Published in final edited form as:

Gastroenterol Clin North Am. 2015 March ; 44(1): 59–68. doi:10.1016/j.gtc.2014.11.015.

Idiopathic Gastroparesis

Henry P. Parkman, MD

Gastroenterology Section, Temple University School of Medicine, Philadelphia, Pennsylvania

Abstract

Gastroparesis is a chronic symptomatic disorder of the stomach characterized by delayed emptying without evidence of mechanical obstruction. The three main causes of gastroparesis are diabetic, postsurgical, and idiopathic. Idiopathic gastroparesis refers to gastroparesis of unknown cause, that is, not from diabetes, not from prior gastric surgery, and not related to other endocrine, neurologic, rheumatologic causes of gastroparesis. The gastroparesis should not be related to medications that can delay gastric emptying, such as narcotic analgesic or anticholinergic medications. There is overlap in the symptoms of idiopathic gastroparesis and functional dyspepsia. A substantial minority of patients with functional dyspepsia can have delayed gastric emptying, blurring the distinction between idiopathic gastroparesis and functional dyspepsia. Patients with idiopathic gastroparesis often have a constellation of symptoms including nausea, vomiting, early satiety, postprandial fullness, and upper abdominal pain. Although the presentation of idiopathic gastroparesis is relatively similar to diabetic gastroparesis, abdominal pain occurs more often in idiopathic gastroparesis, whereas nausea and vomiting are more severe in diabetic gastroparesis. Treatment may employ agents used for diabetic gastroparesis and functional dyspepsia, including dietary management, prokinetics agents, antiemetic agents, and symptom modulators. Current treatment options do not adequately address clinical need for idiopathic gastroparesis.

Keywords

gastroparesis; gastric emptying; idiopathic gastroparesis

Introduction

Gastroparesis is a chronic symptomatic disorder of the stomach manifested by delayed emptying without evidence of mechanical obstruction (1,2). The common causes of gastroparesis include diabetic, postsurgical, and idiopathic (1,2). Idiopathic gastroparesis refers to gastroparesis of unknown cause; that is, not from diabetes, not from prior gastric surgery, and not related to other endocrine, neurologic, rheumatologic causes of

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Correspondence: Henry P. Parkman, MD, GI Section - Parkinson Pavilion 8th Floor, Temple University School of Medicine, 3401 North Broad Street; Philadelphia, PA 19140, FAX : 1-215-707-2684, henry.parkman@temple.edu.

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gastroparesis. In addition, it is not related to medications that can delay gastric emptying. Medications known to delay gastric emptying include opiate narcotic analgesics and anticholinergics (1).

In most series, idiopathic gastroparesis is the most common category for gastroparesis. In the series reported by McCallum et al (3), the etiologies in 146 patients were: 36% idiopathic, 29% diabetic, and 13% postgastric surgery, 7.5% Parkinson's disease, 4.8% collagen vascular disorders, 4.1% intestinal pseudoobstruction, and 6% miscellaneous causes. Miscellaneous causes of gastroparesis include other neurologic diseases, eating disorders, other metabolic or endocrine conditions (hypothyroidism), and critical illness.

This chapter discusses idiopathic gastroparesis, that is, symptomatic gastroparesis not from other known etiologies. This chapter updates the present status of our understanding of this disorder and reviews the recent studies from the NIH NIDDK Gastroparesis Consortium.

Epidemiology

Gastroparesis occurs more often in women than men, often by a 3:1 margin. Interestingly, this is true not only for idiopathic gastroparesis, but also for the other main causes of gastroparesis - diabetic and postsurgical. Patients with idiopathic gastroparesis are typically young or middle-aged women. Even after adjusting for gender differences in gastric emptying, since females in general have slower gastric emptying than males (4), gastroparesis occurs more commonly in women (5).

Outside of gender issues and etiology, the epidemiology of gastroparesis has not been well systematically studied. This stems from the fact that for proper diagnosis, a gastric emptying test is needed; one that presently cannot be done in population studies. Data from the Rochester Epidemiology Project, a database of linked medical records of residents of Olmsted County, Minnesota, showed that the age-adjusted incidence of definite gastroparesis per 100,000 person-years for the years 1996 to 2006 was 9.8 for women and 2.4 for men (6). Definite gastroparesis was defined as diagnosis of delayed gastric emptying by standard scintigraphy and symptoms of nausea and/or vomiting, postprandial fullness, early satiety, bloating, or epigastric pain for more than 3 months. The age-adjusted prevalence of definite gastroparesis per 100,000 persons was 37.8 for women and 9.6 for men. More recent estimates have suggested that the prevalence of gastroparesis were an underestimation and the prevalence is greater, approaching 2% of the general population (7).

Symptoms

Common symptoms of gastroparesis include nausea (>90% of patients), vomiting (84% of patients), and early satiety (60% of patients) (1,2,3). Other symptoms include postprandial fullness and upper abdominal pain (8). There is slight variation in symptoms depending on the etiology of gastroparesis: abdominal pain occurs more often in idiopathic gastroparesis than in diabetic gastroparesis (8), whereas nausea and vomiting are more severe in diabetic gastroparesis than in idiopathic gastroparesis (9). In patients with gastroparesis, weight loss, malnutrition, and dehydration may be prominent in severe cases.

There is overlap in the symptoms of idiopathic gastroparesis and functional dyspepsia. Abdominal pain or discomfort may be present to varying degrees in patients with gastroparesis, but it is not usually the predominant symptom, as it can be in functional dyspepsia (10). A substantial minority of patients (20–40%) with functional dyspepsia can have delayed gastric emptying (10), blurring the distinction between idiopathic gastroparesis and functional dyspepsia. Patients with idiopathic gastroparesis often have a constellation of symptoms including nausea, vomiting, early satiety, postprandial fullness, and upper abdominal pain.

Symptoms may fluctuate, with episodes of pronounced symptoms interspersed with relatively symptom-free intervals. Thus, at times, it can be difficult to differentiate idiopathic gastroparesis from cyclic vomiting syndrome (CVS), especially in the later when there can be a “coalescence of symptoms”, such that they can occur nearly daily rather than as typical for CVS with the vomiting episodes more sporadic on a monthly or less frequent basis (11). In CVS, gastric emptying is normal or often, it can be rapid (11)

The symptom profile and symptom severity of gastroparesis can be assessed with the Gastroparesis Cardinal Symptom Index (GCSI) (12), a subset of the Patient Assessment of Upper Gastrointestinal Symptoms (PAGI-SYM) (13). The GCSI comprises 3 subscales (nausea and vomiting, postprandial fullness and early satiety, and bloating) that the patient scores with reference to the preceding 2 weeks (12). The GCSI daily diary (GCSI-DD) can be used to record symptoms on a daily basis and may be more accurate in recording symptoms (14). This daily diary of symptoms captures symptoms of early satiety, nausea, vomiting, postprandial fullness, and upper abdominal pain. This questionnaire has been shown to capture relevant symptoms of gastroparesis in both patients with diabetic gastroparesis and idiopathic gastroparesis.

Although it has been a common assumption that the gastrointestinal symptoms can be attributed to the delay in gastric emptying characteristic of the disorder, most investigations have observed only weak correlations between symptom severity and the degree of gastric stasis (15,16). In general, the symptoms that appear to be best correlated (significant, but low correlation coefficients of 0.2 to 0.3) with a delay in gastric emptying include nausea, vomiting, early satiety, and postprandial fullness (17,18). Some symptoms present in patients with gastroparesis such as bloating and upper abdominal pain, are not correlated with delayed gastric emptying and might be related to sensory alterations that might also be present in patients with gastroparesis (18).

Most gastroparetic patients are underweight probably because of frequently experienced early satiety, nausea, and vomiting. Some gastroparesis (GP) patients, however, are overweight, for reasons that are not well understood. In a recent study, the factors that influence bodyweight in patients with idiopathic GP and in healthy controls were investigated (19). Thirty-nine healthy controls and 29 subjects with idiopathic GP underwent resting energy expenditure (indirect calorimetry), body composition (bioelectrical impedance), dietary intake (Block Food Frequency Questionnaire), symptoms (Patient Assessment of Upper GI Symptoms), and physical activity (Paffenbarger exercise survey) were assessed. Both median caloric intake (1242 vs 1804 kcal; $p=0.005$) and caloric

expenditure (486 vs 2172 kcal; $p < 0.01$) were significantly lower in patients with GP as compared to controls, although BMI (25.8 ± 5.8 vs 24.3 ± 4.0 kg/m²) and resting energy expenditure (1327 ± 293 vs 1422 ± 243 kcal) were similar. Interestingly, the 12 GP patients who had gained weight since diagnosis had lower symptom severity (12.9 ± 4.4 vs 19.3 ± 6.3 ; $p < 0.05$), consumed more calories (1342 vs 1134 kcal; $p = 0.08$) and expended less calories for activity per week (406 vs 644 median kcal; $p = 0.45$) compared to the 17 GP patients who had lost weight or remained weight neutral. Thus, patients with GP consumed and expended less calories than healthy controls. A subgroup of patients with GP who were less symptomatic, gained weight because of increased caloric intake and reduced energy expenditure.

NIH Gastroparesis Consortium Registry Studies in Idiopathic Gastroparesis

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Gastroparesis Clinical Research Consortium (GpCRC) is a cooperative network of seven clinical centers and one Data Coordinating Center (DCC) funded through the NIDDK of the National Institutes of Health (NIH). The GpCRC Gastroparesis Registry was implemented as an observational study of patients with gastroparesis enrolled prospectively at seven centers (20). Several of the published studies have addressed idiopathic gastroparesis.

The characteristics of 243 patients with idiopathic gastroparesis enrolled in the GpC Registry were recently described (20). This study is the largest study of patients with idiopathic gastroparesis. Patients' mean age was 41 years, and the majority (88%) were female. The most common presenting symptoms were nausea (34%), vomiting (19%), and abdominal pain (23%). Severe delay in gastric emptying ($>35\%$ retention at 4 hours) was present in 28% of patients and was associated with more severe symptoms of nausea and vomiting and loss of appetite compared with patients with mild or moderate delay. Of these patients with idiopathic gastroparesis, 86% met criteria for functional dyspepsia, predominately postprandial distress syndrome. Of interest, 46% of the patients were overweight. Thus, this study shows that idiopathic gastroparesis is a heterogeneous syndrome that primarily affects young women and can also affect overweight or obese individuals.

Although gastroparesis can be diabetic or idiopathic, little is known about differences in their presentation. The GpC compared clinical characteristics, symptoms, and gastric emptying in patients with idiopathic gastroparesis (IG) to patients with type 1 or type 2 diabetic (DG) (21). 416 patients with gastroparesis were analyzed; 254 had IG, and 137 had DG (78 had type 1 and 59 had type 2). Symptoms that prompted evaluation more often included vomiting for DG and abdominal pain for IG. Patients with DG had more severe retching and vomiting than those with IG, whereas patients with IG had more severe early satiety and postprandial fullness subscores. Compared with IG, gastric retention was greater in patients with type 1 DM. Thus, there are many similarities and some differences in clinical characteristics of DG and IG. Gastroparesis is a heterogeneous disorder; the etiology of the gastroparesis impacts on the symptoms and severity.

Abdominal pain can be present in patients with idiopathic gastroparesis. Factors associated with abdominal pain in gastroparesis have not been well studied. The NIH GpC studied the

symptom of abdominal pain and how it relates to other clinical factors in 393 gastroparesis patients (22). Upper abdominal pain was moderate-severe in 261 (66%) patients. Pain/discomfort was predominant in 81 (21%); nausea/vomiting was predominant in 172 (44%). Moderate-severe pain was more prevalent with idiopathic gastroparesis than in diabetic gastroparesis and correlated with scores for nausea/vomiting and opiate use, but not gastric emptying. Gastroparesis severity, quality of life, and depression and anxiety were worse with moderate-severe pain. Predominant pain/discomfort was associated with impaired quality of life. Thus, moderate-severe abdominal pain is prevalent in gastroparesis, impairs quality of life, and is associated with idiopathic etiology, and opiate use. Pain was predominant in one fifth of gastroparetics. Predominant pain has at least as great an impact on disease severity and quality of life as compared to the more classic symptoms of predominant nausea/vomiting.

Bloating is commonly reported in gastroparesis, but is an underappreciated symptom of gastroparesis. The prevalence of bloating in gastroparesis and its severity was assessed in 335 gastroparesis patients (23). Bloating severity of at least severe (GCSI 4) grades was reported by 41% of patients. Bloating severity related to female gender and overweight status and correlated with intensity of nausea, postprandial fullness, visible distention, abdominal pain, and altered bowel function. Antiemetics, probiotics, and antidepressants with significant norepinephrine reuptake inhibitor activity may affect reports of bloating. Disease-specific quality of life and general measures of well-being were progressively impaired with increasing bloating severity. Thus, the symptom of bloating impairs quality of life but is not influenced by gastric emptying rates.

Many patients with gastroparesis have had their gallbladders removed; how this impacts on gastroparesis is not known. The clinical presentations of patients with gastroparesis were compared in those with prior cholecystectomy compared to patients who have not had their gallbladder removed (24). Of 391 subjects with diabetic or idiopathic gastroparesis (IG), 142 (36 %) had a prior cholecystectomy. Patients with prior cholecystectomy were more often female, older, and overweight or obese. Cholecystectomy had been performed in 46% of T2DM compared to 24% of T1DM and 38% of IG. Patients with cholecystectomy had more comorbidities, particularly chronic fatigue syndrome, fibromyalgia, depression, and anxiety. Postcholecystectomy gastroparesis patients had increased health care utilization, and had a worse quality of life. Etiology was not independently associated with a prior cholecystectomy. Thus, symptom profiles in patients with and without cholecystectomy differ: postcholecystectomy gastroparesis patients had more severe upper abdominal pain and retching and less severe constipation. These data suggest that prior cholecystectomy is associated with selected manifestations of gastroparesis.

Pathophysiology

A potential cause in some patients with idiopathic gastroparesis has been suggested to be viral injury to the nerves or muscles of the stomach – postviral gastroparesis. It has been suggested that idiopathic gastroparesis of acute onset with infectious prodrome could constitute postviral or viral injury to the neural innervation of the stomach or the interstitial cells of Cajal in the stomach. In the NIH GpC study of idiopathic gastroparesis, half the

patients had an acute onset of symptoms with a minority of patients (19%) reported an initial infectious prodrome such as gastroenteritis or respiratory infection (20). In the McCallum series, postviral gastroparesis was suspected in 23% of patients with idiopathic gastroparesis (25). This clinical diagnosis of postviral gastroparesis is suggested in previously healthy persons with an acute onset of viral illness with nausea, vomiting, diarrhea, fever, and cramps who have persistence of symptoms (nausea, vomiting, early satiety) for more than 3 months with a delay in gastric emptying. Viruses suspected as potential causes are cytomegalovirus (CMV), Epstein–Barr virus, and herpes varicella-zoster. Symptoms of idiopathic gastroparesis after a presumed viral illness tend to be less severe than in gastroparesis from other causes. Overall, these patients appear to have a good prognosis, with many patients having a slow resolution of their symptoms (25).

Gastric emptying is mediated by the vagus nerve, which helps regulate fundic accommodation, antral contraction, and pyloric relaxation (1). These regional gastric motility changes with food ingestion are then mediated through smooth muscle cells, which control stomach contractions; interstitial cells of Cajal, which regulate gastric pacemaker activity; and enteric neurons, which initiate smooth muscle cell activity (1). The pathophysiology of gastroparesis has not been fully elucidated but appears to involve abnormalities in functioning of several elements including autonomic nervous system, smooth muscle cells, enteric neurons, and interstitial cells of Cajal. Histologic studies in gastroparesis patients demonstrate defects in the morphology of enteric neurons, smooth muscle cells, and interstitial cells of Cajal and increased concentrations of inflammatory cells in gastric tissue (26).

NIH Gastroparesis Consortium Studies on Pathology

Cellular changes associated with diabetic (DG) and idiopathic gastroparesis (IG) have recently been described from gastroparesis patients by the NIH GpC. Full-thickness gastric body biopsy specimens were obtained from 40 patients with gastroparesis (20 diabetic) and matched controls (27). Histologic abnormalities were found in 83% of patients. The most common defects were loss of ICC with remaining ICC showing injury, an abnormal immune infiltrate containing macrophages, and decreased nerve fibers. On light microscopy, no significant differences were found between diabetic and idiopathic gastroparesis with the exception of nNOS expression, which was decreased in more patients with idiopathic gastroparesis (40%) compared with diabetic patients (20%) by visual grading. On electron microscopy, a markedly increased connective tissue stroma was present in both disorders. This study suggests that on full-thickness biopsy specimens, cellular abnormalities are found in the majority of patients with gastroparesis. The most common findings were loss of Kit expression, suggesting loss of ICC, and an increase in CD45 and CD68 immunoreactivity. These findings suggest that examination of tissue can lead to valuable insights into the pathophysiology and possibly treatments for the patient.

The association of these cellular changes in patients with gastroparesis with gastroparesis symptoms and gastric emptying was recently reported (28). Idiopathic gastroparesis with a myenteric immune infiltrate scored higher on the average GCSI and nausea score as compared to those without an infiltrate. Interstitial cells of Cajal counts inversely correlated

with 4 h gastric retention in DG but not in IG. There was also a significant correlation between loss of ICC and enteric nerves in DG but not in IG. Thus, in DG, loss of ICC is associated with delayed gastric emptying. Interstitial cells of Cajal or enteric nerve loss did not correlate with symptom severity. Overall clinical severity and nausea in IG is associated with a myenteric immune infiltrate. Thus, full thickness gastric biopsies can help define specific cellular abnormalities in gastroparesis, some of which are associated with physiological and clinical characteristics of gastroparesis.

Management

Management of gastroparesis is guided by the goals of correcting fluid, electrolyte, and nutritional deficiencies; identifying and treating the cause of delayed gastric emptying (e.g., diabetes); and suppressing or eliminating symptoms (1,2). Treatment of the symptoms may employ agents used for diabetic gastroparesis and functional dyspepsia. Care of patients generally relies on dietary modification, prokinetics medications that stimulate gastric motor activity, antiemetic drug therapy to suppress symptoms of nausea and vomiting, and symptom modulators (psychotropic agents) that reduce symptom expression. Narcotic analgesics should be avoided. Although narcotic analgesics may acutely improve abdominal pain, with chronic use, they delay gastric emptying, may themselves lead to symptoms of nausea and vomiting, may upregulate abdominal pain, and lead to dependence. Total parenteral nutrition, although used in some refractory patients, is associated with complications of infections and thrombosis. Aspects on treatment are discussed in detail in later chapters on treatments for gastroparesis. Particulars of treatment in idiopathic gastroparesis are discussed below.

Dietary aspects in gastroparesis

Gastroparesis can lead to food aversion, poor oral intake, and subsequent malnutrition. In the NIH GPC gastroparesis registry, dietary intake and nutritional deficiencies were characterized in 305 patients with diabetic and idiopathic gastroparesis (29) who completed diet questionnaires (Block Food Frequency Questionnaire). Caloric intake averaged 1168 ± 801 kcal/day, amounting to $58\% \pm 39\%$ of daily total energy requirements (TER). A total of 194 patients (64%) reported caloric-deficient diets. Only 5 patients (2%) followed a diet suggested for patients with gastroparesis. Deficiencies were present in several vitamins and minerals; patients with idiopathic disorders were more likely to have diets with estimated deficiencies in vitamins A, B6, C, K, iron, potassium, and zinc than diabetic patients. Only one-third of patients were taking multivitamin supplements. More severe symptoms (bloating and constipation) were characteristic of patients who reported an energy-deficient diet. Surprisingly, only 32% of patients had nutritional consultation after the onset of gastroparesis; consultation was more likely among patients with longer duration of symptoms and more hospitalizations and patients with diabetes. Multivariable logistic regression analysis indicated that nutritional consultation increased the chances that daily TER were met (odds ratio, 1.51; $P=0.08$). Thus, many patients with gastroparesis have diets deficient in calories, vitamins, and minerals. Most patients are not following a “gastroparesis diet”. Nutritional consultation is obtained infrequently, especially in idiopathic

gastroparesis. A nutritional consultation may be helpful for instructions on dietary therapy and to address nutritional deficiencies.

Psychotropic medications as symptom modulators

Gastroparesis is a challenging syndrome to manage, with few effective treatments and lack of rigorously controlled trials. Symptom modulators (psychotropic agents such as tricyclic antidepressants) are often used to treat refractory symptoms of nausea, vomiting, and abdominal pain. Evidence from well-designed studies for this use is lacking. Tricyclic antidepressants may have benefits in suppressing symptoms in some patients with nausea and vomiting as well as patients with abdominal pain. Doses of tricyclic antidepressants used are lower than used to treat depression. A reasonable starting dose for a tricyclic drug is 10–25 mg at bedtime. If benefit is not observed in several weeks, doses are increased by 10- to 25-mg increments up to 75 mg. Side effects are common with use of tricyclic antidepressants and can interfere with management and lead to a change in medication in some patients. The secondary amines, nortriptyline and desipramine, may have fewer side effects than amitriptyline which itself may delay gastric emptying. The recent NIH gastroparesis consortium study with nortriptyline in idiopathic gastroparesis did not show an effect on overall symptoms of gastroparesis (30). However, there was a suggestion that low nortriptyline doses (10–25 mg qhs) might decrease nausea, whereas higher doses might decrease fullness. The recently completed NIH functional dyspepsia treatment trial showed a favorable effect for amitriptyline for functional dyspepsia – this was seen in patients with normal gastric emptying, but not in those with delayed gastric emptying (31).

Gastric electric stimulation

Gastric electric stimulation is a treatment for refractory gastroparesis involving implantation of neurostimulator. The currently approved stimulator delivers a high-frequency (12 cpm), low-energy signal with short pulses to the gastric muscle along the greater curvature. Based on the initial studies that have shown symptom benefit with low complications, the gastric electric neurostimulator was granted humanitarian approval from the FDA for the treatment of chronic, refractory nausea and vomiting secondary to idiopathic or diabetic gastroparesis (32). Symptoms of vomiting improved with gastric stimulation. This symptomatic benefit was primarily seen in patients with diabetic gastroparesis than in idiopathic gastroparesis (32). In the study by Maranki et al (33), three predictive factors for clinical improvement with gastric electric stimulation were found: 1) diabetic rather than idiopathic etiology; 2) predominant symptoms of nausea and/or vomiting rather than abdominal pain; 3) lack of the use of regular narcotic pain medications. In this series, gastric electric stimulation significantly improved symptoms of nausea and vomiting, but not abdominal pain. In a recently reported, prospective study of gastric electric stimulation for idiopathic gastroparesis (34), there was a reduction in vomiting during the initial 6 week open label ON treatment period. A double-blind 3-month period showed a non-significant reduction in vomiting in the ON vs OFF period, the primary outcome variable. At 12 months with open label ON stimulation, there was a sustained decrease in vomiting and days of hospitalizations.

Conclusions

Idiopathic gastroparesis refers to gastroparesis of unknown cause, that is, not from diabetes, not from prior gastric surgery, and not related to other endocrine, neurologic, rheumatologic causes of gastroparesis. Patients with idiopathic gastroparesis often have a constellation of symptoms including nausea, vomiting, early satiety, postprandial fullness, and upper abdominal pain. Although the presentation of idiopathic gastroparesis is relatively similar to diabetic gastroparesis, abdominal pain occurs more often in idiopathic gastroparesis, whereas nausea and vomiting are more severe in diabetic gastroparesis. Treatment may employ agents used for diabetic gastroparesis and functional dyspepsia, including dietary management, prokinetics agents, antiemetic agents, and symptom modulators. Idiopathic gastroparesis significantly impacts on the quality of life of patients through its chronic symptoms of nausea, vomiting, and abdominal pain. Unfortunately, current approved treatment options do not adequately address clinical need. Development of new effective therapies for symptomatic control is needed.

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Key Points

1. Idiopathic gastroparesis is a common form of gastroparesis, being among the three main causes of gastroparesis: diabetic, postsurgical, and idiopathic gastroparesis.
2. Patients with idiopathic gastroparesis has a constellation of symptoms including nausea, vomiting, early satiety, postprandial fullness, and, in some patients, upper abdominal pain.
3. The presentation of idiopathic gastroparesis is relatively similar to diabetic gastroparesis, although abdominal pain occurs more often in idiopathic gastroparesis, whereas nausea and vomiting are more severe in diabetic gastroparesis.
4. Treatment of the symptoms may employ agents used for diabetic gastroparesis and functional dyspepsia.
5. Idiopathic gastroparesis significantly impacts on the quality of life of patients and development of new effective therapies for symptomatic control is needed.