

Chapter 8

Gastrointestinal Autonomic Disorders



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8.1 Introduction

The relationship between the nervous system and the digestive system is the subject of increasing scientific interest; after all, the enteric nervous system (ENS) has a number of neurons that is analogous to that of the spinal cord, as well as possessing a degree of independence from the central nervous system (CNS) that is unmatched in organs of other systems.

The ANS is the medium between the CNS and the ENS; the latter is involved in a complex manner in the major functions (i.e., storage/secretion, transit/mixing of

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the food bolus, vase-action of vascular perfusion, and excretion/defecation) of the gastrointestinal (GI) tract. The ENS exhibits a high degree of autonomy from central nervous control; it is the only system in the human body to have evolved to develop its own independent organization, scientific knowledge of which has been given a major boost in the last decade mainly regarding enteric sense-motor functions [1].

The activity of the GI system can be spontaneous or evoked by peripheral stimuli (distension and chemical stimulation) and causes motor responses promoted hierarchically in a primary manner by the ENS (Fig. 8.1). The ENS motor response is conditioned by the ANS, which, in turn, is influenced by the various motor and psychic activities pertaining to the CNS. that the complex regulatory mechanisms (still being studied) are also modulated by extra-neuronal systems such as the immune system, the gut microbiota and the neuroendocrine system. Often, primary neurological diseases (but also secondary neurological diseases determined by non-neurological diseases) result in ANS GI impairment that, in some cases, cannot always be counteracted by vegetative compensatory mechanisms, or modified by therapeutic treatment. The GI dysfunction (Box 8.1) determines clinical disorders that often underlie other diseases that could involve the ANS (Table 8.1) [2].

In the ANS impairment, deficits may involve both classical functional compartments (motor and sensory), but the GI disorders that are most evident, for which more clinical findings are available, are mainly entero-motor dysfunction (rather than entero-secretory deficits and those of the sensory compartment); these disorders include dysphagia, gastroparesis, intestinal pseudo-obstruction, constipation, diarrhea, and fecal incontinence. A separate chapter would deserve the oropharyngeal and the rectal sphincter disorder. The dysphagia and the sialorrhea are often associated with other lesions of head/neck structures, and also rectal sphincter disorder have a co-interaction with similar structures of the urinary system [2].

Neurological and non-neurological diseases affecting the neural axis of entero-motor control (CNS-ANS-ENS structures) are many. Those directly affecting the ANS most frequently are diseases with chronic-neurodegenerative course, diffuse in character, slowly progressive, with involvement of both central and peripheral structures (i.e., Parkinson's disease—[PD], other alpha-synucleinopathies and peripheral diabetic neuropathy). These should also include Multiple Sclerosis (MS), which often has an acute onset due to non-traumatic focal injury [2].

The diagnosis of GI motility disorder in the course of neurological disease involves the identification of the neuro-physio pathological context, as well as the non-modifiable preexisting conditions (i.e., evaluation of the possible presence of

Table 8.1 Clinical presentation of gastrointestinal motor disorder

Esophagus	Stomach	Small intestine	Colon	Anus-rectum
Difficulty swallowing (dysphagia); Retro thoracic retrosternal pain; Regurgitation; Heartburn	Nausea and vomiting; Dyspepsia Epigastralgy	Dyspepsia; Abdominal bloating and distension	Abdominal pain; Constipation; Diarrhea; Abdominal bloating and distension; Flatulence/ bloating	Evacuation effort; Incomplete fractional evacuation; Incontinence or encopresis

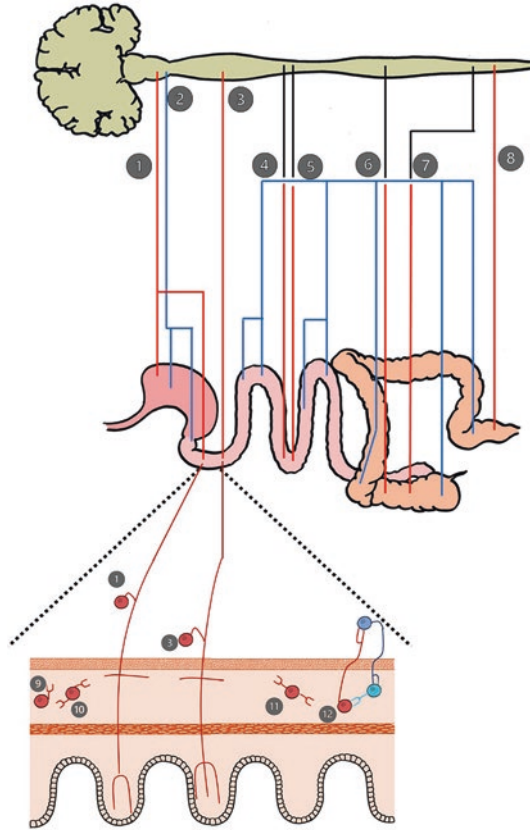


Fig. 8.1 Main extrinsic neural pathways between enteric nervous system and trunk/spinal cord. Main extrinsic motor pathways are shown in blue, afferent pathways in red, and sympathetic pre-ganglionic efferent pathways in black. The motor pathways constitute the parasympathetic and sympathetic nervous systems. In the intestine, sympathetic nerves are inhibitory, parasympathetic nerves are excitatory. In the upper intestinal portions (esophagus and stomach), the main extrinsic sensory nerves are derived from the vagus nerve, while in the lower intestinal portions there is less vagal influence. The main extrinsic sensory nerves in the colon are derived from afferent spinal nerves, whose cell bodies are located in the dorsal root ganglia. (1) vagal afferent; (2) dorsal motor vagal efferent; (3) spinal afferent (*DRG* dorsal root ganglia); (4) coeliac ganglia (sympathetic efferent); (5) superior mesenteric ganglia (sympathetic efferent); (6) inferior mesenteric ganglia (sympathetic efferent); (7) pelvic ganglia (parasympathetic efferent); (8) spinal afferent (*DRG*). In Microstructures: Intrinsic sensory neurons and extrinsic sensory nerve endings in the enteric nervous system. A wide range of intrinsic sensory neurons and extrinsic sensory nerve endings operate within the enteric nervous system. Dogiel's type I neurons [9] are length-sensitive and tension-insensitive myenteric interneurons. Myenteric interneuron in the myenteric plexus [10]. Extrinsic vagal afferent nerve endings [1] innervate the upper intestine and behave predominantly as slowly adapting voltage receptors. Spinal afferent nerve endings [3] provide very abundant sensory innervation to the lower intestine (distal colon) and are potently activated by stretching and increased muscle tension. Dogiel type II neurons in the myenteric plexus [11] are both chemosensory and mechanosensitive and receive fast and slow synaptic inputs from other enteric neurons. Intestino-fugal neurons [12] are generally considered second-order neurons, but they have been shown to be directly mechanosensitive and respond to direct mechanical compression stimuli

congenital or hereditary diseases); as well as potentially modifiable intercurrent conditions determined by non-neurological diseases or other pathologies (i.e., iatrogenic and toxic-food) that secondarily involve the ANS.

Autonomic disorders may occur localized to the GI level, but more often they occur in combination with other autonomic dysfunctions in other body systems (i.e., cardiovascular, thermoregulatory, respiratory, urogenital, pupillomotor, and sudomotor); for example, in parasympathetic dysfunction there may be “sicca” syndrome, light intolerance due to unresponsive dilated pupils, urine retention, erectile dysfunction, resting tachycardia just as sympathetic dysfunction can also be characterized by pupillary miosis, orthostatic intolerance with dizziness or syncope, exercise intolerance, anhidrosis, and heat intolerance.

The examination of the GI system is often strictly the responsibility of the gastroenterology specialist; moreover, clinical investigations for GI motility disorders suffer from the absence of a “gold standard” diagnostic test. Indeed, clinical-instrumental investigations of GI dysfunction often have the limitation of being investigative, invasive, and ultra-specialistic, and the criterion of investigations by refutation is preferred.

Knowledge of the GI autonomic nervous system becomes even more strategic in view of the absence of a specific pharmacological treatment for entero-motor dysfunction. The management of vegetative disorders is aimed at the therapy of the underlying neurological disease, at the search for other modifiable causes, and at the exclusion of non-neurological diseases for which a specific branch specialist is needed. It follows that GI neuro-motor disturbance in the course of neurological disease requires specific expertise, starting with the not obvious restoration of normal hydration, adequate nutrition, and harmonization of pharmacological treatments [3].

In conclusion, GI dysfunction involves a number of disorders that are part of the clinical expression of neurological and not neurological diseases that need, therefore, multidisciplinary for the purpose of an appropriate diagnostic-therapeutic approach; the aim of the paper is to provide indications for the framing of gastrointestinal autonomic impairment, which can also be pauci- or asymptomatic, how it happens in major neurological diseases.

Box 8.1: Vegetative Gastrointestinal Dysfunction

Inefficient response of the gastrointestinal system to food intake, either at rest (stationarity in metabolic homeostasis with circadian adjustments and adaptations to physiological growth/aging), or during adaptation to psychophysiological changes (such as during the performance of common life activities in various environmental conditions) or to chronic/acute decline in health status.

8.2 Structures and Gastrointestinal Motility

Neural Structures (Structures and gastrointestinal motility). The ANS, responsible for extrinsic autonomic motor control of the digestive tract, regulates the major functions of the gastrointestinal tract in an integrated and complex manner.

Sympathetic and parasympathetic fibers of the ANS motor neurons innervate the gastrointestinal (GI) smooth muscle, intra-parietal glands, and those attached to the digestive tract (salivary, liver, and pancreas).

The ENS, also called the meta-sympathetic or intrinsic or visceral control, is an intermediary between the ANS and GI effector organs (smooth muscle and glands). The ENS regulates the functioning of GI motility from the medium part of the esophagus to the anal sphincter; it consists of small clusters of cells, the intramural ganglia, which are interconnected and articulate to form two distinct neural plexuses (Auerbach's myenteric plexus and Meissner's submucosal plexus) organized in a complex and finely coordinated neural network. Congenital or acquired abnormalities of the ENS, associated with a lack of intrinsic neurons in the myenteric and submucosal plexuses of the colon, can result in excessive distension and altered motility of the digestive tract, such as congenital megacolon in Hirschsprung's disease [1].

The CNS, mainly through the ANS, modulates and controls GI tract functioning in an uneven manner. The small intestine and large intestine have a greater degree of independence from extrinsic neural afferents than the esophagus and stomach: removal of extrinsic innervation to the stomach results in disorganized and dysregulated gastric activity that often causes symptoms such as nausea and vomiting, discomfort, and abdominal pain with diarrhea; however, after an initial dysfunctional phase, gastric activity regains an adequate level of normalcy [4].

Probably, motor activity also reverberates from the esophagus and stomach into the distal tracts, which are more independent [4], so it is possible to argue that the control systems present a hierarchy of neuronal control: primary regulation determined by the ENS, which in turn is modulated by the structures of the ANS, which in turn is conditioned by various factors (psychic, motor and others pertaining to the CNS) (Diagram 8.1).

Extrinsic Gastrointestinal Neuro-Motor Control (Structures and gastrointestinal motility). The areas of the ANS centrally are in the forebrain, midbrain, hindbrain, and spinal cord; peripherally, the VNS acts through the parasympathetic and sympathetic nervous systems on the ENS. The extrinsic neural control includes parasympathetic and sympathetic nerves of the PNS; a relatively small number of vagal/sacral preganglionic fibers and sympathetic postganglionic fibers are able to interact with the multiple enteric plexus neurons organized in defined circuits pre-established in the wall of the intestine (Fig. 8.1). The extrinsic parasympathetic component is generally excitatory, while the extrinsic sympathetic component has an inhibitory action on the muscles and acts by activating intrinsic inhibitory systems [1]. Intrinsic control of the ENS contains a variety of cellular components (mechanoreceptors and chemoreceptors, interneurons) that process sensory input and control motor units with direct effects on myenteric. In addition, there are brain astroglia-like cells that support neuronal cells and establish a barrier with capillaries in a manner quite similar to the blood-brain barrier [5].

It follows that the hierarchy of neuronal control (Diagram 8.2) relative to intestinal motor activity is as follows: primary regulation is by the Enteric Nervous System (ENS), followed by the ANS and then the Central Nervous System (CNS). Extrinsic control is in turn conditioned by the CNS, which also participates with the somatic

Nervous System (Central, Peripheral) CNS, PNS				
CNS Brain Brainstem Spinal Cord	Cerebral hemispheres	Telencephalon	Forebrain Central nuclei involved in the regulation of gastrointestinal functions: CeA—Central nucleus of the amygdala BNST—bed nucleus of the stria terminalis	
		Diencephalon	Midbrain The reticular formation.	
	Brainstem	Mesencephalon		
		Pons	Hindbrain Central nuclei involved in the regulation of gastrointestinal functions: PAG—periaqueductal gray; AP—area postrema; dorsal motor nucleus of the vagus; NTS—nucleus of the tractus solitarius; Vestibular N—vestibular nucleus; Trigeminal N—trigeminal nucleus; Raphe N—raphe nuclei	
	Cerebellum	Medulla		
PNS ANS		Efferent projections from the CNS target skeletal muscle (skeletal motor) or the autonomic nervous system, which is divided into three parts: sympathetic, parasympathetic and enteric. Preganglionic motor neurons (Sympathetic and Parasympathetic) located in the CNS synapse with a postganglionic neuron of Auto nomic Nervous System of PNS.		
	Nerves and ganglia	Sympathetic division Parasympathetic division Autonomic responses are mediated by the sympathetic and the parasympathetic systems, which are antagonistic to one another.	Motor efferent compartments, including sympathetic and parasympathetic motor neurons, projecting to the gut wall. Postganglionic sympathetic neurons receive input from the sympathetic neurons in the ILN. Postganglionic parasympathetic neurons from the DMN of the brain stem and from the sacral spinal cord. The postganglionic neurons acts on a target organ.	Sensory afferent compartments: Spinal afferents have their cell bodies in the DRG and project into the dorsal horn of the spinal cord. Vagal afferents have their cell bodies in the nodose and jugular ganglia and project into the nucleus tractus solitarii (NTS) of the brain stem.
Gastrointestinal tract, microstructure				
PNS ANS	Nerves and ganglia	ENS Muscularis propria (externa): smooth muscle layer; there are usually two layers; the inner layer is circular and the outer layer is longitudinal and is thicker than the inner. The myenteric plexus is located between the two layers of muscle layer.	Myenteric (Auerbach's) plexus (Dogiel type I, extrinsic vagal afferent nerve terminals, Dogiel type II) Sensitive afferent, STN; Modulatory "state" DVM; Motor efferent, DVC; tonic input, mostly synaptic, inhibitory (GABA) STN vs DVM (tonically active) excitatory input (ACH) and (Glu) vs DVM pre-ganglilar vagus motor fibers vs ENS ganglia The myenteric plexus primarily regulates gastrointestinal motor activity.	
		Submucosa layer	Submucosal nerve plexus (Meissner plexus) The submucosal plexus controls gastrointestinal secretory activity.	
		Mucosa layer		
Gastrointestinal tract, resident neurogenic pathway and activity				

DMN (dorsomedial nucleus); DVC (dorsal vagal complex); dorsal vagal complex formed by the set of area postrema, the STN and the DVM (dorsal vagal motor) nucleus; DRG (dorsal root ganglia); ILN (intermediolateral nucleus); MMC: migrating motor complex; NTS: nucleus tractus solitarii;

Diagram 8.1 Nervous system (central, peripheral) CNS, PNS. *DMN* dorsomedial nucleus, *DVC* dorsal vagal complex: dorsal vagal complex formed by the set of area postrema, the STN and the DVM (dorsal vagal motor) nucleus, *DRG* dorsal root ganglia, *ILN* intermediolateral nucleus, *MMC* migrating motor complex, *NTS* nucleus tractus solitarii

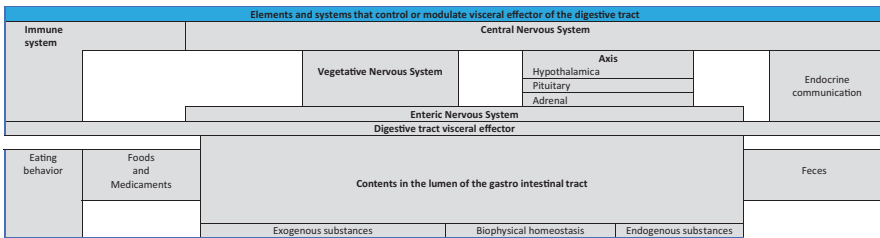


Diagram 8.2 Elements and systems that control or modulate visceral effector of the digestive tract

system in an integrated manner along with the ANS in some activities such as swallowing and defecation. Gut motility is also conditioned by the intrinsic immune system and the endocrine system, including the pituitary-adrenergic axis [5].

The ENS through GI reflexes ensures the proper functioning of the motor activity of the digestive system and coordinates intestinal functions together with the secretory activity.

The GI reflexes (of which the main ones are the peristaltic reflex) promote integrated action (long reflexes, short reflexes and extrinsic reflexes promoted by GI

tract peptides), motor function and communication between different parts of the intestine.

Intrinsic Gastrointestinal Activity (Structures and gastrointestinal motility). The digestive tract, just like the heart, contains cells (not neuronal) with spontaneous depolarization (pacemaker-like potential), not induced by vegetative innervation, between the myenteric syncytium: the Interstitial Cells of Cajal (ICC).

These provide different continuous rhythmic activity in the various tracts of the gastrointestinal tract. The electrical rhythmicity they generate is not required for normal gastrointestinal function, at least in the small intestine. These electrical oscillations in smooth muscle are called slow waves of the migratory motor complex (MMC) and result in phasic contractions. The MMC is a cyclic and recurrent motility pattern that is determined in the stomach and progresses in the small intestine, both in wakefulness and sleep, active during fasting, and deactivated in the postprandial digestive phase.

Serotonergic activity contributes to the regulation of slow wave frequency [6] and is reduced in the colonic cells of patients with irritable bowel syndrome. The motor effects of vagotomy on the MMC seem to have an effect delimited to the stomach and not to the small intestine. The affected cells are morphologically similar to star-shaped muscle cells, CCIs, spontaneously generate slow (3/min) electrical waves that propagate into the surrounding musculature, keeping it in a latent state of excitation and regulating its contractile rhythm. CMMs are characterized by three phases illustrated in Fig. 8.2a. About half of the phase III waves originate from the stomach and the other half from the duodenum.

The physiological role of the MMC is not completely known. It is possible that it has a function analogous to muscle tone in the somatic skeletal system; its absence has been associated with gastroparesis, intestinal pseudo-obstruction, and small intestinal bacterial overgrowth. Measurement of gastrointestinal tract motility may be important in the diagnosis of gastrointestinal disorders [7].

In general, afferent information flow from the digestive tract promotes motor actions both during the interdigestive phase and after food intake and related digestive function, up to stool formation and related excretion. Two completely different motor patterns can be identified: an interdigestive motor pattern and a postprandial digestive motor pattern. During the interdigestive phase, there is high muscle tone in the proximal gastric part while recurrent contractions, MMCs, are present in the distal part. This typical contractile pattern appears after gastric emptying from food and originates from a pacemaker area, located on the great curvature between the fundus and the proximal body. The purpose of these phase III contractions is to ensure a pulsatile flow that keeps the stomach and small intestine free of secretions, waste, and microbes during the fasting period, to prepare the stomach to receive the next meal. During the digestive phase, GI smooth muscle can respond to both excitatory and inhibitory motor neurons of different types depending on the motor activity of the digestive system: peristalsis, segmentation movements (or scrambling) and tonic contractions (Fig. 8.2b). Peristalsis occurs according to a coordinated pattern of activity of the smooth muscles of the esophagus and intestine: contraction upstream and relaxation of the distal tract when a bolus distends the intestine, brought about by inhibition of the circular layer and excitation of the longitudinal

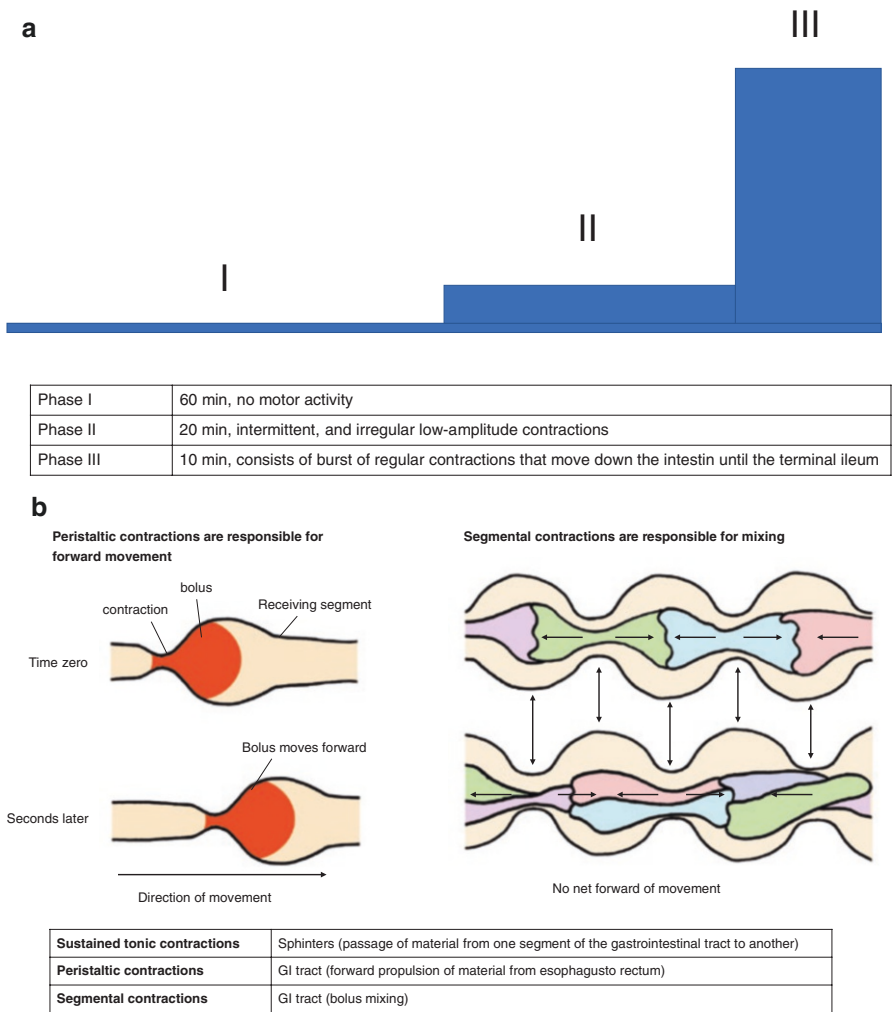


Fig. 8.2 (a) Motor pattern of the MMC. (b) Gastrointestinal motor activity

muscular layer (shortening and widening of the tract); peristalsis normally lets the contents of the digestive tract progress toward the cecum in the aboral direction [8, 9].

Conditioning of intestinal motility (Structures and gastrointestinal motility). Motor function is conditioned by several systems, as well as by psycho-environmental conditions [10].

Numerous endocrine cells are found in the gastrointestinal mucosa that spills into the blood; the endocrine transmission (especially concerning the pituitary-adrenergic axis), intestinal microbiota, immune system,, modulate intestinal motility, through reciprocal interactions with the CNS. They are mostly represented by clear cells (argentaffin or enterochromaffin cells) that produce serotonin through decarboxylation of amine precursors such as 5-hydroxytryptophan; hence, they are referred to by the acronym APUD (Amine Precursor Uptake and Decarboxylation).

Table 8.2 Functions of the intestinal microbiota

Protective action
Pathogen dislocation; competition of nutrients and receptors; production of antimicrobial factors; inhibition of the growth of pathogenic organisms
Metabolic action
Food digestion with SCFA production and energy recovery; regulation of glucose and lipid metabolism (mineral salts); elimination of toxins and drugs; synthesis and absorption of vitamins (folin, biotin, vitamin B12); iron absorption
Immuno-modulatory action
Intestinal barrier fortification; induction of IgA and strengthening of TJ; modulation of inflammation; development of the immune system; modulation in gene expression
Neuro-endocrine action
VNS regulation and development and function; modulation of the endocrine system
<i>SCFA</i> short-chain fatty acids; <i>Tj</i> (tight junction) tight junctions

Such cells are located in the lining epithelia of the small and large intestines in the tubules of the gastric, pyloric, duodenal, and pancreatic glands. The numerous diversities of endocrine cells in the gastrointestinal tract allow it to be considered the largest gastro-entero-pancreatic (GEP) endocrine system.

Bacterial colonization of the intestine is critical for the development and maturation of the ENS [13]. Specifically, ENS interacts with the microbiota via serotonin [5-hydroxytryptamine (5-HT)]. 5-HT is produced in both the ENS and Central Nervous System (CNS), is a key neurotransmitter for motor and secretory responses in the ENS, activates local enteric nervous receptors, which determine secretion and propulsive motility, and acts on vagal afferent pathways to modulate contractile activities [14]. Scientific evidence demonstrates the causal link between inflammation of the intestinal mucosa and altered intestinal secretion/motility [15]. Inflammation-related muscle contractile activity decreases by suppressing the inflammatory response with the use of corticosteroids.

In summary, it is well known that the immune system alters intestinal motility, hence the potential beneficial effects of probiotic treatment. Diet, food intake, medication [16] storage and consumption patterns induce physiopathological effects capable of affecting the whole organism, mediated by the gut microbiota (Table 8.2).

8.3 Functional Gastrointestinal Disorders

Functional Gastrointestinal Disorders (FGIDs) are disorders of gut-brain interaction defined by the presence of GI symptoms related to a variable combination of motility disorders, visceral hypersensitivity and altered immune and mucosal function, altered gut microbiota and altered CNS processing in the presence of predisposing psychosocial, genetic and environmental factors [17]. They cause persistent or recurrent symptoms due to abnormalities in gastrointestinal functioning without organic lesions; it is difficult to arrive at a correct classification by common radiographs or endoscopies alone, which are usually normal. Only accurate evaluation of

symptoms (Rome IV Criteria) and functional diagnostics studying gastrointestinal movement, microbiota, absorption, and local immunity can give the decisive elements to optimize therapy and personalize it so as to improve the patient's quality of life. Twenty-two FGIDs have been identified by global experts, which can affect any part of the gastrointestinal tract, including the esophagus, stomach, bile duct, and intestine [18]. The most common and most studied FGID is Irritable Bowel Syndrome-abdominal pain associated with altered bowel habits with diarrhea, constipation, or alternation. Other frequent FGIDs include Gastroesophageal Reflux without esophagitis (Non Erosive Reflux Disease NERD) often resistant to therapy, Functional Dyspepsia (Box 8.2), Chronic Abdominal Bloating and Functional Abdominal Pain, Constipation, or Chronic Functional Diarrhea.

Box 8.2: Functional Dyspepsia

Defined by the gastroenterologist, it is an expression of vegetative intestinal dysmotility. According to the Rome IV gastroenterological criteria [19], it is defined by the presence of one or more of the four cardinal symptoms (epigastric pain or burning, postprandial heaviness, and early satiety), not associated with organic, systemic, or metabolic pathology, that has been present for more than 6 months (Fig. 8.3).

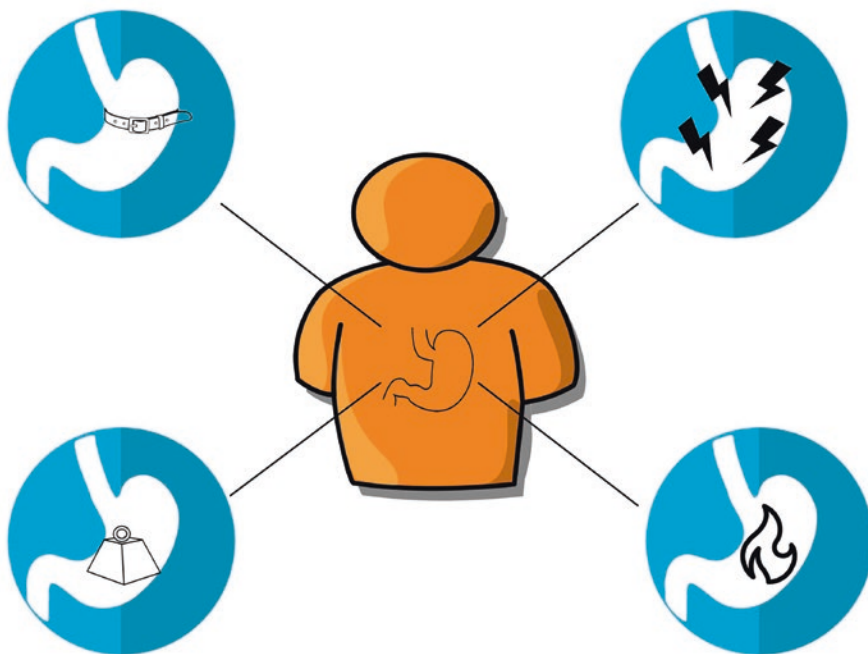


Fig. 8.3 Symptoms of functional dyspepsia according to Rome IV Criteria: epigastric pain, epigastric burning, postprandial fullness, early satiety

8.4 Autonomic Gastrointestinal Dysfunction

GI dysfunction is of strict neurological interest when the GI disorder is among the possible onset manifestations of a neurological disease (i.e., constipation in PD), when it is associated with neurological symptoms/signs not peculiar to the GI district (i.e., functional dyspepsia associated with neurological symptoms), or when it complicates an ongoing neurological disease (i.e., gastroparesis in diabetic neuropathy). GI dysfunction may present in a subclinical form and therefore be difficult to correlate with associated neurological pathology. All segments of the gastrointestinal tract can be affected by GI autonomic dysfunction, contributing to a somewhat variable clinical presentation (Table 8.3) that often, especially for alvus disorders, is not easily reported by the patient [3].

The sympathetic nervous system exerts a predominantly inhibitory effect on GI muscles and is responsible for tonic inhibitory activity on mucosal secretion, as well

Table 8.3 Gastrointestinal motor disorder with vegetative etiopathogenesis

Etiopathogenesis: CNS, VNS, ENS	Main features
Oropharyngeal dysphagia	
Pharyngeal skeletal muscle impairment; disorder of lower motor neuron (e.g., bulbar polio or pseudobulbar palsy), or muscles (e.g., ALS, myasthenia gravis) [2, 20]; oropharyngeal bradykinesia in PD and presence of α -synuclein in motor and sensory nerves [21];	Difficulty swallowing with early aspiration or cough. Often it is accompanied by other symptoms, such as nasopharyngeal regurgitation, voice changes, or the perception of uncoordinated swallowing
Esophageal dysphagia	
Vagal denervation or smooth muscle disease [2, 20] In specific conditions (i.e., MS), dysphagia can be caused by a combination of lesions in several structures: Cerebellum, corticobulbar tract, brainstem and lower cranial nerves, which modulate information to and from the muscles of the respiratory, oropharyngeal and gastrointestinal tracts	Sensation of food or liquid sticking in the esophagus or chest. When it is associated with pain, it takes the name of odynophagia; when it is associated with persistent obstruction and bolus retention, it is classified as food bolus impaction
Gastroparesis	
Gastric motility disorder mainly characterized by uncoordinated antral contractions, pyloric spasm, fundal distention hypersensitivity, and impaired gastric accommodation to a meal, vegetative and vagal neuropathic impairment, and gastric smooth muscle contractility dysfunction The most frequent causes are the idiopathic (60%), and the diabetic (30%) form, successively the post-surgical form. It can be due to vagal myenteric denervation. It may be present in neurological disorders such as stroke, vegetative syndromes, multiple sclerosis, spinal cord injury, neurofibromatosis, peripheral nerve disorders	Continuously or cyclically nausea, vomiting, early satiety, and/or a sense of fullness, it is compatible with gastric retention in the absence of a mechanical obstruction

(continued)

Table 8.3 (continued)

Etiopathogenesis: CNS, VNS, ENS	Main features
Intestinal pseudo-obstruction	
<p>Rare disorder of intestinal motility. It is a severe and disabling disorder characterized by recurrent episodes that mimics the mechanical obstruction, but without organic, systemic, or metabolic disorders, and without physical obstruction detectable by radiographs or surgery</p> <p>The etiology is unknown. The pathogenesis of motor and intestinal transit dysfunctions may involve the impairment of enteric and/or extrinsic nervous system (autonomic neuropathy), of smooth muscle (visceral myopathy), and of interstitial cells of Cajal (intestinal mesenchymal pathology)</p> <p>It may be due by vagal or myenteric denervation, or it may be iatrogenic (narcotics, GLP1 agonists). It may recognize associated to genetic causes: The transmission can be either autosomal dominant (for example mutations of the <i>ACTG2</i> gene, for which the patient inherits a single copy of the mutated gene from a parent, or the mutation can be de novo in the affected individual), or linked to the chromosome X (<i>FLNA</i>), or autosomal recessive (for example mutations in the <i>RAD21</i> and <i>SGOL1</i> genes, for which the affected individual inherits two copies of the mutated gene, one from each parent)</p>	<p>Severe chronic 'obstructive' symptoms: Abdominal pain, distention/satiety, nausea/vomiting, intractable diarrhea and/or constipation, malabsorption. These symptoms cause weight loss and/or growth retardation in children. Biological abnormalities usually reflect the level of malabsorption and malnutrition</p> <p>Affected intestinal traits may be confined (only small bowel involvement in most cases) or generalized. Sometimes the disorder also involves other muscles, such as the bladder</p>
Constipation	
<p>Parasympathetic, vagal, sacral, or myenteric denervation injury. It can be classified in constipation with slow or normal transit, and pelvic floor dyssynergia (due to incoordination, altered recto-anal inhibitory reflex, reduced rectal sensitivity, altered rectal compliance in addition to behavioral factors)</p> <p>Other etiological elements of constipation are: Increased bowel transit time (due to drugs and/or loss of supraspinal modulation), anorectal hyposensitivity, a low-fiber diet, weakness of abdominal muscles</p>	<p>Difficult passage of stools and/or infrequent bowel movements (evacuation less than three times a week), hard stools</p>
Fecal incontinence	
<p>Damage of pelvic nerves, sacral roots, cauda equina, or denervation of spinal cord (pelvic floor and anal sphincters). It can result in abnormal rectal sensation or a deficiency of the internal anal sphincter (sympathetic denervation), or the external anal sphincter (sacral parasympathetic neuropathy)</p>	<p>Involuntary loss of stools and intestinal gas, uncontrolled colonic peristalsis, impaired rectal compliance, prolonged recto-anal inhibitory reflex, weakness of the internal and/or external sphincter muscles, and anorectal hyposensitivity</p>

Table 8.3 (continued)

Etiopathogenesis: CNS, VNS, ENS	Main features
Diarrhea	
Autonomic neuropathy, enteric neuropathy, abnormalities of ICCs, oxidative stress, inflammation. It can result in colon hypermotility, dysfunction of the anal sphincters and rectal hyposensitivity	Liquid stools, with blood, mucus, steatorrhea Symptomatology and signs: Abdominal cramps, tenesmus, marked borborygmi due to the high peristalsis, pelvic floor dyssynergia, possible alterations of the perineal area

as regulating GI blood flow by vasoconstriction. The parasympathetic, in contrast, can exert both an excitatory and inhibitory effect on muscle tone; this dual and antagonistic characteristic allows for finer and more complex control over GI activity, particularly GI motility related to digestive/secretory/defecatory function. The presence of GI autonomic dysfunction is often underestimated, but in some clinical neurological conditions, it can become crucial, such as in Parkinson's disease (PD), where therapeutic efficacy is linked to good gastric transit efficiency.

The main autonomic GI dysfunctional syndromes are manifested by: thoracic dysphagia with gastroesophageal reflux disease (GERD) is associated, gastroparesis, chronic intestinal pseudo-obstruction, constipation, and anal dysfunction (Table 8.3). Sphincters and valves in the GI tube, in fact, exhibit tonic contraction designed to prevent reflux of gastric contents by compartmentalizing the different tracts of the digestive tract. When such motor mechanisms in the proximal part of the stomach are altered, GERD occurs. In general, however, anorectal dysfunction and oropharyngeal dysphagia are associated with alterations in other apparatuses (i.e., urinary autonomic disorders disturbances in anorectal dysfunction) or secondary to encephalic/spinal lesions, respectively.

Several modifiable factors modulate GI activity, including drugs/food/medications (Table 8.4) taken and endogenously produced toxicants. Therefore, collecting a thorough history is the first fundamental approach for these patients to rule out eating disorders (i.e., incongruous psychiatric ingestion of drugs, foods, or otherwise, as well as prolonged fasting).

Table 8.4 Gastrointestinal motility modifiers (drugs)

Motility inhibitors/constipation-inducing drugs	
Clinical field of use	Pharmacological Class (some examples)
Anti-inflammatories/ pain relievers	Opioids (codeine, buprenorphine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine sulfate, oxycodone, Oxymorphone, tramadol), FANS (indometacine)
Anesthetics	Gas anesthetics
Anorectics	Amphetamine
Neuropsychiatrics	Anxiolytics (benzodiazepine), tricyclic antidepressants (amitriptyline, doxepin, imipramine), MAO inhibitors, antipsychotics (Phenothiazines), antiparkinsonians (levodopa, carbidopa, Pergolide, bromocriptine, amantadine)
Gastroenterologists	Antiacids (calcium and aluminum salts, e.g., aluminum hydroxide, calcium carbonate), Antidiarrhoics (Loperamide), Antispastic (Dicycloverine, hyoscine as scopolamine); antiulcer (sucralfate , Bismute)
	Anti-arrhythmics (verapamil), Anticonvulsant/antiepileptic (phenytoin, carbamazepine, gabapentin, oxcarbazepine, Pregabalin), Antihypertensives (clonidine, prazosin, methyl dopa, verapamil), calcium antagonists (verapamil, diltiazem, Nifedipine), diuretics (Benzothiazide, potassium-sparing diuretics), lipid-lowering (cholestyramine, colestipol)
Antibiotics	Broad-spectrum antibiotics without probiotic compensation
Chemotherapy	Derivatives of vinca (vinblastine, vincristine), dacarbazine
Orthopedics/ rheumatologists	Calcium salts
Antihistamines	Anti-H1, Difenedramine
Ear/pneumologists	Anticussion (codeine derivatives, e.g., hydrocodone bitartrate, chlorpheniramine polistirex)
Antispasmodics	Anticholinergics (atropine)
Urologicals	Antimuscarinics (Prociclidine, Ossibutinine)
Antihypertensives	Ganglion blockers (Guanethidine)
Others	Hematinics: Iron salts (e.g., ferrous gluconate, ferrous sulfate), barium sulfate, sympathicomimetics (ephedrine, terbutaline)
Drugs with prokinetic action/diarrhea inducers	
Clinical field of use	Pharmacological class (some examples)
Gastroenterologists	Prokinetics (metoclopramide, Domperidone, levosulpiride, Bromopride), laxatives (osmotics, lactulose-based, anthraquinones, with lactose or sorbitol, macrogol if inappropriate usage of Prucalopride Linaclotide), proton pump inhibitors, H2-antagonists, magnesium
Antibiotics	Broad-spectrum antibiotics without probiotic compensation Diuretics (thiazides)
Anti-inflammatories/ pain relievers	Nonsteroidal (FANS), Opiates , anxiolytics (alprazolam), antidepressants (fluoxetine, lithium), anti-Cholinesterases (donepezil)
Cardiologists	Cardiac antiarrhythmics (propranolol, digoxin, quinidine, procainamide), arterial antihypertensives (ACE inhibitors, hydralazine)
Diabetologists	Oral hypoglycaemics (Clofibrate, metformin)
Anti-cholinergics drugs	Bethanechol, neostigmine
Neurologics	Methyl dopa
Others	Prostaglandins, colchicine, thyroxine, uGastrografin

8.5 Neurological Diseases and GI Autonomic Disorders

Extrinsic neurological diseases are defined as those that result in a deficit of extrinsic GI control; Table 8.5 shows the main neurological diseases that result in GI disorders from possible ANS incompetence. The neurological and non-neurological diseases affecting the neural axis of entero-motor control (CNS-VNS structures) are many, but those that directly affect the ANS most frequently are diseases with a chronic-neurodegenerative course, diffuse in character, slowly progressive, with involvement of central and/or peripheral structures (i.e., Parkinson’s disease (PD) in alpha-synucleinopathies and peripheral vegetative neuropathy in diabetes). Clinically expressing diseases with chronic progressive course without deficits in neurological extrinsic control, such as immunological endocrine/rheumatological diseases, mainly affect the ENS in addition to the GI structure (Table 8.6). The GI control of ENS exhibits greater autonomy from extrinsic control and within certain limits can compensate for the deficit of ANS; however, when the accommodation capacity of GI autonomic control is impaired, GI disorders result. In cases of acute/subacute GI disorder onset, it is possible that the etiologic agent affecting the nervous system and/or GI system may be lesional. In such cases, it is indicated to evaluate the presence of so-called red flags (Box 8.3), i.e., alarm symptoms, situations in which urgent referral to the gastroenterologist, and first-level examinations should be performed to rule out organic pathology, see later Table 8.12.

Table 8.5 Extrinsic neurological diseases with intestinal dysmotility

Brain diseases	Degenerations of the vegetative system	Spinal cord injury	Peripheral neuropathy	Muscle diseases
Stroke; Head trauma; Neurocognitive syndrome (e.g., Alzheimer’s disease; PD); multiple system atrophy; Brainstem injuries;	Pandysautonomy; Familial dysautonomy; Idiopathic orthostatic hypotension and pure autonomic failure; Postural orthostatic tachycardia syndrome;	Spinal cord injury; Multiple sclerosis; Neuromyelitis optica;	Acute peripheral neuropathy; Chronic peripheral neuropathy (i.e., diabetes mellitus; amyloidosis); Paraneoplastic neuropathy; Porphyria; Neurofibromatosis; Nerve lipomatosis; HIV neuropathy; Autoimmune neuropathies ab vs neuronal receptors;	Duchenne/Becker muscular dystrophies; Muscular dystrophies, Polymyositis and dermatomyositis; Mitochondriopathy, Neurogastrointestinal encephalomyopathy, Myotonic dystrophy type 1

Table 8.6 Immunological endocrine/rheumatological diseases with intestinal dysmotility

Autonomic dysfunction	During systemic disease	
		Systemic connectivity
Predominantly sympathetic-stimulatory dysfunction	RAYNAUD'S PHENOMENON GASTROINTESTINAL SYMPTOMS Gastroesophageal reflux symptoms Nasopharyngeal irritation from gas reflux Retrosternal pain (esophagitis/esophageal spasm)	SYSTEMIC SCLEROSIS Rare disease (predominantly female) average age 30/50 years Prevalence 20–40/100000; arterial capillary vasculopathy of the connective tissue of various internal organs and skin including the vasa nervorum with progressive fibrotic evolution
Predominant parasympathetic inibitoria dysfunction	SICK SYNDROME Reduced salivation and reduced tearing GASTROINTESTINAL SYMPTOMS Dysphagia symptoms (especially for dry solid foods)	SJOGREN'S SYNDROME Rare disease with a female predominance, average age 40/50 years. Prevalence 15–25/100000; it predominantly affects the exocrine glands in particular the lacrimal and salivary glands with sclerofibrotic inflammatory progression
Mediators with predominantly sympathetic-stimulatory function	GASTROINTESTINAL SYMPTOMS Gastric hyperacidity, intestinal hypersecretion, pancreatic enzyme secretion and intestinal motility abnormalities	DISEASES OF THE NEUROENDOCRINE SYSTEM Hypothalamic-pituitary-adrenal axis Diffuse endocrine system APUDs that produce serotonin and polypeptides that also function as neurotransmitters

Gastrointestinal autonomic disorders presenting in an acute/subacute mode are often observed in diseases by brain lesion injury (traumatic and nontraumatic) and in the flare-up of chronic-degenerative diseases such as diabetic neuropathy. These disorders will be discussed in other sections.

Box 8.3: “Red Flag”

Age > 50 year;

Familiarity with upper/lower gastrointestinal cancer or chronic inflammatory bowel disease.

High-risk factors for cancer: Previous gastric/colic cancer and/or gastric/colic surgery.

Gastrointestinal bleeding.

Recent onset symptoms (Fever, Progressive and unintentional weight loss, Progressive Dysphagia/Odynophagia, Persistent vomiting, Constipation).

Hematochemical alterations (Ironopenic anemia);

Palpable epigastric/abdominal mass.

8.6 Neurological Diseases and GI Autonomic Disorders: Non-modifiable and Preexisting GI Factors (Aging, Congenital or Inherited GI Diseases)

The impact of aging on the gastrointestinal tract plays a role in worsening GI dysfunction, leading to an age-related selective decline in gut function. In general, nutrient and drug absorption worsens over time, and the defense system against ingested pathogens becomes deficient. Aging is associated with: structural and functional mucosal defense defects, reduced ability to generate protective immunity, and increased incidence of inflammation and oxidative stress. Changes in gut function associated with aging have particular implications for esophageal, gastric, and colonic motility, leading to changes in taste and reduced esophageal sphincter motility and gastric emptying. Older individuals, therefore, are particularly susceptible to malnutrition, postprandial hypotension, dysphagia, constipation, and fecal incontinence. Decreased numbers of myenteric plexus nerve cells, which affect the absorption and plication (surface area) of the small intestine, due to villous degeneration, can lead to reduced nutrient absorption.

Knowledge and evaluation of genetically determined conditions are essential for the appropriate characterization of the disease. Certain factors may alert the clinician, suggesting the search for genetic conditions. These include the age of onset of the autonomic disorder, location, and the possible presence of associated neurological disorders. Tables 8.7 and 8.8 show some of the main recognizable enteric phenotypes and the corresponding clinical-instrumental evaluations useful for correct diagnostic framing or the genes (and thus transmission patterns) to be evaluated.

Table 8.7 Enteric neuronal phenotypes associated with pediatric neuro-intestinal disease

Disease	Epidemiology onset	Autonomic dysfunction (main symptoms)	Clinical-instrumental indications
Congenital achalasia	Incidence 1–3:100000 Insidious onset, mean age at diagnosis 7y	Dysphagia, reflux and regurgitation, chest pain (due to lack of relaxation of the lower esophageal sphincter)	Endoscopy, Esophageal manometry Esophagus x-ray
Hirschsprung disease	1:5000 born alive Infancy onset	Neonatal onset: Abdominal pain, constipation, progressive abdominal distension, vomiting and diarrhea Childhood-onset: Severe constipation and failure to thrive	Anorectal manometry, showing the absence of the anal inhibitory reflex; Rectal biopsy (rectal mucosa and submucosa) showing aganglionosis, thickening of extrinsic nerve fibers, and overexpression of acetylcholinesterase.

(continued)

Table 8.7 (continued)

Disease	Epidemiology onset	Autonomic dysfunction (main symptoms)	Clinical-instrumental indications
Spina bifida	1: 2000 newborns Onset at birth	Two main forms: Open or cystic spina bifida and occult spina bifida (asymptomatic or paucisymptomatic). Open spina bifida involves the spine and spinal cord, it may be present a pocket in the skin that contains only the meninges (meningocele) or also the spinal cord (myelomeningocele). Usually located in the lumbar or sacral portion of the spine, the clinical picture varies according to the region involved. In general, there is paraplegia (paralysis of the lower limbs), hydrocephalus, the Arnold-Chiari malformation, urinary and anorectal incontinence	Prenatal ultrasound and/or MRI
Neuronal intestinal dysplasia, type B	Unknown prevalence Childhood-onset (rarely adult)	Severe constipation or bowel obstruction	Rectal biopsy (rectal mucosa and submucosa) showing colonic submucosal hyperganglionosis
Pediatric gastroparesis	Unknown prevalence Childhood-onset (mean age 8 years)	Nausea, vomiting, abdominal pain, early satiety and/or feeling of fullness	4-h gastric scintigraphy to evaluate gastric emptying rate
CIPO (chronic intestinal pseudo-obstruction)	1:100.000	Abdominal pain, distension/satiety, nausea/vomiting, diarrhea and/or intractable constipation, malabsorption	Clinical diagnosis, supported by radiography showing intestinal dilatation and air-fluid levels (endoscopy, manometry, laboratory tests, biopsy)

CIPO chronic intestinal pseudo-obstruction [2, 22]

Table 8.8 Genetic diseases with vegetative impairment and gastrointestinal dysfunction

Disease	Gene (inheritance)	Locus	OMIM
Neuropathy hereditary sensory and autonomic (HSAN)	HSAN5 – <i>NGF</i> (AR)	1p13.2	162030
	CIPA – <i>NTRK1</i> (AR)	1q23.1	191315
	HSN2C – <i>KIF1A</i> (AR)	2q37.3	601255
	HSN1B (gene unknown) (AD)	3p24–p22	608088
	HSAN7 – <i>SCN11A</i> (AD)	3p22.2	604385
	HSAN2B – <i>RETREG1</i> (AR)	5p15.1	613114
	HSAN6 – <i>DST</i> (AR)	6p12.1	113810
	HSAN1A – <i>SPTLC1</i> (AD)	9q22.31	605712
	HSAN3 – <i>ELP1</i> (AR)	9q31.3	603722
	HSAN8 – <i>PRDM12</i> (AR)	9q34.12	616458
	HSN1F – <i>ATL3</i> (AD)	11q13.1	609369
	HSAN2A – <i>WNK1</i> (AR)	12p13.33	605232
	HSN1D – <i>ATL1</i> (AD)	14q22.1	606439
	HSAN1C – <i>SPTLC2</i> (AD)	14q24.3	605713
HSAN9 – <i>TECPR2</i> (AR)	14q32.31	615000	
HSN1E – <i>DNMT1</i> (AD)	19p13.2	126375	

Hereditary sensory and vegetative neuropathies are a group of disorders of different prevalence. The age at onset is generally related to the model of transmission. In particular, early onset/infantile forms generally recognize an autosomal recessive (AR) etiology, adult-onset forms are generally autosomal dominant (AD) (i.e., HSAN1A – OMIM#162400). Adult-onset forms show a phenotype with minimal vegetative dysfunctions. Clinical phenotype of HSAN1A can include abdominal pain, diarrhea, and weight loss. The neonatal/infantile-onset forms have a phenotype with several signs of gastric vegetative impairment. Gastrointestinal dysfunction and vomiting crises are one of the diagnostic criteria in HSAN3 (OMIM#223900) (present in 40% of patients), the gastroesophageal reflux is typical in HSAN2A (OMIM#201300) and HSAN9 (OMIM#615031)

Familial amyloid polyneuropathy (FAP)	<i>TTR</i> (AD)	18q12.1	176300
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Familial amyloid polyneuropathy (FAP) is also known as amyloid or transthyretin polyneuropathy (*TTR*). FAP is an adult-onset progressive sensorimotor and vegetative neuropathy. Worldwide there are different prevalences of FAP: It is a very frequent disorder (about 5%) in East Africa, and among African Americans, instead in European and Caucasian populations, it has a frequency of about 1:100,000, with some geographical variations. It is characterized by incomplete penetrance with geographical variations. Age at onset and symptoms at onset varies greatly. Patients with adulthood (third to fifth decades) onset often show sensory neuropathy. Patients with earlier onset frequently show symptoms with gastrointestinal involvement (attacks of nausea and vomiting, delayed gastric emptying). About 3% of patients with amyloidosis have gastrointestinal amyloid neuropathy, which can cause dysphagia, constipation, diarrhea, and steatorrhea

Familial autonomic neuropathy	<i>ERBB3</i> (AR)	12q13.2	190151
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Familial visceral neuropathy (OMIM # 243180) is a rare disorder with neonatal onset. Generally, it is transmitted with an autosomal recessive pattern. The phenotype involves a vegetative intestinal dysfunction, with secondary gastric involvement. Vomiting is secondary to aganglionosis or hypoganglionosis of the colon

(continued)

Table 8.8 (continued)

Disease	Gene (inheritance)	Locus	OMIM
Mitochondrial neurogastrointestinal encephalopathy (MNGIE)	TYMP (AR)	22q13.33	131222
	RRM2B (AR)	8q22.3	604712
	POLG (AR)	15q26.1	174763
Mitochondrial neurogastrointestinal encephalopathy (MNGIE) syndrome is characterized by the association of impaired gastrointestinal motility, peripheral neuropathy, chronic progressive external ophthalmoplegia, and leukoencephalopathy. Onset typically occurs in early adulthood (within the fourth decade); gastric symptoms are often present at onset and include cramps, vomiting, diarrhea, intestinal pseudo-obstruction, dysphagia, and gastroparesis			
Ehlers-Danlos syndrome (EDS) type 3 hypermobile	Nessun gene conosciuto		%130020
Ehlers-Danlos syndrome is a heterogeneous group of disorders characterized by fragility of connective tissues, that results in cutaneous, ligament, joint, vascular and/or organic manifestations. Hypermobile Ehlers-Danlos syndrome shows features of a vegetative disorder with impaired gastrointestinal function. Mainly manifestation (33%–67%) includes a functional disorder of the intestine, with frequent gastroesophageal reflux and gastritis. Some patients may show delayed gastric emptying, that can be exacerbated by opioids			
17q12 microdeletion syndrome		17q12	# 614527
17q12 microdeletion syndrome is a rare chromosomal abnormality syndrome resulting from partial deletion of the long arm of chromosome 17. Clinically, it is characterized by cystic kidney disease, juvenile diabetes, and neurodevelopmental disorders (cognitive impairment, developmental delay, and autism spectrum disorder). Less frequently, there are Müllerian aplasia in females, macrocephaly, mild facial dysmorphism (high forehead, deep-set eyes, and plump cheeks), and transient hypercalcemia. Onset is typically in neonatal/infantile age. Patients may have gastroesophageal reflux and dysphagia, in some cases associated with esophageal abnormalities or duodenal atresia			
Episodic ataxia (EA)	EA1 – <i>KCNA1</i> (AD)	12p13.32	176260
	EA2 – <i>CACNA1A</i> (AD)	19p13.13	601011
	EA3 (gene unknown) (AD)		%606554
	EA4 (gene unknown) (AD)		%606552
	EA5 – <i>CACNB4</i> (AD)	2q23.3	601949
	EA6 – <i>SLC1A3</i> (AD)	5p13.2	600111
	EA7 (gene unknown) (AD)		%611907
	EA8 (gene unknown) (AD)		%616055
	EA9 – <i>SCN2A</i> (AD)	2q24.3	182390
Hereditary episodic ataxia (EA) is a group of neurological disorders characterized by recurrent episodes of ataxia and dizziness that may be progressive. Weakness, dystonia, and ataxia may be present in the interictal period. Nine types of AE have been described so far (AE type 1 to AE type 9), with types 1 and 2 being the most frequent (estimated prevalence 1:500,000). The age of onset is highly variable between the different forms, from typical childhood in EA1 and EA2, to adulthood (third–sixth decade) for EA4. GI symptoms include nausea and vomiting and are typically present in the forms EA3, EA4, EA6, and EA9			
Neurofibromatosis type 1 (NF1)	<i>NF1</i> (AD)	17q11.2	613113
The phenotype of neurofibromatosis type 1 include constipation, generally secondary to gastrointestinal malignancies (neurogenic malignancies, disorder of interstitial cells of Cajal, neuroendocrine tumors, adenocarcinomas). It is one of the most frequent genetic pathologies, with a worldwide prevalence of about 1:3000. The age of onset is generally infantile, and dermatological signs (café-au-lait spots, cutaneous neurofibromas) are typically the onset manifestations			

Table 8.8 (continued)

Disease	Gene (inheritance)	Locus	OMIM
Duchenne and Becker muscular dystrophies (DMD/BMD)	<i>DMD</i> (XL)	Xp21.2-p21.1	300377
<p>Dystrophinopathies are a group of X-linked muscular diseases with great phenotypic variability. Dystrophinopathies include severe phenotypes such as Duchenne muscular dystrophy (DMD), milder phenotypes such as Becker muscular dystrophy (BMD), and dilated cardiomyopathy (DCM) and paucisymptomatic or asymptomatic phenotypes such as isolated hyperkalemia. The prevalence is variable according to the different phenotypes but generally varies between 1:5000 and 1:20000. In some cases, dystrophinopathies may be associated with gastroparesis with impaired pharyngoesophageal swallowing</p>			
Myotonic dystrophy type 1 (DM1)	<i>DMPK</i> (AD)	19q13.32	605377
<p>Myotonic dystrophy type 1 is a multisystemic genetic disorder characterized by a wide range of muscular (muscle weakness, myotonia) and systemic (cerebral, endocrine, cardiac, gastrointestinal, uterine, cutaneous and immunological districts) manifestations. The disease is characterized by anticipation: The phenotype is more severe in patients with an early onset than in patients with onset in adulthood. GI manifestations include dysphagia, GI reflux, and megacolon. In childhood-onset forms, gastrointestinal disorders are very frequent (malnutrition and fecal incontinence), furthermore it can be present some intestinal disorders can be associated with inflammation of the myenteric plexus and alteration of smooth muscle (chronic intestinal pseudo-obstructions and megacolon)</p>			
Fabry disease (FD)	<i>GLA</i> (XL)	Xq22.1	300644
<p>Fabry disease (FD) is a progressive, hereditary, multisystemic lysosomal storage disease characterized by neurologic, cutaneous, renal, cardiovascular, cochleovestibular, and cerebrovascular manifestations. The age of onset is highly variable, the classic form has an onset in childhood/adolescence, and the atypical forms (renal and cardiac variant) have an onset in adulthood (after 25 years). The frequency varies worldwide, with higher frequencies in Italian and Chinese populations. In particular, in Italy, the incidence is 1:3100, with a ratio of 11:1 between the atypical form and the classic form. The gastrointestinal symptoms are typical of the classic form and are due to the deposition of glycosphingolipids in small intestine vessels and in intestinal vegetative ganglia. Clinical manifestations of GI impairment include episodic diarrhea, nausea, vomiting, bloating and abdominal cramps, and intestinal malabsorption</p>			
Achalasia-Addisonianism-	<i>AAAS</i> (AR)	12q13	605378
Alacrima syndrome (triple A syndrome)	<i>GMPPA</i> (AR)	2q35	615495
<p>Triple A syndrome is a very rare multisystemic disorder characterized by adrenal insufficiency with isolated glucocorticoid deficiency, achalasia, alacrimia, vegetative dysfunction, and neurodegeneration. The prevalence is not known. Onset occurs between the neonatal period and adulthood. In the neonatal period, phenotype is characterized by alacrimia and achalasia of the cardia; in childhood and adolescence patients show achalasia and adrenal insufficiency (which can cause hypoglycemia and seizures); in adulthood there is a diffuse neurological involvement, with alterations of the vegetative nervous system and polyneuropathy Alachrymia, achalasia, and adrenal insufficiency are the three cardinal features of the triple A syndrome, but they may not be present altogether, or they may be associated with vegetative dysfunction and other neurological signs (“double A” or “quad A,” respectively). The neurological signs are very heterogeneous: Vegetative disorders (dyshidrosis, and digestive, sexual, circulatory and urinary disorders), pyramidal syndrome and peripheral neuropathy (gait disturbance, sensory deficits), bulbar and facial deficits (insufficient velum, atrophy or paresis of the tongue, orbicularis oculi muscle dysfunction, and oropharyngeal dysphagia)</p>			

OMIM online mendelian inheritance in man, *AR* autosomal recessive, *AD* autosomal dominant, *XL* X-linked

8.7 Neurological Diseases and GI Autonomic Disorders: Clinical Expression of Gastrointestinal Autonomic Dysfunction

The mode of onset of GI vegetative disorders can be variable. Neurological diseases with chronic-neurodegenerative courses with diffuse character have slowly progressive GI disorder expression (i.e., alpha-synucleinopathies and peripheral autonomic neuropathy). In contrast, neurological diseases with acute/subacute onset of GI disorder frequently recognize a traumatic or nontraumatic lesional etiology (see “Acute/subacute onset” section); except for flare-ups of alpha-synucleinopathies, peripheral neuropathy or the like. However, the latter diseases may be neurodegenerative in nature (e.g., MS).

Acute/subacute onset (Clinical expression of gastrointestinal vegetative dysfunction). Acute/subacute GI autonomic disorders may occur as a complication of an ongoing neurological disease but also as an expression of an acute condition, e.g., in patients with Chagas disease (a tropical parasitosis characterized by extensive injury of the myenteric plexus), in drug intoxications (e.g., metformin in diabetics), in ganglionitis, or after vagotomy. Acute/subacute onset GI vegetative disorders may have a lesional etiology, which may be traumatic or nontraumatic.

Acute/subacute onset, injury with traumatic VNS injury may involve the encephalon (head injury), spinal cord injury (SCI), and/or spinal and cranial nerve injury, along with related complications (Box 8.4) [23–26].

Box 8.4: Chronic GI Complications from Trauma

Chronic GI dysfunction occurs in 27–62% of patients with spinal cord injury. GI dysfunction is a multifactorial consequence of neurogenic circuits and loss of central (supraspinal) control. Specifically, while post-SCI loss of descending control to lumbosacral reflex circuits is generally considered to play an important role in colonic and anorectal dysfunction, gastric dysmotility is seen as an indirect pathology and secondary to the vagal afferent signaling defect after SCI. Specifically, emerging data indicate a reduced sensitivity of vagal afferents to gastrointestinal neuroactive peptides, neurotransmitters, and possibly macronutrients, while the loss of descending pathways to lumbosacral segmental circuits overlaps with pathophysiological remodeling of the colonic intrinsic neurocircuitry. GI disorders after SCI are mainly related to motility disturbance. Upper GI motility disturbances are rare in the chronic phase after injury, while colonic and anorectal dysfunction are common and result from disruption of supraspinal control, sacral parasympathetic activation at the colon with reduced postprandial motor responses, pelvic floor dysfunction, and anal sphincters, leading to defecation disturbances or fecal incontinence. The most common symptoms are constipation, distention,

abdominal pain, rectal bleeding, hemorrhoids, fecal incontinence, and vegetative hyperreflexia. A biliary stone is observed in 17%–31% of cases [26].

Complications often present in individuals with SCI at the bowel level result in the condition of “neurogenic bowel.” In turn, vegetative dysreflexia, evoked by enteric tube distention, as in severe constipation conditions, triggers increased sympathetic discharge below the level of injury that can be life-threatening, particularly in individuals with SCI at or above the T5-T6 spinal cord. These lesions result in major dysfunction of the colorectum, bladder, and sexual function. The most commonly associated symptoms are slow colonic transit, constipation, and/or bowel obstruction, sometimes associated with episodes of overflow incontinence [26].

In SCI occurring above the mid-thoracic spinal segments, pathophysiologic reductions in emptying and motility of the upper gastrointestinal tract are observed. Studies on gastric motor function have demonstrated a reduction in basal contractions after high spinal cord injury, above T3 but not less than T9 from thoracic contusion in animal guinea pigs, persisting up to 6 weeks after T3-SCI. CCK, released from lipid- and protein-sensitive enteroendocrine cells in the duodenum, has been implicated in the regulation of motility. It is capable of activating the terminals of C-type vagal afferent fibers that project to nucleus cells of the solitary tract in addition to acting on nodose ganglion cells and centrally within the dorsal vagal complex. Activation at each of these levels results in gastro inhibition [28, 29].

Acute/subacute onset, injury with non-traumatic etiology (i.e., MS) recognizes multiple causes: tumors, vascular disease, toxic-parenchymal conditions, and inflammatory conditions; in addition, in the spine, degeneration of the fibrocartilaginous disc and/or osteo-articular arthritic component may result in spinal canal stenosis and/or spinal radiculopathy. Among non-traumatic injuries, acute CNS ischemia due to blood vessel occlusion and/or hemorrhagic bleeding has an important role epidemiologically and by extent of sequelae (Box 8.5).

Compared with traumatic lesional etiologies, nontraumatic ones tend to be age-dependent; some of them affect the structures of the CNS by autoimmune mechanisms (such as autoimmune autonomic ganglionopathy), but also by toxic/iatrogenic mechanisms (as in those from antidiabetic drugs or in carbon monoxide intoxications).

Autonomic dysfunction is a common and significant cause of disability in MS patients, as it produces not only gastrointestinal dysfunction but also cardiovascular, bladder, sexual, thermoregulatory, and pupillary dysfunction, probably also contributing to one of the pivotal symptoms of MS: fatigue [30, 31]. Multiple sclerosis (MS) is an inflammatory-neurodegenerative disease that can have a progressive chronic course. Autonomic dysfunction in MS is attributed to several factors: demyelination in areas of the CNS involved in control or modulation of the ANS, altered interactions between the autonomic and immune systems, and Epstein-Barr virus (EBV) infection.

It has been shown that in the prodromal stages (up to 10 years before the onset of signs and/or symptoms), MS patients experience four main symptoms: pain, cognitive symptoms/fatigue, psychiatric symptoms, and autonomic dysfunction affecting the upper gastrointestinal, urinary, and anorectal tracts [32]. In MS, an increase in catecholamine production takes place in response to hyperactivation of the immune system [33]. It has also been found that autonomic dysfunction in MS follows a dual pattern: while disease activity (demonstrable as clinical relapses/presence of demyelinating lesions on radiological examinations) is associated with sympathetic system dysfunction, disease progression (demonstrable as increased neurological disability) is associated with parasympathetic system dysfunction [34].

The main gastrointestinal autonomic symptoms in MS involve both the upper and lower gastrointestinal tracts and are dysphagia, fecal incontinence, constipation, and diarrhea (Table 8.9).

Box 8.5: Main Causes of Injuries of the Brain and Spinal Cord

Acute cerebral ischemia. Dysphagia in stroke is the most common occurrence; it can be brought on by involvement of motor neurons of the related cranial nerves of swallowing (trigeminal V, facial VII, glossopharyngeal IX, vagus X, accessory XI, and hypoglossal XII). Over time, it can complicate with malnutrition or ab ingestis pneumonia, normally of the oropharyngeal type, thus not caused by a VNS disorder. Conversely, pseudo-obstruction of the colon could have a vegetative basis, although this represents a rare occurrence. The second most incident gastrointestinal symptom is constipation, which affects about 45% of subjects in the acute phase and persists at least in the subsequent rehabilitation phases. This disorder is prevalent in brain, rather than brainstem, localizations; it is associated with decreased rectal sensitivity and overall delay of colonic transit in at least ¼ of cases [26, 27].

Brainstem lesions. Brainstem lesions can present in the acute phase, even in the absence of intracranial hypertension, with various gastrointestinal complaints: isolated gastrointestinal motor dysfunction or vomiting from the involvement of the vomiting center on the floor of the fourth ventricle. Compression of the brainstem and lower cranial nerves can cause neurogenic dysphagia in patients with Arnold-Chiari malformations. The presence of more widespread vegetative dysfunction, in particular if adrenergic pathways are involved, is always an indication to look for a CNS lesion [26].

Table 8.9 Symptoms and signs of gastrointestinal vegetative dysfunction in Multiple Sclerosis and complications

Disease	Epidemiology	Clinical presentation	Evaluation
Oropharyngeal dysphagia	Frequency: 30–40% [35, 36] More common in adults moderately and severely impaired (expanded disability status scale, EDSS score: 8–9) [37]	Symptomatology: Coughing during or after eating and/or drinking, food sticking in their mouth and/or throat, throat clearing, gagging, drooling, slowness and fatigue while eating, dyspnea, weight loss and any episodes of either unexplained fever or pneumonia Complications: Reduced eating desire; social withdrawal; mealtime anxiety/distress; critical impact in quality of life (QoL) of the patients [38] Dehydration, malnutrition, and food aspiration [39], increased risk of ab ingestis pneumonia, morbidity, and death; reduced ability to perform activities of daily living (ADL)	See Table 8.14 for clinical exam and instrumental tests
Faecal incontinence	Frequency: About 50% of the patients [40, 41] Type – Passive: If the patient has not awareness of the incontinence – Urge incontinence: If fecal incontinence is accompanied by a degree of urgency	Symptomatology: Fecal incontinence, associated or not with urinary incontinence Complications: Perianal dermatitis (anal eczema, perianal eczema), pruritus ani, pressure sores, higher risk of urinary and vaginal infections	See Table 8.14 for clinical exam and instrumental tests
Constipation	Frequency: 18–43% [40, 41] More common in the early stages of the disease and with a low level of disability (lower EDSS scores: 0–3,5): Severe constipation is often the first symptom of MS	Symptomatology: Absence of evacuation stimulus, presence of hard stools, difficulty in expelling stools Complications: Intestinal occlusion, hemorrhoids, thrombosis hemorrhoidal, rectal prolapse	See Table 8.14 for clinical exam and instrumental tests

(continued)

Table 8.9 (continued)

Disease	Epidemiology	Clinical presentation	Evaluation
Diarrhea	<p>Higher prevalence of diarrhea in patients with MS which present:</p> <ul style="list-style-type: none"> – Comorbidity: IBD (Crohn’s disease, ulcerative colitis), probably due to genetic predisposition, damage to the intestinal microbial flora and the role of the immune system present at the gastrointestinal level [42, 43, 44] – Therapy with dimethyl fumarate used in relapsing-remitting forms [45] 	<p>Symptomatology: Abdominal cramps, tenesmus</p> <p>Complications: Dehydration and hydroelectrolytic imbalance</p>	See Table 8.14 for clinical exam and instrumental tests

8.8 Chronic Progressive Course and Exacerbation (Clinical Expression of Gastrointestinal Autonomic Dysfunction)

Neurological disorder presentation can occur acute/subacutely, as is observed in pathologies with lesional etiology; one of the distinguishing features in chronic-degenerative pathologies could be the intra-individual fluctuation of the disorders over time, as it is observed frequently in diabetic neuropathy.

In some pathological conditions, gastrointestinal disorders can progress slowly with progressive chronic features, as it has been observed in degenerative neurological diseases, such as PD and SM. Other systemic pathologies can cause peripheral neuropathy determined by the involvement of small-fibers, as it occurs in DM, and they have a chronic progressive course. The related autonomic disorders can progress over time to become frankly disabling, while gastrointestinal autonomic disorders must often be subclinical or clinically irrelevant and therefore it has to be actively investigated.

Neurodegenerative diseases, such as α -synucleinopathies, alter gastrointestinal function with a chronic progressive course. In PD, GI symptoms are observed in the very early stages of the disease, in the “premotor” phase of the disease. GI symptoms involve the entire digestive tract and are evident throughout the course of the disease. Indeed, constipation, in particular, may precede the onset of motor symptoms, even more than 10 years. The GI tract seems to play a crucial role in the neurodegenerative process leading to PD, being an entrance door from the external environment to the ENS. Indeed, α -synuclein would spread with a rostro caudal gradient, from the GI, at the ENS, and through the sympathetic and parasympathetic nervous system to the CNS, causing the typical neuropathological changes of PD [46] (Table 8.10).

Table 8.10 Symptoms and signs of gastrointestinal autonomic dysfunction in Parkinson's disease and complications

Disease	Epidemiology	Clinical presentation	Evaluation
Drooling	Frequency: 10–81% of patients From impaired swallowing of saliva rather than from increased production;	Symptomatology: Anamnestic evidence of hypersalivation, loss of saliva, sialorrhea; Complications: Psychosocial discomfort; wounds, skin lesions, angular cheilitis, skin infections;	See Table 8.14 for clinical exam and instrumental tests
Dysphagia	Frequency: More than 80% of patients during the course of their disease; all phases are affected (oral, pharyngeal and esophageal); the onset of severe dysphagia in the first year of the disease is a red flag for atypical Parkinsonism (Multy systemic atrophy-MSA; progressive Supranuclear palsy-PSP);	Symptomatology: Coughing during or after eating and/or drinking; weight loss, drooling, recurrent respiratory infections; chronic inflammatory state not otherwise justified; inefficacy of drug dose that can be stuck in valleculae; Complications: Aspiration pneumonia;	<i>Questionnaires: The swallowing disturbance questionnaire (SDQ) and the Munich dysphagia test-Parkinson's disease (MDT-PD) [47, 48];</i> See Table 8.14 for clinical exam and instrumental tests
Reduced gastric emptying/ gastroparesis	Frequency: Up to 100% of patients	Symptomatology: Nausea, bloating, reduced effectiveness of dopaminergic drugs; Complications: Lack of efficacy of dopaminergic therapy; nutritional and weight changes;	See Table 8.14 for clinical exam and instrumental tests
Faecal incontinence	Frequency: 10–24% of patients	Symptomatology: Loss of stools; Complications: Recurrent urinary and vaginal infections; psychosocial discomfort;	See Table 8.14 for clinical exam and instrumental tests
Constipation/ reduced intestinal transit	Frequency: 20–89% of patients; it can be a premotor symptom of PD	Symptomatology: Abdominal bloating; Complications: Fecal impaction; bowel obstruction;	See Table 8.14 for clinical exam and instrumental tests
Difficulty in defecation	Frequency: 60% of patients; it can be due to the impaired release (dystonic phenomenon) of the anal sphincter;	Symptomatology: Excessive effort, pain and incomplete evacuation; Complications: Pain and failure to evacuate;	See Table 8.14 for clinical exam and instrumental tests

Peripheral sensory and autonomic neuropathy of large and small fibers may be present in metabolic disorders (DM, hypothyroidism, uremia), cobalamin deficiency, infections, immune-mediated conditions (gammopathies, vasculitis, and celiac disease), neurotoxic exposure (alcoholism and drug treatment), and in inherited conditions (inherited sensory and autonomic neuropathy, Fabry disease, and transthyretin-mediated hereditary amyloidosis).

Gastrointestinal autonomic symptoms occur frequently in DM and result in a major impact on quality of life. In particular, DM represents the most common cause of chronic gastroparesis, a condition of altered gastric motility resulting in delayed gastric emptying in the absence of mechanical obstruction [46, 49] (Table 8.11). The pathogenesis is complex and heterogeneous, being determined by

Table 8.11 Symptoms and signs of gastrointestinal autonomic dysfunction in Diabetes Mellitus and complications

Disease	Epidemiology	Clinical presentation	Evaluation
Functional dyspepsia	Prevalence up to 50% in DM1 and DM2	Symptoms: Epigastric fullness, early satiety, nausea, vomiting, pyrosis, abdominal pain Signs and complications: Hypo-hyper-nutrition, effect on glycemic control, weight modifications	See Table 8.14 for instrumental tests
Gastroparesis	Prevalence 9.6% in men and 37.8% in women (defined by scintigraphy; Olmsted County) Incidence 5.2% in DM1 and 1% in DM2 over 10 years (Olmsted County)	Symptoms: Dysphagia, nausea, vomiting, abdominal bloating, post-meal fullness, early satiety, abdominal pain, weight loss Signs and complications: Impaired balance between intestinal absorption of glucose and the action of exogenously administered insulin, or other antidiabetics; poor glycemic control (episodes of ketoacidosis); dehydration and nutritional deficiencies; weight modifications	Questionnaire Gastroparesis cardinal symptom index (GCSI) Gastrointestinal domain of the composite vegetative symptom score 31 (COMPASS 31) See Table 8.14 for instrumental tests
Diarrhea	Prevalence 15.6%	Signs and complications: Fecal incontinence, abdominal pain, dehydration and nutritional deficiencies, bowel malabsorption, weight modifications	Intestinal diary recording: Frequency and characteristics (liquid stools, with blood, with mucus, steatorrhea) See Table 8.14 for instrumental tests
Faecal incontinence	Prevalence 1–8.6%	Signs and complications: Possible association with diarrhea	Intestinal diary recording Perineum evaluation and RE See Table 8.14 for instrumental tests

Table 8.11 (continued)

Disease	Epidemiology	Clinical presentation	Evaluation
Costipation	Prevalence 30%	Symptoms and complications: Feeling of incomplete evacuation, need for manual maneuvers during defecation, possible association with diarrhea	Intestinal diary recording Perineum evaluation and RE See Table 8.14 for instrumental tests

Abbreviations in table: *DM1* type 1 diabetes mellitus, *DM2* type 2 diabetes mellitus; RE, rectal exploration

vegetative neuropathy and enteric neuropathy, abnormalities of *interstitial cells of Cajal*, and acute fluctuations in blood glucose. These mechanisms result in reduced *fundus* release, antral hypomotility with subsequent dilatation, and pylorospasm, all of which are responsible for dyspeptic symptoms. Moreover, unpredictable gastric emptying can impair the balance between intestinal absorption of glucose from food and the action of exogenously administered insulin, as well as other antidiabetics, resulting in postprandial glyceemic fluctuations and poor glyceemic control.

Chronic diarrhea and fecal incontinence, in addition to symptoms of gastroparesis, are common in diabetic patient [50, 51]. Hypo- and hyper-colonic motility have been demonstrated in DM and together with internal anal sphincter dysfunction, contribute to fecal incontinence [50, 51]. The management of diabetic patient with gastrointestinal autonomic symptoms, due to the above, is often suboptimal: therapy aims to control gastric symptoms, improve glyceemic control, and promote maintenance of optimal hydration and nutritional status. Treatment is essentially based on dietary and behavioral measures and use of prokinetic drugs, although these are not effective in all patients. Surgery and gastric electrostimulation represent alternative forms of therapy to be reserved for cases refractory to drug therapy.

8.9 Laboratory and Instrumental Tests for the Diagnosis of Dysmotility of the Gastrointestinal System

Currently, we do not have a commercially available *in vivo* diagnostic test for the diagnosis of enteric dysmotility, and GI symptoms are generally not predictive of objective motility dysfunction. This condition would always recommend a specialized objective evaluation by verifying the type and extent of GI motor disturbance; available clinical-instrumental diagnostic findings that can provide useful information to support the diagnosis of enteric dysmotility are helpful in guiding its treatment. However, although the finding of GI motor impairment in a patient with GI dysmotility significantly increases the likelihood of enteric neuropathy, some patients may have enteric dysmotility despite normal motility measurements. The pathophysiology underlying GI system dysmotility varies among patient groups, but the methods of assessing dysfunction are overall identical.

Table 8.12 Instrumental tests for diagnosis of vegetative dysmotility of the GI system

First-line testing
Esophagogastroduodenoscopy; Anoscopy/colonoscopy; colon-CT; X-ray barium enema
Further insights
(a) Radiological tests (X-ray video-Fluoroscopy; Scintigraphic gastric emptying; intestinal transit time study; Defecography or defeco-MRI)
(b) Functional/metabolic tests (high-resolution esophageal, gastroduodenal, anorectal manometry; balloon expulsion test; wireless motility capsule; Fibrolaryngoscopy)
(c) Hydrogen and methane breath test

Diagnosis involves exclusion of primarily gastro-enterological disease; then, identification of neurologic disease and its distribution; and documentation of segmental bowel dysfunction, usually using noninvasive imaging, transit measurements, or intraluminal measurements of pressor activity and motility coordination.

In patients with moderate symptoms without any warning symptoms, noninvasive motility testing should be considered in the first instance. Otherwise, however, digestive endoscopy is one of the most widely used methods to which the patient should be referred immediately. This technique is both diagnostic and therapeutic, useful for the study of many gastroenterological pathologies, as it allows not only a direct view, from the inside, of certain organs but also allows histologic typing or/and removal of lesions by biopsy or endoscopic operative techniques (e.g., polypectomy) (Table 8.12).

8.10 Laboratory and Instrumental Tests for the Diagnosis of Dysmotility of the Gastrointestinal System: First-Line Testing

This group of tests is indicated to rule out organic pathologies. The symptoms of GI motor disorders are nonspecific, and dysmotility cannot be differentiated from organic pathology on the basis of the patient's history alone. For example, epigastric pain, early satiety, and abdominal fullness are typical symptoms of gastroparesis but may also be due to gastroduodenal ulcers or gastric cancer. Therefore, it is important to first rule out other etiologies, especially mucosal and obstructive lesions, by appropriate investigations such as upper and lower gastrointestinal endoscopy, imaging techniques, and laboratory investigations. Such tests are mandatory in patients with warning symptoms (i.e., age, low hemoglobin levels, weight or blood loss, consistent episodes of vomiting, recent onset constipation).

First-line testing: Virtual colonoscopy is a simple low-dose x-ray CT scan. The anatomical data acquired in a few seconds with the CT scan are then processed by specific software, which reconstructs the bowel virtually and three-dimensionally on the screen, allowing "navigation" within it, but also visualizing the thickness of the colon wall and other organs.

Table 8.13 First-line test to disprove GI organic pathologies

	Esophagogastroduodenoscopy EGDS	Colonoscopy/ anoscopy	COLON-CT	Double-contrast opaque enema
Evaluated bodies	Esophagus stomach duodenum	Anus-rectum, colon, terminal ileum	Colon	Colon
Biopsies	Yes	Yes	NO	NO
Operating procedures	Yes	Yes	NO	NO
RX	NO	NO	Yes	Yes
Preparation	Yes	Yes	Yes	Yes

First-line testing: *Double-contrast opaque schism* is a technique that is now rarely performed because it has been replaced by colonoscopy and virtual colonoscopy. It is an x-ray of the colon and rectum performed by using first a suspension of water and barium introduced rectally and then air, which allows the structure of the organ in which it is placed, i.e., the colon in toto, to be visible on x-rays. It is indicated in suspicion of an abnormality in the rectum or colon, or in cases of irregular bowel function (sudden onset of constipation even alternating with diarrhea). It may show neoplasms and diverticula (small extroversions of the intestinal wall) and mucosal changes (Table 8.13).

8.11 Laboratory and Instrumental Tests for the Diagnosis of Dysmotility of the Gastrointestinal System: Further Investigation

Radiological tests are indicated to assess swallowing dynamics, morphology of the esophagus and esophago-gastric junction, to measure gastric and gastrointestinal emptying time, to morpho-functionally evaluate all pelvic floor structures and study their dysfunction underlying symptoms. Functional/metabolic tests are useful to assess the motor activity and sensitivity of the GI system. Finally, a niche examination, Breath tests are tests that through exhaled breath provide reliable indications of various diseases, such as lactose intolerance, bacterial contamination, malabsorption.

Radiological tests. X-ray videofluoroscopy (or radiologic study of swallowing or morphodynamic Rx of swallowing) is a radiologic investigation, indicated in cases of dysphagia, which is minimally invasive, well-tolerated, easily performed, lasting only a few minutes and with minimal radiologic exposure. It allows, by video recording, to accurately study the entire dynamics of the complex mechanism of swallowing, esophageal motility, the presence of endoluminal pathology, and the position of the gastroesophageal junction. It is also of great help in identifying the

most useful rehabilitation techniques for the purpose of improving swallowing efficiency and reducing the risk of aspiration. The test allows precise correlation between pressure events (esophageal contractions) and the actual propagation of the radio-opaque bolus from the oral cavity to the pharynx, esophagus and, through the cardia, to the stomach. It can be performed with boluses of various sizes and nature (liquid or solid). The technique in recent years has evolved a great deal thanks in part to the recent introduction of digital elements that make it possible to acquire, using minimal doses of radiation the entire investigation, from the introduction of the meal into the oral cavity to the passage of the bolus into the stomach and the first loops of the mesenteric tenous, with dynamic reconstructions of up to 15 images per second.

Scintigraphic gastric emptying: it is indicated in patients with early satiety, nausea, vomiting, regurgitation, bloating, postprandial fullness, visible upper abdominal distension, abdominal pain and weight loss, in whom a risk factor such as long-standing diabetes mellitus has been identified, in suspected gastroparesis and in all cases in which objective evidence of delayed gastric emptying is required. Scintigraphy is the gold standard for measuring gastric emptying: it involves the use of harmless radioactive materials administered with a meal or beverage or intravenously. Radiation emitted by the radiopharmaceutical (^{99m}Tc -Nanocolloid) is detected by the gamma chamber and transformed into images. Alternatively, ^{13}C gastric emptying breath tests can be used [52].

Several substrates including octanoic acid (medium chain fatty acid) and *Spirulina platensis* (edible seaweed) are labeled with a stable carbon (nonradioactive- ^{13}C) Unclear and subsequently incorporated into the solid component of low-calorie meals. After transiting the stomach, these are digested and absorbed in the proximal small intestine and metabolized by the liver so that ^{13}C is excreted from the lungs and its increase from baseline in breath samples can be measured by mass spectrometry. Thus, alterations in the $^{13}\text{C}:^{12}\text{C}$ ratio in breath samples collected at multiple postprandial time points reflect gastric emptying. Given the strong correlation with scintigraphy obtained simultaneously, the ^{13}C spirulina technique has been approved by the U.S. Food and Drug Administration (FDA). It is a noninvasive, repeatable, simple and relatively inexpensive technique and can be centralized. The main limitations are artifacts in patients with intestinal malabsorption and liver or lung disease.

8.12 Laboratory and Instrumental Tests for the Diagnosis of Dysmotility of the Gastrointestinal System: Other Diagnostic Options in Highly Specialized Centers

8.12.1 Two/Three-Dimensional Transabdominal Ultrasound

Intestinal Transit Time Study, measures the rate at which fecal waste moves in the colon by monitoring intestinal progression of radiopaque markers administered p.o. (20 markers \times 3 days every 24 h) with direct Rx of the abdomen [53]. The patient,

after having had a spontaneous or provoked evacuation (in this case preferably by enema) 24–36 h before the start of the investigation and maintaining usual eating habits, should take during breakfast 20 radiopaque markers (1 sachet), at 9 a.m. for 3 consecutive days. Each day, the indicators will have a different form. On day 4 and, if necessary, on days 7 and 10, the patient will undergo a direct examination of the abdomen, in postero-anterior projection, on large-format film (35 × 43), taking care to include in the radiograms the entire pelvic excavation (including the pubic symphysis) and the two colic flexures. A radiogram in lateral projection (on 24x39 film) will be performed, including sacrum and coccyx, where the indicators reach the pelvic excavation. The day and time of any evacuations should be reported on a sheet throughout the investigation. Once the radiograms have been taken, a line passing through the vertebral spinous apophysis on the P-A radiogram and one perpendicular to the sacrum, passing through the S1-S2 intervertebral space on the lateral radiogram, should be drawn so as to roughly distinguish right colon (CD: cecum, ascending and mid-transverse) from left colon (CS: left mid-transverse, descending and sigma) and rectum (Re). Then it will be necessary to count and report the number of radiopaque indicators of each type present in the CD, CS and Re, respectively. Data analysis: (i) the parameters considered are total oro-anal transit time, which is equal to the evacuation time of 80% of the indicators administered (of at least one type); (ii) normal values in adults <96 h, children <33 h; (iii) segmental transit of the CD, CS and Re is assessed by the transit index, which is the average percentage of indicators cleared daily from each segment considered; normal values are in adults CD < 82, CS < 62, Re < 64, children < 60 for all segments.

Defecography and Defeco-RMN, are indicated for the diagnosis of organic and functional pelvic floor pathology. Defecography is the radiologic study that simulates defecation, allowing its pathophysiology to be studied and related disorders to be highlighted by video recording of evacuation after rectal filling with barium. It allows visualization of the pelvic floor and wall of the rectum in both basal and dynamic conditions and the detection of functional and anatomical changes that are only evident during evacuation effort. Rx of the pelvis in lateral projection: at rest, in contraction, in ponxation, and during evacuation. Defeco-RMN: Allows morphological evaluation with simultaneous study of various segments of the pelvis and soft tissues in both static and dynamic.

8.13 Laboratory and Instrumental Tests for the Diagnosis of Dysmotility of the Gastrointestinal System: Subsequent Insights Functional/Metabolic Testing

High-resolution esophageal manometry, allows the motility of the esophagus and upper and lower esophageal sphincter to be studied by introducing a catheter into the viscera that can measure pressure changes occurring in the lumen of the organ. It is indicated in the presence of nonorganic dysphagia, non-cardiac chest pain, GERD, systemic diseases (collagenopathies, amyloidosis, diabetes, etc.).

High-resolution esophageal manometry represents an advancement of the classic technique to study the muscular function of the esophagus: the probe incorporates up to 36 sensors, which allow the entire esophagus to be scanned from the pharynx to the stomach and allow precise measurement of pressure, esophageal peristalsis, and upper and lower esophageal sphincter activity. The examination is performed by introducing, through the nostril a flexible nasogastric tube about 5 mm in diameter. The patient will be lying down and will have to swallow water or solids when required. The investigation takes 20 min. This procedure is considered safe.

High-resolution gastroduodenal manometry is an invasive and expensive technique, but it provides important information about the frequency and strength of antral and proximal bowel contractions, antra-duodenal coordination, and the presence or absence of stage III MMC. It is performed only in specialized centers dedicated to research.

High-resolution anorectal manometry is a method that can provide important data on the physiology and pathology of the defecatory act. It studies the prevailing pressures in the rectum and anal canal at rest, during stimulation and dynamic testing, gives information on anorectal function expendable in clinical practice, for diagnostic, evaluative and therapeutic-rehabilitative purposes. It also assesses rectal sensitivity. It is commonly used in cases of fecal incontinence, difficulty evacuating, anal fissure, rectal prolapse, hemorrhoids, or rectal pain. Currently, high-resolution manometry allows measurement and analysis of the pressure activity of the rectum and anal sphincter with a single placement of a catheter and allows reconstruction of the anal canal through the 36-point recorder readings that ensure optimal diagnostic accuracy. Technique of execution: a tube of about 5 mm in diameter is introduced into the rectum for about 10 cm after evacuation enemas. The patient will be lying on the left side, with thighs overlapping and flexed on the trunk at 90°. The investigation takes 20–30 min. It has virtually no complications or contraindications.

The balloon expulsion test is to assess expulsive capacity in suspected abdominopelvic dyssynergy. This test is not a standardized method, but it is part of the tests indicated by the guidelines to be performed in cases of defecatory difficulty. The method is simple and inexpensive; it is performed by filling a rectal balloon with 50 ml of warm water, sitting the patient on the sanitary vessel, or a comfortable one, and recording the time of expulsion, which must be less than 2 min.

The Wireless Motility Capsule (WMC) is a noninvasive technique to indirectly measure gastric emptying and intestinal transit times. Once ingested, the capsule records pH, pressure, and temperature signals that are analyzed by an external receiver. This smart pill has the limitation that, being a large indigestible solid, even when ingested with a test meal, it does not reflect the emptying of its calorically digestible components as it is eliminated separately during the fasting state. However, it does allow the assessment of global transit abnormalities that may be useful in the evaluation and management of comorbidities, such as constipation, that are associated with gastroparesis [54]. In studies conducted, WMC has enabled correct diagnosis in more than 50% of patients with suspected gastroparesis (or

slow intestinal transit). In a recent study WMC detected delayed gastric emptying in 10% more individuals and in almost twice as many diabetics as scintigraphy [55].

Fiberoptic Endoscopic Evaluation of Swallowing (FEES), is an additional instrumental examination for the study of vegetative gastrointestinal dysfunction dysphagia, also called functional dyspepsia [56]. It has the advantage of being a well-tolerated, modestly invasive outpatient procedure that can be performed even in uncooperative patients.

The main goals of FEES are to identify the oropharyngeal swallowing deficits underlying neurogenic dysphagia, to evaluate the efficacy and safety of oral feeding, to identify rehabilitative and adaptive therapeutic maneuvers, along with the most appropriate food consistencies and postural strategies for the individual patient. FEES also makes it possible to detect indirect signs of esophageal dysphagia such as post-deglutition reflux that can occur because of GI autonomic dysfunction; by allowing to examine of the entire intake of a meal in real time, it also enables the detection of swallowing muscle fatigue with late esophageal regurgitation [57].

The method therefore allows for a complete evaluative picture of the larynx and pharynx morphology, motility, and functions [58]. It follows that the evaluation of pharyngeal stagnations, in relation to their location, extent, management, degree of penetration and aspiration into the larynx, is particularly indicated in pathologies such as PD and Parkinsonism, where the differential diagnosis between oropharyngeal dysphagia and indirect pharyngeal phase impairment due to gastropharyngeal-laryngeal reflux from related esophageal autonomic dysfunction, both of which are present but not always simultaneously, is necessary because of the different therapeutic approach that ensues (Box 8.6).

Box 8.6: FEES in the Evaluation of the Patient with Vegetative Dysphagia

FEES in the evaluation of the patient with v dysphagia allows for an evaluation of GERD, an extremely common pathology characterized by typical symptoms (heartburn and regurgitation) and influenced by diet, stress, and lifestyle, and which, due to the alterations induced on the pharyngolaryngeal mucosa, simulates pharyngeal deglutition alterations that are actually absent.

This type of reflux always originates from the stomach and, due to incompetence of the upper esophageal sphincter (SES), is able to reach the mucosa of the larynx and pharynx [59]. These structures are extremely sensitive to gastric juice, so inflammation sets in very rapidly for even minute amounts of refluxed material, resulting in the symptoms described earlier.

The atypical symptomatology of GERD is represented by dry, hacking cough; pharyngeal foreign body sensation (throat knot); difficulty swallowing saliva; mucous stagnation sensation; hoarseness or voice disturbance; need to have to clear the voice frequently; dry mouth and throat; and sore and burning

throat. The above symptoms always require consultation by an Otolaryngologist or Phoniatician, whose history and clinical evaluation should be complemented by fibroendoscopy with swallowing tests.

At FEES signs suggestive of gastroesophageal reflux are hyperemia of the mucosa of the arytenoid cartilages, inter-arytenoid mucosa, true vocal cords, tracheal mucosa; inter-arytenoid pachydermia; ulcers of the mucosa of the arytenoid cartilages, inter-arytenoid mucosa; laryngeal granulomas; of the mucosa of the arytenoid cartilages, inter-arytenoid mucosa. However, the swallowing act both spontaneous and on demand of saliva and food, appears normal.

However, the significance of endoscopic exploration in subjects with vegetative dysfunction is also to avert the presence of swallowing deficits that could give rise to the same symptoms (i.e., aspiration cough in the dysphagic oropharyngeal subject) of different prognostic impact as well as a therapeutic approach.

In the GI dysfunction of patients with Parkinsonism, FEES can detect characteristic dysphagia signs such as predeglutatory dropping, bolus fragmentation, stagnation in the glossoepiglottic vallecula and piriform sinus, delayed pharyngeal phase initiation, and deficits in laryngeal movement, bolus penetration (when it reaches the vocal cords), and aspiration (when the bolus passes the true vocal cords). The extent, location, and management of stagnation influence the risk of penetration and aspiration [60].

Being able to assess numerous swallowing acts and detect altered swallowing parameters even in patients at an unadvanced stage of disease, FEES is a highly sensitive method that also allows early diagnosis of asymptomatic dysphagia [61]. In addition to the standard FEES protocol, specific testing protocols have been developed and validated for various neurogenic disorders; the FEES-L-Dopa-Test is for the evaluation of L-Dopa-sensitive dysphagia in patients with Parkinson's syndrome [62].

Several useful scales are also available for quantifying salient endoscopic findings such as the Aspiration and Penetration Scale (PAS), according to Rosenbek [63], the Yale Residual Scale [64], and the Secretion Severity Scale [60].

8.14 Laboratory and Instrumental Tests for the Diagnosis of Dysmotility of the Gastrointestinal System: Ultra-Specialty Evaluation

Hydrogen breath test (H₂-breath test) and respiratory methane test are used for the study of bacterial contamination of the small intestine and for the diagnosis of mal-absorption of certain sugars (lactose, sorbitol, glucose). In case of bloating,

distension, alterations in alvus. They also provide important data on intestinal transit times. They are noninvasive, easy to perform, and excellently tolerated by patients. They are based on the failure of the intestinal mucosa to absorb certain sugars, resulting in the production of hydrogen (H₂) and methane (CH₄), which are found in the exhaled air [65].

8.15 Suggestions for the Management of Gastro-Enteric Failure

Functional dyspepsia, as an expression of intestinal dysmotility, is a clinical problem that is not easy to treat because the available drugs are often ineffective; moreover, to the little benefit adduced, one can add the side effects inherent in any therapy.

Some relevant GI autonomic dysfunctions benefit from treatment with resolution of the problem or, at least, management of the disorders determined by the underlying disease. Thus, in addition to treatment of the underlying neurological disease, management focuses mainly on restoration of normal hydration and nutrition and pharmacological treatment of GI neuromuscular deficit. The main autonomic dysfunction syndromes with recalls of pathogenesis and diagnostic-therapeutic suggestions are presented in Table 8.14 [2].

Table 8.14 Visceral dysfunctional syndromes: reminders of pathogenesis and diagnostic-therapeutic suggestions

Clinical presentation	Neurological mechanism	Diagnosis/assessment	Management
Oropharyngeal dysphagia	Pharyngeal skeletal muscles; lower motor neuron (i.e., bulbar polio or pseudobulbar palsy) or muscle (e.g., ALS, myasthenia gravis)	Physical exam: Dentition, movement of the uvula (IX and X cranial nerves) Jaw snap Instrumental examination: Video fluoroscopy; HR esophageal manometry; FEES	Nutritional support Prevention of pulmonary aspiration
Thoracic dysphagia, GERD	Vagal denervation Or smooth muscle disease	Instrumental examination: Video fluoroscopy; FEES; HR esophageal manometry; PH impedancemetry of the 24 h	PPI Prokinetics Antacids

(continued)

Table 8.14 (continued)

Clinical presentation	Neurological mechanism	Diagnosis/assessment	Management
Dyspepsia nausea-vomiting (gastroparesis)	Vagal, myenteric denervation; Drug iatrogenic (narcotics, GLP-1 agonists)	Instrumental examination: Gastric emptying test (scintigraphy/GEBT) GD manometry Self-tests	Hydration and nutrition support Prokinetic therapy and antiemetics in refractory patients pyloromyotomy feeding PEG nasogastric tube
Abdominal pain, distension/satiety, nausea/vomiting, diarrhea and/or intractable constipation, malabsorption (chronic intestinal pseudo-obstruction)	I wander Myenteric denervation Drug iatrogens (narcotics, GLP-1 agonists)	Physical exam: EO abdomen; E.R EMG (myopathy/neuropathy) Instrumental examination: Gastric emptying test (scintigraphy/GEBT) GD manometry EMG (myopathy/neuropathy)	Prokinetics for gastroparesis + enteral or parenteral nutrition Treating small intestinal bacterial overgrowth related to myopathic disease small intestine transplant
Constipation	Vagal or sacral parasympathetic Myenteric denervation	Physical exam: EO abdomen; E.R Associated neuropathy or spinal disease Instrumental examination: HR anorectal manometry with balloon expulsion Colon transit times VEDI note del testo	Diet Osmotic laxatives Secretory or prokinetic Pelvic floor rehabilitation TAI (transanal irrigation) Rarely colectomy or colostomy
Fecal incontinence	Pelvic nerves Sacred roots Cauda equina and spinal cord injury, pelvic floor and anal sphincters	Physical exam: Rectal exploration Instrumental examination: HR anorectal manometry EMG (myopathy/neuropathy)	Medicines Diet Pelvic floor rehabilitation Hygiene and skin care TAI Sphincter reconstruction and rarely colostomy or ileostomy

Table 8.14 (continued)

Clinical presentation	Neurological mechanism	Diagnosis/assessment	Management
Passive diarrhea/incontinence	Loss of sympathetic inhibitory control (may manifest with bowel motor activity, including diarrhea)	Physical exam: Abdomen exam Rectal exploration Instrumental examination: Chemical/physical and cultural and parasitological examination of feces Laboratory tests (i.e., celiac disease, pancreatic enzymes, dysthyroidism) Colonoscopy with ileoscopy + esophagoduodenoscopy with biopsy Anorectal manometry	Medicines Diet Pelvic floor rehabilitation Hygiene and skin care TAI Sphincter reconstruction and rarely colostomy or ileostomy

ALS amyotrophic lateral sclerosis, *EO* objective examination, *ER* digital rectal exploration, *GD* gastroduodenal, *GEBT* gastric emptying with breath test, *GERD* gastroesophageal reflux disease, *HR MAR* high-resolution anorectal manometry, *PEG* percutaneous endoscopic gastrostomy

In the absence of protocols validated through randomized, controlled trials, research has turned toward the study and evaluation of para pharmaceuticals capable of modifying GI activity; today a wide range of dietary supplements based on nutrients or other substances with a “physiological” effect (e.g., plant extracts and preparations) are also available; as well as other “natural” products (Table 8.15). These are to date widely consumed in the population and aimed at seeking health and wellness benefits [66].

Although in the body, the main responsible for the contractility of gastrointestinal muscles, as already mentioned, is acetylcholine, most prokinetic drugs act at higher levels than it itself is released, resulting in important systemic side effects that limit the use of cholinergic agonists. For the treatment of all propulsive-type motor disturbances of the gastrointestinal tract, to stimulate motility of both stomach and intestines, in cases of GERD, dyspepsia, nausea, vomiting, and constipation from slowed transit, prokinetics capable of more selectively coordinating contractile activity and transit of intestinal contents are currently used. Those mainly involved are dopaminergic (D2) subtype, serotonergic (5-HT3 and 5-HT4), muscarinic-type cholinergic and motilin receptors.

Prokinetic drugs that act on dopaminergic receptors block the effects of dopamine, which normally reduce motility in the gastrointestinal tract. Their activity results in increased motility and reduced nausea and vomiting, the latter mechanism mediated by activity on dopaminergic receptors centrally. The activity on serotonergic receptors is agonist, which causes stimulation of peristalsis and gastric emptying.

Table 8.15 Parapharmaceutical drugs capable of modifying GI activity

Symptom	Active ingredient	Action
Gerd-dyspepsia	Iberis Amara, Matricaria chamomilla Carum carvi, Mentha piperita Glycyrrhiza glabra Melissa officinalis Chelidonium majus Silybum marianum Angelica archangelica, Perilla, ginger, melatonin, alginate, pectin carbenoxolone	Mucoprotective effects Prokinetic effects Anti-inflammatory effects Enzymatic effects
Nausea-vomiting	Ginger Vitamina B6 Perilla	<ul style="list-style-type: none"> – Prokinetic effect at the gastroduodenal level – Essential for the synthesis of serotonin – Prokinetic and anti-inflammatory effects
Diarrhea	Probiotics Diosmectide Psillium/guar gum Berberine	<ul style="list-style-type: none"> – They colonize the intestine and compete with pathogens (bacteria, viruses and protozoa) responsible for acute and/or chronic diarrhea (secretory/inflammatory) – Clay that covers the mucous membrane and protects it by increasing the resistance of the mucus and binding to pathogens, bacteria, viruses and toxins. – Mass forming – Antimicrobial, eubiotic and intestinal antisecretive actions; reduces intestinal motility
Constipation	Senna cascara aloe Lactulose Psyllium	<ul style="list-style-type: none"> – Anthraquinone laxatives – Osmotic laxative – Mass forming
Bloating	Probiotics Charcoal	They compete with the methanogenic microbiota The porosity is exploited to trap substances and gases in order to avoid their absorption or accumulation in the digestive system

GERD gastroesophageal reflux disease

Serotonin is important for both motor and secretory functions of the gastrointestinal tract, so it is found in high concentrations. Activity on muscarinic receptors stimulates smooth muscle contraction, so there is increased motility. Finally, motilin is a hormone that promotes the flow of intestinal contents, as it acts by stimulating the release of acetylcholine. Metoclopramide reduces nausea and vomiting, often in cases from chemotherapy therapies, by facilitating gastric emptying; it can

be administered either orally or parenterally. Domperidone has a more specific action on D2 receptors at the gastric level unlike Metoclopramide, increasing gastric emptying.

It can also be used in the treatment of acid reflux in children. Second-generation prokinetics include those that act on serotonergic receptors (Cisapride, Renzapride, and Zelopride). Finally, third-generation ones include Prucalopride and the antibiotic Erythromycin. The latter owes its effect to its agonist action on motilin receptors. Third-generation drugs do not act on dopaminergic receptors and therefore lack the antiemetic effect and related adverse reactions.

Regardless of the mechanism of action, among the most widely used prokinetics are Betanechol; Neostigmine; Levosulpiride; Linaclotide; Domperidone; Bromopride; Metoclopramide.

8.16 Conclusion

The relationship between the nervous system and the digestive system is also ensured by the ANS. Extrinsic GI autonomic dysfunction can complicate the course of various vegetative nervous system disorders; recognizing and treating autonomic disorder is important. Autonomic dysfunction of other body districts (e.g., cardio autonomic disorders with reduced heart rate variability, arrhythmias, increased blood pressure variability, and neurogenic orthostatic hypotension), moreover, is associated with increased morbidity and mortality.

The activity of the GI system is promoted from the periphery and has a complex and peculiar peripheral control system through the ENS; this has a high degree of independence from the CNS. In GI disorders in the course of neurological disease, multidisciplinary management with the gastroenterologist is advisable. GI motility dysfunction is a varied and frequent disorder in both gastroenterology and neurology, although often underdiagnosed by neurologists. GI autonomic dysfunction may be driven by an ANS deficiency. Excluding other non-ANS pathologies, the mode of onset of GI autonomic disorders, its expression, and clinical progression can be helpful in the diagnosis and management of GI disorder; it can sometimes present in slowly progressive subtle ways, as when autonomic dysfunction may be the first sign of an underlying paraneoplastic condition.

The tempestive recognition of GI dysfunction is important to provide early administration of treatments which, however, are currently limited, as well as to allow prevention of GI complications in the course of neurological disease. Finally, autonomic tests support monitoring the course of autonomic disorders and the treatment response, even if specific GI tests should be performed in a multidisciplinary program with the support of gastroenterological experts.

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