Revista da Sociedade Brasileira de Medicina Tropical 48(5):629-632, Sep-Oct, 2015
http://dx.doi.org/10.1590/0037-8682-0073-2015

Case Report

Long-term follow-up of a patient since the acute phase of Chagas disease (South American *trypanosomiasis*): further treatment and cure of the infection

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ABSTRACT

A woman had been followed since 1957 for acute phase Chagas disease. Parasitological and serological tests were positive, and treatment included benznidazole in 1974. Following treatment, parasitological test results were negative and conventional serology remained positive until 1994, with subsequent discordant results (1995-1997). The results became consistently negative since 1999. She had an indeterminate chronic form until 1974. Only two minor and transitory nonspecific alterations on electrocardiogram were noted, with the last nine records normal until June 2014. This case confirms the possibility of curing chronic disease and suggests the benefit of specific treatments for preventing long-term morbidity.

Keywords: Chagas disease. Specific treatment. Evolution. Cure.

INTRODUCTION

This case has been part of a longitudinal study on human Chagas disease (CD) by the Emmanuel Dias Research Center (EDRC) of Bambuí, State of Minas Gerais, Brazil since its acute phase[1] [2] [3]. The World Health Organization (WHO) strongly recommends long-term studies to understand the natural history of CD and to establish main risk factors involved in its evolution, with a focus on the possible impact of specific treatments[3] [4]. The municipality of Bambuí was free of CD vector transmission since 1972, maintaining regular and active epidemiological surveillance since 1974[3].

Laboratory evaluations such as parasitological tests [direct blood examination, xenodiagnosis, hemocultures, and polymerase chain reaction (PCR)] were performed at the EDRC and in the parasitology departments of the Federal Universities of Minas Gerais and Uberaba, according to standard techniques[4] [5] [6]. Until 1960, serological tests included the complement fixation technique at the Oswaldo Cruz Foundation [*Fundação Oswaldo Cruz* (FIOCRUZ), Brazil]; since then, the indirect hemagglutination test (IHAT, cutoff = 1:16) and immunofluorescence test (IMFT, cutoff = 1:40) have been used in FIOCRUZ, Belo Horizonte, State of Minas Gerais. Since 1992, simultaneous IHAT and IMFT (using the aforementioned cut-off values), and enzyme-linked immunosorbent assays (ELISA, positive in optical densities 1.2 and upper) have been performed by the Ezequiel Dias Foundation [*Fundação Ezequiel Dias* (FUNED)]. As most serological results are recorded qualitatively, no titers are included in the present report. Clinical follow-up, electrocardiography, and heart radiography were performed in compliance with the WHO and classic Brazilian protocols[3] [6]. Esophageal and colon radiography were performed according to the Haddad, Godoy, and Rezende techniques[5] [7] [8].

Ethical considerations

Clinical revisions by the EDRC were approved by the René Rachou Ethical Committee since 2002, with a new approval in 2011.

CASE REPORT

We report of CD in a 68-year-old half Caucasian female born in Bambuí, Minas Gerais, Brazil (EDRC registration # 2,931).

Acute phase

The patient lived in a mud hut highly infested with *Triatoma infestans,* in the Sapé Village of Bambuí. On April 25, 1957, the patient (aged 3 years) was examined at the EDRC; she presented with fever (37.9°C), light asthenia, generalized edema, several engorged preauricular and subaxillar lymph nodes, tachycardia,

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Received 6 March 2015
Accepted 27 April 2015

hepatosplenomegaly, and the typical Romaña sign (right eye). An electrocardiogram (EKG) showed tachycardia and low-voltage QRS complex, and chest radiography showed moderate global cardiac enlargement. In addition to a xenodiagnosis with 12 *Trypanosoma infestans* nymphs, direct blood examination results for *Trypanosoma cruzi* were positive. She was treated with available anti-thermic drugs, oral hydration, and two daily chloroquine pills. The fever began to decrease after 3 weeks, with normal EKG findings after 4 months, normal chest radiography after 8 months, and disappearance of hepatosplenomegaly and ocular signs after 12 months.

Chronic evolution and specific treatment

Between 1957 and September 2014, she was examined 27 times at 1-3-year intervals. At the end of 1974, she weighed 58kg and with her consent, she was treated with a new drug at that time, benznidazole, which was in the experimental stage at the Evandro Chagas Hospital (FIOCRUZ). She received 100mg of the active ingredient every 8 hours (5.17mg/kg/day) for 2 months. The drug was well tolerated, with transient urticaria occurring between days 10 and 14 that did not necessitate suspension. During the pre-treatment period, two xenodiagnosis (1966 and 1972), one hemoculture (1975), and five serological tests (the first three by complement fixation technique alone and the last two by IHAT plus IMFT) were positive. After treatment, four xenodiagnosis, five hemocultures, and a single PCR test showed negative results. Seven conventional serology test results using two or three techniques remained positive between 1975 and 1995, following four discordant results between 1996 and 1997. Since 1998, seven serological test results were negative **(Table 1)**.

The clinical evolution was very good since the acute phase, with only the first signs of gut constipation for 2 or 3 days detected in 1974, occurring 3-4 times monthly. In 1976, a single barium enema showed moderate elongation and slight enlargement of the rectosigmoid segment, with similar results in 2002 and 2014. Common esophageal and cardiac symptoms of chronic CD such as dysphagia, palpitation, dyspnea, easy fatigue, dizziness, and vespertine leg edema were never reported. Between 1976 and 2014, results of nine radiological examinations of the esophagus and 13 of the cardiac shadow were normal. Conventional EKG was normal in almost all the medical revisions, with a unique extrasystole detected in March 2009, and a transient pattern of incomplete bundle branch block in November 2011. The last nine records between 2012 and 2014 were normal. In 2005, a bi-dimensional Doppler echocardiogram showed normal findings, according to Prof. Adriana Mizziara (Uberaba Medicine School).

The patient was working in domestic and agrarian jobs until 1972. She married in 1972, having two normal children (serology negative for *T. cruzi* antibodies) and no abortions. Family history of CD was reported, with a few sudden deaths. She had experienced common childhood diseases such as measles, varicella, and pertussis and underwent appendectomy at 19 years of age. Since 2001, she has reported general articular and muscular pain, which was diagnosed as an autoimmune rheumatic disease and was treated with analgesic and anti-inflammatory drugs. Gut constipation remains unchanged since 1974, but has been successfully controlled by an anti-constipation diet and the eventual use of saline purgative drugs such as magnesium hydroxide[6][7][8].

TABLE 1 - Summary of the etiological diagnosis of Chagas disease of the present case since 1957 (the acute period) until 2014.

Year	Etiological diagnosis		Observations
	Serological	Parasitological	
1957 (April)	Not done	Fresh examination: pos. (2×) Xenodiagnosis: pos. (1×)	Acute phase, specific treatment not available
1957-1975	CFT: pos. (3×)	Xenodiagnosis: pos. (1963, 1×)	Pre-treatment period
	IHAT and IMFT: pos. (2×)	Hemoculture: pos. (1974, 1×)*	
Specific treatment with benznidazole in November 1974 (5.7mg/k/day × 60 days)			
1976-1995	IHAT and IMFT: pos. (3×) IHAT, IMFT, and ELISA: pos. (2×)	Not done	
1996-1997	Discordant results among IHAT, IMFT, and ELISA (4×)	Hemoculture: neg. (1×)	
1998-2013	IHAT, IMFT and ELISA: neg. (1999, 2001, 2006, 2009, 2011, 2012, and 2013)	Hemoculture: neg. (1×)	PCR: neg. (1×)

pos: positive; **neg:** negative; (…x): the number of tests; **CFT:** complement fixation test; **IHAT:** hemagglutination test; **IMFT:** immunofluorescence test; **ELISA:** enzyme-linked immunosorbent assay; **PCR:** polymerase chain reaction. *The *Trypanosoma cruz*i discrete typing unit was TC-II (IIb), the more prevalent detected group in chagasic individuals of the Bambuí Region, where TC-I is also detected in wild triatomines and reservoirs, as well as in some human cases(3).

Present situation

At the last clinical evaluation (June 2014), she complained of the same muscle and joint pain and the aforementioned occasional constipation episodes, with no mention of dyspnea, dizziness, peripheral edema, or dysphagia. Physical examination was generally normal, with some signs of aging characteristics such as venous engorgement of the lower limbs and solar dermatitis. Wrist and finger pain was noted, but no joint edema was detected. Heart auscultation was normal, with a cardiac rate of 64 beats/minutes and arterial blood pressure of 126/82mmHg. No signs of liver enlargement, ascites, or fecaloma were observed. Neurological examination results were normal. Results of serological tests for *T. cruzi* antibodies (ELISA, IHAT, and IMFT) remained negative, and EKG and chest radiography findings (heart shadow and esophageal emptying) were normal. An opaque enema showed the same rectal sigmoid elongation and small enlargement (7.5cm) previously detected in the colon **(Figure 1)**.

Other laboratory findings

Normal findings: the complete blood count; levels of fasting glucose, cholesterol (total and fractions), and triglyceride; uric acid and antistreptolysin test results; and results of urine (routine) and feces (parasitological) analyses were normal.

FIGURE 1 - Double contrasted opaque enema scan of the patient at *Nossa Senhora do Brasil* Hospital by Dr. Helvécio Telles in Bambuí, Brazil on April 29, 2014.

Positive findings: the antinuclear factor-HEP2 for nuclear and metaphasic chromosomal plaque showed a titer 1/160, rheumatic factor was >128UI/mL, and PCR was >96mg/L. The erythrocyte sedimentation speed test was 23mm (30 minutes) and 59mm (1 hour).

DISCUSSION

This case is interesting owing to its long follow-up and particularly because of the clinical evolution after successful antiparasitic treatment was performed 40 years ago. According to Köberle's observations and previous clinical studies, an acute phase with abnormal EKG findings during childhood can predict evolution to later cardiac and digestive chronic forms[3,4,7,9]. Without specific treatment in the acute period, the immediate evolution of this case was similar to those already described in classic longitudinal studies: the patient remains in an indeterminate chronic phase since 16 years, when the first symptoms of colon peristalsis were noted. This is not the most typical evolution, because megacolon was the last clinical alteration to appear over the course of CD, generally following chronic cardiopathy and/or esophagopathy[2,3,7,10]. Some cases of single and precocious colopathy have been described, even in young individuals. For instance, Rezende and Moreira detected megacolon in 13.4% of 463 CD cases <30 years old in Central Brazil, whereas Dias found isolated chronic colopathy in 25% of 115 individuals in Bambuí, with 20.4% detected before 30 years old[3,8].

Treatment with benznidazole was effective in our patient 17 years after the acute phase, thus curing the infection according to current criteria[6,11,12]. The persistent negative conventional serology was only detected 22 years after drug administration, similar to observations of other treated and cured chronic patients[7,11,12]. The treatment seemed to have been successful, preventing clinical evolution for 40 years, despite pre-existing acute myocarditis and chronic colopathy. A similar evolution was described by Cançado[11] in a chronic patient 17 years posttreatment. A discrete megacolon, detected before treatment, has remained radiologically and clinically unaltered to date. No esophagopathy evolution was detected posttreatment, despite undeniable evidence of autonomic denervation (colopathy) in contrast with the classical evolution of digestive CD[6,8]. Likewise, no evidence of cardiac chagasic involvement was detected in this long-term follow-up. Isolated extrasystoles in a single EKG record and a transient pattern of incomplete bundle branch block in another EKG do not characterize the evolution to CD, and these are commonly found in the non-infected population, as reported by many comparative studies[2,4,6,10]. In summary, given that the main goal of CD treatment is to stop or at least slow the clinical evolution, the present case suggests such a possibility[6,10,12].

ACKNOWLEDGMENTS

The authors are indebted to the Ezequiel Dias Foundation, Federal Medicine School of Triângulo Mineiro (Uberaba), Bambuí Municipal Policlinics, *Hospital Nossa Senhora do Brasil*, and the University of Minas Gerais for their invaluable help in the complementary study of this patient.

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