

New evidence of spontaneous cure in human Chagas' disease

Novas evidências da cura espontânea da doença de Chagas humana

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Abstract A new case of spontaneous cure of human Chagas' disease is described in Uruguay. An 87-year-old man who had a typical acute phase of *Trypanosoma cruzi* infection in 1947 and never received specific treatment against the disease, when examined in 1998 revealed several completely negative parasitological and serological tests, including traditional serology, PCR and flow cytometry. As a whole, such findings fulfill the current criteria to define the cure of Chagas' disease. Clinical data suggest the possibility of a benign evolution of Chagas' disease in this case, but the basic findings (slight cardiac and esophageal impairment) could also be due to the advanced age of the patient.

Key-words: *Trypanosoma cruzi*. Chagas' disease. Spontaneous cure.

Resumo Um novo caso de cura espontânea da doença de Chagas humana é descrito no Uruguai. Um homem de 87 anos de idade que teve um quadro típico de doença de Chagas aguda em 1947 e nunca recebeu tratamento específico, revelou-se em 1998 completamente negativo para exames sorológicos e parasitológicos, inclusive por PCR e citometria de fluxo. Estes achados, no conjunto, preenchem os critérios correntes para a definição de cura da doença de Chagas. O quadro clínico atual sugere a possibilidade de uma evolução benigna da doença de Chagas, mas os achados principais (comprometimento leve do coração e do esôfago) poderiam também dever-se à avançada idade do paciente.

Palavras-chaves: *Trypanosoma cruzi*. Doença de Chagas. Cura espontânea.

Since his pioneering works, Carlos Chagas stated that once infected by *Trypanosoma cruzi* (*T. cruzi*), a chagasic individual generally would continue with the infection for the rest of his life, always presenting high levels of specific antibodies in the chronic phase of Human Chagas' Disease (HCD)⁴. Several longitudinal studies in endemic and non-endemic areas have shown this persistence of antibodies in chagasic individuals during many years. On the other hand, some naturally or experimentally infected mammals, such as pigs, goats, horses and cattle have shown very discrete parasitaemia at the beginning of the infection which frequently disappears totally at the chronic phase. In larger animals, serology has also become negative after a brief period of parasitaemia, immediately after the inoculation, suggesting an elimination of infection^{1 5 17 20}.

In human beings, after successful parasitological treatment in both acute and chronic phase serology becomes negative, thereby indicating the absence of the parasite from the organism, signifying cure of the infection^{3 5 12 13 14 15}. However, spontaneous cure of HCD had never been detected before 1988, when Zeledón et al. reported some cases that became serological and parasitologically negative without specific treatment three decades after their acute onset²⁵. Likewise, this possibility has been mentioned in Chile and Brazil but, in general, the authors consider that spontaneous cure must be understood as an exceptional situation in the natural history of HCD^{5 2 13 20 25}. Similarly, another similar case was reported in Uruguay that was detected in 1998, during a routine international supervision of the National Chagas Disease Program in the city of Paysandu.

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CASE REPORT

PER, 78 years old, male, Caucasian, agriculture worker, Russian immigrant. Arriving in Uruguay during 1946, he was immediately transferred to the rural zone of Paysandu county, where he has been living until today. At that time, this entire region was highly infested by *Triatoma infestans* infected by *T. cruzi*, resulting in numerous acute cases, several of them published by Talice et al²². The patient himself informs clearly that his first rural house in Paysandu was infested by *vinchucas* at that time and that many times he was bitten by them during the night. In July 1998, PER presented himself as a volunteer for blood donation at the Paysandu Blood Bank, where serology for HCD was performed and resulted negative*. Nevertheless, during the routine medical examination, the patient declared that he had HCD since 40 years ago, having been attended by Prof. Rodolfo Talice at the Hospital Maciel (Ministry of Health) in Montevideo. The original hospital records indicate that this patient was attended by Prof. Talice on May 7, 1947, with fever and Romaña's sign, positive direct blood examination (concentrated drop) for *T. cruzi*. EKG showed only general disturbances of repolarization and synusal rhythm with normal PR interval and a frequency of 90 hb/minute. According to the patient, xenodiagnosis was also positive at that time, but no official records were found. No specific treatment was performed and the

patient left the hospital without fever, within two weeks. A picture of his very typical Romaña's sign was taken and published in the Salveraglio's *Enfermedades Infecciosas* Medical textbook by Talice, page 394 (Figure 1)²¹. In Paysandu PER remained healthy and asymptomatic during the last 40 years, never again being examined or specifically treated for Chagas' Disease. No information about serology for HCD was available or referred by the patient between 1947 and 1998. During this time the patient reports good health, never requiring medical assistance, hospitalization, surgery or blood transfusion. **Present medical examination:** the only complaint is a first degree stable dyspnea (on major physical effort) in the last two years. No swallowing disturbances or constipation were referred throughout his life. Physical examination showed no evident alterations and the basal blood pressure was 130/80mm³Hg., with a regular pulse of 65 bpm. Normal heart auscultation, only an hyperphonetic pulmonary second murmur being detected. No signs of heart failure. Lungs, kidney, spleen, liver and descendent colon were clinically normal. In the face, a very slight reduction of the right eyelid rift can be noted (Figure 2). Other subsidiary exams at the present time included: EKG: synusal rhythm, with rare ventricular and supraventricular ectopic beats and



Figure 1 - Mr. PER in 1947. Note Romaña's sign (right eye). (photo by Prof. R. Talice).

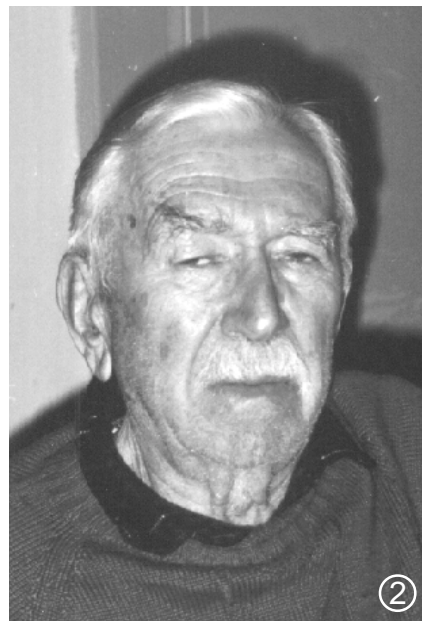


Figure 2 - Mr. PER in 1998. Note reduction of the right eyelid rift. (photo by J.C. Pinto Dias).

*Indirect haemagglutination and indirect immunofluorescence.

isolated complete bundle branch block (CRBBB), with a ventricular QRS axis = 100° (positive). A cycloergometric test was sufficient and normal for the age, reaching 600 kgmts/min. with an adequate elevation of arterial blood pressure (170/90mmHg and CF of 120 bpm) and no disturbances in the recuperation. During the test, basal ventricular extra-systoles disappear and no T waves alterations were revealed. The basal CRBBB remained unaltered. The interruption of the test was caused by leg muscle fatigue. Chest X-ray in PA position was normal (aortic discrete hypertrophy), but esophageal X-ray showed a very discrete retention of contrast one minute after swallowing (borderline from normal to anectasic first degree esophagopathy). Several specific tests to detect *T. cruzi* infection were then performed on this patient between August 1998 and December 1999, all of them resulting negative

(Table 1). **Observation.** To meet ethical aspects, the medical examination was made with the full voluntary cooperation of the patient, who was completely informed about his case and the clinical and laboratory examinations to which he would be submitted, as well as the right he would have to leave the examination and/or to refuse any medical procedure at any time, according to his will. Local and Ministerial Health Authorities as well PAHO Office (Montevideo) were also informed about this case study, none of them manifesting any doubts about the work to be done. Finally, Mr. PER continues to receive permanent medical attention from one of the authors (A.F.A.) until the date of this publication. In 2001 the patient was submitted to an inguino-crural hernia surgery in Paysandu with peridural anesthesia, presenting very good follow up and no intrasurgical complications.

Table 1 - Laboratory examinations for *Trypanosoma cruzi* infection in the patient PER between 1998 and 2000.

Date	Test	Result	Observations
July/1998	IIT and IHT	negative	Paysandu Blood Bank
August/1998	IIT, ELISA & IHT	negative	FUNED/Belo Horizonte, Brazil
August/1998	IIT & IHT	negative	Fac Medicine/Montevideo, Uruguay
August/1998	IIT, ELISA	negative	CDC/Atlanta, USA
August/1998	flow cytometry	negative	FIOCRUZ/Belo Horizonte, Brazil
September/1998	PCR	negative	FIOCRUZ/Belo Horizonte, Brazil
November/1998	PCR	negative	FIOCRUZ/Belo Horizonte, Brazil (repetition)
February/1999	IIT, ELISA & IHT	negative	Fac Medicine/Goiânia, Brazil
June/1999	xenodiagnosis	negative	Fac Medicine/Montevideo, Uruguay
December/1999	xenodiagnosis	negative	Fac Medicine/Montevideo, Uruguay

IIT = indirect immunofluorescence test; IHT = indirect hemoagglutination test;

Xenodiagnosis: 40 *Triatoma infestans* nymphs, examined at 30 and 60 days

The parasite DNA research was made by PCR technique, utilizing the phenol-chloroform method for extraction, according to Diaz et al⁸.

DISCUSSION

This case probably confirms prior very rare reports of spontaneous cure of chronic Chagas' disease described in Costa Rica, Brazil and Chile^{12 17 25}. According to the present consensus among HCD experts, a permanent absence of specific antibodies and parasitic evidence strongly suggests the nonexistence of chagasic infection, this criterion being utilized to indicate the cure of treated patients^{3 7 13 15 24 25}. Very singular cases of absence of antibodies in immunodeficient chagasic individuals have been reported, but generally such patients show high peripheral parasitaemia, easily detected by xenodiagnosis and/or PCR^{8 9 13}. The evidence of an acute phase of the disease 41 years ago in this patient was stated by direct examination (official records) and xenodiagnosis (referred by the patient), as well as the fact that his picture was published by Prof. Talice in a Medical textbook, to illustrate a typical case of acute HCD^{6 10 11 20}. Unfortunately, no records of serology were found in this patient's antecedents. According to all available records and evidence, PER presented a typical

and benign acute phase of HCD and naturally entered in the chronic phase within a few weeks of clinical course, without specific treatment. The typical Romaña's sign (Figure 1) and both information from the patient and Dr. Talice's records leave no doubt that PER presently examined is the same person registered in 1947 and that he was contaminated by the vector route. This route is most probable since the patient had just arriving from Russia (a non-endemic country) and never received blood transfusion in his life. On the other hand, Paysandu region was highly infested by *T. infestans* at that time, with a general infection rate due to *T. cruzi* of 47%. According to Talice et al²². It should also be underscored that Paysandu was the origin of the first case of HCD registered in Uruguay and that 35% of the cases reported by Talice et al originated from this region²². Electrocardiographical benign alterations in the acute phase of this patient show a diffuse and slight myocardial involvement, with favorable prognosis, chiefly in the absence of clinical signs of acute heart failure^{5 11 20 24}. Another factor of good prognosis was the age of this

patient during the acute onset, since deaths and severe clinical pictures are always detected in younger patients and experimental animals^{14 10}. To date, the clinical course of this patient was very good and specific treatment was never initiated. It must be emphasized that at that time no effective drugs against *T. cruzi* were available and that Dr. Talice himself had tried in 1945 an arsenical drug in acute HCD cases, with no influence in clinical course and only slight influence in the parasitaemia of only a few cases studied²³. The central aspect of this case concerns the complete and permanent disappearance of his IgG antibodies 41 years after the acute phase of HCD, which indicates the absence of the parasite in healthy individuals or, in other words, cure of the infection^{13 14 15 25}. Such a hypothesis is also reinforced here by the negative result of flow cytometry, a very specific test to detect the lytic protector antibodies which indicate the existence of live parasites^{3 13 14 15}. The cure was also supported by parasitological tests, namely two negative xenodiagnosis and two PCR assays^{8 12 15}. Clinically, the present examination of this patient shows an elderly man with slight heart and esophageal impairment which could be due to *T. cruzi* infection, according to several observations in Latin American endemic countries^{7 16 18 24}. Nevertheless, the cardiac

involvement (CRBBB & extra-systolic beats) as well as the first degree esophageal dysperistalsis can also appear in elderly non-chagasic individuals, as a result of myocardial sclerosis and physiologic esophagus denervation (*presby-oesophagus*), thus making it almost impossible to determine the central etiological component of the present clinical picture^{7 18}. As a general rule and considering a series of longitudinal studies, the most probable is that both factors have been involved in this evolution, since the patient certainly had an acute phase of HCD, in which myocytolysis and autonomic denervation generally occurs^{1 25 10 20}. The basic difference between this case and the ones detected earlier in Costa Rica is just the present clinical picture, because those cases were in the chronic indeterminate form, with no cardiac and/or digestive detected disturbances²⁵. Not only the age of the patients can explain this clinical difference, since the Costa Rican individuals were much younger than PER^{5 25}. Also geographical differences might be involved, since the parasite strains are not the same, as well as the regional vectors (*Triatoma dimidiata* in Costa Rica; and *T. infestans* in Uruguay); since in general terms, it is accepted that the morbidity of HCD is usually more severe in the Southern Cone than in Central America^{7 20 24 25}.

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