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Review

Clinical aspects of the Chagas' heart disease

Gopikrishna Punukollu [a], Ramesh M. Gowda [a], Ijaz A. Khan [b,*], Victor S. Navarro [a], Balendu C. Vasavada [a]

[a] *Division of Cardiology, Long Island College Hospital, Brooklyn, NY, USA*
[b] *Division of Cardiology, University of Maryland School of Medicine, 22 South Greene Street - S3B06, Baltimore, MD 21201, USA*

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Abstract

Chagas' heart disease, caused by protozoan *Trypanosoma cruzi*, is a common cause of cardiomyopathy in the Americas. Transmission of *T. cruzi* occurs through Reduviids, the kissing bugs. Less common ways of transmission are blood transfusion, congenital transmission, organ transplantation, laboratory accident, breastfeeding, and oral contamination. Infestation results in cardiac dysautonomia, myocardial apoptosis, and myocardial fibrosis. In acute phase, death is mostly caused by myocarditis and in chronic phase, it is mostly by irreversible cardiomyopathy. A majority of the patients with Chagas' disease remain in the latent phase of disease for 10 to 30 years or even for life. Specific anti-Chagas' therapy with trypanocide drugs is useful in acute phase but the management of chronic Chagas' heart disease is mostly empirical. The mortality during the acute phase of cardiac Chagas is around 5%. Five-year mortality of chronic Chagas' disease with cardiac dysfunction is above 50%. The clinical aspects of the Chagas' heart disease are concisely reviewed.

Keywords: Chagas' heart disease; *Trypanosoma cruzi*; Chagasic cardiomyopathy; Neurogenic cardiomyopathy; Congestive heart failure

Cardiac Chagas' results from an infection due to the hemoflagellate protozoan *Trypanosoma cruzi*. In 1909, Carlos Chagas from Brazil first described the human case of disease in a 9-month-old child [1]. Cardiac Chagas is a common form of cardiomyopathy in Latin-American countries [2,3]. Initially a rural disease in endemic countries, Chagas' disease has spread to cities with increased surge of urban migration. In non-endemic countries, it can be transmitted vertically and by blood transfusion or organ transplantation [4].

1. Epidemiology

Reduviids ("kissing bugs") nests in crevices within the walls and roofs of the substandard houses ("simple houses") primarily found in South and Central America [3]. Insects become infected with the organism *T. cruzi* after biting an animal or person with Chagas' disease. Spread of infection to humans occurs when an infected bug deposits feces on a person's skin, usually at night while the person is sleeping. With manual rubbing the feces gets into the bite wound, an open cut, the eyes, or mouth. Following skin contact with the infected reduviids and after a 7–10 day incubation period, a local swelling occurs at the portal of entry (chagomas). On conjunctiva, it may result in unilateral periorbital edema and eyelid swelling (Romana's sign). Infestation can also occur through blood transfusion, congenital transmission, organ transplantation, laboratory accident, breastfeeding, and oral contamination (Table 1). Micro-epidemics of acute Chagas' disease have been reported, probably due to oral transmission [4].

Majority of patients are infected during childhood. The early stage of infection is usually not severe, but occasionally leads to death, particularly in infants. However, in about one-third of those who are infected, chronic symptoms develop after 10–20 years [5]. For those patients who develop chronic symptoms, the average life expectancy decreases by an average of 9 years [4]. An estimated >750 thousand-years

* Corresponding author. Tel.: +1 410 328 2251; fax: +1 410 328 2255.
E-mail address: ikhan@medicine.umaryland.edu (I.A. Khan).

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Table 1
Mechanisms of transmission

- Vectorial: infective feces contacting eyes, mouth, or open cuts
- Oral: by eating uncooked food contaminated with infective feces of "kissing bugs"
- Vertical: mother to baby during pregnancy, at delivery, or while breastfeeding
- Blood transfusion
- Organ transplantation
- Laboratory accident

of productive life are annually lost, due to premature deaths associated with cardiac Chagas [6].

2. Pathophysiology

The pathophysiology of Chagas' disease is still incompletely understood [4]. Persistence of parasites in the heart, autoimmune responses, and cardiac autonomic imbalance are the leading hypothesis on the pathogenesis of the chronic Chagas' heart disease [5]. Parasite persistence is considered to result in lymphocytic infiltration of the myocardium, which is a common finding in Chagas' hearts [7]. Myocardial cell loss by both fibrosis and apoptosis contribute to heart failure in the chronic phase of Chagas' disease [8]. Nonetheless, a definitive cause–effect relationship between progression of the disease and parasite persistence has not conclusively demonstrated, and an imbalance in the cardiac autonomic system seems to play an equal part in the progression of the Chagas' heart disease. Autonomic ganglia and nerves are frequently abnormal and lesions of cardiac nerves are frequently encountered in cardiac Chagas [9]. The parasympathetic dysautonomia is an early phenomenon and it may precede left ventricular systolic dysfunction [10]. Consequently, cardiac sympathetic system remains unopposed, and the cardiotoxic effects of a permanent sympathetic activation may result in progression of the myocardial damage by catecholamine cardiotoxicity [11]. Dysfunction of the sympathetic nervous system occurs during the later stages of the disease [12,13]. This reduced sympathetic activity results in lower plasma norepinephrine levels in patients with Chagas' heart disease who have class III or IV heart failure in contrast to sympathetic hyperactivity and elevated plasma norepinephrine levels in class III or IV heart failure patients without Chagas' disease [12,13]. Dysautonomia in Chagas' disease is likely of autoimmune origin. Sterin-Borda and Borda [14] have demonstrated the existence of circulating auto antibodies in Chagas' disease that react against the second extracellular loop of the human heart beta-1-adrenergic and M2 muscarinic cholinergic receptors.

T. cruzi infection causes a generalized vasculitis of several vascular beds, manifested by vasospasm, decreased blood flow, focal ischemia, platelet thrombi, increased platelet aggregation, and elevated plasma levels of thromboxane A-2 and endothelin-1 [15,16]. In animal models of Chagas' disease myocardial myonecrosis and vasculitis of the aorta, coronary artery, smaller myocardial vessels, and the endocardial endothelium have been observed [15].

3. Clinical presentation

3.1. Acute phase

In acute phase of Chagas' disease, the main features include fever, myalgias, malaise, muscle pains, sweating, hepatosplenomegaly, heart failure from myocarditis, pericardial effusion, and, less often, meningoencephalitis. Cardiac involvement is present in over 90% of cases [17]. There is intense parasitism noted on microscopic examination in most of the organs, with prominent inflammatory changes near ruptured infected cells (pseudocystis). The diagnosis is established in <10% of cases [18], probably owing to mild symptoms. Laboratory findings are nonspecific and include leukocytosis with an absolute increase in lymphocyte count [18]. The electrocardiogram may show low voltage, diffuse ST-T changes and various conduction abnormalities. Complement fixation and other serologic tests for *T. cruzi* infection are usually negative during the first weeks but the circulating parasites can be detected by xenodiagnosis. Spontaneous recovery occurs over a period of a few months in >95% of patients. Mortality at this stage is usually secondary to myocarditis. Chagas' disease may reactivate in immunocompromised patients who have the chronic form [19].

3.2. Latent phase

The latent (indeterminate) phase usually lasts for 10 to 30 years, but in a majority it can persists throughout life. During latent phase, the patients remain asymptomatic with positive serology, and no physical signs or clinical evidence of organ involvement [20]. Nonetheless, virtually all patients in the latent phase have a subclinical degree of cardiac involvement when tested by Holter monitoring and echocardiography [21].

3.3. Chronic phase

Symptoms and physical signs of chronic Chagas' heart disease arise from heart failure, cardiac arrhythmias, and arterial or venous thromboembolism. Atypical chest pain is common in patients with Chagas' heart disease. Heart failure is usually biventricular. Heart failure caused by cardiac Chagas is the most frequent and severe clinical manifestation of Chagas' disease and is associated with poor prognosis and high mortality rates when compared with heart failure from other causes [22]. Cardiac dysfunction can be systolic or diastolic. Diastolic dysfunction has been noted in the absence of regional or global left ventricular systolic dysfunction [23]. Cardiac examination typically reveals prominent apical impulse, regurgitant murmurs from mitral and tricuspid values, wide splitting of the second heart sound due to right bundle branch