Review Article

Pathogenicity of Chagas Disease Cardiopathy

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Abstract

Chagas disease is a protozoonoses caused by *Trypanosoma cruzi*. After chronification, human infection may present with several clinical manifestations, ranging from asymptomatic disease to severe cardiomyopathy. Currently, it is estimated that about 7 million people are infected, of which approximately 30% develop heart disease. Chronic Chagas cardiomyopathy (CCC) is the main cause of morbidity and mortality in Chagas patients. CCC presents with particular characteristics, such as extensive fibrosis, thromboembolism, arrhythmogenicity, destruction of the intrinsic cardiac nervous system, microvascular alterations, and sudden death. Here we present an overview of cardiomyopathy in Chagas disease.

ABBREVIATIONS

CCC: Chronic Chagas Cardiomyopathy; ICF: Indeterminate Clinical Form; ECG: Electrocardiogram; Mmps: Matrix Metalloproteinase's; ECM: Extracellular Matrix; TIMPS: Tissue Inhibitors Of Metalloproteinase's; TGF-β: Transforming Growth Factor Beta; PDGF: Platelet-Derived Growth Factor; BFGF: Basic Fibroblast Growth Factor; CCL2/MCP-1: Monocyte Chemoattractant Protein-1; CCL3/MIP-1a: Macrophage Inflammatory Protein 1alpha; TNF-A: Tumor Necrosis Factor Alpha; IL-1:Interleukin-1; IL-4: Interleukin-4; IL-10: Interleukin-10; IL-12: Interleukin-12; IL-13: Interleukin-13; IL-18: Interleukin-18; IL-5: Interleukin-5; IL-8: Interleukin-8; IL-13: Interleukin-13; IFN-γ: Interferon Gamma; ODC: Ornithine Decarboxylase; OAT: Ornithine Amino Transferase; ANS: Autonomic Nervous System; IL-13Rα2: Interleukin-13receptor Subunit Alpha-2; CIAI: Cardiac Intrinsic Autonomic Innervation; ACEI: Angiotensin-Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blockers; ICD: Implantable Cardioverter Defibrillator

INTRODUCTION

Chagas disease, also called American *trypanosomiasis,* is a neglected illness caused by *Trypanosoma cruz* (*T. Cruzi*). At one time, this disease was restricted to Latin American countries; however, due to global mobility, currently, *T. cruzi* infection has spread all over the world, affecting approximately 7 million people [1].

The transmission of the protozoan parasite is possible through contact with feces of contaminated bug vectors (Figure 1), ingestion of food contaminated with *T. cruzi*, blood transfusion, organ transplantation, as well as through congenital transmission [2].

After infection, the disease presents in two distinct phases: acute and chronic. The acute phase lasts approximately 4-8 weeks and is characterized by the presence of the parasite in the blood, as well as some nonspecific symptoms, such as fever, inoculation site edema, and headache. A cure can be achieved in this phase of the disease if the individual receives early treatment with trypanocidal drugs [3]. If the infected individual is not treated or cured, the disease will progress to the chronic phase, which can be symptomatic or asymptomatic. The asymptomatic form is called the indeterminate clinical form (ICF) and is characterized by the absence of pathological signs. Patients with the ICF present with positive serological or parasitological tests of infection, associated with a normal electrocardiogram (ECG), as well as normal radiological examinations of the chest, esophagus, and colon. The symptomatic forms of Chagas disease progress from indeterminate status to clinical Chagas Cardiopathy and/or gastrointestinal disease. The transition from acute to symptomatic forms occurs within 10 to 20 years, progressively [4]. The outcome of the disease depends on parasite characteristics and the host's immune system and genetics (Figure 2).

About one third of Chagas disease patients will develop heart disease with wide spectrum of clinical presentation and severity [5]. Chronic Chagas Cardiopathy (CCC) is responsible for the morbidity and mortality of chagasic patients and, among the cardiomyopathies, is the one presenting with the worst prognosis, higher lethality, higher arrhythmogenicity,
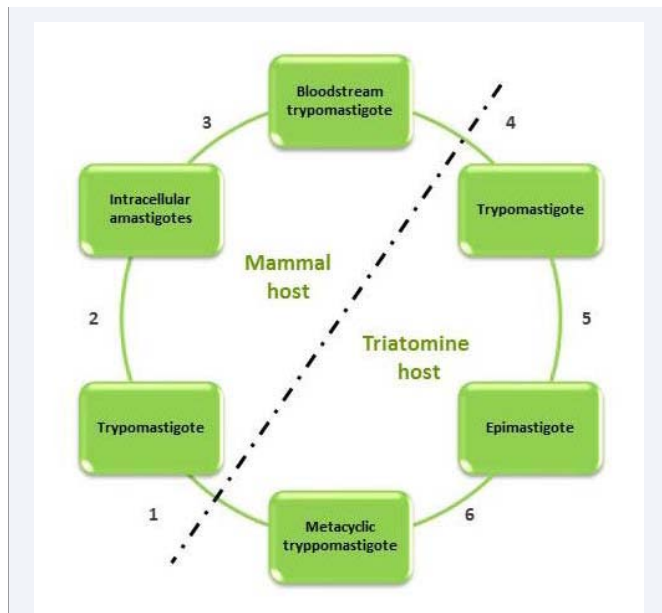
Figure 1 T. cruzi life cycle. While feeding, infected triatomines defecate and parasites present in the feces (metacyclictrypomastigotes) enter the host through skin lesions caused by scratching the bite (1). The parasite is internalized by the host cells where the parasites differentiate in amastigotes, the proliferative form (2). After multiplication, the amastigotes differentiate to trypomastigotes that are able to infect and disseminate to other cells (3). If those parasites are ingested by a triatomine bug (4), it will be converted, in the bug midgut, to epimastigote forms (5), and, in the posterior intestine, epimastigotes are transformed in trypomastigotes (6).
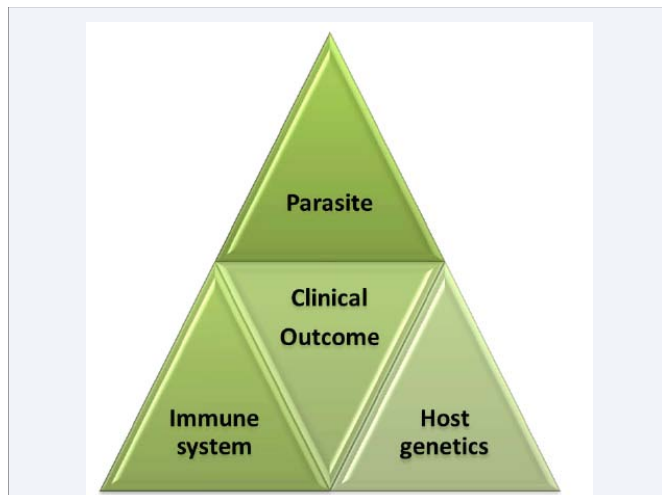

Figure 2 Factors influencing clinical outcome in Chagas disease. Chagas disease can be associated with different outcomes. Infected individuals may develop the indeterminate form and continue this asymptomatic form for life or, progressively, present characteristic symptoms of cardiac and/or digestive clinical forms. There are several factors that lead an individual to the development of different clinical forms. The most critical factors are the presence of parasitic components, which trigger the immune response, important in controlling parasitemia in the acute phase. After the acute phase, the immune response can persist as controlled or exacerbated, which may be important for the maintenance of the asymptomatic form or contribute to the development of tissue injury, respectively. Genetic components will drive the kind of interaction between the parasite and the immune system, and consequently, clinical results of this interaction.

frequent and complex ventricular extra systoles associated with conduction disturbance, thromboembolism, and sudden death [6,7]. CCC is characterized by chronic myocarditis that involves all cardiac chambers and damage to the conduction system [6,8]. All those characteristics establish CCC as a valuable model of clinical and pathogenic studies for other cardiomyopathies. This work will present several distinct aspects of CCC.

Mechanisms of chagas disease pathogenesis

Different mechanisms are proposed to explain the pathogenesis of CCC. One of them relies on the role of parasite persistence and direct tissue destruction. This theory proposes that parasites would continue the process of invading myocardial cells and, when new parasites were released, the host cells would be destroyed. In fact, parasites are not easily found in heart tissue of chronic chagasic patients, but are in patients in the acute phase [9]. However, using more sensitive molecular biological techniques, it is possible to detect parasite DNA in those tissues [10,11]. The low rate of parasitism during the chronic phase, in which the worst symptoms are observed, prompted the suggestion of another hypothesis to explain the disease, involving the immune system auto reactivity.

The hypothesis of auto reactivity mechanisms is based on the activation of the immune system during the acute phase and the persistence of this activation due to molecular mimicry between parasite and host molecules. Several studies support this hypothesis, showing the presence of an inflammatory infiltrate rich in lymphocytes, especially CD8+ T cells, in hearts during the chronic phase, and the detection of antibodies and T cells reactive to auto antigens, as myocardium proteins that mimic parasite components [12-18].

Besides those two main theories, the pathogenesis of Chagas disease may involve autonomic damage by the destruction of heart parasympathetic ganglion cells [19-21] and micro vascular abnormalities [22-25]. All the theories are logical possible explanations for the pathogenesis of Chagas disease, and reflect the multi factorial and complex character of this disease (Figure 3).

Chronic chagas cardiopathy characteristics

Despite the enormous clinical - epidemiological importance of chronic Chagas Cardiopathy, the definitions of clinical management regarding the care of patients with this condition usually come from the acquisition of knowledge gained from the study of other diseases [26-28].

According to Bogliolo [29], Chagas cardiopathy is the most severe form of known myocarditis and the one that disorganizes the most myocardial architecture and structure and the relationship of its components. It is also the most fibrosing [29], and represents the most common cause of myocarditis worldwide [30]. It is an inflammatory myocarditis, probably caused by activation of the immune system, and can lead to arrhythmias, cardiomegaly, heart failure, and often sudden death. In general, it is known that sudden death accounts for 60-65% of deaths from Chagas disease, heart failure for 25-30%, and the remainder from thromboembolic events (10-15%). Death usually occurs one year after the first sign or symptom of congestion
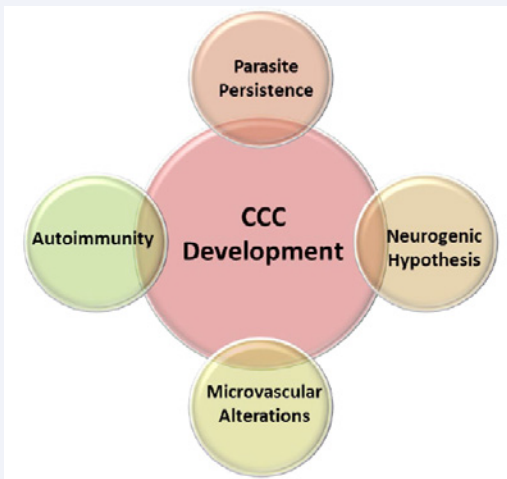
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Figure 3 Chagas disease pathogenesis. The pathogenesis of CCC involves parasite persistence in cardiac tissue, continuous low - grade parasitemia, and immune-mediated myocardial injury, with the contribution of autonomic damage and micro vascular disturbances.
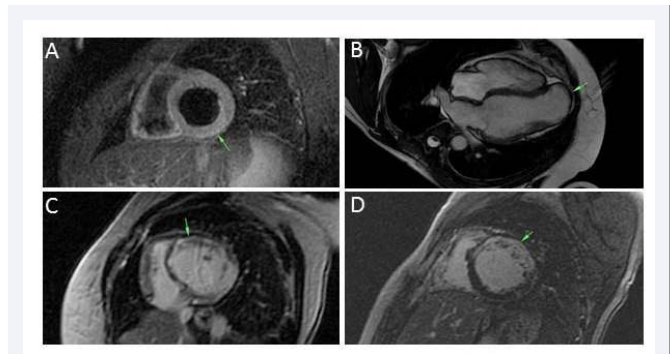

Figure 4 Chagas cardiomyopathy tissue characterization by cardiovascular magnetic resonance (CMR). Myocardial edema (green arrows) shown in a fast spin - echo sequence of the left ventricle (A). Apical aneurysm characteristic of the Chagas cardiomyopathy (arrow) shown by long - axis steady - state free precession image of the left ventricle (B). Myocardial fibrosis and/or necrosis in the mesocardial region (C) or subendocardial region (D) of the anterior segment of the left ventricle shown by a short axis gradient-echo myocardium delayed - enhancement image (green arrows). Photos provided by Dr. Eduardo B Falchetto.

[31]. CCC has important peculiarities, characterized by variable intensity in focal inflammation, consisting of lymphonuclear cells, structural derangement, hypertrophy, myocardial edema, dilatation, which predominates, and intense reactive and reparative fibrosis (Figures 4A,C,D) [29,32]. Signs of chronic congestion, cardiomegaly, and thromboembolic events are the primary gross pathological changes. Heart enlargement is due to the combination of hypertrophy and dilation, and aneurysms occur in 20-40% of the cases, which is a striking feature of chronic Chagas myocarditis (Figure 4B) [32]. When compared to other forms of dilated cardiomyopathy, it is the one that most frequently leads to sudden death, myocardial remodeling, and more severe heart failure [33]. Chagas disease characteristically presents with a slow and progressive clinical course, although sometimes it may rapidly evolve. Sudden death may be its first manifestation [31,34].

From the pathophysiological aspect, i.e., hemodynamic, inflammatory, and neurohormonal factors, CCC does not appear to differ from forms of idiopathic and ischemic cardiomyopathies. It is usually believed that the results of large clinical trials in heart failure can be extrapolated to those patients with dilated cardiomyopathy, including those with Chagas disease. However, it is known that CCC presents with pathogenic and immunopathogenic characteristics, such as more extensive inflammation and fibrosis. There is also autonomic dysfunction with various forms of atrioventricular and intraventricular blockage, autoimmunity with antibodies directed toward myocyteproteins, beta receptors, and adrenergic neurons, making it unique in many respects (Table 1).

Thromboembolism and arrhythmia

Thromboembolic events are relatively frequent in CCC and constitute the third most frequent cause of death [35]. Brain embolism is the most common clinically recognized event, followed by limb and pulmonary embolisms. Stroke can be the first manifestation of the disease in asymptomatic patients [36-

Table 1: Curiosities and characteristics of Chagas disease and Chronic Chagas Cardiopathy

Summary of information about Choronic Chagas Cardiopathy
Chagas disease was named in honor of Carlos Chagas, a Brazilian researcher who discovered its etiological agent, transmission forms, and symptoms related to the disease in 1909.
Chagas disease is known as American *Trypanosomiasis*, however, due to globalization, it is now not confined to Latin America.
Chronic Chagas Cardiomyopathy (CCC) is the most debilitating form of the disease and affects young adults who may become unable to work.
Global costs for Chagas disease are $7.19 billion per year. A substantial proportion of those costs come from lost productivity due to cardiovascular disease-induced early mortality.
CCC is the most fibrosing cardiomyopathy, leading to myocardium commitment, fiber, and matrix disorganization, which produce an arrhythmogenic environment.
CCC is the most arrhythmogenic cardiopathy, associated with conduction disorders of distinct magnitude. The more frequent the arrhythmia is, the worse the prognosis.
Reentry is the most common ventricular arrhythmia mechanism in CCC. The presence and magnitude of non-sustained ventricular tachycardia is associated with a worse prognosis and precedes the risk of sustained ventricular tachycardia and ventricular fibrillation, responsible for sudden death.
Ventricular dysfunction is a determinant prognostic factor of arrhythmia in CCC.
Microcirculation disturbances and sympathetic system imbalance also contribute to arrhythmia development.
Echocardiography is a useful, cheap, non-invasive tool to study morphofunctional cardiac alteration and ventricular function.
Myocardial perfusion scintigraphy evaluates perfusion in cardiac muscle, especially the left ventricle and inter-ventricular septum. A MIBG (metaiodobenzylguanidine) scan evaluates myocardial sympathetic denervation.
Cardiac magnetic resonance imaging evaluates morphofunctional myocardium conditions and conveys information about systolic and diastolic functions, myocardial perfusion, fibrosis, necrosis, edema and presence of inflammation.

41]. Therefore, chronic Chagas disease has been considered an often - unrecognized cause of stroke and should be regularly included in its differential diagnosis in Latin American patients. Left ventricular systolic dysfunction, left atrial volume enlargement, apical aneurysm, mural thrombus, and cardiac arrhythmias seem to be important risk factors in the genesis of ischemic stroke related to Chagas Cardiopathy [36,38,42].

Complete atrioventricular block may occur with Stokes - Adams syndrome and there is danger of sudden death [43]. This wide range of manifestations of chronic Chagas heart disease led to the development of a classification system based on clinical, radiological, electrocardiographic, and echocardiographic evidence. Our group use the follow classification system: CCC 1: asymptomatic patients, without significant alteration on ECG; CCC 2: patients presenting minor ECG alterations; CCC 3: patients presenting considerable ECG alterations, mainly advanced conduction abnormalities; CCC 4: patients presenting severe ECG alterations, predominantly rhythm disorders and CCC 5: patients presenting signs of heart enlargement [44].

An important consequence of myocardial lesions is ventricular dysfunction. With the destruction of the myocardial fibers and their replacement by fibrous tissue, compensatory mechanisms are triggered through hypertrophy of intact fibers and dilation of the ventricular cavity to maintain cardiac output, blood pressure, and tissue perfusion at appropriate levels. However, with the progression of myocarditis and excessive distention of the remaining myocytes, this compensation process becomes inappropriate, leading up to the clinical manifestations of heart failure [45].

The presence of inflammatory foci and areas of fibrosis in the contractile myocardium or Purkinje network can produce multiple electrophysiological changes and favor the appearance of the reentry phenomenon, which is the primary electrophysiological mechanism of ventricular tachyarrhythmia [46]. All types of arrhythmias are extremely frequent in patients with Chagas disease and, like other cardiomyopathies, their presence, and, in particular, their severity, influence the prognosis [47]. There is evidence that the intensity of the ventricular arrhythmia is significantly higher in heart failure due to Chagas disease, as compared to other etiologies. Sudden death is one of the most significant phenomena of the natural history of chronic Chagas disease, affecting individuals in the most productive stages of their lives and is the leading cause of death in this disease [48].

Immune response and cardiac remodeling in chagas disease

The immune response following infection with *T. cruzi* is an important factor in determining the course of the disease. However, the same factors controlling parasitemia may also contribute to the appearance of inflammatory lesions in Chagas disease [49].

Chagas cardiomyopathy patients present with an inflammatory immunological profile, observed *in situ* and systemically. There is a predominance of IFN-γ and TNF-α production in relation to IL-10 production that is also observed in those patients [50-53]. The imbalance between inflammatory

and anti - inflammatory cytokine expression may favor the aggravation of cardiac disease [54]. The higher TNF-α production is related to worse cardiac function and worse prognosis of disease and a higher IFN- expression is related to a more severe degree of cardiomyopathy [55,56]. The presence of elevated levels of cytokines and chemokines induced by *T. cruzi* in the inflammatory infiltrate in the myocardium can lead to chronic changes in the cardiac structure, such as collagen deposition and fibrosis [57,58].

Fibrosis

In CCC, as well as other dilated inflammatory cardiomyopathies, fibrosis occurs as a result of massive and constant infiltration of inflammatory cells in the myocardium. This process is mediated by cytokines and growth factors that regulate the migration, proliferation, and differentiation, as well as the production and degradation of different extracellular matrix components.

Progressive and fibrosing chronic myocarditis and/or hypertrophy of the heart can be seen by the change in the hearts' shapes [59,60]. Myocarditis, one of the major pathological processes observed in Chagas disease, occurs in the acute and chronic phases, but in the chronic phase, it is disproportionate to the tissue parasitism [61]. Some authors have noted that the inflammatory infiltrates appear to be more harmful to the cardiac fibers than to the parasites themselves [18]; at this stage, myocarditis is characterized by infiltration of mononuclear cells, and the destruction of myocardial fibers in the inflammatory focus, areas of fibrosis, and rare parasites [62]. Studies show that the destruction of cardiac fibers in patients with Chagas disease could be related to mechanisms established soon after infection with *T. cruzi* and may be caused by continuous stimulation of antigens during the illness [32].

Chronic Chagas disease myocarditis presents as a dynamic process that is periodically reactive in foci, which evolve to fibrosis, at which point lesions can be observed in different stages of development [63]. Fibrosis is prominent, and all types of described fibrosis (focal, diffuse interstitial, perivascular, and plexiform) can be found, even in the same tissue section [64].

The production of the cytokine TGF-β in areas near the lesions may contribute to myocyte hypertrophy and the deposition of extracellular matrix [67]. In addition to TGF-β, other molecules also participate in the genesis and regulation of fibrosis: endothelin, PDGF (Platelet-derived growth factor), bFGF (basic fibroblast growth factor), CCL2/MCP-1, CCL3/MIP-1a, TNF-α, IL-1, IL-5, IL-8, and IL-13, which are described as pro - fibrogenic factors, and IFN-γ [65].

IL-13 is a powerful mediator of fibrosis in asthma and schistosomiasis, acting as a regulator of extracellular matrix production. The regulation of IL-13 production is influenced by several factors, including the cytokines IL-4, IL-12, IL-18, IFN-γ, IL-10, TGF-β, TNF-α, and IL-4/IL-13 receptor [66]. The primary mechanism by which IL-13 exerts its fibrogenic effect is through the alternative macrophage activation and preferential activation of the arginase-1 enzyme, leading to the production of L-ornithine. L-ornithine, in turn, serves as a substrate for the enzymes ornithine decarboxylase (ODC) and ornithine amino transferase (OAT), resulting in the generation of polyamines and

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proline, respectively. Proline is an essential amino acid used in collagen production. IL-13 also acts on fibroblasts, directly or indirectly, by stimulating and activating TGF-β by macrophages. In addition, the type 2 immune response stimulates the expression of the IL-13Rα2 receptor (IL-13 decoy receptor), which regulates the effector activity of IL-13. The type 1 immune response, as triggered by infection with *T. cruzi*, typically antagonizes the expression of this receptor *in vivo*, which may lead to an increased effect of IL-13 when produced in low amounts or when type 1 and type 2 responses together predominate [66]. The role of IL-13 in myocardial fibrosis during Chagas cardiomyopathy has not yet been explored. Preliminary data in experimental model show that IL-13 expression in the myocardium correlates with the degree of susceptibility of the animal to an acute infection with *T. cruzi*; susceptible mice C3H/HeSnJ, which also succumb to infection during the acute phase, have an enhanced expression of IL-13 and cardiac inflammation, and intense fibrosis [67].

Based on immunological aspects, the chronic phase of *T. cruzi* infection may be characterized by the balance between the accumulation of efficient immune response (innate and adaptive) and the presence of a few parasites in the host tissue. This balance could lead to a lengthy asymptomatic period of the disease, but in a significant proportion of patients, for unknown reasons, there is a disturbance in this regulation, which leads to the onset of severe clinical manifestations of the disease in the chronic phase (Figure 5) [68].

Intrinsic cardiac nervous system commitment

The autonomic nervous system (ANS) coordinates and integrates the relationship between an organism and the environment. The ANS also influences heart and vascular system functioning by modulating heart rate and cardiac output. The heart autonomic nervous system consists of sympathetic and parasympathetic branches. Stimulation of the sympathetic branch leads to an increase of heart rate and myocardial contractility, whereas the parasympathetic branch stimulation leads to a decrease of heart rate and contractility. The interplay between these two branches is an important homeostatic process in an organism [69].

Alterations in autonomic function linked to the heart are a hallmark of Chagas disease, occurring in the acute phase and may progress during all chronic forms. Cardiac intrinsic autonomic innervation (CIAI) lesions are less pronounced in the indeterminate form, shown by discrete neuroganglionitis [70]. In the cardiac and/or digestive forms, CIAI is more severely damaged by alterations due to inflammatory and degenerative processes, which results in neuronal depopulation [71]. Parasympathetic fibers are preferentially destroyed; however, sympathetic fibers are also affected [23].

The disturbance of the autonomic system presents with variable intensity between individuals; therefore, different consequences of dysautonomia are observed individually. Generally, indeterminate patients and patients presenting with border line electrocardiograms show less intense autonomic dysfunction. Conversely, the most severe alterations are observed in the digestive and cardio - digestive forms. Dysautonomia in cardiac patients is less severe when compared with that in
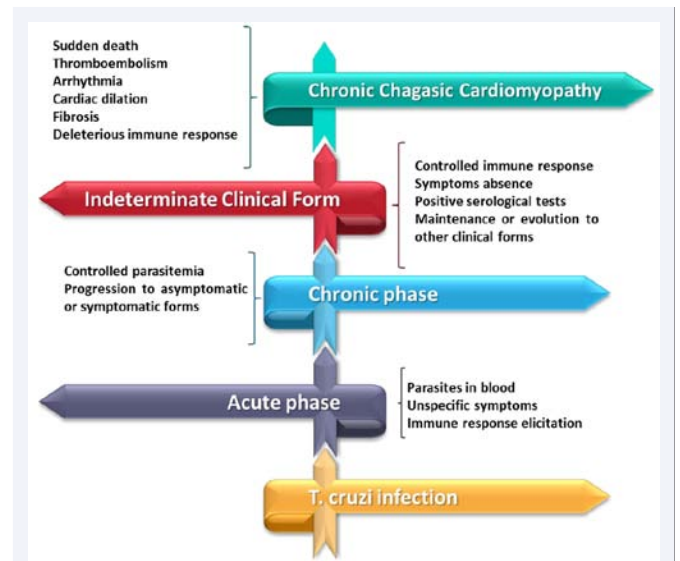

Figure 5 Chronic Chagas Cardiomyopathy (CCC) development timeline. After infection with T. cruzi, the individual will follow an acute phase, which could last for about 8 weeks and usually has no specific symptoms. If not treated and/or cured, the individual will develop an asymptom.

patients with the digestive and cardio - digestive clinical forms. Interestingly, normal cardiac autonomic function might also be encountered in patients with any form of Chagas disease [72-74]. Whether or not dysautonomia is a cause or consequence of secondary cardiac disturbances is controversial; however, there is a consensus that CIAI alteration in combination with myocardial damage and excite - conducting system lesions may enhance patient outcome.

Considering the modulatory role of the ANS over electrophysiological heart properties, it is logical to associate alterations in this system and the arrhythmogenesis phenomenon, common in CCC. Axonal regeneration and proliferation of sympathetic fibers, after the damage, was observed in myocardial infarction lesions and other cardiac lesions. This phenomenon may cause electrical instability and, consequently, arrhythmias, due to an imbalance between those areas poorly enervated and those more abundantly enervated in the damaged myocardium [75,76]. It is possible that the same occurs in cardiac Chagas disease, leading to an imbalance, due to the preferential destruction of parasympathetic fibers to the detriment of sympathetic ones. Arrhythmia development in CCC is a result of a combination of lesions in the myocardium, alteration of the excite - conducting system, and ANS imbalance. An intense ventricular arrhythmia may result in sudden death [77].

Other consequences of dysautonomia in cardiac Chagas disease patients are systemic alterations of metabolism, hormone releasing, and immune response, since the ANS modulates many of those processes.

Micro vascular alterations

Myocardial cell destruction and ischemia observed in CCC occur with the contribution of cardiac micro vascular alteration that modifies the blood distribution in chagasic heart. Studies in experimental models of chronic Chagas disease demonstrated an

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association between necrosis, degeneration, and intravascular platelet aggregation in the myocardium of infected mice, suggestive of microcirculation participation via transient ischemia and hypoxic changes in the pathogenesis of chagasic cardiomyopathy [78,79].

In humans, studies of the myocardium of chagasic patients demonstrated collapse of intramyocardial arterioles, which presented with intimal thickening [25]. Some years later, a similar study indicated that the micro vascular abnormalities were responsible for the myocytolysis observed in a CCC necroscopic study [80]. Abnormal perfusion has also been confirmed in chagasic patients. In a study using myocardial perfusion scintigraphy (MPS), at least one perfusion defect was detected in each CCC patient evaluated [81]. The same group observed that the majority of individuals with CCC and normal epicardial coronary circulation also presented with perfusion defects [81]. Corroborating these findings, a morphologic study using confocal microscopy, characterized micro vascular alterations in hearts from patients with CCC. This study observed a severe and diffuse arteriolar dilation in association with micro vessel tortuosity, which may cause unbalanced blood flow distribution, focal worsening in tissue perfusion, and multiple infarctions. Additionally, the fibrotic tissue causes obstruction in vessel trajectory, which may contribute to blood deviation, leading to the appearance of ischemic areas [25]. A recent study using magnetic resonance imaging (MRI) described a pattern of delayed enhancement, especially for the apical and inferolateral segments of the left ventricle, similar to observations of ischemic and non ischemic heart diseases. Then, the myocardial involvement in CCC may be due to micro vascular disturbances and chronic myocardium inflammation [82].

Chronic chagas cardiopathy management

Treatment of CCC comprises treatment of cardiac alterations. Specific treatment with trypanocidal drugs is indicated for patients at the acute phase of the disease, preventatively in organ transplantation to the donor and the recipient, in reactivation of disease in immune suppressed patients, in patients with recent chronic infections (within the past 5-12 years), and all children infected with *T. cruzi*. There are few studies appointing the efficacy of the specific therapeutic in preventing the evolution of the disease which contribute to the controversial role of the trypanocidal drugs use in chronic Chagas patients [83,84].

The treatment of heart failure caused by Chagas disease is based on the use of a combination of medications, such as angiotensin-converting-enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), diuretics, beta - blockers, and aldosterone inhibitors. According to the General Guidelines of Heart Failure, the treatment should start with an ACEi or ARB, diuretics, and aldosterone inhibitors. After optimization, beta - blockers might be added [27,85].

Treatment and prevention of thromboembolic phenomena in CCC patients are done, if clinically recommended, by the use of anticoagulation. Medication should be considered for patients presenting with atrial fibrillation, preceding mural thrombus, embolic events, or an apical aneurysm [27,85].

Antiarrhythmic treatment of CCC patients is controversial, however, the use of an implantable Cardioverter defibrillator (ICD) might be benign in patients presenting with malignant, sustained ventricular tachycardia or those resuscitated from sudden cardiac arrest, with a low left ventricular ejection fraction. Pacemaker biventricular resynchronization benefits CCC patients with left bundle branch block and severe systolic left ventricular dysfunction [77]. Amiodarone is usually used as antiarrhythmic drug in patients with CCC [26,86].

Finally, heart transplantation for severe Chagas heart disease should be considered as a treatment option [87].

CONCLUSION

Chronic Chagas cardiopathy, the most debilitating clinical manifestation of Chagas disease is a complex disease, involving parasite presence, interaction of the parasite and host immune systems, as well as autoimmune reactions. Host - parasite interactions result in cellular destruction with consequent damage of the autonomic and micro vascular systems, which may affect heart function and structure.

There is not a consensus on the use of anti - parasitic drugs in the chronic phase of Chagas disease, since its efficacy is not completely proven. CCC treatment is focused on managing the symptoms of heart failure. The search for biomarkers to identify the progression of the indeterminate form of CCC and research for specific treatment to avoid the advance of cardiac symptoms is urgent, considering the large number of infected individuals, the great prevalence of the disease, and the poor prognosis associated with the high lethality of the cardiac form of Chagas disease.

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