New evidence of spontaneous cure in human Chagas' disease
Novas evidências da cura espontânea da doença de Chagas humana

Sonia S. Francolino¹, Antonio Fernandez Antunes², Rodolfo Talice³, Rachel Rosa⁴, Joel Selanikio⁵, Joffre Marcondes de Rezende⁶, Álvaro J. Romanha⁷ and João Carlos Pinto Dias⁷

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.


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). 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. 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. 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 onset. 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. 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.
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 al. 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 80 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). 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 130/80 mmHg., 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 $\text{ÄQRS}$ axis = 100° (positive). A cyclo-ergometric 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 reported, but generally such patients show high immunodeficient chagasic individuals have been 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 region. The parasite DNA research was made by PCR technique, utilizing the phenol-chloroform method for extraction, according to Diaz et al.

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<th>Date</th>
<th>Test</th>
<th>Result</th>
<th>Observations</th>
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<tr>
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<td>IIT and IHT</td>
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<td>Paysandu Blood Bank</td>
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<tr>
<td>August/1998</td>
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<td>Fac Medicine/Montevideo, Uruguay</td>
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<tr>
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**DISCUSSION**

This case probably confirms prior very rare reports of spontaneous cure of chronic Chagas’ disease described in Costa Rica, Brazil and Chile. 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. 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. 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. 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 Romana’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 al 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 region. 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. 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. 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 studied. 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. 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. The cure was also supported by parasitological tests, namely two negative xenodiagnosis and two PCR assays. The conclusion drawn here is therefore 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 studied.

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REFERENCES

15. Martins Filho OA, Pereira MES, Carvalho JF, Cançado JR, Brener Z. Flow cytometry, a new approach to detect anti-live


