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Characteristics of Patients with Chronic Unexplained Nausea and Vomiting and Normal Gastric Emptying

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Conflict of Interest Statement

None of the authors report any conflict of interest with respect to this manuscript or the data in it

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Abstract

Background & Aims—Chronic nausea and vomiting with normal gastric emptying is a poorly understood syndrome; we analyzed its characteristics.

Methods—We collected and analyzed data from 425 patients with chronic nausea and vomiting, enrolled at 6 centers by the Gastroparesis Clinical Research Consortium in the National Institute of Diabetes and Digestive and Kidney Diseases Gastroparesis Registry.

Results—Among the patients, 319 (75%) had delayed emptying, defined by the results of a standardized, low-fat meal, and 106 had normal gastric emptying. Patients with or without delayed emptying did not differ in age, sex, or race, although those with normal gastric emptying were less likely to be diabetic. Symptom severity indices were similar between groups for nausea, retching, vomiting, stomach fullness, inability to complete a meal, feeling excessively full after meals, loss of appetite, bloating, and visibly larger stomach. There were no differences in health care utilization, quality of life indices, depression, or trait anxiety scores. However, state anxiety scores were slightly higher among patients with delayed gastric emptying. Total gastroparesis cardinal symptom index scores were not correlated with gastric retention after 2 or 4 hours in either group. Patients with the syndrome were not adequately captured by the stand-alone criteria for the Rome III diagnoses of chronic idiopathic nausea and functional vomiting. With rare exceptions, the diagnosis remained stable after a 48-weeks follow-up period.

Conclusions—Patients with nausea and vomiting with normal gastric emptying represent a significant medical problem and are, for the most part, indistinguishable from those with gastroparesis. This syndrome is not categorized in the medical literature—it might be a separate clinical entity.

Keywords

GCSI; digestion; PGI-SYM; PGI-QOL

Introduction

Chronic nausea and vomiting, in the absence of an obvious structural abnormality, is a relatively uncommon but important cause of morbidity. When associated with a delay in gastric emptying, the syndrome has been called gastroparesis. However, a number of patients with chronic nausea and vomiting have no demonstrable abnormality in gastric emptying using current methodologies and present a significant challenge in terms of both diagnosis and management. Little is known about this group of patients and the few reports that exist are based on single-center experiences and small numbers of patients.¹⁻⁴ The Rome III classification of functional gastroduodenal and bowel disorders lists several

disorders with nausea and or vomiting as a major symptom including “chronic idiopathic nausea” and “functional vomiting” and we used Rome III diagnostic questionnaire for screening potential participants in Gastroparesis Registry. This large multi-center patient registry organized by the NIH-funded Gastroparesis Clinical Research Consortium, enrolling patients with both gastroparesis and those with chronic nausea and vomiting but with normal gastric emptying has provided the opportunity to study these patients in a more comprehensive and systematic manner (ClinicalTrials.gov Identifier: NCT00398801).

The primary aim of this study was therefore to examine the clinical and demographic features in patients with chronic unexplained nausea and vomiting with normal gastric emptying. In addition, our aim was to examine the differences, if any, between this group and patients with gastroparesis to determine if a delay in gastric emptying conferred a distinct clinical presentation.

Methods

Patients

Patients were recruited through the Gastroparesis Registry (see supplement) To meet entry criteria, patients had to have symptoms of at least a 12 week duration, delayed gastric emptying and no abnormality causing obstruction as seen by upper endoscopy. Further, by design, recruitment of patients with symptoms suspicious of gastroparesis but with normal gastric emptying was allowed as a comparison group, but not to exceed about 20% of the total number in the registry. We refer to this group of patients as chronic unexplained nausea and vomiting (CUNV) with normal gastric emptying. In addition to the upper endoscopy, a rigorous history and physical was required to exclude any other plausible explanation for these symptoms in both groups of patients before enrollment, and appropriate tests (e.g. biliary imaging or gastrointestinal contrast studies) were ordered as indicated.

Human Subjects Approval

The study was approved by the Institutional Review Board of all the participating institutions as well as the consortium’s Data and Safety Monitoring Board.

Symptom scoring and grading of severity

Symptoms were scored using the PAGA-SYM (Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index) questionnaire, which also contains the Gastroparesis Cardinal Symptom Index (GCSI), a validated scale of severity (from 0 to 5) in patients that utilizes three symptom clusters (nausea/vomiting, post-prandial fullness/satiety, and bloating) measure over the preceding two weeks.^{5, 6} The clinical severity of gastroparesis was graded globally into three (1= mild, 2 =compensated and 3 = severe) by the investigators as previously described.⁷

Gastric Emptying

A consensus protocol was used to assess gastric emptying by scintigraphy using a low-fat, egg white meal labeled with radioactive technetium with imaging at 0, 1, 2, 4 hours after meal ingestion.⁸ As per this consensus report, delayed gastric emptying was defined as greater than 60% retention at two hours and/or 10% at 4 hours. Rapid emptying was defined as <30% retention at 1 hour.

PAGI-QOL

The Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life is a 30-item instrument that has been validated as a reliable and sensitive measure of quality of life in

patients suffering from dyspepsia, gastroesophageal reflux disease (GERD) or gastroparesis.⁹

IDIOMS

The investigator derived independent outcomes measure score (IDIOMS) includes three parameters associated with healthcare resource use: intensity of service (e.g. outpatient, home health, inpatient), severity of illness (e.g. still working, on disability), and number of non-GI organ systems involved. Each parameter was rated on a 10-point scale, and the parameters are summed for a total score ranging from 0 to 30; the three components are added for a total score.¹⁰

Pain Inventory and Psychological Measurements

We used the short form of the Brief Pain Inventory (BPI)¹¹, Beck Depression Inventory (BDI)¹² and State-Trait Anxiety Inventory (see supplemental material for details).¹³

Rome III Classification

A portion of the Rome III Diagnostic Questionnaire relating to functional gastroduodenal and bowel disorders was administered to each patient during the registration period. An analysis program developed by the Rome Foundation was utilized to obtain Rome III diagnoses. (http://www.romecriteria.org/rome_iii_sas/, accessed 03 February 2010).

Statistical Analysis

Unadjusted comparisons of patient characteristics by gastric emptying (patients with nausea and vomiting but with normal gastric emptying and patients with gastroparesis or delayed gastric emptying) were conducted using Fisher's exact test for categorical variables and Wilcoxon rank sum test for measured variables. In addition, the Cochran-Armitage test for trend was used to detect a linear relationship between symptom severity and gastric emptying. Multiple logistic regression models were used to compare patients with nausea and vomiting but with normal gastric emptying from patients with gastroparesis on various variables, a full description of which is found in the supplement. All statistical analyses were performed using SAS for Windows, version 9.1 (SAS Institute Inc., Cary, NC).

Results

Patients

From January 2007 to August 2009, 425 patients were enrolled in the Gastroparesis Registry. Of these 319 (75%) had delayed emptying and 106 (25%) had normal gastric emptying with chronic unexplained nausea and vomiting (CUNV). As expected, CUNV patients had gastric emptying rates that were faster than patients with gastroparesis (Median % retentions at 1 hour: 62 versus 84.6; 2 hour: 28.5 versus 66; 4 hour: 3 versus 25). 2 patients (0.6%) in the gastroparetic group and 6 patients in the CUNV group (5.7%) had rapid emptying at 1 hour (defined as < 30% retention). Overall, however, as the graph in Supplemental Figure 1 shows, the gastric emptying values in the CUNV group are almost identical to the median range of the widely accepted normative data.⁸ Amongst diabetic patients, glycemic control at baseline (as measured by HbA1c levels) was similar in the CUNV (median: 7.85; range: 7.1–8.75) and gastroparetic groups (median 7.35; range: 6.55–8.65).

Demographics, lifestyle and anthropometric measures

Table 1 shows the distribution of demographic, lifestyle and anthropometric characteristics in the two patient groups. As for gastroparetics, patients with CUNV were predominantly

young to middle-aged females. There were no significant differences between the two groups across a wide variety of parameters, with the exception of the patients who were currently employed and those who were binge drinkers (as defined by six or more alcoholic drinks on one occasion), with both proportions being higher in patients with CUNV and normal gastric emptying.

Clinical Features and Presentation

Patients with CUNV were as a group significantly symptomatic. Table 2 represents the answers to questions in the PAGI-SYM questionnaire, regarding symptom severity during the past two weeks. Table 3 describes the symptoms that the patients reported as having prompted evaluation for gastroparesis. Overall, the severity, pattern and nature of symptoms were indistinguishable in the two groups. Diabetes appeared to be less common as a putative etiology in patients with normal emptying compared to those with gastroparesis (18.9% versus 31.4%; $P=0.04$). Amongst symptoms that prompted evaluation, only early satiety appeared to be higher in patients with normal gastric emptying compared to gastroparesis (68% versus 57%; $p=0.05$). There were also no differences in any of the items in the Brief Pain Inventory.

There were no significant differences between the two groups in terms of a previous diagnosis of gallbladder disease or prior cholecystectomy (Supplemental Table 1). Patients with CUNV were far less likely to be on prokinetics as compared with patients with gastroparesis (36.8% versus 54.9%; $P=0.001$) and somewhat less likely to be on acid-suppressive therapy (67% versus 76.8%; $P=0.05$). The use of other medications including antiemetics, antidepressants, anxiolytics or pain relievers was not different amongst the two groups (Supplemental Table 1).

Psychometric and quality of life comparisons

Patients with CUNV had a significant burden of health, comparable to that of patients with gastroparesis, as shown by PAGI-QOL scores. No differences were seen in depression or trait anxiety scores; however state anxiety scores were higher in patients with delayed gastric emptying (Table 4).

Physician-measured indices of gastroparesis severity and healthcare utilization (Table 4)

Patients with CUNV were perceived to have a heavy burden of disease. However, as a group, patients with normal gastric emptying had a smaller proportion of patients with the most severe grade of symptoms (23% versus 33%, grade 3, see methods). This also corresponded to a lower perception of healthcare utilization, as assessed by the IDIOMS score (12.5 versus 14; $P=0.007$).

Differences in laboratory parameters

We examined a variety of blood tests and no striking abnormalities were seen either in the CUNV or gastroparetic group. Comparing the two groups, statistically significant differences were seen in a small number of tests such as beta-globulin levels and hematocrit/hemoglobin (supplemental Table 1).

Regression Analysis

We performed separate and multiple logistic regression analyses (Table 5) and found that factors associated with the presence of normal gastric emptying are: early satiety as a presenting complaint, binge drinking, higher beta-globulin levels and currently being employed whereas factors associated with the presence of delayed gastric emptying are a higher IDIOMS score and higher state anxiety scores.

Analysis by Rome III criteria

CUNV and gastroparesis patients classification with Rome III diagnostic questionnaire is summarized in Table 6. The majority (>80%) of patients in either group satisfied the Rome III criteria for “functional dyspepsia”. These numbers did not change substantially even when we included patients with mildly delayed gastric emptying (<20% retention at four hours) in the “normal emptying group” (supplemental Table 2). There was also overlap between “functional dyspepsia” and the two other major categories of nausea or vomiting—chronic idiopathic nausea (CIN) and functional vomiting (FV). According to Rome III criteria, about 45% of patients with CUNV and 26% of patients with gastroparesis would be classified as “chronic idiopathic nausea”. On the other hand only 30% of patients with CUNV but 42% of patients with gastroparesis would be classified as “functional vomiting”. Further, very few patients satisfied the criteria for either CIN or FV without overlap with functional dyspepsia. Patients with CIN alone represented 6.3% and 10.7% of the CUNV and gastroparesis groups respectively while the corresponding numbers for patients with FV alone were 12.5% and 8.2%. Interestingly, the majority of patients in both CUNV and gastroparesis groups also met the Rome III criteria for irritable bowel syndrome.

48 week follow-up

222 patients with gastroparesis and 66 patients with CUNV had completed 48 weeks of follow-up at the time of this manuscript. Patients remained significantly symptomatic with no difference between the two groups in terms of GCSI scores at this time period (2.60 ± 1.13 in the gastroparesis group versus 2.53 ± 1.25 in the CUNV group; $P = 0.5$). Of the CUNV patients, only two patients had an additional diagnosis that could explain their symptoms (one patient with Addison’s disease and one with a pyloric channel ulcer).

Correlation of gastric emptying with GCSI scores

Gastric emptying rates at two or four hours did not correlate with severity of symptoms (as measured by total GCSI scores) in the group as a whole ($R=0.03$; $P=0.53$), or separately in the group with gastroparesis ($R=0.04$, $P=0.43$) and in the group with chronic nausea and vomiting and normal emptying ($R=0.03$, $P=0.78$) (Figure 1).

Discussion

The syndrome of chronic nausea and vomiting but with normal gastric emptying has been clinically obscure in part because of the paucity of reports in the literature. In this regard our multicenter study is unique because it represents the largest and most comprehensive analysis of this group of patients, included very rigorous inclusion and exclusion criteria and employed standardized evaluations for both clinical symptoms and gastric emptying. Further, the cohort in this study has now been followed for at least a year with little change in the initial diagnosis, suggesting the stability of this diagnosis.

The most important lesson from this multicenter study is that patients with normal gastric emptying and symptoms of nausea and vomiting have a clinical presentation and course that is virtually indistinguishable from those with delayed gastric emptying (i.e. classical gastroparesis). Although the literature on these patients is extremely limited, it is generally supportive of our results. Thus, in one study, the efficacy of gastrointestinal electrical stimulation on seven patients with chronic nausea and vomiting but with normal gastric emptying was compared to eight patients with classical gastroparesis.² The groups did not differ in symptoms and quality of life and the response to electrical stimulation was also comparable, similar to what was reported in another small study of 12 patients.³ In the largest series to date, seventeen patients with chronic nausea and vomiting and documented normal gastric emptying were compared to 52 patients with delayed gastric emptying.¹ The

two groups were similar with respect to symptomatic burden and the response to conservative treatment. However, there was a disproportionate number of males in the group with normal emptying, similar to what has been mentioned in a recent review, describing “vomiting of unclear etiology or VUE” nearly half of whom were males.⁴ By contrast, in this large multicenter study, we found that patients with CUNV had a similar gender profile to that of gastroparesis, with the vast majority being female.

When dealing with these patients, it is also important to exclude potentially confusing syndromes. One of these is rumination syndrome, which is distinguished by lack of nausea and very early postprandial regurgitation that may be mistaken for vomiting.¹⁴ Only 2 patients in our cohort of CUNV satisfied the Rome III criteria for rumination. Cyclic vomiting syndrome is another entity increasingly being recognized in adults.¹⁵ A significant subset of patients with cyclic vomiting may have accelerated emptying. A small percentage of our patients had a cyclic pattern but they appeared to be equally represented in the two groups. Further, although rapid emptiers were disproportionately represented in the group with normal emptying, their number was very small (six). A more controversial condition that may be confused with this syndrome is “psychogenic vomiting”. Historically, this has been the default diagnosis for chronic unexplained nausea and vomiting, with many patients being labeled as either suffering from a conversion disorder or depression.^{16, 17} Although patients with vomiting of unexplained origin have been reported to be more likely to be disabled and have a history of physical or sexual abuse, no significant psychiatric differences were found when compared with a control group with vomiting secondary to gastroesophageal reflux or diabetic gastroparesis.⁴ In our study, we evaluated psychological indices using validated symptom questionnaires and found that patients with chronic nausea and vomiting and normal gastric emptying were comparable to those with gastroparesis both in terms of depression scores and trait anxiety scores. If anything, these patients had better state anxiety scores and more likely to be currently employed, minimizing a role for psychosocial confounders in the development of this syndrome.

The group with normal gastric emptying had a smaller proportion of patients (23% as compared with 33% in the delayed emptying group) with grade 3 severity (“gastric failure”), and this was accompanied by a decreased IDIOMS score, corresponding to lower healthcare utilization. Overall these results suggest that patients with normal gastric emptying may have a slightly less severe illness or are better adjusted to their clinical condition. However, it should be noted that nearly a quarter of patients with normal gastric emptying still met the criteria for “gastric failure”, attesting to the considerable burden of suffering in the CUNV group.

The results of our regression analysis suggest six factors correlated with the presence of normal gastric emptying (Table 5). Three of these- employment history, decreased state anxiety scores and decreased IDIOMS scores have been discussed above. It is difficult to speculate on the clinical relevance of two others- a history of binge drinking or an increase in beta-globulin levels (which includes transferrin, lipoprotein, complement components and other proteins) and a more hypothesis driven research will need to be conducted to determine their clinical significance as potential correlates with symptoms. The sixth factor is early satiety. The presence of early satiety as a presenting complaint conferred a nearly 2-fold increase in the odds of having normal gastric emptying. However, this did not translate into differences in the frequency or severity of early satiety, so it is difficult to determine the importance of this statistically significant finding.

Our study has also brought into question the importance of gastric emptying in the pathogenesis of nausea and vomiting. It is becoming increasingly apparent that the correlation between individual symptoms and delayed gastric emptying is poor¹⁸⁻²¹; in

particular, delayed gastric emptying may have partial correlation with complaints of fullness, upper abdominal pain and reduced hunger but not with nausea and vomiting.^{20, 22} Our study supports the notion that delayed gastric emptying may not be the primary causative factor in nausea and vomiting because of two reasons. First, similar degrees of nausea and vomiting are seen in patients with and without delayed gastric emptying. Secondly, within each group, there is no correlation between the degree of emptying and severity of symptoms.

The pathogenesis of nausea and vomiting in these patients therefore is unexplained. At this point it is not clear whether these patients represent a distinct syndrome, a heterogenous collection of different unidentified etiologies or are really part of the spectrum of gastroparesis with scintigraphic values that change with time. Our study was not designed to answer these questions but several speculations may be made. After being followed for nearly a year, the diagnosis remained unchanged in all but a very small number of patients, suggesting that it was unlikely that we were failing to identify significant underlying illnesses. It remains possible that these patients do have abnormalities in gastric function that are more subtle than those found in classical gastroparesis. First, it is feasible that current solid gastric emptying techniques by themselves do not capture the entire spectrum of gastric dysfunction in these patients. It has been recently shown that nearly a third of patients with suspected normal solid gastric emptying have delayed liquid gastric emptying.^{23, 24} Secondly, changes in autonomic nervous function may play an important role in tying together symptoms with changes in gastric emptying.^{25, 26} More importantly, aberrant afferent signaling via either vagal or splanchnic nerves or both, remains an attractive hypothesis to explain symptoms as it has been shown that even physiological degrees of gastric distension can induce nausea, bloating and upper abdominal pain in diabetics with autonomic neuropathy.²⁷ It is also possible, that unexplored changes in hormonal levels or subtle pathology in the central nervous system may exist in these patients. Finally, it is possible that over time, these patients will manifest delay in emptying, thus qualifying for the diagnosis of gastroparesis.

It is also worthwhile to consider issues of nomenclature when dealing with patients with chronic nausea and vomiting but with normal gastric emptying. Although the term functional dyspepsia has been used in the past, the new Rome III system excludes patients with predominant nausea or vomiting from this category, using instead new terms such as “chronic idiopathic nausea” (CIN) which includes “bothersome nausea, not usually associated with vomiting” and “functional vomiting” (FV) which includes vomiting that is not explained by an eating disorder, rumination, major psychiatric disease or other primary disorders.²⁸ Our analysis also suggests functional dyspepsia, as defined by Rome III, is an imprecise diagnostic category as even patients with relatively severe gastric emptying (i.e. those who fit the classic definition of gastroparesis) would be classified as such. It is also not clear whether there is any utility to the terms CIN or FV as a significant number of patients in both groups met these criteria, albeit in different proportions. More importantly, as a stand-alone diagnosis, the criteria for either CIN or FV only captured a very small proportion of these patients (less than 12.5% at most). Other terms that have been used for these patients includes gastroparesis-like syndrome (GLS)¹ and ‘vomiting of unexplained etiology’ (VUE).⁴ In this study, we have used the term chronic unexplained nausea and vomiting (CUNV) although this too is descriptive and not particularly informative. Thus, it is clear that this is a syndrome that does not fall easily into any pre-existing category in the current medical literature.

In conclusion, patients with symptoms of chronic nausea and vomiting but normal gastric emptying are indistinguishable from patients with classical gastroparesis by most demographic and clinical criteria and gastric emptying does not correlate with symptom

severity in either group of patients. Further investigation is needed to determine conclusively whether these patients are part of a spectrum of the same syndrome as gastroparesis or represent distinct disorder(s) and we hope that this study forms the basis of future research into this important clinical problem.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic, lifestyle and anthropometric characteristics

	CUNV with normal gastric emptying [†] (N = 106)	Gastroparesis* (N = 319)	P [‡]
Demographics			
Age, median (IQR)	39.5 (30, 50)	42 (32, 52)	0.43
Race and ethnicity, N (%)			0.17
White, non-Hispanic	86 (81.1)	269 (84.3)	
Black, non-Hispanic	6 (5.7)	28 (8.8)	
Hispanic	6 (5.7)	13 (4.1)	
Asian or Pacific Islander	3 (2.8)	3 (0.9)	
American Indian or Alaska native	0 (0.0)	1 (0.3)	
More than one race	5 (4.7)	5 (1.6)	
Gender, N (%)			0.89
Male	20 (18.9)	58 (18.2)	
Female	86 (81.1)	261 (81.8)	
Marital status, N (%)			0.94
Single, never married	27 (25.5)	83 (26.0)	
Married or similar	62 (58.5)	190 (59.6)	
Separated, divorced or annulled	13 (12.3)	37 (11.6)	
Widowed	4 (3.8)	9 (2.8)	
Currently employed, yes vs. no, N (%)	64 (60.4)	143 (44.8)	0.007
Occupational history, N (%)			0.59
Never employed	3 (2.8)	7 (2.2)	
Laborer	9 (8.5)	40 (12.5)	
Clerical	20 (18.9)	56 (17.6)	
Professional	51 (48.1)	165 (51.7)	
Homemaker	6 (5.7)	10 (3.1)	
Other	17 (16.0)	41 (12.9)	
Household income ≥ \$50,000, yes vs. no, N (%)	55 (51.9)	172 (53.9)	0.74
Education level, N (%)			0.52
Did not complete high school	4 (3.7)	19 (6.0)	
High school	20 (18.9)	77 (24.1)	
Some college or post-high school training	52 (49.1)	136 (42.6)	
Bachelor's degree or higher	30 (28.3)	87 (27.3)	
Lifestyle characteristics			
History of cigarette smoking, N (%)			0.27
Never	59 (55.7)	200 (62.7)	
Past smoker	30 (28.3)	66 (20.7)	
Current smoker	17 (16.0)	53 (16.6)	
Average cigarettes per day among regular smokers, median (IQR)	10 (7, 20)	10 (7, 20)	0.65
Abstain from alcohol during past year, N (%)	70 (66.0)	216 (67.7)	0.81
Frequency of having six or more drinks on one occasion, N (%)			0.004

	CUNV with normal gastric emptying [†] (N = 106)	Gastroparesis* (N = 319)	P [‡]
Never	93 (87.7)	303 (95.0)	
Less than monthly	7 (6.6)	14 (4.4)	
Monthly	6 (5.7)	2 (0.6)	
Formal nutrition consult, yes vs. no, N (%)	35 (33.0)	113 (35.4)	0.72
<i>Anthropometric measures</i>			
Height, m, median (IQR)	1.65 (1.60, 1.72)	1.64 (1.60, 1.70)	0.10
Weight, kg, median (IQR)	71.7 (58.0, 86.6)	68.9 (56.7, 86.2)	0.47
BMI, median (IQR)	26.3 (21.6, 31.2)	25.4 (20.7, 31.6)	0.54

* Gastroparesis; based on delayed gastric emptying scintigraphy >60% retention at 2 hours or >10% retention at 4 hours.

^{††} Chronic Unexplained Nausea and Vomiting

[‡] P values based on Fisher's exact test for categorical variables and Wilcoxon rank sum test for measured variables.

Table 2

Symptoms of gastroparesis

	CUNV with normal gastric emptying [†] (N = 106)	Gastroparesis with delayed emptying* (N = 319)	P [§]
Nausea, N (%)			0.85
None	5 (4.7)	15 (4.7)	
Very mild	5 (4.7)	26 (8.2)	
Mild	11 (10.4)	35 (11.0)	
Moderate	26 (24.5)	78 (24.5)	
Severe	27 (25.5)	85 (26.7)	
Very severe	32 (30.2)	80 (25.1)	
Retching, N (%)			0.66
None	37 (34.9)	102 (32.0)	
Very mild	13 (12.3)	37 (11.6)	
Mild	18 (17.0)	40 (12.5)	
Moderate	14 (13.2)	62 (19.4)	
Severe	15 (14.2)	49 (15.4)	
Very severe	9 (8.5)	29 (9.1)	
Vomiting, N (%)			0.23
None	44 (41.5)	106 (33.2)	
Very mild	9 (8.5)	31 (9.7)	
Mild	11 (10.4)	29 (9.1)	
Moderate	10 (9.4)	61 (19.1)	
Severe	17 (16.0)	44 (13.8)	
Very severe	15 (14.2)	48 (15.1)	
Stomach fullness, N (%)			0.71
None	2 (1.9)	10 (3.2)	
Very mild	4 (3.8)	18 (5.7)	
Mild	7 (6.6)	31 (9.8)	
Moderate	34 (32.1)	83 (26.2)	
Severe	32 (30.2)	86 (27.1)	
Very severe	27 (25.5)	89 (28.1)	
Unable to finish meal, N (%)			0.56
None	7 (6.6)	20 (6.3)	
Very mild	3 (2.8)	19 (6.0)	
Mild	12 (11.3)	38 (11.9)	
Moderate	24 (22.6)	77 (24.1)	
Severe	24 (22.6)	84 (26.3)	
Very severe	36 (34.0)	81 (25.4)	
Feeling excessively full after meals, N (%)			0.28
None	4 (3.8)	12 (3.8)	
Very mild	2 (1.9)	20 (6.3)	
Mild	6 (5.7)	34 (10.7)	

	CUNV with normal gastric emptying [†] (N = 106)	Gastroparesis with delayed emptying* (N = 319)	P [§]
Moderate	25 (23.6)	74 (23.2)	
Severe	31 (29.3)	80 (25.1)	
Very severe	38 (35.9)	99 (31.0)	
Loss of appetite, N (%)			0.90
None	8 (7.6)	32 (10.0)	
Very mild	9 (8.5)	22 (6.9)	
Mild	20 (18.9)	70 (21.9)	
Moderate	23 (21.7)	67 (21.0)	
Severe	22 (20.8)	66 (20.7)	
Very severe	24 (22.6)	62 (19.4)	
Bloating, N (%)			0.07
None	10 (9.4)	28 (8.8)	
Very mild	2 (1.9)	31 (9.7)	
Mild	13 (12.3)	44 (13.8)	
Moderate	29 (27.4)	60 (18.8)	
Severe	26 (24.5)	79 (24.8)	
Very severe	26 (24.5)	77 (24.1)	
Stomach visibly larger, N (%)			0.84
None	23 (21.7)	64 (20.1)	
Very mild	10 (9.4)	21 (6.6)	
Mild	14 (13.2)	38 (11.9)	
Moderate	19 (17.9)	63 (19.8)	
Severe	15 (14.2)	58 (18.2)	
Very severe	25 (23.6)	75 (23.5)	
Gastroparesis cardinal symptom index (GCSI), median (IQR)	3.2 (2.3, 3.7)	3.1 (2.2, 3.7)	0.84

Symptoms shown were collected from the Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM). Severity as assessed for period covering the past two weeks.

[†] Gastroparesis; based on delayed gastric emptying scintigraphy >60% retention at 2 hours or >10% retention at 4 hours.

^{‡‡} Chronic Unexplained Nausea and Vomiting

[§] P values based on Fishers exact test.

[¶] P values based on Cochran-Armitage test for trend.

Table 3

Clinical presentation

	CUNV with normal gastric emptying [†] (N = 106)	Gastroparesis* (N = 319)	P [‡]
<i>Gastroparesis characteristics</i>			
Etiology of gastroparesis, N (%)			0.04
Diabetes	20 (18.9)	100 (31.4)	
Idiopathic	78 (73.6)	199 (62.4)	
Other	8 (7.6)	20 (6.3)	
Infectious prodrome, yes vs. no, N (%)	19 (17.9)	52 (16.3)	0.76
Symptoms among patients with initial infectious condition, N (%)			
Upper respiratory symptoms, yes vs. no	3 (2.8)	14 (4.4)	0.58
Food poisoning like symptoms, yes vs. no	4 (3.8)	13 (4.1)	1.00
Gastroenteritis, yes vs. no	5 (4.7)	16 (5.0)	1.00
Other, yes vs. no	7 (6.6)	10 (3.1)	0.15
Symptoms that prompted evaluation for gastroparesis, N (%)			
Nausea, yes vs. no	89 (84.0)	269 (84.3)	1.00
Vomiting, yes vs. no	67 (63.2)	219 (68.7)	0.34
Bloating, yes vs. no	67 (63.2)	178 (55.8)	0.21
Early satiety, yes vs. no	72 (67.9)	182 (57.1)	0.05
Postprandial fullness, yes vs. no	67 (63.2)	175 (54.9)	0.14
Abdominal pain, yes vs. no	75 (70.8)	229 (71.8)	0.90
Diarrhea, yes vs. no	48 (45.3)	126 (39.5)	0.31
Constipation, yes vs. no	50 (47.2)	138 (43.3)	0.50
Anorexia, yes vs. no	20 (18.9)	47 (14.7)	0.36
Weight loss, yes vs. no	58 (54.7)	157 (49.2)	0.37
Weight gain, yes vs. no	29 (27.4)	61 (19.1)	0.08
Reflux symptoms, yes vs. no	55 (51.9)	172 (53.9)	0.74
Problems with diabetes or glycemic control, yes vs. no	13 (12.3)	45 (14.1)	0.74
Predominant symptom, N (%)			0.36
Nausea	46 (43.4)	110 (34.5)	
Abdominal pain	15 (14.1)	63 (19.8)	
Vomiting	21 (19.8)	70 (21.9)	
Other	24 (22.6)	76 (23.8)	
Onset of symptoms, N (%)			0.10
Acute start	47 (44.3)	163 (51.1)	
Insidious	56 (52.8)	154 (48.3)	
Other	3 (2.8)	2 (0.6)	
Nature of symptoms, N (%)			0.51
Chronic, but stable symptoms	28 (26.4)	77 (24.2)	
Chronic, but worsening symptoms	36 (34.0)	108 (34.0)	
Chronic symptoms with periodic exacerbations	34 (32.1)	103 (32.4)	
Cyclic pattern of exacerbations with periods of feeling well	7 (6.6)	30 (9.4)	

	CUNV with normal gastric emptying [†] (N = 106)	Gastroparesis* (N = 319)	P [‡]
Other	1 (0.9)	0 (0.0)	
Brief pain inventory scores [§] , median, (IQR)			
Worst pain	6 (5, 8)	7 (5, 8)	0.33
Least pain	2 (1, 4)	3 (1, 4)	0.23
Average pain	5 (4, 6)	5 (4, 7)	0.27
Current pain	4 (2, 7)	5 (2, 7)	0.26
Percent relief from treatments	50 (10, 70)	40 (10, 70)	0.32
Pain interference in general activity	5 (3, 7)	6 (3, 8)	0.26
Pain interference in mood	6 (3, 8)	6 (3, 8)	0.28
Pain interference in walking ability	5 (1, 7)	5 (1, 7)	0.51
Pain interference in normal work	6 (3, 9)	6 (4, 8.5)	0.34
Pain interference in relationships	5 (2, 8)	5 (2, 8)	0.57
Pain interference in sleep	7 (3, 8)	7 (3, 8)	0.74
Pain interference in enjoyment of life	6 (3, 9)	7 (3.5, 9)	0.85

* Gastroparesis; based on delayed gastric emptying scintigraphy >60% retention at 2 hours or >10% retention at 4 hours.

^{††} Chronic Unexplained Nausea and Vomiting

[‡] P values based on Fishers exact test for categorical variables and Wilcoxon rank sum test for measured variables.

[§] Among patients reporting pain in the past 24 hours. N=264 for delayed emptying group and N=90 for normal emptying group.

Table 4

Other parameters: Depression, anxiety, quality of life, severity and healthcare utilization

	CUNV with normal gastric emptying [†] (N = 106)	Gastroparesis* (N = 319)	P [‡]
<i>Beck Depression Inventory</i>			
Inventory score, median (IQR)	17 (6, 25)	17 (11, 25)	0.13
Score>28 (severely depressed), yes vs. no, N (%)	14 (13.2)	59 (18.5)	0.13
Feelings of hopelessness, yes vs. no, N (%)	9 (8.5)	40 (12.5)	0.30
Suicidal wishes, yes vs. no, N (%)	0 (0.0)	5 (1.6)	0.34
<i>State-Trait Anxiety Inventory</i>			
State anxiety score, median (IQR)	41.5 (30.0, 51.0)	46.0 (34.0, 54.0)	0.02
Trait anxiety score, median (IQR)	43.0 (31.0, 50.0)	44.0 (34.0, 52.0)	0.09
<i>PAGI-QOL</i>			
Daily activities subscore, median (IQR)	2.4 (1.4, 3.5)	2.1 (1.3, 3.1)	0.14
Clothing subscore, median (IQR)	3.0 (1.5, 5.0)	3.0 (1.5, 5.0)	0.85
Diet subscore, median (IQR)	1.4 (0.6, 2.4)	1.3 (0.4, 2.3)	0.23
Relationship subscore, median (IQR)	3.3 (2.0, 4.7)	3.0 (2.0, 4.0)	0.15
Psychological subscore, median (IQR)	3.0 (1.8, 4.0)	2.8 (1.6, 3.9)	0.22
Total score, median (IQR)	2.7 (1.7, 3.4)	2.5 (1.6, 3.3)	0.21
<i>Global Severity Grade, N (%)</i>			
Grade 1: mild gastroparesis	21 (19.8)	39 (12.3)	
Grade 2: compensated gastroparesis	61 (57.6)	175 (55.0)	
Grade 3: gastroparesis with gastric failure	24 (22.6)	104 (32.7)	
<i>Investigator Derived Independent Outcome Measure Scores (IDIOMS), median (IQR)</i>	12.5 (10, 16)	14 (11, 18)	0.007

*Gastroparesis; based on delayed gastric emptying scintigraphy >60% retention at 2 hours or >10% retention at 4 hours.

^{††}Chronic Unexplained Nausea and Vomiting[‡]P values based on Fishers exact test for categorical variables and Wilcoxon rank sum test for measured variables.

Logistic regression analyses of characteristics that discriminate patients with CUNV with normal gastric emptying from patients with gastroparesis

Table 5

	Unadjusted* models			Adjusted† model		
	OR‡	95% CI	P	OR	95% CI	P
Early satiety, yes vs. no	1.58	0.99 – 2.52	0.05	2.10	1.27 – 3.49	0.004
Currently employed, yes vs. no	1.87	1.19 – 2.92	0.006	1.71	1.07 – 2.76	0.03
Frequency of having six or more drinks on one occasion, ever vs. never	2.64	1.22 – 5.69	0.01	3.10	1.37 – 7.00	0.007
Beta-Globulin, g/dL	3.74	1.52 – 9.17	0.004	6.53	2.49 – 17.10	0.0001
State anxiety score	0.98	0.96 – 1.00	0.02	0.98	0.96 – 0.99	0.01
Investigator Derived Independent Outcome Measure Scores (IDIOMS)	0.93	0.89 – 0.98	0.005	0.95	0.90 – 1.00	0.05

* Separate logistic regression models for each characteristic with the outcome measure: nausea and vomiting with normal gastric emptying vs. gastroparesis.

† Multiple logistic regression model relating outcome measure nausea and vomiting with normal gastric emptying vs. gastroparesis to characteristics early satiety, current employment, frequency of binge drinking, beta-globulin level, State anxiety score and IDIOMS score. Characteristics: global severity grade, reason for gastroparesis, presence or symptoms of infectious prodrome, symptoms that prompted evaluation (including nausea, vomiting, bloating, postprandial fullness, abdominal pain, diarrhea, constipation, anorexia, weight loss, weight gain, reflux), problems with diabetes management, onset and nature of symptoms, nutritional consult, history of cigarette smoking, abstinence from alcohol, age, race/ethnicity, gender, education level, occupational history, marital status, household income, BMI, height, weight, antinuclear antibody positive, CRP level, albumin level, alpha 1 globulin level, alpha 2 globulin level, gamma globulin level, SPEP total protein level, hemoglobin level, hematocrit level, erythrocyte sedimentation rate, Beck Depression Inventory score, Trait anxiety score, symptom severity measures collected from PAGI-SYM (including nausea, retching, vomiting, stomach fullness, inability to finish a meal, feeling excessively full, loss of appetite, bloating, and visibly larger stomach), quality of life scores from PAGI-QOL (including daily activities, diet, psychological, clothing, relationship subscores and total score), were analyzed but not related to the outcome at P=0.05 level of significance, using forward stepwise selection (P=0.05 for entry).

‡ Relative odds of nausea and vomiting but with normal gastric emptying versus gastroparesis

Table 6

Rome III Classification of Patients with Chronic Nausea and Vomiting

	CUNV with normal gastric emptying [†] N=106			Gastroparesis* N=319			P [‡]
	N	%		N	%		
<i>Functional dyspepsia, if no structural disease explains it</i>							0.87
Yes	92	86.8		273	85.6		
No	14	13.2		46	14.4		
<i>Functional dyspepsia: Postprandial Distress Syndrome or PDS</i>							1.00
Yes	93	87.7		280	87.8		
No	13	12.3		39	12.2		
<i>Functional dyspepsia: Epigastric Pain Syndrome, EPS</i>							0.50
Yes	4	3.8		8	2.5		
No	102	96.2		311	97.5		
<i>Chronic idiopathic nausea, or CIN if no abnormalities with upper endoscopy or no metabolic disease</i>							0.0004
Yes	48	45.3		84	26.3		
No	58	54.7		235	73.7		
<i>Functional vomiting, if no eating disorder/rumination/major DSM-IV classification</i>							0.03
Yes	32	30.2		135	42.3		
No	74	69.8		184	57.7		
<i>Rumination Syndrome in Adults</i>							1.00
Yes	2	1.9		8	2.5		
No	104	98.1		311	97.5		

* Gastroparesis; based on delayed gastric emptying scintigraphy >60% retention at 2 hours or >10% retention at 4 hours.

[†] Chronic Unexplained Nausea and Vomiting[‡] P values based on Fishers exact test