Lectures

I

GLOBALIZATION OF CHAGAS DISEASE
(AMERICAN TRYPANOSOMIASIS): THE SITUATION IN EUROPE AND BELGIUM

par

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1. Infection with Trypanosoma cruzi and Chagas disease

Chagas disease (American trypanosomiasis) is caused by the protozoan parasite Trypanosoma cruzi. Both the extracellular form of the parasite (called “trypomastigote”), susceptible to diffuse in the whole body, and its intracellular form (called “amastigote”), required for its division, are present in humans. This infection is endemic in Latin America, where 25% of population would be at risk of infection. Ten million people are estimated to be infected in 21 countries, with an incidence of 20,000 new cases per year. One to three millions of infected people suffer from cardiac and digestive clinical forms of chronic Chagas disease, responsible of 11,000 deaths per year (1).

The parasite can be transmitted by insect vectors (Hemiptera reuvida, such as Triatoma infestans, Rhodnius prolixus, Triatoma dimidiata, etc.) by making contact between their parasite-contaminated feces with break in the skin, the eyes or the mouth. This mode of transmission has been significantly reduced by the programmes of vector control developed in many of the endemic countries. A second transmission mode is the transfusion of infected blood, equally decreasing through the blood bank control. Another transmission mode, which is increasingly important in relation to the regression of the latter two, is the congenital transmission, occurring in 1 to 12% of acutely as well as chronically infected pregnant women (2). Transmission can also occur by oral route, through food or drink contaminated with parasites (mainly eliminated by vectors), and after transplantation of infected organs (1).

Chagas disease can present acute or chronic clinical phases. The acute phase lasts 30 to 60 days and is frequently asymptomatic and undiagnosed. However some signs can indicate parasite entrance in case of vector contamination, such as the Romaña’s sign (unilateral oedema of the upper and lower eyelids) or the cutaneous chagoma. Some non-specific and self-limited symptoms, such as fever, enlarged lymph nodes, hepatomegaly and oedema can also appear. Cardiac and/or neurological alterations are mainly observed in case of co-infection with HIV. Such acute phase evolves spontaneously toward either a rapid aggravation (often associated with active myocarditis), leading up to death (over all in children under two years), or the indeterminate chronic phase in 90% of cases. The latter is asymptomatic and can last
throughout whole life. However, 30 to 40% of such infected subjects can develop, 10 to 20 years later, cardiac and/or digestive clinical forms of Chagas disease. The chronic chagasic myocarditis associates arrhythmias, cardiac failure and thromboembolism. Its evolution is irreversible and often results in sudden death or congestive cardiac failure. Chagas disease is the main cause of cardiovascular death in Latin America. The chronic disease also induces enlargements of oesophagus (megaoesophagus) and colon (megacolon). The mechanisms on such lesions involve destructions of muscular cells and of the autonomous nervous system of heart and digestive tube (1).

The laboratory diagnosis of *T. cruzi* infection in the acute phase is based on parasitological tests, such as microscopic examination of fresh blood, thick blood smears stained with Giemsa, or blood centrifuged in heparinized capillary tubes. Multiplication of parasites from blood samples can also be obtained by hemoculture and xenodiagnosis (the patient is bitten by uninfected *reduviidae* insects of which intestinal content is examined 30, 60 and 90 days later). Immunological tests are useful for the diagnosis of the chronic phase. Standard serological tests, such as immunofluorescence, ELISA or indirect hemagglutination, as well as rapid immunochromatographic tests can be used. Molecular diagnosis based on PCR and qPCR (amplifying *T. cruzi* kinetoplast or satellite nuclear DNA) are also available (1).

The treatment of *T. cruzi* infection uses two drugs: benznidazol (5 to 7 mg/kg/day, given during two months) and nifurtimox (8-10 mg/kg/day given during two months). Such drugs are available through World Health Organization (WHO). They induce side effects in 30% of patients (allergic dermatitis, digestive problems, peripheral polyneuritis and rarely neutropenia). Both drugs are active overall during the acute phase (in 100% of children below 1 year, and in 60 to 70% of adult patients). In chronic phase, 50 to 60% of patients with infection evolving from less than 10 years and much less of those infected from a longer time can be effectively cured. The etiological treatment of patients in the indeterminate phase reduces the frequency and the severity of the cardiac clinical form (1).

2. Historical milestones of Chagas disease

In 1909, Carlos Chagas, a Brazilian MD (Minas Gerais, Brazil) discovered the parasite, the insect vector, described the human infection and its parasitological diagnosis (unique case in the history of medicine). From 1930 to 1950, the disease is mainly studied in Argentina by Salvator Mazza and Cecilio Romaña, and the clinical aspects of chagasic cardiopathy are detailed. In the 1970s-1980s, massive migrations of farmers toward the Latin American cities lead to an urbanization of the disease (with urban transmission by vectors and blood transfusion). From the 1990s, important programmes aiming to control transmission by vectors and blood transfusion are launched in collaboration with the Pan American Health Organization (PAHO) (against *T. infestans*, in 1991, through the South cone initiative; against *R. prolixus* in 1997, with the Andean and Central America initiatives; in 2004, with the Amazonian initiative) (3). From the 2000s,
congenital infection begins to be controlled. A consensus on the strategy to be applied has been defined through an international meeting organized in 2002 by ULB and UMSS with the help of the Belgian cooperation, and validated in 2004 by WHO/PAHO (4, 5). In 2007, WHO and PAHO, in a historical meeting in Geneva, considered the important changes having occurred in the epidemiology of *T. cruzi* infection/Chagas disease. They acknowledged its reduced incidence in endemic countries and its extension toward non-endemic areas (see below), i.e. its recent globalization and launched an additional initiative to deal with Chagas disease in non-endemic countries (6).

3. Epidemiological evolution of Chagas disease in Latin American endemic countries

Since the 1990s, a constant decrease of prevalence of infection and incidence in children and young adults is observed in countries applying the recommended vector control programmes and improvement of blood banks. The number of infected subjects has decreased from 18 million in 1980 to 10 million in 2009. During the same period, the annual incidence has been also reduced from 700,000 to 20,000 cases and the mortality from more than 45,000 to 11,000 per year. Interruption of vector transmission by *T. infestans* and blood transfusion transmission is acknowledged in Uruguay, Chile, Brazil and partially in Argentina (1). Countries of Central America (Belize, Costa Rica, Guatemala, Honduras, El Salvador, Nicaragua, and Panama) have received the certification of the interruption of the vector transmission by *R. prolixus*. The prevalence of *T. cruzi* infection in pregnant women, as well as the incidence of congenital infection in areas where vector transmission has been controlled have also decreased significantly (as e.g. in Cochabamba, Bolivia, from a prevalence of 28% in 1992 to 16% in 2006, and an incidence of 1.4% to 0.3% in the same period ; 2, 7).

4. *T. cruzi* infection and Chagas disease in non-endemic countries

In the last decades, important migration flows were observed from Latin America towards North America (United States and Canada), the Western Pacific region (Australia and Japan), and, more recently, to Europe, and particularly Spain (8). The main challenges of the occurrence of such infection in non-endemic countries are the management of infected subjects, the prevention of transmission by blood transfusion and organ transplantation, and the control of congenital infection.

Presently in US, the number of infected subjects is estimated to be 300,200 (over 22,850,000 Latin American migrants) with 30,000–45,000 cardiomyopathies and 63 to 315 congenital cases per year. More than 5,000 infected blood donors have been detected since 2007, when a screening test for Chagas disease has been approved by FDA and recommended to the American blood banking industry. Some cases of Chagas disease associated with blood transfusion have been reported. Insect vectors susceptible to transmit *T. cruzi* are present in US and active in the enzootic cycle involving wild and
domestic animals (mainly dogs). Some cases of vector transmission in humans have been reported in Texas, California, Tennessee and Louisiana (9, 10).

The question of the presence of vectors susceptible to transmit *T. cruzi* in the old world has been raised. Analysis of available data indicate that potential vectors (such as *Triatoma rubrofasciata* and others, present in Latin America) are encountered in various harbours of the African coast and mainly in harbours and cities of India and other countries of South-East Asia. Contacts between such insects and humans have been documented in Vietnam, India and Thailand. However, these insects are not harbouring infective parasites since up to now there are no infected humans or animals in such areas. They have been probably brought with goods transiting by the maritime commercial routes (11).

5. *T. cruzi* infection and Chagas disease in Europe

From the beginning of 1980s, there were only sporadic publications on cases of transmission by blood transfusion, congenital route and laboratory accidents, and in some infected tourists and adopted children in Europe. A considerable increase in the number of reported cases is noted from the beginning of 2000s, mainly in Spain, when important migrations between Latin America and Europe occurred for economic hardship, tightening of visa regimes in US (after 2001), appeal to dual nationality (for migrants having European ancestors). A feminization of such migration, relevant for congenital transmission, was also observed. In 2009, WHO launched a network of European experts on Chagas disease in order to exchange information and experience and define a common strategy for the epidemiological surveillance of *T. cruzi* infection (12, 13).

In 2008, 4,180,000 Latin American migrant people from endemic countries lived in Europe (i.e. 11% of all migrants). However, this does not include undocumented migrants, those having acquired an European citizenship, and children adopted by European families. The Latin American nationalities with the greatest presence in Europe are the Brazilian (mainly in Portugal), Ecuadorian, Colombian, Bolivian (mainly in Spain), Peruvian, Surinamese (mainly in the Netherlands) (13).

WHO has analysed the data of countries with more than 400 cases of Chagas disease in 2009: Belgium, France, Germany, Italy, Netherlands, Portugal, Spain, Switzerland and United Kingdom (UK). The diagnosed cases for all these countries were only 4,290 (89% in Spain), i.e. 1.3% of migrants from endemic countries, whereas the expected cases were estimated to be 68,000 to 123,000, i.e. 1.8 to 2.8% of such migrants (according to the distribution of migrants per nationality and the known prevalence of *T. cruzi* infection in the respective countries). The Latin American nationalities with the greatest number of infected people were: Bolivian, Ecuadorian, Argentinean, Brazilian, and Colombian. The estimated numbers of newborns with congenital Chagas disease were 20 to 184 per year (i.e. an incidence of 0 to 3% pregnancies in migrant women
from endemic countries, 90% being in Spain). The index of underdiagnosis of *T. cruzi* infection was 94 to 96% (99% in Netherlands, Portugal and UK). The reasons for such underdiagnosis are likely related to the fact that:

1) most European health professionals have little or no experience with the detection and management of Chagas disease;

2) the access to specialized laboratory diagnosis for the community at risk is very limited, since only few institutions offer such screening;

3) the diagnosis of chronic phase is usually delayed as most patients remain asymptomatic for many years. The European countries with *T. cruzi* infection/Chagas disease are classified in three groups:

   a) Spain with more than 50,000 cases (75% of all expected cases in Europe);

   b) France, Italia and UK, with 2,000 to 12,000 expected cases;

   c) Belgium, Germany, the Netherlands, Portugal and Switzerland, with 700 to 2,000 expected cases (13).

Some directives of the European Commission mention the exclusion of Chagas disease carriers for donation of blood (2004), tissue and cells (2006). In agreement with such European Union directives, Spain and France have implemented mandatory screening of Latin American blood donors, and Italia and UK have prohibited blood donation by migrants from endemic countries (their country of origin being recorded by questionnaire). Protocols in Spain (Valencia and Cataluña) have been established to screen pregnant women from Latin America in order to control congenital infection (12, 13).

6. *T. cruzi* infection and Chagas disease in Belgium

The serodiagnosis of *T. cruzi* infection is performed in two Belgian centres:

1) the Institute of Tropical Medicine (ITG) in Antwerp (M. Van Esbroeck, E. Bottieau), by ELISA;

2) the Laboratory of Parasitology of the Erasmus Hospital (ULB) in Brussels (C. Truyens, Y. Carlier) by immunofluorescence and ELISA (this lab also performs *T. cruzi*-specific PCR and qPCR).

From 01/01/1999 to 12/31/2010 (12 years), both centres have performed *T. cruzi* serology for 1939 patients, from which 48 were detected positive (2.5%), i.e. about four positive patients per year. From these 48 patients, 23 lived in Belgium and 25 lived in other European countries (Netherlands, Luxembourg, France, Italia, Sweden, Norway) and were referred to ULB/ITG laboratories for serodiagnosis. Comparison of data obtained for periods of four years indicated a relative stability in the number of *T. cruzi*-specific serology asked by Belgian MD, and a significant increase in the proportion of patients displaying positive serodiagnosis in the last four years period (about five to six per year) compared to the previous periods (Fig. 1). The analysis of individual data available for the 23 infected patients living in Belgium showed that most were migrants from Latin
America (21/23, 91.3%), and only two were Belgians having made multiple stays in various Latin American countries. The countries of origin of migrant infected patients were mainly Brazil (41%), Bolivia (29%) and Ecuador (18%). Approximately one third of infected patients (32%) displayed a symptomatic chronic Chagas disease (cardiac: 50%; digestive with megaoesophagus: 17%; cardiac and digestive: 33%).

A survey performed in the maternity ward of the Saint-Pierre Hospital (Brussels), from April 2007 to February 2010 (Dabiri C., Ronsenberg S., Barlow P., Truyens C., Vandenberg O. and Carlier Y.) showed that among 8926 births, 473 were from Latin American mothers (5.3%). Surprisingly, 74% of them were undocumented. The countries of origin of such mothers were mainly Brazil (63%) and Ecuador (28%). Less than 2% came from other Latin American countries (1.5% from Bolivia). Only one mother was detected seropositive for *T. cruzi* (1/418, 0.24%). This mother was Brazilian and suffered from a megaoesophagus treated surgically in Brazil. Her newborn and siblings were not infected (according to parasitological, PCR and serological investigations). Beside this case at the Saint-Pierre Hospital, three other neonates of *T. cruzi*-infected mothers have been also studied in other maternity wards and shown free of *T. cruzi* infection.

![Graph showing the percentage of patients with positive T. cruzi-specific serodiagnosis](image)

**Fig. 1**
*T. cruzi*-specific serodiagnosis performed at ITG and ULB from 1999 to 2010 (n= number of positive serodiagnosis ; N= total number of serodiagnosis ; *= p<0.05)
The data mentioned above are of limited scope. A more realistic estimate of expected cases of *T. cruzi* infection in Belgium can be obtained considering the number of Latin American migrants, their nationalities and the mean prevalence of *T. cruzi* infection in endemic countries. In 2009, 28,880 Latin American migrants were officially registered in Belgium (all regions) (National Register, DGSIE, Brussels, Belgium). The number of undocumented Latin American migrants could be reasonably estimated to 50%, i.e. 14,440. The adopted Latin American children were 490 in 2009, i.e. a total of 43,810 Latin American migrants. Considering the prevalences of *T. cruzi* infection in endemic countries (1.6%-2.1% ; 14), the number of cases of infection in Belgium could be estimated at 683 to 921 (including 218 to 295 cases of cardiac and/or digestive Chagas disease). However, considering the mean prevalence of 3.3% observed in the last period of ULB/ITG laboratory studies (see above), the estimated number of infected people increases to 1,446 (with 463 cases of cardiac and digestive Chagas disease). The numbers of Latin American blood donors in Brussels and Wallonia in 2008 was 389 (D. Sondag, O. Bertrand, Service du sang, Croix Rouge, Belgium), i.e. 6 to 13 potentially infected blood donors (considering the prevalences of 1.6% and 3.3%, respectively). An estimation of pregnant women and newborns infected with *T. cruzi* could also be performed for all Belgian regions. In 2009, 722 Latin American pregnant women gave birth to live newborns. The numbers of infected mothers were estimated being 12 to 24, according to the calculation mode indicated above, with 0 to 1 congenitally infected neonates per year, considering maternal-foetal transmission rates of 5 to 10% (2).

So, in Belgium, there are various cases of *T. cruzi* infection (asymptomatic indeterminate, as well as cardiac and digestive clinical forms of Chagas disease), with an estimate of 700 to 1500 expected cases in migrants coming from endemic areas. However, as far as we know up to now, there is no case report of *T. cruzi* infection due to local blood transfusion, organ transplantation or maternal-foetal transmission.

7. Conclusion

These data indicate an urgent need in Europe and Belgium:

1) to reinforce teaching on *T. cruzi* infection and Chagas disease (in the frame of courses of Medical Parasitology, Infectious Diseases and/or Tropical Medicine);
2) to train health professionals to detect cases and to take care of the existing cases (creating specific task forces in hospitals);
3) to implement screening programmes of target populations (with focus on migrants without legal residency permit having potential difficulty in accessing care). A greater involvement of European and Belgian health authorities in controlling Chagas disease would be highly desirable. Based on legislation or protocols already used in Spain and France (European surveillance), regulations on blood and organ donation, and control of congenital infection should be implemented.
SUMMARY

Trypanosoma cruzi, the protozoan agent of Chagas disease infects ten million people in Latin America where it is the main cause of cardiac failure. It is transmitted by insect vectors in endemic areas, and also congenitally, by transfusion of infected blood, transplantation of infected organs and oral route in both endemic and non-endemic areas. Since the 1990s, a constant decrease of incidence of infection is observed in Latin America, where vector control programmes and improvement of blood banks have been implemented. However, the important migration flows in the last decades for economic reasons have brought considerable numbers of Latin American subjects infected with T. cruzi, in US, Europe, Japan and Australia. Such globalization of T. cruzi infection/Chagas disease has been confirmed in an WHO historical meeting in 2007, emphasizing the importance of a wise management of such patients and the need of implementing control measures in blood banks, transplantation centres and maternities of involved countries in non-endemic areas. This paper considers these elements and the present situation of Chagas disease in Europe and Belgium.

RÉSUMÉ

Trypanosoma cruzi, le protozoaire agent de la maladie de Chagas, infecte dix millions de personnes en Amérique latine où il est une cause majeure d’insuffisance cardiaque. Il est transmis par des insectes vecteurs en zone endémique, et également par voie congénitale, transfusion sanguine, transplantation d’organe et voie orale, en zones endémique et non endémique. On assiste depuis les années 1990 à une diminution constante de l’incidence de cette infection en Amérique latine, suite à la mise en place de programmes de lutte anti-vectorielle et de contrôle des banques de sang. Cependant les migrations importantes, pour raisons économiques, de ces dernières décennies, ont amené un nombre considérable de sujets latino-américains infectés par T. cruzi aux USA, en Europe, au Japon et en Australie. Cette « mondialisation » de l’infection à T. cruzi/maladie de Chagas a été confirmée lors d’une réunion historique à l’OMS en 2007, soulignant l’importance d’une prise en charge avisée de ces patients et la nécessité de mettre en place des mesures de contrôle dans les banques de sang, les centres de transplantation et les maternités des pays concernés dans les zones non endémiques. Le présent exposé envisage ces éléments et la situation actuelle de la maladie de Chagas en Europe et en Belgique.
BIBLIOGRAPHY


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Discussion

M. M. Lamy. – En matière de transfusion sanguine et de transplantation d’organes, quelles règles préconisez-vous ? Sérologie, cela implique, pour la Belgique, des échantillons sanguins vers Anvers ou Bruxelles ? Quel est le délai de réponse des laboratoires ? En transplantation d’organe, on est en effet parfois assez pressé par le temps.

M. Y. Carlier. – Réaliser une sérologie pour T. cruzi chez tout donneur de sang ou d’organe, originaire de ou ayant séjourné en Amérique latine, est une mesure facile à prendre. Ces sérologies sont effectivement disponibles à l’ULB et à l’ITG. Ces tests sont réalisés en quelques heures (ELISA) et, en prévenant le laboratoire de l’urgence, il est possible d’obtenir ce résultat plus rapidement.

M. L. Hue. – Connaît-on le mode d’action des deux médicaments utilisés dans le traitement de la maladie de Chagas ?

M. Y. Carlier. – Le(s) mode(s) d’action du benznidazole et du nifurtimox étaï(en)t peu connu(s) jusqu’il y a peu. On pensait que le benznidazole agissait sur l’ADN parasitaire, en empêchant la synthèse protéinique et en augmentant la phagocyte et la production de cytokines, et que le nifurtimox agissait par la production de radicaux libres (anions super oxydes et oxyde nirelque). Récemment il a été montré que ces deux médicaments nitrohétérocycliques étaient des promédicaments transformés par une nitroréductase parasitaire de type 1 (absente des cellules de l’hôte) et produisant ainsi des métabolites toxiques pour le parasite, sans génération de superoxydes.

M. J.-C. Schoevaerds. – La migration vectorielle dans le monde a-t-elle été influencée par la lutte antivectorielle dans les pays d’Amérique latine, qui a abaissé le taux d’infection vectorielle en Amérique latine ? Ou est-ce que cette migration est une pure constatation actuelle ? Y-a-t-il eu des cas d’infection en phase « aiguë » constatés en Belgique ?

M. Y. Carlier. – Non, les migrations vectorielles en Afrique et en Asie sont le fait du commerce maritime à partir de l’Amérique latine et ne sont pas en rapport avec la diminution des vecteurs dans ce continent. Il n’y a pas encore, à ma connaissance, eu de cas d’infection aiguë constatée en Belgique (par transfusion sanguine ou par voie congénitale).

M. A. Albert. – Vous avez évoqué l’œdème oculaire comme un des premiers signes de la maladie de Chagas. S’agit-il d’un signe lié à la transmission vectorielle ? Pourriez-vous élargir sur ce point ?

M. Y. Carlier. – L’œdème oculaire bipalbrépal unilatéral, appelé signe de Romaña, est en effet un signe d’entrée du parasite par voie vectorielle. Il est lié à la réaction inflammatoire provoquée au contact de l’œil par les déjections du vecteur associées au parasite. Cet œdème peut également être observé au cours du contact oculaire avec des déjections d’insectes sans parasite. Dans ce cas la durée de l’œdème est moindre.
M. G. Casimir. — Est-il pensable de réaliser un test de dépistage néonatal avec une bonne sensibilité, par exemple sur papier Guthrie ?

M. Y. Carlier. — Le dépistage néonatal d’une infection à *T. cruzi* à partir d’une goutte de sang prélevée sur papier filtre n’est pas possible. Les anticorps détectés seront ceux provenant de la mère et pas ceux du nouveau-né. Par ailleurs les essais de PCR que nous avons réalisés pour rechercher de l’ADN parasitaire sur ce type de matériel ont échoué, les concentrations d’ADN parasitaire présentes dans les prélèvements étant beaucoup trop faibles. Par contre ce dépistage pourrait tout à fait permettre de dépister les mères séropositives pour *T. cruzi*, ce qui devrait conduire à la recherche du parasite chez leurs nouveau-nés par d’autres techniques.

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