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Pseudo-obstruction, enteric dysmotility and irritable bowel syndrome

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ABSTRACT

New diagnostic techniques have advanced our knowledge about the irritable bowel syndrome. The majority of patients that we believed to have a psychosomatic disorder have received other diagnoses explaining their symptoms. Endoscopy makes it possible to diagnose celiac disease before it leads to malnutrition and allows the detection of microscopic colitis as a cause of watery diarrhea. At the severe end of the symptom spectrum enteric dysmotility marks the border at which IBS ceases to be a functional disorder and becomes a genuine motility disorder. Joint hypermobility or Ehlers-Danlos syndrome is present in a substantial proportion of patients with enteric dysmotility. Chronic intestinal pseudo-obstruction is the end-stage of a large number of very rare disorders in which failed peristalsis is the common denominator. Nutritional needs and symptom control are essential in the management of pseudo-obstruction. Home parenteral nutrition is life saving in more than half of patients with chronic intestinal pseudo-obstruction.

The irritable bowel syndrome (IBS) is defined by the presence of recurrent abdominal pain associated with defecation or a change in bowel habits [1]. Symptoms should have duration of at least 6 months and there should be no organic cause for symptoms. During the latest 40 years a number of distinct diseases have been identified among those believed to suffer from IBS. These include coeliac disease, lactose malabsorption, microscopic colitis, bile acid diarrhea, and exocrine pancreatic insufficiency. In recent years, genetic aberrations leading to disturbed function of ion channels or enzymes for carbohydrate digestion were identified in subgroups of patients with IBS-like symptoms [2,3]. Still, there remain a fair number of people in whom no explanation for their symptoms has yet been found. Cross-sectional population studies have estimated that 6.2–12.5% of European populations may suffer from symptoms compatible with the diagnosis of IBS [4,5]. However, studies using diagnosis registers in primary care found that only 1.2% of patients seeking medical advice from general practitioners in Sweden received a diagnosis of IBS [6]. The discrepancy between surveys and actual diagnoses makes it difficult to understand where does IBS as a disease begin and where does natural variation of gut perceptions end.

At the other end of the spectrum of symptom severity is chronic intestinal pseudo-obstruction (CIP). In pseudo-obstruction the propulsive forces of intestinal peristalsis has lost their ability to overcome the natural resistances to flow [7] and this leads to a clinical picture resembling mechanical obstruction of the bowel. The diagnosis rests upon symptoms and radiological findings. Recurrent sub-occlusive events are the most common clinical presentation and the radiological finding of episodic or persistent intestinal dilatation defines pseudo-obstruction, when mechanical causes have been carefully excluded. CIP is not a singular disease but the end-stage of a large number of rare neuromuscular disorders of the gut. The majority of these have genetic causes. In adults, pseudo-obstruction secondary to connective tissue diseases like scleroderma and polymyositis, neurological diseases such as Parkinson and autonomic dysfunction, and paraneoplastic or autoimmune pseudo-obstruction are more prevalent than primary neuromuscular disorders.

It had long been recognized that there was an empty space in diagnostic classifications between on one hand the functional gastrointestinal disorders and on the other the end-stage of motor dysfunction. In an attempt to fill this gap an international working group at the 2002 World Congresses of Gastroenterology in Bangkok suggested a new diagnostic entity ‘enteric dysmotility’ to account for patients with symptoms and objective signs of dysmotility but no dilatation of the intestines [8]. Objective dysmotility meant abnormal contractile activity on small bowel manometry or delayed small bowel transit. Clinical features, small bowel manometry findings and histopathology from full thickness

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jejunum biopsies were described from one Swedish center [9,10]. Similarly, enteric dysmotility was found in 105/145 patients with severe gastrointestinal symptoms and a negative work-up for organic disease in a case series from an Italian center [11]. Enteric dysmotility was somewhat more prevalent (74.5%) among 110 patients who were malnourished than among those without malnutrition (65.7%).

Enteric dysmotility is one way of filling the gap between functional gastrointestinal disorders and intestinal pseudo-obstruction. Fig. 1 depicts the relation between diagnostic entities. Similar to gastroparesis, the diagnosis of enteric dysmotility is based on physiological measurements. Gastroparesis is defined by an abnormal gastric emptying test, whereas abnormal small bowel manometry or small bowel transit defines enteric dysmotility. The gap between diagnostic entities can possibly be filled by other means of classification such as underlying pathology or pathogenesis but as will be detailed later there is considerable heterogeneity in all of the above entities and for the moment no other candidate classification has been put forward.

Irritable bowel syndrome

History has taught us that IBS is a heterogeneous concept. The language of the gastrointestinal tract is poor and a lot of diseases can lead to similar symptoms like diarrhoea or constipation and abdominal pain. It is no surprise that a large proportion of those believed to suffer from IBS in the early 1980's were later found to have other diseases. There is also no reason to believe that what we know today about IBS is all there is to know. It is far more likely that future research will uncover yet undefined mechanisms leading to IBS-like symptoms, thus further narrowing the scope of the term IBS. However, a substantial proportion of the population will likely continue to have symptoms that fulfil the Rome Criteria for IBS [1] and about 10% of them will continue to seek medical help for their problems [12].

Diagnosis

IBS is diagnosed on the basis of symptom criteria and currently we use the Rome-IV set of criteria [1]. It is reasonable to exclude other causes for similar symptoms and to search for alarm symptoms. The latters include signs or symptoms from gastrointestinal bleeding (anemia, blood in stools or vomits, and melena), dysphagia, and weight loss. A change in bowel habits after the age of 50 is also considered an alarm symptom and an onset of IBS after the age of 50 is by definition consistent with such an alarm symptom. Patients with alarm symptoms need to be further investigated. If the family history includes colorectal cancer, inflammatory bowel disease, or celiac disease, this should be taken into account when deciding on further investigations.

A basic investigation including full blood count and differential count, C-reactive protein, serum albumin, thyroid function tests, and tissue transglutaminase antibody level should be done in all patients considered for the diagnosis of IBS. In those who have diarrhea further tests may include lactose tolerance test or genetic testing for lactase persistence, stool examination for ovas and parasites, and fecal calprotectin. Bile acid diarrhea should be screened for using the serum level of 7-OH-kolestenon or measurement of bile acids in feces. Microscopic colitis may need to be excluded using colonoscopy with biopsies and exocrine pancreatic insufficiency can be screened for using fecal elastase.

Management

Management options in IBS have been reviewed in detail elsewhere [13–15]. Pharmacological treatment is usually symptom-directed but some treatments aim for presumed mechanisms of disease. The latter is true for antidepressants, which are believed to address the brain-gut-axis both at the central and the peripheral level. Apart from pharmacological treatment, the management of IBS includes general lifestyle measures (exercise, pedagogical treatments), diet modifications, and psychological treatment.

General lifestyle measures

Physical exercise like walking, cycling, swimming, or jogging for 20–60 min 3–5 days a week during 12 weeks was shown to improve symptoms in a randomized controlled trial from Sweden [16]. Interestingly, a follow-up after 5.2 years indicated that physical exercise can have a long-term effect both on symptom severity and psychological parameters in IBS [17].

Many patients with IBS feel insufficiently informed about their disease, particularly in relation to risk of serious disease and role of

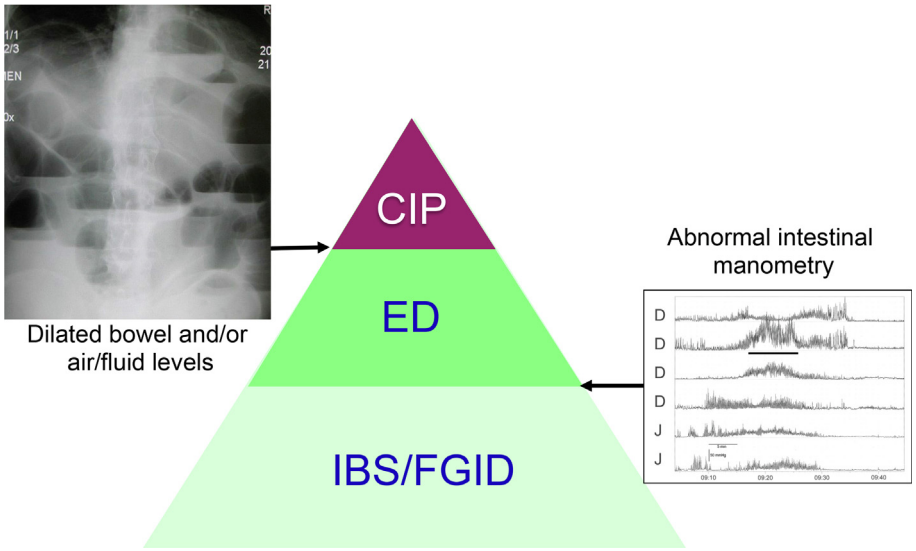

Fig. 1. Classification of small bowel motility disorders. IBS = irritable bowel syndrome; FGID = functional gastrointestinal disorder; ED = Enteric dysmotility; CIP = Chronic intestinal pseudo-obstruction. Link to source for X-ray picture: "https://commons.wikimedia.org/wiki/File:Upright_X-ray_demonstrating_small_bowel_obstruction.jpg".

diet [18]. There seems to be a gap in the communication between patients and gastroenterologists and many patients do not acknowledge their diagnosis of a functional gastrointestinal disorder [19]. Various forms of patient education have therefore been tried [20,21]. Structured patient education in the format of an IBS-school was shown to better reduce symptom severity and gastrointestinal-specific anxiety compared to self-education using an IBS guidebook in a randomized controlled study [22].

Diet modifications

There is almost always a relation between food intake and symptom worsening in patients with IBS. There are several possible mechanisms, including accentuated motor or sensory responses of the gut to food ingestion, alterations of the gut microbiome, and immune activation by dietary antigens. Elimination diet based on IgG antibody titers was found to improve symptoms with a number needed to treat (NNT) of 9 [23]. However, a population study from Norway found no difference in the levels of IgG and IgG4 antibodies to food items between IBS and non-IBS controls [24]. It was suggested that IgG antibodies against food might reflect the diet.

A different mode of diet modification is to reduce the intake of fermentable oligo-, di-, and monosaccharides, and polyols (FODMAP). Researchers from Australia suggested a low FODMAP diet for alleviating symptoms in patients with IBS [25]. A recent meta-analysis of nine randomized trials found a significant short-term benefit of a low FODMAP diet for overall gastrointestinal symptoms, abdominal pain, and quality of life in patients with IBS [26]. The effect was more pronounced in patients with IBS-D. No conclusion could be drawn regarding the long-term effect of a low FODMAP diet.

A large study of increasing the dietary content of soluble fiber (psyllium) or insoluble fiber (bran) in patients with IBS showed that psyllium was superior to placebo (NNT = 4) and bran for symptom severity and that bran was no better than placebo [27]. Similarly, a systematic review and meta-analysis of 14 randomized controlled trials, mostly though of low quality, found that psyllium but not bran had a beneficial effect on symptoms in patients with IBS (NNT = 7) [28].

Psychological treatment

Cognitive behavioral therapy, relaxation therapies, multi-component psychological therapy, hypnotherapy, mindfulness meditation training, dynamic psychotherapy, and stress management have been studied in comparison with control therapy (usual care, symptom monitoring, or supportive therapy) in IBS and were included in a recent systematic review and meta-analysis [29]. The evidence base was greater for four of the therapies: cognitive behavioral therapy improved IBS symptoms in 58.5% compared to 36.4% following control therapy and NNT with cognitive behavioral therapy was 4; relaxation training or therapy led to improvement of IBS symptoms in 31.9% compared to 16.0% in those receiving control therapy (NNT = 6); multi-component psychological therapy improved IBS symptoms in 42.9% compared to 19.2% among controls (NNT = 4); and hypnotherapy improved symptoms in 45.6% compared to 22.6% (NNT = 5).

Pharmacological treatment

The main symptoms in IBS are abdominal pain, diarrhea, constipation, and abdominal distension. Symptom-directed treatment is the most common approach in absence of a common disease mechanism.

Abdominal pain. Tricyclic antidepressants (TCA) were shown in a meta-analysis to be superior to placebo for improvement of abdominal pain in IBS with NNT = 4.5 for TCA [29].

Spasmolytic agents that have been investigated for the treatment of IBS include dicyclomine, trimebutine, otilonium, pinaverum bromide, scopolamine, and peppermint oil. The best evidence for a beneficial effect on pain comes from studies of pinaverum bromide and trimebutine [30].

Diarrhea. Loperamide is widely available at low cost as a treatment for diarrhea in general. However, the evidence for its usefulness in IBS with diarrhea is lacking. Eluxadoline is a new drug that is a mu-opioid receptor agonist and a delta-opioid receptor antagonist. In a meta-analysis of two studies comparing different doses of eluxadoline against placebo NNT = 8 for adequate relief of symptoms after 26 weeks of treatment [31]. Eluxadoline is currently not available in Europe.

Alosetron and cilansetron are serotonin-5-HT_3-receptor antagonists that were developed for treatment of IBS with diarrhea in the United States. They were shown to be beneficial with NNT = 4 for global improvement of symptoms in patients with non-constipated IBS [32] but the use of alosetron became restricted and the development of cilansetron was stopped due to concerns about ischemic colitis [33].

Bile acid sequestrants have received a lot more attention in recent years as it has been found that bile acids contribute to diarrhea in 28% of patients with IBS and diarrhea [34]. However, the efficacy of bile acid sequestrants in IBS is yet unknown. No randomized controlled study of bile acid sequestrants in IBS has yet been performed. Studies are limited to open-label studies of colestipol 1 g twice a day for 8 weeks [35] and colesevalam 1875 mg twice a day for 10 days [36]. Both studies indicated that bile acid sequestration leads to improvement of diarrhea.

Luminal antibiotics for IBS with diarrhea were initially put forward as a remedy for presumed small intestinal bacterial overgrowth (SIBO) [37]. The diagnosis of SIBO was based on lactulose hydrogen breath testing. Later studies could not confirm then validity of the lactulose breath test for detecting SIBO [38,39]. This didn't prevent further studies and a meta-analysis of 5 studies showed that rifaximin had a beneficial effect for patients with non-constipated IBS with NNT = 9 [40].

Constipation. IBS-C and chronic constipation are now viewed as a continuum rather than separate diagnoses [1]. Soluble fiber [41] and macrogol [42], which are well established in the treatment of chronic constipation, have been shown to improve constipation also in patients with IBS-C.

Serotonin-5-HT_4-receptor agonists are prokinetic drugs that have been developed for chronic constipation and IBS-C. Tegaserod was shown to be an effective treatment for IBS-C both in terms of overall symptoms (NNT = 6–11) and individual symptoms including abdominal pain, bloating, and constipation [43]. In 2007 tegaserod was withdrawn from most markets following concerns about its cardiovascular safety. Prucalopride was developed for chronic constipation where it was shown to effectively increase complete spontaneous bowel motions (NNT = 7) [44] but studies in patients with IBS-C were not done.

A new principle for the treatment of IBS-C is to increase intestinal secretion. Lubiprostone is a prostaglandin E_1 derivative that activates intestinal type 2 chloride channels. Linaclotide and plecanatide are peptides that increase secretion by stimulating guanylate-cyclase-C receptors on the enterocytes. Tenapanor is a small molecule that inhibits the gastrointestinal sodium-hydrogen exchanger NHE3. All these drugs have been shown in large randomized controlled trials to be superior to placebo for the treatment of IBS-C. A network meta-analysis indicated that linaclotide 290 μg once daily was ranked first in efficacy for abdominal pain and complete spontaneous bowel motions, whereas tenapanor

50 mg twice daily was ranked first for decreasing bloating [45]. Only linaclotide is currently available in Europe, whereas in the United States lubiprostone, linaclotide, and plecanatide have been approved for the treatment of IBS-C.

Abdominal distension. Abdominal distension and bloating occurs in patients with IBS-C but also in those with functional dyspepsia, functional constipation, and functional abdominal bloating. Bloating or distension have been studied as secondary endpoints or as part of a composite symptom score. Thus, tegaserod and lubiprostone were shown to improve bloating in patients with IBS-C, whereas rifaximin and some probiotics such as Bifidobacterium infantis 35624 and B. animalis significantly improved bloating in patients with non-constipating IBS, IBS in general, and IBS-C, respectively [46]. As mentioned above, the NHE3-inhibitor tenapanor may reduce bloating and in the only study yet published as a full article the abdominal bloating responder rate was 59.5% among those taking tenapanor 50 mg twice daily compared to a responder rate of 41.6% in the placebo group (NNT = 6) [47].

Enteric dysmotility

A case series from Sweden described clinical features, long-term prognosis and small bowel manometry findings in 70 adult patients with enteric dysmotility [9]. The median time from onset of symptoms to diagnosis was 4.7 years. Abdominal pain was the most common (96%) symptom, followed by abdominal distension (77%), nausea (50%), constipation (46%) and diarrhea (44%). More than half of the patients (54%) had suffered a significant (>10%) weight loss. The main indication for ordering small bowel manometry was that patients had particularly severe symptoms. In a separate paper the same group reported findings from histopathological examination of full thickness bowel biopsies in 65 patients with enteric dysmotility [10]. The most common finding was lymphocytic ganglionitis (74%); two patients had this finding in combination with alpha-actin deficiency and one patient in combination with leiomyositis. Degenerative neuropathy was found in 13 patients (20%); two of these had coexisting alpha-actin deficienty and three patients also had degenerative myopathy. One patient had intestinal neuronal dysplasia and three patients had degenerative myopathy. Thus, there is considerable variation of the underlying pathology in patients with enteric dysmotility.

At follow-up in 2015 a total of 125 patients had been diagnosed with enteric dysmotility at the same unit in Karolinska University Hospital. At that time it became possible to group the patients according to various co-morbidities (Fig. 2). The largest subgroup comprised 42% of patients that had idiopathic enteric dysmotility, i.e. enteric dysmotility without a reasonable explanation. The diagnosis of enteric dysmotility rests heavily upon findings in small bowel manometry and there are some important caveats with this definition. Several drugs, but most importantly opioids (and their metabolites) and anticholinergic drugs, can severely affect small bowel motor activity. It is somewhat contra-productive to misinterpret opioid-induced dysmotility as enteric dysmotility, since the latter diagnosis can lead the caring physician to believe that their patient has a severe motility disorder. In our series we were able to document 26 cases of opioid-induced dysmotility masquerading as enteric dysmotility.

It is no surprise that patients with slow transit constipation constitute an important subgroup among those with enteric dysmotility. Many of the underlying pathologies leading to slow transit constipation are generalized gastrointestinal neuromuscular diseases and the presence of enteric dysmotility may indicate a higher risk for an unsatisfactory outcome of colectomy [48].

Another important subgroup with enteric dysmotility is patients with joint hypermobility syndrome or Ehlers-Danlos syndrome. Joint hypermobility was reported from England as a risk factor for severe functional gastrointestinal disorders [49]. Experiences from the Mayo Clinic indicated that patients with Ehlers-Danlos syndrome often exhibited abnormal gastrointestinal physiology including abnormal esophageal motility, gastric emptying, colon transit, and ano-rectal function [50]. Our findings indicate that patients with joint hypermobility or Ehlers-Danlos syndrome may also have enteric dysmotility.

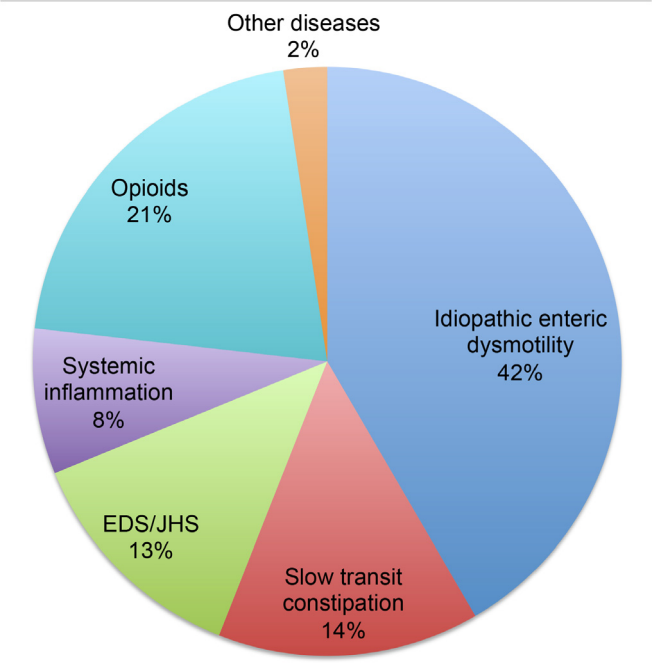

Fig. 2. Causes of enteric dysmotility in a case series of 125 patients from Sweden. JHS = joint hypermobility syndrome; EDS = Ehlers-Danlos syndrome.

Systemic inflammatory disease like systemic sclerosis, mixed connective tissue disease, SLE, and Sjögren's syndrome may also exhibit enteric dysmotility, some of them before they progress to pseudo-obstruction. A few other diseases with a causal relation to enteric dysmotility were myotonic dystrophy and mitochondrial disorders.

Diagnosis

Small bowel manometry is the preferred method for diagnosing enteric dysmotility and both stationary water-perfused manometry over 5 or 8 h [9,11] and ambulatory 24-h recordings [9] have identified patients with enteric dysmotility. The availability of small bowel manometry is limited to highly specialized units and there is an unmet need for more accessible methods for diagnosing enteric dysmotility. Transit studies showing delayed transit using contrast radiography or radio-opaque markers [51,52] have been used in more severe cases of dysmotility and recently the wireless motility capsule was shown to identify general dysmotility in patients with diabetes mellitus [53].

Management

No controlled studies have been performed to assess the usefulness of pharmacological agents in patients with enteric

dysmotility. This means that all attempts to treat symptoms as well as motor dysfunction in these patients are experimental. Many of the drugs used for treatment of symptoms in IBS can probably be tried also in enteric dysmotility. However, since patients with enteric dysmotility do have a motility disorder, drugs that enhance peristalsis may have a greater potential in enteric dysmotility. Impaired peristalsis has long been suggested as a risk factor for developing SIBO [54] but solid data supporting such a suggestion has been difficult to attain not least because SIBO lacks at firm definition [55].

Removing the offending drug is the best treatment in opioid-induced enteric dysmotility and if patients have developed narcotic bowel syndrome graded withdrawal of opioids is strongly recommended [56]. The role of peripherally acting μ-opioid receptor antagonists like methylnaltrexone, naloxegol, and naldemedine is well established in the treatment of opioid-induced constipation [57]. It is yet unclear to what extent such drugs influence enteric dysmotility.

Prucalopride is a prokinetic drug that facilitates colon transit by inducing high-amplitude propagated contractions [58]. It is less clear how prucalopride enhances motility in the small bowel but experiments in patients undergoing capsule enteroscopy clearly show that prucalopride shortens the time it takes for the capsule to pass through the small bowel [59]. Other prokinetics that may have a place in the treatment of enteric dysmotility are octreotide and erythromycin. Octreotide was first described for treatment of SIBO in patients with intestinal pseudo-obstruction secondary to scleroderma [60]. Octreotide induces propagated activity complexes similar to phase-III of the migrating motor complex in the small intestine. When administered as a subcutaneous injection of 50 μg at bedtime, octreotide is believed to enhance the ability of fasting motor activity to keep the small bowel free of debris and bacteria. Erythromycin is a motilin agonist that induces phase-III activity in the stomach that is propagated into the small bowel [61]. Initial studies in patients with enteric dysmotility indicate that azithromycin is superior to erythromycin as a small bowel prokinetic [62].

Antibiotics may have a role in the management of enteric dysmotility but there is yet no evidence for this.

Chronic intestinal pseudo-obstruction

CIP is the end-stage of a large number of mostly very rare diseases. In children CIP usually results from genetic aberrations but in adults secondary forms of pseudo-obstruction are more common. Onset of CIP in older children and young adults is more likely to result from mitochondrial disorders. It is difficult to ascertain the true prevalence and incidence of CIP. A nationwide survey in Japan estimated the prevalence of CIP in children to be 3.7 per 10^6 children [63]. In adults, the prevalence of CIP in another Japanese survey was 0.9 per 10^5 inhabitants and the incidence in the same population was 0.23 per 10^5 inhabitants [64].

Familial forms of CIP have repeatedly been described in the literature. However, only a few genetically defined causes for pseudo-obstruction have been identified so far. Mutations in SOX10 [65] and ACTG2 [66] have been shown to cause autosomal dominant forms of neuropathic and myopathic CIP, respectively. Autosomal recessive forms of CIP have been reported for mutations in RAD21 [67], SGOL1 [68], TYMP [69], and POLG [70]; the latter two causing MNGIE (mitochondrial neurogastrointestinal encephalomyopathy) and multiple mitochondrial DNA deletions. Two genes on the X chromosome, L1CAM [71] and FLNA [72] have been identified to harbor mutations leading to X-linked CIP. In addition, CIP may occur in patients with primary mitochondrial disorders such as MELAS (mitochondrial myopathy, epilepsy, lactic acidosis, and stroke-like episodes) [73] and MERRF (myoclonus epilepsy associated with ragged-red fibers) [74].

Secondary forms of CIP dominate among adults and a large number of diseases can lead to CIP [7]. The most common association is scleroderma or systemic sclerosis [75], but CIP can occur also in systemic lupus erythematosus [76] and other systemic inflammatory diseases. In Brazil the chronic phase of Chagas' disease leads to megaesophagus and megacolon, but less commonly to dilatation of the small intestine [77]. Other reasonably common secondary forms of CIP are paraneoplastic CIP [78] and CIP in myotonic dystrophy [79].

Drug-induced pseudo-obstruction has been described as a rare side effect of cytotoxic drugs like oxaliplatin [80] and vincristine [81]. Far more common is opioid-induced dysmotility. Patients who have developed narcotic bowel syndrome [56] can easily be mistaken for pseudo-obstruction but opioids as a cause of CIP has rarely been reported [82].

A proportion of adults with CIP have no associated disease explaining their pseudo-obstruction and these are referred to as chronic idiopathic intestinal pseudo-obstruction. Little is known about causality in these cases but certain DNA-viruses including Herpes virus and JC virus have been implicated in some cases [83].

Diagnosis

The diagnosis of CIP rests upon clinical findings. Usually there is a history of sub-occlusive events and radiological findings of dilated bowel with air/fluid levels. Findings mimic those seen in mechanical obstruction and in order to confirm the diagnosis of pseudo-obstruction a mechanical cause has to be ruled out. Small bowel manometry can lend support to the diagnosis by confirming the presence of abnormal motor activity, but as discussed above, abnormal motor activity is also seen in enteric dysmotility. Analysis of full thickness bowel biopsies can help identifying the underlying pathology [84] and determine the significance of observed pathologies [85]. An important caveat regarding histopathology is that findings from the analysis of a full thickness bowel biopsy are insufficient for diagnosing CIP. Abnormal histopathology can be found in many less severe cases with abdominal symptoms [10], even in the irritable bowel syndrome [86].

The workup in adults must consider the spectrum of diseases that can lead to secondary CIP. Connective tissue diseases should be screened for using antinuclear antibody and antibodies to double-stranded DNA and SCL-70 and muscle diseases using creatine phosphokinase and aldolase [87]. Diabetes mellitus, celiac disease, and hypothyroidism need to be ruled out. Whenever appropriate neurotropic viruses like Cytomegalovirus and Epstein-Barr virus and serology for Chagas' disease should be investigated. Urinary catecholamines and porphyrins serve to identify patients with pheochromocytoma and porphyria, respectively. Type 1 antinuclear neuronal antibodies (Anti-Hu) are typical for paraneoplastic CIP but can rarely indicate autoimmune CIP, without underlying malignancy.

Management

Two problems dominate the management needs of patients with CIP: nutrition and symptom control. CIP is a common cause of intestinal failure [88,89] and parenteral nutrition is life-saving in more than half of adult patients with CIP [9]. Long-term results of home parenteral nutrition are good with 68% surviving at least 15 years when monitored from a highly specialized center [88]. Isolated small bowel or multi-visceral transplantation is an option in children when they fail on parenteral nutrition [90]. In adults, failure on parenteral nutrition is less common but loss of venous

access, life-threatening complications of parenteral nutrition, and disease-related poor quality of life despite optimal parenteral nutrition can be considered as indications for transplantation [91]. Other surgical procedures that can help patients with CIP are venting enterostomy and resection or by-pass in the case of localized disease [92]. In those that can tolerate oral feeding low residue, low fiber, and low fat, small but frequent meals can help maintaining nutritional needs [93]. Liquid meals are often better tolerated than solid food and the latter needs to be soft and easily digestible. Enteral feeding is useful in some patients with CIP and should be tried using nasojejunal tube feeding before embarking on long-term home parenteral nutrition. A gastro-jejunal feeding tube placed through a gastric stoma using endoscopy and fluoroscopy (PEG-J) can be used both for decompression and enteral nutrition [94].

Symptom control is difficult, in particular since abdominal pain is a common symptom in CIP. The use of opioids is hazardous because opioids worsen the already impaired motor activity of the gut. It is yet unclear if the addition of a peripherally acting μ-opioid receptor antagonist would benefit patients who cannot do without opioids. Gabapentinoids, like gabapentin and pregabalin, and tricyclic antidepressants can be tried for amelioration of pain in CIP. There is a reasonable theoretical basis for these drugs in patients with neuropathic CIP but firm evidence is yet lacking.

The most common complication of CIP is SIBO and antibiotics represent a mainstay in the management of CIP. Ideally, less absorbable antibiotics like neomycin and rifaximin should be used but empirical therapy has included many antibiotics like amoxicillin with clavulanic acid, metronidazole, tetracycline, doxycycline, and ciprofloxacin [95]. In my experience, SIBO is also the most common cause of exacerbations of CIP with subocclusive events. Cyclic treatment with antibiotics every fourth week can possibly prevent such exacerbations.

Treatment aimed at improving peristalsis might benefit both nutrition and symptoms. Octreotide is a somatostatin analog that induces activity complexes similar to phase-III of the migrating motor complex in the small bowel. Subcutaneous injections with 50 μg octreotide in the evening reduced breath hydrogen excretion and symptoms indicating a beneficial effect on SIBO [60]. No controlled study has been done in other types of CIP but whenever SIBO is a problem in a patient with CIP it is reasonable to perform a therapeutic trial with octreotide. Erythromycin is a macrolide antibiotic that acts as an agonist on motilin receptors, thus inducing activity complexes in the stomach. Erythromycin showed efficacy at a dose of 1.5–2 g/day (i.e. antibacterial doses) in 6/15 adults with CIP [96].

Neostigmine, an acetylcholinesterase inhibitor is a safe and effective option at doses ranging 2–5 mg intravenously for 3–30 min in patients with acute colonic pseudo-obstruction [97]. Pyridostigmine is an oral acetylcholinesterase inhibitor that has been used with some success at doses starting from 20 mg/day in patients with CIP [98].

Prucalopride is a selective serotonin-5-HT_4-agonist that has been developed for the treatment of chronic constipation [44]. In a randomized n = 1 trial, prucalopride showed beneficial effects on abdominal pain, bloating, and need for analgesics in patients with CIP [99].

Summary

The three concepts of IBS, enteric dysmotility, and CIP all exhibit significant diversity and none of the diagnoses can be viewed as a singular entity. CIP is merely the end-stage of many very rare disorders leading to inability of peristalsis to overcome the natural resistances to flow. In adults many of the patients with CIP suffer the complications to a systemic disease. Treatment of the underlying disease can be helpful in some patients but for many damage to muscles and nerves has become irreversible and the only thing left is to manage their intestinal failure. At the other end the irritable bowel syndrome has been shown to be an umbrella term for many different diseases causing similar symptoms. Development will not stop here. The future is likely to reveal yet unknown causes for IBS-like symptoms that perhaps can be amenable to treatments already available or in the pipeline. Enteric dysmotility represents one way of bridging the gap between CIP and IBS. It looks as if enteric dysmotility is yet another umbrella term for several different diseases whose common denominator is abnormal small bowel motor activity. Treatment aimed at restoring motility is an unmet need both for patients with enteric dysmotility and those with CIP. Symptom improvement, in particular abdominal pain, is difficult in all of the above groups. Better understanding of mechanisms behind symptoms may lead to improved means for treatment. As for now, we do not know enough about motility disorders and it is yet difficult to form a hypothesis about the best way to move forward.

Practice points

- IBS is a multifactorial disease. Future research will likely clarify further subgroups that can be treated for the underlying cause of symptoms.
- Enteric dysmotility is a physiologically defined diagnosis. Treatment aimed at enhancing peristalsis can help the intestines to clear debris and bacteria.
- CIP is a severe motility disorder that often necessitates long-term parenteral nutrition. Highly specialized units are needed for evaluation of patients and monitoring of treatment.

Research agenda

- The role of microbiota in IBS needs to be further explored. The interactions between the immune system in the gut, microbiota and food components need better understanding and so do the mechanisms of gut permeability.
- Therapeutic trials are needed in subgroups with enteric dysmotility in order to clarify the relative importance of microbiota and the migrating motor complex and its “housekeeping” function.
- Multinational protocols are needed to advance our knowledge about treatment effects in CIP. The diagnosis is too rare and too multifaceted to attract the interest of pharmaceutical industry.

Conflicts of interest

None.

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