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Understanding the Etiology and Spectrum of Idiopathic Gastroparesis


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Gastroparesis is a debilitating disease of delayed gastric emptying (GE) which affects approximately 10 million people in the United States. Diabetes-related and post-surgical gastroparesis are well-known entities, but the majority of patients with gastroparesis have no identifiable etiologies and are labeled as idiopathic (IG). Although post-infectious causation has been implicated in IG, the pathophysiology of IG remains elusive. Vagal nerve impairment, changes in enteric neurons, and depletion of interstitial cells of Cajal have been demonstrated. The diagnosis of IG is based on clinical symptoms and an abnormal scintigraphic gastric emptying study. This article aims to review new discoveries in "idiopathic gastroparesis" and update entities that may be incorrectly labeled idiopathic gastroparesis.

INTRODUCTION

Gastroparesis (GP) is a disease of delayed gastric emptying where mechanical obstruction of the upper gastrointestinal tract has been excluded. Often, disordered gastric emptying is accompanied by post-prandial nausea, vomiting, early satiety, bloating and abdominal pain. Estimated to occur in 10 million (3%) people in the Unites States, gastroparesis can be categorized into diabetic (DG), post-surgical (PSG) and idiopathic (IG). Idiopathic gastroparesis accounts for up to 50-60% of cases and primarily affects females (88%) with an average age of onset of 41 years.[1] Case reports and case series have linked an infectious prodrome (gastroenteritis or flu-like symptoms) to IG, and this particular sub-category is termed post-infectious GP. It had previously been reported that post-infectious GP accounts for approximately 21% of all IG cases,[2] however, this number will be higher with new data. Also, post-infectious GP patients seem to have a higher likelihood for spontaneous recovery.[2]

The majority of the data for understanding IG comes from the NIDDK Gastroparesis Clinical Research Consortium (GpCRC), a collaborative effort

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from experts at a few specialized academic motility centers in the U.S. The consortium has led multiple studies with the aim of improving the understanding of the pathophysiology, clinical presentation, and response to therapy in GP. Symptoms of nausea, vomiting, and abdominal pain have been associated with a poor quality of life among all GP patients.[3,4] Data from the NIDDK Gastroparesis Registry revealed that among 159 patients with gastroparesis (107 IG, 52 DG), nausea was the predominant symptom in both groups, vomiting was more common in DG (81% vs. 57% p=0.004),[5] and abdominal pain was more common in IG.[6] Also, psychological profiles have identified depression along with physical and sexual abuse as present in up to 62% of the female patients with IG.[7] These factors contribute to visceral hypersensitivity and could help explain the higher prevalence of abdominal pain in IG. The limited understanding about the pathogenesis in IG has led to a non-tailored approach in the management of symptoms. Additionally, many entities (i.e scleroderma), which can cause delayed GE, may be inappropriately labeled as IG. Knowledge of this evolving field will lead to a more focused approach to treatment. The goal of this article is to review this entity of "idiopathic gastroparesis" while also emphasizing these other diagnoses that may mimic IG.

Methods

Pubmed (MEDLINE) was searched using the MESH and non-MESH search terms: "idiopathic", "post-infectious", "autoimmune", "connective tissue diseases", "paraneoplastic syndromes", "eating disorders", "delayed gastric emptying", "gastroparesis" and "diagnosis". This search was complemented by the extensive clinical experience of the Center for Neurogastroenterology and GI Motility at Texas Tech University Medical Center in El Paso.

Pathophysiology

Although the pathophysiology of idiopathic gastroparesis remains unclear, some mechanisms and explanations are evolving (Figure 1). Vagal function and regulation have been shown to be impaired among patients with DG, however, to a lesser extent in IG.[8,9] Also, the role of the vagus nerve in ghrelin secretion has been proposed. Ghrelin is released mainly

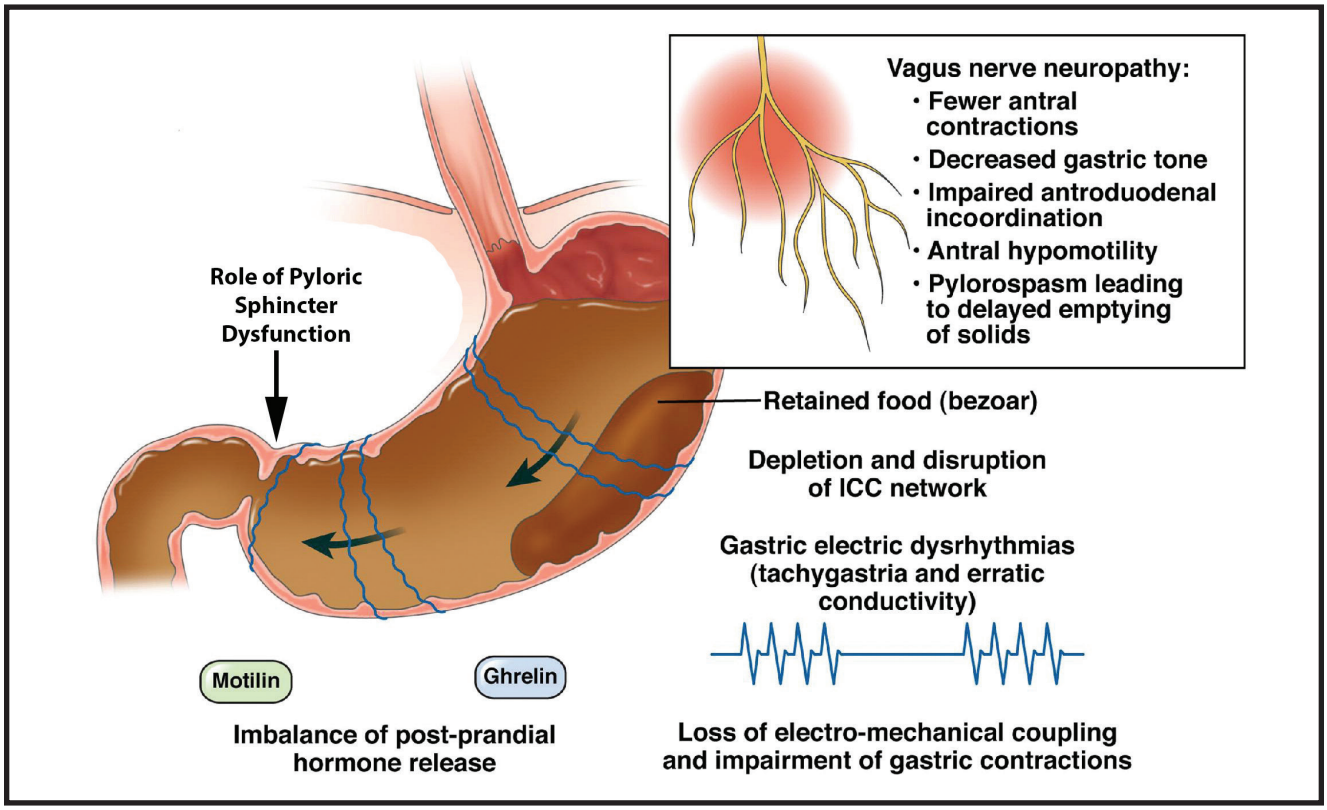

Figure 1. Pathophysiology of Idopathic Gastroparesis

by neuroendocrine cells in the gastric fundus and duodenum and has been suggested to function as an appetite-stimulating hormone acting centrally through vagal afferent pathways.[8] Ghrelin also has also been shown to stimulate gastric contractility and improve meal related symptoms and gastric emptying (GE) in IG patients.[10]

Full thickness gastric biopsies in patients with gastroparesis (compared to matched-controls) revealed that nNOS expression was more frequently decreased in IG than in DG (40% vs 20%). Increased connective tissue stroma, however, was visualized in both IG and DG via electron microscopy.[11] Loss of interstitial cells of Cajal (ICC) has been a predominant finding among patients with both DG and IG,[11] being present in up to 50% of cases and has been correlated with delayed gastric emptying in DG.[12] Interstitial cells of cajal are regarded as the origin of the gastric electric activity and the loss of ICC impairs and disorganizes the electrical signal resulting in reduced peristalsis. Previous studies revealed differences in gastric myoelectrical patterns among patients with IG and non-GP as assessed by electrogastrography (EGG). Idiopathic gastroparesis patients had a more irregular EGG pattern, with reduced 3-cycles-per-minute (cpm) EGG activity, whereas patients with mechanical pyloric outlet obstruction had high-amplitude, regular 3 cpm EGG patterns.[13,14] In patients with IG, clinical severity and nausea has been associated with immune-mediated infiltration of the myenteric plexus.[15] Evidence of ganglionitis in full thickness gastric biopsies infers a diagnosis of IG. There is also an evolving role of pyloric pathophysiology in the development of GP. Loss of ICC in the pylorus occurs twice as commonly as in the antrum, and fibrosis in pyloric smooth muscle is three times more common than in the antrum on biopsies of patients undergoing gastric electric stimulation with pyloroplasty.[16] Therefore, one unifying concept is that gastroparesis has similarities to "achalasia". In achalasia, there is both denervation of the esophageal body producing loss of peristalsis, in addition to a non-relaxing lower esophageal sphincter (LES) resulting in esophageal obstruction. In GP, there is impairment of the enteric neurons, ICC loss in the smooth muscle of the antrum, and an impaired relaxation/compliance of the pyloric sphincter resulting in retention of a meal. One of these "dual mechanisms" may be more dominant in an individual GP patient, but both need to be considered and addressed when planning therapies.

How to Diagnose IG: Re-visiting the Gastric Emptying (GE) Diagnostic Criteria

Grading for severity of delayed gastric emptying, adopted from the consensus paper of a Joint Report of the Society of Nuclear Medicine and the American Neurogastroenterology and Motility Societies, is based on the percentage of gastric retention at 4 hours. The following grading system has been proposed: grade 1 (mild): 11–20% retention at 4 h; grade 2 (moderate): 21–35% retention at 4 h; grade 3 (severe): 36–50% retention at 4 h; and grade 4 (very severe): >50% retention at 4 h.[17] A recent study by the NIDDK GP Research consortium suggests that the severity of gastric retention significantly correlated with the severity of symptoms when there was more than 35% retention of isotope at 4 hours. This correlation was not significant in the large number of patients with retention of 11-34%.[18] To readdress normal gastric emptying criteria (since the original "egg meal" dates back 20 years ago), we recently studied the range of gastric emptying in 25 healthy individuals aged to 30 to 70 years, both male and female, with equal distribution for each decade. Four-hour retention values of up to 17% can be observed in asymptomatic healthy volunteers.[19] Therefore, in interpreting the current "gold standard" meal for GE, we recommend that gastric retention > 15% at 4 hours should be considered the appropriate criteria to apply the label of "gastroparesis" and not the >10% standard currently used. Hence the term "idiopathic" gastroparesis needs to be applied with more rigorous GE criteria. Patients with symptoms of postprandial distress and normal GE are generally regarded as having functional dyspepsia (FD). There is more attention being directed to the role of impaired fundic accommodation and rapid filling of the antrum in explaining symptoms of early satiety, fullness, abdominal pain and nausea, which may be more dominant in some patients, categorized as having FD.

Pharmacologic Explanation for Delayed GE

Effect of Marijuana on GE

Cannabis has been shown to delay GE in previous studies. In the first study investigating the effect of delta-9-tetrahydrocannabinol (THC) on gastric emptying, smoking THC was shown to significantly delay GE compared to placebo in normal volunteers who did achieve symptoms of being "high". The mean

percentage of retention was significantly greater in the THC group compared to placebo at all times from 30 min to 2 hours after the test meal.[20] Chronic (daily) marijuana use has been linked to the newly recognized syndrome of cannabis hyperemesis and patients may be misdiagnosed as having gastroparesis as a cause of vomiting. More recently, use of recreational marijuana has been approved in many states. It is important to take a careful history and stop all marijuana use for at least 72 hours prior to GE being studied.[17]

Effect of Medications on GE

There are many classes of medications that can slow GE. In this article, we will emphasize the most commonly encountered medications (Table 1).

Opioids are the most commonly associated medication inducing delayed GE. A randomized controlled trial evaluating 75mg of Tapentadol immediate-release (IR) TID or 5mg Oxycodone IR TID vs. placebo revealed a significant delay in GE with narcotics compared to placebo.[21] Medications used for the management of hyperglycemia in type 2 diabetics including Pramlintide,[22] an amylin analogue, and Exenatide,[23] a GLP-1 agonist, have been associated with delayed GE due to inhibition of vagal function.

Proton pump inhibitors can mildly delay GE to solids by impairment of the acid-dependent peptic activity, which interferes with trituration of ingested food.[24]

Table 1 lists all the classes of medications that should be considered as possibly slowing GE and emphasizes that a detailed social and medication history is paramount when IG is in the differential.

Table 1. Classes of Medications Associated with Delayed Gastric Emptying

- Anticholinergics
- Antihypertensive
  - Calcium channel blockers
  - Clonidine
- Anti-psychotics
  - Tricyclic antidepressants
  - Lithium
- Diabetic medications
  - Exenatide
  - Liraglutide
  - Pramlintide
- Dopamine agonists
- Nicotine containing agents
- Opioids
- Octreotide
- Progesterone containing agents
- Proton pump inhibitors
- Tetrahydrocannabinol (THC)
  - THC derivatives

Hypothesized Etiologies for IG

Post-Infectious Gastroparesis

Post-infectious GP has been reported in both pediatric and adult populations and it has been linked to various pathogens. The pathophysiology of post-infectious GP could be neuropathic or myopathic in origin. The proposed mechanism is believed to be due to inflammation, an immune-mediated phenomenon or an exacerbation or unmasking of an underlying dysmotility.[25] There is also literature suggesting possible viral mediated damage to the ICC.[13]

Viral Pathogens Linked to IG

In the pediatric literature, reports have linked rotavirus to IG. Two cases series reported that among children with post-viral GP, positive for rotavirus, all had full recovery of their gastric emptying over 6-24 months.[15,26]

Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) have been linked to gastroparesis. In a large cohort of 143 adult patients with IG, 11 patients were identified with a post viral etiology of which four had antibody titers against CMV and two against EBV, while the remaining five had a clinical history and presentation consistent with viral etiology based on an illness consistent with gastroenteritis.[2] Seven patients (age three months to 47 years old) with a viral prodrome prior to development of GP revealed CMV and EBV as culprits in two cases.[13] CMV was also linked to GP in an immunosuppressed patient who developed neurological symptoms and delayed gastric emptying with confirmatory CSF PCR positivity for

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CMV. This patient later had clinical improvement with ganciclovir.[27]

Enterovirus (EV) has been linked as a possible causative etiology in IG.[28] Seventeen adult patients reported having flu-like symptoms or gastroenteritis prior to diagnosis of IG and 11 subjects had immunoperoxidase staining for EV on mucosal gastric biopsies. Nine patients had active EV infection as noted on endoscopic gastric biopsies and eight patients underwent treatment with antivirals and/or immune therapy. Four out of the eight patients treated experienced symptomatic improvement.

Among other viral etiologies, Norwalk virus and Hawaiian virus have been associated with IG in up to 50% of patients thought to be affected with the viruses.[29] Varicella-Zoster has also been associated with IG in a setting of a 52 year-old male with Ramsay-Hunt syndrome who developed GP and had symptomatic improvement with metoclopramide.[30]

A case series of three adolescent female patients also revealed viral gastroenteritis as a possible culprit for GP.[25] Viral GP was identified in seven out of 103 GP cases from the Mayo Clinic. Among the seven cases (three male, four female), the mean age was 26.9 years and symptoms experienced prior to onset of GP included, low-grade fever, fatigue, myalgia with or without diarrhea. A mean follow-up of 32.3 months revealed complete resolution of gastroparetic symptoms in five of the seven subjects while the remaining two had significant improvement in symptoms[31] suggesting that post-infectious GP appears to have an overall good prognosis. Neither article specified the pathogens, but it was presumed to be viral as per clinical presentation.

Table 2. Possible Etiology and Medical Entities which Can Mimic Idiopathic Gastroparesis

Hypothesized Etiology
• Post Infectious
Medical Entities Mimicking IG
• Anorexia Nervosa/Bulimia
• Autoimmune Diagnosis
• Celiac Axis Compression (Median Arcuate Ligament Syndrome)
• CNS Degenerative Diseases
• Connective Tissue Disorder
• Demyelinating Diseases
• Functional Dyspepsia
• Gastroesophageal Reflux
• Hypermobility Syndrome
• Miscellaneous e.g. Cystic fibrosis, radiation, chemotherapy, atrophic gastritis, mastocytosis, eosinophilic gastroenteritis
• Paraneoplastic Syndrome

Other Pathogens Linked to IG

In an outbreak of 1300 subjects with waterborne Giardia lamblia, 139 continued to have abdominal symptoms after an initial infection. Of this cohort, twenty-two patients who had a negative follow-up stool analysis for Giardia were compared with 19 controls using GE. There was a significant delay in GE among subjects previously infected with Giardiasis, $p<0.01$.[32]

Medical Entities that May be Un-recognized and Inappropriately Labeled as "Idiopathic Gastroparesis"

Connective Tissue Disorder

The esophagus, small intestine and colon are commonly affected in patients with systemic sclerosis (SSc).[33] Approximately 47-66% of patients with SSc have delayed gastric emptying to solids.[33,34] Dyspeptic symptoms such as nausea, vomiting and epigastric fullness are often observed in SSc patients.[33] In one study, 80% patients with abnormal esophageal motility also had significantly delayed GE.[33] Similarly, delayed GE with liquids was seen via ultrasonography in 20 patients with SSc vs 20 healthy controls.[35] It is hypothesized that collagen replacement of the gastric smooth muscle may lead to subsequent stomach hypomotility in SSc.[36]

Autoimmune Diagnosis

Gastroparesis in patients with myasthenia gravis with subacute autonomic failure shows clinical improvement after administration of an acetylcholinesterase inhibitor.[38] In this report seven patients had antibodies against muscle AChR, and three had antibodies against neuronal ganglionic AChRs (all had thymoma). Autoimmune autonomic neuropathy in association with ganglionic neuronal acetylcholine receptor and N-type voltage-gated calcium channel autoantibodies

was also reported in a 60 year-old non-diabetic woman with a 15-year history of GP.[39] Patients with Sjogren's syndrome who have serum antimuscarinic antibodies (IgG) can also have delayed GE.[37]

Demyelinating Diseases

Acute demyelinating disease is a rare cause of GP, but it should be suspected when symptoms of GP are associated with neurological deficits. Antibodies against the water channel protein aquaporin (AQP)-4 can cause a spectrum of inflammatory, demyelinating, central nervous system disorders termed neuromyelitis optica spectrum disorders (NMOSDs) which can present with GI symptoms similar to GP with intractable nausea, vomiting and hiccups. However, AQP4-IgG positive patients have not demonstrated delayed GE.[40]

In a case report, a 31-year-old female with acute gastroenteritis developed gastroparesis and suffered a cardiac arrest during the hospitalization. A post-mortem autopsy revealed decreased myelinated axons with vacuolar degeneration consistent with Guillain-Barre syndrome.[41] Two cases of patients with focal deficits and demyelinating disease, seen on magnetic resonance imaging (MRI), have also been associated with abnormal GES. Both patients improved with intravenous corticosteroids and one of the patients later developed multiple sclerosis.[42]

Multiple sclerosis (MS) is a demyelinating disease, which damages the brain and spinal cord. Similar to IG, more patients with MS are women. The most common GI complaints reported in MS patients are diarrhea or constipation and dysphagia.[43] Previous studies have demonstrated delayed GE in MS patients. In a study of 49 patients with defined MS and 20 controlled subjects, 47.7% demonstrated slow emptying, 34.1% normal and 18.2% had rapid emptying compared with controls.[43] In other reports, the complaints reported in MS patient who presented with symptoms of delayed GE were mainly a sense of fullness, nausea, persistent vomiting, recurrent hiccups and gastroesophageal reflux.[44] However, there has been no correlation noted between the severity of MS and gastric emptying abnormalities.

Paraneoplastic Syndrome

Paraneoplastic syndrome can be manifested as esophageal dysmotility (pseudoachalasia), gastroparesis, intestinal pseudo-obstruction or constipation.[45] Factors related to cachexia have been theorized as an explanation for paraneoplastic syndrome. Inflammatory lymphocytic and plasma cell infiltrate of the myenteric plexus as well as loss of ganglion cells can be seen on full thickness biopsy in patients with paraneoplastic dysmotility of the GI tract.[45]

Gastroparesis was reported to be the most common paraneoplastic syndrome associated with type 1 antineuronal nuclear (ANNA-1, also called anti-Hu) antibodies, and small cell lung cancer (SCLC) of the lung is the most common tumor expressing this antibody.[45] Plasmapharesis was effective in overcoming the antibodies. The second most common antibody in paraneoplastic syndrome and GP is the P/Q-type calcium channel antibodies, which are predominately seen in patients with Lambert Eaton myasthenic syndrome (LEMS) in association with SCLC.[46] Patients with LEMS can present with proximal muscle weakness, depressed tendon reflexes, post-tetanic potentiation and autonomic changes, which can be similar to that of myasthenia gravis. Similarly, a ganglionic acetylcholine receptor antibody has been associated with GP in a patient with bladder cancer but also in patients with no underlying cancer.[47]

Pancreatic cancer has also been associated with GP. A cohort of 15 patients with pancreatic carcinoma without invasion or obstruction revealed that nine (60%) patients had delayed solid-food GE. Symptoms of nausea and/or vomiting were more frequent among patients with delayed GE as opposed to those with normal GE.[48] Other tumors that have been linked with delayed gastric emptying include cholangiocarcinoma,[49] as well as intestinal[50] and retroperitoneal leiomyosarcoma.[51] In the two cases where leiomyosarcoma was linked to delayed GE, both patients had resolution of symptoms after tumor resection.

CNS Degenerative Diseases

Patients with Parkinson's disease (PD) have been noted to have delayed gastric emptying to solids.[52] In a randomized study, 80 patients with untreated PD were compared to 40 healthy controls with solid or liquid gastric emptying. A total of 88% of PD patients had delayed GE with solids and 38% with liquids. Abnormal gastric myoelectrical activity in untreated Parkinson's disease may be responsible for delayed GE.[53] Lewy bodies have also been identified in the smooth muscle and enteric neurons of Parkinson's disease patients.[54] In an animal study, 6-hydroxy-dopamine (6-OHDO) was unilaterally injected into the substantia nigra pars compacta of mice. The mice developed delayed

gastric emptying four weeks after a 6-OHDO injection, as measured by a [13C]-octanoic acid breath test. Thus, the authors postulated a neurofunctional and neuroanatomical alteration of the brain-gut axis as a potential etiology for delayed GE in PD.[55]

Dopamine agonists used in the treatment of PD have been regarded as being a risk for delaying GE. However, treatment with the dopamine agonist as a transdermal patch, rotigotine, has recently shown improvement in gastric emptying.[56]

Functional Dyspepsia

Approximately 40% of patients with the working diagnosis of functional dyspepsia (FD) may have delayed GE as the explanation for their symptoms.[57] Idiopathic gastroparesis patients are more likely to have frequent nausea and vomiting, whereas FD patients have postprandial distress syndrome manifested by early satiety and abdominal discomfort. A meta-analysis of 17 studies with 868 dyspectic subjects and 397 controls revealed that GE was delayed with a relative risk of 1.46 (CI 1.23-1.69).[57] Recent reports of duodenal eosinophilia in a subgroup of dyspepsia patients may be another marker for separating FD from GP where eosinophilia in the duodenum was infrequent among the latter group.[58]

Gastroesophageal Reflux

Delayed GE has been reported in 28 to 56% of the patients with gastroesophageal reflux (GERD) and is a co-existing entity, which can exacerbate GERD symptoms.[59] Theoretically, the slow GE induces gastric distention, which increases the frequency of transient lower esophageal sphincter relaxation increasing GERD. A gastric emptying study should be considered in patients whose heartburn is resolved with anti-reflux medication but who continue to report persistent nocturnal regurgitation.

Anorexia Nervosa/Bulimia

Anorexia and bulimia have been associated with dyspeptic symptoms and delayed gastric emptying. In a study of 16 female patients with anorexia nervosa, GE of solid food phase was significantly delayed in 80% of patients.[60] In this study, patients with anorexia nervosa were observed to have better tolerance to liquid diet compared to solid meals. Patients with bulimia have had conflicting results. Two studies reported normal GE to solids and liquids,[61,62] however, a cohort of female patients with bulimia revealed delayed GE in 38% of the patients.[63]

Anorexia nervosa in childhood or early adulthood results in an unused or atrophic gastric emptying function, where despite subsequent improvement of eating habits, it does not lead to recovery of the "gastric atrophy." In another scenario, some patients may still be "closet anorexics" and have hidden their eating behaviors. Some important clues suggesting an eating disorder are excessive dental caries, finger excoriations and unexplained hypokalemia. Another possible explanation for delayed GE could be secondary to endocrine dysfunction (i.e hypoadrenalism) observed in patients with eating disorders.

Celiac Axis Injury or Compression

Compression or injury to the celiac plexus ganglion can affect parasympathetic signaling to the stomach, resulting in loss of myenteric coordination. Compression of the celiac axis by a fibrous band (the median arcuate ligament) connecting the diaphragmatic crura is called median arcuate ligament syndrome (MALS) which is characterized by abdominal pain, nausea and vomiting. A case report of a patient presenting with postprandial epigastric pain, weight loss, gastroparesis and gastric dysrhythmias was diagnosed with MALS and had significant improvement of symptoms and GE after surgical decompression of the celiac axis. The patient was able to return to a full diet within four weeks without nausea or vomiting.[64] This entity is not explained by vascular insufficiency but by compression of the celiac ganglion via the the fibrous ligament. Clinical clues include nausea, vomiting and upper abdominal pain which is out of proportion to abdominal examination

Hypermobility Syndrome

Joint hypermobility syndrome (JHS), a type of Ehlers-Danlos Syndrome (EDS) (formally called type III), is a new addition to an association with GI symptoms. Patients with JHS have hypermobility of the joints, skin hyper extensibility and easy brushing. In a case-controlled study of the 336 patients with functional gastrointestinal disorder (FGID), 39% were also diagnosed with JHS. More specifically 51% of the FGID patients whose predominant symptom was postprandial distress were diagnosed with JHS.[65] Postural orthosthetic tachycardia syndrome (POTS), caused by dysfunctional autonomic control mechanism,

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is accompanied by JHS in up to 60% of patients.[66] In a large cohort study of 163 patients with POTS, 34% had normal, 18% has delayed and 48% had rapid GE.[67] In JHS patients, autonomic dysfunction and decrease in compliance of the gut wall may influence GE. Review of literature suggests that rapid gastric is more common in JHS patient with POTS but in absence of POTS, occurrence of rapid and delayed GE were similar.[68]

Miscellaneous Causes for Delayed GE

Cystic fibrosis (CF) can be associated with GI dysmotility including GP, GERD and chronic constipation. The average life span of patients with CF who live to adulthood is 37 years. In a systemic review, patients with CF had a high frequency of GP (38%) and it was more prevalent among patients older than 18 years of age.[69] The co-existence of GP and CF may pose significant nutritional challenges.

Cases of GP in patients receiving abdominal, pelvic and total spine radiation have also been documented.[70] There is also a report of GP in patients who received high dose chemotherapy and stem cell transplant.[71] Post-chemotherapy treatment GP is rare and pathophysiology behind the process is not well established but could relate to being part of the paraneoplastic syndrome or neuropathy from the chemotherapy agent.

Delayed solid emptying is also noted in atrophic gastritis with or without pernicious anemia,[72] which is explained, by a combination of achlorhydria and thinning of smooth muscle. Other diseases associated with delayed GE include mastocytosis[73] and eosinophilic gastroenteritis.[74]

TAKE HOME POINTS

A wide spectrum of contributing factors and unappreciated entities can result in the label of "idiopathic gastroparesis". Idiopathic gastroparesis is also a term that may be overused as the etiology for unexplained upper gastrointestinal symptoms. The diagnosis of IG must be rigorously made with particular attention to the interpretation of a scintigraphic GE study, where abnormal should be >15% retention at 4 hours, not the current >10%. Medications, specifically opioids and marijuana, are key factors to consider in interpreting a gastric emptying study. This article helps the reader gather enough data to differentiate idiopathic gastroparesis from other diagnoses while at the same time emphasizing the importance of a thorough evaluation of the patients' history for factors that can have a long term effect on gastric motility and present as gastroparesis. In the future, the diagnostic approach will benefit from a non-surgical way of obtaining gastric smooth muscle tissue to examine enteric neurons, and ICC, which will be achieved by endoscopic ultrasound-guided biopsies of gastric antrum smooth muscle. Patients with suspected post-infectious gastroparesis appear to have an overall good chance of recovery. Idiopathic gastroparesis, the most common subset of gastroparesis patients, remains a challenging diagnostic and clinical entity. We hope this article will give you new expertise in addressing this in your practices. ■

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Answers to this month's crossword puzzle:

1 X	E	2 N	O	3 G	R	4 A	F	5 T	■	6 C	E	7 C	U	8 M
R	■	E	■	E	■	L	■	U	■	A	■	A	■	R
9 A	D	R	E	N	A	L	■	10 M	I	D	■	11 N	O	N
Y	■	V	■	E	■	E	■	O	■	U	■	A	■	A
■	12 T	E	N	S	O	R	■	13 R	E	C	A	L	14 L	■
15 R	■	■	■	I	■	G	■	■	■	E	■	16 S	A	17 P
18 A	M	19 P	■	20 S	21 O	Y	■	22 N	E	U	R	O	N	S
S	■	E	■	■	V	■	23 G	I	■	S	■	24 F	D	A
25 H	E	P	A	26 T	O	L	O	G	Y	■	■	H	■	■
■	■	T	■	W	■	■	27 O	H	■	28 C	29 H	E	30 M	O
31 T	R	I	G	O	N	32 E	■	T	■	33 R	A	R	E	■
H	■	C	■	■	■	O	■	■	34 B	I	L	I	N	■
35 R	X	■	■	36 G	A	S	T	37 R	I	C	■	38 N	D	39 A
O	■	40 C	■	A	■	I	■	41 E	L	K	■	42 G	E	L
43 B	U	D	E	S	O	N	I	D	E	■	■	■	L	■