

Urban outbreak of acute Chagas disease in Amazon region of Brazil: four-year follow-up after treatment with benznidazole

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ABSTRACT

The objective of this report is to describe treatment outcomes over a four-year period of patients with acute Chagas disease in the Amazon region of Brazil. An outbreak of Chagas disease in a low-income district of urban Belém, in September 2000, affected 11 people simultaneously, indicating the likelihood of indirect, oral transmission of *Trypanosoma cruzi*. Prior to treatment, patients underwent physical and clinical tests; blood samples were processed with immunofluorescence assay (IFA) and quantitative buffy coat (QBC). Following treatment with benznidazole, parasitological and serologic tests (artificial xenodiagnosis and blood culture for *T. cruzi*), electrocardiogram, and echocardiogram were administered at intervals over a four-year period. Four years after treatment for acute Chagas disease, all patients presented with negative parasitological tests and persistent IgG anti-*T. cruzi* antibodies with lowered titers; three patients presented electrocardiogram abnormalities consistent with chronic Chagas disease or sequel of acute disease. The satisfactory response to treatment and relevance of serial parasitological examinations of patients with acute Chagas disease are discussed.

Key words

Benznidazole; Chagas cardiomyopathy; Chagas disease; disease outbreaks; disease transmission; immunologic tests; *Trypanosoma cruzi*; Brazil.

Despite efforts to eliminate American trypanosomiasis (Chagas disease) through vector control, the disease continues to

be a public health problem in Latin America. The infection is caused by *Trypanosoma cruzi*, a parasite transmitted primarily by triatomine vectors found in Mexico and Central and South America. Chagas disease is a complex zoonosis, and the life cycle of the parasite involves a variety of mammal hosts. *T. cruzi* infection in humans manifests with acute symptomatic or asymptomatic phases and progressive chronic forms with myocardial, esophageal, and intestinal involvement.

An estimated 15 million people in Latin America are infected with *T. cruzi*, but acute cases are detected in only 1%–2% of those infected (1). Some authors point out that there has been an increase in the number of acute cases recorded in some Latin American countries, leading to predictions that the situation regarding Chagas at the beginning of the 21st century will be similar to that in the early years of the 20th century (2, 3).

Prior to 1996, acute Chagas disease was rarely reported in the Amazon re-

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gion of Brazil, despite evidence of the complete enzootic cycle of *T. cruzi* in the region. Outbreaks have since been reported in the region, characterized as short outbreaks involving 2 to 16 acute cases per episode (4). Only five chronic cases are considered autochthonous to the Amazon region. Two of the five patients were symptom-free, two had dilated cardiomyopathy, and one had the digestive form of Chagas disease (5–7).

Acute Chagas disease in the Amazon region of Brazil was first documented by Shaw et al. in 1969 in a low-income area of Belém, Pará state (8). The outbreak involved four family members who fell ill simultaneously in 1968. The absence of triatomine vectors in the family dwelling suggested oral transmission of *T. cruzi* for the first time in Brazil's Amazon region (8).

Belém is located between Guajará Bay and the Guamá River and has an urban area of 516 km² with some 1.3 million inhabitants. Preserved forest areas, such as Utinga National Park are on the outskirts of the city. Between 1967 and 1977, single adult insects infected with *T. cruzi*, particularly *Panstrongylus geniculatus* and *Rhodnius pictipes*, were found in households of poor, low-lying suburbs of Belém (9, 10). Mammals trapped in forest areas bordering the Pedreira district of Belém, where the 1968 outbreak occurred, had a high prevalence of *T. cruzi*-like trypanosomes (9, 10).

Outbreaks in the Amazon region are a target of epidemiological surveillance programs by the Brazilian Ministry of Health because of suspected oral transmission of the parasite. It is problematic to distinguish clinical features of acute Chagas disease in patients infected by vectors and those infected by the oral route. In part this is due to difficulties in obtaining data on acute cases from endemic areas where transmission typically occurs through vectors. Outbreaks involving oral transmission show prolonged febrile illness, a broad spectrum of symptoms, high mortality rates between outbreaks, and no inoculation sites on the body (11, 12).

When the acute phase of *T. cruzi* infection is not detected and treated, it can persist in the indeterminate phase for the life of a patient. Treatment of the acute infection with tripanocidal drugs (benznidazole) has moderate efficacy (60%) in eradicating parasites, mainly in patients with a prolonged subacute phase (11, 12). Tri-

als with patients suffering from chronic or indeterminate phase Chagas disease do not indicate a treatment benefit (13, 14). Andrade et al. presented encouraging findings regarding the efficacy of benznidazole in a randomized controlled trial of children with early chronic *T. cruzi* infection. Their data showed negative seroconversion at the end of a three-year follow-up study in 55.8% of the children treated with benznidazole, when compared with the placebo group (15). Results from a study in the same cohort of children using the polymerase chain reaction (PCR) method support the notion that negative serology post-treatment corresponds to cure (16).

Better evidence about the clinical profile and treatment outcome of acute phase Chagas disease patients is needed.

We describe an outbreak of acute trypanosomiasis that occurred in September 2000, in the city of Belém. Eleven members of four neighboring families were affected simultaneously, likely as a result of ingesting contaminated food. We describe clinical and laboratory findings during the outbreak and in a four-year follow-up study. The treatment outcome and relevance of serial parasitological examinations of patients with acute Chagas disease are discussed.

MATERIALS AND METHODS

Eleven patients from four families were enrolled in the study. The first two patients, a 17-year-old female and her 58-year-old mother, visited the Evandro Chagas Institute in Belém following diagnosis with supposed typhoid fever and treatment with chloramphenicol. Both mother and daughter showed negative results for typhoid fever. Based on clinical evidence of prolonged fever and information about febrile illness in a relative and in neighbors, acute Chagas disease was suspected.

These two patients and nine of their relatives or neighbors with the same history of extensive febrile illness were subsequently diagnosed with trypanosomiasis by parasitological and serologic tests. As far as could be ascertained, all 11 of these individuals were born in the city of Belém and had always lived in the district of Pedreira.

Forty contacts (relatives and neighbors) of the infected individuals were questioned about febrile illness and underwent blood sample collection, re-

gardless of whether symptoms were present. Blood samples were examined using immunofluorescence assay (IFA) for immunoglobulin M (IgM) and immunoglobulin G (IgG), and indirect hemagglutination assay (IHA).

The houses of all patients and their contacts were rigorously searched for triatomine bugs, but none were found.

Case definition

The case definition for acute Chagas disease is a positive *T. cruzi* parasitological test (Strout method or thick smear) or a positive serologic test for immunoglobulin M (IgM) anti-*T. cruzi* antibodies by IFA. When a case is detected, contacts (relatives or neighbors) are immediately screened for infection with blood and parasitological exams, whether or not they are symptomatic (17). Infection cure is defined when three sequential serologic tests, using two different methods, give negative results (17).

A suspicious case is defined as a contact of a diagnosed case who presents febrile illness \pm 15 days from the time the first diagnosed patient became ill.

Clinical and laboratory evaluation

During the initial evaluation (acute phase), all patients were submitted to clinical and physical examination and blood sampling. Seven series of blood samples were collected: one before onset of treatment (initial), one during treatment (30 days after the onset of treatment), and five following the conclusion of treatment (at 60 days and at 12, 24, 36, and 48 months post-treatment).

The samples collected before treatment were processed using IFA and quantitative buffy coat (QBC) (18).

We added two indirect parasitological methods—artificial xenodiagnosis and blood culture for *T. cruzi*—to the follow-up series of examinations. For serum blood culture, a 3 mL sample of heparinized blood was overlaid on a Hoff agar slant. The overlay was examined by phase contrast microscopy at 400 \times magnification every 2 weeks; cultures were discarded as negative after 10 weeks. Xenodiagnosis was performed using 40 fifth-stage nymphs of *Triatoma infestans*, *Triatoma maculata*, *Triatoma tibiamaculata*, *Triatoma dimidiata*, *Panstrongylus megistus*, and *Dipetalogaster maximus*. Rectal contents of individual insects were ex-

amined for trypanosomes at 400× magnification one and two months after feeding. Leukocyte counts and hemoglobin concentration studies were made before and after treatment.

Standard 12-lead electrocardiograms (ECG) with the patient at rest and echocardiograms were performed during the first week of treatment and in the third month and fourth year of post-treatment follow-up.

Treatment procedures

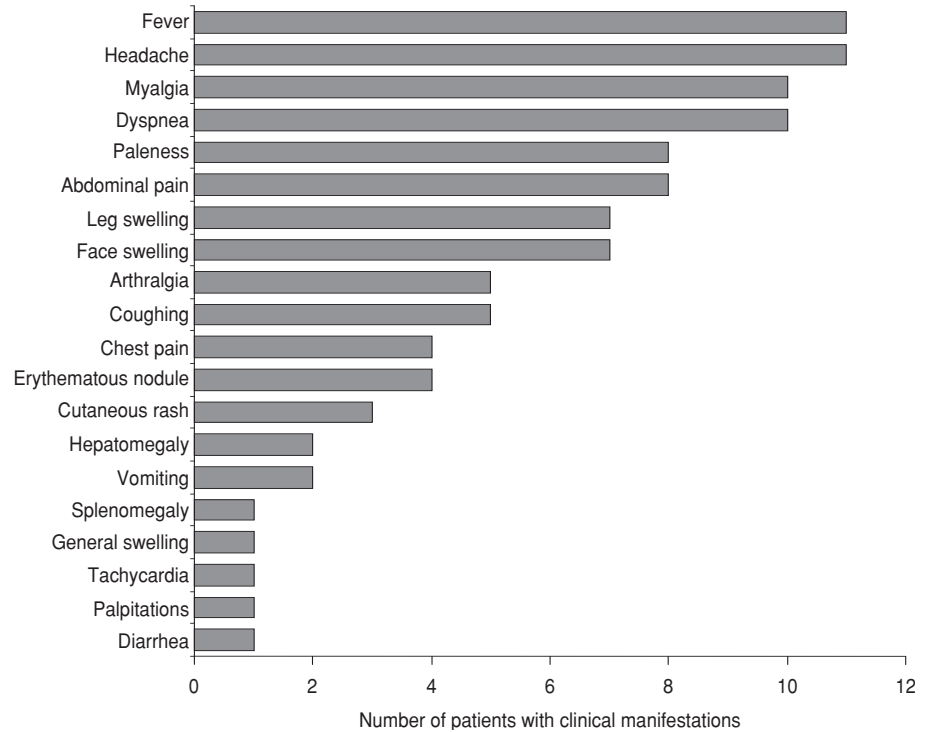
The 11 confirmed cases in the study were treated with benznidazole at doses of 5 to 7 mg/Kg daily for 60 to 90 days (17). Ten patients received daily treatment for 60 days and, because of treatment failure, one patient received treatment for 90 days.

The ethics committee of the Evandro Chagas Institute approved the study, and all subjects gave informed consent for their participation in this investigation.

RESULTS

All 11 patients included in this study presented febrile illness and asthenia beginning 7 or 9 September 2000, lasting between 23 and 43 days. Other reported symptoms and signs were dyspnea, chills, abdominal pain, vomiting, paleness, myalgia, arthralgia, leg swelling, face swelling, cutaneous rash, coughing, and variable degrees of myositis, mainly in the females (Figure 1). Three patients had palpitations, tachycardia, and chest pain. Six patients developed myocarditis and five presented with myopericarditis during the acute phase. Two had serious cardiac manifestations during the acute phase of the disease and required hospitalization. Neither Romaña sign nor other indication of insect inoculation was found on physical examination of the patients.

FIGURE 1. Manifestation of signs and symptoms in 11 patients with acute Chagas disease in Belém, Brazil, 2000



Parasitological tests made immediately after the completion of 30 days of treatment were negative in nine patients. Xenodiagnosis was positive for one 31-year-old female at the 30th day of treatment and positive for another 58-year-old female on the 60th day of treatment, indicating treatment failure (Table 1).

Follow-up serologic tests in all patients detected IgM antibodies for a short period and persistent IgG anti-*T. cruzi* antibodies four years after acute infection. No patients had negative serologic tests until September 2004, four years after treatment (Figure 2).

During the acute phase, five patients presented with anemia (hemoglobin 8.9–10.2 g/dL). Leukocyte counts increased

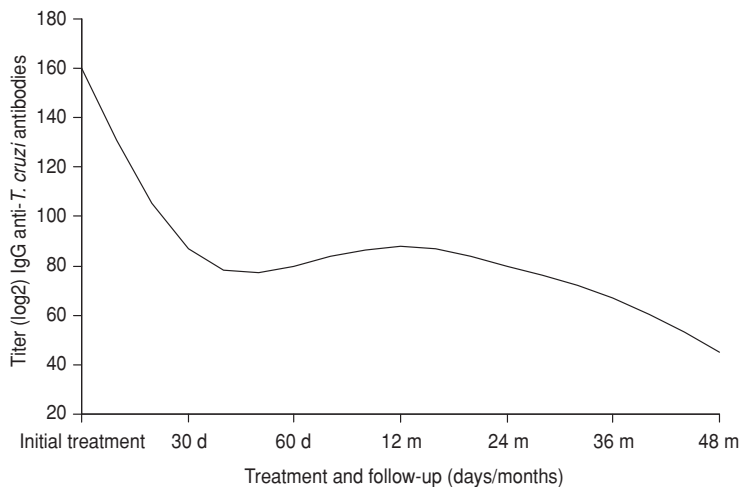
in two patients who presented with acute pulmonary infections simultaneously with acute Chagas disease. Four patients had lymphocytosis (1 702–8 979 lymphocytes/mm³) during the acute illness, with improvement after two months. Three patients presented with leukopenia (3 200–4 700 leukocytes/mm³).

ECG and echocardiogram results during the acute illness and at four years post-treatment are shown in Table 2. Five patients had no ECG changes through the follow-up period. One patient had low QRS voltage due to pericardial effusion. Four patients presented non-specific ventricular repolarization with or without associated conduction disturbances. Of these four, the ECGs of two patients

TABLE 1. Parasitological results in follow-up of treatment of 11 patients presenting acute Chagas disease, Belém, Brazil; 2000–2004

Days following treatment	Test results for patients											
	Quantitative buffy coat				Blood culture				Xenodiagnosis			
	Positive		Negative		Positive		Negative		Positive		Negative	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
First day	8	72.3	3	27.3	8	72.3	3	27.3	11	100	0	
30 days	0		11	100	0		11	100	2	18	9	82
60 days	0		11	100	0		11	100	1	9	10	91
1 year	0		11	100	0		11	100	0		11	100
3 years	0		11	100	0		11	100	0		11	100

FIGURE 2. Change in titers of IgG anti-*Trypanosoma cruzi* antibodies by immunofluorescence assay (IFA) during the acute phase and four years following treatment in 11 Chagas disease patients in Belém, Brazil, 2000–2004



normalized, one 17-year-old female remained with atrioventricular (AV) dissociation and intermittent left bundle-branch block, and one 15-year-old female developed right bundle-branch block plus fascicular left bundle-branch block.

Three patients presented pericardial effusion that resolved shortly after onset

of treatment. One 28-year-old male had a moderate amount of fluid in the pericardium and significant myositis in both lower limbs. Echocardiography of a 70-year-old female with prior history of arterial hypertension showed abnormalities before and after treatment that were consistent with diastolic dysfunction and

signs of hypertrophy due to her previous condition. None of the patients presented decreased ejection fraction either during acute illness or later (see Table 2).

All 40 contacts (relatives and neighbors) examined were asymptomatic and had negative serologic tests.

DISCUSSION

The signs and symptoms described in the Chagas outbreak reviewed in this study reveal a prolonged, febrile syndrome illness and positive parasitological and serologic tests. All patients showed persistent titers of IgG anti-*T. cruzi* antibodies four years after acute infection, but with an important decrease over time. While these lowered titers suggest a high possibility of cure, the outcomes for the patients remain uncertain.

Despite the low sensitivity of parasitological tests in cure assessment, we performed these tests during, before, and after treatment. Xenodiagnosis showed that two patients had persistent parasitemia at days 30 and 60 of treatment. Both continued medication for an additional 30 days. There was no difference in response to treatment between the pa-

TABLE 2. Results of electrocardiograms and echocardiograms during acute phase and four years post-treatment in 11 Chagas disease patients in Belém, Brazil, 2000–2004

Case No.	Age (years)	Gender	Acute phase electrocardiogram results	Post-treatment electrocardiogram results (fourth year)	Acute phase echocardiogram results	Post-treatment echocardiogram results (fourth year)
1	24	M	Low QRS voltage	Normal	Mild pericardial effusion; EF = 64%	Normal
2	28	F	Normal	Normal	...	Normal
3	31	F	Left axis deviation	Left axis deviation, left anterior fascicular block	Normal; EF = 69%	Normal
4	70	F	Non-specific repolarization changes	Normal	Left ventricular hypertrophy; diastolic dysfunction; pericardial effusion; EF = 66%	Diastolic dysfunction; left ventricular hypertrophy
5	28	M	First-degree atrioventricular block; non-specific repolarization changes	Normal	Moderate pericardial effusion; EF = 63%	Normal
6	17	F	Non-specific repolarization changes; atrioventricular dissociation; left axis deviation	Atrioventricular dissociation; intermittent left bundle-branch block	Mild pericardial effusion; left ventricular dilatation with diffuse hypokinesia; moderate mitral regurgitation; EF = 56%	Normal
7	22	M	Normal	Normal	Normal; EF = 66%	Normal
8	19	M	Normal	Normal	...	Normal
9	15	F	Non-specific repolarization changes	Right bundle-branch block, left posterior fascicular block	Normal; EF = 74%	Normal
10	24	F	Normal	Normal	Mild pericardial effusion; EF = 70%	Normal
11	58	F	Normal	Normal	Left ventricular hypertrophy; EF = 68%	Normal

QRS= QRS complex; EF = Ejection fraction; ... = echocardiogram not carried out.

tient receiving benznidazole for 90 days and the patient receiving it for 60 days. Four years after treatment, both of these patients showed low IgG antibody titers (1/40) and negative parasitological tests. We cannot be certain that these two patients followed the prescribed dosing schedules during the first 60 days of treatment.

Our findings show the potential benefits of benznidazole for clinical improvement of acute cases. However, the failure of benznidazole to clear parasitemia (as shown by xenodiagnosis and blood culture) in two patients by days 30 and 60 of treatment, suggests the need for new treatment schedules with longer duration. In addition, we do not know the significance of low IgG titers during the follow-up series of tests, but we hypothesize that it represents immunological memory rather than parasite persistence. More extensive follow-up or other effective tests are necessary to evaluate cure.

The rates of ECG abnormalities and cardiac disease during the acute phase reported in this study are similar to those reported in endemic areas (19, 20). Abnormalities compatible with acute Chagas disease showed rapid clinical improvement following treatment. One patient showed minimal echocardiography alterations consistent with acute myocarditis that disappeared after treatment. Similar results were encountered in a study of 37 patients with acute Chagas disease in an endemic area. These patients had temporary alterations of the cardiac autonomic conduction system (19, 3).

Early lesions of the cardiac conduction system have been documented in patients from a Chagas endemic area in Brazil. Pazin-Filho et al. showed that mild segmental left ventricular wall motion abnormalities in echocardiograms of patients with chronic disease could indicate future worsening of systolic function (21). In our post-treatment follow-up, chronic Chagas disease is indicated in three patients on the basis of these ECG findings: left anterior fascicular block, atrioventricular dissociation and intermittent left bundle-branch block, and right bundle-branch block and left posterior fascicular block, despite there being no clinical manifestation of these conditions. We do not know if the persistent ECG abnormalities indicate chronic phase of Chagas disease despite all patients having undergone treatment dur-

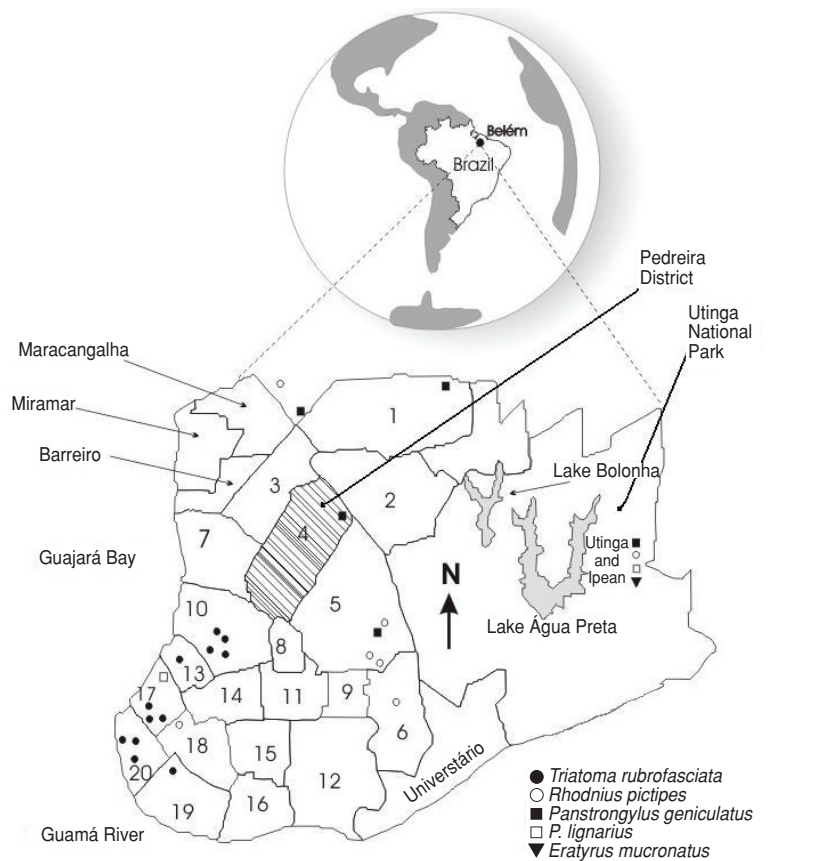
ing the acute phase, or if these abnormalities represent sequelae of acute myocardial attack in patients who are free of the parasite. Patients with abnormal ECGs four years after treatment suggest that these early lesions are common and can go undetected, as we observed in the follow-up of patients. Long-term observation is needed to determine whether overt clinical disease will appear or if these abnormalities persist as mild sequelae of the acute phases.

Pericardial effusion resulting in death has been documented in patients with acute Chagas disease in outbreaks in the municipalities of Abaetetuba and Cametá, both in Pará state in Brazil's Amazon region. In the Cametá outbreak, two deaths due to acute myopericarditis occurred (22, 23). In our study, three patients presented mild pericardial effusion without relationship either to ECG conduction disturbances or low ejection fraction in echocardiogram. This sug-

gests that the presence of pericardial effusion may be part of a generalized process of inflammation with important repercussions for the pericardium rather than the myocardium. While myocarditis is more consistent with acute Chagas disease, pericarditis is described as a consequence of direct parasite lesions in acute cases from endemic areas, and should not be disregarded in cases in the Amazon region.

Epidemiologic investigation found no signs of triatomine vectors in the households of the patients and their contacts in our study. Onset of symptoms occurred within two to four days for all 11 of the affected individuals, suggesting oral transmission due to indirect contact with triatomine bugs. The presence of triatomines infected with *T. cruzi* in Pedreira district has been documented, as well as a 17.4% *T. cruzi* infection rate in wild mammals on the outskirts and in forests bordering Belém, mainly in the

FIGURE 3. Location of triatomine bugs collected in districts of Belém, Brazil, 1967–1977



Districts: 1. Marambaia; 2. Souza; 3. Sacramento; 4. Pedreira; 5. Marco; 6. Terra Firme; 7. Telégrafo; 8. Matinha; 9. Canudos; 10. Umarizal; 11. São Braz; 12. Guamá; 13. Reduto; 14. Nazaré; 15. Cremação; 16. Condor; 17. Comércio; 18. Batista Campos; 19. Jurunas; 20. Cidade Velha

Source: Adapted by N. Veiga from Lainson et al, 1979. Used with permission.

National Park of Utinga located near the Pedreira district (see the map in Figure 3) (9). This could be evidence of indirect and accidental human contact with this vector in this well-defined area of Belém, where acute cases of Chagas disease have occurred. The four families included in this study did not participate in gatherings where they would have shared food. It is improbable that infected triatomine bugs could infect three or more people concurrently, and that symptoms would present nearly simultaneously. We suggest that transmission of *T. cruzi* in this group of patients occurred orally, possibly involving an unprocessed beverage frequently consumed by this population. When prepared in unclean conditions this drink could be contaminated, as documented in a similar outbreak in Amapá state (24).

Brazilian researchers suggest that the increased risk for endemic Chagas disease in the Amazon is related to deforestation, population settlements, shifting cultivation, human colonization of the

vector's natural ecotopes, and human migration to the Amazon region from endemic areas. Chagas disease in humans has been described in limited geographic areas in the Amazon region, especially northeastern Pará state and southeastern Amapá state, related to sylvatic and port areas or areas that have experienced rapid urbanization and increased population density in the last 10 years (4, 25–29). In northeastern Pará state, an extensive highway project may have caused an important ecological imbalance that has contributed to disturbing triatomine ecotopes.

There are many unanswered questions regarding contact between sylvatic vectors and human hosts of Trypanosomas in the Brazilian Amazon. We know that acute infection is benign in the majority of cases of Chagas, but poor clinical outcomes are possible when delayed diagnosis and delayed host response occurs. Serious pericarditis may be lethal to patients in the acute phase of the disease.

Clinical outcomes of patients during this brief follow-up of an urban Trypanosomiasis outbreak suggest that chronic Chagas disease in the Amazon region may be underestimated, although all patients in this study were symptomatic during the acute phase, unlike those affected in endemic areas. The authors underscore the need for a strong surveillance system for Chagas disease in the Amazon region of Brazil.

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RESUMEN

Brote urbano de enfermedad aguda de Chagas en la región amazónica de Brasil: seguimiento de cuatro años después del tratamiento con benznidazol

El objetivo de este informe es describir los resultados del tratamiento para la enfermedad aguda de Chagas durante un seguimiento de cuatro años en pacientes de la región amazónica de Brasil. Un brote de la enfermedad de Chagas en un distrito de bajos ingresos de la parte urbana de Belém afectó simultáneamente a 11 personas en septiembre de 2000; al parecer, la transmisión de *Trypanosoma cruzi* fue indirecta por vía oral. Antes del tratamiento, los pacientes se sometieron a un examen físico y pruebas clínicas; las muestras de sangre se estudiaron mediante inmunofluorescencia indirecta y análisis cuantitativo de la capa leucocitaria (*buffy coat*). Después del tratamiento con benznidazol se realizaron pruebas parasitológicas y serológicas (xenodiagnóstico artificial y hemocultivo de *T. cruzi*), electrocardiogramas y ecocardiogramas periódicos durante cuatro años. Cuatro años después del tratamiento por enfermedad aguda de Chagas, todos los pacientes eran negativos en los análisis parasitológicos y disminuyeron los títulos de anticuerpos IgM anti-*T. cruzi* persistentes; tres pacientes presentaron alteraciones electrocardiográficas indicadoras de enfermedad crónica de Chagas o de secuelas de la enfermedad aguda. Se discute la respuesta satisfactoria al tratamiento y la importancia de los análisis parasitológicos seriados de los pacientes con enfermedad aguda de Chagas.

Palabras clave

Cardiomiopatía chagásica, enfermedad de Chagas, brotes de enfermedades, transmisión de enfermedad, pruebas inmunológicas, *Trypanosoma cruzi*, Brasil.