RESEARCH NOTE

Chagas Disease and Immunosuppression

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Chagas disease, caused by a hemoflagellate, *Trypanosoma cruzi*, is a parasitic disease widely distributed throughout Latin America. It is transmitted to man by hematophagous vectors (reduviid bugs), blood transfusion and, more rarely, by oral route, laboratory accidents, and from mother to fetus. About 18 million people are chronically infected by this parasite in the Americas. The majority of these individuals do not display signs or symptoms of the disease (indeterminate phase), but as time goes by around 30% of the infected individuals develop signs of cardiopathy and/or megaesophagus/magacolon (MS Ferreira et al. 1997a *Clin Infect Dis 25*: 1397-1400).

From several decades, cases of reactivation of Chagas disease in immunocompromised individuals have been recognized. The literature registers cases of *T. cruzi* meningoencephalitis and/or myocarditis occurring in patients with hematologic cancers (leukemias and lymphomas), kidney, bone marrow and heart transplantation, and in individuals using high doses of corticosteroids and other immunosupressors. The epidemic of acquired immunodeficiency syndrome (Aids) opened the possibility of the appearance of this parasitosis in individuals seriously immunocompromised by the human immunodeficiency virus (HIV) and coinfected with *T. cruzi*. In Brazil, nowadays, the majority of carriers of this infection live in big cities, where cases of Aids are commoner; therefore it is expected the occurrence of a growing number of these reactivations in coinfected individuals. In chagasic patients with hematologic cancers who reactivate the infection it was observed the development of severe cases of meningoencephalitis and myocarditis; the parasite, in general, can be easily seen by direct examination of a blood smear. The mortality in these cases has been high, particularly in those whose diagnosis is delayed. Treatment with nifurtimox or benznidazole can lead to remission and decrease mortality substantially (MS Ferreira et al. 1997b p. 365-379. In JC Pinto Dias & JR Coura, *Clínica e Terapêutica da Doença de Chagas. Uma Abordagem Prática para o Clínico Geral*, Fiocruz, Rio de Janeiro).

The reactivation of chagasic infection also occurs in patients submitted to kidney or heart transplant who are treated with immunosupressive therapy. *T. cruzi* infection can also be acquired, in these cases, by the organ transplanted from a chagasic donor. In patients submitted to kidney transplant the clinical manifestations can be indistinguishable from the acute phase, with occasional involvement of the central nervous system. Cardiac transplants carried out in patients with chronic chagasic cardiopathy have been uncommon, but reactivation of the trypanosomiasis occurs in the majority of the individuals, with clinical manifestations characterized by fever, signs of acute myocarditis, characterized by cardiac failure or atrioventricular block, and erithematous-infiltrative cutaneous lesions whose histopathological study reveals the presence of paniculitis with a large number of nests of *T. cruzi* within macrophages (Ferreira et al. 1997b *loc. cit.*).

In patients with kidney transplant with reactivated Chagas disease, the finding of the parasite in the blood smear is key to the diagnosis, but this finding is rare in patients with cardiac transplants. Therapy with benznidazole with usual doses (5 mg/kg/day for 60 days) suppresses efficiently the clinical symptoms, but obviously does not cure the parasitosis. Another drug, allopurinol (600mg/day) seems to be safe and effective in the treatment of Chagas disease reactivation after heart transplantation (DR Almeida et al. 1996 *Ann Thorac Surg 61*: 1727-1733). Secondary episodes of reactivation can occur. It is important to note that American trypanosomiasis is not a contraindication to any form of transplant, given that specific therapy is able, as already mentioned, to rapidly suppress the clinical manifestations of reactivation (Ferreira et al. 1997b *loc. cit.*).

About 60 cases of Chagas disease reactivation in patients with Aids have been documented as of December 1998, the majority of them only reported in congresses and symposiums of the speciality; 19 cases are published and the details of them can be found in two recent publications, where the subject is discussed (Ferreira et al. 1997a *loc. cit.*, AMC Sartori et al. 1998 *Clin Infect Dis 26*: 177-179).

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Curiously, the first case of reactivation of the disease in patients with Aids occurred in the United States, but the majority of the subsequent cases was diagnosed in Brazil and Argentina. In our hospital (Uberlândia, MG), in na endemic area of Chagas disease, 6% of the HIV positive who were submitted to autopsy had reactivated Chagas disease (3 out of 52 cases) (MS Ferreira et al. 1991 *Am J Trop Med Hyg 45*: 723-727, D Gluckstein et al. 1992 *Am J Med 92*: 429-432, Ferreira et al. 1997a *loc. cit.*).

Although in the majority of the patients so far reported there are no data regarding their immunologic status, it is possible to presume that reactivation of this protozoosis tends to occur, similarly to what is seen with other opportunistic infection in Aids, when the T CD4 lymphocyte count is below 200 cells/mm^3 (Ferreira et al. 1997a *loc. cit.*). In fact, in ten published cases where this information was available, the number of T CD4 lymphocyte number varied from 35 to 382 cells/mm^3, and in seven of them the levels were below 200 cells/mm^3 (Ferreira et al. 1997a *loc. cit.*).

The two organic sites more frequently involved in cases of reactivation were the central nervous system and the heart (Ferreira et al. 1991 *loc. cit.*, D Gluckstein et al. 1992 *Am J Med 92*: 429-432, A Rocha et al. 1993 *Rev Inst Med Trop São Paulo 35*: 205-208, A Rocha et al. 1994 *Am J Trop Med Hyg 50*: 261-268, AMC Sartori et al. 1995 *Clin Infect Dis 21*: 1297-1299, Ferreira et al. 1997a *loc. cit.*, RS Pacheco et al. 1998 *Mem Inst Oswaldo Cruz 93*: 165-169). In the former, it is observed the presence of na acute meningoencephalitis, uni or multifocal, which occurs in about 75 to 80% of the cases. Fever, headache, vomiting, focal signs, seizures and, rarely, meningeal signs constitute the major clinical manifestations. Cerebrospinal fluid, in these cases, displays a mild lymphomononuclear pleocytosis, with raised proteins, and the parasite is usually present in this fluid. Also in this phase, it is constant the presence of *T. cruzi* in the blood, given that it is sought in a systematic way and with appropriate technique (Strout, thick blood, microhematocrit). Documentation of parasitemia by xenodiagnosis or blood culture should not be considered as evidence of reactivation, given that positivity by these methods can occur in any phase of the disease, including in chagasic patients not infected with HIV (Ferreira et al. 1997a *loc. cit.*).

Computed tomography of the brain reveals, in the patients with meningoencephalitis, one or more hypodense lesions, predominantly in subcortical areas, with ring enhancement after contrast injection. Such lesions are very similar to those seen in toxoplasmosis of the nervous system, although the encephalic areas involved in this parasitosis are mainly thalamic and in the periventricular basal nuclei. Magnetic ressonance is another method of high sensitivity to detect cerebral lesions in the reactivation of *T. cruzi* infection (Rocha et al. 1994 *loc. cit.*).

Histologically, the brain shows severe memingoencephalitis, with intense inflammatory, predominantly perivascular infiltrate, with the presence of countless amastigotes of *T. cruzi* parasitizing glial cells and, rarely, neurons. The meninges also show parasitism within macrophages, what could be an explanation for the high frequency of the finding of tripomastigote forms in the cerebrospinal fluid (Rocha et al. 1994 *loc. cit.*).

The heart is another organ involved during the process of reactivation of Chagas disease. The frequency of this involvement is difficult to be calculated, given that the majority of the reactivated patients did not have their heart systematically examined after their death. Contrary to meningoencephalitis, cardiac involvement can be overlooked particularly when its involvement is mild. In the cases so far published this organ was involved in about 45% of the patients. The three patients who had reactivation in the serie of Sartori et al. had myocarditis (Sartori et al. 1998 *loc. cit.*). The clinical manifestations, when present, are consequent to the development of cardiac failure (tachycardia, edema, hepatomegaly) or arrhythmias. One of our cases, whose reactivation occurred only at the cardiac level, had extensive pericardial effusion, with presence of tripomastigote forms of the parasite on direct examination of the pericardial fluid. Endomyocardial biopsy can be of great value in the diagnosis of reactivated acute chagasic myocarditis; anatomopathologically, acute myocarditis in these patients is severe, with presence of numerous amastigote nests within myocardial fibres. Sometimes only segments of the organ are involved, as it occurred in one of our patients who had involvement only of the left atrium (Rocha et al. 1994 *loc. cit.*). Confirmation of the identity of the parasite by immunohistochemical techniques is mandatory in this situation, as concurrent parasitism of the myocardium by *T. cruzi* and *Toxoplasma gondii* has already been documented in one of the patients submitted to autopsy by us.

It is fundamental that the diagnosis is done quickly, given that the early administration of treatment is very important for a better prognosis. The mean survival in these patients has been short, on average ten days, with only three patients surviving longer than three months (Ferreira et al. 1997 *loc. cit.*).

The only drug available for therapeutic with reactivated trypanosomiasis in patients with Aids is benznidazole, which is recommended in the dose of 5 mg/kg/day, twice a day for a minimum of 60 days (SA Nishioka et al. 1993 *Mem Inst Oswaldo*

Cruz 88: 493-496, Ferreira et al. 1997a *loc. cit.*, Sartori et al. 1998 *loc. cit.*). Adverse effects, such as skin rash, peripheral neuropathy and granulocytopenia can be observed during the use of the medication. Nifurtimox, not available any longer in Brazil, can also be used in the dose of 8-10 mg/kg/day in three daily doses for 60 to 90 days. Side effects are also commonly described during the use of this medication, such as weight loss, peripheral neuropathy, skin rash, psicosis and leukopenia. Triazole derivatives (itraconazole, fluconazole) have already been used in more than one occasion, apparently successfully, for the treatment of Chagas' disease reactivation in patients with Aids (AMC Solari et al. 1993 *Clin Infect Dis 16*: 255-259). We do not recommend them, however, as first line therapy for patients with severe forms of *T. cruzi* meningoencephalitis or myocarditis.

Remission of the disease can be documented after a few days of the start of the treatment, with disappearance of the fever and other symptoms, improvement of neurologic signs and arrhythmias and/or cardiac failure developed by the patient. Direct examination, blood cultures and xenodiagnosis become negative within the first weeks of therapy. Secondary prophylaxis is indicated for the patients who achieved complete remission of the clinical manifestations, given that new reactivations can occur in the following months. The introduction of antiretroviral therapy in these patients can theoretically, by improvement of the immunitary state, decrease the likelihood of new reactivations. A committee of experts meeting in Uruguay in 1996 under the sponsorship of the Pan American Health Organization recommended for secondary prophylaxis the use of benznidazole in the dose of 5 mg/kg/day three times a week indefinitely. Nifurtimox can be used alternatively. Triazole derivatives and allopurinol are theoretical alternatives for this indication. Consensus has not been achieved yet for the utilization of primary prophylaxis in chagasic patients carriers of HIV (Anonymous 1996 *Bol Oficina Sanit Panam 121*: 377-403).