Reactivation of Chagas disease with central nervous system involvement in HIV-infected patients in Argentina, 1992—2007

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SUMMARY

Objectives: The objective of this study was to evaluate clinical and microbiological characteristics of Chagas disease (ChD) with central nervous system (CNS) involvement in AIDS patients.

Methods: This was a retrospective study of clinical and laboratory findings of HIV-infected patients with a confirmed diagnosis of ChD involving the CNS during the period 1992—2007 at the “Francisco J. Muñiz” Infectious Diseases Hospital, Buenos Aires, Argentina.

Results: Of a total of 15 patients, 14 were male and the median age was 33 years (range 25—54 years). Seven out of nine had lived in a Chagas endemic area and 7/10 were intravenous drug users (IDUs). The disease was reactivated during corticosteroid therapy in three patients. Clinical manifestations were: headache (11/15), focal neurological deficits (9/15), fever (9/15), meningismus (7/15), seizures (7/15), altered mental status (5/15), and cardiac involvement (3/10). The median CD4 T-cell count at the time of reactivation was 64 cells/µl (range 1—240). Twelve of 14 had positive serology for Trypanosoma cruzi; the two negative were IDUs. Cerebrospinal fluid (CSF) findings (median (range)): cell count 5/mm³ (2—90), protein level 0.68 g/l (0.1—1.84), and glucose level 0.45 g/l (0.13—0.73). CSF direct examination for T. cruzi was positive in 11/13.

Neuroimaging findings showed a single hypodense lesion in 7/14 and normal images in 2/14. Twelve patients were treated with benznidazole. The global mortality was 79% (11/14).

Conclusions: ChD reactivation should be considered as a differential diagnosis of meningoencephalitis in HIV patients with low CD4 T-cell counts, previous residency in an endemic area, and/or IDUs. Whenever possible, lumbar puncture should be performed because of the high accuracy for early diagnosis.

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Introduction

Chagas disease, or American trypanosomiasis, is a zoonotic disease caused by Trypanosoma cruzi, a flagellated protozoan. It extends from the southern USA to the south of South America. T. cruzi is transmitted mainly by vectors (triatomine bugs) more common in rural areas. Other mechanisms of transmission are transfusion of infected blood, transplacental route, organ transplantation from an infected donor and, more rarely, oral route and laboratory accidents. Sharing intravenous needles with an infected person is another possible means of transmission.2,3

In Latin America, the disease affects about 25% of the population, with 16 to 18 million people infected and about 100 million at high risk of infection.4 Following urban migration, Chagas disease has become a health problem in non-endemic cities and countries.1,5 In the USA, approximately 50 000 to 100 000 immigrants have evidence of chronic T. cruzi infection,6 and the estimated seroprevalence is one in 4655 blood donations for T. cruzi antibodies.7 In recent years many non-vector-associated cases have been published in the literature, most of them from Latin America,1,5 in endemic cities and countries.3,16 However, limited data from prospective and retrospective studies of reactivations involving the central nervous system (CNS) are available. The aim of this study was to evaluate clinical and microbiological characteristics of 15 HIV-infected patients with a confirmed diagnosis of Chagas disease reactivation with CNS involvement.

Methods

This was a retrospective study of clinical and laboratory findings for 15 HIV-infected patients with a confirmed diagnosis of Chagas disease involving the CNS, for the period 1992–2007, at the “Francisco J. Muñiz” Infectious Diseases Hospital, Buenos Aires, Argentina. Data recorded included epidemiological information, clinical findings, time from the onset of symptoms to diagnosis, serological and direct microscopic examination (DME) tests for Trypanosoma cruzi infection, neuroimaging findings, CD4 cell count, cerebrospinal fluid (CSF) examination, treatment, and clinical outcome.

Screening for HIV infection was done by ELISA; positive results were confirmed by Western blot. Serological diagnosis of T. cruzi infection was defined as at least two different positive serological tests (indirect immunofluorescence assay, indirect hemagglutination assay, ELISA, complement fixation for anti-T. cruzi antibodies). Detection of parasites was done by Strout method7 in blood and by direct microscopic examination and Giemsa-stained smear in CSF.

CNS Chagas disease was defined as the detection of: (1) T. cruzi trypomastigote forms through DME of CSF; (2) amastigote forms in histologic examination of brain tissue; (3) trypomastigote forms through DME of blood, with neurological manifestations and clinical response to treatment without another concomitant neurological disease.

Results

Of a total of 15 patients, 14 were men; the median age was 33 years (range 25–54 years). Ten out of fifteen were aware of their previous HIV seropositive status and 6/15 had a concomitant opportunistic infection (OI; category C of the CDC classification) at admission. None of them were receiving highly active antiretroviral therapy (HAART) and only three were under co-trimoxazole prophylaxis. In only 4/15 had the diagnosis of T. cruzi infection been done before admission. Seven out of nine had lived in a Chagas endemic area. Seven out of ten were intravenous drug users (IDUs) and in three patients this was the only risk factor for T. cruzi infection. In three patients the disease was reactivated while they were receiving high dose corticosteroid therapy (prednisone equivalent 20 mg/day or higher for more than 21 days) for another OI (Pneumocystis jirovecii pneumonia, Toxoplasma encephalitis, and oral plasmablastic lymphoma).

The main clinical manifestations are shown in Table 1 and were: headache (11/15), focal neurological deficits (9/15), fever (9/15), meningismus (7/15), seizures (7/15), altered mental status (5/15), and concomitant cardiac involvement (3/10). The median CD4 T-cell count at the time of Chagas disease reactivation was 64 cells/μl (range 1–240); 77% of the patients had a count of <100 CD4 T-cells/μl. Twelve out of fourteen had positive serological tests for T. cruzi infection; the two who were negative were IDUs. T. cruzi parasitemia was detected in only 1/7.

Lumbar puncture was performed in 13 patients. In the other two patients this diagnostic procedure was contraindicated. CSF findings were (median range): cell count 5/mm³ (2–90), protein level 0.68 g/l (0.1–1.84), and glucose level 0.45 g/l (0.13–0.73). One of the patients had normal CSF values. CSF direct examination for T. cruzi was positive in 11/13 (85%) (Figure 1).

Neuroimaging studies were performed in 14 patients. The most frequent finding was a single supratentorial hypodense lesion (50%) compatible with abscess, involving predominantly the white matter of the brain lobes (83%) (Figure 2). Two patients had normal neuroimaging studies (14%) (Table 2).
Table 1 Clinical manifestations in HIV positive patients with a confirmed diagnosis of Chagas disease involving the central nervous system

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Headache</td>
<td>11/15</td>
<td>73</td>
</tr>
<tr>
<td>Focal neurological deficits</td>
<td>9/15</td>
<td>60</td>
</tr>
<tr>
<td>Fever</td>
<td>9/15</td>
<td>60</td>
</tr>
<tr>
<td>Meningismus</td>
<td>7/15</td>
<td>47</td>
</tr>
<tr>
<td>Seizures</td>
<td>7/15</td>
<td>47</td>
</tr>
<tr>
<td>Altered mental status&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5/15</td>
<td>33</td>
</tr>
<tr>
<td>Concomitant cardiac involvement&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3/10</td>
<td>30</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes confusion, delirium, or a declining level of consciousness ranging from lethargy to coma.

<sup>b</sup> Includes signs and symptoms of acute myocarditis evaluated with electrocardiogram and echocardiogram without a history of previous cardiomyopathy. Not confirmed by isolation of parasites in heart tissue.

Figure 1 Trypanosoma cruzi trypomastigote in a smear of cerebrospinal fluid (Giemsa).

Figure 2 Magnetic resonance imaging showing a single periventricular white matter lesion, with gadolinium enhancement and perilesional edema corresponding with cerebral chagoma.
Diagnosis was achieved by DME of CSF in 11/15, by stereotactic brain biopsy and histologic examination of smear tissues in 3/15 (Figure 3), and by Strout method in 1/15. The median time between the onset of clinical manifestations and diagnosis was 15 days (range 1—60). Twelve out of 15 patients were treated with oral benznidazole (5 mg/kg/day divided into two daily doses), six of whom (50%) experienced side effects during hospitalization (Table 3). Three patients had not received specific treatment; in two of them diagnosis was done postmortem, and the other was discharged after diagnosis with no follow-up data available.

Eleven of fourteen died (79%) with a median time of survival of 21 days (range 0—180). Of the survivors, one was discharged and followed up at another center and information on his outcome was not available. The other two survivors continued on secondary prophylaxis with benznidazole 200 mg three times a week and were started on antiretroviral therapy. In one of them the secondary prophylaxis was interrupted after immune reconstitution without any relapse of T. cruzi infection to date.

Discussion

To the best of our knowledge, this is one of the largest reported series of HIV-infected patients with neurological involvement due to Chagas disease. History of living in an endemic area is still the major risk factor for T. cruzi transmission. However, we should not rule out the diagnosis of Chagas disease in the absence of this precedent. Sharing an intravenous needle is a new means of urban transmission of T. cruzi infection. In our study, one of the patients had positive serological tests for T. cruzi at admission, but 14 years previously he had had a negative one. He had never been in an endemic area or been transfused, and there was no family history of the disease. Sharing intravenous needles was the only risk factor present, which suggests that in this case the infection was acquired by this route.

Positive serological tests for T. cruzi were present in 12 out of 14 patients (86%). Therefore, the absence of T. cruzi antibodies makes a diagnosis of Chagas disease unlikely. In our series the only two patients with negative tests were IDUs. Reviewing the literature, of five cases of Chagas disease reactivation with negative serological tests, four had as the possible means of transmission the sharing of intravenous needles. This association may be related to the time at which the infection was acquired, probably when there was profound immunosuppression due to HIV. In this context, the humoral response cannot occur properly. Serology should not be relevant in the diagnosis of Chagas disease in these cases.

Lumbar puncture had a high sensitivity for diagnosis in our study (85%), hence this procedure should always be performed in the absence of contraindications to it. The high frequency of trypomastigote forms in CSF could be explained histologically by the presence of inflammation and amastigote forms in the leptomeninges in patients with chagasic meningoencephalitis. HIV infection leads to a significant exacerbation of T. cruzi parasitemia in patients with chronic Chagas disease. Parasitemia detected by DME may precede the clinical manifestations or be detected later. However, positive blood cultures or xenodiagnostic tests for T. cruzi should not be interpreted as evidence of reactivation since they are positive in the majority of the patients with chronic Chagas disease. In our study T. cruzi parasitemia was detected in 1/7. The small number of patients in which the Strout method was performed is explained in part by the fact that if the diagnosis was first achieved by DME of CSF, no further examinations were done. The low accuracy of the Strout method in our study in comparison with the literature can be explained by the fact that serial samples were not examined for all patients; this is necessary to increase the sensitivity of this test.

Among the patients in our series, headache, focal neurological deficits, and fever were the most common manifestations of CNS involvement, indistinguishable from other causes of meningoencephalitis, like toxoplasmosis. Cardiac involvement is another form of Chagas disease reactivation in AIDS patients. It presents alone (19%) or associated with CNS involvement (25%). Similar to the literature, in our study 30% of the patients for whom systematic electrocardiograms and echocardiograms were performed had cardiac involvement. The patients who had cardiac involvement had a longer time to diagnosis when compared to the patients who had only CNS involvement (median time between onset of clinical symptoms and diagnosis: 28 days versus 3 days). It is probable that cardiac involvement appears later in the natural evolution of the reactivation, but more studies must be done to confirm this theory.

All patients but two had abnormal neuroimages. As has already been pointed out, the most frequent finding was a single supratentorial hypodense lesion compatible with abscess, predominantly involving the white matter of the brain. This is similar to findings reported in the literature.

Table 3  Benznidazole side effects in 12 patients with central nervous system Chagas disease

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Hematological a</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>Gastrointestinal b</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>None</td>
<td>6</td>
<td>50</td>
</tr>
</tbody>
</table>

a Thrombocytopenia, anemia, or agranulocytosis.

b Anorexia, nausea, vomiting, or abdominal pain.
our series, infratentorial lesions were always associated with a supratentorial compromise. The imaging pattern of the brain is similar to that found in cerebral toxoplasmosis in which involvement of the thalamus and basal ganglia is more common. In our study, only two (17%) had this location. Normal neuroimaging cannot rule out the diagnosis of CNS involvement since there are cases without pathological images (two cases in our series; 17%).

There is evidence that the use of corticosteroid therapy in patients with serological evidence of Chagas disease increases the risk of reactivation and the intensity and the frequency of \textit{T. cruzi} parasitism. However, there are few reports of clinical reactivations in these patients. Most have shown an association with the use of another immunosuppressive drug or another concomitant disease such as lymphoma or leukemia. The role of primary prophylaxis with benznidazole is uncertain and controversial in these patients. There are no reports in the literature of Chagas disease reactivations associated with the use of corticosteroid therapy and AIDS. In three patients in our series, reactivation of their disease occurred while they were receiving corticosteroid therapy for another OI or neoplasm. One of these patients was admitted with the diagnosis of meningoencephalitis; he had positive serological tests for \textit{Toxoplasma gondii} and \textit{T. cruzi}. DME for \textit{T. cruzi} in blood and CSF were negative. Empirical treatment for \textit{Toxoplasma} encephalitis was started and corticosteroid therapy was added for mass effect. After neurological and radiological improvement and still under corticosteroid therapy he presented a contralateral neurological deficit. Neuroimaging showed the presence of new lesions, and CSF direct examination showed trypanomastigote forms of \textit{T. cruzi}. Treatment with benznidazole was started with clinical and radiological improvement. The positive serological test for \textit{T. gondii}, response to anti-\textit{Toxoplasma} therapy, and initial negative DME for \textit{T. cruzi}, suggest that Chagas disease reactivation could have been caused by the high dose of corticosteroid therapy the patient received.

Only two drugs are effective for the treatment of patients with Chagas disease, nifurtimox and benznidazole. The main limitations of these drugs are that only oral formulations are available and the high frequency of adverse side effects. Limited data are available on the efficacy of these agents in patients with AIDS and Chagas disease reactivation. In the present series all patients were treated with benznidazole; 50% experienced side effects, most of them hematological disorders. Secondary prophylaxis with benznidazole (5 mg/kg three times a week) is recommended. Two of our patients continued under secondary prophylaxis with no relapses of the disease. In one of them, secondary prophylaxis was interrupted after immune reconstitution, with no reactivations after 5 years.

The global mortality in our study was 79% with a median time of survival of 21 days. This high mortality rate may be related to the delayed diagnosis (median 18 days). This could be associated to the clinical and radiographic similarities to \textit{Toxoplasma} encephalitis and to the low index of suspicion. Another explanation for the high mortality rate could be the profound immunosuppression in these patients. All but one had <200 CD4 T-cells/\(\mu L\) and 77% of the patients had <100 CD4 T-cells/\(\mu L\). The high prevalence of concomitant OIs at admission could be another reason for the high mortality rate in our series.

In conclusion Chagas disease reactivation is associated with a high mortality rate in patients with AIDS, probably related to delayed diagnosis and profound immunosuppression. It should be considered as a differential diagnosis of meningoencephalitis in HIV patients with very low CD4 T-cell counts, previous residency in an endemic area, and/or IDUs. A positive serological test is relevant to the diagnosis of \textit{T. cruzi} infection, however the absence of \textit{T. cruzi} antibodies cannot rule out the diagnosis, especially in IDUs.

Corticosteroid therapy should be used with caution since they could promote a reactivation of \textit{T. cruzi} infection in these patients. Because of this, in our opinion, all patients with AIDS and Chagas disease undergoing high corticosteroid therapy or therapy with another immunosuppressive drug, should routinely undergo DME for \textit{T. cruzi} in order to prevent reactivations. Whenever possible, lumbar puncture should be performed because of the high accuracy for early diagnosis. All patients should be systematically evaluated for cardiac involvement. Finally, we think that early diagnosis followed by specific treatment, immune reconstitution associated with HAART, and secondary prophylaxis, should improve the poor prognosis in these patients.

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Conflict of interest: No conflict of interest to declare.

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