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Diagnosis and Treatment of Congenital Chagas Disease in a Premature Infant

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BACKGROUND

Chagas disease is caused by *Trypanosoma cruzi*, a protozoan parasite transmitted by Triatominae insects, predominantly in rural areas of Latin America [1]. Other important modes of transmission include blood transfusion from an infected donor and oral transmission, reported in the Amazon region of South America, and from an infected mother to her unborn child. If untreated, Chagas disease can cause serious cardiac manifestations in chronically infected patients, including heart failure, stroke, and sudden death. The World Health Organization has estimated that more than 5 million people are infected with *T cruzi* in Latin America, and approximately 1.2 million of them are women of child-bearing age [1]. The risk of congenital transmission is estimated to be 5% in endemic regions of Latin

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America. On the basis of immigration estimates and seroprevalences reported by countries of origin, an estimated 300 000 people with chronic Chagas disease are living in the United States. On the basis of that estimate and reported congenital transmission rates, the US Centers for Disease Control and Prevention (CDC) has estimated that 63 to 315 babies are born every year with congenitally transmitted Chagas disease [2]. With the migration of people from endemic regions of Latin America to other parts of the world, including the United States, healthcare providers should consider this disease as a possibility in patients at risk and conduct a thorough evaluation to confirm the diagnosis of Chagas disease and provide appropriate treatment when indicated.

CASE PRESENTATION

The patient was a male infant born in 2015 at 30 weeks' gestation via Cesarean section performed because of placental abruption, possibly precipitated by the mother's reported history of a fall. His Apgar scores at 1 and 5 minutes were 3 and 7, respectively, and his birth weight was 1785g. The infant was intubated shortly after birth. In utero ultrasound revealed pericardial effusion and ascites. Because of the concern for hydrops fetalis, the patient was transferred to our neonatal intensive care unit from an outside hospital on day of life (DOL) 4. After arrival, the infant was begun on parenteral nutrition and received 5 days of ampicillin and gentamicin for clinical sepsis. On approximately DOL 7, as a result of the in utero ultrasound findings, the outside hospital performed a histopathologic examination of the placenta and reported intracellular parasites, and the infectious diseases service was consulted. He remained hemodynamically stable and was extubated on DOL 10, but he required oxygen via nasal cannula for respiratory support until DOL 23.

The patient's mother was 37 years old and previously in good health; her prenatal care began in the first trimester. She was from Bolivia and had traveled to Santa Cruz, a region of Bolivia endemic for Chagas disease, for 1 month during her last trimester of pregnancy. She denied any symptoms of acute illness, including fever, lymphadenopathy, malaise, rashes, or chagoma (a focal nodular inflammatory reaction that develops at the region of parasite penetration into the subcutaneous tissue), during pregnancy. She denied animal or insect exposure and ingesting undercooked meats or unpasteurized dairy products. She had a nonreactive rapid plasma reagin test result, and she tested negative for hepatitis B surface antigen and human immunodeficiency virus (HIV) antibody. Her group B *Streptococcus* colonization status was unknown, her baseline tuberculin skin test result was negative, and she was immune to rubella.

In the initial evaluation on DOL 7, the patient's vital signs were within the normal range for age, and his oxygen saturation level was 95% to 98% on 2 liters of oxygen via nasal cannula. On physical examination, the infant showed no signs of acute distress. The anterior fontanelle was open and flat. The conjunctivae were nonicteric. There were no oral lesions. The infant's neck was supple, and his lungs were clear to auscultation. He had a grade 2/6 systolic murmur. His abdomen was soft, and he had no hepatosplenomegaly. There was no generalized lymphadenopathy, and he had no rash.

The initial laboratory test results included a peripheral white blood cell count of 17 470/μL with 44% lymphocytes, 37% segmented neutrophils, 7% reactive lymphocytes, 4% monocytes, 2% eosinophils, 1% band neutrophils, and 5% immature myelocytes. The patient's hemoglobin concentration was 14.5 g/dL, and his hematocrit level was 42.1%. His platelet count was 105 000/μL. The results of electrolyte and renal and liver function tests were all within normal limits. Results of a rapid plasma reagin test were negative, and serum HIV and parvovirus B19 polymerase chain reaction (PCR) assay results were negative. A cytomegalovirus urine PCR test was negative at <200 copies per mL. Maternal and infant *Toxoplasma* serologic testing results were negative. Ophthalmology was consulted, and a dilated-eye examination revealed no evidence of chorioretinitis or cataracts.

An echocardiogram performed on admission was notable for tricuspid valve hypoplasia and a hypoplastic right ventricle with echo brightness of the right ventricular outflow tract with concern for endomyocardial fibroelastosis. The electrocardiogram showed normal sinus rhythm and findings consistent with right atrial enlargement and left ventricular hypertrophy with repolarization abnormality. A moderate patent ductus arteriosus with a left-to-right shunt was noted. The atrial and ventricular septa were intact. His left ventricular function was normal, and there was no pericardial effusion noted. A chest radiograph revealed cardiomegaly. An abdominal ultrasound was negative for ascites or organomegaly, and an intracranial ultrasound was normal, and no evidence of intracranial calcifications or ventriculomegaly was found.

Congenital Chagas disease was suspected on the basis of the patient's clinical presentation and the mother's previous residence and travel within Bolivia, initial concern of hydrops fetalis in the infant, and the abnormal placenta. The mother's and infant's blood samples were sent to the CDC. The mother's serology results were consistent with chronic Chagas disease, and the infant's blood tested positive for *T cruzi* by PCR (Table 1). Review of the infant's peripheral smears by hematology revealed rare trypomastigotes, which confirmed the diagnosis of congenital Chagas disease (Figure 1). After further questioning, the mother revealed that her sister had been diagnosed with Chagas disease and that her father (the maternal grandfather) has cardiomegaly attributable to Chagas disease.

The patient was treated with benznidazole at a dose of 6 to 9 mg/kg per day divided in 2 doses via nasogastric tube for 60 days. Benznidazole was obtained from the CDC under an investigational protocol because the drug has not been approved the US Food and Drug Administration. Therapy was initiated on DOL 28, and the first negative CDC multitargeted PCR test result was on a sample collected on DOL 49 (21 days from the initiation of benznidazole therapy) (Table 1). The patient remained stable without evidence of acute illness and tolerated the medication well. At 7 months of age, the infant had a follow-up echocardiogram that revealed endocardial fibroelastosis of the right ventricle adjacent to the tricuspid valve annulus with normal tricuspid valve function and no clinical consequences. The serology of the patient's 2-year-old brother for Chagas disease and *T cruzi* PCR results were negative. The infant's mother was referred for care for her chronic Chagas disease.

DISCUSSION

This case highlights the importance of having a heightened suspicion of Chagas disease among pregnant women at risk and, if the mother is infected, providing a thorough evaluation of their infants for congenital Chagas disease when epidemiologically indicated. Although the annual incidence of congenitally acquired Chagas disease in the United States has been estimated to be 63 to 315 cases per year [2], only 1 previous case of congenital Chagas disease has been reported. In this 2012 case report from Virginia, the male infant was born in 2010 at 29 weeks' gestation as a result of fetal hydrops and was noted to have ascites and pleural and pericardial effusions. The mother was originally from Bolivia and had a previous history of untreated Chagas disease [3].

The risk of congenital infection of infants born to an infected mother is estimated to be approximately 5% [4]. Of congenitally infected infants, 10% to 40% are symptomatic [5], and the clinical diagnosis can be difficult to make, because the infant might have only nonspecific symptoms, including those observed in the setting of other congenital infections such as those with cytomegalovirus, herpes simplex virus, *Toxoplasma gondii*, and rubella [6]. Clinical findings include anasarca, hepatosplenomegaly, respiratory distress, and rare severe morbidities such as cardiomyopathy and meningoencephalitis [6]. In this infant's case, endocardial fibroelastosis of the right ventricle was found on echocardiogram, which can be representative of past infection or scarring caused by congenital Chagas disease. Ongoing research has been focused on identifying the risk factors for congenital Chagas disease, such as the strain of the parasite, geographic location, and the immunologic state of the mother and infant [6].

The most sensitive test for diagnosing congenital and acute Chagas disease is the *T cruzi* PCR assay. However, false-positive results can occur, possibly as a result of low detectable levels of circulating maternal *T cruzi* DNA that can be present in uninfected infants born to an infected mother. Thus, an early positive PCR test should be repeated to confirm the diagnosis. Diagnosis also can be made by direct microscopic detection of *T cruzi* trypomastigotes in cord blood or in the infant's blood, although this method is less sensitive than molecular detection. If initial test results are negative, testing should be repeated at 4 to 6 weeks, because the level of parasitemia might increase over this period. Serology can be diagnostic in children older than 9 months after maternal antibodies have waned [2-4]. The CDC reference diagnostic laboratory currently uses a multitargeted PCR testing algorithm using the *T cruzi* minicircle TaqMan real-time PCR and the nuclear *T cruzi* minisatellite TaqMan real-time PCR assays.

Early treatment of acute congenital infection can have a cure rate of greater than 90% and can prevent severe complications of chronic Chagas disease, which mainly affects the cardiac and gastrointestinal systems. Cardiac complications include arrhythmias, cardiomyopathy that can lead to congestive heart failure, and thromboembolism. Severe gastrointestinal complications are less common and include megasyndromes of the esophagus or colon. Thus, early recognition and therapy are crucial, but they are especially challenging because the majority of infected patients are asymptomatic [7]. Either benznidazole or nifurtimox can be used for treatment, and both of them are generally well

tolerated in the infant population [2, 3, 7]. The CDC currently recommends benznidazole at an oral dose of 5 to 7.5 mg/kg per day in 2 divided doses for children aged 11 years or younger.

Another potential issue for an infant born to an infected mother is the risk of transmission through breastfeeding. A recent review summarized the few studies that examined this question and determined that there is insufficient evidence of transmission through breast milk to recommend discontinuation of breastfeeding in mothers with chronic Chagas disease, especially in resource-poor settings where infant formula may not be readily available. A caveat is made that if the mother has fissures or bleeding nipples, which can lead to contamination of breast milk with blood containing the parasite, then temporary discontinuation of breastfeeding or thermal treatment of expressed milk is suggested. However, the risk for transmission through breastfeeding is considered to be higher for any infant whose mother has acute or reactivated disease and thus higher levels of parasitemia [8].

Obstetricians, gynecologists, and pediatricians in both endemic and nonendemic areas should consider the risk for Chagas disease and routinely screen for *T cruzi* infection in pregnant women who have emigrated from or resided in regions with epidemiological risk of Chagas disease, such as Mexico, Central America, and South America. All infants born to an infected mother should be monitored clinically and tested at birth, at 4 to 6 weeks of age, and finally at 9 to 12 months of age for evidence of congenital infection. Treatment is generally recommended for any infant found to be positive for Chagas disease. Assistance with questions about the diagnosis, management, and treatment of Chagas disease can be obtained from the CDC; more information is available at http://www.cdc.gov/chagas.

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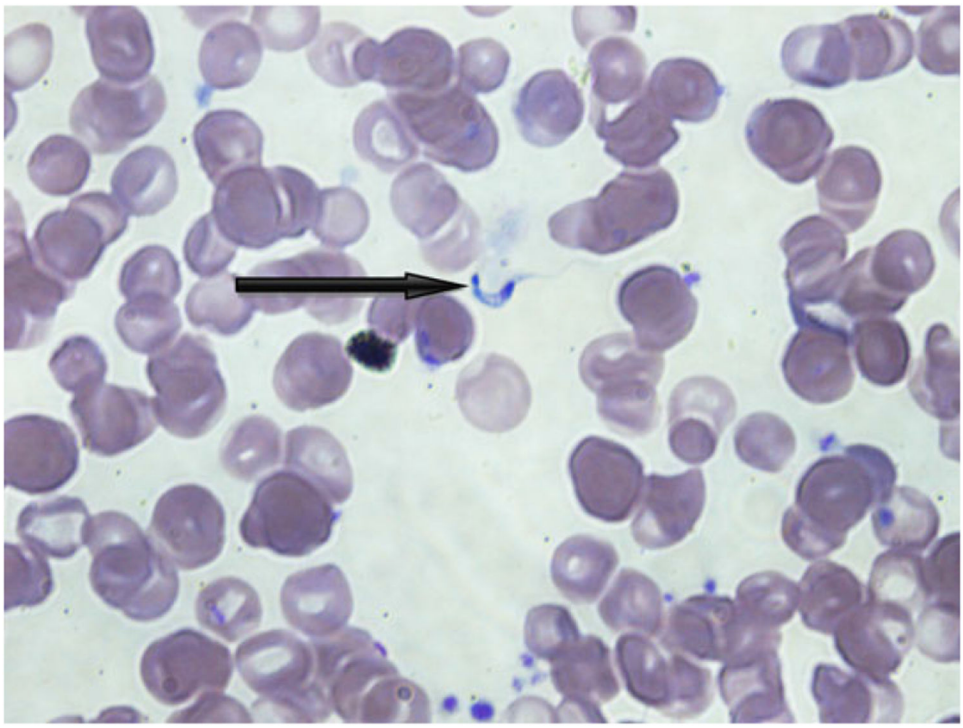

Figure 1.
Trypanosoma cruzi trypomastigote at 1000× magnification in the patient's blood smear stained with Wright Giemsa stain.

Table 1.

Results of CDC Multitargeted PCR Testing of Blood for *Trypanosoma cruzi* Infection in an Infant Born to a Chronically Infected Mother

DOL of Collection[a]	MNC TaqMan (Ct)	TCZ TaqMan (Ct)	Interpretation
20	Positive (22)	Positive (17)	First positive
25	Positive (21)	Positive (17)	Subsequent positive
42	Positive (29)	Positive (25)	Subsequent positive
49[b]	Negative	Negative	Negative
55	Negative	Negative	Negative
116[c]	Negative	Negative	Negative

Abbreviations: CDC, Centers for Disease Control and Prevention; Ct, cycle threshold; MNC, *T cruzi* minicircle TaqMan real-time polymerase chain reaction; PCR, polymerase chain reaction; TCZ, *T cruzi* minisatellite TaqMan real-time polymerase chain reaction.

[a]Benznidazole therapy was initiated on day of life (DOL) 28 and completed on DOL 88.

[b]First negative CDC multitargeted polymerase chain reaction test for *T cruzi* infection (21 days into therapy).

[c]Twenty-eight days from completion of 60 days of therapy with benznidazole.