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Case Report

Uneventful benznidazole treatment of acute Chagas disease during pregnancy: a case report

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ABSTRACT

This report describes the case of a patient with acute Chagas disease in Tocantins, Brazil, who was unaware of her pregnancy during benznidazole treatment. She presented with impaired cardiac function during the acute phase (pericarditis and incomplete right bundle-branch block) that resolved favorably after benznidazole therapy. Serological results also became negative, as determined by hemagglutination assays, enzyme-linked immunosorbent assays, and immunofluorescence assays. The child was born without sequelae and showed no evidence of congenital *Trypanosoma cruzi* infection at birth or 24 days later.

Keywords: Acute Chagas disease. Benznidazole. Pregnancy.

INTRODUCTION

Twelve million people are estimated to have Chagas disease (CD), and 25,000 CD-related deaths occur each year in the world. The resulting morbidity and mortality have highlighted CD as one of the most important parasitoses in Latin America[1].

In 2006, the elimination of *Triatoma infestans*, the main vector of CD was certified in Brazil. Since this time, oral and congenital transmissions of CD have gained prominence[2]. Maternal infection can cause adverse effects during pregnancy relating to fetal growth and maturity, abortion, prematurity, retarded intrauterine growth, and fetal malformations[3,4]. Congenital transmission of *Trypanosoma cruzi* is diagnosed when a neonate is born from an infected mother with positive serology or *T. cruzi* parasites circulating in the blood; when *T. cruzi* parasites are detected in the neonate at birth or shortly thereafter, or when *T. cruzi* antibodies not of maternal origin are detected after birth; and when transmission to the neonate by vectors or blood transfusion has been ruled out.

Here, we describe the case of a woman with acute CD due to an oral infection, who was unaware of her pregnancy during benznidazole treatment.

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CASE REPORT

A 22-year-old woman with intermittent fever, tachycardia, cervicalgia, nausea, vomiting, inappetence, hepatomegaly, and ascites was treated at the Tropical Diseases Hospital of Araguaína. During the epidemiological investigation, the patient reported that 11 cases of CD had occurred during the previous 30 days in her family and neighbors, who were residents of Ananás, Tocantins, Brazil, in November 2011. Chagas disease symptoms arose in the 11 infected individuals following their ingestion of bacaba juice on the same day. An investigation by the Araguaína Centre for the Control of Zoonoses identified the probable bacaba contamination site that caused the outbreak in the locality of Quatro Bocas. According to information from the Secretariat of Health from the State of Tocantins, the CD transmission cycle is well established among wild animals in Quatro Bocas, and encroachment of positive Triatominae (*Rhodnius negletus* and *Rhodnius pictipes*) has been observed.

The patient had a positive direct parasitological examination result on November 3, 2011, as well as positive serology according to hemagglutination inhibition (HAI) and enzyme-linked immunosorbent assay (ELISA) analyses. Only the indirect immunofluorescence assay (IFA) analysis was inconclusive at admission **(Table 1)**.

An electrocardiogram (ECG) was performed and revealed sinus tachycardia, Incomplete right bundle-branch block (IRBBB), and pericarditis, with a heart rhythm suggestive of sinus tachycardia (ST) elevation and and nonspecific alterations of ventricular repolarization (NSAVR), **(Table 2)**. Echocardiography testing indicated a thickened pericardium with mild effusion and no signs of impaired cardiac function.

TABLE 1 - Follow-up of serological and parasitologial tests during mother treatment and follow-up.

	Date				
Diagnostic test	March 3, 2011	November 21, 2011	January 18, 2012	July 5, 2012	January 1, 2013
HAI	reactive	reactive	—	reactive	—
ELISA	non-reactive	reactive	non-reactive	non-reactive	non-reactive
IFA	inconclusive (1/40)	reactive (1/160)	reactive (1/80)	reactive (1/80)	inconclusive (1/40)
CD-Direct Parasitological	positive	—	—	—	—

HAI: hemagglutination inhibition; **ELISA:** enzyme-linked immunosorbent assay; **IFA**: indirect immunofluorescence assay. **CD:** Chagas disease.

TABLE 2 - Electrocardiographic alterations: sinus tachycardia, incomplete right bundle-branch block and nonspecific alterations of ventricular repolarization.

	Date			
Diagnostic test	June 6, 2011	January 1, 2012	September 9, 2012	January 1, 2013
Rhythm	ST	sinus	ST	sinus
Heart rate	119	66	122	68
Repolarization	discreet supra ST IRBBB	NSAVR	NSAVR	NSAVR

ST: sinus tachycardia; **IRBBB:** incomplete right bundle-branch block; **NSAVR:** nonspecific alterations of ventricular repolarization.

The patient was treated with 300mg/day of benznidazole on November 6, 2011 after receiving guidance regarding the risks and side effects associated with the medication. The patient's condition resolved with ECG normalization **(Table 2)** and reductions in symptoms. The benznidazole dose was reduced to 200mg/day in December due to elevated liver enzyme levels (aspartate aminotransferase [142mg/dl]; alanine aminotransferase [209mg/dl]) and thrombocytopenia (89,000 platelets/mm^3).

The treatment ended in February 2012 and the patient remained asymptomatic. Upon re-evaluation in May 2012, the patient had no complaints and the HAI and IFA were positive **(Table 1)**. The patient also reported that she was in the twelfth week of gestation, indicating that at least 2 weeks of benznidazole treatment had been administered after conception. Follow up testing in June and October 2012 revealed that the patient had recessed and remained asymptomatic, with normal laboratory results. According to the patient, the prenatal period progressed normally.

On November 5, 2012, an uneventful Caesarean delivery was performed. At 24 days of age, the newborn was referred to the outpatient clinic for a CD evaluation. The child was asymptomatic and showed no signsin the physical examination. Chagas disease diagnostic tests and a negative direct parasitological thick film examination were performed with negative results **(Table 3)**.

The mother and child were re-evaluated in January 2013. The mother was asymptomatic, and the child weighed 6.3kg, was asymptomatic, showed no alterations in the physical examination, and presented with normal growth and weight gain. Both were subjected to new serological tests, and all results were negative (**Tables 1** and **3**).

TABLE 3 - The newborn's serological and parasitologial tests after birth and follow-up.

	Date	
Diagnostic test	November 11, 2012	January 21, 2013
ELISA	non-reactive	non-reactive
IFA	non-reactive	non-reactive
CD direct parasitological	negative	—
Thick drop malaria	negative	—
Thick drop Chagas	negative	—

ELISA: enzyme-linked immunosorbent assay; **IFA**: indirect immunofluorescence assay; **CD:** Chagas disease.

DISCUSSION

Campaigns to control and eradicate *Triatoma infestans,* the main CD vector, have decreased the incidence of CD throughout Brazil[5,6]. Oral transmission, which had occurred rarely and under specific conditions in humans, was diagnosed with increasing frequency in the Amazon region, mainly in the Northern region[5].

Currently, oral and vertical transmissions are important CD transmission methods. The prevalence of CD infection in pregnant women, which is the main risk factor for congenital infections, varies from 5-30%, depending on the geographical area. However, up to 30% of pregnant women may be infected in areas with the highest prevalences. According to the Ministry of Health, congenital transmission in Brazil is estimated to occur in less than 1% of pregnancies in chagasic women[6]. Despite the high rates of maternal infection, mother-to-child transmission has been identified in approximately 5-6% of pregnancies[2]. However, vertical CD transmission remains an important route of infection, and uninformed carriers comprise a limiting factor in disease control. Therefore, it is relevant to include CD investigative exams in prenatal care of pregnant women who reside in endemic areas. Although treatment is contraindicated during pregnancy, such examinations would allow the identification of CD as the cause of miscarriages, prematurity, low birth weight, retarded intrauterine growth, and malformation[4,7].

Most reported congenital CD transmission cases are related to mothers who are chronic disease carriers because of the high disease prevalence during this phase. After the chronic disease phase, carriers present with low parasitaemia, which might decrease the risk of transplacental transmission. Pregnant women with acute CD are more likely to transmit the infections to their children because they present with significantly high parasitaemia, along with the characteristic immunosuppression during pregnancy[4]. Congenital infection occurs in 71% of cases of acute infection during pregnancy and in 1.6% of cases in chronic infection[8]. Given the likelihood of transmission during the acute phase, the early diagnosis of childbearing-aged women is an important step towards the goal of reducing congenital transmission rates. In the case reported herein, transmission to the newborn did not occur because the mother received proper treatment during the acute disease phase before pregnancy. Guidance regarding the importance of effective contraception during treatment is another critical action because once pregnancy is established, treatment should be interrupted because of the potential teratogenic effects of the medication[4,6].

Vertical transmission can occur transplacentally, usually after the sixth month of pregnancy (between 22 and 37 weeks), and seems to depend both on parasite and host factors[9]. Transmission may even occur during delivery due to contact between the newborn's mucous membranes and infected blood[6]. After crossing the villus epithelium, *T. cruzi* invades the villus stroma, proliferates in its amastigote form, and induces changes; the degree of placental involvement is usually related to the intensity of fetal injuries[5]. The placenta is altered in most congenital CD cases, a fact that is associated with increased risks for morbidity and mortality. Additionally, transmission through oral contamination can occur via the amniotic fluid, breast milk from women during the acute disease phase, or bleeding nipples[9].

There is no single clinical profile of congenital CD; the disease ranges from the absence of symptoms to serious clinical statuses, thus reinforcing the need for laboratory diagnoses[10]. Overall, 60-90% of congenitally infected children are asymptomatic (Consenso, 2005). A small percentage of infected children present with clinical conditions common to other congenital infections, including hepatosplenomegaly, sepsis, myocarditis, hepatitis, meningoencephalitis, edema, fever, anemia, and jaundice[11,12].

During the acute disease phase, treatment should be given in all cases following diagnostic confirmation regardless of the transmission route, excepting pregnant women. The clinical forms of maternal *T. cruzi* infection (particularly the cardiac and digestive forms) require further investigation. Since etiological treatment of infected women is not recommended during pregnancy, treatment should be considered after delivery and breastfeeding[4].

In Brazil, benznidazole is the only available CD drug. Benznidazole is highly toxic; thus, its use contraindicated during pregnancy and breastfeeding. The teratogenicity of benznidazole was confirmed in experimental models study of rats at 20 days of gestation, and the drug was found to cross the placental barrier and bind to fetal proteins[4,6].

Treatment is mandatory in all cases of congenital infection. Serology should be repeated at 6-9 months after birth in asymptomatic children with positive and/or inconclusive results. Seropositivity requires the initiation of specific treatment[4,6] direct parasitological examination is recommended for children with clinical manifestations suggestive of a congenital infection[4].

In the present report, accidental administration of benznidazole to a pregnant woman in the acute phase of DC proved to be beneficial for mother and son, as regression of clinical symptoms and cure of infection in the mother was observed. The treatment probably helped to prevent transmission vertical, and no teratogenic effects were noticeable during examinations through the first year of life.

It is timely to review the effects of benznidazole treatment in pregnant women in the acute phase of CD infection that is likely to continue to occur, especially in endemic areas with known cases of vertical or oral transmission.

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