EDITORIAL

Myocardial Involvement in Chagas disease: From Parasite to Immune Response

Compromiso miocárdico en la enfermedad de Chagas: Del parásito a la respuesta inmune

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Chagas cardiomyopathy (CC) is a unique and fascinating model of myocardial involvement within the spectrum of cardiovascular disease. Chagas disease (CD) is an acute zoonotic infection caused by the hemoflagellate protozoan parasite Trypanosoma cruzi. (TC). After the acute phase, which is oligosymptomatic in most cases, the disease mysteriously cools down and evolves into a quiescent phase. Several decades after the acute infection, in less than 30% of asymptomatic carriers, selective organ involvement inexplicably develops, in most cases involving the cardiovascular system. (1) At this point, we must deal with one of the most lethal cardiomyopathies known in the field of human medicine, which almost invariably involves prototypical compromise of the conduction system, a furious generation of supraventricular and ventricular arrhythmias associated with high risk of sudden cardiac death, heart failure rapidly evolving towards refractory disease and, to top it all off, the heart becomes an efficient thromboembolic factory. (2) The latter characteristic is not only explained by the frequent occurrence of the paradigmatic apical aneurysm and the increased number of cases of atrial fibrillation, but also by probable intrinsic factors of hypercoagulability inherent to the pathogen itself. (3)

But how is it possible for this microscopic protozoan to produce all this damage? Dysautonomia, microvascular impairment, microembolic phenomena and focal fibrosis are the mechanisms most closely related with cardiac involvement; nevertheless, they are actually only epiphenomena that barely let us see the surface of the pathogenesis of Chagas disease. The true determinants are cast in deep shadows, hidden by the paucity of research resources, minimal interest in the disease, or simply by insufficient understanding of all the variables of human biology. Two of them are usually suspected and are the main lines of investigation in CD. The first determinant is related with direct parasite pathogenicity and the second with the specific immune response to T. cruzi antigens either by direct cellular/humoral cytotoxicity or by autoimmunity secondary to molecular mimicry that transforms the cardiomyocyte into a collateral victim of the response to the pathogen. (4) In summary: parasite or immunity.

In this issue of the Argentine Journal of Cardiology, Principato et al. shed light on this topic, laying on the table an interesting study aimed at determining the presence of a distinctive inflammatory pattern in patients with incipient myocardial abnormalities secondary to CC. (5) For this purpose, the researchers evaluated the inflammatory profile of 22 patients with a diagnosis of Chagas disease with preserved systolic function. Ten of these patients presented intraventricular conduction disturbances (IVCD) and were compared with the remaining 12 patients without IVCD. Despite the small sample size, a differential inflammatory profile was convincingly evident with a statistically significant increase in inflammatory cytokines such as MP1α, IL-2, IL-12, IL-15 and INF-γ in the IVCD group with respect to the comparator. Additionally, there were no significant differences when the inflammatory profile of the subjects without IVCD was compared with a control group without disease. In summary, inflammatory cytokines were increased in patients with stage B1 CC but not in the group without interventricular conduction disturbances or in the control group.

There are several findings supporting immune involvement as a key factor in the genesis of CC. Interestingly, despite the universal exposure to the parasite, only one third of infected subjects progress to the determinate stage, suggesting that the parasite itself is not sufficient. Familial aggregation of CC cases is another striking finding that has been previously described, suggesting an element of genetic susceptibility or predetermined immune responses. (6) Another interesting observation is the low correlation between the intensity of the inflammatory reaction and the number of parasites. (7) In the same sense, our research group has recently described how, remarkably unexpectedly, patients with CC with low parasitemia had greater impairment of systolic function and myocardial strain, a statistically significant increase in cardiac biomarkers and higher mortality at two years of follow-up com-

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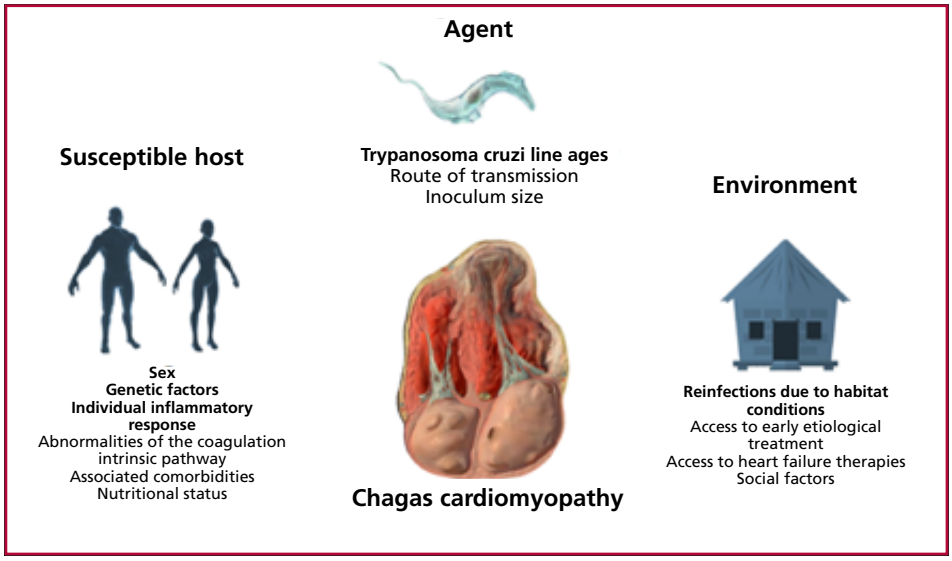

Fig. 1. Ecological triad of Chagas disease where the interaction between the host, agent and environment creates multiple possibilities for the different developments of the disease

pared with those with high parasitemia. (8) All these data support the hypothesis that immunological clearance of the parasite may be even more important than the presence of the parasite itself, and that the particular inflammatory reaction of each organism is potentially the key to the puzzle of myocardial damage in CC. Another important topic is to determine how this immunological activity causes damage. Could Trypanosoma Cruzi be our evolutionary distant relative and do we preserve some family traits that turn out to be our ruin? The evolutionary preservation of the primary sequences of many proteins and structural substances of protists in the evolution to Homo sapiens indicates such direction; therefore, the detection of cross-reacting antigens between the two species does not appear to be surprising. Previous publications have reported the presence of immunological cross reactions and antigenic mimicry between T Cruzi and host autoantigens. (9) Three decades ago, Vermelho et al. described that the presence of glycosphingolipids in heart muscle cells were strikingly similar to those constitutive of T. cruzi and could induce immunological reactivity. (10)

It is clear that in CC, as in many other diseases, the combination of infective agent, host, and environmental factors (described by Leavell and Clark in their legendary book on preventive medicine more than 50 years ago) (11) is critical for the development of diseases. An example of this lies on the parasite itself. The linage of T. cruzi seems to largely determine the type of organ involved (T cruzi I preferentially involves the heart, and T cruzi V and IV involve the heart and gastrointestinal tract) while the environmental factors influence the possibility of reinfection and of acquiring synergistic comorbidities. Finally, the innate immune response appears to be the key to the onset and extent of organ damage (Figure 1).

In conclusion, despite the limitations of the article, such as the small sample size and the absence of correlation with other more robust parameters of cardiovascular involvement, the investigation by Principato et al. provides key knowledge to understand the puzzle of CC and, above all, constitutes a brave invitation to cardiologists, internists and other health care professionals to explore beyond the visible spectrum of our understanding, leaving our comfort zone in an attempt to answer by our own means the main questions of the most Latin American of all cardiovascular diseases.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

Ethical considerations

Not applicable.

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