes of heart failure.³ Through both globalization and immigration, the prevalence of CD in the United States is expected to increase.⁴

All authors had access to the data and a role in writing the article.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Epidemiology

Until recently, CD was confined to those areas of South and Central America in which *T cruzi* is endemic. In these regions, the triatomine bug—the main vector for human transmission—thrives in poor housing conditions; therefore, rural populations are most commonly infected.² In the 1980s, the number of individuals infected with *T cruzi* in endemic areas of Latin America was estimated at 16 to 18 million. However, following the institution of parasite and vector control programs along with blood-bank screening in this region, there has been a steady decline in the prevalence of CD to about 11 million cases in the mid-to-late 1990s, and 7.6 million cases in 2006. Conversely, as the prevalence of CD in Latin America decreased, the number of Latin American immigrants in the United States rose, with more than 7 million people from *T cruzi*-endemic countries becoming legal US residents from 1981 to 2005, resulting in a surge of this disease in the United States.⁵ According to preliminary estimates, the United States now ranks seventh in the Western Hemisphere in number of individuals infected with *T cruzi*.⁴

Transmission/Life Cycle

T cruzi is excreted in the feces of an infected triatomine bug onto human skin or near mucous membranes. The parasites breach the dermis through excoriations in the skin and gain systemic access. Once within host cells they reproduce, which leads to cell lysis and hematogenous dissemination, at which point parasites are apparent on peripheral blood smear. The cycle is complete when a triatomine vector

feeds on the human host, ingesting *T cruzi* from the blood.⁶ Chagas disease can also be transmitted through nonvectorial mechanisms, such as blood transfusion or vertically from mother to infant. Cases of direct oral transmission have also been documented.⁷ Transfusion-based and congenital transmissions are the main forms of human infestation in urban zones and nonendemic countries, and are therefore the major targets for the reduction of spread.⁸

Pathogenesis

Inoculation is followed by a short incubation period of 1 to 2 weeks after which the acute phase of the disease begins. This phase typically lasts 8 to 12 weeks and is characterized by parasitemia and subsequent immune response. Following the acute phase, about 30% of patients directly enter the determinate (final) phase, but the majority of patients proceed to the indeterminate phase (Figure 1). The latter phase involves host-parasite equilibrium and is without progressive host damage.⁹ Approximately one-third of patients progress from indeterminate to determinate phase, in which cardiac symptoms and signs arise from progressive myofibril fibrosis and conduction system injury.¹⁰ Remodeling of the collagenous matrix with fibrosis leads to increased myocardial stiffness, systolic and diastolic dysfunction, and ultimately a severe, dilated cardiomyopathy.

Clinical Manifestations

The acute phase of CD has multiple clinical manifestations, most common of which are nonspecific viral-like signs and symptoms including fever, malaise, and lymphadenopathy (Table 1). For this reason, many infected individuals are not identified, as they often do not seek medical care. A small number of patients may present with a Chagoma, an inflammatory nodule at the site of inoculation, or Romana sign, which is described as periorbital soft tissue swelling after *T cruzi* enters through the conjunctiva. During the acute phase, patients may manifest arrhythmias and transient electrocardiogram (ECG) abnormalities.¹¹ In <5% of cases, more severe illness, including myocarditis and meningoencephalitis, can occur.

After the acute phase of the disease, most patients enter a clinically asymptomatic chronic phase, with both indeterminate and determinate subgroups. Although serologic and parasitologic testing are positive for *T cruzi*, a majority of patients have no subjective complaints or objective findings. This phase generally carries an excellent prognosis with survival rates similar to those of noninfected individuals.¹² The clinical or serologic indicators in patients who progress to the determinate phase of the disease (eg, symptomatic and often fatal) remain unclear. Elucidation of methods to identify these patients remains an area of active investigation, and possible targets include ECG abnormalities, dysautonomia, ventricular segmental wall motion impairment, and magnetic resonance imaging to detect cardiac fibrosis and diastolic dysfunction.^{13–16}

For infected individuals, 20% to 30% will progress from the indeterminate to the determinate phase of the disease. Importantly, progression to the determinate phase

Table 1. Clinical Manifestations of Chagas Disease

Acute phase (duration: weeks)
Fever
Malaise
Lymphadenopathy
Chagoma — inflammatory nodule at site of inoculation
Romana's sign — periorbital swelling
ECG abnormalities: sinus tachycardia, first-degree AV block
Myocarditis (rare)
Indeterminate phase (duration: decades)
Asymptomatic (most)
Conduction abnormalities, regional LV wall motion abnormalities, or sudden cardiac death (rare)
Chronic phase (duration: decades)
Asymptomatic
Cardiac: LV dilatation, congestive heart failure, conduction abnormalities, ventricular arrhythmias, thromboembolic disease, sudden cardiac death
Abbreviations: AV, atrioventricular; ECG, electrocardiogram; LV, left ventricular.

can occur after a prolonged (eg, decades) indeterminate phase. The chronic form of CD ranges from absence of signs and symptoms (indeterminate phase) to severe illness (determinate phase). The most common cardiac complications of chronic CD are left ventricular dilation and dysfunction, aneurysm, congestive heart failure, thromboembolism, ventricular arrhythmias, and SCD, which is the leading cause of mortality in patients with Chagas heart disease.¹⁷ In this regard, a study of ambulatory Chagasic patients revealed that 67% of mortality at 9 years was secondary to SCD.¹⁸ Additionally, a strong association has been reported between seropositivity for CD and cardiac conduction system abnormalities such as prolongation of the QRS complex and QT interval, right bundle branch block, and/or left anterior fascicular block.¹³ Chagas cardiomyopathy also carries a significantly elevated risk of stroke. This complication is related to intracardiac mural thrombi resulting from depressed left ventricular function and/or aneurysm with subsequent embolization.⁶ Although the brain is most commonly affected, thrombi may also shower to other vital organs.

Diagnosis

The diagnosis of chronic CD is based on serology to detect trypomastigotes (the mature form of the parasite) or immunoglobulin G antibodies to *T cruzi*. In the acute phase of the disease, the level of parasitemia is high, and trypomastigotes can be detected on blood microscopy. Polymerase chain reaction can also be utilized for tissue diagnosis during the acute phase, as it offers both a qualitative and quantitative assessment of *T cruzi* burden.

Figure 1. Natural history of Chagas disease. Adapted from Mattu UK, Singh GD, Southard JA, et al. *Am J Med.* 2013;126:864–867.

The level of parasitemia decreases within the first 90 days of infection and *T. cruzi* is not detectable in the chronic phase, during which diagnosis focuses on detection of serum antibodies to the parasite for which there are 3 serologic tests: indirect hemagglutination, indirect immunofluorescence, and enzyme-linked immunosorbent assay.

Although its findings are nonspecific, the ECG provides the initial evidence of cardiac involvement. The most common abnormalities are right bundle branch block, left anterior fascicular block, and diffuse ST-T changes.⁸ Patients who exhibit ECG changes suggestive of cardiac involvement should undergo further assessment to determine severity of disease. Excellent prognosis for almost a decade has been reported for patients with a normal ECG.¹⁹ Echocardiography can demonstrate both structural and functional alterations in the early stages of cardiac involvement, including regional wall motion abnormalities and diastolic dysfunction. With progression of the disease, ventricular dilation and severe, global hypokinesia ensue.²⁰

Due to the high incidence of ventricular arrhythmias and sudden death in chronic Chagasic patients, screening of those at risk has been proposed. Ambulatory ECG

monitoring has been suggested for patients with an abnormal resting ECG or ventricular wall motion abnormalities on echocardiography. If nonsustained ventricular tachycardia is detected, invasive electrophysiologic study has been considered.¹⁹ However, at this time, a uniform and consensus-based approach to screening patients has not been established.

Treatment

Anti-infective Agents

The 2 antiparasitic drugs available for the treatment of CD are benznidazole and nifurtimox. These agents are most effective in the acute phase of the disease, with the rates of parasitological cure of 60% to 80% (Figure 1). Treatment is recommended for all cases of acute, reactivated, or congenitally transmitted infection, and also for children up to age 18 years old with chronic infection.⁸ Indications for treatment of patients in the chronic phase are currently unclear. A meta-analysis of 9 studies showed that compared with placebo or no treatment in patients with chronic Chagas infection, benznidazole increases the probability

of a response to therapy by 18-fold.²¹ Additionally, there is an ongoing prospective international trial of antitrypanocidal treatment assessing the efficacy of benznidazole in patients with chronic Chagas heart disease.²² Both benznidazole and nifurtimox have significant adverse side effects, but early discontinuation of the latter has been more frequent.²³ Although neither drug is approved for use in the United States, both can be obtained from the CDC and used under investigational protocols. Posaconazole is an additional agent that has been noted to have antitrypanocidal activity in murine models. A recent study assessing the efficacy of posaconazole compared to benznidazole for the treatment of patients with chronic CD showed antitrypanosomal activity in these patients. However, a significant proportion had treatment failure during follow-up.²⁴

Heart Failure

Chagas heart disease results in neurohumoral activation similar to other etiologies of dilated cardiomyopathy, and the mainstay of therapy is in accord with the American College of Cardiology/American Heart Association guidelines for management of patients with heart failure.²⁵ In the last 3 decades, there have been multiple small studies in patients with CD that have shown that neurohumoral inhibition can improve both symptoms and left ventricular function, and may also reduce ventricular arrhythmia burden and mortality.^{26–29} However, patients with CD frequently have lower blood pressure and a higher incidence of bradyarrhythmias than non-Chagasic patients and may not tolerate target doses of angiotensin converting enzyme inhibitors and β -adrenergic blockers. However, outcomes are improved even at nontarget doses, and these agents should be utilized.^{30,31}

Cardiac resynchronization therapy can also be considered for patients with severe systolic dysfunction (left ventricular ejection fraction <35%) and prolonged QRS complex. Resynchronization therapy is shown to significantly improve New York Heart Association Functional Class, increase left ventricular ejection fraction, and enhance survival in patients with chronic Chagas cardiomyopathy.³² In those patients who fail maximal medical treatment for heart failure, a left ventricular assist device and ultimately cardiac transplantation are therapeutic options, although there is a paucity of data on these methods in patients with Chagas heart disease.

Antiarrhythmic Treatment

Recommendations for antiarrhythmic therapy in patients with Chagas heart disease are based on limited observational data and extrapolation of results from other patient populations. Some data suggest that amiodarone can improve survival in patients who are at high risk of arrhythmic death; thus, amiodarone has been recommended as the treatment of choice for all patients with sustained ventricular tachycardia, and also for those with nonsustained ventricular tachycardia with myocardial dysfunction.⁸ In addition to its ability to suppress ventricular arrhythmias, it has been reported that amiodarone has direct activity against *T cruzi*.³³

The implantable cardioverter-defibrillator (ICD) has been used to prevent SCD in patients with Chagas cardiomyopathy. Only a small number of observational studies have examined the efficacy of ICD therapy exclusively in patients with chronic Chagas heart disease. A retrospective analysis of these patients reported that ICD therapy was effective in both primary and secondary prevention of SCD.³⁴ In addition, therapy with ICD plus amiodarone was superior to amiodarone alone for secondary prevention of sudden death in patients with Chagasic heart disease, resulting in a 72% reduction in all-cause mortality and a 95% decrease in sudden cardiac death (SCD) in the ICD group compared to those receiving amiodarone alone. The survival benefit in the amiodarone and ICD combination group was greatest in patients with left ventricular ejection fraction <40%.³⁵ Patients with high-degree atrioventricular block or with symptomatic bradycardia warrant treatment with permanent cardiac pacing.³⁶ These patients often require high pacing thresholds and have an increased incidence of new onset atrial fibrillation following device implantation.³⁷

Anticoagulation

Prevention and treatment of thromboembolic complications in patients with CD should be directed by guideline recommendations. Oral anticoagulants are indicated for those with atrial fibrillation, previous embolism, and ventricular aneurysm with thrombus.⁶

Prevention

In endemic areas, preventive measures to reduce the spread of disease have been established through housing improvements and the use of insecticides to eliminate the triatomine vector.² Blood transfusion screening has been an additional measure to prevent disease transmission in this region. In the United States, strategies to control disease focus primarily on preventing transmission through both organ transplantation and blood transfusion.

Prognosis

Mortality from CD is almost entirely due to cardiac involvement. Chagasic heart failure patients have a higher death rate than their non-Chagasic heart failure counterparts.³⁸ Sudden death accounts for ~60% of the mortality due to chronic CD, whereas heart failure causes 25% to 30% of deaths, and stroke is responsible for 10% to 15%.¹⁷ As previously noted, the ECG also provides prognostic information. Seropositive patients <60 years old with a normal ECG at the time of diagnosis have long-term survival rates similar to seronegative Chagas patients.¹⁹

Conclusion

Chagas disease is increasing in importance in the United States. In the past, this disease was primarily limited to regions in South America; however, with globalization it is now on the rise in this country. Diagnosis can be suspected based on clinical symptoms and confirmed with serologic testing. The treatment of acute infection is highly effective, but oftentimes these patients do not present in this phase

due to the nonspecific symptoms. Chronic infection often ensues, causing marked cardiac derangements including heart failure, arrhythmias, and thromboemboli. The optimal treatment strategy in this crucial phase remains an active area of investigation. The current mainstay of treatment focuses on heart failure management and both medical and device therapy for arrhythmia management. The primary method for controlling the disease is prevention of transmission. This goal is being approached by increasing awareness of CD to identify and treat patients, and by legal requirements to optimize the safety of blood supply.

References

- Schofield CJ, Dias JC. A cost-benefit analysis of Chagas disease control. *Mem Inst Oswaldo Cruz*. 1991;86:285–295.
- Centers for Disease Control and Prevention. Parasites—American trypanosomiasis (also known as Chagas Disease). <http://www.cdc.gov/parasites/Chagas>. Accessed May 1, 2014.
- Traina M, Sanchez D, Hernandez S, et al. Chagasic cardiomyopathy is associated with increased morbidity and mortality compared with nonischemic cardiomyopathy among Latin American immigrants in Los Angeles. *Circulation*. 2012;126:A18171.
- Bern C, Montgomery S. An estimate of the burden of Chagas disease in the United States. *Clin Infect Dis*. 2009;49:e52–e54.
- Schmunis G. Epidemiology of Chagas disease in non-endemic countries: the role of international migration. *Mem Inst Oswaldo Cruz*. 2007;102(suppl 1):75–85.
- Rossi M, Ramos S, Bestetti R. Chagas' heart disease: clinical-pathological correlation. *Front Biosci*. 2003;8:e94–e109.
- Shikanai-Yasuda M, Carvalho N. Oral transmission of Chagas disease. *Clin Infect Dis*. 2012;54:845–852.
- Rassi A Jr, Rassi A, Marin-Neto J. Chagas disease. *Lancet*. 2010;375:1388–1402.
- Andrade Z, Andrade S, Sadigursky M, et al. The indeterminate phase of Chagas' disease: ultrastructural characterization of cardiac changes in the canine model. *Am J Trop Med Hyg*. 1997;57:328–336.
- Rossi M. Patterns of myocardial fibrosis in idiopathic cardiomyopathies and chronic Chagasic cardiopathy. *Can J Cardiol*. 1991;7:287–294.
- Alvarado-Tapia E, Miranda-Pacheco R, Rodríguez-Bonfante C, et al. Electrocardiography repolarization abnormalities are characteristic signs of acute Chagasic cardiomyopathy. *Invest Clin*. 2012;53:378–394.
- Ribeiro A, Nunes M, Teixeira M, et al. Diagnosis and management of Chagas disease cardiomyopathy. *Nat Rev Cardiol*. 2012;9:576–589.
- Williams-Blangero S, Magalhaes T, Rainwater E, et al. Electrocardiographic characteristics in a population with high rates of seropositivity for *Trypanosoma cruzi* infection. *Am J Trop Med Hyg*. 2007;77:495–499.
- Dias J. The indeterminate form of human chronic Chagas' disease. A clinical epidemiological review. *Rev Soc Bras Med Trop*. 1989;22:147–156.
- Molina R, Matsubara B, Hueb J, et al. Dysautonomia and ventricular dysfunction in the indeterminate form of Chagas disease. *Int J Cardiol*. 2006;113:188–193.
- Regueiro A, Garcia-Alvarez A, Sitges M, et al. Myocardial involvement in Chagas disease: insights from cardiac magnetic resonance. *Int J Cardiol*. 2013;165:107–112.
- Rassi A Jr, Rassi S, Rassi A. Sudden death in Chagas' disease. *Arq Bras Cardiol*. 2001;76:75–96.
- Rassi A Jr, Waktare J, Rassi SG, et al. Chagas heart disease: long term prognostic significance of nonsustained ventricular tachycardia and left ventricular dysfunction. *Pacing Clin Electrophysiol*. 1999;22(part II):862.
- Maguire J, Hoff R, Sherlock I, et al. Cardiac morbidity and mortality due to Chagas disease: prospective electrocardiographic study of a Brazilian community. *Circulation*. 1987;75:1140–1145.
- Acquatella H. Echocardiography in Chagas heart disease. *Circulation*. 2007;115:1124–1131.
- Perez-Molina J, Perez-Ayala A, Moreno S, et al. Use of benznidazole to treat chronic Chagas' disease: a systematic review with a meta analysis. *J Antimicrob Chemother*. 2009;64:1139–1147.
- Marin-Neto J, Rassi A Jr, Avezum A Jr, et al. The BENEFIT trial: testing the hypothesis that trypanocidal therapy is beneficial for patients with chronic Chagas heart disease. *Mem Inst Oswaldo Cruz*. 2009;104(suppl 1):319–324.
- Bern C. Antitrypanosomal therapy for chronic Chagas' disease. *N Engl J Med*. 2011;364:2527–2534.
- Molina I, Prat J, Salvador F, et al. Randomized trial of posaconazole and benznidazole for chronic Chagas' disease. *N Engl J Med*. 2014;370:1899–1908.
- Yancy C, Jessup M, Butler J, et al. 2013 ACCF/AHA. Guideline for the management of Heart Failure. *J Am Coll Cardiol*. 2013;62:e147–e239.
- Roberti R, Martinez E, Andrade A, et al. Chagas cardiomyopathy and captopril. *Eur Heart J*. 1992;13:966–970.
- Botoni F, Poole-Wilson P, Ribeiro A, et al. A randomized trial of carvedilol after renin-angiotensin system inhibition in chronic Chagas cardiomyopathy. *Am Heart J*. 2007;153:544.e1–e8.
- Bestetti R, Otaviano A, Cardinali-Neto A, et al. Effects of β -blockers on outcome of patients with Chagas' cardiomyopathy with chronic heart failure. *Int J Cardiol*. 2001;151:205–208.
- Quiros F, Morillo C, Casas J, et al. CHARITY: Chagas cardiomyopathy bisoprolol intervention study: a randomized double-blind placebo force-titration controlled study with bisoprolol in patients with chronic heart failure secondary to Chagas cardiomyopathy. *Trials*. 2006;7:21.
- Bestetti R, Muccillo G. Clinical course of Chagas heart disease: a comparison with dilated cardiomyopathy. *Int J Cardiol*. 1997;60:187–193.
- Braga J, Reis F, Aras R, et al. Clinical and therapeutic aspects of heart failure due to Chagas disease. *Arq Bras Cardiol*. 2006;86:297–302.
- Aruajo E, Chamlian E, Peroni A, et al. Cardiac resynchronization therapy in patients with chronic Chagas cardiomyopathy: long-term follow up. *Rev Bras Cir Cardiovasc*. 2014;29:31–36.
- Benaim G, Sanders J, Garcia-Marchan Y, et al. Amiodarone has intrinsic anti-*Trypanosoma cruzi* activity and acts synergistically with posaconazole. *J Med Chem*. 2006;49:892–899.
- Pereira F, Rocha E, Monteiro Mde P, et al. Long-term follow-up of patients with chronic Chagas disease and implantable cardioverter-defibrillator. *Pacing Clin Electrophysiol*. 2014;37:751–756.
- Gali W, Sarabanda A, Baggio A, et al. Implantable cardioverter-defibrillators for treatment of sustained ventricular arrhythmias in patients with Chagas' heart disease: comparison with a control group treated with amiodarone alone. *Europace*. 2014;16:674–680.
- Epstein A, DiMarco J, Ellenbogen K, et al. ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Circulation*. 2008;117:e350–e408.
- Arce M, VAN GRIEKEN J, Femenia F, et al. Permanent pacing in patients with Chagas' disease. *Pacing Clin Electrophysiol*. 2012;35:1494–1497.
- Traina M, Sanchez D, Hernandez S, et al. Chagasic cardiomyopathy is associated with increased morbidity and mortality compared with nonischemic cardiomyopathy among Latin American immigrants in Los Angeles. *Circulation*. 2012;126:A18171.