Gastrointestinal Chagas Disease

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Abstract The chronic phase of Chagas disease is presented in three clinical forms: indeterminate (no clinical manifestations), cardiac disease, and megaviscera syndromes. The latter comprise up to 18% of the infected individuals and most often present a compromise of the esophagus and colon. The physiological function of these organs depends on a perfect coordination/synchronization of muscular constriction and relaxation waves, in order to push a rather hard material (alimentary bolus and feces) through their cavity, and a coordinated transposition of two sphincters. When this function is hampered, a progressive increase in the diameter of both organs is produced, termed megaesophagus and megacolon. A clue for the cause of this dysfunction is the selective destruction of parasympathetic plexus neurons by the etiological agent of the disease, *Trypanosoma cruzi*. Besides motor alterations, secretory and absorptive functions may be affected. Why these features are observed in only some of the infected is not clear. A markedly discrete geographical distribution of digestive Chagas disease cases below the equatorial line suggests it may be due to the type of circulating *T. cruzi* lineages (TcII and TcV). Different incidences according to gender and age are also seen. A number of neurotransmitters and neuropeptides have been linked to Chagas disease-associated megaviscera syndromes. Dysphagia and obstipation are clinical hallmarks of this disease, but serological

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diagnosis is necessary to exclude other possible causes, like idiopathic megaviscera. Association with cardiac involvement is observed in 20–30% of the cases, and 40% of the cases exhibit both megaesophagus and megacolon. Progression from mild to severe disease is seen in some of the cases, in which surgery is ultimately required. Fecaloma and volvulus are common complications of megacolon. In recent years, new methods have significantly improved post-surgery prognosis. Alternative treatments with botulinum toxin and by mechanical dilatation are indicated for specific cases. Other hollow viscera may be involved, albeit at lower frequencies, such as the stomach, duodenum, gallbladder, ureter, bladder, and others. However, these are usually also associated with megacolon and/or megaesophagus.

1 Introduction

T. cruzi produces overt disease in only half of the infected individuals. The other half will remain chronically infected in the indeterminate or asymptomatic form of the disease for life. The reasons for this are not clearly known. The evolution to symptomatic forms of the disease is slow, with an estimated 2% of the patients progressing into cardiac and/or digestive compromise every year. Cardiac manifestations are the most frequent, and they have been detected since the discovery of the disease in 1909. Conversely, the association between Chagas disease and megaviscera was only acknowledged 47 years later by Koberle [1] who unequivocally showed denervation of the myenteric plexus in infected individuals with megaesophagus and megacolon. The reasons for this delay include low frequency of cases, geographical differences, lack of parasites in the scrutinized lesions at the time of examination, similarity with idiopathic megaviscera, and difficulties to reproduce these syndromes in experimental animal models. Nevertheless, megaesophagus and megacolon had been described in Chagas disease endemic areas (Central Brazil) by historians in 1823 [2] and 1857 [3], long before the discovery of the disease, and in frequencies that recalled that of *T. cruzi* infection. Also, mummies with megacolon were found [4].

1.1 Pathophysiology

The parasite destroys, mainly during the acute phase, the nervous intramural plexuses of hollow viscera, with an unpredictable and uneven distribution. Coordinated motor activity of the digestive tract is directed by myenteric plexuses, and it is essential for the alimentary bolus and feces to traverse it. Furthermore, both the esophagus and the colon have a sphincter at their ends, which need to coordinately open in order for the material to pass through. This explains the compromise of mainly the esophagus and the distal segment of the colon. With a lower frequency, dilation of other segments of the digestive tract, i.e., the megagastria, megaduodenum, megajejunum, dilated gallbladder, and urinary tract dilations, may be found, nearly always

Table 1 Frequency of megaesophagus and megacolon in Central Brazil

Megaviscera involved	*n*	%
Megaesophagus	1183	47.6
Megacolon	288	11.6
Megaesophagus + megacolon	1013	40.8
Total	2484	100.0

In all cases diagnosis was performed by barium swallow and barium enema. All patients had four serological positive tests. Data from Núcleo de Estudos da doença de Chagas (NEDoC), Federal University of Goias, Goiania, Brazil

Table 2 Association of megaesophagus and megacolon in Central Brazil

	Colon		Esophagus			
Primarily considered megaviscera	Normal	Mega	Normal	Mega	Total	Association, %
Megacolon	–	–	288	1013	1301	77.9
Megaesophagus	1183	1013	–	–	2196	46.1
Group I/II	696	521	–	–	1217	42.8
Group III/IV	487	492	–	–	979	50.3

Megaesophagus cases were divided in non-severe (compensated, groups I and II) and severe (groups III and IV). In all cases diagnosis was performed by barium swallow and barium enema. All patients had four serological positive tests. Data from Núcleo de Estudos da doença de Chagas (NEDoC), Federal University of Goias, Goiania

associated with megaesophagus and/or megacolon. In fact, in endemic areas, megacolon-megaesophagus association is frequent (~40%, Table 1).

When we consider the degree of association of both main megasyndromes, almost all megacolon cases are associated with megaesophagus, but megaesophagus cases present lower frequency of association with megacolon. The latter seems to be related to the severity of megaesophagus: 43% of the patients with compensated megaesophagus have megacolon, while half of those with severe megaesophagus also exhibit megacolon (Table 2), indicating a widespread compromise of the enteric nervous system.

Koberle [5] attributed the development of megaviscera after variable periods of time to the natural aging and progressive loss of neurons in the enteric nervous system. According to the serial count of neurons in the wall of hollow viscera, the denervation required to develop megaesophagus is at least of 90% and for megacolon 55%. These figures may be attained in elderly noninfected individuals (presbyesophagus) but are seen in young *T. cruzi*-infected subjects due to an accelerated destruction of such cells.

1.2 Geographical Differences

Geographical differences in incidence and pathology are recognized and are probably related to the differential distribution of *T. cruzi* variants. At least six different discrete typing units (DTU) of this parasite have been described (TcI to TcVI), out

of which three are the most clinically relevant [6]. TcI is found mainly in endemic regions above the equatorial line, including part of Brazil, Colombia, Venezuela, Central America, and Mexico. Even though sporadic cases of megaesophagus and megacolon were described, examples of megaviscera are rare in this area. Human infection with *T. cruzi* TcII is mainly found in Central Brazil, where most of the megaviscera cases are seen, with a higher proportion of megaesophagus (Table 1 [7]). TcV is found in humans all across the Southern Cone, including south of Brazil. Cases of megacolon and megaesophagus have been reported, but in lower proportions than in Central Brazil. Interestingly, in Chile, the number of patients with Chagas disease-associated megacolon is higher than that of megaesophagus patients [8].

T. cruzi-related megaviscera should be distinguished from other similar clinical entities, such as high-altitude megacolon (Andean megacolon), occurring in Peru. This is in fact a type of dolichocolon (increase in the length of the colon, without diametral enlargement), causing volvulus, and for which maize-based diet has been appointed as the main cause.

1.3 Epidemiology

For symptomatic individuals, megaesophagus usually appears before cardiopathy, while megacolon has a later onset than cardiac symptoms. Both may evolve differently, from slight alterations that remain so for decades to early severe organ dilation [9]. The reasons behind these different patterns are not clear. Apart from age-associated variation, gender differences are remarkable: megaesophagus is clearly more frequent in males, especially in its more severe forms [10]. This gender difference is less clear in chronic Chagas cardiopathy, even though male patients tend to present more severe evolution. Megacolon patients are predominantly female. Clinical manifestations also differ: it is unusual for a patient with megaesophagus to have no complaints. Dysphagia is the clinical hallmark, present in nearly all patients, and is the main reason leading them to medical consultation and treatment. On the contrary, up to 1/3 of the megacolon cases, diagnosed by barium enema, present no obstipation [11]. This has consequences on treatment: patients only undergo surgery if severe obstipation is present, irrespective of the radiological findings. Other reasons that oblige them for medical attention are volvulus and fecaloma, frequent in megacolon patients. Conversely, some *T. cruzi*-infected subjects with severe obstipation and positive serology have no dilation, but need to be treated. Clearly, the physiopathology of megacolon deserves more investigation. The occurrence of megaviscera during the acute phase, or shortly after it, has been described, but it is infrequent. Acute phase Chagas disease is seldom diagnosed in endemic areas nowadays, as vector-borne transmission has been effectively controlled by insecticides in most endemic countries.

1.4 Other Causes of Megaviscera

Cases with megaviscera may have other etiologies, i.e., idiopathic megaesophagus, caustic megaesophagus, cancer, and others. Congenital megacolon (Hirschsprung disease) is seen mainly in children, and megacolon may also be acquired by traumatisms and alimentary habits, as in severe psychiatric disturbances. For all these reasons, epidemiological history should be thoroughly enquired, endoscopy should be performed, and serological tests should be asked for [9]. Idiopathic cases of megaviscera are seen also in endemic countries, in similar frequencies as in non-endemic regions, which are rare (1 in 100,000). Interestingly, association of chagasic megaesophagus with cancer has been recorded (up to 2%), but the association of chagasic megacolon has not, suggesting a protective effect of the parasite [12, 13].

1.5 Serological Diagnosis and Megaviscera

Search for anti-*T. cruzi* antibodies is mandatory for all cases of megaviscera. Diagnosis should be performed by at least two serological tests of different principles, as recommended by the World Health Organization [14]. Any of the conventional methods (indirect immunofluorescence, indirect hemagglutination, or ELISA) are suitable, and a second test may be performed with rapid tests or non-conventional methods (see Chap. 2.4). Antibody titers may be evaluated, and they are generally high. Parasitological tests are not appropriate, as parasitemia is usually low during the chronic phase of Chagas disease. The presence of megaviscera strongly suggests Chagas disease, not only in endemic regions but around the globe, due to large migratory movements implying a dispersion of infected Latin American natives residing in non-endemic countries. The predictive value of these syndromes is very high in endemic areas, in the order of 95%, as seen in Table 3 [15]. Obviously, these values are lower in non-endemic areas, and subjects with a positive association may have lived in endemic countries for some time in the past.

Table 3 Positive serology in megaesophagus and megacolon

	Serology				
	Positive		Negative		
Megaviscera	*n*	%	*n*	%	Total
Megaesophagus	2902	94.6	167	5.4	3069
Megacolon	1747	94.3	105	5.7	1852
Both megasyndromes	1013	98.6	14	1.4	1027
Total	5662		286		5948

Data from Núcleo de Estudos da doença de Chagas (NEDoC), Federal University of Goias, Goiania, Brazil

1.6 Some Features on Immune System and Enteric Nervous System in Chagasic Megaviscera

In 1916, the first indication of the existence of the digestive form of Chagas disease arose by the observation of patients with dysphagia who required the aid of water to complete food intake. Even the ingestion of fluids could be difficult, requiring them to be taken in small doses. This phenomenon, without pathogenic explanation at the time, was denominated "choking sickness" [16].

Megacolon is characterized as intestinal dilation associated with an inflammatory infiltrate. This infiltrate consists mainly of $CD3^+$ T lymphocytes, $CD20^+$ B lymphocytes, and also natural killer cells, macrophages, and mast cells [17, 18]. Pathogen-specific B and T lymphocytes take part in adaptive immunity. An effective T cell response requires adequate stimulation by other host cells (Fig. 1).

Constipation is a typical symptom of megacolon, and both the clinical and anatomical diagnoses are usually late, after dilatation appears. Macroscopically, lack of motor coordination, sphincter achalasia, and distension caused by the accumulation of fecal contents result in chagasic megacolon [19]. According to Tafuri [20], a progressive lesion in the plexus is likely to occur, which aggravates according to the development of the megacolon. Considering the stasis of fecal content, one of the main factors leading to megacolon, we may state that the accumulation of fecal content in the lumen provokes compression of the mucosa and consequent dilation of the organ. The changes resulting from compression cause the mucosa to undergo ischemia, favoring the diffusion of the inflammatory process through the nervous plexus and muscle layers. Muscle cells are also affected as a consequence of the

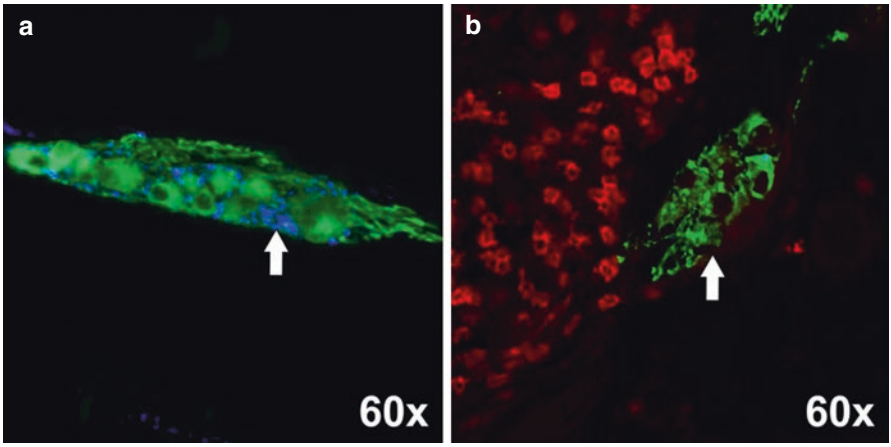

Fig. 1 Relation among neurons (green), serotonin (blue), and $CD8^+$ lymphocytes (red). (**a**) Noninfected individual presented serotonin near to neuronal ganglia associated with low concentrations of $CD8^+$ lymphocytes. (**b**) Chagasic patient with megacolon displaying high incidence of $CD8^+$ lymphocytes adjacent with neuronal ganglia combined with serotonin absence. Micrography courtesy of Dr. A.B. Morais da Silveira

greater contraction effort, due to the greater resistance of the medium, with the development of hypertrophy over time. Since the submucosal plexus is closely related to muscle cells, it is easy to understand how the inflammatory process can aggravate the process of neuronal destruction.

Studies from the last decades indicate that, in addition to inflammatory processes, the lesions in Chagas disease depend on the presence of *T. cruzi* DNA and the parasite itself, albeit in small numbers. A close correlation between the presence of parasite antigens and the intensity of the inflammatory infiltrate has been demonstrated [21]. It is now accepted that the inflammatory process is primarily responsible for the destruction of the enteric nervous system (ENS) components [17, 18].

1.7 Enteric Neurons, Neuropeptides, and Other Markers

The ENS organization is similar in humans and other mammals. The physiological control exerted by the enteric neurons on motility, secretion, and other digestive processes and the mechanism of action of drugs that affect neurotransmission are similar between different species [22]. It has approximately the same number of nerve cells than the spinal cord, around 200–600 million neurons, which demonstrates its great importance [23]. Such neurons can be identified by function, morphology, and neurochemical correlation. Functionally, they can be divided into excitatory motor neurons, inhibitory motor neurons, interneurons, and intrinsic primary afferent neurons. More than 30 potential neurotransmitters affecting neuronal, muscle, and epithelial cell activity are present in the ENS. Moreover, a single neuron may harness several neurotransmitters, in addition to other neuro-specific proteins. The combination of chemical attributes related to neural function and their locations in the nerve circuit provide a chemical code by which neurons may be identified. In general, more than one substance contributes to the transmission process [24]. The myenteric plexus is a network of small neuronal ganglia, which are interconnected by nerve bundles between the internal and external muscular layers of the gastrointestinal tract. This plexus forms a continuous network around the section and throughout the extension of the digestive system (Fig. 2). The lymph nodes found in this plexus vary in size and shape, depending on the portion of the intestine and the animal species under analysis [25].

Intrinsic primary afferent neurons (IPAN) are numerous, approximately 500 by square millimeter in length of the small intestine and are best identified by immunohistochemical staining of the intracellular protein calretinin. They are transducers of physiological stimuli, including mucosal villus movement, intestinal muscle contraction, and chemical changes in intestinal contents. IPANs are the first neurons in intrinsic reflexes that influence the patterns of gut secretion and motility. Therefore, they are directly sensitive to mechanical and chemical stimuli from the intestinal mucosa, and the sum of synaptic events caused by the transmission of IPAN results in the activation of numerous interneurons and motor neurons [26, 27].

Excitatory motor neurons innervate the longitudinal and circular smooth muscle and the muscular mucosa of all digestive tract. The primary transmitter of these

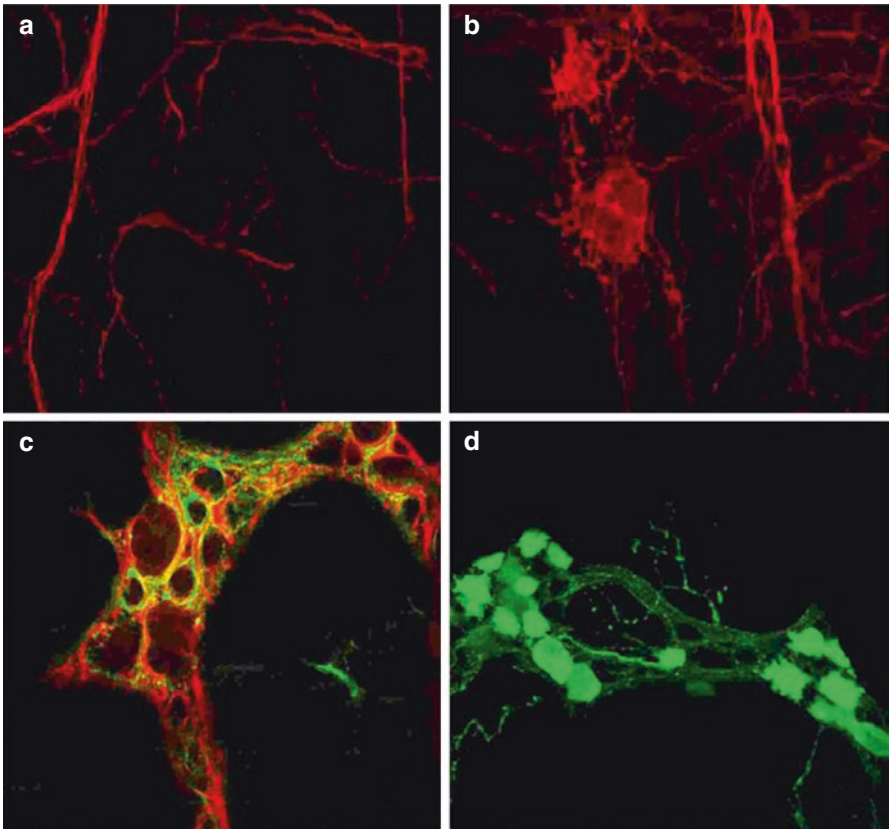

Fig. 2 Whole mount fluorescent immunohistochemistry of myenteric plexus in a colon sample from a Chagas disease patient. (**a**) Presence of nerve fibers emerging from the myenteric plexus toward the muscular layers; (**b**) interconnection between neuronal bodies in the myenteric plexus and its relationship with nerve fibers; (**c**) relationship between nerve fibers and neural bodies (red) and enteric glial cells (green); (**d**) nervous ganglion in the myenteric plexus where nerve fibers are observed in close relation with neurons. Micrography courtesy of Dr. A.B. Morais da Silveira

neurons is acetylcholine (ACh) which acts on muscle cells through muscarinic receptors. The major marker of excitatory motor neurons is the precursor enzyme of ACh, choline acetyltransferase (ChAT). Tachykinins, represented by substance P (SP), neurokinin A, neuropeptide K, and neuropeptide gamma (γ), contribute to excitatory transmission, but play a secondary role compared to ACh [22, 24].

In contrast, inhibitory motor neurons release a combination of transmitters that contribute to relaxation of the gastrointestinal tract. The primary neurotransmitter of these neurons is nitric oxide (NO), which receives a secondary contribution from other substances such as the vasoactive intestinal peptide (VIP) and adenosine triphosphate (ATP). It is possible that there is more than one primary transmitter for this neural subclass. However, the relative roles of these transmitters differ between

regions and species. The main marker of inhibitory motor neurons is the NO-producing enzyme nitric oxide synthase (NOS) [22, 24].

In addition to neurotransmitters, neuropeptides also have considerable activity on the immune system, influencing ENS activities through the secretion of various types of compounds. Substance P is a protein that, in addition to its function as neuromodulator, has a pro-inflammatory action on immune cells. It stimulates lymphocyte proliferation, lymphocyte trafficking through lymph nodes, and IL-2 production. In addition, substance P acts as a natural killer (NK) cell activator and has chemotactic action for mast cells, macrophages, and neutrophils [28].

VIP has anti-inflammatory effect, by inhibiting the response of NK cells and T lymphocytes, as well as the production of IL-2 and IL-4 by these cells and antigen presentation. On the other hand, it also stimulates macrophage chemotaxis and IL-5 production by lymphocytes [29]. The pro-inflammatory effects of NO are not evident under acute physiological conditions. Among its anti-inflammatory effects, we can mention the inhibition of neutrophil adhesion, cyclooxygenase activity, cytokine formation, and bone reabsorption [30].

Currently, denervation is accepted as one of the causes of development of chagasic megacolon [5, 26]. Neuronal destruction in acute Chagas disease is due to the great concentration of the parasite in the tissue, but in the chronic phase, specific segments, such as the stomach, small intestine, and colon [31], are also involved in this inflammatory process [32, 33]. The interrelationship between the nervous, endocrine, and immune systems is very important for the understanding of the intestinal compromise and may be definitive for the determination of clinical manifestations and for the development of inflammatory processes in the intestine [34]. The earliest descriptions relating changes in the myenteric plexus and Chagas disease date back to 1930. However, they still lacked anatomopathological evidence. This was provided by Koeberle, starting in 1953, by his quantitative studies on neurons of the esophagus.

Some studies have confirmed neuronal destruction in the myenteric plexus of chagasic patients and demonstrated a relation with the inflammatory process in portions of the gastrointestinal tract [18, 32, 33]. Later it was evidenced that this neuronal destruction could be selective, that is, some neuron types would be preferentially destroyed [26]. The question then arises as to what would be the regenerative process in the different neuron types of the ENS, whether a type is actually destroyed or its immunoreactive area is reduced because it did not present a satisfactory regenerative process.

The regeneration process was found to be greatly increased in VIP- and NOS-positive neurons. This indicates that the organism activates regeneration processes as an attempt to compensate for the loss of inhibitory neurons caused by the parasite.

These basic results are in agreement with the clinical observation of relaxation capacity loss in the muscular layers of the colon in Chagas disease patients who develop megacolon. This produces alterations in the motility of the colon, leading to fecal accumulation and, consequently, to organ dilation. Incoordination of the rectosigmoid segment, hyperactivity to cholinergic stimuli, and achalasia of the internal anal sphincter are the most common symptoms in chagasic megacolon [31].

1.8 Etiological Treatment

Etiological treatment (see Chap. 2.5) may be prescribed in chagasic patients with megaviscera, but in the case of severe megaesophagus, surgical treatment should be performed in advance, in order to allow the drug to be ingested and absorbed.

2 Megaesophagus

2.1 Epidemiology

Idiopathic megaesophagus is a rather unusual entity, with a prevalence of 1/100,000 in global population. In Latin America, the prevalence of megaesophagus is higher due to chagasic etiology. The pathogeny, physiopathology, symptoms, evolution, and treatment of this entity are similar to the idiopathic one, the main difference being the presence of antibodies against the parasite, as well as the association with cardiopathy and/or megacolon in some cases. The term "mega" may be misleading since the anectasic forms have no dilatation of the esophagus.

Geographical distribution of chagasic megaesophagus has been recognized and is limited to the south of the Amazon River, with a higher prevalence in Central Brazil. This has been linked to the *T. cruzi* DTU (TcII) preferentially isolated from humans in this large area [7]. In the Southern Cone, the prevalence of megacolon is higher.

Age range is wide, and, in our case studies' history, we have recorded patients from 2 years old to over 100 years old. It usually appears earlier than the other clinical forms, most often between 20 and 40 years of age. Our case studies comprise more than 3200 cases, beginning in 1975. In the last decades (1990–2010), the case distribution is shifting to older age, and patients usually consult after some years after symptoms have appeared [35] (Table 4). Gender has been found to correlate

Table 4 Distribution of 2925 cases of megaesophagus and relation with age (by the time of first consultation) and gender

	Female		Male		Total	
Age group (years)	*n*	%	*N*	%	*N*	%
<10	6	**66.7**	3	33.3	9	0.3
11–20	19	34.5	36	**65.5**	55	1.9
21–30	82	46.3	95	**53.7**	177	6.1
31–40	159	43.6	206	**56.4**	365	12.5
41–50	295	45.3	356	**54.7**	651	22.3
51–60	361	47.4	401	**52.6**	762	26.1
61–70	299	47.8	327	**52.2**	626	21.4
> 70	126	45.0	154	**55.0**	280	9.6
Total	1347	46.1	1578	53.9	2925	100.0

Data from Núcleo de Estudos da doença de Chagas (NEDoC), Federal University of Goias, Goiania, Brazil

The values in bold represents P<0.05

Table 5 Distribution by radiological groups of 2475 non-treated cases with megaesophagus and relation with gender

	Female		Male		Total	
Radiological group	*n*	%	*N*	%	*N*	%
I	391	60.4	256	39.6	647	26.1
II	414	46.6	477	**53.5**	891	36.0
III	216	36.9	370	**63.1**	586	23.7
IV	113	32.2	238	**67.8**	351	14.2
Total					2475	100.0

Non-treated means not submitted to dilatation by pneumatic balloon or to surgery previously that may change the classification of group. Data from Núcleo de Estudos da doença de Chagas (NEDoC), Federal University of Goias, Goiania, Brazil
The values in bold represents P<0.05

with the severity of the involvement, being the female more frequent among the less severe (anectasic) cases, similar frequencies for both sexes in group II, and male predominance in the decompensated severe groups (III and IV) (Table 5). Male predominance is observed in all age groups (Table 4).

2.2 Clinical Findings

Dysphagia is a common complaint among these patients; it is generally progressive and initially implies solid and cold food. As it worsens, patients begin to suffer regurgitation during meals and later regurgitation while laying down, in those cases with advanced megaesophagus. Patients also present heartburn, hiccups, cough, ptyalism, and constipation. Enlargement of salivary glands may be found in physical exam.

Barium swallow is the main complementary evaluation, as it allows to see the degree of dilation and evaluate the stomach. In advanced cases, it may be necessary to substitute the affected esophagus by a gastric tube.

Endoscopy is necessary in all cases before surgical treatment. When this is the first exam performed on the patient, an experienced endoscopist may suspect megaesophagus diagnosis in patients within groups with early phase pathology, as group I or II. Esophageal cancer and other esophageal diseases may be excluded by endoscopy.

Esophagus manometry is not a routine exam. It gains relevance in cases of symptomatic patients without dilation or in patients who have undergone surgery and report recurrent symptoms. The usual findings are lower esophageal sphincter achalasia and uncoordinated contractions of the esophageal body.

2.3 Classification: Groups I–IV

Rezende et al. [36] proposed a radiological classification of chagasic megaesophagus in four groups (Fig. 3):

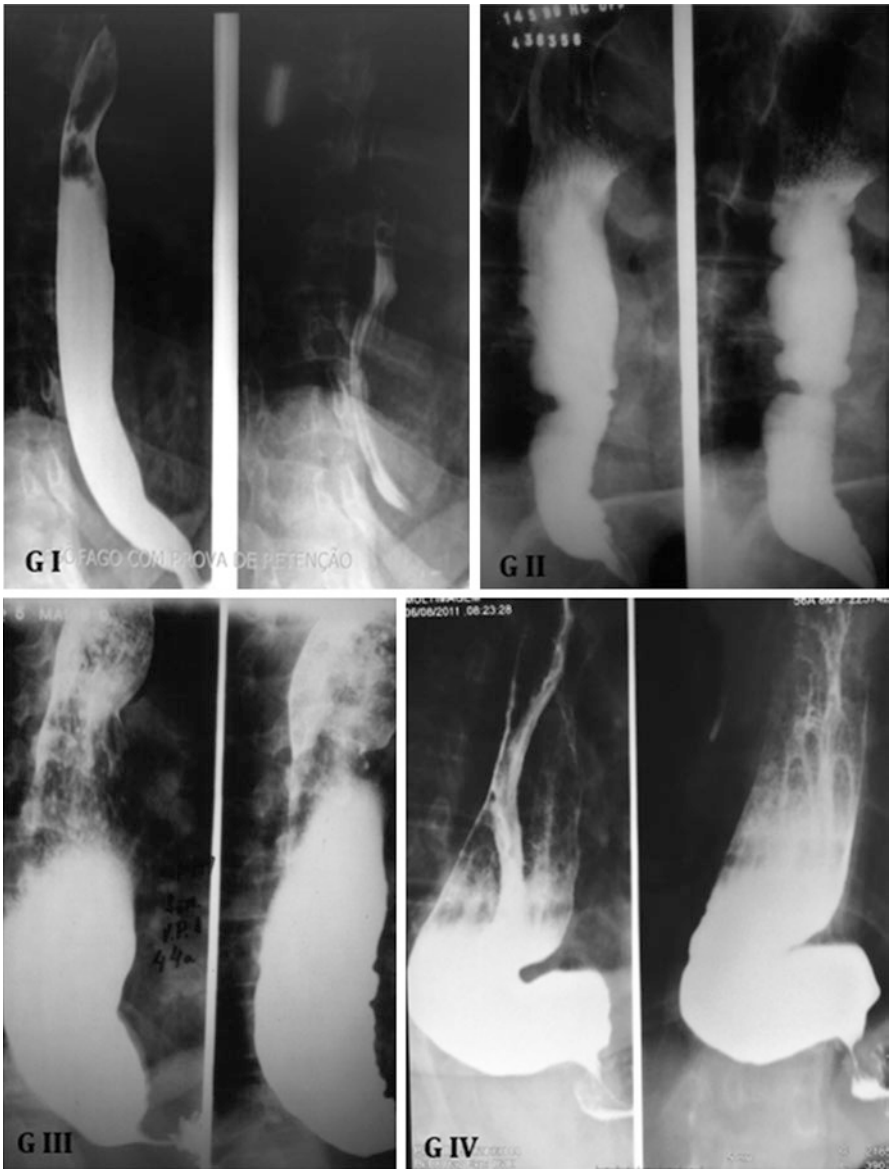

Fig. 3 Megesophagus classification [36]. X-ray images courtesy of Dr. Ê. Chaves de Oliveira

- Group I—anectasic and with barium transit delay in the esophagus. One minute after barium swallow, a barium column in the lower esophagus and an air column above are visible.
- Group II—small dilation and frequent tertiary uncoordinated contractions.
- Group III—major dilation, may present tertiary contractions.
- Group IV—most severe form, dolichomegaesophagus with dilation and sigmoid-like aspect in radiography.

2.4 Differential Diagnosis

The differential diagnosis should mainly consider esophagus neoplasia. Idiopathic megaesophagus and congenital megaesophagus are less frequent, but should also be taken into account.

2.5 Treatment

Most cases of initial megaesophagus (group I) do not require treatment. Patients with mild dysphagia may be treated with prokinetic drugs. Prokinetics such as cisapride, metoclopramide, and domperidone may be administered 15 min before meals for relief of dysphagia and regurgitation.

Surgical treatment is properly indicated in patients with megaesophagus groups II, III, and IV. We usually divide groups II and III as non-advanced and group IV as advanced.

Several different surgical techniques were developed to treat megaesophagus, but the main procedure performed in group II and III patients is cardiomyotomy with anti-reflux valve. The most practiced method in many centers in Brazil is the Heller-Pinotti operation. This surgical technique has low outcome complication rates, and most patients improve their symptoms [37]. Laparoscopic surgery may be carried out according to surgeon experience, with outcome as good as that of open surgery [38]. The laparoscopic approach has become the gold standard practice, and it is considered the procedure of choice for the treatment of achalasia [39].

Treatment of group IV patients is controversial. Some authors advocate the Serra-Doria operation owing to its low mortality and morbidity [40], while others suggest that the best approach is esophagectomy, whereby the sick esophagus must be removed and replaced by the stomach or colon [41, 42]. Esophagectomy has a higher morbidity, even in experienced hands. Robotic surgery has been introduced to treat chagasic megaesophagus [43] presenting the same advantages of this technology for other diseases [44].

Balloon dilation was commonly used some decades ago to treat megaesophagus groups I and II patients. Nonetheless, follow-up studies revealed that the relief of symptoms was temporary, and most of them needed additional surgical treatment. Besides, the dilated cardia evolved with fibrosis after two or more sessions of dilation making surgery more difficult. Therefore, dilation was deprecated as first-line treatment for megaesophagus, and currently it is reserved only to patients with severe comorbidities, such as chronic obstructive pulmonary disease, cardiopathy, or pregnancy.

Botulinum toxin has been used as treatment of non-severe megaesophagus, with good transitory results [45].

Recently, a new endoscopic technique was reported for the treatment of achalasia: per oral endoscopic myotomy (POEM) [46]. It is a minimally invasive endoscopic therapy that has not been used yet to treat chagasic megaesophagus.

3 Megacolon

Colon involvement in Chagas disease may be as frequent as megaesophagus, but diagnostic approaches make it less reported in statistic records. Megacolon is the dilatation of the colon caliber over 6.3 cm, as measured by barium enema radiographic exam [47].

3.1 Epidemiology

Chagasic megacolon is more frequent after the fifth decade of age, with slight predominance in the female (Table 6). It is frequent in Central Brazil and rare in Northern Brazil. A similar clinical entity has been recognized, Andean megacolon, described as elongated colon (dolichocolon), with similar radiological aspect to chagasic megacolon. However, Andean megacolon patients have negative serology for Chagas disease. These patients usually live in high altitudes in the Andes [48].

3.2 Pathophysiology

The pathophysiology of colon dilation is similar to that of megaesophagus, as ENS neuron destruction is required (Fig. 4).

After infection, *T. cruzi* shows a tropism to ENS neurons and destroys them. Myenteric and submucous plexuses' damage occurs with different intensities. Some patients display broader neuron destruction in one plexus than the other, and this seems to influence the clinical symptoms. Destruction of myenteric neurons leads to colon enlargement, while destruction of submucous neuron cells is responsible for dysmotility, and, consequently, the patient suffers from chronic constipation [49].

Table 6 Distribution of 1748 cases of chagasic megacolon and relation with age and gender

	Female		Male		Total	
Age group (years old)	*N*	%	*N*	%	*n*	%
<10	1		0	0.0	1	0.1
11–20	5	29.4	12	70.6	17	1.0
21–30	42	**56.8**	32	43.2	74	4.2
31–40	112	**57.7**	82	42.3	194	11.1
41–50	190	**54.0**	162	46.0	352	20.1
51–60	259	**52.4**	235	47.6	494	28.3
61–70	193	48.6	204	51.4	397	22.7
> 70	108	49.3	111	50.7	219	12.5
Total	910	52.1	838	47.9	1748	100.0

All patients were diagnosed by barium enema and had at least four positive serological tests. Data from Núcleo de Estudos da doença de Chagas (NEDoC), Federal University of Goias, Goiania, Brazil

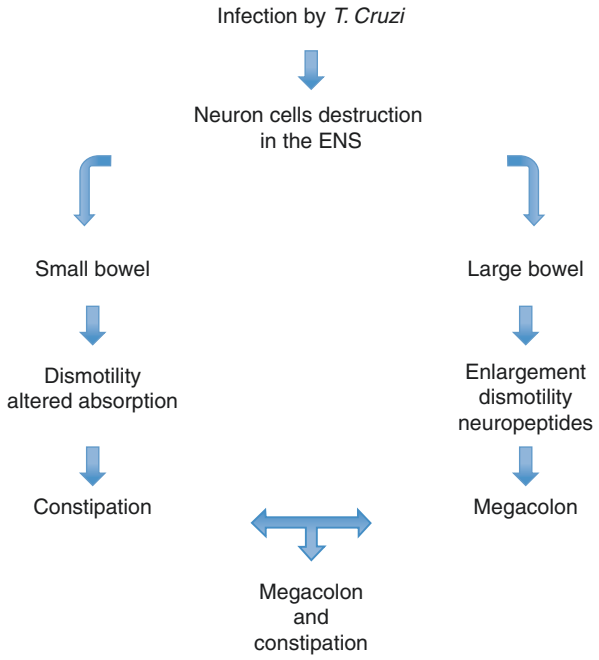

Fig. 4 Pathophysiology of chagasic megacolon. *ENS* enteric nervous system

Besides ENS damage in the colon, the small intestine ENS seems to be damaged in acquired megacolon and may also play a role in clinical symptoms [50].

The reason behind the dilation occurring only in the sigmoid portion of the colon is not clear. It is thought to be related to the proximity of the anal sphincters. Internal anal sphincter achalasia has been reported by some authors. Nevertheless, these findings were not consistent with studies by our group and others [51, 52]. Besides there are many patients with megacolon without constipation, showing that constipation and dilation are different factors that interact only sometimes [49, 53]. The rectum may be dilated or not. The role of dilated rectum in constipation is not clear but seems to be a non-relevant factor [54].

3.3 Clinical Findings

The main complaint from patients with megacolon is constipation, which is usually long-lasting and severe. Patients frequently report constipation ranging from 10 to 60 days, spanning several years. Abdominal cramps, abdominal distention, flatulence, scybalous-type feces, and straining are frequent as well.

On physical examination, patients with megacolon usually present slight abdominal distention, sometimes tenderness on palpation. After a long period without evacuation, the fecal mass may be felt as a moldable mass when the abdominal wall is pressed which, upon release of this pressure, produces a sensation similar to the

detachment of a nurse tape from the skin, owing to the colon wall displacement from the fecal mass (i.e., Gersuny sign).

Rectum digital examination is mandatory for all patients with obstipation, mainly for differential diagnosis with other diseases. Diagnosis is based in epidemiology, clinical findings, and complementary exams (barium enema and serology for Chagas disease, Fig. 5). Differential diagnosis should discard any other cause of slow transit and constipation, as neoplasias or diverticular disease, for example.

3.4 Complications

Megacolon has three main complications:

- Volvulus—the torsion of the colon over its own axis, usually occurring just above the rectum-sigmoid transition (Fig. 6).
- Fecaloma or fecal impaction—after 10 or more days without evacuation, patients may present fecal impaction. The mass of solid and hard feces may accumulate in the sigmoid colon and may be felt by digital examination (lower fecaloma), but sometimes it cannot be thereby reached (high fecaloma). Most times, the feces are removed by slow instillation with saline solution into the rectum (Fig. 7).
- Colonic perforation—hard feces may erode the colonic wall and perforate it. Also, ischemic points due to prolonged volvulus may evolve toward necrosis and puncture (Fig. 7).

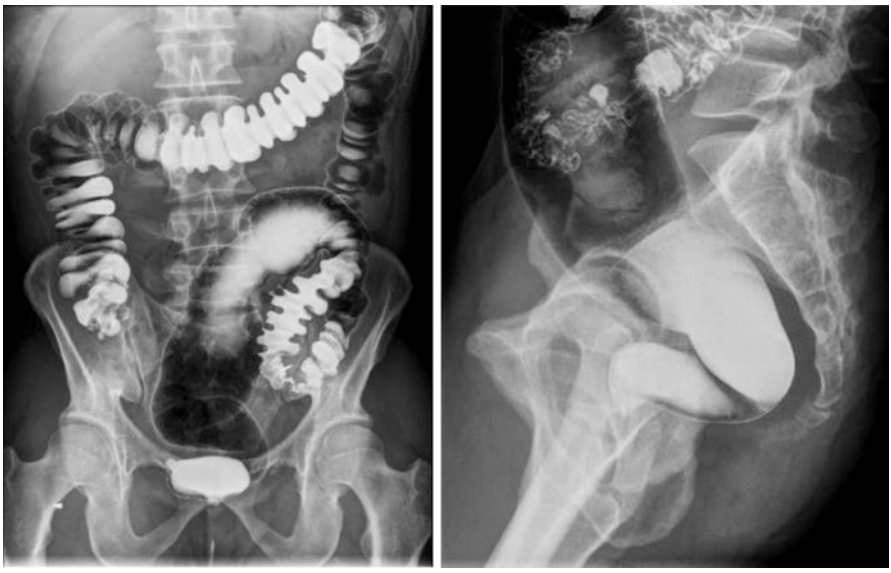

Fig. 5 Barium enema showing a dilation of the sigmoid colon and rectum. X-ray images courtesy of Dr. Ê. Chaves de Oliveira

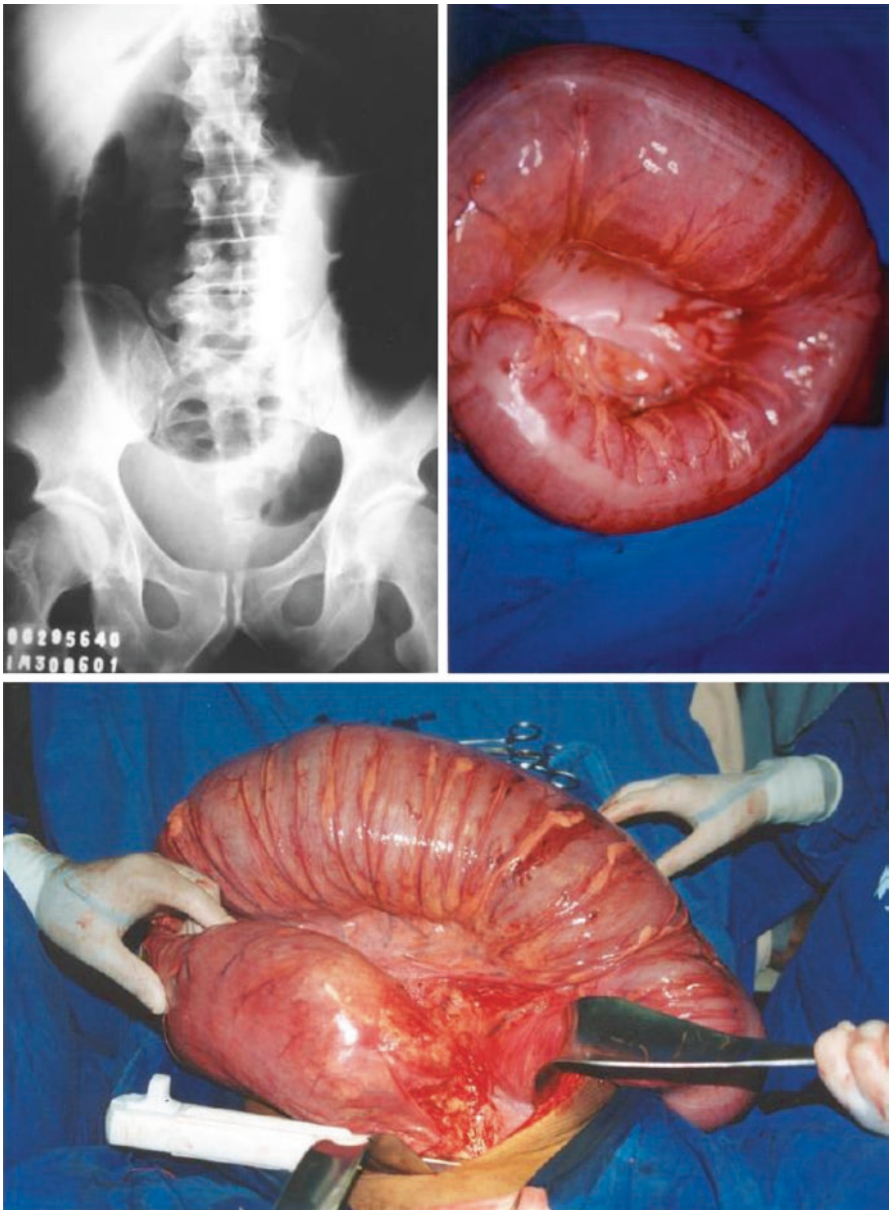

Fig. 6 Sigmoid volvulus: abdominal plain X-ray and surgical treatment. Pictures courtesy of Dr. Ê. Chaves de Oliveira

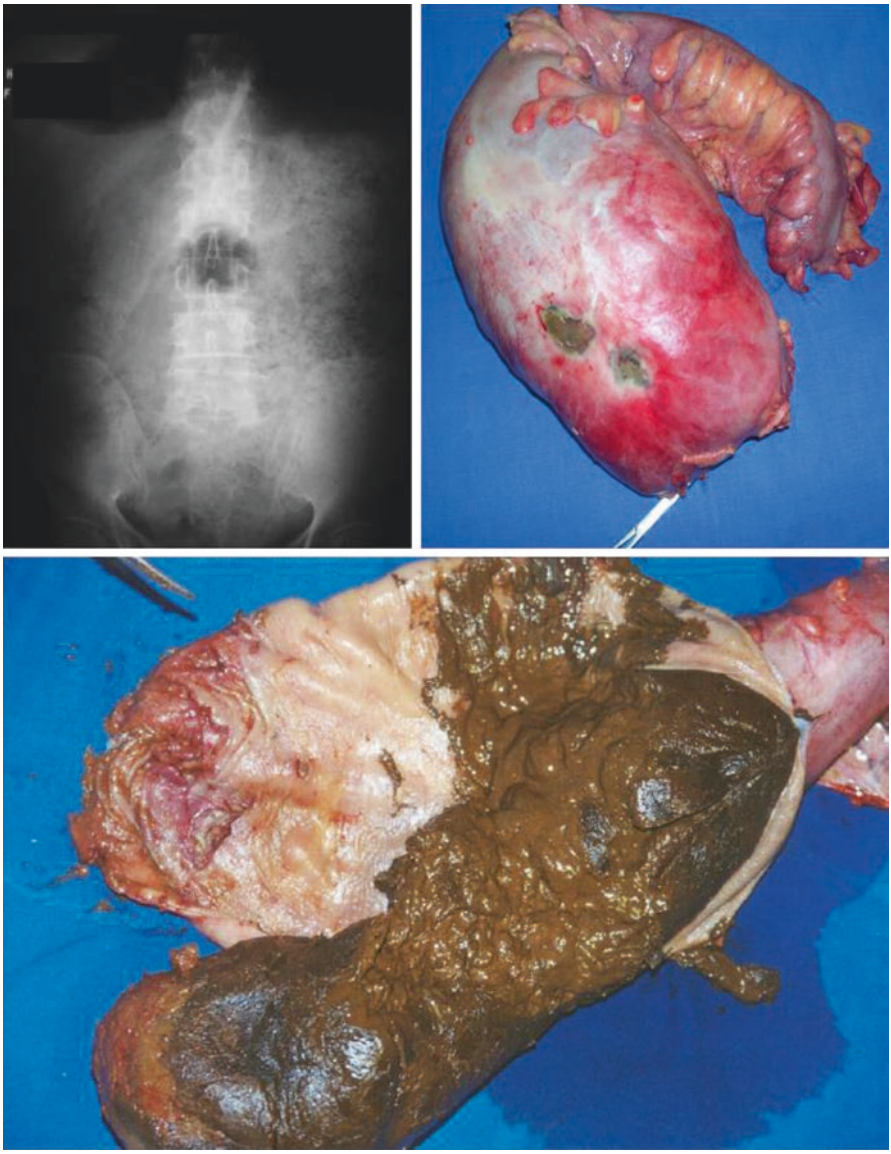

Fig. 7 Plain abdominal X-ray showing large fecaloma; colon perforation due to fecaloma; partial colectomy and fecaloma. Picture courtesy of Dr. Ê. Chaves de Oliveira

3.5 Treatment

Patients with megacolon without constipation (nearly one in three) do not need medication. Advice about possible complications of dilated bowel, such as unexpected fecal impaction or volvulus, should be given. Preventive surgery may be indicated according to age, comorbidities, or labor characteristics.

Constipated patients with megacolon should undergo left colectomy, with removal of the dilated colonic portion. Historically, many surgical techniques have been applied to these cases, but two have been employed the most:

- Duhamel operation—due to similarities between acquired and idiopathic megacolon, authors used the same technique described by Duhamel [55, 56]. This technique was modified by Haddad [57] and has been carried out on megacolon patients with satisfactory results [58].
- Low anterior resection is primarily indicated for patients without megarectum. It has been made simpler by the introduction of mechanical suture. This technique may be performed by laparotomy and laparoscopy.

The choice of technique should consider the presence of megarectum. Patients with megarectum are easier to operate by the Duhamel procedure, because there is a great difference in the calibers of the rectum and the normal proximal colon. Duhamel operation is a construction of a side-to-side anastomosis, so the caliber is not an obstacle [59].

Early outcomes are similar for both methods, although fecal incontinence is more frequent in the Duhamel procedure. Functionally, both techniques are equivalent [60].

4 Other Digestive Involvements

Despite a much lower incidence than megaesophagus and megacolon, other viscera may be enlarged in Chagas disease, nearly always associated with the former.

Megagastria may be present in up to 20% of patients with megaesophagus and is due to intrinsic denervation of the stomach. In cases of gastric emptying difficulty, pyloric muscle hypertrophy may be seen [15].

Duodenum is frequently dilated at the bulb, with eventual compromise of the whole arcade. Jejunum or ileum are rarely involved. An abnormal increase in the absorption of glucose has been described. Gallbladder and the Oddi sphincter are seldom involved as well. Parotid hypertrophy is seen in some patients with megaesophagus.

5 Conclusion

Megaesophagus and megacolon are the main digestive manifestations in individuals infected with *T. cruzi*. Other organs may be affected, but generally associated with the former. In regions endemic for Chagas disease, or in patients who used to live there, chagasic etiology should be investigated by serology. Of note, it is confirmed in more than 95% of the cases. Less than 20% of the infected people will develop megaviscera syndromes, with a marked geographical distribution, probably related to the parasite subspecific variants circulating in humans (DTU TcII or TcV). Contrasted radiological diagnosis is necessary, and the degree of involvement may

be important for the decision of an appropriate treatment. Surgery is advised in patients with advanced compromise. Fecaloma and volvulus are frequent in subjects with megacolon. The association of megaviscera with cardiac compromise is seen in around 30% of the cases and needs to be investigated, among other reasons, to account for surgical risk. Surgical advances in the last decades have significantly improved success and prognosis of these approaches.

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