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The Management of Functional Constipation



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ABSTRACT

Functional constipation is a very common disease among the healthy population and is a cause of serious social discomfort in young and working-age patients. In older people and in defeated patients, it can be cause and contributory cause of aggravation of existing pathologies. For these reasons, this pathology is an important source of expenditure for the national health service and also for the nation and the economy, given the absences of work. The problem, often limited to situations that can be handled in outpatient care, sometimes takes on important dimensions, requiring hospitalization and, in particularly severe cases, the need for surgical intervention. In this review article, I try to highlight the importance of targeted diagnostics before proceeding with a therapeutic intervention. The focus is done on attention on the differential diagnosis between functional constipation and irritable bowel syndrome with prevalent constipation because this can change the pathology management. I also point out the importance of dividing the disease into subclasses, because this also radically affects the therapeutic approach.



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ABBREVIATIONS

FC (Functional Constipation), IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed bowel habits (IBS-M), IBS unclassified (IBS-U), HPPC (High Pressure Propagated Contractions), CTT (Colic Transit Time), ET (Expulsive test), PEG (Polyethylene glycol), FGD (Functional Gastrointestinal Disorders)

INTRODUCTION

Brain-intestinal interaction is a group of disorders classified by the presence of gastrointestinal symptoms (GIs) related to a variable combination of motility disorders, visceral hypersensitivity, impaired immune and mucosal function, altered microbial intestinal tract and altered CNS(Central Nervous System) processing (Drossman, 2016). This new definition is more consistent with the evolution of knowledge about the multiple pathophysiological processes that in part or together determine the characteristic symptoms of the classification of Rome. Although Functional Gastrointestinal Disorders (FGDs) share common physiological characteristics, their relative contribution may differ according to body location, duration of symptoms, and between individuals or the same person over time. Functional gastrointestinal disorders include constipation. The pelvic floor rehabilitation therapies, valid for expulsion constipation, dietary and behavioral advice, evaluating its effectiveness, and drug therapies, the latest of which deals with 5-HT₄ receptor agonist drugs (5-hydroxytryptamine that is serotonin) and with a new agonist of cyclanecguanilate C (GC-C) receptors. Corrective surgery of anorectal malformations finds its space, preceded by an appropriate correction of the pathophysiological defect. Demolitive surgery, in the case of slow-transit constipation, is reserved for cases of particular gravity. In conclusion, this review wishes to convey is that aimed at both family Doctors and Specialists not to underestimate, since early childhood, the disorder of constipation, but to face it in its clinical complexity, to reach an exact diagnostic definition, providing the most appropriate dietary, behavioral, pharmacological and surgical therapies.

Definition of Constipation

One of the first definitions of constipation was given by Sandler RS and Drossman DA (1) and indicates an evacuative frequency of less than three per week, as a work by Connell et al. (2) reported an average of evacuations in the English population between three daily and three weekly. But Sandler and Drossman emphasize above all the aspect of the problem,

pointing out that only a third of the constipated population complains of infrequent defecation, while all of them complain of a difficulty in evacuating. The Author also cites the most recent definition by Andrew and Storr (3) who talk of difficult transit of stools through the colon and/or rectum.

The definition of constipation given by the American College of Gastroenterology (4) Task Force in 2005 is the one that most closely matches the definitions of the Study Roma Group's Experts. This definition indicates constipation as a defective defecation characterized by unusual evacuations and/or difficult expulsion. Difficult expulsion including necessity of marked straining, hard or lumpy stools (like nuts), sensation of difficult evacuation, feeling of incomplete evacuation, need for prolonged time to get the evacuation and need for manual maneuvers. Symptoms must be present for > 3 months.

The road to Rome Criteria goes through four stages: Rome I in 1994, Rome II in 2000, Rome III in 2006 and Rome IV in 2016. The criteria of Rome IV say that the diagnosis of functional constipation must include 2 or more of the following : lumpy or hard stool in more than 25% of defecations (Bristol 1-2 scale) (5), straining in more than 25% of defecations, sensation of anorectal obstruction / blockage in more than 25% of defecations, sensation of incomplete evacuation in more than 25% of defecations, manual maneuvers to facilitate in more than 25% (eg, digital evacuation, support of the pelvic floor), fewer than 3 spontaneous bowel movements per week. Moreover, loose stools must be rarely present without use of laxatives and they must be insufficient criteria for irritable bowel syndrome. These criteria must be present for the last three months with symptom onset at least 6 months prior to diagnosis. This definition also indicates that abdominal pain and/or bloating can be present but are not predominant and Patient must not meet the criteria for IBS (Irritable Bowel Syndrome). This supports the concept that Functional Constipation (FC) and IBS-C (Irritable Bowel with predominant Constipation) are disorders that exist in a continuous spectrum.

Classification and differential diagnosis

Chronic constipation can be idiopathic or secondary. It can be secondary to mechanical and/or surgical, endocrine and/or metabolic, myopathic and/or neurological and to pharmacological causes. Surgical causes are a rectal or colonic cancer, extraintestinal masses, post-diverticulitis, post-ischemia and post-anastomotic stenosis. Metabolic or endocrine causes are diabetes, hypothyroidism, increased calcium for an excess of parathormone, a reduction in

potassium and magnesium in case of chronic renal insufficiency, a heavy metal poisoning.

Connective pathologies such as amyloidosis and scleroderma can cause constipation and thus neurological disorders such as stroke, traumatic or neoplastic cerebrospinal cord disease, multiple sclerosis, disability.

Other causes of secondary constipation include depression, dementia, immobility, cardiopathy.

Using some medications may be a cause of constipation. Some are self-prescription drugs, such as anti-diarrhoeals, antacids, anticholinergics, antihistamines, martial therapies, non-steroidal anti-inflammatory drugs (NSAIDs) and others are medicines subject to medical prescription such as opiates, sympathomimetics, antiparkinsonian, tricyclic antidepressants, antipsychotics, calcium-antagonists, diuretics, antispasmodics, 5-HT₃-antagonists.

Idiopathic Chronic Constipation: assessment and classification

Two are the factors that are taken into account in the ethio-pathogenetic classification of constipation: Colic transit times (CTT) and Expulsive Tests (ET).

Gastrointestinal Transit Times is measured with radiopaque pellets. The patient, after a direct RX of the abdomen, ingests a number of radiopaque pellets and, after 96 hours, a control RX is made. The normal elimination range is > 80%.

The expulsion test is the anorectal manometry with the balloon ejection test, which can be accompanied by the imaging tests of defecography, colpo-cysto-defecography and defecation RM resonance imaging test.

If both of these factors are normal, one cannot talk about constipation, but it will be irritable bowel syndrome or other pathology to investigate.

If there is a distal delay of CTT (Colic Transit Time) and there is an altered ET (Expulsive Test), then there will be expulsive constipation.

If we have a delay of CTT and Normal ET, then it is a slow transit constipation (inertia coli).

In case of delay of CTT and altered ET, we talk about mixed constipation.

Slow transit constipation

Many studies have been made regarding the motility of the colon, which led to the distinction of colic motility in segmenting activity and propagated activity (6). The first is composed of single contractions and bursts of contractions (rhythmic and arrhythmic) that do not produce intestinal material progression. The peristaltic activity that propagates is characterized by low amplitude contractions that function as a cleansing of the bowel and by propagated contractions of high amplitude (mass movements) that determine the propulsion of the stools.

The motility of the small intestine was studied in patients with coli inertia (7)

Anorectal chronic idiopathic constipation

There are two conditions related to this pathology: the anismus and the descending perineum syndrome. In the first case, there is a paradoxical anal contraction or an inadequate anal release. In the second case, there is hypotonia of perineal muscles, sometimes associated with megarectum. The first condition is documented by physio-pathological examination of standard or high-resolution anorectal manometry (8). The second condition is diagnosed with defecography showing a downward curvature of the perineal plane greater than 4 cm (9).

Diagnostic Flow Diagram

The first step should be to evaluate and exclude patients with a condition that may be the cause of constipation, such as allergies, intestinal infections or other.

The second step, if clinical conditions allow and if there are no symptoms of alarm, is the use of therapeutic trials such as fiber, laxatives, appropriate water intake and dietary modifications.

Next, we go through the first level specialistic tests, which are gastroenterologic/proctological visits and colonoscopy, colic transit time test (CTT), anorectal manometry with ballon ejection test.

In case of slow transit constipation, you can proceed with a small intestine study (CT, contrast ultrasonography (SICUS that is Small Intestine Contrast Ultra-Sonography), MR (Magnetic Resonance) Enterography, Manometry). If everything is normal, the diagnosis can be isolated colic slowing, irritable bowel syndrome (IBS) or inertia coli. If there is some abnormality, the

diagnosis can be diffused motor disorders, IBS, or pseudo intestinal chronic obstruction.

If the Colic Transit Time (CTT) is normal, this may be a technical error or the diagnosis will be IBS or psychological disorders.

If the Colic Transit Time (CTT) shows a distal delay, defecography procedure should be used to diagnose pelvic floor dysfunction or anatomical alterations.

Clinical approach to functional chronic constipation

Many patients mistakenly believe that daily evacuation is needed: modifying this misguided belief can improve the perception of regular bowel syndrome. In some patients, it may be necessary to have a daily diary to determine the nature of the disturbances in frequency of evacuation, intensity, and duration of the expulsion effort (10).

It is necessary to consider the possibility that constipation is induced by medication. Eliminating the potentially harmful drug may improve constipation (11).

It is important not to suppress the evacuation stimulus. Inhibition of stimulation at evacuation may result in stagnation and further dehydration of the stool resulting in greater difficulty in expulsion (12).

Fiber intake

It is believed that in Western populations an inadequate fiber supply is commonly associated with constipation. It is interesting to note that there are few studies aimed at assessing the role of dietary fiber in subjects with chronic constipation. There are no differences in controls and the transit times are usually prolonged and the fecal volume is generally reduced in the constipated subjects compared to the controls, regardless of the supply of dietary fibers.

A meta-analysis study (13) showed that constipated patients exhibited reduced fecal weight and slow transit even if they assumed ≥ 20 grams of bran per day.

Therefore, although a higher fiber content can increase fecal weight in constipated subjects, the results obtained will, in any case, remain lower than the standard. For this reason, the results of a high-fiber diet may be disappointing in constipated patients (14,15).

In a study, patients with chronic constipation were treated with psyllium 15-30g/day for at

least 6 weeks. Some patients may benefit from fibers, but in many cases with severe constipation, fibers can lead to worsening symptoms (16). Patient compliance with a fiber-rich diet is modest, due to side effects such as flatulence, meteorism, abdominal distension. To improve compliance, it is advisable to increase the dose of fibers gradually: 5 gr per week until reaching the recommended daily dosage of 20-35 gr. The benefits of the fibers are observed not before 3-5 days of intake; in any case, it is advisable to continue for at least one month in order to be able to express a judgment of effectiveness on constipation.

In conclusion, it is useful to recommend a fiber supplement to the constipated patients with an excessively refined diet; grade C recommendation (17). But, in constipated patients, fibers should not be given indiscriminately or aggressively. It is necessary to evaluate the subjective tolerability and to modify, if necessary, how to administer the fibers.

Liquid intake

Proper hydration is important to modulate intestinal motility. However, despite the opinion that a lack of liquids could increase the risk of constipation, studies available did not make any significant evidence that fluid intake could affect the frequency and consistency of stools.

In healthy volunteers, a relatively short period of time dehydration reduces the frequency and volume of stools (18). Therefore, it is reasonable to assume that a reduced water intake may favor the appearance of constipation in some patients. Dehydration, then, must be corrected. But there is no evidence, however, that an increase of contribution of liquids, within tolerable limits, can improve chronic constipation. In fact, a study shows that the increase of isotonic fluids up to 2 Lt per day does not increase the fecal output (19).

In conclusion, available data suggest that fecal output cannot be significantly altered by fluid ingestion. There is also no evidence that constipation can be relieved by increased mouth fluids, except in dehydrated patients (14,20).

Regular physical activity: what role?

The National Health and Nutrition Examination Survey has shown that poor physical activity doubles the risk of constipation. The Nurses' Health Study, comprising a cohort of 62,036 women, has shown that physical activity from 2 to 6 times a week reduces the risk of constipation by 35%. But other studies show that the risk of constipation in adults is

independent from physical activity (21) and with a stable dietary intake, physical activity does not affect colic function (22).

In conclusion, physical activity can affect bowel function, but it certainly is not the predominant factor in constipation. The relationship between physical activity and constipation seems to be more evident in the elderly, although other factors seem to play a predominant role: drugs, diet, cognitive disorders...

Although it is good to encourage patients to exercise regularly, whenever possible, there is no significant evidence of an important role in physical activity in relieving constipation.

Pharmacological therapy

The main objectives of the pharmacological therapy are to modify the stool consistency and modify the intestinal transit.

In the physiological also the total H₂O content in faeces is 75-80%, in bacteria/food residues is 70% and H₂O dilution is 5-10%. In Patients with constipation, total H₂O content in faeces is 70%, H₂O in bacteria/food residues is 70% and H₂O dilution is 0%.

The bidirectional brain-gut interactions are fundamental to the etiopathogenesis of constipation. The Central Nervous System (CNS) brain is linked to the autonomic nervous system (ANS) and to the enteric nervous system (ENS). IPANs, intrinsic primary afferent neurons, transmit signals to the interneurons and ultimate neurons of the muscles, secretion glands and vascular cells. The signals come from the ENS (enteric nervous system) to the CNS (central nervous system) through IPAN, the intrinsic primary afferent neuron, and the ESN, extrinsic neuronal sensory. The affected transmitters are 5-HT (serotonin), Ach (acetylcholine), NO (nitric oxide), NKA (neurokinin A), VIP (vasoactive intestinal peptide), CGRP (calcitonin gene-related peptide) and PACAP (pituitary adenylate cyclase -activating peptide) present in myo-enteric plexus, in the mucosa and in the submucosa (23).

Classification of laxatives

The laxatives can be classified in:

a) lumenally active agents like hydrophilic colloids, bulk-forming agents like bran, psyllium, osmotic agents, nonabsorbable inorganic salts or sugars, polyethylene glycol, stool-wetting

agents (surfactants) and emollients (docusate sodium per enemas, mineral oil);

b) non-specific stimulants or irritants like diphenylmethanes (bisacodyl), anthraquinones (senna and cascara), castor oil;

c) prokinetic agents like 5-HT₄ receptor agonists, opioid receptor antagonists, agonist of cyclanlicguanilate C (GC-C) receptors (24, 36).

Another classification distinguishes them in:

I. Bulking or hydrophilic agents like dietary fiber, psyllium (*Plantago*), polycarbophil, methylcellulose, carboxymethylcellulose;

II. Osmotic agents like poorly absorbed ions, poorly absorbed disaccharides, sugar alcohols, glycerin, polyethylene glycol;

III. Stimulant laxatives that are surface-active agents, diphenylmethane derivatives, ricinoleic acid (castor oil), anthraquinones;

IV. Lubricating agent or mineral oil;

V. Neuromuscular agents that are cholinergic agonists, 5-HT₄ agonists, prostaglandin agonist, Colchicine, opiate antagonists, cyclase C guanilate receptor agonist (GC-C) (25, 37, 26).

Bulking or hydrophilic agents

A study on wet bran in constipated Patients concluded that bran can be expected to be only partially effective in restoring normal stool weight and transit time in patients who are constipated (27).

Osmotic agents

The most common osmotic agents are lactulose and macrogols. The former recalls sodium, chlorine and water, binds them and prevents their reabsorption, through metabolism and fermentation. Macrogol binds a definite amount of water, increases the secretion of chlorine and water in the lumen, but without metabolization and fermentation (27).

The lactulose arrives unchanged in the colon, generates bacterial fermentation and production of gas (carbon dioxide). This results in flatulence and acid faeces. Short chain acids (acetic,

propionic, butyric acid) facilitate the growth of bifidus lactobacilli with increased osmotic pressure, subsequent reduction of water absorption and increased stool volume and increased peristalsis. Thus, disaccharides call water for osmosis in the intestinal lumen, they are digested in lactic acid and acetic acid and their metabolism causes meteorism and colic distention.

Polyethylene glycols determine an increase in water with osmotic mechanism and molecular bond, but they are not metabolized and do not produce meteorism (28).

Among the studies concerning lactulose and polyethylene glycols are interesting those that compare the correlation between daily stool weight and Mean Residence Time (MRT) of the colon during ingestion of therapy. It has been found that the mean residence time throughout the whole colon, the right colon and, above all, in the distal colon was for the benefit of polyethylene glycols (29).

In conclusion, both lactulose and PEG-4000 are effective and well tolerated.

However, although lactulose can be considered pre-biotic in constipated patients, PEG produces signs of decreased colonic fermentation in the stool (30).

Stimulant laxatives

The stimulant laxatives act on the myenteric plexus and prevent the reabsorption of chlorine and water. Thus they stimulate peristalsis, increase the secretion of water and electrolytes in the intestinal lumen, promoting fecal progression.

A study on the effect of bisacodyl has shown an increase in the number of patients with at least two bowel movements (BMs) per day during the run-in and treatment phases (31).

Most of these types of laxatives lose their effectiveness over time and create the problem of tachyphylaxis (32).

Laxatives, like all medicines, have side effects, each of a different type.

The bulking or hydrophilic agents can give bloating, flatulence, intestinal obstruction, asthma (psyllium), reduced drug absorption.

The mineral oil can cause anal leakage, decreased absorption of fat-soluble vitamins, lipoid

pneumonia, foreign body reactions.

The osmotic agents can cause dehydration, bloating, flatulence, congestive heart failure, magnesium intoxication, hyperphosphatemia, hypocalcemia (33).

Secretagogues laxatives and agents with direct effects on epithelial, nerve, or smooth muscle cells can give cramps, electrolyte depletion, hyperreninemia, renal failure, fixed drug eruption (phenolphthalein), protein-losing enteropathy (phenolphthalein), Stevens-Johnson syndrome (phenolphthalein), Lupus-like reaction (phenolphthalein), melanosis coli (anthraquinones), cathartic colon, increased drug absorption (docusates) (33).

The bulk forming agents have the advantage of possible long-term use in patients with normal intestinal motility and uncomplicated constipation, but the disadvantages of slow onset of action (48-72h), no acute resolution, mechanical obstruction risk, excessive gas formation, meteorism, cramps, possible addiction, unpleasant taste and laxatives containing psyllium can cause anaphylaxis and other allergic reactions.

The saline osmotic laxatives have the advantage of rapid onset of action, but they are not usable in the long run, they can provide dehydration for diarrhea, magnesium-containing laxatives can cause hypermagnesemia, sodium phosphate can cause severe acute hyperphosphataemia, especially in the elderly.

The non-absorbable disaccharides have the advantage of onset of action in 24-72 hours, but they can give meteorism, flatulence, abdominal pain and have a bad taste.

The Poly-Ethylene-Glycol PEG 4000, with or without electrolytes, have the advantage of efficacy and long-term safety, negligible absorption, lack of metabolism, efficacy independent of colic flora, miscibility with liquids and food, no caloric intake. But they have the disadvantage of possible aftertaste salt.

The stimulants have the advantage of rapid onset of action, but they give abdominal pain and cramps (colon cathartic), are long-term use limited and you need to take precaution in pregnancy (carcinogenicity?).

A systematic review of the efficacy and safety of traditional medical therapies for chronic constipation has resulted in a good evidence (grade A) for supporting the use of PEG and tegaserod (neuromuscular agent). A moderate evidence (grade B) was found to support the

use of psyllium and lactulose. Paucity of quality data was found for many commonly used agents including milk of magnesium, senna, bisacodyl, and stool softeners (34).

A recent multicentre study showed that macrogol was the most prescribed laxative, and prucalopride and pelvic floor rehabilitation represented a "second line" approach. Diagnostic tests and prescribed therapies increased by increasing chronic constipation severity (35).

Since a few years, Linaclotide is the first member of a new class of drugs to be extensively evaluated for the treatment of chronic constipation (CC) and irritable bowel syndrome with constipation (IBS-C). Linaclotide is a minimally-absorbed 14-amino acid peptide which acts in the intestinal lumen on guanylate cyclase-C (GC-C). This results in the generation of cyclic guanosine monophosphate (cGMP), which stimulates the secretion of the chloride, resulting in increased luminal fluid secretion and acceleration of intestinal transit (36).

Expectations for this new drug were high. Studies on its use have shown great quality and performance. Some adverse events, the most important of which is diarrhea, have resulted in a reduction in its use or intake in occasional doses (37).

I only report two studies on new research in this area. One on the possibility of using sildenafil to accelerate intestinal transit and another on a new molecule, empagliflozin, a novel selective sodium glucose co-transporter 1 (SGLT1) inhibitor, for the amelioration of chronic constipation (38,39).

The constipation surgical therapy provides:

- 1) the surgical correction of pelvic malformations
- 2) direct stimulation of sacral nerves with surgical positioning of the stimulator
- 3) the surgery of slow transit constipation (inertia coli)

The *surgery of pelvic malformations* should be performed after physiotherapeutic remediation to prevent the restoration of anatomical anomaly (for example prolassectomy in stressed rectum, surgical intervention for laparocoele correction due to pelvic dyssynergia).

The *direct stimulation of sacral nerves* (Sacral Neuro Modulation) involves the percutaneous placement of an electrode in the third sacral foramen and implanting a stimulating device under the skin in the buttocks. It is generally accepted that the mechanism of action is

modulation rather than stimulation so it is called sacral neuromodulation (SNM).

Slow transit or *inertia coli surgery* is reserved for well-defined and well-studied cases.

A) Surgical correction of pelvic malformations.

The surgical correction of pelvic malformations is related to these major malformations:

Lonely rectal ulcer: common rectal ulcer is the consequence of repeated rectal microtrauma of rectal mucosa in patients with complete rectal prolapse or internal.

Rectocele: Herniation of rectum wall: can be either front or rear. The front is a herniation on the back wall of the vagina. It can be: 1) relaxed rectocele, in which the vaginal dome is in a normal position; 2) displaced rectocele, as occurs when the back wall of the vagina descends with the vaginal dome and drags the front wall of the rectum. This is a condition often due to uterus and/or vaginal genital prolapse. It is a frequent pathology in multipare, in 80% of cases, it is asymptomatic.

The rectocele pocket alters the defecation dynamics as it seals off the fecal bolus. Typing is a consequence. Depending on site respect to the back vaginal wall, it can be high, middle and low.

Low rectocele is at the perineal body level due to separation of the anus muscle bundles, often as a result of a non-well-repaired episiotomy.

Medium rectocele is the most common, also linked to obstetrical laceration with the damage of recto-vaginal septum support systems.

High rectocele = high swelling of the back vaginal wall. According to Mellgren, three types of rectocele can be distinguished: small, medium or large, depending on size 2, 2 to 4 cm and > 4 cm (40). The most common symptoms are incomplete and difficult evacuation, anorectal weight or anorectal pain that may radiate to the sacrococcygeal area. Tenesmus and soiling often associated with mucoemorrhoid prolapse. The patient performs perineum typing for evacuation and lifting maneuvers in 20-75% of cases. Vaginal entrance due to excessive laxity may be painful due to the presence of micro-abrasions and bleeding.

Cystocele = drop of the base of the bladder beneath the pubo-coccygeal plane. Modest = 0-2 cm vertical descent, moderate 2 to 4 cm, extended > 4 cm.

Enterocoele = drop of intestinal limbs below the pubic coccyx line. Modest = 0-2 cm vertical descent, moderate from 2 to 4 cm, extended > 4 cm.

Peritoneum cele = descent of the peritoneum below the line of pubic coccyx.

Pelvic floor dyskinesia (but after physiotherapy of the pelvis).

The main interventions to correct these anomalies can be distinguished in interventions with a transanal or perineal approach and interventions with an abdominal approach.

Transanal or perineal approaches are:

Delorme technique (mucosectomy)

Altemeier (rectum sigmoidectomy)

Thiersch procedure (provides a physical barrier by anal encircling)

STARR with double circular suturing machine

Trans SATRR with Contour suture machine

Mucosal plication (Gant-Miwa procedure) with anal encircling for rectal prolapse

Abdominal approaches (laparotomy / laparoscopic / robotic) are:

Laparoscopic Posterior Rectopexy (Wells) for Full-Thickness Rectal Prolapse

Anterior rectopexy: Orr-Loygue Rectopexy

Transabdominal posterior rectopexy with resection of the redundant left colon (Frykman-Goldberg operation)

Ventral rectopexy.

Neuromodulation treatment

Patients are placed in a lead to perform a sacral neuromodulation treatment test. This procedure is performed in general anesthesia with antibiotic prophylaxis and is performed by an experienced surgeon. A radiograph is used to determine the position of S3 and to place a needle in the foramen.

The electrode is connected to the external stimulator and a trial period of 3-5 weeks is performed to evaluate the benefit of the treatment and decide on the permanent stimulator system. To qualify for a permanent device, the frequency of defecation must be reset at a frequency of at least three times a week.

The permanent stimulator is implanted in local anesthesia and placed in a subcutaneous gluteal pocket under antibiotic prophylaxis. Initial pacing settings are standard and initially, a pulse width of 210 μ s (microseconds) and a frequency of 16 Hz are used. In the case of unpleasant feel or suboptimal treatment, the settings can be changed from 120 to 330 μ s, respectively 10 to 21 Hz.

Neuromodulation is altering function of an organ by altering neural activity. The neuromodulation, used to treat constipation, includes direct stimulation of sacral nerves and stimulation across the skin. Direct stimulation of sacral nerves is the most well developed method. It is generally accepted that the mechanism of action is modulation rather than stimulation so it is called sacral neuromodulation (SNM). SNM involves percutaneous placement of an electrode in the third sacral foramen and implanting a stimulating device under the skin in the buttocks.

SNM is founded on the physiological principle that activity in one neural pathway modulates pre-existing activity in another through synaptic interaction. The mechanism of action in constipation may be neuromodulation of the extrinsic neural control of the large bowel or modulation of reflexes inhibiting large bowel function. Limited evidence is available to assess the outcome of SNM in constipation.

Results in the medium term seem promising for selected patients with idiopathic slow and normal transit constipation not responding to optimal conservative treatment. Adverse events include electrode migration and infection. The availability of a testing phase provides a predictor of treatment outcome. In addition, transcutaneous stimulation using sticky pad electrodes over the lumbosacral region or acupuncture points has been reported to improve constipation symptoms. In general, the level of evidence is low and further studies are needed (41).

Surgery in low transit constipation (inertia coli).

Surgical treatment of chronic functional constipation slow transit type should be considered

only in the most severe cases of slow-colonic-transit constipation for those patients who do not respond to aggressive medical therapy.

Prior to surgery, patients should be carefully evaluated for existence of other gastrointestinal conditions and symptoms, particularly abdominal pain and irritable bowel syndrome.

It is crucial to inform the patient that the surgical procedure is aimed to ease constipation but is not likely to alleviate other gastrointestinal symptoms.

A detailed work-up should include: (1) exclusion of known causes of constipation, such as medications (eg, opiates and anticholinergics); low-fiber diet; mechanical obstruction (eg, colon cancer or stricture); metabolic disorders (eg, hypothyroidism, hypercalcemia); psychological disorders (severe depression); and others; (2) confirming the diagnosis of severe functional colonic inertia (slow transit)-type constipation by studying colonic transit time (eg, radiopaque marker studies); and (3) exclusion of other possible treatable conditions, such as disturbed defecation, as assessed by anorectalmanometry (eg, for Hirschsprung's disease and other pelvic floor dysfunctions) and defecation studies (eg, for rectocele and rectal prolapse); and chronic intestinal pseudo-obstruction, as assessed by radiologic or manometric studies.

The recommended surgical procedure is subtotal colectomy with ileorectal anastomosis. Partial colectomy has not been found to be helpful and should therefore not be considered. A comprehensive review of 13 reported studies of 362 patients who underwent colectomy and who were followed for 1.2-8.9 years reported a success rate of 88% (42). A recent prospective long-term (mean follow-up of 56 months) study of 52 patients who were carefully evaluated and underwent surgery for slow-transit constipation showed that over 90% of patients were satisfied with the results of surgery, and reported a good or improved quality of life (43). Postoperative complications may include small-bowel obstruction, prolonged ileus, abdominal pain, and diarrhea.

More recently, *antegrade continent enema* has been suggested as an alternative approach in patients who are unable or unwilling to undergo colectomy. Conduits can be created from the appendix, cecum, or ileum. A recent retrospective study of 32 patients who underwent this procedure, with a median of 36 months' (range, 13-140 months) follow-up, reported satisfactory long-term results in approximately half of the patients, although revision procedures were often required (44). However, the procedure is reversible and does not

preclude subsequent surgical intervention.

CONCLUSIONS.

In conclusion, in this review, the author traces the steps that have led to a correct definition and classification of functional chronic constipation, recalling the main diagnostic investigations. In particular, he emphasizes, recalling the criteria of Rome IV, on the distinction between functional chronic constipation and irritable bowel syndrome with a constipation component.

Consequently, the many therapeutic possibilities are mentioned, ranging from non-pharmacological, which emphasizes life habits and the type of nutrition, to all the laxative medicines on the market. Particular emphasis the author puts on the indications of the latest high performing pharmaceuticals. He also mentions the possibilities of a surgical approach, which should be carefully evaluated and framed in a multi-disciplinary management.

Conflict of interest

Declare no financial interest and no conflict of interest exists.

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