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Original Article

Clinical and manometric investigation in constipated Chagasic patients with and without megacolon

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ABSTRACT

Background: Chagasic colopathy is the second most common digestive manifestation, and constipation is the main symptom. The absence of the Rectoanal Inhibitory Reflex plays an important role in constipation and anal manometry is crucial for appropriate evaluation.
Purpose: Evaluate anal manometry findings (mainly Rectoanal Inhibitory Reflex) in Chagasic patients with chronic constipation, with and without megacolon and correlate these findings with clinical and demographic data.
Methods: Cross-sectional study of patients with chronic constipation who underwent Chagasic serologic test, barium enema, and anal manometry. The absence of Rectoanal Inhibitory Reflex was evaluated using the mid-P Exact Test.
Results: 64 Patients were included: 23 Chagasic patients with megacolon/megarectum (G1), 21 Chagasic patients without megacolon/megarectum (G2) and 20 non-Chagasic patients without megacolon/megarectum (G3). Chagasic patients with megacolon had a higher incidence of fecaloma (39%) compared to the other two groups (9.5% and 10% for G2 and G3, respectively, $p = 0.03$). Rectal capacity on manometry was statically higher for G1 patients. Rectoanal Inhibitory Reflex was absent in 91.3% of patients in G1, 47.29% in G2 and present in all patients in G3. There was a significant difference in the absence of the Rectoanal Inhibitory Reflex when comparing the groups (G1 vs. G2: $p = 0.002$, G1 vs. G3: $p < 0.001$, G2 vs. G3: $p < 0.001$).

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Conclusion: The absence of RAIR confirms the diagnosis of Chagasic colopathy and endorses surgical treatment whenever clinical treatment fails. The presence of the RAIR in patients with positive serology for Chagas disease without megacolon/megarectum might not be due chagasic colopathy and other causes should be considered.

Investigação clínica e manométrica de pacientes chagásicos constipados com e sem megacolon

Palavras-chave:
Doença de Chagas
Diagnóstico
Constipação intestinal
Reflexo
Canal anal
Ausência
Megacolon

RESUMO

Fundamento: A colopatia chagásica é a segunda manifestação digestiva mais comum e a constipação é o principal sintoma. A ausência do Reflexo Inibitório Retoanal desempenha um papel importante na constipação e a manometria anal é crucial para avaliação adequada.
Objetivo: Avaliar os achados da manometria anal (principalmente o Reflexo Inibitório Retoanal) em pacientes chagásicos com constipação crônica, com e sem megacólon, e correlacionar esses achados com dados clínicos e demográficos.
Métodos: Estudo transversal de pacientes com constipação crônica submetidos ao teste sorológico para doença de chagas, enema de bário e manometria anal. A ausência de Reflexo Inibitório Retoanal foi avaliada por meio do Teste Exato de Ponto Médio.
Resultados: Foram incluídos 64 pacientes: 23 chagásicos com megacólon/megarreto (G1), 21 chagásicos sem megacólon/megarreto (G2) e 20 não chagásicos sem megacólon/megarreto (G3). Os pacientes chagásicos com megacólon apresentaram maior incidência de fecaloma (39%) em comparação aos outros dois grupos (9,5% e 10% para G2 e G3, respectivamente, $p = 0,03$). A capacidade retal na manometria foi estatisticamente maior nos pacientes do G1. O Reflexo Inibitório Retoanal estava ausente em 91,3% dos pacientes do G1, em 47,29% no G2 e presente em todos os pacientes do G3. Houve diferença significativa na ausência do Reflexo Inibitório Retoanal quando comparados os grupos (G1 vs. G2: $p = 0,002$, G1 vs. G3: $p < 0,001$, G2 vs. G3: $p < 0,001$).
Conclusão: A ausência de RIRA confirma o diagnóstico de colopatia chagásica e endossa o tratamento cirúrgico sempre que o tratamento clínico falhar. A presença de RIRA em pacientes com sorologia positiva para doença de Chagas, sem megacólon/megarreto, pode não ser devida à colopatia chagásica e outras causas devem ser consideradas.

Introduction

Chagas' disease is an infection caused by the protozoan *Trypanosoma Cruzi* discovered by Carlos Chagas in 1909.[1] The disease is transmitted by a Triatominae, however, other modes of transmission are reported, including blood transfusion,[2,3] organ donation, congenital infection, oral infection by contaminated food and laboratory accidents.[4,5]

Cases of American trypanosomiasis or Chagas' disease have been diagnosed in non-endemic countries due to the large number of Latin American emigrants. Japan, Australia, EUA, Spain and Canada have received a substantial number of Hispanic Americans. Spain for example, received around 287.760 argentines and 238.605 Bolivians of which approximately 19.000 were contaminated.[6] Worldwide, it is estimated that there are about 10 million infected people[7] and 75 to 90 million are at risk of becoming infected.[8]

Thirty to 60% of infected patients will develop some clinical manifestation of the disease including the cardiac form, digestive form (Chagasic Esophagopathy, or Chagasic Colopathy) and mixed form (cardiodigestive).[9–11] Chagasic colopathy is considered the second most common digestive manifestation of Chagas' disease[12] resulting in chronic constipation, a common symptom in the general population, making its diagnosis challenging. Patients with chronic constipation may develop in distinct functional, anatomical, biochemical and infectious scenarios, and may be classified in groups of individuals with normal bowel transit time, slow-transit time and patients with an outlet obstruction, as occurs in Chagas' disease colopathy.[13] Sometimes, constipation is a consequence of multiple causes whereas slow transit time and an outlet obstruction is presented.

Constipated patients with positive serology for Chagas' disease may not suffer from Chagasic colopathy and their

symptoms might be due to other causes, commonly seen in the general population.[14] Anal manometry, allows the assessment of anorectal disorders, including the Recto-Anal Inhibitory Reflex (RAIR), which has been reported to be negative in patients with Chagasic colopathy. Therefore anal manometry may be crucial for a definitive diagnosis and indicate a medical or a surgical treatment.[15] This study aimed to evaluate the incidence of the RAIR in Chagasic patients with constipation, with and without megacolon and in non-Chagasic constipated patients.

Patients and methods

Type and location of study

Cross-sectional study, comparing the absence of RAIR among groups of patients who presents chronic constipation with and without Chagas' disease, and with and without megacolon. The study was conducted in a tertiary hospital of education in the mid-west of Brazil, an endemic area for Chagas Disease.

Ethical aspects

The study was conducted in accordance with the Helsinki Declaration and local regulations. The project was approved by the Research Ethics Committee (Clinical Hospital, Federal University of Goiás). All participants of this study were informed about the purpose of the tests that were performed and signed a Free and Informed Consent Form.

Patients and eligibility

Patients with chronic constipation, who underwent at the Coloproctology Unit, were selected prospectively between January 2009 and October 2011, using consensual random selection. The symptoms of chronic constipation were diagnosed according to criteria of Roma III. The Organogram illustrates the recruitment of patients for the study (Fig. 1).

Anal manometry was performed using a Dynamed® Dynapack model MPX 816 (São Paulo, SP, Brazil), with an eight radial channels silicone catheter, and a constant rate of 0.3 mL/min of distilled water was perfused. The water pressure required to overcome the resistance offered by the wall of the anal canal was continuously recorded by a polygraph, which converted mechanical pressure into electrical signals. Dynamed® ProctoMaster 5.1 software recorded graphs of mmHg in each of the anal canal quadrants. We defined rectal threshold and capacity before eliciting RAIR, using up to 150% of the volume needed to trigger the initial sensation of rectal filling, considering that, in normal individuals, intra-rectal balloon insufflation up to 2/3 the volume of the rectal threshold is enough to elicit the RAIR.[16,17] Therefore, the volume used to elicit the RAIR was individually defined for each patient.

Rectal enema performed 2 h before the test. Rectal examination was avoided immediately before the test. The technique used was stationary manual traction. Patients were informed about the objectives and details of the procedure (sphincter resting, squeezing and pushing).

Normal values of anal manometry were considered: resting pressure from 40 to 70 mmHg, squeeze pressure from 100 to 180 mmHg; length of the high-pressure zone of 2 to 3 cm for women and 2.5 to 3.5 cm for men, presence of recto-anal inhibitory reflex; sensory threshold of 10 to 30 mL and rectal capacity from 100 to 350 mL.

Demographic and clinical data, bowel habits, water and fiber intake on current diet, complications related to constipation, use of laxatives and previous surgery was prospectively collected and compared between the three group of constipated patients.

Statistical analysis

For each group of patients descriptive data analysis was performed. Statistical comparisons were obtained among groups of patients using Chi-squared and Kruskal–Wallis tests; calculation and comparison of the absence of the recto-anal inhibitory reflex was obtained using the mid-P Exact Test, with respective Confidence Intervals of 95%. For all the analysis we considered the value of $p < 0.05$ as statistically significant.

Results

The study included 64 patients with chronic constipation, divided into three groups: 23 with positive serology for Chagas' disease with megacolon and/or megarectum (G1), 21 with positive serology for Chagas' disease without megacolon and/or megarectum (G2) and 20 with negative serology for Chagas disease without megacolon and/or megarectum, considered the control group (G3).

The average age was 53.5, 49.0 and 47.7 years in groups G1, G2 and G3, respectively. There was a female predominance in all groups of patients. However, G1 presented 69.6% of women, whereas G2 and G3 had 95.2% and 95.0%, respectively ($p = 0.019$). The average time of constipation onset was 13.6 years in G1, 14.3 years in G2 and 18.4 years in G3, without significant difference ($p = 0.428$). Bowel frequency was, on average, 9.3 days in G1, 8.0 days in G2 and 11.9 days in G3, without significant difference ($p = 0.128$) (Table 1).

In G1, abdominal distention was reported in 60.9%; G2 reported 61.9% and G3 55.0%, without significant difference ($p = 0.889$). Patients with abdominal pain were reported in 47.8%, 61.9% and 75.0%, in G1, G2 and G3, respectively, with no statistical difference ($p = 0.189$). Sensation of incomplete evacuation were present, in 56.5% of G1 patients, while G2 and G3 incidence were 57.1% and 50.0%, respectively, without any significant difference ($p = 0.878$). The incidence of previous report of fecaloma was significantly different between the three groups. Group 1 presented 39% of fecaloma development event, versus 9.5% for G2 ($p = 0.036$) and 10% for G3 ($p = 0.03$). However, it did not reach statistical difference between G2 and G3 ($p = 1$). Although sigmoid volvulus was more frequent in G1 (8.5% vs. 0% and 5% for G2 and G3, respectively), the difference was not statistically significant ($p = 0.489$ and 1). Past history of pelvic surgery was more commonly described in G2 (71.4% vs. 39.1% and 65%, respectively). Comparison between G1 and G2 was statistically significant ($p = 0.032$). Perineal surgery was more common in G3 group (60%), with

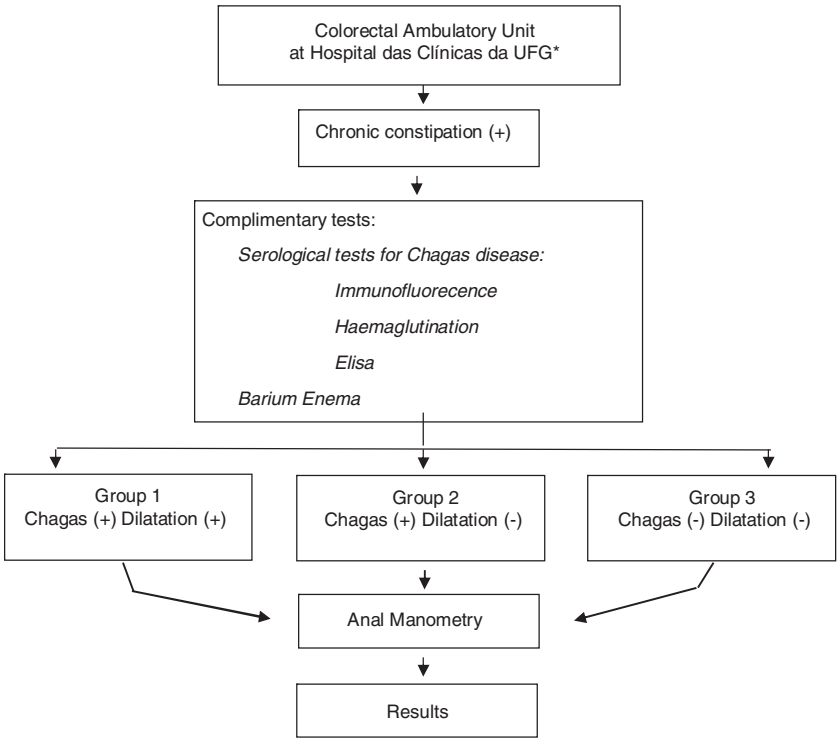

Fig. 1 – Organogram. Patient recruitment for the study. Colorectal Ambulatory Unit at Hospital das Clínicas da UFG.*

Table 1 – Demographic and severity of constipation reported by all three groups of patients.

	Group 1	Group 2	Group 3	*p*-value		
				G1 vs.G2	G1 vs G3	G2 vs G3
Age (Y.O.)[a]						
Mean	53.52	49	47.7	0.219	0.133	0.73
Standard deviation	12.44	11.51	12.4			
Time of constipation (years)[b]						
Median	10	14	15			
Minimum	1	1	2	0.786	0.367	0.388
Maximum	50	30	60			
Bowel frequency (days)[b]						
Median	10	7	15			
Minimum	1	1	4	0.364	0.113	0.037
Maximum	20	20	30			

[a] Test: ANOVA.
[b] Test: *U* Mann Whitney.
Group 1, Chagasic patient with megacolon; Group 2, Chagasic patient without megacolon; Group 3, non-Chagasic patient without megacolon.

statistical significance between Group 1 (17.4%, $p = 0.005$) and Group 2 (23.8%, $p = 0.019$). Associated comorbidities, including hypothyroidism, diabetes and high blood pressure were significantly more common in Group 3 (80% vs. 47.8% when compared to Group 1, $p = 0.056$). However, despite of a higher incidence of comorbidities in G3 when compared to G2 (80 vs. 52.4%), it did not reach statistical difference – $p = 0.1$ (Table 2). The percentage of patients with adequate fiber and water intake was statistically significant in G1 patients when compared to the G3 group (39.1% vs. 5%, $p = 0.011$).

Resting and squeeze anal pressure were similar between the three groups, without any statistical difference. However, median rectal capacity was higher in G1 (320 mL) with statistical difference between the other two groups (G2 = 150 mL, $p = 0.001$ and G3 = 145 mL, $p < 0.001$ (Table 3).

The incidence of anal achalasia in Group 1 was significantly higher when compared to the other two groups: G2 ($p = 0.002$) and G3 ($p < 0.001$). The proportion of anal achalasia in Group 2 was significantly higher when compared to Group 3 ($p < 0.001$) (Fig. 2).

Table 2 – Comparison of demographic and clinical features reported by the patients of the three groups of study.

	Group 1	Group 2	Group 3	*p*-value		
				G1 vs. G2	G1 vs. G3	G2 vs. G3
Gender[a]						
Male	7 (30.4%)	1 (4.8%)	1 (5%)			
Female	16 (69.6%)	20 (95.2%)	19 (95%)	0.048	0.05	1
Laxatives						
Yes	19 (82.6%)	15 (71.4%)	15 (75%)	0.481	0.711	0.796
No	4 (17.4%)	6 (28.6%)	5 (25%)			
Abdominal distention						
Yes	14 (60.9%)	13 (61.9%)	11 (55%)	0.944	0.697	0.654
No	9 (39.1%)	8 (38.1%)	9 (45%)			
Abdominal pain						
Yes	11 (47.8%)	13 (61.9%)	15 (75%)	0.349	0.069	.368
No	12 (52.2%)	8 (38.1%)	5 (25%)			
Incomplete evacuation						
Yes	13 (56.5%)	12 (57.1%)	10 (50%)	0.967	0.669	0.647
No	10 (43.5%)	9 (42.9%)	10 (50%)			
Fecaloma						
Yes	9 (39.1%)	2 (9.5%)	2 (10%)			
No	14 (60.9%)	19 (90.5%)	18 (90%)	0.036	0.03	1
Volvolus						
Yes[a]	2 (8.7%)	0 (0%)	1 (5%)			
No	21 (91.3%)	21 (100%)	19 (95%)	0.489	1	0.488
Pelvic surgery						
Yes	9 (39.1%)	15 (71.4%)	13 (65%)	0.032	0.091	0.658
No	14 (60.9%)	6 (28.6%)	7 (35%)			
Perineal surgery						
Yes	4 (17.4%)	5 (23.8%)	12 (60%)	0.716	0.005	0.019
No	19 (82.6%)	16 (76.2%)	8 (35%)			
Comorbidity						
Yes	11 (47.8%)	11 (52.4%)	16 (80%)	0.763	0.056	0.1
No	12 (52.2%)	10 (47.6%)	4 (20%)			
Fiber intake						
Yes	9 (39.1%)	5 (23.8%)	1 (5%)			
No	14 (60.9%)	16 (76.2%)	19 (95%)	0.276	0.011	0.184
Water intake						
Yes	8 (34.8%)	3 (23.8%)	1 (5%)			
No	15 (65.2%)	17 (76.2%)	19 (95%)	0.175	0.024	0.605

[a] Test: Exact Fisher, $p < 0.05$.
Group 1, Chagasic patient with megacolon; Group 2, Chagasic patient without megacolon; Group 3, Non-Chagasic patient without megacolon.

Discussion

In this study, the majority of Chagasic patients were females, in disagreement with the literature, where males are more commonly predominant.[18] This result was expected because the patients involved in this study were from the Ambulatory of functional anorectal disorders of the colorectal unit, where most of the patients enrolled are women. According to epidemiological studies, about 80% of patients who complain constipation are female.[19–22] Constipation used to be considered as a reduced bowel frequency. However, it is more complex and subjective, and may be reported as a difficulty in evacuation, sensation of incomplete evacuation, abdominal distention, discomfort and pain.[19] The comparison among the three groups in Table 2, showed no significant difference in abdominal distention, abdominal pain and sensation of incomplete evacuation. Patients with negative serology for Chagas disease present more severe symptoms of constipation when compared to the other two groups of patients with positive serology for Chagas disease. Although this was not statistically significant, it was different from what we would expect. This numbers demonstrate homogeneity among the analyzed groups regarding to the severity of constipation. It also shows how impossible it is to distinguish, using only clinical criteria, which patient is constipated due to Chagasic

Table 3 – Anorectal manometry findings in the three studied groups, including anal resting and squeeze pressures, rectal capacity, length of high pressure zone and the Recto-Anal Inhibitory Reflex (RAIR).

	Group 1	Group 2	Group 3	*p*-value		
				G1 vs. G2	G1 vs. G3	G2 vs. G3
RP (mmHg)[a]						
Meadian	65	64	64	0.411	0.301	0.557
Minimum	28	38	27			
Maximum	141	87	138			
SP (mmHg)[a]						
Meadian	134	125	118			
Minimum	79	58	53	0.518	0.374	0.715
Maximum	251	207	244			
Rectal capacity (mL)[a]						
Meadian	320	150	145			
Minimum	85	105	80	**0.001**	**<0.001**	0.229
Maximum	600	270	300			
Length of HPZ (cm)[a]						
Meadian	2	2	3			
Minimum	1	2	1	0.371	0.389	0.808
Maximum	4	4	4			
RAIR[b]						
Positive	8.70%	52.40%	100%	**0.002**	**<0.001**	**<0.001**
Negative	91.30%	47.60%	0			

RP, resting pressure; SP, squeeze pressure; HPZ, high pressure zone.
[a] Test 1: *U* Mann Whitney.
[b] Test 2: Exact fisher.
Group 1, Chagasic patient with megacolon; Group 2, Chagasic patient without megacolon; Group 3, non-Chagasic patient without megacolon.

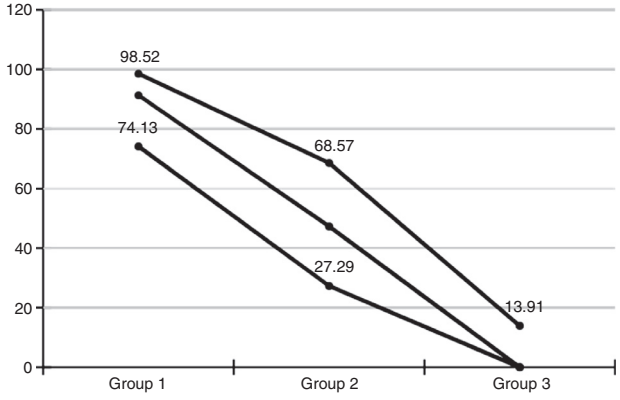

Fig. 2 – Proportions of anal achalasia and respective confidence intervals elicited by anal manometry in chronic constipated patients with Chagas disease and megacolon (Group 1), Chagasic patients without megacolon (Group 2) and non-Chagasic patients without megacolon (Group 3)

colopathy or to other functional disorders, without performing additional diagnostic tests.

Fecaloma was more commonly seen in G1 patients, which corroborates to anal manometry and barium enema findings (higher rectal capacity on anal manometry and megarectum on barium enema determines that there is a higher chance of developing fecaloma as the rectal stool content may dehydrate before the desire of evacuation occurs).

It is interesting to notice that Chagasic patients with megacolon/megarectum were more likely to adhere clinical treatment of constipation as the percentage of patients with adequate fiber and water intake was statistically significant when compared to the G3, the control group (39.1% vs. 5%, $p = 0.011$). Although it was more commonly seen in G1, the comparison to G2 patients (23.8%) did not show statistical difference – $p = 0.276$. These results demonstrate that causes of constipation other than Chagasic colopathy may play a role in the development of constipation, more specifically in G2 patients, whereas over 75% of individuals have inadequate fiber and water intake.

Abnormalities of Recto-Anal Reflex (RAIR) have been associated with anorectal disorders, including constipation and anal incontinence.[23,24] In addition, the RAIR may be abnormal in Chagas' disease,[25,26] due to lack of relaxation of the internal anal sphincter.[27] Some studies have used anorectal manometry in patients with Chagasic megacolon, to assess the anal pressure and rectal sensitivity and correlate the findings with abnormal anorectal reflex.[28]

Our study demonstrated that the absence of RAIR was significantly different between the three groups (Fig. 2). It was absent in 91.3% of patients with Chagas' disease with megacolon or megarectum; in 47.6% of Chagasic patients without megacolon; and present in all patients in G3 (without Chagas' disease)[26] evaluated 29 Chagasic patients with megacolon and reported absence of RAIR in 79% of the sample[29] in a group of 39 Chagasic patients with megacolon. They considered that RAIR may be not reported in patients with Chagas' disease due to the use of inadequate volume of intra-rectal insufflation. In

that study, RAIR was present in 43.6% of cases with volumes up to 300 mL with an average of approximately 196 mL.

During our study of anorectal anal manometry, we defined rectal threshold and capacity before eliciting RAIR, using up to one and a half times the volume needed to trigger the initial sensation of rectal filling. The average of volume used to evaluate the RAIR was 90 mL and 60 mL for the groups of patients with mega and without mega, respectively. These values are lower than those used.[29] Several authors have shown that in normal individuals, intra-rectal balloon insufflation up to 2/3 the volume of the rectal sensitivity threshold would be enough to elicit the RAIR.[16,17] Increasing 50% of that volume, as we do, reduces the possibility of miss-interpretation of the patient during the test (identification of the moment in which the instillation of water inside the intra-rectal balloon produces some sensation). Consequently, this maneuver objectively reduces the possibility of a false negative RAIR. Regardless of different methodologies used to elicit the RAIR, we believe that induction of the reflection with very large volumes does not constitute a normal physiological state, and can, as reported,[26] be the anal manometry evidence of the anal canal opening caused by a significantly abnormal increase of intra-rectal pressure, other than RAIR.[30]

RAIR was absent in 47.3% of constipated patients with positive serology for Chagas but without megacolon, while no patients with negative serology for Chagas disease presented anal sphincter achalasia ($p < 0.001$). This data shows the importance of anal manometry to definitively provide the diagnosis of Chagasic colopathy in this subgroup of constipated patients.

The possibility of a Chagasic patient develops symptoms is approximately 40%.[31] It means that 60% will remain asymptomatic during their entire lives. It is reasonable to consider that some of these patients will become constipated due to other different causes.[30] In our study, more than half (52.4%) of Chagasic patients without megacolon demonstrates the presence of RAIR. This finding suggests that causes other than Chagasic colopathy are evolved in the subset of symptoms. They might be part of the indeterminate form of Chagas' disease, whose symptoms occur for other reasons, such as, the inadequate diet, outlet obstruction, colonic inertia, irritable bowel syndrome, hypothyroidism, etc.

The presence of RAIR in patients with Chagasic colopathy remains controversial because it suggests the existence of normal cells in the intramural plexus nerve.[28]

However, it does not allow us to completely exclude the diagnosis as it should be considered the existence of different gradations of the disease in the colorectal segment, due to:

The severity of intramural neural destruction after *T. cruzi* infection; factors such as the parasite strain, the amount of inoculated parasite in the patient, the immunity and nutritional status of the host may play an important role.

An early stage of evolution of a chronic and progressive disease, which just did not have enough time to evolve to a megacolon, neither to present internal anal sphincter achalasia[32] suggested that patients with Chagasic colopathy, unlike that observed on those with megaesophageus, presents initially intestinal lengthening followed by dilatation.

Comparing clinical manifestations of Chagasic patients with megacolon and/or megarectum, to Chagasic patients without megacolon and/or megarectum and non-Chagasic constipated patients without megacolon and/or megarectum, no statistical difference was observed that could distinguish patients with constipation due to Chagasic colopathy to those with functional constipation.

Finally, careful analysis should be carried out when the rectoanal inhibitory reflex is identified by anal manometry in Chagasic patients without megacolon and/or megarectum Other causes of constipation must be ruled out before any attempt of surgical treatment is recommended as we usually do for patients with Chagasic colopathy.

Conclusion

This study brings important implications in the diagnosis of constipated patients with Chagas' disease. The presence of megacolon and/or megarectum is an important indicator of the absence of RAIR (achalasia of the internal anal sphincter), as commonly seen in patients with Chagasic colopathy. However, a constipated Chagasic patient with no radiological evidence of megacolon and/or megarectum, presents anal sphincter achalasia approximately in 50% of the cases. It should be noted that the absence of RAIR confirms the diagnosis of Chagasic colopathy, and, consequently, endorse the indication of surgical treatment in those patients whose conservative medical treatment was ineffective. Conversely, the presence of the RAIR determines the need of further investigation and should change the approach with more conservative options.

More studies are necessary to determine the existence of sub-groups of Chagasic colopathy patients, which might include those without anal sphincter achalasia. It will eventually determine different medical or surgical approaches, according to the pathophysiological changes.

Conflicts of interest

The authors declare no conflicts of interest.

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