

REVIEW

THE CHRONIC GASTROINTESTINAL MANIFESTATIONS OF CHAGAS DISEASE

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Chagas disease is an infectious disease caused by the protozoan *Trypanosoma cruzi*. The disease mainly affects the nervous system, digestive system and heart. The objective of this review is to revise the literature and summarize the main chronic gastrointestinal manifestations of Chagas disease. The chronic gastrointestinal manifestations of Chagas disease are mainly a result of enteric nervous system impairment caused by *T. cruzi* infection. The anatomical locations most commonly described to be affected by Chagas disease are salivary glands, esophagus, lower esophageal sphincter, stomach, small intestine, colon, gallbladder and biliary tree. Chagas disease has also been studied in association with *Helicobacter pylori* infection, interstitial cells of Cajal and the incidence of gastrointestinal cancer.

KEYWORDS: Enteric nervous system; Gastrointestinal tract; Motility disorders; Chagas disease, *Trypanosoma cruzi*.

INTRODUCTION

Chagas disease, named after the Brazilian physician, bacteriologist and epidemiologist Carlos Chagas who first described it a hundred years ago, is a tropical parasitic disease caused by the flagellate protozoan *Trypanosoma cruzi* (*T. cruzi*).¹⁻³

The parasite *T. cruzi* is commonly transmitted to humans and other mammals by a vector insect, the blood-sucking bugs of the subfamily Triatominae.^{1,2} This disease can also be transmitted by blood transfusion, organ transplantation, from a mother to her fetus and by ingestion of food contaminated with the parasites.^{4,5}

Several years or even decades after the initial infection, approximately 30% of infected people develop medical problems from Chagas disease over the course of their lives.⁴ Chagas disease mainly affects the nervous system, gastrointestinal tract and heart. Most people suffer

cardiac damage, including cardiomyopathy, heart rhythm abnormalities and often an apical aneurysm.^{3,4}

Approximately one third of patients can develop dilation of the gastrointestinal tract (megacolon, megaesophagus, megastomach, megaduodenum, megajejunum, megagallbladder, megacholedochus) and gastrointestinal motor disorders, such as achalasia of the cardia, disturbances of gastric emptying, altered intestinal transit and colon and gallbladder motor disorders.^{3,4,6-18} Chagas disease is known to cause both central nervous system and enteric nervous system injury.^{3,4} The chronic gastrointestinal manifestations of Chagas disease are mainly a result of enteric nervous system injury caused by *T. cruzi* infection.¹⁹⁻²⁵

The objective of this review is to revise the literature and summarize the main chronic gastrointestinal manifestations described in association with Chagas disease in the year of the hundredth anniversary of the first description of Chagas disease.

DISCUSSION

The chronic gastrointestinal manifestations of Chagas disease are described in the salivary glands, esophagus, lower esophageal sphincter, stomach, small intestine, colon, gallbladder and biliary tree.^{3,4,6-18,26} These alterations seem to develop from both excitatory and inhibitory enteric motor

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innervation impairments.¹⁹⁻²⁴ The chronic gastrointestinal manifestations of Chagas disease are described in association with *Helicobacter pylori* (*H. pylori*) infection, damage to the interstitial cells of Cajal and the incidence of gastrointestinal cancer.²⁷⁻³⁴

From a total of 4,690 autopsies, 1,708 chagasic chronic post-mortem examinations were performed, and megacolon was the most frequent gastrointestinal manifestation, followed by megaesophagus. Megacolon associated with the megaesophagus was the third most common finding.³⁵

The salivary gland manifestations of Chagas disease

Sialorrhea has been described in association with megaesophagus in both patients with Chagas disease and those with idiopathic megaesophagus.³⁶ Salivary gland hypertrophy and sialorrhea have been described not only in association with chagasic megaesophagus and idiopathic achalasia, but also in association with other eating disorders, including bulimia and anorexia nervosa.³⁶⁻³⁸ Both salivary gland hypertrophy and sialorrhea seem to be related to the symptoms of vomiting and regurgitation described in these eating disorders and idiopathic and chagasic achalasia.³⁶⁻³⁸

The esophagus and the lower esophageal sphincter manifestations of Chagas disease

Chagasic achalasia and its consequence of chagasic megaesophagus are common findings in Chagas disease, and dysphagia may be the first symptom of digestive disturbances that may lead to malnutrition and severe weight loss.^{8,9,35,39,40}

The nitric oxide (NO) donor drugs were used at the first half of the last century to increase emptying of the megaesophagus and to improve the symptoms of dysphagia in idiopathic achalasia.⁴¹⁻⁴⁴ In chagasic achalasia, there are reports of the use of such drugs for the same purpose in the middle of the last century. However, the presentation of NO-donor drugs and their side effects has limited their use. Only later, with the presentation of such drugs in the form of tablets to be administered orally or sublingually, it was demonstrated that NO-donor drugs decrease lower esophageal sphincter pressure, improve the symptoms of dysphagia and increase megaesophagus clearance in both idiopathic achalasia and chagasic achalasia.⁴⁵⁻⁵³ Researchers finally demonstrated similarities between the inhibitory non-adrenergic non-cholinergic mediator and the substance released from NO-donor drugs in the late 1980s.^{54,55}

Although chagasic achalasia presents with symptoms and radiological findings similar to those of idiopathic achalasia, some important differences are described.^{9, 56-}

⁵⁸ It has been demonstrated that, in patients with Chagas disease, pressure in the lower esophageal sphincter is lower than in normal patients, whereas the pressure is higher in patients with idiopathic achalasia.^{7,40} Higher pressure in the lower esophageal sphincter in idiopathic achalasia relative to that in controls has also been demonstrated by others researchers.^{59,60} Reduced pressure in the lower esophageal sphincter in chagasic achalasia further demonstrates that both innervations, excitatory and inhibitory, are damaged in contrast to idiopathic achalasia, where the excitatory innervation is preserved, thereby causing the pressure to be higher than in the normal subjects.^{39,40,59-61} Similarities are also observed in the treatments, including pharmacological, endoscopic and surgical procedures.^{62,63} In both cases, treatment is palliative, with an objective of decreasing lower esophageal sphincter pressure, improving esophageal emptying and relief of the symptoms of dysphagia.^{62,63}

The stomach manifestations of Chagas disease

The megastomach is neither a common nor an important finding of gastrointestinal manifestation in Chagas disease, although alterations in both motility and secretion have been described. Delayed gastric emptying of solid meals has been demonstrated. The explanation provided for this observation is that the excitatory motor enteric neurons are damaged in Chagas disease.^{13,64} Fast gastric emptying of liquid meals was also demonstrated, and the explanation was related not only to impairment of the excitatory enteric neurons, but also to impairment of inhibitory enteric neurons.^{12, 15}

Given that inhibitory innervation is responsible for gastric accommodation after a meal, the stomach is not able to relax after a liquid meal once inhibitory enteric innervation is damaged, which results in rapid gastric emptying.^{12,15}

Moreover, electrogastrography performed in patients with Chagas disease showed a higher incidence of gastric dysrhythmias in the chagasic patients than in the normal subjects.²⁶ Another alteration demonstrated in patients with Chagas disease is that both basal and stimulated acid gastric secretion were lower than in normal subjects.^{65,66}

The small intestine manifestations of Chagas disease

Abnormalities of interdigestive motility of the small intestine in Chagas disease have been described.⁶⁷ Manometric studies of gastrointestinal motility showed abnormally slow propagation of the interdigestive migrating motor complex, which was also excessively prolonged.^{66,67}

Although not common, dilation of the small intestine, such as megaduodenum and megajejunum, has also been

described.^{14,18} However, fast transit in the dilated small intestine in Chagas disease has been associated with bacteria overgrowth with chronic diarrhea, malabsorption, steatorrhea and hypocalcemia that improved with oral antibiotic therapy.^{14,18} Patients with Chagas disease have a combination of very fast gastric emptying and abnormally delayed transit of liquids through the more distal segments of the small bowel.¹⁵ Also, disorders of absorption in the small intestine were demonstrated in Chagas disease as an abnormal increase in the absorption of carbohydrates.^{2,10}

The colonic manifestations of Chagas disease

Another common manifestation of Chagas disease in the gastrointestinal tract is chagasic megacolon. Chronic constipation is the main symptom related to megacolon.^{4,6,8,35} Although chagasic megacolon presents with symptoms and radiological findings similar to congenital megacolon, differences are also related to damage in both excitatory and inhibitory innervations.^{19,20,22,24,25} Manometric studies in chagasic patients have demonstrated the basal motility index and wave frequency of the sigmoid colon and rectum to be lower than in normal subjects. In addition, the studies show a lack of relaxation of the internal sphincter of the anus in the chagasic patients.^{6,11} Others have demonstrated an absence of the rectoanal inhibitory reflex in the chagasic megacolon, similar to that in Hirschsprung's disease.^{68,69} Alteration of the rectoanal inhibitory reflex in most of the chagasic patients with megacolon was demonstrated by several researchers and can be justified by the destruction of enteric motor innervations.^{6,11,19,20,22,24,25,68,70} The choice of surgical treatment appears to have the same indication as a solution for constipation in both chagasic and idiopathic megacolon.^{71,72}

The incidence of diverticula in the sigmoid colon of the non-chagasic group was higher than in both the chagasic group with and without megacolon.⁷³ Among the patients with megacolon and diverticular disease, the diverticula were always located in the non-dilated portions of the large bowel, suggesting that unfavorable conditions for the genesis or maintenance of diverticula exist in the dilated colon of the chagasic patients.⁷³

The gallbladder and the biliary tree manifestations of Chagas disease

Gallbladder neuron counts in cholelithiasis in patients with Chagas disease have demonstrated a reduction in the number of neurons in the gallbladder wall.²¹ Given that the enteric excitatory motor neurons are damaged in Chagas disease, the prevalence of cholelithiasis, megagallbladder and megacholedochus is higher.^{74,75} Despite controversial

results, a scintigraphic study of gallbladder emptying in Chagas disease showed that the gallbladder of the chagasic patients was much more sensitive to an exogenous cholecystokinetic agent and contracted in a more intense manner, with contraction starting earlier and lasting longer than among the controls, suggesting more severe impairment of the inhibitory enteric innervations.¹⁷

H. pylori infection and Chagas disease

In addition to studies in developing countries, which have a higher incidence of infection by *H. pylori*, Chagas disease has a higher incidence of peptic changes and a high frequency of peptic disease associated with *H. pylori* infection.^{29,76} Another study showed that the prevalence of infection by *H. pylori* was higher in the chagasic patients than in non-chagasic subjects from both urban and rural areas.³¹ Furthermore, *H. pylori* was considered a possible factor related to the etiopathogenesis of chronic superficial and atrophic gastritis, since it was frequently observed in patients with the gastrointestinal manifestations of Chagas disease.^{34,77}

The interstitial cells of Cajal and Chagas disease

Injury to the interstitial cells of Cajal as well as the enteric nervous system have been considered important in gastrointestinal motility control.^{78,79}

Despite the controversy regarding the pathogenic role of defects in the interstitial cells of Cajal in idiopathic constipation and other gastrointestinal motor disorders, changes in the distribution of the interstitial cells of Cajal have been reported in various conditions, such as achalasia, chronic intestinal pseudo-obstruction, infantile hypertrophic pyloric stenosis, Hirschsprung's disease, inflammatory bowel disease and slow transit constipation.⁷⁷⁻⁸⁷ In addition, altered distribution of the interstitial cells of Cajal has been demonstrated in chagasic megaesophagus and in chagasic megacolon.^{27,28,30}

The incidence of gastrointestinal cancer and Chagas disease

The association of cancer of the esophagus and megaesophagus has been demonstrated to be both higher and lower in chagasic patients than in normal subjects.^{33,88} Since a higher prevalence of gastric lesions and infection by *H. pylori* has been demonstrated, an increased incidence of cancer in the chagasic megaesophagus can be expected.^{34,89-91}

A review of 4,690 necropsies and 24,209 surgical specimens showed that the prevalence of malignant tumors

of the large bowel was not higher in chagasic megacolon.³² Other authors also showed no association between chagasic megacolon and an increased incidence of cancer.³³ Thus, Chagas disease affects several gastrointestinal regions, but there is no apparent relationship with the increased incidence of cancer and chagasic megacolon, and the main causes of death in elderly chagasic patients are commonly related instead to heart disease.^{32,33,92}

SUMMARY

Chagas disease is an infectious disease that is described to mainly affect the central nervous system, heart and gastrointestinal tract. The objective of this review is to revise and summarize the main chronic gastrointestinal manifestations described in association with Chagas disease.

Chagas disease is related to several chronic gastro-

intestinal disorders resulting from damage to both excitatory and inhibitory enteric motor innervations, leading to megaesophagus, megacolon, megasmall intestine, megagallbladder, megacholedochus, achalasia of the cardia, changes in gastric receptive relaxation, fast gastric emptying of liquid meals, delayed gastric emptying of solid meals, altered small intestine transit and impairment of colon and gallbladder motility.

Chagas disease is also related to hypertrophy of the salivary glands, increased saliva production, decreased acid gastric production and altered small intestinal absorption. In addition, more peptic gastric lesions, a higher incidence of *H. pylori* infection, a similar incidence of cancer in the colon, a higher incidence of cancer in esophagus and altered distribution of the interstitial cells of Cajal in the megaesophagus and megacolon have also been demonstrated in association with Chagas disease.

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