Published in final edited form as:

Neurogastroenterol Motil. 2012 July ; 24(7): 597–603. doi:10.1111/j.1365-2982.2012.01942.x.

What Are the Important Subsets of Gastroparesis?

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Abstract

Gastroparesis is often divided into subsets based on etiology and pathophysiology; however, the utility of these subsets in the diagnosis and treatment of gastroparesis is not well defined. The objectives are to consider the subsets of gastroparesis from the perspectives of etiology and pathogenesis, pathophysiology, histopathology, and clinical associations, with particular focus on similarities and differences between diabetic and idiopathic gastroparesis and consideration of the potential subset of painful gastroparesis. We conclude that idiopathic and diabetic gastroparesis have similar initial presentations and manifestations, except that idiopathic gastroparesis tends to be associated more frequently with pain. Myopathic disorders are uncommon. Extrinsic denervation was considered the most common etiology; however, with the decline in surgery for peptic ulceration and in depth study of full thickness gastric biopsies, the most common intrinsic defects are being recognized in the interstitial cells of Cajal (ICC-opathy) and with immune infiltration and neuronal changes (intrinsic neuropathic gastroparesis). Histomorphological differences at the microscopic level between diabetic and idiopathic gastroparesis are still of unclear significance. Two gastroparesis subsets worthy of special mention, because they are potentially reversible with identification of the cause, are post-viral gastroparesis, which has a generally good prognosis, and iatrogenic gastroparesis, especially in patients with non-surgical gastroparesis, such as diabetics exposed to incretins such as pramlintide and exenatide.

Keywords

neuropathy; myopathy; interstitial cells of Cajal; vagus; diabetes

Introduction

Gastroparesis is a syndrome characterized by delayed gastric emptying in absence of mechanical obstruction of stomach (1). The cardinal symptoms include postprandial fullness (early satiety), nausea, vomiting, and bloating. Abdominal pain has been reported as an additional symptom in a significant percentage of patients with gastroparesis (2,3). Bloating is prevalent in gastroparesis, particularly among female and overweight patients, and is severe in many individuals (4).

Gastroparesis is often divided into subsets based on etiology or associated conditions, pathogenesis, pathophysiology, histopathology or ultrastructure, and association with pain or

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Disclosures

The authors have no competing interests.

Authors' Contributions

Drs. Michael Camilleri, Madhusudan Grover, and Gianrico Farrugia wrote the manuscript.

bloating; however, the utility of these subsets in the diagnosis and treatment of gastroparesis is not well defined.

Etiological Subsets

In one tertiary referral series, Soykan et al. (5) reported that diabetes and idiopathic causes each accounted for almost one-third of cases of gastroparesis; the remaining cases included post-surgical, collagen-vascular, and neurological disorders. Symptoms attributable to gastroparesis are reported by 5–12% of patients with diabetes in epidemiological studies (6,7). There are several associated symptoms and diseases in the group called “idiopathic”, in which it is unclear whether the association might be the etiological factor causing the gastroparesis, such as hypothyroidism, or post-viral gastroparesis. In the National Institute of Diabetes and Digestive and Kidney Diseases Gastroparesis Clinical Research Consortium, which represents the collective experience of several tertiary referral centers, approximately 60% of patients with gastroparesis were idiopathic (8).

The subset of post-viral gastroparesis is well accepted as a clinical entity, but it remains ill defined. It may also overlap with post-infectious functional dyspepsia which may also be associated with delayed gastric emptying and other motor or sensory dysfunctions of the stomach (9). The distinction between idiopathic gastroparesis associated with a significant pain component and functional dyspepsia is a matter of continuing controversy, and no biomarkers have been established to differentiate the two conditions (10). When characterized by acute or insidious onset of symptoms and the presence of an initial infectious prodrome with resultant chronic gastrointestinal symptoms, 19% of patients with idiopathic gastroparesis can be classified as post-infection, likely post-viral (8). Among patients with **post-viral gastroparesis**, there are at least three subsets. The first is the transient gastroparesis associated with acute viral gastritis. This was probably first proven by Meeroff et al. (11), who administered parvoviruses (Norwalk and Hawaii virus) to healthy volunteers and showed that all 5 of the 10 subjects who developed illness had severe delays in gastric emptying.

A viral prodrome (with the agent not specified, but often associated with acute phase inflammatory reactions) (9) as well as intestinal immune activation (12) are associated with post-infectious functional dyspepsia. Similarly, the acute “infectious state” may be followed by gastroparesis (13). This condition generally has a good prognosis; when followed for ~1 year, most patients had recovered sufficient gastric function to require only conservative treatments such as diet or prokinetics (13).

The literature has documented rare associations with herpes family virus-induced selective or pan-dysautonomia such as Epstein Barr virus (14), cytomegalovirus, and herpes virus (15), or with a Guillain-Barré-type syndrome associated with degeneration of sympathetic chain (16), which are associated with worse prognosis.

Iatrogenic gastroparesis is most commonly due to prior surgery typically causing vagotomy or vagal injury such as fundoplication (17), bariatric surgery including gastric bypass or vertical banded gastroplasty which are associated with bezoar formation (18), or peptic ulcer surgery. In the latter group, the likelihood of developing post-operative symptoms suggestive of gastroparesis is more likely with truncal vagotomy with antrectomy than with proximal gastric vagotomy or truncal vagotomy with drainage (19), or after Roux-en-Y gastrectomy (20). A study based on the NIDDK gastroparesis consortium (21) showed that Nissen fundoplication is now the most common cause of post-surgical gastroparesis (52%), followed by partial gastric resection (22%), myotomy or esophago-gastrectomy (9% each), and stomach stapling and vagotomy (4% each). Such surgical procedures may result in

acceleration of the emptying of liquids (which may be associated with dumping symptoms) in association with gastric stasis of solids (22). Hence, in such patients with symptoms suggesting gastroparesis, it is important to investigate with tests of gastric emptying of solids.

Medications causing delayed gastric emptying include medications used to treat type 2 diabetes such as amylin analogs [e.g. pramlintide (23)] or GLP-1 agonists [e.g. exenatide (24)] that inhibit vagal function. This does not apply to the dipeptidyl peptidase IV inhibitors [vildagliptin, sitagliptin (25)] which inhibit metabolism of endogenous GLP-1. In fact, in a clinical trial, the prevalence of nausea was 39% with exenatide and 15% with sitagliptin, and vomiting was observed in 19% with exenatide and 5% with sitagliptin treatment (26).

In patients with prior pancreatic transplantation treated with anti-rejection treatment with cyclosporine, there may be delay in gastric emptying (27). This does not apply to another calcineurin inhibitor, tacrolimus, which is derived from a macrolide molecule and retains prokinetic properties (28).

Other agents that commonly retard gastric emptying are the μ opiate agonists, including tramadol (29) and tapentadol (30).

Subtypes Based on Pathogenesis

Subtypes of gastroparesis based on pathogenesis include extrinsic autonomic neuropathy affecting the vagus nerve, intrinsic or enteric neuropathy, pathology of the interstitial cells of Cajal (ICC), and myopathy. Myopathy is usually characterized by increased fibrosis of the muscle layer, hypoplasia or degeneration of smooth muscle cells (31).

The most common causes of extrinsic autonomic neuropathy are diabetes and post-surgical vagal injury. Another neuropathic subtype of gastroparesis results from intrinsic neuropathy affecting excitatory and inhibitory intrinsic nerves, with loss of nNOS expression being the most common defect reported (32).

Pathology of the ICC or Cajalopathy is the most common cellular defect identified on full-thickness biopsies of the stomach in patients with gastroparesis (32). In some conditions, it is possible that the neuropathic gastroparesis represents a combined diathesis affecting both intrinsic and extrinsic nerves, such as in diabetic and post-viral gastroparesis. In addition, patients with gastroparesis evaluated in the NIDDK clinical research consortium were found to have defects in more than one cellular population such as ICC and enteric nerves (32). A relatively less well understood subtype is an immune infiltrate found in about 40% of gastroparesis (32). The exact identity of the immune cell and the effects of immune cells on other cell types, including nerve, ICC and smooth muscle, are unknown.

Myopathic gastroparesis typically involves infiltrative disorders such as amyloidosis and scleroderma or other collagen vascular diseases. Invariably, gastric involvement is a component of a more generalized motility disorder affecting other organs, such as the small bowel, lower esophageal sphincter, and esophagus (33,34).

Other less common diseases associated with myopathic gastroparesis are hollow visceral myopathy and mitochondrial cytopathy. A subtype of patients without systemic disease has distinct smooth muscle changes as documented by abnormalities in smoothelin expression (32). Fibrosis was previously reported as a significant feature of gastroparesis (35). More recent studies suggest that, while present, fibrosis is less marked than the previous studies on “burned out” gastroparesis had suggested. It is important to keep in mind that cellular defects may not pick up important functional defects. For example, smooth muscle is a

significant source of steel factor, the ligand for Kit, required for ICC phenotype maintenance (36).

Subtypes Based on Pathophysiology

Gastric emptying profiles cannot distinguish neuropathic from myopathic gastroparesis, either from the lag time or the post-lag gastric emptying rate (37). Antroduodenojejunal motility can differentiate neuropathic from myopathic processes (38). Extrinsic neuropathic gastroparesis (e.g. diabetic or post-vagotomy) is characterized by increased frequency of migrating motor complexes during fasting, reduced frequency of distal antral contractions postprandially (typically <1/min during the first postprandial hour), and poorly developed intestinal fed pattern with return of the migrating motor complex (MMC)-like activity within 2 hours of the ingestion of a 500 kcal solid-liquid meal (39). Incoordinated bursts of high amplitude duodenal and jejunal motor activity are less consistently observed. When the same manometric features are present, but there is no evidence of autonomic neuropathy, it is assumed that the underlying disturbance involves the intrinsic neuromuscular apparatus or ICCs. The presence of increased numbers of phase III MMCs during the fasting period and the occurrence of MMCs in the early postprandial period are manometric features that appear to be more prevalent in extrinsic (22) compared to intrinsic neuropathic processes. Thus, manometry cannot completely differentiate extrinsic from intrinsic neuropathic gastroparesis. Therefore, special tests of abdominal vagal function (e.g. plasma pancreatic polypeptide response to modified sham feeding) can aid this differentiation. In idiopathic gastroparesis (possibly a surrogate for enteric neuropathic gastroparesis), the motility patterns are qualitatively similar to those of extrinsic neuropathies, but the one study comparing postprandial antral motility showed idiopathic (n=21) and secondary gastroparesis (17 neuropathic, 3 myopathic) had similar amplitude, but reduced frequency and overall antral motility index in secondary conditions (40).

Antroduodenal manometry in myopathic disorders is characterized by normal patterns of motility with low amplitude; typically, the average postprandial distal antral pressure activity is <40mmHg, and the duodenojejunal pressure activity is <10mm Hg (33,40). Interstitial cells of Cajal generate the slow wave that regulates smooth muscle contractility, set the smooth muscle membrane potential, and also participate in nerve to smooth muscle communication. A defect in ICC may, therefore, appear as a mixed pattern on antroduodenal manometry.

Does Histopathology Identify Subsets of Gastroparesis or Associations with Gastroparesis?

From the largest collection of data in the NIH Gastroparesis Clinical Research Consortium study, Grover et al. reported significant quantitative cellular changes in diabetic and idiopathic gastroparesis (41). The most common defect observed was loss of ICC, followed by an immune infiltrate and loss of nNOS expression in enteric neurons. Thus, ICC counts were inversely correlated with 4 hour gastric retention in diabetic gastroparesis, but the same relationship was not observed in idiopathic gastroparesis (diabetic $r = -0.6$, $p=0.008$; idiopathic $r=0.2$, $p=0.4$). The reason for this difference is unclear, but it may reflect the differences in etiology (41).

In addition, there was significant correlation between loss of ICC and enteric nerves in diabetic gastroparesis, but not in idiopathic gastroparesis (diabetic $r=0.5$, $p=0.03$; idiopathic $r=0.3$, $p=0.16$). In contrast, idiopathic gastroparesis was associated with myenteric plexus immune infiltrate, and such patients with the immune infiltration scored higher on the average gastroparesis cardinal severity index score [GCSI (3.6 ± 0.7 vs. 2.7 ± 0.9 , $p=0.05$)] and

nausea score (3.8 ± 0.9 vs. 2.6 ± 1.0 , $p=0.02$) than those without an infiltrate. Thus, overall clinical severity and nausea in idiopathic gastroparesis are associated with a myenteric immune infiltrate. In contrast, ICC or enteric nerve loss did not correlate with symptom severity (41).

On light microscopy, no significant differences in specific neuronal populations were observed between diabetic and idiopathic gastroparesis, with the exception of nNOS expression (32). nNOS expression was decreased in 40% of patients with idiopathic gastroparesis compared to 20% of patients with diabetic gastroparesis, by visual grading. These observations need to be cautiously interpreted, as the numbers in the different histological subsets were small.

Transmission electron microscopy was also used to study the ultrastructure of the neuromuscular and ICC networks. In contrast to light microscopy, ultrastructural changes in ICC and nerves differed between diabetic and idiopathic gastroparesis and were more severe in idiopathic gastroparesis. Electron microscopy correctly classified idiopathic gastroparesis and diabetic gastroparesis. A thickened basal lamina around smooth muscle cells and nerves was characteristic of diabetic gastroparesis, whereas idiopathic gastroparesis was characterized by fibrosis, especially around the nerves. In general, overall nerve and ICC damage was more prominent in idiopathic gastroparesis (42).

Are There Differences in the Presentations of Patients with Idiopathic and Diabetic Gastroparesis?

From the NIH Gastroparesis Clinical Research Consortium database, Parkman et al. (43) evaluated the data of 254 patients with idiopathic gastroparesis (mostly female, white), and 137 patients with diabetic gastroparesis (78 type 1 diabetes and 59 type 2 diabetes). The main differentiations were in the demographics, symptoms at presentation, predominant chronic symptoms, results of gastric emptying measurements, and selection of therapy. Patients with type 2 diabetes were, on average, 13 years older at the onset of symptoms of gastroparesis and heavier than the patients with idiopathic gastroparesis. At the time of presentation or diagnosis, patients with type 1 diabetes had more hospitalizations in the past year than patients with idiopathic gastroparesis. Symptoms that prompted evaluation more often included vomiting for diabetic gastroparesis and abdominal pain for idiopathic gastroparesis. Among the chronic symptoms, patients with diabetic gastroparesis had more severe retching and vomiting than those with idiopathic gastroparesis, whereas patients with idiopathic gastroparesis had more severe early satiety and postprandial fullness subscores. On scintigraphic gastric emptying tests, compared with idiopathic gastroparesis, gastric retention was greater in patients with type 1 diabetes. More than 50% of patients with type 1 diabetes had severe retention (35% at 4 hours). Patients with diabetic gastroparesis took prokinetic agents more frequently and were more likely to receive gastric electric stimulation. In the patients with idiopathic gastroparesis from the same cohort, 46% were overweight or obese (44); yet, formal surveys showed many had dietary intake that was paradoxically deficient in calories, vitamins, and minerals.

Recent studies have addressed the symptoms presented by diabetic patients with delayed gastric emptying (diabetic gastroparesis) and non-diabetic, non-surgical patients with delayed gastric emptying (idiopathic gastroparesis). Among 157 patients with gastroparesis (increased gastric retention at 4 hours; 43 diabetic, 114 idiopathic) at a single center, nausea and vomiting were significant symptoms, with vomiting prevalence was greater in diabetic compared with idiopathic gastroparesis [72% vs. 55% (45)]. In addition, both vomiting severity score and number of vomiting episodes per day were significantly greater in diabetic compared to idiopathic gastroparesis. In contrast, nausea prevalence and severity

were similar in the two groups. There was modest correlation between symptom severity of vomiting and gastric emptying at 4 hours [$r=0.169$, $p=0.035$ (45)]. These single center data are consistent with the findings in the multicenter NIDDK gastroparesis consortium: patients with severe retention (4 hour retention $>35\%$) reported more severe nausea, vomiting, retching, loss of appetite, upper abdominal discomfort, and had higher gastroparesis cardinal symptom index (GCSI) scores compared to patients with moderate or mild retention (8). On the other hand, patients with idiopathic gastroparesis had increased bloating and upper abdominal pain (46).

While there is not a perfect correlation between severity of gastric emptying delay and symptom severity, there is general concordance between presence of symptoms and delay in gastric emptying in both idiopathic and diabetic gastroparesis, with the only difference being a greater propensity for idiopathic gastroparesis patients to present with abdominal pain as a significant feature.

Is the Response to Therapy Different According to Type of Gastroparesis?

In general, it is considered that myopathic gastroparesis may not respond as well to prokinetic medications. However, cisapride and erythromycin were effective in relief of symptoms and enhancing gastric emptying in patients with scleroderma (47,48). Based on a 1-year follow-up study in 50 pediatric patients with the related gastrointestinal motility disorder, chronic intestinal pseudo-obstruction (CIP), Hyman et al. reported that patients with hollow visceral myopathy and those who did not have any migrating motor complexes (MMCs) during a 4-hour fasting period had a decreased response to cisapride (49). In 42 adult patients, it was demonstrated that generalized sympathetic and vagal dysfunctions influenced the response of patients with neuropathic CIP to cisapride, and that idiopathic cases unassociated with abdominal vagal dysfunction were more likely to respond to cisapride (50). The response to therapy may, however, also be determined by inherited genetics, unrelated to idiopathic or diabetic gastroparesis. Parkman recently provided provocative data suggesting that polymorphism rs3815459 in *KCNH2*, the gene determining the function of the delayed-rectifier potassium channel that influences neuronal responses, was associated with effectiveness of domperidone and that the efficacious dose of domperidone was associated with polymorphism in *ABCB1* gene, which influences the function of P-glycoprotein that determines drug absorption (51). Conversely, Parkman et al. (52) reported that genetic polymorphism rs1805123 in *KCNH2* was associated with reduced efficacy of metoclopramide, another dopamine D2 antagonist.

Is Painful Gastroparesis a Subset of the Disease?

There is an increasing literature on abdominal pain as an “under-recognized” symptom in gastroparesis. In the NIH Gastroparesis Clinical Research Consortium study, 72% of patients had abdominal pain, and it was the dominant symptom in 18% of patients. In the tertiary referral study at Temple University (3), 90% of 68 patients with delayed gastric emptying (18 diabetic and 50 idiopathic) reported pain; pain was induced by eating (72%), was nocturnal (74%), and interfered with sleep (66%). Severity of pain was not correlated with gastric emptying rate, but with quality of life. The presence of daily pain in 43%, and even constant pain in 38%, may suggest tertiary referral bias. Given the nature of the pain and the lack of association of both pain and bloating with gastric emptying rate, associated conditions may be contributing to these symptoms. In fact, many patients in the NIH Gastroparesis Clinical Research Consortium database frequently had diagnosis of co-morbid conditions, including irritable bowel syndrome, migraines, fibromyalgia, functional dyspepsia (postprandial distress syndrome in 86% of those with idiopathic gastroparesis),

depression, and ~40% of patients received opiate treatment for pain or they were being concurrently treated with antidepressants (8).

Conclusions

The manifestations and presentation of idiopathic gastroparesis are similar to those of diabetic gastroparesis, with the exception of the predominance of pain in idiopathic gastroparesis. Histomorphological differences documented in these two groups are still of unclear biological significance. The relative preservation of enteric nerves and the rapid turnover of ICC suggest a degree of reversibility of the cellular defects. Post-viral gastroparesis generally is associated with a good prognosis; it is not known if this reflects such reversibility in the causative defect(s). Myopathic gastroparesis is an uncommon subtype of gastroparesis and is usually accompanied by other organ manifestations. Iatrogenic, non-surgical gastroparesis is potentially reversible and should always be considered, as its identification and use of alternative medications may relieve the patients' problems. In those with predominant pain, especially those requiring opiate treatment, there should be skepticism as to the relationship of the pain to the gastric emptying. Attention to the subsets of gastroparesis has the potential to allow more precise diagnosis and optimize treatment.

Acknowledgments

Funding Support

Grant P01-DK068055 from National Institutes of Health to Drs. Camilleri and Farrugia.

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