MYOCARDIAL DISEASE

Neglected tropical cardiomyopathies: I. Chagas disease

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Cardiomyopathies, defined as diseases of the myocardium associated with cardiac dysfunction, are classified into dilated, hypertrophic, restrictive and arrhythmogenic right ventricular cardiomyopathy, as well as unclassified.[1] More recently, molecular classification has been suggested.[2] Cardiomyopathies continue to be a significant cause of morbidity and mortality in the developed world.[w1] In developing countries, however, there appears to be an increased incidence of the "usual" forms of cardiomyopathy, with a modified clinical course possibly due to genetic differences or environmental factors such as malnutrition, infections and pollution.[w2] In addition, there are specific cardiomyopathies endemic to the tropics such as Chagas and endomyocardial fibrosis, which cause a considerable amount of death and suffering and have been classified as neglected diseases. We here describe what is known about these two diseases, their aetiologies, pathogenesis and management and outline directions for further research. The present article will discuss Chagas disease, and a subsequent article will address endomyocardial fibrosis.

CHAGAS DISEASE

Chagas disease is the leading cause of cardiac disease in many countries in Latin America, and the World Health Organization has estimated that 16–18 million people are currently infected and 90 million are at risk of infection.[3] Chagas disease has been classified as one of the most neglected diseases in the world,[w3] with no new drug development in the past 30 years.[w4] Yet there are still 200 000 new cases of Chagas disease reported each year and some rural communities in Latin America have seroprevalence rates as high as 40%.

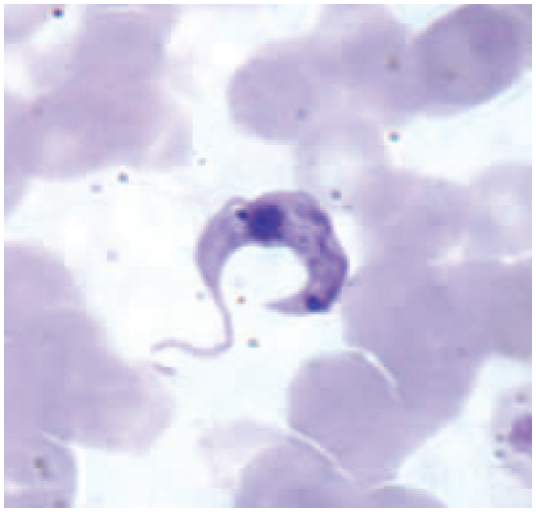

Figure 1 *Trypanosoma cruzi*, the causative agent of Chagas disease.

EPIDEMIOLOGY

Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi* (fig 1), which is spread by triatomine bugs (fig 2). The disease is mainly constrained geographically to countries where its vector is endemic, ranging from South America to Mexico and southern USA. Transmission has also been shown to occur via blood transfusions, organ transplants as well as transplacentally and by ingestion of triatomine contaminated food or drink.[w5] The bug lives in the mud walls and thatched roofs of poor quality houses in rural areas; therefore, Chagas disease is linked to socioeconomic status with the rural poor being most exposed.

With increasing immigration from Latin America to the United States there was concern relating to safety of blood donations in the USA. A study between 2006 and 2007 identified one in 4655 blood donations in three centres in California and Arizona as being positive for *T cruzi* antibodies.[w6] There have been seven reported transfusion acquired infections for Chagas disease in the USA and Canada.[w7,w8] The Food and Drug Administration has recently licensed a new *T cruzi* enzyme-linked immunosorbent assay (ELISA) test system to screen blood donors in the USA.[w9] Vector borne transmission of Chagas disease can also occur in the southern United States, but with five reported cases ever it remains rare, so the potential for misdiagnosis is significant.[w10]

LIFE CYCLE OF THE PARASITE

The triatomine bug becomes infected when it takes a blood meal from an infected mammal, and the parasite develops over a few weeks within the bug's intestine as the epimastigote. When an infected bug bites a person, contaminated faeces may enter the body through the wound, other areas of broken skin, or the conjunctiva of the eyes, introducing the infectious form of the parasite (the metacyclic trypomastigote) into the host. These

Figure 2 *Triatoma infestans*, the vector for Chagas disease.

parasites penetrate most commonly host phagocytic cells and multiply intracellularly as amastigotes. They are then released into the blood stream as trypomastigotes able to infect a variety of host cells, most commonly myocardial cells. The trypomastigotes may also be taken up by feeding triatomine bugs, thus continuing the life cycle.[w11]

DISEASE STAGES

The acute phase of the infection with *T cruzi* is characterised by a self limiting syndrome lasting between 4–8 weeks, with fever, malaise, lymphadenopathy, hepatosplenomegaly and myocarditis. A chagoma may occur at the site of entry or, if this is at the conjunctiva, a unilateral periorbital oedema can occur called Romañas sign. During this stage parasites can be demonstrated in the blood and there is direct invasion of myocardial fibres. Rarely, it can cause a meningoencephalitis in younger children, which carries a poor prognosis. Overall the acute infection has around a 10% mortality rate.[4 w12]

In the majority of cases, through the development of immunity, the infection is controlled and the disease progresses to a latent period or indeterminate phase. Dilated cardiomyopathy constitutes the chronic phase which develops in up to 30% of infected individuals between 10–20 years later.[w12] This may present as congestive cardiac failure, symptomatic arrhythmias, thromboembolic disease or sudden death.[w13 w14] The left ventricular wall becomes thinner, allowing the formation of an apical aneurysm, a distinctive feature of Chagas cardiomyopathy. Thrombi are often present in such aneurysms, easily explaining the common occurrence of thromboembolisms.

Cardiac dysautonomia is a hallmark of chronic Chagas disease resulting in varying degrees of heart block in the initial stages, plus a frequent occurrence of malignant arrhythmias.[w13] Ventricular premature contractions are common. Runs of ventricular tachycardia, complete heart block, malignant arrhythmias and thromboembolic disease could all be contributing to the high prevalence of sudden death in chagasic patients. The overall 5 year mortality for patients with established Chagas cardiomyopathy is over 50%.[w13]

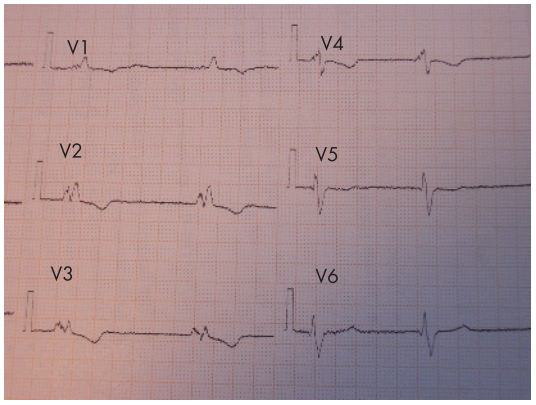

Figure 3 ECG from a patient with early Chagas cardiomyopathy showing right bundle branch block.

ECG AND ECHOCARDIOGRAPHY FINDINGS

We studied early echo and ECG changes in patients with Chagas disease in Honduras and found 36% of asymptomatic patients infected with *T cruzi* already had myocardial functional impairment and 29% had ECG changes, most commonly right bundle branch block (RBBB) alone or with left anterior hemi-block.[5] (fig 3).

In the later symptomatic stages the majority of patients have grossly abnormal echocardiograms, representative of the widespread cardiac involvement including dilated ventricles, thinned walls and large left and right atria, and significant overall ventricular functional impairment (fig 4). ECG changes in these later stages are also pronounced, with both conduction disturbances and arrhythmias being found far more frequently than in dilated cardiomyopathies of other aetiologies.[w13]

DIAGNOSIS

T cruzi parasites can often be detected by direct blood smear in the acute phase of the disease, but due to low levels of parasitaemia in the indeterminate and chronic phases, diagnosis has previously relied on xenodiagnosis and serological tests including ELISA and indirect immunofluoresence assay (IFF).[w15] Recently, molecular based assays using polymerase chain reaction (PCR) have been shown to be the most sensitive technique to diagnose patients with chronic Chagas disease,[6] and has also been shown to be the most effective way for evaluation of cure following anti-trypanosome treatment.[w16]

PATHOGENESIS

In the acute phase of the disease the myocarditis that develops has been associated with the parasitaemia affecting the target organ. The damage results from direct destruction due to intracellular parasitism, necrosis related to inflammation, and other cytotoxic mechanisms involving CD8 T cells and, less frequently, CD4 T cells. Such cells recognize *T cruzi* epitopes at the surface of infected cells, which

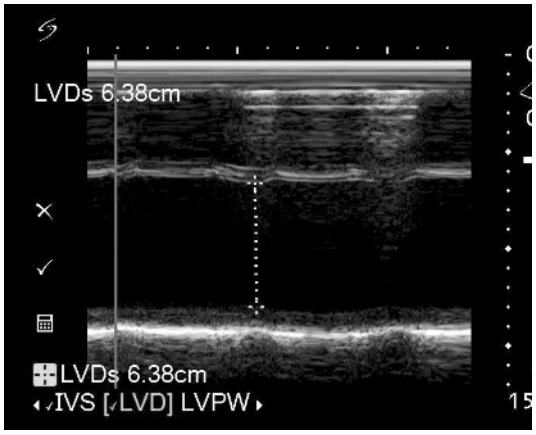

Figure 4 M mode echocardiogram showing a dilated left ventricle (6.38 cm in systole) of a patient with severe Chagas cardiomyopathy, with pronounced hypokinesia of the thinned septum and posterior wall.

contain amastigotes, and non-infected cells, which have processed parasite antigens.[7]

The histopathological picture of the myocardium in chronic Chagas disease is characterised by a chronic inflammatory process in all four chambers of the heart (with the right side often worst affected), with focal thickening, tissue destruction and interstitial fibrosis, either focal or later becoming diffusely distributed.[7 8]

The progression to this chronic stage and the factors determining why only a certain proportion of patients develop this stage remains poorly understood. Due to the scarcity of parasites in the myocardium in these later stages, and the occurrence of myocardial inflammatory infiltrate, many theories have implicated autoimmune and inflammatory processes in the pathogenesis. One of us (SY) is currently investigating the role of cytokines as mediators of disease progression in patients with different stages of Chagas disease and the role of cytokine gene polymorphisms as a predisposing factor to disease.[w17]

Recent developments in molecular and immunohistochemistry have demonstrated *T cruzi* antigen in the inflammatory foci in chronic Chagas hearts. This suggests that parasite persistence is driving the immune response, causing the low grade tissue destruction and chronic inflammation. However, the *T cruzi* antigen remains scarce and not always associated with the inflammatory foci in the myocardium. It is likely that the pathogenesis of chronic Chagas cardiomyopathy is a complex interplay between parasite and the host's immune response.[9] Further research is needed to investigate the mechanism of cardiac injury and why 30% of people infected progress to cardiomyopathy.

PROGNOSIS

Patients with Chagas cardiomyopathy have a different clinical progression to other cardiomyopathies, often with a worse prognosis.[4] A study of heart failure patients with cardiomyopathies of different aetiologies in Brazil showed Chagas disease to be the most important determinant for mortality.[w18] A risk score for predicting mortality has recently been developed and validated for Chagas cardiomyopathy.[10] Of the six independent prognostic factors identified, the first three were related to functional class, cardiomegaly and systolic dysfunction, plus demonstration of ventricular arrhythmias. Management therefore should be aimed at aggressive treatment of the heart failure and prevention of malignant arrhythmias.

MANAGEMENT

This consists of treating the different manifestations of the disease and, importantly, controlling the infection and applying preventive measures.

Cardiac failure treatment

Due to a lack of specific clinical trials for Chagas cardiomyopathy patients, treatment has traditionally relied upon the same heart failure medications as have been used to treat other cardiomyopathies, including diuretics, angiotensin converting enzyme (ACE) inhibitors and digoxin.[w19] In particular, ACE inhibitors, which have been shown to improve survival in the latter group,[w20] have been utilised in studies investigating the specific effect of these agents on chagasic patients. Captopril has been shown to improve cardiac function but not mortality from Chagas heart disease.[11] Captopril is also an anti-inflammatory agent, acting through the immunomodulatory actions of angiotensin II and the downstream effects of bradykinin. In a mouse model of acute Chagas myocarditis, captopril significantly reduced cardiac necrosis and fibrosis without increasing parasite burden.[12] β-blockers currently used in standard heart failure treatment have been postulated to be beneficial in Chagas cardiomyopathy; however, data to confirm this are lacking. A recent study has demonstrated in a small cohort beneficial effect with the addition of the β-blocker carvedilol to an ACE inhibitor in cardiac function and clinical status of patients with chagasic cardiomyopathy.[13] Larger randomised controlled trials, including other β-blockers as well, are needed to verify these findings.

Treatment of rhythm disturbances

Due to the high frequency of atrioventricular (AV) nodal block in Chagas disease, pacemakers are often used and are a very effective treatment option, but they do not alter the progression of the disease.[5] The use of these devices is life saving with a need for humanitarian organisations, individual professionals and commercial companies to donate devices to the local physicians who are capable and willing to help deprived individuals free of charge.[5]

For tachyarrhythmias, antiarrhythmics such as amiodarone are used, and more recently implantable cardioverter-defibrillators (ICDs). Chagas disease patients have indications for ICD implantation similar to those of other patients.[14] However, in patients with cardiomyopathies of different aetiologies receiving ICDs, Chagas

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patients had the highest cumulative incidence of life threatening ventricular arrhythmias[w21] and significantly more had received an appropriate shock in the first 6 months after implantation.[w22]

Transplantation

Heart transplantation for end stage Chagas cardiomyopathy has been shown to be a valuable treatment option, with old fears of reactivation of the disease in the allograft and therefore poor survival rates being disproved.[15] In Brazil, follow-up of patients undergoing heart transplantation showed significantly better survival rates for Chagas cardiomyopathy compared to other types of cardiomyopathy.[w23] Reactivation of *T cruzi* remains a concern, but improved molecular based diagnostics allows early identification of parasitaemia and successful treatment with antiparasitic agents.[w24]

Antiparasitic treatment

In the 1970s the antiparasitic agents benznidazole and nifurtimox were introduced for clinical treatment of Chagas disease, but high toxicity and variable efficacy, especially in the chronic phase, limited their use.[w4] More recent data suggest favourable outcomes in children and young adults treated with benznidazole in the early chronic phase of *T cruzi* infection, with 55.8% showing negative seroconversion of *T cruzi* antibodies at 3 year follow-up compared to controls.[16]

In addition, a non-randomised trial in 2006 showed that the use of benznidazole in patients in indeterminate phase with no heart failure was associated with reduced progression to chronic Chagas cardiomyopathy.[17] A Cochrane Review in 2002 also suggests potential for trypanocidal drugs in asymptomatic patients, but emphasises the need for large randomised controlled trials including newer agents to confirm these findings.[18]

New antiparasitic drug developments

Although there have been no new licensed antitrypanosomal drugs since the 1970s, the recent sequencing of the *T cruzi* genome in 2005 opens up possibilities for the development of novel therapeutics.[19]

Currently experimental antifungal triazoles are reported to show good trypanocidal effects in acute and chronic murine models.[w25 w26] Itraconazole in particular has shown excellent parasitological cure in animal models and human Chagas disease.[w27 w28] Allopurinol has also shown encouraging results in treating chronic *T cruzi* infections with far fewer side effects than conventional anti-trypanosomal treatments.[w28 w29]

Other potential chemotherapeutic agents against *T cruzi* in development include tricyclic drugs, antiproliferative lysophospholipid analogues (already in clinical trials as the first oral treatment for visceral leishmaniasis), and cysteine proteinase (cruzipain) inhibitors.[w25]

There is an urgent need for human clinical trials of these new therapeutic agents for the 18 million people currently infected with *T cruzi* for which there are grossly inadequate treatment options.

CONTROL OF DISEASE

In the early 1990s the "southern cone initiative" included many countries in South America and saw great reductions of transmission, through vector elimination from residual spraying with synthetic pyrethroids, housing improvements and health education.[20] More recently the Andean and Central American countries have adopted similar control programmes plus universal screening of blood products to control transfusion related infections.[21] In July 2007 the WHO launched a "global network for Chagas elimination" with the goal of coordinating efforts to eliminate Chagas disease by 2010. However, as *T cruzi* has many animal reservoirs, completely eradicating the disease seems almost impossible. As new rural housing developments spread and insecticide spraying is labour intensive and expensive, without continued vigilance and surveillance resurgence of Chagas disease will remain a threat.[w30] An integrated approach to prevention, diagnosis and management is badly needed.

CONCLUSION

Chagas disease is no longer a sole problem for the rural poor of South America. An estimated 12.7 million Latin Americans are currently resident in the USA, with up to 0.5 million thought to be infected with *T cruzi*.

The management of Chagas disease depends on the stage, with patients in the acute and indeterminate phase most likely to benefit from antiparasitic treatment. Management of patients in the advanced stages should be aimed at aggressive heart failure treatments and antiarrhythmics, including ICDs and heart transplantation considered for those with end stage disease. Further research is still needed to elucidate the complex immunology underlying the pathogenesis of Chagas disease, which in turn may lead to the well needed development of novel therapeutics.

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Chagas disease remains a major cause of cardiac morbidity and mortality in the Americas, and although there has been success in reducing transmission in the past decade, areas of resurgence are occurring as well as spread to new areas. Global awareness of Chagas disease needs to be promoted in the medical and general community if any impact is to be made on this neglected disease.

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