Gastrointestinal Dysfunction

6

Roberta Granata, Eschlböck Sabine, Herbert Tilg, and Gregor Wenning

Contents

The present chapter is divided into three sections. In the first part, the diagnostic work-up of gastrointestinal (GI) dysfunction is discussed. The second focuses on specific disorders that involve gastrointestinal autonomic system followed by the last section, which provides an overview of specific management.

R. Granata • E. Sabine • G. Wenning (✉)
Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria
e-mail: roberta.granata@i-med.ac.at; gregor.wenning@i-med.ac.at

H. Tilg
Department of Gastroenterology, Medical University of Innsbruck, Innsbruck, Austria

W. Struhal et al. (eds.), *Bedside Approach to Autonomic Disorders*,
DOI 10.1007/978-3-319-05143-7_6

6.1 Diagnostic Work-Up

6.1.1 Gastrointestinal Dysfunction

Gastrointestinal autonomic dysfunction may result from primary dysautonomias (e.g. pure autonomic failure (PAF), multiple system atrophy (MSA)), but a more common scenario is a systemic disorder (e.g. diabetes mellitus) resulting in autonomic dysfunction [3] (see Fig. 6.1). Gastrointestinal autonomic dysfunction is mostly non-specific and manifests with a combination of various symptoms and different degrees of severity. The entire gastrointestinal tract can be affected leading to a plethora of features. Symptoms of the proximal GI tract include for example dysphagia, nausea or epigastric pain and involvement of distal GI tract results in obstipation, diarrhoea and faecal incontinence (see Fig. 6.2). Diagnosis and

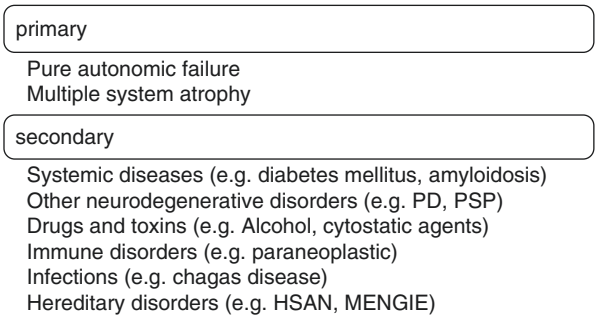

Fig. 6.1 Aetiology of gastrointestinal autonomic dysfunction (Modified from Bittinger et al. [3] with permission from Springer Science and Media)

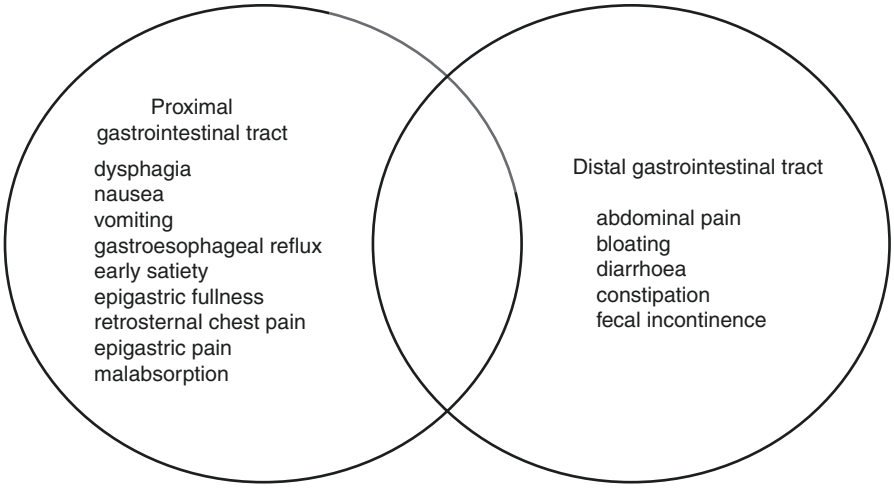

Fig. 6.2 Gastrointestinal manifestations arising from autonomic dysfunction [12]

treatment of gastrointestinal autonomic disorders are still challenging in clinical practice and require a detailed assessment and specific management.

For pathophysiology see Sect. 1.2.3.

6.1.2 History Taking and Red Flags

Gastrointestinal autonomic dysfunction includes a variety of unspecific symptoms. Accurate history taking and identification of red flags are pivotal for diagnosis. Detailed assessment of gastrointestinal complaints encompasses symptom onset, chronology as well as frequency, character and location of current GI symptoms. Frequency of defaecation as well as stool colour and consistency and events of haematochezia or melaena are essential for diagnosis. Patients should be asked about dietary habits and aggravating and alleviating factors of symptoms. Further evaluation includes comorbidities, past surgical history, current treatment as well as family and social history. Red flags that may suggest gastrointestinal autonomic dysfunction are summarised in Fig. 6.3 – See also Sect. 2.2.4.1 for reference.

6.1.3 Physical Examination

Based on historical features, general physical examination needs to be performed. In the first step, physical examination should focus on signs of gastrointestinal diseases (ascites, gynaecomastia, abdominal bruits, hernial orifices, alterations of the

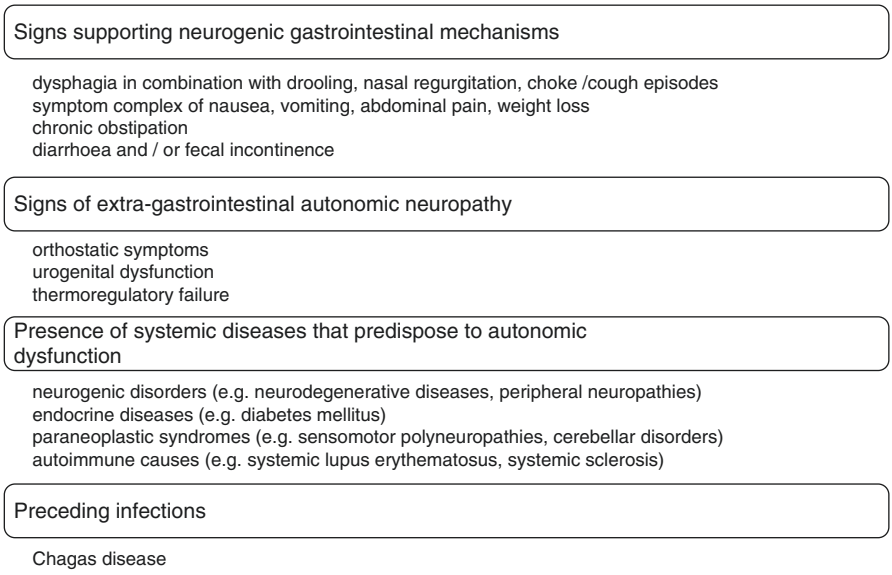

Fig. 6.3 Red flags suggesting gastrointestinal autonomic involvement [3, 44]

skin, eyes and hands), which are important for differential diagnosis, and further encompasses abdominal auscultation, percussion and palpitation. Digital rectal examination should be conducted to complete physical examination.

6.1.4 Laboratory Tests

According to the predominating symptoms and differential diagnosis, the following laboratory tests should be considered: full blood count, C-reactive protein, erythrocyte sedimentation rate, thyroid function tests, liver function tests, amylase, creatinine, urea, electrolytes, calcium, glucose, vitamin B12, electrophoresis, plasma autoantibodies and urinalysis [26, 31]. Special laboratory tests may be necessary in selected cases.

Autonomic Neuropathies Antibodies (anti-Hu, anti-nicotinic acetylcholine receptor antibodies, anti-Ri, cytoplasmic antigens (amphiphysin, anti-Yo), voltage-gated neuronal potassium channel complex (VGKC), calcium channel antibodies, glutamic acid decarboxylase 65 (GAD65), peripherin-IgG) are detected in serum or cerebrospinal fluid. Specific genetic tests may be considered for the diagnosis of inherited neuropathies [31]. For diagnostic work-up of autoimmune autonomic ganglionopathy, antiganglionic nicotinic acetylcholine receptor (AChR) (α3 subunit) antibodies may provide additional information [48]. Nonetheless, seronegativity has been reported in about 50% of cases with clinical features of subacute onset of multidomain autonomic failure suggesting an immune-mediated autonomic ganglionopathy [36].

Chagas Disease In acute phase, organisms may be detected in Giemsa-stained smears from tissue or cultivated in special media. Chronic phase serology or molecular biological tests may be helpful for diagnosis [4].

6.1.5 Investigations

Diagnostic work-up is difficult, because no specific assessment for GI autonomic neuropathy is available and limited to the detection of its sequela [3]. Nevertheless, detailed evaluation (see Fig. 6.4) is mandatory to define aetiology and fundamental for tailored therapy.

Dysphagia is a common symptom and may occur due to mechanical block or dysmotility. Difficulties in swallowing associated with drooling, nasal regurgitation, choke and cough episodes suggest neurogenic mechanisms [8], which result from sensorimotor impairment and can affect oral, pharyngeal or oesophageal phase of swallowing [44]. Although upper GI endoscopy including endoscopic biopsy per se does not diagnose motility disorders, endoscopy should be considered if structural abnormalities are suspected. Further investigations include videofluoroscopy to assess oropharyngeal dysfunction [33] and radiological investigation with barium swallow for detection of oesophageal dysmotility and structural abnormalities. In

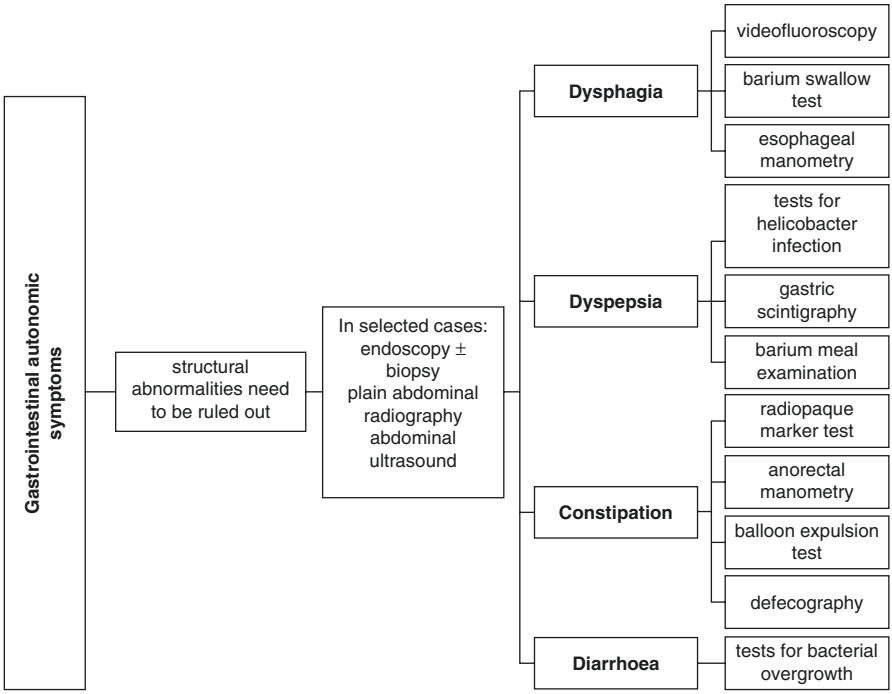

Fig. 6.4 Investigations of gastrointestinal symptoms (Modified from Fasano et al. [14] with permission from Elsevier)

case of normal barium swallow test and unexplained dysphagia or suspicion of oesophageal motility disorder, oesophagus manometry is of particular value [4].

Upper GI endoscopy is the predominant diagnostic modality to evaluate dyspepsia, and non-invasive tests including urea breath test, stool antigen test and serology are available to detect helicobacter infection [14]. Gastroparesis and delayed gastric emptying need to be evaluated by gastric scintigraphy, which is performed with radiolabelled digestible solids or liquids [10]. Although barium meal examination may be performed to detect gastric dysmotility, gastric scintigraphy remains the gold standard [4].

Assessment of chronic constipation resulting from neurologic disorders requires specific examination. In the first step, anorectal diseases, intestinal obstruction, metabolic/endocrine causes and drugs need to be ruled out. Therefore, to exclude structural diseases, patients younger than 50 years and without alarm signs (e.g. fever, weight loss, blood in the stools) should undergo sigmoidoscopy. In patients older than 50 years, colonoscopy or sigmoidoscopy in combination with barium enema examination is recommended [28]. For the assessment of colonic transit time, radiopaque marker test is considered as the standard measurement. In patients, which have clinical features that suggest a defecatory disorder, physiological testing is further recommended and includes anorectal manometry and balloon expulsion test. Defecography may be necessary to definitively exclude structural abnormalities in the rectum [26].

The pathomechanisms of diarrhoea are multifactorial. Common causes comprise infections (viral, bacterial, parasites, protozoa), inflammatory diseases (Crohn's disease, ulcerative colitis), colorectal cancer, coeliac disease and drug-induced diarrhoea, which need to be ruled out in the first step. Colonoscopy in combination with biopsy may be performed to definitely exclude malignancy and colitis. In the setting of gastrointestinal autonomic dysfunction, increased bacterial colonisation of the small intestine may lead to diarrhoea and malabsorption of nutrients [4] and can be established by breath hydrogen testing and jejunal aspirate [17].

6.2 Autonomic Dysfunction and the Gastrointestinal Nervous System

6.2.1 Gastrointestinal Autonomic Dysfunction in Neurodegenerative Diseases

In the last years, an increasing similarity of pathological mechanisms involving both the central and the peripheral gastrointestinal nervous system has been recognised in most neurodegenerative diseases. Intra- and extracellular inclusions of misfolded proteins are present in numerous CNS structures and sympathetic and spinal ganglia, as well as in the gastrointestinal plexus, with a different pattern and density of distribution in various neurodegenerative diseases. Like prion disorders, these protein aggregates can migrate from periphery (myenteric, submucosal plexus via autonomic innervation) to spinal cord, brainstem and other CNS structures or vice versa [13]. Some authors postulate the gastrointestinal tract as the origin of some neurodegenerative diseases, such as Parkinson's disease or MSA, dysfunction of the GI tract being a common premotor sign in these conditions [5, 7, 37, 49].

α-Synuclein aggregates forming Lewy bodies and Lewy neurites represent the pathological hallmark of Parkinson's disease and dementia with Lewy bodies and are found in early phases of the disease (according to Braak PD pathology stages) [6] in the dorsal vagal nucleus, olfactory bulb, midbrain and neostriatum. Lewy bodies are also widely present in the spinal cord, sympathetic ganglia, parasympathetic nervous system and enteric nervous system accounting for common gastrointestinal premotor symptoms such as slowing of gastrointestinal motility inducing dyspepsia, oesophageal achalasia and constipation [7, 38]. The presence of Lewy bodies in the submandibular gland and the related sympathetic and parasympathetic structures might explain the reduced salivary secretion in early stages of PD. Constipation is much more frequent in PD patients than in the healthy population [22], and people suffering of constipation have a 3.3- to 4.2-fold risk of developing PD [29]. Almost 90% of PD patients suffer of constipation, frequently worsening with disease progression [14]. Reduced gastric emptying is also present, causing upper gastrointestinal symptoms, but also interfering with optimal absorption of levodopa and consequently with optimal therapy efficacy and worsening levodopa long-term side effects such as fluctuations [32].

Dopaminergic medications can also produce gastrointestinal side effects, such as reduced gastrointestinal motility, whereas subthalamic nucleus-deep brain stimulation (STN-DBS) has been reported to improve gastrointestinal PD symptoms, such as delayed gastric emptying [32].

In MSA filamentous α-synuclein glial cytoplasmic inclusions (GCIs) are widely distributed. Massive autonomic dysfunction characterises these neurodegenerative diseases such as MSA and PAF including dysphagia and anal incontinence.

Gastrointestinal dysfunction may also be present in patients with AD and related tauopathies such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). These features likely reflect deposition of tau-positive neurofibrillary tangles (NFTs) in autonomic areas of the brain and spinal cord. Comorbid Lewy body pathology may also contribute to gastrointestinal dysfunction in Alzheimer's disease (AD). No NFTs have been reported in the myenteric plexus.

6.2.2 Gastrointestinal Autonomic Dysfunction in Peripheral Autonomic Neuropathies

Sympathetic and parasympathetic autonomic nerves (ANS) are constituted of small myelinated and unmyelinated fibres, the latter being predominant (about 80%). Most metabolic, hereditary, autoimmune, paraneoplastic and toxic neuropathies involve autonomic nerve fibres and may cause gastrointestinal autonomic dysfunction.

Among the metabolic neuropathies, the diabetic neuropathy is the most common. Hyperglycaemia increases apoptosis-activating ATP-sensitive K+-channels leading to loss of enteric neurons within myenteric and submucosal plexus, sympathetic ganglia and vagus nucleus, as well as of interstitial cells of Cajal (ICC). Other pathogenetic mechanisms of neuronal damage in diabetes mellitus (DM) involve decreased neuronal growth factor, increased circulating free fatty acids, altered transforming growth factor beta and decreased antioxidants such as glutathione [50]. Also reduced blood circulation and autoimmune/inflammatory response may play a role in neural damage.

Denervation mainly involves sympathetic nerve terminals, which have the function of reducing gut motility, and parasympathetic excitatory nerves being at least at the beginning spared from damage. Loss of ICC is associated with impaired relaxation of gastric fundus and the absence of slow-phase peristaltic movements. Delayed gastric emptying and increased distal retention lead to gastroesophageal reflux, early satiety sensation, gastric pain and vomiting [23, 39, 50]. Symptomatic gastroparesis is a rare complication of diabetic neuropathy accounting for 4.8% in type 1 diabetes and 1% in type 2 diabetes. The decrease of NO release from vagal efferent fibres and of the enzyme responsible for its generation, nNOS, has been postulated to play an important role in pathogenesis of delayed gastric emptying [21].

Reduced gut movements produce bacterial overgrowth and diarrhoea, which, together with faecal incontinence, is a common symptom of diabetic neuropathy.

Other mechanisms potentially accounting for diarrhoea include the presence of accelerated intestinal transit as suggested by some animal models [50].

Hereditary sensory and autonomic neuropathies (HSAN) represent a group of rare disorders characterised by degeneration of peripheral sensory and autonomic neurons leading to variable sensory and autonomic symptoms. HSAN type 3 is the disorder which shows most autonomic symptoms. HSAN 3, also known as Riley-Day syndrome or familiar dysautonomia, is a rare autosomic recessive disorder affecting principally Ashkenazi Jews. It is due to a mutation on chromosome 9q leading to depletion of IKAP/EPL1 protein which affects cell motility [45]. This genetic mutation results in a marked depletion of small C-fibres in the sensory and autonomic nervous system which can be demonstrated in the skin and on peripheral blood vessels. Children develop early and severe symptoms such as sensory loss (with frequent trauma and self-mutilation as consequence), the absence of tears, swallowing difficulties, pneumonia, orthostatic blood pressure dysregulation, autonomic crises with vomiting and gastrointestinal dysmotility. Oropharyngeal problems occur early in children with HSAN 3 which present with poor sucking, swallowing difficulties and consequent drooling. Vomiting can occur daily in response to physical or emotional stress [42].

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an autosomal recessive disease caused by mutations of the gene encoding thymidine phosphorylase. External ophthalmoplegia, gastrointestinal motility disorders, peripheral neuropathy and leukoencephalopathy are the main characteristics of this disease. Patients are often cachectic and suffer neuropathic pain [41].

Idiopathic, postinfectious or paraneoplastic autoimmune neuropathies can cause acute or subacute autonomic failures, including severe gastrointestinal dysmotility or pseudo-obstruction. Symptoms, such as vomiting, abdominal pain and constipation, are similar to those occurring due to mechanical obstruction. Oesophageal dysmotility (including achalasia) may also be present. Gastrointestinal hypermotility may occur in autoimmune dysautonomias. The term autoimmune gastrointestinal dysmotility (AGID) is generally accepted to indicate gastrointestinal manifestations of autoimmune autonomic neuropathies. In paraneoplastic disorders, dysautonomia can occur as isolated disorder or in combination with other neurological findings, such as sensorimotor polyneuropathies, cerebellar disorders and limbic encephalitis.

6.2.3 Gastrointestinal Autonomic Dysfunction in Infections: Chagas Disease

Autonomic dysfunction of gastrointestinal tract can occur in case of a parasite infection, the so-called American trypanosomiasis or Chagas disease, which is caused by the flagellate protozoan *Trypanosoma cruzi* [43]. The chronic form has a variable

course, 60% of individuals are asymptomatic and 20–40% of affected people present cardiomyopathy or gastrointestinal dysautonomia.

6.3 Therapy of Gastrointestinal Autonomic Dysfunction

Non-pharmacological treatment of gastrointestinal dysmotility includes dietary measures. Patients should avoid excessive food intake and instead eat small frequent meals, chew their food well and avoid fibre and fats. The judicious use of some drugs which affects gastrointestinal motility such as anticholinergics and opiates is also recommended.

In general, symptomatic therapies of gastrointestinal autonomic dysfunction include antidopaminergic agents, cholinesterase inhibitors and drugs which improve gastrointestinal motility, such as erythromycin or serotoninergic agents (i.e. the selective 5-HT4 receptor agonists prucalopride or mosapride), antiemetics and laxatives. Simple analgetics may be useful in the treatment of abdominal pain (*see* Table 6.1).

Table 6.1 Symptomatic treatment of gastrointestinal autonomic symptoms

	Drug	Doses	Action	Side effects
Prokinetics	Metoclopramide	10 mg/3×	Antidopaminergic (central and peripheral)	Drowsiness, fatigue, extrapyramidal effects
	Itopride	50 mg/3×	Antidopaminergic (peripheral), acetylcholinesterase inhibitor	Abdominal pain and diarrhoea
	Domperidone	10 mg/3×	Antidopaminergic (peripheral)	Dizziness, dry mouth, nervousness
	Prucalopride	2–4 mg/1×	Selective 5-HT4 receptor agonists	Headache, nausea, abdominal cramps and diarrhoea
	Lubiprostone	24 mg/2×	Activates type-2 chloride channels	Nausea, diarrhoea, abdominal pain
	Linaclotide	195/290 mcg/×1	Activates guanylate cyclase C	Diarrhoea
	Macrolide antibiotics (erythromycin)	250–500-mg/×2	Motilin agonists	Antimicrobial effect

(continued)

Table 6.1 (continued)

	Drug	Doses	Action	Side effects
Antiemetics	Prochlorperazine	5–10 mg	Antidopaminergic, anticholinergic (central)	Extrapyramidal effects
	Ondansetron and granisetron	8 mg	5-HT3 antagonists	Diarrhoea or constipation, headache, drowsiness, fatigue
	THC (tetrahydrocannabinol)	5–10 mg/×2–3	CB1 and CB2 receptor agonist in the CNS	Unsteadiness, dizziness, drowsiness, confusion
	Diphenhydramine	50 mg/×1–3	H1 receptor agonists, antimuscarinic	Sedation, drowsiness, increased heart rate, urinary retention
Analgetics	Gabapentin	300–800 mg/×3	GABA receptor agonist	Dizziness, fatigue
	Pregabalin	75–150 mg/×2–3	GABA analogue	Dizziness, fatigue
	Oxycodone	10–40 mg/day	μ-Opioid receptor antagonist	OIBD, dependence, addiction
	Naloxone	10–40 mg/day	μ-Opioid receptor antagonists	OIBD, dependence, addiction
	Tricyclic antidepressants	Dose depends on formulation	Serotonin-norepinephrine reuptake inhibitors	Dry mouth, urinary retention, constipation, cognitive impairment
Laxatives	Saccharin, lactulose, sorbitol macrogol, polyethylene glycol 3350, magnesium hydroxide, sodium biphosphate	Dose depends on formulation	Osmotic activity	Abdominal distention and pain, diarrhoea, dehydration

The dopamine receptor antagonist metoclopramide is used in case of gastroparesis [1]. It has both a peripheral (in the upper gastrointestinal tract) and a central effect. Being an inhibitor of CYP2D6, enzyme 45 should not be used in combination with antidepressants such as tricyclics, selective serotonin reuptake inhibitors and antidepressants acting as serotonin-noradrenalin reuptake inhibitors

(venlafaxine or duloxetine), which could increase the risk of extrapyramidal side effects. Drowsiness and fatigue represent the most common side effects of metoclopramide. Due to possible extrapyramidal effects, it should be avoided as a long-term treatment in patients with extrapyramidal diseases and in younger patients and children [27].

Itopride is a peripheral antidopaminergic drug that also increases acetylcholine levels due to acetylcholinesterase inhibition and can be used as prokinetic agent. It is metabolised through a mono-oxidase system, and it can be used relatively safely with other drugs such as antidepressants. Due to its exclusive peripheral antidopaminergic effects, itopride can be used also in patients with extrapyramidal diseases (i.e. PD) [27].

Domperidone, a dopaminergic receptor D-2 antagonist which does not cross the blood-brain barrier, is very useful to accelerate gastric emptying and represents the first-choice treatment for delayed gastric emptying, nausea and vomiting in PD or MSA patients [40].

The use of macrolide antibiotics may be considered in improving gastrointestinal dysmotility accelerating, such as motilin agonists, the MMC (migrating motor complex). Their chronic use is however limited due to the contemporary antimicrobial effect [25, 32].

Prucalopride and mosapride such as selective 5-HT4 receptor agonists; lubiprostone, which activates type-2 chloride channels; and linaclotide which activates guanylate cyclase C represent newer prokinetic drugs [9, 27].

Some prokinetic agents, such as the gastric-derived hormone ghrelin, ghrelin agonists and motilin, represent interesting treatment options for reduced gastric motility in diabetic neuropathies and PD. Some of these drugs are available only for study purposes, and controlled studies are needed to further evaluate the safety and efficacy of these medications [34, 46].

Linaclotide is a prokinetic drug that modulates chloride secretion of the intestinal epithelial cells through activation of guanylate cyclase C. Linaclotide improves defaecation by stimulating GI secretion and motility, increasing stool frequency as well as stool weight. The main adverse event of linaclotide is diarrhoea [35]. Linaclotide can be used for chronic constipation and may be useful also in case of opioid-induced bowel dysfunction (OIBD) [9, 27].

Phenothiazines such as prochlorperazine are potent neuroleptics and commonly utilised as therapy for nausea and vomiting. The antiemetic effect is due to the central action on dopaminergic and cholinergic receptors; however, their use is limited due to a potential risk of extrapyramidal side effects. Other antiemetic drugs include the 5-HT3 antagonists ondansetron and granisetron, cannabinoids, opioid agonists, benzodiazepines and H1 receptor agonists, such as diphenhydramine.

Laxatives can be used in patients with chronic constipation although their side effects such as dehydration and intestinal occlusion have to be considered [18, 24]. The most commonly used group of laxatives comprises osmotic agents such as lactulose, sorbitol, macrogol, polyethylene glycol 3350, magnesium and sodium salts

or detergents that increase GI secretion and decrease surface tension, such as docusate and stimulants like sennosides and bisacodyl that promote gastrointestinal motility [27].

In case of chronic abdominal pain, antineuralgic therapy with gabapentin and pregabalin, also in combination with tricyclic and tetracyclic antidepressants, may be helpful. Other analgetic drugs including weak opiates, such as naloxone and oxycodone, should be used very sparsely and only in refractory cases due to their gastrointestinal side effects such as opioid-induced bowel dysfunction (OIBD) and physical dependence and addiction [27].

In severe cases of pseudo-obstruction and ileus, surgical procedures may be necessary. Gastric electric stimulation is an effective treatment in severe cases of gastroparesis and drug-refractory vomiting [20].

Intrapyloric injection of botulinum toxin injection in some case of pylorospasm has been reported as efficacious in some open-label studies. Controlled trials have not confirmed this improvement [16, 19].

AGID (autoimmune gastrointestinal dysmotility) due to postinfectious dysautonomia is usually self-limited and requires symptomatic treatment only in the acute phase. Other forms of AGID (i.e. paraneoplastic or as manifestation of an idiopathic autoimmune disorder) may require immunotherapy with intravenous immune globulin (IVIG) or methylprednisolone (IVMP), especially if neural-specific immunoglobulins are detected in serum, although data regarding efficacy of this therapy are controversial. In case of a good response, long-term maintenance immunotherapy can be considered [15].

Two nitro-heterocyclic drugs currently represent the only treatment options for Chagas disease: benznidazole and nifurtimox. However, these drugs provide a lot of side effects, such as intolerance, allergic reactions and fever, being often very challenging to treat patients properly. Other effective drugs are currently needed, and at the present, a few drug trials are ongoing [11].

In patients suffering of synucleinopathies (PD, MSA), domperidone and selective 5-HT4 receptor agonists (i.e. prucalopride, mosapride) represent useful drugs to accelerate gastrointestinal motility especially in case of gastroparesis augmented by L-dopa fluctuations [30, 47]. Improved gastric emptying increases L-dopa absorption and induces an improvement of motor symptoms. Interesting data of improved gastrointestinal motility have been reported after subthalamic nucleus-deep brain stimulation (STN-DBS) which represent an effective therapy option in selected PD patients. STN-DBS may improve autonomic gastrointestinal dysmotility directly due to the connections of STN and autonomic centres or indirectly due to the reduction of dopaminergic therapy after STN-DBS [2]. Further treatment options in PD patients may be considered and include liquid levodopa formulations and parenteral routes (e.g. rotigotine transdermal patch, subcutaneous apomorphine, intrajejunal levodopa infusion) [14].

Case Report 1

A 64-year-old male patient with a history of Parkinson's disease and disease duration of 10 years complains about dysphagia and dyspepsia.

At neurological examination, a left-sided Parkinsonian syndrome with bradykinesia, rigidity and classic pill-rolling tremor is present. Furthermore, gait disturbances and bilaterally reduced arm swing are present. The patient reports no further signs of autonomic dysfunction. Although the patient usually has a good levodopa response, he suffers from disabling motor fluctuations.

Examinations to evaluate upper gastrointestinal symptoms include videofluoroscopy, which excludes oropharyngeal pathology. For the assessment of oesophageal motility, barium swallow exam is performed and demonstrates oesophageal dysmotility. Upper GI endoscopy, which is performed to rule out ulcers and malignancy, shows food residue in a fasted stomach suggesting gastric stasis. Therefore, gastric scintigraphy is conducted and confirms delayed gastric emptying.

Because of impairment of oesophageal and gastric motility, which leads to reduced absorption of levodopa and worsening of levodopa long-term side effects, subcutaneous apomorphine is recommended and provides improvement of motor symptoms.

Case Report 2

A 30-year-old woman is examined because of abdominal pain, weight loss, intractable obstipation and vomiting. The patient is cachectic and physically weakened because food ingestion is nearly impossible.

Medical history taking reveals gastrointestinal symptoms for 10 years. Additionally, the patient suffers from multidomain autonomic failure including urinary retention, recurrent syncope, hypohidrosis, sicca syndrome and Raynaud's phenomenon. Extensive examinations including autonomic function testing and immunological laboratory have been conducted and have ruled out other immunological disorders.

Broad examination of proximal and distal gastrointestinal tract confirms gastroparesis and severe colonic motility dysfunction but shows normal duodeno-cecal transit time. In the course of the disease, the patient is reliant on parenteral nutrition, and after double-barrel colostomy, she undergoes subtotal colectomy because of persistent gastrointestinal dysfunction. Histopathological examination reveals segmental hypogangliosis and

T-lymphocytic ganglionitis. The patient is given immunosuppressive therapy, which immediately leads to improvement of gastrointestinal symptoms. Autoimmune autonomic ganglionopathy (AAG) is suspected, but screening for antibodies to the ganglionic nicotinic acetylcholine receptor is negative.

Despite negative ganglionic nicotinic acetylcholine antibodies, which are found in only 50% of patients with AAG, clinical presentation and response to immunosuppressive therapy indicate the presence of AAG. The patient receives steroid therapy and tacrolimus stabilising the clinical disease course.

References

1. Abell TL, Bernstein RK, Cutts T, Farrugia G, Forster J, Hasler WL, McCallum RW, Olden KW, Parkman HP, Parrish CR, Pasricha PJ, Prather CM, Soffer EE, Twillman R, Vinik AI (2006) Treatment of gastroparesis: a multidisciplinary clinical review. Neurogastroenterol Motil 18(4):263–283
2. Arai E, Arai M, Uchiyama T, Higuchi Y, Aoyagi K, Yamanaka Y, Yamamoto T, Nagano O, Shiina A, Maruoka D, Matsumura T, Nakagawa T, Katsuno T, Imazeki F, Saeki N, Kuwabara S, Yokosuka O (2012) Subthalamic deep brain stimulation can improve gastric emptying in Parkinson's disease. Brain 135:1478–1485
3. Bittinger M, Barnert J, Wienbeck M (1999) Autonomic dysfunction and the gastrointestinal tract. Clin Auton Res 9(2):75–81
4. Boulton R, Cousins C, Gupta S, Hodgson H (2011) Gastroenterology, 2nd edn. London: Manson Publishing. ISBN: 978–1–84076-068-2
5. Braak H, de Vos RA, Bohl J, Del Tredici K (2006) Gastric alpha-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. Neurosci Lett 396:67–72
6. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 24:197–211
7. Braak H, Sastre M, Bohl JR, de Vos RA, Del Tredici K (2007) Parkinson's disease: lesions in dorsal horn layer I, involvement of parasympathetic and sympathetic pre- and postganglionic neurons. Acta Neuropathol 113:421–429
8. Buchholz DW (1994) Dysphagia associated with neurological disorders. Acta Otorhinolaryngol Belg 48(2):143–155
9. Busby RW, Kessler MM, Bartolini WP, Bryant AP, Hannig G, Higgins CS, Solinga RM, Tobin JV, Wakefield JD, Kurtz CB, Currie MG (2013) Pharmacologic properties, metabolism, and disposition of linaclotide, a novel therapeutic peptide approved for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation. J Pharmacol Exp Ther 344(1):196–206
10. Camilleri M, Shin A (2013) Novel and validated approaches for gastric emptying scintigraphy in patients with suspected gastroparesis. Dig Dis Sci 58(7):1813–1815
11. Chatelain E (2015) Chagas disease drug discovery: toward a new era. J Biomol Screen 20(1):22–35
12. Chelimsky G, Chelimsky TC (2003) Evaluation and treatment of autonomic disorders of the gastrointestinal tract. Semin Neurol 23(4):453–458
13. Cushman M, Johnson BS, King OD, Gitler AD, Shorter J (2010) Prion –like disorders: blurring the divide between transmissibility and infectivity. J Cell Sci 123:1191–1201
14. Fasano A, Visanji NP, Liu LW, Lang AE, Pfeiffer RF (2015) Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurol 14(6):625–639

15. Flanagan EP, Saito YA, Lennon VA, McKeon A, Fealey RD, Szarka LA, Murray JA, Foxx-Orenstein AE, Fox JC, Pittock SJ (2014) Immunotherapy trial as diagnostic test in evaluating patients with presumed autoimmune gastrointestinal dysmotility. Neurogastroenterol Motil 26(9):1285–1297
16. Friedenberg FK, Parkman HP (2006) Delayed gastric emptying: whom to test, how to test, and what to do. Curr Treat Options Gastroenterol 9(4):295–304
17. Grace E, Shaw C, Whelan K, Andreyev HJ (2013) Review article: small intestinal bacterial overgrowth – prevalence, clinical features, current and developing diagnostic tests, and treatment. Aliment Pharmacol Ther 38(7):674–688
18. Holzer P, Ahmedzai SH, Niederle N, Leyendecker P, Hopp M, Bosse B, Spohr I, Reimer K (2009) Opioid-induced bowel dysfunction in cancer-related pain: causes, consequences, and a novel approach for its management. J Opioid Manag 5(3):145–195
19. Hoogerwerf WA, Pasricha PJ (1999) Botulinum toxin for spastic gastrointestinal disorders. Baillieres Best Pract Res Clin Gastroenterol 13(1):131–143
20. Jayanthi NV, Dexter SP, Sarela AI (2013) Gastric electrical stimulation for treatment of clinically severe gastroparesis. J Minim Access Surg 9(4):163–167
21. Kashyap P, Farrugia G (2011) Oxidative stress: key player in gastrointestinal complications of diabetes. Neurogastroenterol Motil 23:111–114
22. Kaye J, Gage H, Kimber A, Storey L, Trend P (2006) Excess burden of constipation in Parkinson's disease: a pilot study. Mov Disord 21(8):1270–1273
23. Kinekawa F, Kubo F, Matsuda K, Fujita Y, Tomita T, Uchida Y, Nishioka M (2001) Relationship between esophageal dysfunction and neuropathy in diabetic patients. Am J Gastroenterol Hepatol 96(7):2026–2032
24. Larkin PJ, Sykes NP, Centeno C, et al.; European Consensus Group on Constipation in Palliative Care (2008) The management of constipation in palliative care: clinical practice recommendations. Palliat Med 22(7):796–807
25. Larson JM, Tavakkoli A, Drane WE, Toskes PP, Moshiree B (2010) Advantages of azithromycin over erythromycin in improving the gastric emptying half-time in adult patients with gastroparesis. Neurogastroenterol motil 16(4):407–413
26. Lembo A, Camilleri M (2003) Chronic constipation. N Engl J Med 349(14):1360–13608
27. Leppert W (2015) Emerging therapies for patients with symptoms of opioid-induced bowel dysfunction. Drug Des Devel Ther 9:2215–2231
28. Lieberman DA, Weiss DG (2001) One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. N Engl J Med 345(8):555–560
29. Lin C, Lin J, Liu Y, Chang C, Wu R (2014) Risk of Parkinson's disease following severe constipation: a nationwide population-based cohort study. Parkinsonism Relat Disord 20:1371–1375
30. Liu Z, Sakakibara R, Odaka T, Uchiyama T, Uchiyama T, Yamamoto T, Ito T, Asahina M et al (2005) Mosapride citrate, a novel 5-HT4 agonist and partial 5-HT3 antagonist, ameliorates constipation in parkinsonian patients. Mov Disord 20:680–686
31. Longmore M, Wilkinson IB, Davidson EH, Foulkes A, Mafi AR (2012) Oxford Handbook of clinical medicine, 8th edn. Oxford University Press, Oxford
32. Marrinan S, Emmanuel AV, Burn DJ (2014) Delayed gastric emptying in Parkinson's disease. Mov Disord 29(1):23–32
33. Martin-Harris B, Jones B (2008) The Videofluorographic Swallowing Study. Phys Med Rehabil Clin N Am 19(4):769–785
34. McCallum RW, Lembo A, Esfandyari T, Bhandari BR, Ejskjaer N, Cosentino C, Helton N, Mondou E, Quinn J, Rousseau F, TZP-102 Phase 2b Study Group (2013) Phase 2b, randomized, double-blind 12-week studies of TZP-102, a ghrelin receptor agonist for diabetic gastroparesis. Neurogastroenterol Motil 25(11):705–717
35. Müller-Lissner S (2013) Pharmacokinetic and pharmacodynamic considerations for the current chronic constipation treatments. Expert Opin Drug Metab Toxicol 9(4):391–401
36. Muppidi S, Vernino S (2013) Autoimmune autonomic failure. Hand Clin Neurol 117: 321–3277

37. Natale G, Pasquali L, Paparelli A, Fornai F (2011) Parallel manifestations of neuropathologies in the enteric and central nervous system. Neurogastroenterol Motil 23:1056–1065
38. Natale G, Pasquali L, Ruggieri S, Paparelli A, Fornai F (2008) Parkinson's disease and the gut: a well known clinical association in need of an effective cure and explanation. Neurogastroenterol motil 20:741–749
39. Nishida T, Tsuji S, Tsujii M, Arimitsu S, Sato T, Haruna Y, Miyamoto T, Kanda T, Kawano S, Hori M (2004) Gastroesophageal reflux disease related to diabetes: Analysis of 241 cases with type 2 diabetes mellitus. J Gastroenterol Hepatol 19(3):258–265
40. Nishikawa N, Nagai M, Tsujii T, Iwaki H, Yabe H, Nomoto M (2012) Coadministration of domperidone increases plasma levodopa concentration in patients with Parkinson disease. Clin Neuropharmacol 35(4):182–184
41. Nishino I, Spinazzola A, Papadimitriou A, Hammans S, Steiner I, Hahn CD, Connolly AM, Verloes A, Guimarães J, Maillard I, Hamano H, Donati MA, Semrad CE, Russell JA, Andreu AL, Hadjigeorgiou GM, Vu TH, Tadesse S, Nygaard TG, Nonaka I, Hirano I, Bonilla E, Rowland LP, DiMauro S, Hirano M (2000) Mitochondrial neurogastrointestinal encephalomyopathy: an autosomal recessive disorder due to thymidine phosphorylase mutations. Ann Neurol 47(6):792–800
42. Norcliffe-Kaufmann L, Kaufmann H (2012) Familial dysautonomia (Riley-Day syndrome): when baroreceptor feedback fails. Auton Neurosci 172:26–30
43. Pereira PCM, Navarro EC (2013) Challenges and perspectives of Chagas disease: a review. J Venom Anim Toxins Incl Trop Dis 19:1–34
44. Perkin GD, Murray-Lyon I (1998) Neurology and the gastrointestinal system. J Neurol Neurosurg Psychiatry 65(3):291–300
45. Slaugenhaupt SA, Blumenfeld A, Gill SP, Leyne M, Mull J, Cuajungco MP, Liebert CB, Chadwick B, Idelson M, Reznik L, Robbins C, Makalowska I, Brownstein M, Krappmann D, Scheidereit C, Maayan C, Axelrod FB, Gusella JF (2001) Tissue-specific expression of a splicing mutation in the IKBKAP gene causes familial dysautonomia. Am J Hum Genet 68(3):598–605
46. Shin A, Wo JM (2015) Therapeutic applications of ghrelin agonists in the treatment of gastroparesis. Curr Gastroenterol Rep 17(2):430
47. Ueno N, Inui A, Satoh Y (2010) The effect of mosapride citrate on constipation in patients with diabetes. Diabetes Res Clin Pract 87:27–32
48. Vernino S, Sandroni P, Singer W, Low PA (2008) Invited article: autonomic ganglia: target and novel therapeutic tool. Neurology 70(20):1926–1932
49. Wakabayashi K, Mori F, Tanjo K, Orimo S, Takahashi H (2010) Involvement of the peripheral nervous system in synucleopathies, tauopathies and other degenerative proteinopathies of the brain. Acta Neuropathol 120:1–12
50. Yarandi SS, Srinivasan S (2014) Diabetic gastrointestinal motility disorders and the role of enteric nervous system: current status and future directions. Neurogastroenterol Motil 26(5):611–624