

## Gastro-intestinal Chagas disease in migrants to Spain: prevalence and methods for early diagnosis

A. PÉREZ-AYALA\*, J. A. PÉREZ-MOLINA\*, F. NORMAN\*, B. MONGE-MAILLO\*, M. V. FARO† and R. LÓPEZ-VÉLEZ\*

\*Tropical Medicine and Clinical Parasitology Unit, Infectious Diseases Department, Ramón y Cajal Hospital, Carretera Colmenar Viejo, Km 9.1, 28049 Madrid, Spain

†Gastro-intestinal Motility Unit, Gastro-enterology Department, Ramón y Cajal Hospital, Carretera Colmenar Viejo, Km 9.1, 28049 Madrid, Spain

Received 31 August 2010, Revised 11 October 2010,

Accepted 15 October 2010

Each year in Spain, the number of Latin American immigrants who present with chronic *Trypanosoma cruzi* infection increases. Although gastro-intestinal abnormalities are not as common as cardiomyopathy in such infection, they can still lead to an impaired quality of life. In a recent study based in Madrid, the frequencies of gastro-intestinal involvement in a cohort of Latin American immigrants infected with *T. cruzi*, and the role of early diagnostic techniques in the detection of such involvement, were explored. Between January 2003 and April 2009, all Latin Americans who attended the Tropical Medicine Unit of the Hospital Universitario Ramón y Cajal were tested for *T. cruzi* infection, in IFAT and ELISA. Each subject found both IFAT- and ELISA-positive was considered to be infected (chronically) and checked for symptoms indicative of Chagas disease. Each infected subject giving informed consent was investigated further, using an electrocardiogram, an echocardiogram and oesophageal manometry. Between January 2003 and June 2008, every infected subject who consented was also explored using a barium swallow and barium enema. After July 2008, however, only subjects showing oesophageal and/or colonic symptoms were investigated in this manner.

Of the 248 patients found infected with *T. cruzi*, 118 underwent oesophageal manometry, 75 a barium enema and 48 a barium swallow. Thirteen (11%) showed evidence of oesophageal involvement (incomplete relaxation of the lower oesophageal sphincter; three cases) or bowel involvement (five cases of dolichosigma, three of dolichocolon and two of megacolon). Only six of these 13 had any gastro-intestinal symptoms (all six were suffering from constipation). None of the barium swallows revealed any pathology. It appears that oesophageal manometry can reveal mild abnormalities not detected by barium swallow, even in asymptomatic patients, while barium enemas are useful in the detection of colonic involvement.

Nowadays, American trypanosomiasis or Chagas disease may be diagnosed in almost every country in the western world thanks to increased emigration from Latin America to countries where the causative parasite, *Trypanosoma cruzi*, is non-endemic. Worldwide, after the U.S.A., Spain has the largest number of Latin American immigrants and, consequently, surprisingly large and increasing numbers of cases of chronic Chagas

disease (Schmunis, 2007; Perez de Ayala *et al.*, 2009).

Decades after the primary infection, between 20% and 40% of humans infected with *T. cruzi* will develop detectable organ involvement such as cardiomyopathy (20%–30%) or gastro-intestinal manifestations (15%–20%) or both (10%) (Prata, 2001).

Given its relatively high frequency and the severe morbidity and mortality it may cause, cardiac involvement is the most important consequence of *T. cruzi* infection but gastro-intestinal involvement, although

---

Reprint requests to: A. Pérez-Ayala.  
E-mail: aperezd.hrc@salud.madrid.org.

less frequently observed, may also lead to great suffering and deterioration in quality of life. The prevalence of gastro-intestinal involvement varies between geographical areas, probably reflecting subspecific variation in the *T. cruzi* circulating in each region (Prata, 2001). Such morbidity is relatively rare in countries north of the Equator and also more commonly observed in central and northern Brazil than in the rest of the countries in the Southern Cone (Rassi *et al.*, 2010). It occurs secondary to a progressive destruction of intramural neurons and affects mainly the oesophagus, producing megaesophagus with identical clinical and manometric features to those present in idiopathic achalasia (Meneghelli *et al.*, 2005). Although the entire gastro-intestinal tract can be affected, colonic abnormalities (mainly megacolon) are the second most common form of gastro-intestinal morbidity, often occurring relatively late in the course of the disease (Iantorno *et al.*, 2007).

Chagas disease has been identified as a 'neglected' tropical disease. The presence of the infection in the Western world provides an excellent opportunity for initiating research studies that could be extended into endemic countries at a later date. Several recent studies have focused on progression of the cardiac disease (Marin-Neto *et al.*, 2008) but there have been few publications on the gastro-intestinal involvement.

The main aims of the present study were to determine, in Spain, the frequency of gastro-intestinal involvement in a cohort of immigrants (from *T. cruzi*-endemic areas) who were chronically infected with *T. cruzi*, and to assess the value of oesophageal manometry, barium swallow and barium enema in the early detection of such involvement.

## SUBJECTS AND METHODS

The subjects of the observational, cohort, longitudinal and prospective study were Latin American immigrants who attended

the Tropical Medicine Unit of the *Hospital Universitario Ramón y Cajal* in Madrid, Spain, between January 2003 and April 2009 and were tested for *T. cruzi* infection by both IFAT and ELISA (Flores-Chávez *et al.*, 2008). Each subject found positive in both the IFAT and ELISA was considered to have a chronic *T. cruzi* infection.

Each infected subject was checked for symptoms of Chagas disease and, after giving informed consent, investigated further, via an electrocardiogram (ECG), an echocardiogram (ECC) and oesophageal manometry. Between January 2003 and June 2008, each infected subject who consented was explored using a barium swallow and barium enema. After July 2008, however, only subjects showing oesophageal and/or colonic symptoms were investigated in this manner.

In the absence of another possible cause, dysphagia for solids and/or liquids, retrosternal pain, increased salivation, enlarged parotid glands, halitosis, nocturnal regurgitation or progressive weight loss were considered indicative of chagasic oesophageal involvement whereas progressive constipation, rectal faecalomas or acute abdominal pain due to volvulus were considered indicative of chagasic colonic involvement (De Rezende and Moreira, 1988; Bern *et al.*, 2007).

Test results considered indicative of chagasic gastro-intestinal involvement were aperistalsis and/or a non-relaxing or partially relaxing lower oesophageal sphincter (LOS) in the oesophageal manometry, slow transit, retention of contrast, oesophageal dilatation and/or dolichomegaesophagus in the barium swallow, and dolichocolon or megacolon in the barium enema (De Oliveira *et al.*, 1998).

Once clinical assessment was complete, all the infected patients aged <50 years who had no severe cardiac involvement and had not previously received appropriate treatment in their country of origin were treated with benznidazole, at 5 mg/kg.day (in two or three divided doses each day) for 60 days.

## RESULTS

Overall, 248 subjects (169 females and 79 males) were diagnosed with chronic *T. cruzi* infection. They had a median age of 36 years (range=16–70 years). All but nine (i.e. 96.4%) came from Bolivia, with the rest originating in Ecuador (two), Paraguay (three), Argentina (one), Chile (one), Brazil (one) or Honduras (one). Most (84%) had seen triatomine bugs in their old houses in Latin America, most (79%) had lived in rural areas of Latin America, and most (60%) had family members who had been identified as cases of Chagas disease.

Gastro-intestinal symptoms were present in 84 (33.9%) of the infected patients, mainly constipation on its own (seen in 50% of those with gastro-intestinal symptoms), followed by dysphagia on its own (12%), abdominal pain (4.8%) and both constipation and dysphagia (3.6%).

Overall, 130 of the 248 infected subjects could not be investigated further for gastro-intestinal morbidity because they were lost to follow-up or would not give consent. Of the other 118 subjects, who were investigated by oesophageal manometry (118), barium enema (75) and/or barium swallow (48), 13 (11%) showed evidence of gastro-intestinal involvement in the tests performed. Three showed oesophageal involvement (incomplete relaxation of the LOS) while the other 10 all showed bowel involvement (five dolichosigma, three dolichocolon and two megacolon). Of the 13 who gave test results indicative of gastro-intestinal involvement, only six had any gastro-intestinal symptoms, all six suffering from constipation. Both subjects found to have megacolon (via barium enemas) had been complaining of constipation for years, and one of these two cases had a faecaloma.

None of the 48 barium swallows performed revealed any pathology and none of the subjects showed both oesophageal and colonic involvement. The results of the tests performed are summarized, separately for the subjects with and without symptoms, in the Table.

Of the 165 infected subjects who were given both ECC and ECG, 37 (22.4%) of them showed chagasic cardiomyopathy without gastro-intestinal involvement and four (2.4%) showed chagasic cardiomyopathy with gastro-intestinal involvement.

Although benznidazole treatment was initiated in 119 of the subjects, 24 (20%) of them had to stop treatment before the 60-day course was completed because of adverse side-effects. At the time of the data analysis for the present study, 28 subjects were still receiving treatment and the remaining 77 had completed treatment (56 without any adverse effects and 21 with mild adverse effects). The adverse effects observed, in 45 (38%) of the subjects given benznidazole, were mainly attributable to cutaneous toxicity (morbilliform rash, pruritus and/or occasional mucosal involvement).

## DISCUSSION

In the present study, eight of the subjects infected with *T. cruzi* (including four suffering from constipation) were found to have dolichocolon or dolichosigma. There were three asymptomatic subjects who showed incomplete relaxation of the LOS and two subjects with long-term symptoms and megacolon. No barium-swallow abnormalities were found. Based on these results a number of issues arise.

Firstly, barium swallows did not reveal any cases of oesophageal involvement (whether the subjects tested were symptomatic or asymptomatic) whereas oesophageal manometry revealed minor gastro-intestinal involvement in three subjects, all of whom were asymptomatic. Although the manometric abnormalities observed were not specific to Chagas disease, it appears that manometry may be more useful than barium swallow for the detection of early oesophageal involvement, as Dantas *et al.* (1999) suggested. Manometric abnormalities can occur relatively frequently among asymptomatic patients who give normal results in barium

TABLE. Test results for subjects with and without gastro-intestinal symptoms

Test	No. of subjects:			
	With gastro-intestinal symptoms:		Without gastro-intestinal symptoms	
	Investigated	Giving abnormal result	Investigated	Giving abnormal result
Oesophageal manometry	3	0	115	3*
Barium enema	38	6 <sup>†</sup>	37	4
Barium swallow	23	0	25	0

\*Including one subject with cardiomyopathy.

<sup>†</sup>Including three subjects with cardiomyopathy.

studies. In Spain, it would appear that barium swallow may reasonably be omitted from the investigation (or, at least, the initial investigation) of *T. cruzi*-infected Bolivian immigrants with few or no symptoms whereas manometry should perhaps be included. With the exception of advanced cases, and knowing that, once established, the progression of the disease is slow (Meneghelli *et al.*, 2005), the detection of oesophageal involvement should not, however, modify case management and therefore manometry may not be indicated for all asymptomatic patients. In addition, some doubt remains over whether asymptomatic individuals with *T. cruzi* infection and manometric abnormalities will ever develop gastro-intestinal Chagas disease (Herbella *et al.*, 2004). The results of some recent studies have shown that patients with early cardiac involvement may benefit from treatment with benznidazole, with decreased progression towards established cardiomyopathy (Viotti *et al.*, 2006). Early treatment with benznidazole may offer similar benefits in gastro-intestinal involvement but little is known about disease progression in this type of involvement. All of these considerations may become unnecessary in the future because the current trend seems to be toward the treatment of all asymptomatic patients with *T. cruzi* infections. If such treatment becomes standard practice, routine manometry may be both unnecessary and unethical, as patients would receive treatment regardless of the results of such investigation.

Secondly, barium enemas revealed megacolon in two of the subjects of the present study, although both subjects had presented with long histories of constipation. Barium enemas also revealed dolichocolon or dolichosigma in four asymptomatic subjects but it remains unclear whether these abnormalities (which can also be found in apparently healthy and uninfected subjects) were the result of the *T. cruzi* infections. At the study centre in Madrid, as there are no plans to modify the therapeutic approach of the clinicians as a result of this discovery, not every *T. cruzi*-infected asymptomatic subject who presents in the future may be given a barium enema (even though the results might still reveal incipient colonic morbidity).

All patients with gastro-intestinal involvement should be tested for cardiac involvement. Various studies have shown that approximately 50% of patients with oesophageal involvement also have ECG abnormalities indicative of chagasic cardiomyopathy (Prata, 2001). In the present study, four subjects (one of the three who had oesophageal involvement and three of the six who had symptomatic colonic involvement) had both cardiomyopathy and gastro-intestinal morbidity.

The indications for treatment in the chronic phase of Chagas disease remain a matter of controversy. Bern *et al.* (2007) recommended treatment of every case of *T. cruzi* infection except those for whom treatment seems to offer little if any benefit: those showing clear organ involvement and those aged >50 years.

Before prescribing benznidazole treatment, a careful risk–benefit assessment should be performed on an individual basis, especially given the risks of adverse effects. A long-term follow-up of treated patients, using both serological and PCR-based techniques, would be of interest in order to evaluate the responses to treatment.

In conclusion, in the present study, gastrointestinal involvement was observed less frequently than in earlier investigations (11% *v.* 15%–20%; Prata, 2001) and was generally mild. In immigrants from Bolivia who are seropositive for *T. cruzi*, barium enemas (which, in the present study, revealed both mild and severe involvement in both symptomatic and asymptomatic individuals) seem to be indicated. In contrast, barium swallows appear to be of little use in detecting the early stages of oesophageal involvement, in asymptomatic or symptomatic patients. The symptoms associated with oesophageal involvement are confusing (in the present study, none of the subjects with manometric abnormalities presented with dysphagia) and abnormalities may be detected by oesophageal manometry in asymptomatic individuals (in the present study, three asymptomatic subjects had manometric abnormalities). Further studies, including long-term follow-ups, are clearly justified.

**ACKNOWLEDGEMENTS.** The authors acknowledge the financial support provided by the *Red de Investigación de Centros de Enfermedades Tropicales* (RD06/0021/0020). They thank Dr C. Cañavate and M. Flores, both of the *Instituto de Salud Carlos III*, for performing the *T. cruzi* serology.

## REFERENCES

- Bern, C., Montgomery, S. P., Herwaldt, B. L., Rassi Jr, A., Marin-Neto, J. A., Dantas, R. O., Maguire, J. H., Acquatella, H., Morillo, C., Kirchoff, L. V., Gilman, R. H., Reyes, P. A., Salvatella, R. & Moore, A. C. (2007). Evaluation and treatment of Chagas disease in the United States: a systematic review. *Journal of the American Medical Association*, **298**, 2171–2181.
- Dantas, R. O., Deghaide, N. H. & Donadi, E. A. (1999). Esophageal manometric and radiologic findings in asymptomatic subjects with Chagas' disease. *Journal of Clinical Gastroenterology*, **28**, 245–248.
- De Oliveira, R. B., Troncon, L. E., Dantas, R. O. & Menghelli, U. G. (1998). Gastrointestinal manifestations of Chagas' disease. *American Journal of Gastroenterology*, **93**, 884–889.
- De Rezende, J. M. & Moreira, H. (1988). Chagasic megaesophagus and megacolon. Historical review and present concepts. *Arquivos de Gastroenterologia*, **25** (Spec. No.), 32–43.
- Flores-Chávez, M., Fernández, B., Puente, S., Torres, P., Rodríguez, M., Monedero, C., Cruz, I., Gárate, T. & Cañavate, C. (2008). Transfusional Chagas disease: parasitological and serological monitoring of an infected recipient and blood donor. *Clinical Infectious Diseases*, **46**, e44–e47.
- Herbella, F. A., Oliveira, D. R. & del Grande, J. C. (2004). Are idiopathic and chagasic achalasia two different diseases? *Digestive Diseases and Sciences*, **49**, 353–360.
- Iantorno, G., Bassotti, G., Kogan, Z., Lumi, C. M., Cabanne, A. M., Fisogni, S., Varrica, L. M., Bilder, C. R., Munoz, J. P., Lissere, B., Morelli, A. & Villanacci, V. (2007). The enteric nervous system in chagasic and idiopathic megacolon. *American Journal of Surgical Pathology*, **31**, 460–468.
- Marin-Neto, J. A., Rassi Jr, A., Morillo, C. A., Avezum, A., Connolly, S. J., Sosa-Estani, S., Rosas, F. & Yusuf, S. (2008). Rationale and design of a randomized placebo-controlled trial assessing the effects of etiologic treatment in Chagas' cardiomyopathy: the BENznidazole Evaluation For Interrupting Trypanosomiasis (BENEFIT). *American Heart Journal*, **156**, 37–43.
- Meneghelli, U. G., Darezzo, F. M., Peria, F. M., Almeida, F. H., Rodrigues, C. M., Aprile, L. R. & Dantas, R. O. (2005). Clinical, radiographic, and manometric evolution of esophageal involvement by Chagas' disease. *Dysphagia*, **20**, 40–45.
- Perez de Ayala, A., Perez-Molina, J. A., Norman, F. & Lopez-Velez, R. (2009). Chagasic cardiomyopathy in immigrants from Latin America to Spain. *Emerging Infectious Diseases*, **15**, 607–608.
- Prata, A. (2001). Clinical and epidemiological aspects of Chagas disease. *Lancet Infectious Diseases*, **1**, 92–100.
- Rassi Jr, A., Rassi, A. & Marin-Neto, J. A. (2010). Chagas disease. *Lancet*, **375**, 1388–1402.
- Schmunis, G. A. (2007). Epidemiology of Chagas disease in non-endemic countries: the role of international migration. *Memórias do Instituto Oswaldo Cruz*, **102** (Suppl. 1), 75–85.
- Viotti, R., Vigliano, C., Lococo, B., Bertocchi, G., Petti, M., Alvarez, M. G., Postan, M. & Armenti, A. (2006). Long-term cardiac outcomes of treating chronic Chagas disease with benznidazole versus no treatment: a nonrandomized trial. *Annals of Internal Medicine*, **144**, 724–734.