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STATE-OF-THE-ART REVIEW

Chronic Chagas Heart Disease Management

From Etiology to Cardiomyopathy Treatment

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ABSTRACT

Trypanosoma cruzi (T. cruzi) infection is endemic in Latin America and is becoming a worldwide health burden. It may lead to heterogeneous phenotypes. Early diagnosis of *T. cruzi* infection is crucial. Several biomarkers have been reported in Chagas heart disease (ChHD), but most are nonspecific for *T. cruzi* infection. Prognosis of ChHD patients is worse compared with other etiologies, with sudden cardiac death as an important mode of death. Most ChHD patients display diffuse myocarditis with fibrosis and hypertrophy. The remodeling process seems to be associated with etiopathogenic mechanisms and neurohormonal activation. Pharmacological treatment and antiarrhythmic therapy for ChHD is mostly based on results for other etiologies. Heart transplantation is an established, valuable therapeutic option in refractory ChHD. Implantable cardioverter-defibrillators are indicated for prevention of secondary sudden cardiac death. Specific etiological treatments should be revisited and reserved for select patients. Understanding and management of ChHD need improvement, including development of randomized trials. (J Am Coll Cardiol 2017;70:1510–24)

Chagas heart disease (ChHD) data were reviewed to guide management planning of this disease, which is endemic in Latin America and is becoming a worldwide health burden due to migration (1,2). This review of evidence in the diagnosis and management of Chagas disease (ChD) was done to assist clinicians who are caring for patients with ChHD in common clinical scenarios found in everyday practice.

EPIDEMIOLOGY

In Latin America, about 6 million people are infected by *Trypansosoma cruzi* (*T. cruzi*), and an unknown proportion of them are *T. cruzi* carriers (3,4). *T. cruzi* infection may cause ChD (4). There are several ways to transmit the protozoan *T. cruzi* to human beings, including through the feces of a kissing bug, congenitally, blood transfusion, oral transmission, laboratory contamination, and organ transplantation (4,5). The main bug vectors well-adapted to living with humans are *Triatoma infestans*, *Rhodnius prolixus,* and *Triatoma dimidiata* from the Reduviidae family, subfamily Triatominae. Blood/platelet concentrate transfusion and congenital transmission continue to be a threat in areas where vector control measurements have been taken and in nonendemic countries (5–7). Due to migration, *T. cruzi*-infected individuals have spread throughout the world; it is estimated that 400,000 infected persons live in nonendemic countries, mainly in the United States and Europe (6,7). A recent meta-analysis of European

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studies that, in aggregate, screened 10,000 Latin American immigrants, found a positive serological test prevalence of 4.2% (8). Based on published seroprevalence in Latin American immigrant populations (1.31%), it was estimated that approximately 300,000 individuals with *T. cruzi* infection live in the United States, with 30,000 to 45,000 cardiomyopathy cases and 63 to 315 congenital infections annually (9). In Latin American immigrants residing in Los Angeles with conduction abnormalities on electrocardiogram, a significant prevalence of ChD has been reported; the highest prevalence rate was among those with right bundle branch block and left anterior fascicular block (17.9%) (10). Among 499 individuals seropositive for *T. cruzi*, 120 (24%) had definite ChHD, and, among 488 *T. cruzi* seronegative individuals, 24 (5%) had cardiomyopathy, for an incidence difference of 1.85/100 person-years attributable to *T. cruzi* infection. Of the 120 seropositive persons classified as having ChHD, 31 (26%) presented with left ventricular ejection fraction (LVEF) <50% and 11 (9%) were classified as New York Heart Association (NYHA) functional class II or higher (11). ChD was the etiology of heart failure (HF) in 19% of Latin-American immigrants diagnosed with advanced nonischemic cardiomyopathy at a Los Angeles hospital (12). Because *T. cruzi* infection is an emerging infectious disease in the United States and Europe, physicians must be able to recognize and treat the most frequent and serious complications of chronic ChD. Also, public health policies should include screening programs for access to diagnosis and treatment, and to avoid nonvectorial transmission (13).

PHENOTYPES: DIAGNOSIS OF *T. CRUZI* INFECTION AND ChD

T. cruzi infection may lead to heterogeneous phenotypes and clinical manifestations in acute infection, chronic phases, and reactivations (14,15) (**Table 1**). Several mechanisms have been proposed for the polymorphic manifestation, such as the form of transmission, lineage of *T. cruzi* with diversity in pathogenicity and histiotropism, reinfection, parasite load, increased genetic susceptibility, immune status of the infected patient, immunosuppression, and coinfection (e.g., human immunodeficiency virus or other viruses). The early diagnosis of previous *T. cruzi* infection is crucial for disease management and prognosis in endemic and nonendemic areas. This permits specific treatment to be offered to people <18 years of age, to babies born to infected mothers (16), and to transplanted patients receiving organs from infected individuals (7). Spain and Italy have adopted control measurements for pregnant women and prompt treatment for newborns (17). Immigrants from Latin American should also undergo screening for *T. cruzi* infection. Screening for Chagas disease in asymptomatic Latin-American adults living in Europe was reported to be a cost-effective strategy (18). As parasites are seldom seen in the blood circulation in the chronic stage, the diagnosis of a previous *T. cruzi* infection is essentially serological, and should be performed using a test with high sensitivity (enzyme-linked immunosorbent assay) with total antigen or indirect immunofluorescence in conjunction with another method with high specificity, such as indirect hemagglutination (14,15).

DIAGNOSIS OF ChHD IN CLINICAL PRACTICE

In clinical practice, the most appropriate diagnostic strategy depends on the clinical stage of the infection. Patients with confirmed positive serological tests should also undergo electrocardiography and echocardiography (**Central Illustration**) (10). In nonendemic regions, the diagnosis should always be suspected by clinicians in immigrant patients with a nonischemic etiology of HF. Because previous *T. cruzi* infection is frequent in endemic areas, the diagnosis of chronic ChHD is based on positive epidemiology and serology associated with typical ChD phenotypes. Some of these phenotypes include bradycardia; right bundle branch block, left anterior fascicular block, or both conditions on electrocardiography; biventricular cardiomyopathy or predominant right ventricular (RV) dysfunction without evidence of another etiology; age generally younger than 60 years; thromboembolism; arrhythmias; sudden death; and syncope. Nonspecific findings suggesting ChHD diagnosis can be obtained on electrocardiography, echocardiography, and cardiac magnetic resonance without high specificity; however, these findings can mimic both ischemic and nonischemic cardiomyopathies (18). The **Central Illustration** shows a clinical practice algorithm for diagnosis and management of patients who are at risk of *T. cruzi* infection without or with cardiovascular symptoms.

ROLE OF SEROLOGICAL BIOMARKERS IN CLINICAL PRACTICE IN ChHD

Because *T. cruzi* infection is usually followed by a long, clinically silent period before the development of an overt clinical presentation of ChHD, detection

ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

ChD = Chagas disease

ChHD = Chagas heart disease or chagasic cardiomyopathy

HF = heart failure

HTx = heart transplantation

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

NSVT = nonsustained ventricular tachycardia

PCR = polymerase chain reaction

RV = right ventricle/ventricular

SCD = sudden cardiac death

SVT = sustained ventricular tachycardia

T. cruzi = *Trypanosoma cruzi*