Review Article

Renal Disfunction in Chagas Disease

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Abstract

Background: Chagas' disease has a wide distribution in South America, having several forms of transmission. The disease's evolution varies according to the parasite/host relationship, presenting diversified progression through the acute, indeterminate and chronic forms. In the cardiac form, there are several clinical and laboratory alterations due to the involvement of several organs, including the kidneys. Actually, a lot of mechanisms are employed for the control and detection of renal damage. It has been proven that before the cardiac inflammatory changes were established, alterations in renal function could be observed due to elevated levels of urea, creatinine and other alterations compatible with the clinical picture of uremia. As well it was possible to verify an anemic state in laboratory animals, thus, it could be a condition known as cardio-anemic-renal syndrome described in patients with heart failure. Although there are studies correlating clinical and laboratory findings of renal dysfunction in Chagas' disease, there is still a need to elucidate some pathways of interaction between chagasic physiopathogeny and renal function.

Aim: The present study addresses a review of articles from the current and classical scientific literature, correlating the function and/or loss of renal function with Chagas' disease.

Conclusion: The information base of renal pathophisyology is crucial in order to better understand this problem of public health that involves several countries and populations.

Keywords: Chagas' disease; Neglected diseases; Trypanosomiasis; *Trypanosoma cruzi*; Kidney; Nephritis

Introduction

Chagas' disease is a disorder of wide distribution in South America and it is caused by the protozoan *Trypanosoma cruzi* (*T. cruzi*) [1]. For many years, the primary means of transmission was through the triatomine hematophagous vector; however, other pathways of infection such as blood transfusion, organ transplantation, transplacental and oral infection are more frequent [2-4].

This parasitosis is characterized by an initial acute phase that later becomes chronic, and it may evolve to myocarditis and affect other organs, such as the kidney [5-7]. There are few reports correlating the involvement of renal function with the pathophysiology of Chagas' disease, and most of them involve organ transplantation or the reactivation of the disorder [8,9]. A study by Lenzi [10] demonstrated the relationship between the disseminated form of infection, tissue damage in the acute phase and the presence of the parasite in the tissue. Other authors have also described the relationship between *T. cruzi* parasitism and acute infection in other organs, such as the kidney and intestines [11-13].

Inflammatory response is important for the pathogenicity of renal injury, along with other factors such as impairment of endothelium, which releases reactive oxygen species (ROS), and produce mediators of damaged tubular cells [14]. This dysfunction involves increased production of nitric oxide (NO), reactive oxygen species (ROS) and endothelin, as well as decreased vascular smooth muscle sensitivity to NO and prostacyclin. Under these conditions, endothelial cells lose the ability to regulate vascular tone, perfusion, permeability, inflammation and cell adhesion [15]. In summary, several mechanisms may be involved with tissue aggression in Chagas' disease (whether local or systemic), which would interfere with renal physiology.

Development

Etiologic agent and evolutionary cycle

Chagas' disease is one of the most widespread diseases in the Americas and its vectors was already found from the southern United States to Argentina. For many years, the transmission of *T. cruzi* was

primarily through triatomine vectors, which proliferate in abundance in precarious housing conditions environments [16]. This phenomenon limited the incidence of the disorder to certain countries and social classes. Due to the other transmission routes - blood, transplacental (congenital) and oral [4,7] for example, - Chagas' disease also affects individuals under better socioeconomic conditions.

T. cruzi performs its biological cycle in both invertebrate and vertebrate hosts, which leads to several evolutionary forms. In their cycle in humans, trypomastigotes eliminated in the feces and urine of the invertebrate vector penetrate the site of the bite and interact with macrophages of the skin or mucosa, differentiating in amastigotes, and multiplying in this place by simple binary division. Sequentially, the differentiation of the amastigotes into trypomastigotes occurs and they are released into bloodstream, reaching other cells of any tissue or are destroyed by immunological mechanisms of the host.

The triatomine vectors become infected by ingesting trypomastigote forms present in the bloodstream of vertebrate host; in the insect's stomach they differentiate into rounded epimastigote forms. In the middle intestine, epimastigotes are multiplied by simple binary division, being responsible for the maintenance of infection in the vector. In the rectum, epimastigotes differentiate into metacyclic trypomastigotes, being eliminated in feces or urine [17,18].

Evolution of Chagas' disease and the related immune response

The onset of chagasic infection in humans is marked by the acute phase, in which parasites are detected in a direct blood test, lasting one to two months. At this stage, a non-specific inflammatory process may occur, the chagoma of inoculation or Romaña sign (a typical manifestation of ocular infection with unilateral bi-palpebral edema and lymph node infarction) [16]. However, in most individuals the acute phase is asymptomatic and may have some nonspecific symptoms such as malaise and fever [19]. At this stage, the immune response is essential both in chronifying the disease and in reducing parasitaemia [20].

In the bloodstream, the interaction of trypomastigotes with host cells initiates an immune response based on the induction of Natural Killer cell activation and subsequent lymphocyte T cell expansion. First, the parasite is phagocytosed by macrophage and then begins the multiplication of amastigote forms within this cell, inducing the inflammatory response, leading to the production of cytokines such as TNF-α and IL-12, in addition to nitric oxide, generating macrophagic enhancement. These cytokines activate Natural Killer (NK) cells, which are important sources for the synthesis of other cytokines, such as IFN-γ and TNF-α, responsible factors for the activation of macrophages and consequent destruction of intra- and extracellular microorganisms [20-22]. On the other hand, the production of IL-4 and IL-10 inhibits the activation of macrophages and the differentiation of Th1 cells, inducing differentiation of Th2 cells, more commonly observed in bacterial infections [23,24].

Following macrophage activation, the antigens are exhibited on the macrophage membrane, initially for CD4+ T lymphocytes (produced by Th0 differentiation in Th1), which also release type I cytokines (IFN-γ and TGF-β), in order to eliminate the parasite and produce a cytotoxic TCD8+response. Finally, the activation of T lymphocytes generates IgG antibodies [20,25,26].

The evolution from the acute phase to the chronic one is perceived through diminution of the sanguine parasitism and the intensity of inflammatory process. This parasitism persists for the whole life of the host, and no cases of spontaneous cures have been known so far [27]. At first in the chronic phase, the individual may not present clinical signs and symptoms, which characterizes the indeterminate form of Chagas' disease. However, there are other patients who may manifest symptoms during the chronic phase and these will determine distinct anatomic-clinical forms (cardiac, digestive, cardiac and digestive, nervous, reactivation of Chagas disease, cardio-anemic-renal syndrome [28-31].

Chagas disease and renal damage

The cardiac form is the most serious clinical manifestation of the disease. The most common symptoms are: palpitations (tachycardia) and out-of-rhythm heart beats (extra-systoles and arrhythmias), dizziness, chest pain, shortness of breath in physical exertion, and progressive heart failure [32].

In an experimental study, Oliveira et al. [33] demonstrated that before the cardiac inflammatory alterations were established, alterations in renal function were already observed by the increase of urea and creatinine. Further study of renal function showed the presence of leukocyturia and high concentrations of urobilinogen in the urine, besides oliguria and polaciuria (compatible clinical picture of uremia). It was also possible to verify an anemic state in laboratory animals, leading to the establishment of cardio-anemic-renal syndrome described in patients with heart failure [33]. Such anemic state may be related to a deficit in renal function which results in a lower release of the renal hormone erythropoietin, which stimulates erythrocytic production in the bone marrow.

Before cardiac lesions were established, rats infected with *T. cruzi* showed renal inflammatory infiltration. This inflammatory process, in addition to kidney damage, caused ischemic/reperfusion injury due to the increase of pro-inflammatory cytokines and NO. In addition, it was seen that in the absence of Fas-L (binding proteins of tumor necrosis factor (TNF)), there was a lower cardiac inflammatory infiltration, but a higher systemic inflammatory response and renal injury. These data suggest that the damage of renal tissue leads to an irreversible dysfunction of renal and cardiac function, promoting death, even after blockade of the renin-angiotensin system (RAS) [34-36].

In relation to morphometry, Peña et al. [37] described the application of the stereological method in the evaluation of some parameters, such as the number and volume of glomeruli per mm^3 and the results obtained showed the variation of this compartment in relation to age and also to several diseases. Such analysis could be applied in renal biopsies of nephropathic patients in order to reach the estimation not only of the risks but also the prognosis of renal damage in chagasic patients [38]. Similarly, human experimental studies have been performed, being possible analyse several organs [39-41], including heart [42,43] and kidney [37]. These studies demonstrated important structural changes in the architecture of each tissue in Chagas' disease.

The cytokines involved in the inflammatory process are responsible for the morphological changes found in the damage tissue. In this sense, the role of polymorphonuclear cells (PMN) in the renal injury process has been discussed, since in cases of Ischemic Renal Insufficiency, PMN are not observed histologically in the tissue even with increased activity of Myeloperoxidase (MPO). The MPO enzyme

is present in the PMN cytoplasm and is directly related to the oxygen-dependent bactericidal mechanisms, acting as a catalyst protein in the formation of highly reactive radicals such as hypochlorous acid (HCLO), from H_2O_2 and halogen ions [44]. This enzyme represents an important defense mechanism against pathogenic microorganisms, like *T. cruzi* [44]. Thus, intense recruitment of these cells into renal tissue is expected to explain the elevation of enzyme activity, degranulation of PMN and consequent release of intracellular stocks of MPO, which would remain bound to the cellular membranes of renal tissue [45].

Another way of assessing kidney damage in Chagas' disease is based on biochemical parameters measured in both blood plasma and urine. Rosa [46] and other studies have shown that male Wistar rats infected with *T. cruzi* have hidroelectrolytes disorders in response to water deprivation for a period of 8 h. These alterations were represented by a lower conservation and a higher excretion of water and sodium, which indicated a decreased rate of glomerular filtration. In addition, creatinine excretion was lower in infected rats than controls, which corroborates to the reduced rate of glomerular filtration.

Conclusion

The pathophysiology of Chagas' disease is complex and involves several mechanisms in response to the presence of the parasite. The innate immunity of the host plays a crucial role in such response, through the action of NK cells that limits parasite growth, as well as promotes the development of acquired cellular immunity. Infection of macrophages by *T. cruzi* can induce IL-12 secretion, which leads to increased production of IFN-γ and TNF-α, resulting in parasitemia and mortality control. On the other hand, the development of this effective response against parasitic dissemination (depending on the parasite / host relationship) can provide tissue damage.

Chagas' disease, in its chronic phase, may compromise tissue physiology, as well as loss of function (cardiac and/or digestive). In addition, in its cardiac manifestation (Chagas' heart disease), systemic decompensation is observed, leading to injury of several organs.

There are some studies that investigate the function/loss of renal function due to *T. cruzi* infection. Most of these studies involve renal lesions (correlating them with cardiac lesions) or are aimed at infection or reactivation of the disease in renal transplantation, with scarce literature involving renal pathophysiology in Chagas' disease.

It is important to note that although there are studies correlating clinical and laboratory findings of renal dysfunction in Chagas' disease, this relationship is still poorly studied. Therefore, it's necessary to elucidate some routes of interaction between the disease and renal dysfunctions.

Conflict of Interest

None

Acknowledgements

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