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Current insights on chronic intestinal dysmotility: pseudo-obstruction and enteric dysmotility

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Abstract:

Chronic intestinal dysmotility is a rare and debilitating digestive disorder characterized by symptoms of mechanical obstruction without an organic lesion. It has diverse causes and involves various pathological mechanisms. Small bowel manometry is the preferred diagnostic method, particularly for patients with severe and progressive symptoms. The condition can be categorized as intestinal pseudo-obstruction and enteric dysmotility, both entities share abnormal small bowel motility, but with important differences in prognosis and management.

The small bowel is a crucial component of the digestive system that carries out most of the digestion of ingested food. Indeed, the small bowel is the only organ of the gastrointestinal tract that human beings cannot live without. The main functions of small bowel are the efficient absorption of nutrients and the maintenance of aboral

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movement of indigestible waste products. Normal small bowel motility is critical to achieve both of these important goals (1).

Clinical features and etiologies

Small bowel motility disorders are characterized by the failure of the gut to propel the luminal contents (2). Clinically, patients with chronic intestinal dysmotility present with symptoms and signs suggestive of intestinal obstruction: abdominal pain, abdominal distension and nausea with or without vomiting. During acute episodes, radiological evidence of distended bowel loops and air-fluid levels in the upright position may be seen. Acute episodes can last from a few hours to days. Between these crises, patients generally complain of severe, non-specific digestive symptoms. Constipation is usually the predominant bowel habit, but diarrhea and even steatorrhea can occur because of small bowel bacterial overgrowth (SIBO). Food ingestion often exacerbates digestive symptoms, and consequently patients tend to reduce normal oral nutrition and lose weight (3).

Chronic intestinal dysmotility may be caused by many heterogeneous conditions, primary or secondary, and can be congenital, idiopathic or acquired (Table 1) (4). Since small bowel motor activity is controlled by neuromuscular mechanisms, dysmotility can be caused by derangements of the extrinsic or intrinsic nerve pathways, the enteric plexus or the smooth muscle (5,6) (Table 1). Furthermore, more than one component can be affected at the same time in any given patient.

In the adult population, chronic intestinal dysmotility is the second most common cause of chronic intestinal failure, after short bowel syndrome, and therefore an indication for parenteral nutrition or fluid support (1). It is also an important indication for small bowel transplantation in the western world (7). Regretfully, chronic intestinal dysmotility is diagnosed late. This delay in the diagnosis can be mostly attributed to one important reason: symptoms and signs of chronic intestinal dysmotility are non-specific and the typical initial work-up including laboratory, imaging, and endoscopic studies is often unsuccessful, therefore patients are frequently misdiagnosed with a disorder of gut-brain interaction like functional dyspepsia or irritable bowel syndrome (8) (Table 2). Late diagnosis of chronic intestinal dysmotility is associated with decreased quality of life, decreased nutritional status, increased healthcare

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consultation, repeated testing with negative results and unnecessary surgeries (9).

Diagnosis

The diagnosis of chronic intestinal dysmotility depends first on the exclusion of a mechanical obstruction or structural disease and second on the objective assessment of small bowel motor function by measurement of small bowel motility pressure patterns. Manometry studies measure the lumen-generated pressure inside any tubular organ and are useful to evaluate the strength, propagation, and coordination of muscle contractions, offering direct evaluation of the velocity, force, integrity and coordination of peristalsis and sphincter functions. Regretfully, manometric studies of small bowel motor function are not as commonly performed compared to manometric studies of the esophagus or the anorectum, mainly because only a few specialized centers offer the technique.

In manometry studies, the small bowel produces a series of coordinated contractions in various spatial and temporal patterns that are characteristic of fasting and fed states. During fasting, small bowel motor activity shows a repetitive cyclic motor pattern known as the migrating motor complex (MMC) . The MMC is composed of three distinctive phases; Phase I is characterized by motor quiescence and succeeds phase III, phase II is characterized by irregular contractile activity, both propagated and shortly propagated, which increases in activity over time and precedes phase III; Phase III is the most easily recognizable of the MMC, is characterized by repetitive contractions at the maximal rate (10-12/min) rapidly propagating aborally. After food ingestion, small bowel motor activity changes to a postprandial pattern, characterized by an increase in irregular contractile activity and absence of the MMC phases. Postprandial motility promotes efficient digestion by mixing and propelling the luminal content in an aboral direction (Figure 1)(10).

Abnormal small bowel motility patterns detected during fasting and the fed state are used to diagnose intestinal dysmotility. Due to the significance of the diagnosis, the criteria for abnormal intestinal motility in manometry studies are very strict (11). Two studies evaluated the diagnostic yield of small bowel manometry in the real-world setting in patients with suspected chronic intestinal dysmotility. Both concluded that small bowel manometry has a high negative predictive value, and that it is most useful

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ruling out intestinal dysmotility (12,13). Traditionally, abnormal small bowel motility patterns have been classified as neuropathic, myopathic and obstructive. Even though there is a poor correlation between manometric patterns and histology results, abnormal small bowel motility by manometry is associated with abnormal histology in full thickness biopsies(14). In a subset of patients, small bowel manometry will determine treatment choices and offer prognostic information. For example, small bowel manometry can be suggestive of a missed obstructive lesion and be useful to select patients for re-evaluation of organic diseases with more precise imaging or endoscopic tests(15). It can also be used to decide whether to perform a full-thickness biopsy to rule out inflammatory myoneuropathies in patients with abnormal small bowel motility by manometry, severe gastrointestinal symptoms and no evidence of the underlying cause after a thorough work-up(16).

Small bowel manometry evaluation is also susceptible to pharmacological and physiological interventions(17), and for these reason it has been used to tailor treatment with parenteral prokinetics, like octreotide or erythromycin (18). Small bowel manometry can be used to detect intestinal dysmotility in systemic disorders associated with small bowel involvement, like patients with systemic sclerosis(19) and patients with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)(20) even before radiological signs of pseudo-obstruction develop. Lastly, small bowel manometry also provides prognostic information, since myopathic patterns have been associated with increased mortality(21) and complete absence of fasting migrating motor complex is associated clinically with stasis of small intestinal contents, malabsorption, and SIBO(3).

Evolution and prognosis

Once the diagnosis of chronic intestinal dysmotility is established, it is imperative to search for the underlying disorder causing a neuropathy and/or myopathy (3,22) (table 1). Over the last 20 years, there has been an increasing recognition that patients with chronic intestinal dysmotility can be divided in two broad categories based on radiological findings and objective motility studies: chronic intestinal pseudo-obstruction (CIPO) and enteric dysmotility (ED)(23).

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CIPO is the most severe form of chronic intestinal dysmotility, in which abnormal small intestinal motility is associated with the presence of radiological signs suggestive of intestinal obstruction but without a mechanical cause in imaging studies. Enteric dysmotility (ED) is defined by objective evidence of abnormal small bowel motility (as CIPO), but without radiological findings suggestive of intestinal obstruction (i.e. absence of intestinal dilatation or air-fluid levels).

Demographic and clinical characteristics are similar between CIPO and ED patients(24), and the objective motility abnormalities evidenced by small bowel manometry studies are the same in both entities, which suggests that CIPO and ED are closely related. Indeed, some authors advocate that ED and CIPO could be different stages of small intestinal motor disturbance. Another important similarity is that both CIPO and ED have a high incidence of neuro-muscular abnormalities in small bowel full thickness biopsies, however with some differences. CIPO patients have a higher incidence of visceral myopathies, whereas ED patients have a higher incidence of enteric neuropathies, and particularly important, a higher incidence of inflammatory neuropathies which could benefit from immunosuppressive treatment(16). There are some important differences regarding prognosis and treatment options, which validates the distinction between these two entities. CIPO patients require more intensive nutritional support compared to ED patients, and in follow-up studies, CIPO patients are less likely to wean off total parenteral nutrition(25). Still, the mortality rate is similar in both entities, therefore it is important to recognize and diagnose ED early to offer management, avoid malnutrition and improve survival.

Conclusion

In conclusion, chronic intestinal dysmotility is a rare but severely disabling gastrointestinal disorder characterized by symptoms of mechanical obstruction in the absence of an organic cause. Chronic intestinal dysmotility has multiple causes (primary, secondary, or idiopathic) and various pathological mechanisms involved (muscle, ENS, intrinsic or extrinsic pathways). Small intestinal manometry is currently the gold standard for the diagnosis and should be considered in patients with severe progressive symptoms of uncertain etiology, especially when alarm features are present to avoid delay in the diagnosis. Chronic intestinal dysmotility can be divided in

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two categories, CIPO and ED, which have distinct prognostic and management considerations. Since ED without any identifiable primary or secondary cause is associated with inflammatory neuromyopathies, small bowel full thickness biopsy should be considered in the diagnostic approach.

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Table 1: Causes of chronic intestinal dysmotility

Primary	Congenital	Visceral myopathies	• Multisystemic smooth muscle dysfunction syndrome (ACTA2 gene) • Visceral myopathy 1 (ACTG2 gene)
		Mitochondrial cytopathies	• X-linked intestinal pseudo-obstruction (L1CAM, FLNA genes) • Megacystis microcolon intestinal hypoperistalsis syndrome (MYH11, MYL9, ACTG2, MYLK genes) • Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) (MT-TL1 MT-ND5 genes) • Myoclonic epilepsy with ragged red fibers (MERRF) (MTTK gene) • Mitochondrial neurogastrointestinal encephalopathy(MNGIE) (TYMP, LIG3, POLG genes)
		Visceral neuropathies	• Chronic atrial and intestinal dysrhythmia (SG1 gene) • Familial visceral neuropathy (ERBB3, ERBB2 genes) • Neuropathic pseudo-obstruction (SOX10 gene)
		Abnormalities in myenteric plexus development	• Aganglionosis • Neural dysplasia
		Mesenchymopathies	
	Idiopathic		
Secondary	Paraneoplastic	• Small cell lung cancer, Carcinoid, Thymoma (anti-Hu	

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Secondary	syndromes	antibodies)

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Secondary		

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	Paraneoplastic syndromes	• Small cell lung cancer, Carcinoid, Thymoma (anti-Hu antibodies)	
	Neurological	Central nervous involvement	• Cerebrovascular accident, central nervous system tumors
		Medullar involvement	• Post-trauma, vascular accidents
		Autonomic systemic dysfunction	• Diabetes mellitus, amyloidosis, multiple system atrophy
	Neuromuscular	• Muscular dystrophy, mitochondrial cytopathy, myasthenia gravis	
	Endocrine	• Hypothyroidism, MEN2b, hyperparathyroidism, hyperthyroidism	
	Post-infectious	• Epstein-Barr virus, JC virus, Varicella-Zoster Virus, Chagas disease, Herpes simplex virus, Cytomegalovirus	
	Autoimmune	Antibody mediated	• ANNA-1 or anti Hu, anti CRMP-5/anti-CV2, anti gAChR, Guillain-Barre syndrome
		Inflammatory	• Autoimmune myositis or ganglionitis, lymphocytic ganglionitis, eosinophilic ganglionitis
		Connective tissue diseases	• Systemic sclerosis, mixed-connective tissue disease
		Autoimmune diseases	• Systemic lupus erythematosus, dermatomyositis, polymyositis, Sjögren syndrome
	Hereditary connective tissue disorder	• Ehlers Danlos syndrome	
	Medication related	• Opioids and narcotics, anti-cholinergic, anti-psychotics	

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	Miscellaneous	• Celiac disease, sarcoidosis, cystic fibrosis, intestinal ischemia, porphyria, Fabry´s disease, anorexia nervosa, radiation enteritis

Table 2: Indications for manometric evaluation of small bowel motility

Patients with severe chronic digestive symptoms and signs of malnutrition in whom organic lesions have been reasonably excluded.
Patients with recurrent or sustained symptoms of intestinal sub-occlusion in whom mechanical obstruction has not been substantiated by radiological studies.
Patients with systemic disorders associated with intestinal dysmotility and severe gastrointestinal symptoms
Patients who develop chronic digestive symptoms after abdominal surgery or radiotherapy.
Patients with segmental gut motor disorders (gastroparesis, colonic inertia) to determine the extent of the disorder prior to considering respective surgery such as gastrectomy or colectomy.

Figure 1: Examples of normal and abnormal small bowel motility by high-resolution jejunal manometry. Above, in a healthy subject, a normal migrating motor complex characterized by first, a period of irregular propagated contractions (phase II), followed by a period of repetitive regular propagated contractions (phase III) and then a period of motor quiescence (phase I). Below, in a patient, abnormal configuration of phase III (simultaneous, non-propagated contractions) is observed, indicative of a neuropathic intestinal dysmotility pattern.

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