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## Review Article

# Colonic Inertia: approach and treatment



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### ABSTRACT

**Objective:** Revision of the state of the art of the knowledge regarding pathophysiology, diagnosis and treatment of Colonic Inertia, which predominantly affects young women and has a significant socio-economic impact.

**Methods:** A search was made in “colonic inertia”, “colon inertia” and “slow transit constipation” in PubMed database for articles of the last 5 years, in Portuguese or English with available abstract and full text. 59 articles and 2013 guidelines of the American Gastroenterological Association on constipation were included.

**Results:** The pathophysiology is not completely elucidated and the reduction of the interstitial cells of Cajal is the most consistent histological finding. Diagnosis requires the exclusion of secondary causes of constipation and obstructed defecation syndrome, to which contribute several complementary diagnostic tests. Given the frequency of failure of the medical treatment, surgery is often the only possible option. Sacral nerve stimulation seems to be a promising therapeutical alternative.

**Conclusion:** A deeper investigation of the pathophysiological mechanisms is fundamental to acquire a more global and integrated vision. Rigorous patient selection for each treatment and the discovery of new therapeutical targets may avoid the use of surgical therapies.

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### Inércia Cólica: abordagem e tratamento

#### RESUMO

**Objetivo:** Revisão do estado da arte do conhecimento da patofisiologia, diagnóstico e tratamento da Inércia Cólica, que afeta predominantemente mulheres jovens e tem um impacto socioeconómico significativo.

**Métodos:** Pesquisou-se na base de dados PubMed por “colonic inertia”, “colon inertia” e “slow transit constipation” por artigos apenas dos últimos 5 anos, em português ou em inglês com resumo e texto completo disponíveis. Incluíram-se 59 artigos e as recomendações de 2013 da Associação Americana de Gastroenterologia para a obstipação.

#### Palavras-chave:

Obstipação

Motilidade gastrointestinal

Trânsito gastrointestinal

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**Resultados:** A patofisiologia ainda não está completamente esclarecida, sendo que a redução das células intersticiais de Cajal constitui o achado histológico mais consistente. O diagnóstico requer a exclusão de causas secundárias de obstipação e de síndrome de obstrução defecatória, para o qual contribuem vários exames complementares de diagnóstico. Dada a frequência do insucesso do tratamento médico, a cirurgia é, muitas vezes, a única opção possível. A estimulação nervosa sagrada parece ser uma alternativa terapêutica promissora. **Conclusão:** É fundamental uma investigação mais profunda dos mecanismos patofisiológicos envolvidos para adquirir uma visão mais global e integrada. A seleção rigorosa de pacientes para cada tratamento e a descoberta de novos alvos terapêuticos poderão evitar a utilização de terapêuticas cirúrgicas.

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## Introduction

Severe/intractable colic inertia or slow transit constipation is the inability that the colon has to modify stool consistency, so as to make them move from the cecum to rectosigmoid at least once every three days. There is a significant delay in colonic transit, not attributable to any other cause.<sup>1-4</sup>

Slow transit constipation is responsible for a variable percentage (13–37% in recent studies) of cases of idiopathic chronic constipation (lasting more than 3 months). This condition is classified as a functional one according to ROME III criteria, contrary to the American Gastroenterological Association.<sup>5-11</sup>

The condition predominantly affects young women and has a significant economic impact.<sup>6,11-14</sup>

In addition to constipation, a lack of desire to defecate, abdominal distension, abdominal pain, feeling of incomplete evacuation, nausea, and decreased food intake may also be present.<sup>11,15</sup>

The diagnosis is established by clinical examination and ancillary diagnostic tests, including colonic transit studies; but these procedures are not sufficient to select patients with a view to the most appropriate treatment. The treatment of slow-transit constipation is not standardized, and the failure of medical treatment (which often occurs) is a surgical indication. But surgery, though with potential good functional results, cannot solve all the symptoms.<sup>8,16,17</sup>

One must know the pathophysiology of this entity in order to give the best treatment for each patient, with the help of complementary diagnostic tests.

## Methods

The search for this review was conducted in July and August 2015, and PubMed was the database used. “Colonic inertia,” “colon inertia,” and “slow transit constipation” were searched, always using as filters the abstract and full-text availability, articles from the last five years, and articles only in Portuguese and English. Seventeen, 11 (7 repeated) and 100 articles (6 repeated) were obtained, respectively. Of these 115 articles, we did not have access to one. After reading and analyzing these 114 articles, 59 were selected for their relevance and importance to the subject studied. The 2013 American

Gastroenterological Association recommendations for constipation were also included.

## Pathophysiology

In order to have a normal bowel function, there must be integrity of the gut–brain–microbiome axis. Suppose if problems can occur at any level, some more get localized (at the colon wall level), other get more widespread. Manometric studies have shown that colonic motor activity is a complex, intermittent, and variable in time and space phenomenon, and this occurs also among different segments of the colon. It is known that in cases of slow transit constipation there is a change of intestinal motility, in terms of frequency, amplitude and duration, but the underlying mechanisms are not well known. Various explanations of possible etiologies related to myopathy, neuropathy (myenteric plexus, changes in the levels of neuroendocrine transmitters, central neuropathy), or a reduction of the interstitial cells of Cajal have been proposed, and seemingly the latter proposition is the most consistent histological finding. There have been several observations that support every possible etiology.<sup>8,16-19</sup>

### *Decrease of spontaneous high-amplitude propagating sequences, after meals and upon waking*

The high-amplitude propagating sequences are one of several motor patterns observed in healthy individuals. They correspond to the mass movements in the colon that occur after food intake (gastrocolic reflex), consisting of a set of pressure events that always progress in an anterograde direction and whose maximum amplitude is, in most cases, >116 mmHg. Most of them originate in the proximal colon, propagating by varying distances, and do not spread beyond half of the colon; <5% reach the rectum. The sequences (in fasting, or postprandial) occur spontaneously in response to pharmacological agents or to the distention of the colon, increasing in number when the person wakes up (the sequences are most common during the day) and after meals. They have a speed of propagation of 1–2 cm/s in the right colon, increasing as the waves advance caudally, often reaching synchronicity, and followed by defecation.<sup>20-22</sup>

As the central nervous system appears to play a role in increasing the propagation pressure after meals and in inducing their nocturnal suppression, a decreased or inhibited response to these stimuli, such as that found in cases of slow transit constipation, possibly suggests a neuropathy, or myopathy. Moreover, this reduced response also suggests the possible involvement of clock genes, which are central or peripheral (in colonic epithelium and myenteric plexus) and, in turn, can control directly or indirectly colonic gene groups that regulate motility. In slow transit constipation, one can also observe a decreased response to chemical stimuli, for example, to bisacodyl, which may indicate a neuromuscular dysfunction; this can draw attention, more specifically, to a change of the myenteric plexus, in the cholinergic pathways, or in colonic and rectal neural pathways.<sup>14,19,20,23</sup>

#### **Decrease in the number and frequency of cyclic motor patterns after high-calorie meals**

Cyclic motor patterns are another type observed in healthy subjects. These are repetitive propagating pressure events with a cyclic frequency of 2–6 min<sup>-1</sup> (corresponding to slow waves) which, for the most part, are observed in the sigmoid colon and which can progress in an anterograde or retrograde direction. These patterns increase in number after meals. The retrograde cyclic motor patterns stand out; their function is to prevent a premature rectal filling and provide sufficient time in order to allow the reabsorption of water and electrolytes during the formation of feces. It is believed that the interstitial cells of Cajal are the source of these patterns, which are modulated by excitatory stimuli. Therefore, the observation of a decreased post-prandial response also suggests the existence of an extrinsic neuropathy, namely parasympathetic (extrinsic sympathetic stimuli inhibit the intestinal motility) neuropathy. Another study failed to get a response after applying an electric or distensible stimulation, suggesting the existence of a problem intrinsic to the colon of the patients in the enteric nervous transmission.<sup>20,21,24</sup>

#### **Changing the spatial-temporal organization of propagating sequences**

The propagating sequences are organized so as to allow a continuous flow. Slow transit appears to be documented more frequently in the left colon than in the ascending and transverse colon. A pan-colonic spatial-temporal mapping study using manometry even showed a decrease in the propagating extension of the waves originating from the proximal colon, and an increase of the frequency of retrograde propagating sequences in the proximal colon, suggesting the existence of an adynamic zone at the level of the splenic angle, corresponding to the junction zone of two different embryological segments and, therefore, possibly with a disruption of the innervation zone (probably more important in subjects with constipation at a very early age). It is assumed that the colonic vagal innervation ends at the level of the splenic angle. The remainder of the colon and the rectum receive sensory innervation from pelvic nerves. The absence of the normal suppression of nocturnal waves also suggests a central neuropathic cause.<sup>7,14,20,22</sup>

#### **Decrease of interstitial cells of Cajal**

Interstitial cells of Cajal are considered as intestinal pacemakers, playing a critical role in the regulation of spontaneous electrical activity (“slow waves and enteric transmission”). These cells can be found particularly at the level of mucosa and myenteric plexus. Despite the frequent observation of their decrease in histologic findings in patients with slow transit constipation, there is still doubt whether this is a primary cause, or if it is a secondary change. Together with this decrease, a reduction in enteric nerves and hypoganglionosis are findings also often observed, suggesting two possibilities: the existence of a factor that induces both decreases, or the decreases influence their mutual survival.<sup>9,15,17,18</sup>

#### **Other observations**

Other changes have been observed in patients with slow transit constipation. The endocannabinoid system has a controversial role in the regulation of intestinal motility and may be bidirectional. However, a decrease in fatty acid amide hydrolase (FAAH) activity would lead to an increase of two endocannabinoids: anandamide and 2-araquidonilglicerol (2-AG) which, through their action on cannabinoid receptor type 1 (CB1), would lead to a reduction of intestinal motility.<sup>25</sup> The brain-derived neurotrophic factor (BDNF) appears to influence the maintenance and survival of the enteric nervous system, accelerating the colonic emptying and increasing the frequency of bowel movements. Studies in mice have suggested that a change of BDNF would lead to a change in the neural structure of the intestinal innervation, with denervation, causing atrophy and secondary smooth muscle degeneration [with a decrease in smooth muscle  $\alpha$ -actin ( $\alpha$ -AML) expression] through the kinase tropomyosin B receptor-phospholipase C/inositol triphosphate (TrkB-PLC-IP3) pathway. A decrease of this factor in human patients has been demonstrated.<sup>26</sup> An increase in the number of intact (not degranulated) mast cells in the colon of these patients was also observed, but it was suggested that this would be a potential compensatory mechanism, in order to repair any damaged neuroenteric circuits, taking into account that they constitute a source of nerve growth factors.<sup>27</sup> Furthermore, a study with mice suggested that mast cell deficiency could lead to an inflammatory condition that would decrease muscle contractility by reducing the reactivity to acetylcholine (ACh), regardless of the decrease in the number of the interstitial cells of Cajal.<sup>28</sup> Apparently, the peptide YY (PYY) is increased in the ascending colon in some patients, constituting a possible etiological factor, by leading to an increased absorption and to a decreased secretion of water and electrolytes, and resulting in an increase of the ileal brake force and in the inhibition of intestinal motility.<sup>29</sup> The downregulation of microRNA128 in the colon of these patients appears to lead to increased numbers of macrophages, which could lead to loss or dysfunction of the interstitial cells of Cajal.<sup>9</sup> A decrease in the expression of esmotelin, that supposedly plays a role in muscle contractile activity by interacting with  $\alpha$ -MLA in the outer layer of the muscularis propria, may have implications in the pathogenesis of colic inertia in some patients.<sup>30</sup>

## Role of progesterone

There is evidence that colonic transit is more intense during the luteal phase of the menstrual cycle, and that the speed of propagation of phase III of the migrating motor complex is slowed in women. Although women with slow transit constipation have normal levels of progesterone, there appears to be an overexpression of progesterone receptors in the circular muscle layer of the colon, which slows its contractility. Progesterone activates two nuclear receptors, A and B. The stimulation of A receptors increases muscle relaxation induced by vasoactive inhibitory peptides, whereas the stimulation of B receptors down-regulates cyclooxygenase-1 (COX-1) and decreases thromboxane A<sub>2</sub> (TXA<sub>2</sub>) and prostaglandin F<sub>2α</sub> (PGF-2α) levels, which would lead to muscle contraction. This latter receptor appears to be responsible for which normal muscle cells will respond to physiological concentrations of progesterone.<sup>31,32</sup>

## Diagnosis

### Clinical diagnosis

The initial approach of a chronically constipated patient consists in taking a comprehensive collection of medical history and in a thorough physical examination. It is important that, as early as possible, warning symptoms and signs (weight loss, blood loss, and family history of colon carcinoma) and secondary causes (improper diet, lack of physical activity, use of pharmaceutical agents, metabolic diseases, psychiatric or neurological disorders, complications of perineal-pelvic-abdominal or obstetric-gynecologic surgery) are excluded. It is particularly important that malignancy in older patients is excluded.<sup>2,17</sup>

It may be useful to apply the Wexner constipation scale that simplifies and objectify complaints, and the Constipation Severity Instrument (CSI) which, in addition to identifying the various types of constipation, also scores its severity; on the other hand, to assess the impact of constipation on quality of life, the SF-36 questionnaire and the Constipation-related quality of life (CRQOL) are useful tools.<sup>2,11,12,17,33</sup> The Rome III Criteria for the Diagnosis of Functional Constipation and the Bristol stool scale (a classification based on the shape of feces) are also emphasized.<sup>2,7,11,34,35</sup>

### Complementary diagnostic tests

In an initial approach, a complete blood count should be obtained; there is controversy if biochemical tests would be of interested.<sup>10,17,36</sup>

### Colonoscopy and barium enema

Colonoscopy allows a structural evaluation of the colon and excludes anatomical/mechanical causes of constipation. This test should be done particularly if the patient has warning symptoms, shows a sudden onset of constipation, or if is aged over 50 and have never done a colorectal cancer screening. The colonoscopy also allows the achievement of biopsy samples

(ideally reaching the muscular layer) to evaluate histological changes.

A barium enema may be indicated in cases of a difficult bowel preparation and of colonic tortuosity.<sup>1,10,17,36</sup>

### Defecography, anorectal manometry and balloon expulsion test

It would seem that a significant overlap occurs between slow transit constipation and constipation caused by pelvic floor changes. The differential diagnosis is essential to delineate an appropriate therapeutic strategy.

Defecography is a dynamic morphological radiological study that provides information about the anatomical and functional changes that occur in the anus and rectum at rest and during defecation. This test identifies several causes of failure in the evacuation (defecatory dyssynergia, defecatory obstruction). The pelvic dynamic MRI is an alternative.

Anorectal manometry is a very useful tool in the investigation of anorectal physiology: it evaluates the sphincter pressure at rest, during contraction, and during a defecation effort. The balloon expulsion test can also measure the anorectal coordination during defecation. In analyzing the action potentials of the pelvic muscles, electromyography provides further information.<sup>1,2,4,37-39</sup>

### Transit studies

The most commonly used test for diagnosis of slow transit constipation is the transit study, which relies on the measurement of transit speed. The patient should refrain from taking laxatives, enemas or suppositories, and should report any bowel movement as long as the test is on. The test consists of the intake of 24 radiopaque markers on day 0 and obtaining abdominal radiographs on days 1, 3 and 5. If there are 5 or more markers in the colon at day 5, i.e. more than 20% retention of markers or no expulsion of more than 80% of the markers, the existence of slow transit constipation is documented. This test allows distinguishing patients with segmental or total slow transit, depending on the site of accumulation of radiotracers. If the markers are scattered throughout the colon but with accumulation especially in the ascending colon, the patient will probably have colic inertia. If the accumulation of markers predominates in the rectosigmoid region, then this is probably a case of defecatory obstruction. Many variations of this test have been already described, particularly with respect to the number of ingested markers and the number of radiographs, which can complicate the subsequent comparison of results. The protocol developed by Metcalf, that is, the intake of 3 different types of markers on 3 separate days (0, 1, and 2), with radiography obtained on day 4 and, if necessary, also on day 7 (which will be more useful for the diagnosis of segmental areas of colic inertia), is emphasized. Some studies have replaced the use of radiotracers by barium suspensions and suggested that these suspensions, in addition to being cheap and simple, may allow a more accurate measurement of bowel transit in the various intestinal segments since they blend better with the contents of the gastrointestinal tract and allow a more exact definition of the location of the suspension.



A disadvantage of these methods is the higher radiation exposure.<sup>1,2,12,15,37,40-42</sup>

#### Colon manometry

Colon manometry is of interest in the diagnosis and to the therapeutic decision-making, which should not be based exclusively on radiologic studies. This test shows the daily motor patterns of bowel activity by measuring multiple regions of the colon, and changes in their characteristics help to characterize dysmotility. This technique has undergone changes which mainly consist in increasing the number of data-collection sensors into the colon and in reducing the spacing between these sensors, namely, the low-resolution manometry becomes a high-resolution test. Taking into account that the motor patterns are not evenly distributed throughout the colon, this resulted in an increase in our power to correctly identify the propagating events and their direction and frequency. Colon manometry reveals that there is a significant pathophysiological heterogeneity among patients with slow transit constipation, dividing them into three subtypes based on three physiological responses: high-amplitude propagating contractions, gastrocolic response, and colic response when awakening. If two of these three responses are absent, this suggests neuropathy (probably caused by nerve circuit damage, with secondary muscle dysfunction). If two or three responses are present, but in an attenuated form (pressure activity less than two standard deviations from the normal motor response), then this will suggest myopathy (probably caused by target organ or muscle damage, but with intact neural circuits). If the 3 responses are present, or if there is a slight change of only one of two responses, the manometric pattern is considered normal. A relationship between these patterns and the clinical evaluation and transit studies has not been established. Thus, it can be concluded that manometry is particularly important for refractory slow transit constipation, serving as a guide for subsequent treatment; and this technique may also predict the therapeutic effectiveness.

To assess colonic tone and sensitivity, one can connect a barostat in the manometer. This procedure is useful because studies show that, in addition to motor dysfunction, a sensory dysfunction – or even an isolated sensory neuropathy – may also be present. However, this may also be only an effect, not a cause.

Challenge studies with bisacodyl or neostigmine may be useful to test the residual propulsive activity, thus helping in a proper selection of patients with severe colic inertia or with slow transit constipation for surgery.<sup>8,17,19,42-44</sup>

#### Scintigraphy and capsule endoscopy

Scintigraphy and capsule endoscopy are more advanced, but more expensive, methods, which limits their application. These methods allow measuring gastric, small intestine, and colon transit times in a single test; thus, these tests are important to assess the regional transit time and exclude a suspected gastrointestinal diffuse dysmotility. This information may have prognostic significance in predicting the results of aggressive therapies.<sup>2,40,45,46</sup>

## Treatment

### Conservative measures

The first line of treatment in cases of chronic constipation is to change behavior, with modification of the lifestyle and diet.

These patients should be advised to discontinue drugs that can cause secondary constipation, not to postpone defecation when they feel comfortable, and to defecate every day at the same time, preferably in the morning upon waking and after meals. It is known that constipation is more frequent in subjects with a sedentary lifestyle; thus the assumption that increased exercise improves intestinal transit time. Such patients should also increase their fluid intake (1.5–2L/day) and fiber (25 g/day). However, attempts to obtain improvement of slow transit constipation with fiber supplements are usually unsuccessful, despite many studies that have tested the use of fiber in the diet of subjects with chronic constipation that pointed in the opposite direction.<sup>2,3,16,47,48</sup>

### Medical therapy

#### Laxants

For many constipated patients, the use of laxatives is a constant reality. Besides the use of fiber in the diet, several studies have already proven the effectiveness of osmotic and stimulant laxatives in chronic constipation, because these drugs improve some symptoms and accelerate the intestinal transit. While laxatives have a significant impact on the frequency and form of the stool, these drugs have little effect on abdominal pain, sense of abdominal distension, the feeling of complete evacuation, and efforts made to defecate (which may suggest the presence of a concurrent defecatory obstruction).

Typically, one begins the treatment with fiber and an osmotic laxative (i.e., magnesium salt or polyethylene glycol) and, if necessary, with the addition of a stimulant laxative (i.e. bisacodyl).<sup>16,35,47,48</sup>

#### Prokinetics and intestinal secretagogues

Prokinetics and intestinal secretagogues are agents that can restore the colon function in cases of constipation.

Prokinetics accelerate the colonic transit and have laxative potential when inducing quick excitatory postsynaptic potentials in intrinsic neurons, releasing excitatory neurotransmitters, and activating submucosal neurons, which leads to an increased mucosal secretion. The highly selective agonists of the 5-HT<sub>4</sub> receptor (i.e. prucalopride, naronapride, and velusetrag), besides being very effective, have a better safety profile, especially for cardiovascular system.

The use of prucalopride (so far the best-studied drug) should be considered when symptomatic relief is not obtained after the change of lifestyle and the use of laxatives. However, and despite leading to the generation of high-amplitude propagating contractions in the colon, its effect on the slow transit constipation is not what is expected.

Intestinal secretagogues are useful for alleviating constipation, taking into account the production of softer stools and intestinal transit acceleration by reducing the effort to defecate. These drugs promote intestinal secretion activation in

two different ways. On the one hand, type 2 intestinal chloride channels can be activated by promoting secretion of fluid (lubiprostone). On the other hand, by acting on the guanylyl cyclase receptors of enterocytes, these drugs potentiate the increase in chloride and bicarbonate secretion into the intestinal lumen (linaclotide).<sup>6,7,13,16,47,48</sup>

#### *Other pharmaceuticals*

It may be advantageous to treat a possible bacterial overgrowth with antibiotics, due to the reduced intestinal transit.

The effects of probiotics in chronic idiopathic constipation are not well known, but it is thought that these effects will modestly decrease the intestinal transit in constipated patients.<sup>16,47,49</sup>

#### *Nerve stimulation*

Neuromodulator therapy, or sacral nerve stimulation, is an established treatment in urological pathology (incontinence and retention) and in fecal incontinence. Studies that tested its applicability in slow transit constipation have shown promising results, as there is a direct involvement in the pathophysiology of the disease. Despite this, the underlying mechanisms are not completely understood, and it is believed that the action occurs in central, sensory and motor levels. Apparently, this technique induces pan-colonic pressure waves (including sequences of retrograde propagation, which at first may seem counterproductive).

The great advantage of this technique is that it allows the testing of results and the effectiveness of a temporary stimulation, pre-selecting patients who will receive a permanent implant (a 3-week temporary stimulation appears to have a higher negative than positive predictive value, but perhaps there is a need for a longer treatment, to obtain results). Strict selection criteria for the application of this technique are not established. In general, the technique is applied when the conventional therapy failed. A better understanding of the pathophysiology allows a better selection of patients and, therefore, better results (some studies report that the results will be better in the presence of an isolated or concomitant defecatory obstruction).

The stimulation site varies from the transcutaneous stimulation to the direct stimulation of specific nerves. Normally S3 is the stimulated nerve, but it is thought that the stimulation of posterior tibial nerve fibers, by containing 2nd and 3rd nerve roots, will be of potential interest, thanks to the easy accessibility of the nerve. There is no consensus as to the optimal stimulation. Oversensitive stimulus levels appear to be more effective, but more studies are needed to test the subsensitive stimulation that would be more tolerable and, therefore, more attractive to patients. A study in dogs found that the use of pulse waves, a technique used in most animal studies, will be more effective than the use of long isolated repetitive pulses, which is the technique normally used in human studies. A deepening of the knowledge related to methods of direct electrical stimulation (intramuscular, serous or intraluminal) of the colon, and of interferential therapy for treatment of slow-transit constipation in adults (stimulation

of the parasympathetic fibers increases the colonic transit) is required.<sup>14,16,33,47,50-57</sup>

#### *Other options*

Other options that should be considered in relieving symptoms and that induce some improvements in chronic constipation are rectal/transanal irrigation (its advantages include: a less invasive technique versus surgery, it cleans the bowel more proximally versus enemas, it can be done on an outpatient basis, and the patient can decide the frequency and timing of the procedure, allowing a greater control of symptoms), or anterograde colon enemas (which should be considered for patients who are satisfied with the results of the rectal irrigation, but who find it inconvenient).<sup>47,58</sup>

#### *Surgical options*

The American Gastroenterological Association recommends surgical intervention for patients with symptomatic slow transit constipation where the colonic motor dysfunction has been appropriately documented (manometry, barostat) and in cases whose long and aggressive therapy with laxatives, fiber, and prokinetic agents failed (proof of refractoriness to medical treatment).<sup>10,36</sup>

Some studies claim that the finding of manometric characteristics of neuropathy constitutes a surgical indication, whereas this option should be discouraged in patients with a normal colonic manometry, or a with manometry suggestive of myopathy.<sup>3,8,11,47</sup>

The two main surgical treatments for slow transit constipation are total colectomy with ileorectal anastomosis and subtotal colectomy. A segmental colectomy may also be performed.<sup>1,11,59</sup>

#### *Total colectomy with ileorectal anastomosis*

This is the surgery of choice for colic inertia. When one opts for a total colectomy, the anastomosis is made at the superior rectum by laparotomy, laparoscopy or hand-assisted laparoscopy. As most of the patients are young and active, they are good candidates for a laparoscopic surgery, with the advantages associated with this procedure.

A proper selection of patients for this surgery results in excellent outcomes (exceeding 85–90%). However, other studies show that patient satisfaction levels vary widely (39–100%); it is likely that this has to do with the possibility of some degree of persistence of symptoms and morbidity. The most frequent postoperative complication is a small bowel obstruction (by occlusion or neuropathic dysfunction of the myenteric plexus, which affects intestinal motility). The mortality of this surgery is also variable. Some studies report less than 1%, while in other the mortality ranges from 0 to 15%.<sup>1,3,11,12,15,34,52,59-61</sup>

#### *Subtotal colectomy*

This surgery is a valid alternative for some patients. The resection is carried out at a point about 10 cm distally to the ileocecal junction and in the upper part of the rectum. The preservation of the terminal ileum, ileocecal valve and cecum permits the reabsorption of electrolytes, bile salts, vitamin B12 and about 2 L of water per day. In terms of efficacy and safety,

this technique appears to be similar to total colectomy with ileorectal anastomosis, with lower rates of diarrhea and post-surgical incontinence. However, preservation of the ileocecal valve and cecum appears to result in a higher rate of recurrent or persistent constipation.

Colonic reservoirs of different sizes may be created, but there is still no consensus about what is the best option. However, it seems that the shortening of the ascending colon portion above the ileocecal junction results in a better quality of life (less distention of the cecum and less abdominal pain).<sup>1,3,47,59-61</sup>

### Segmental colectomy

Although an attractive option, it is difficult to determine, by means of transit studies, in which specific part of the colon occurs the dysmotility, or if it occurs throughout the colon, which may lead to recurrence of symptoms and to persistent constipation; also, an additional surgical resection may be needed. The same problem occurs in patients treated with subtotal colectomy.<sup>1</sup>

## Discussion

Investigations and observations conducted on patients with colic inertia led to the proposal of various etiologies, suggesting the existence of multiple causes. However, to determine if some of them are the cause or consequence of the disease is a challenging task. This question is particularly relevant in relation to the findings related to myopathy, since the vast majority of studies suggest the existence of neuropathy (leading consequently to the belief that the primary cause lies at this point). It would be important to have a concatenated, comprehensive and integrated view of the mechanisms, in order to clarify which changes are occurring, particularly at the level of enteric nervous transmission, regulation and modulation with food intake, and a possible role of clock genes.

In view of the predominance of cases in young women, it would be interesting to investigate the possible occurrence of a variety of complaints with menstrual cycle and its relation with the overexpression of progesterone receptors. This may project a new focus on different therapeutic targets.

Despite the fact that the evolution of manometry allowed an in-depth knowledge of the propagation characteristics of the colon, there is still no standardization of the technique, which can result in a potential loss of relevant information. It would be appropriate to clarify whether the retrograde propagation sequences have some active etiological role.

As mentioned earlier, some studies state that neuropathic characteristics obtained with colonic manometry constitute an indication for surgery, while patients with a normal colonic manometry, or one suggestive of myopathy are not candidates for surgery. One why is this, because patients with myopathic features could benefit from a more localized intervention.

Standardization in the evaluation of the results of different surgical interventions is very important, in order to obtain a more accurate assessment of the advantages and disadvantages of each procedure, in the decision-making of an individualized therapeutic choice. If the surgeon has to choose a surgical treatment, the advantage offered by a

segmental colectomy is undeniable, because in this situation this would allow the most conservative therapy possible. Therefore, we must emphasize the importance of the various complementary diagnostic studies, not only to confirm the surgical indication but also for the exclusion of other comorbidities that could be associated with a worse outcome.

A broader understanding of the pathophysiology also allows a better selection of patients for sacral nerve stimulation, which is an attractive alternative therapy versus surgery. The stimulation of different nerve roots and the direct stimulation of the colon would help circumvent the fact that sacral nerve stimulation seems to produce better results in the case of defecatory obstruction or in patients in whom this condition occurs simultaneously with the slow transit constipation.

## Conclusion

Although the medical community has witnessed a considerable improvement in understanding the pathophysiology of colic inertia over the past years, this is still insufficient. The evolution of slow transit constipation as a pathology should be further studied, in order to eventually find predictive markers of its progression, as well as ways to prevent the worsening of this condition.

It is mandatory to register the lines of conduct that should be taken into account in the guidance of these patients; and it is essential to find new clinical targets, particularly considering that this entity affects a significant percentage of the population, in whom the most affected individuals are young people, and also because the end of the therapeutic line is a surgical procedure.

More studies providing a global perspective are welcome. A more consistent bet in randomized clinical trials, in order to produce higher-value scientific evidence, could result in more effective therapeutic implementations.

## Conflicts of interest

The authors declare no conflicts of interest.

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