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Research Article

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Gastric Myoelectrical Activity and Autonomic Nervous System Abnormalities in Patients with Chronic Unexplained Nausea and Vomiting and in Patients with Gastroparesis

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Abstract

Background: Patients with chronic unexplained nausea and vomiting (CUNV) and Gastroparesis (GP) have similar symptoms, suggesting they share pathophysiological abnormalities along a continuum of disease.

Objectives: To determine the incidence of gastric myoelectrical, accommodation dysfunction and autonomic abnormalities in patients with CUNV and GP.

Methods: Outpatients with CUNV and GP who underwent standard 4-hr solid phase gastric emptying, upright tilt table test and electrogastrogram (EGG) recordings with water load satiety test (WLST) were identified from chart review. Subjects with normal emptying were in the CUNV group; those with delayed emptying were in the GP group. EGGs were recorded before and 30 minutes after the WLST and symptoms were recorded on a 100mm visual analog scale.

Results: 44 patients (35 women and 9 men, ages 17-76 years) were identified: 24 had normal gastric emptying and CUNV and 20 had GP. Gastric dysrhythmias were found in 70% of CUNV and 69% of GP patients. Twenty percent of CUNV patients and 44% of GP patients ingested abnormally low volumes (< 300mL) during the WLST. Nausea increased similarly after the WLST in the subjects with CUNV and GP (Ps > 0.05). Postural orthostatic tachycardia syndrome (POTS) was diagnosed in 17% of CUNV patients and 20% of GP patients.

Conclusions: Gastric myoelectrical and accommodation abnormalities and autonomic nervous system (ANS) dysfunctions frequently occur in subjects with CUNV and GP. These pathophysiological abnormalities support the idea that CUNV and GP occur along the same continuum of gastric neuromuscular dysfunction and may be targets for therapeutic approaches.

Keywords: Gastroparesis, Nausea, Vomiting, POTS, Gastric dysrhythmias

Abbreviations: GP: Gastroparesis; CUNV: Chronic Unexplained Nausea and Vomiting; OI: Orthostatic Intolerance; WLST: Water Load Satiety Test; ICC: Interstitial Cells of Cajal; ANS: Autonomic Nervous System; POTS: Postural Orthostatic Tachycardia Syndrome; NCS: Neurocardiogenic Syncope; GMA: Gastric Myoelectrical Activity; EGG: Electrogastrogram

Introduction

Patients with chronic unexplained nausea and vomiting (CUNV) have normal gastric emptying, normal laboratory tests and endoscopy [1,2]. The pathophysiology of CUNV is poorly understood [1]. Gastroparesis (GP) is a neuromuscular disorder of the stomach defined by delayed gastric emptying in the absence of mechanical obstruction [3]. Nausea and vomiting are common and noxious symptoms associated with GP [3]. However, symptoms such as nausea and vomiting do not correlate with the delayed rate of gastric emptying [4]. Thus, it is important to investigate other pathophysiological mechanisms that may have a role in the genesis of nausea symptoms in patients with CUNV and GP.

Gastric dysrhythmias have been recorded in patients with functional dyspepsia, postprandial distress syndrome and in patients with GP [5,6]. Interstitial cells of Cajal (ICC) are the pacemaker cells that mediate normal 3 contractions per minute (cpm) gastric myoelectrical activity (GMA) that coordinate gastric peristaltic contractions and produce normal gastric emptying [7-9]. In patients with GP the ICCs are severely depleted, the 3cpm GMA is reduced and gastric dysrhythmias are present [9]. ICCs are depleted to a lesser degree in patients with CUNV and gastric dysrhythmias are also present in these patients [10].

Unexplained gastrointestinal symptoms may also be related to orthostatic intolerance (OI) which includes postural orthostatic tachycardia syndrome (POTS), neurocardiogenic syncope (NCS)and orthostatic hypotension(OH) [11,12].POTS is associated with chronic nausea and vomiting [11] and gastrointestinal motility disorders, including gastroparesis and gastric dysrhythmias [13]. Studies to assess autonomic function and gastric emptying in patients with POTS scant [14-16]. A recent review suggested ANS dysfunction may have an underappreciated role in the pathophysiological mechanisms of symptoms in patients with unexplained gastrointestinal symptoms [13].

In the current study we identified patients with CUNV and GP who underwent electrogastrography with water load satiety test (WLST) to assess GMA and gastric accommodation and upright tilt table test to assess ANS function. We hypothesized ANS dysfunction and abnormalities in GMA and accommodation defects would be present in both CUNV and GP patients, but would be less prevalent in CUNV patients when compared to GP patients. CUNV and GP may represent disorders on a continuum of gastric neuromuscular dysfunction and shared pathophysiological abnormalities would support that concept.

Methods

Forty-four patients who were referred to gastroenterology clinic for evaluation of chronic nausea and vomiting from 10/2012-02/2016 were identified from the electronic medical records. Inclusion criteria include the following: 1) 4-hour solid phase gastric emptying, 2) upright tilt table test and 3) electrogastrogram with WLST. All patients had endoscopy that excluded mucosal disease and pyloric stenosis. CT abdomen, CT head, biliary imaging and other laboratory tests were ordered as indicated for each individual patient and had failed to reveal the cause of symptoms. None of the patients had an underlying organic disorder that explained the gastrointestinal symptoms. Patients with hypothyroidism were on proper medical therapy (levothyroxine) and their TSH levels were within normal limits. None of the patients had hyperthyroidism. Patients with well controlled gastroesophageal reflux disease (GERD) on proton pump inhibitor (PPI) therapy were included in the study cohort. The study was approved by the Wake Forest Baptist Medical Center IRB.

Gastric-emptying scintigraphy

Gastric emptying was assessed by solid phase scintigraphy. Patient fasted after midnight and consumed a standardized meal (eggbeaters, toast, jam) labeled with 0.535 mCi Tc99m sulfur colloid. Diabetic patients were asked to self-report fingerstick blood glucose reading prior to the meal to ensure level <270 mg/dL. Serial imaging up to four hours was performed in the anterior and posterior projections and the corrected counts of geometric mean of decay were obtained. Normal ranges are as follows: 37-90% at 1 hour, 30-60% at 2 hours, 10-29% at 3 hours and 0-9% at 4 hours. Delayed emptying was defined as values > 60% retained at 2 hours or > 10% at 4 hours [17]. Medications such as metoclopramide, narcotics, erythromycin, and domperidone were stopped five days before gastric scintigraphy and electrogastrogram with WLST.

Tilt table testing

Each subject was positioned supine for 15 mins before the tilt test began during which the patient was tilted to a 70-degreeangle and remained in the upright position for up to 45 minutes. The patient was monitored at baseline on the supine position and then tilted to a 70-degree

angle with continuous electrocardiogram monitoring and pulse oximetry with intermittent blood pressure recording. Positive test indicates the presence of OI which includes POTS, neurocardiogenic syncope or orthostatic hypotension. POTS was defined as an increase in HR > 120bpm or a 30 bpm increase from baseline in the first 10 minutes of upright tilt, sustained > 2 minutes, without evidence of orthostatic hypotension. Neurocardiogenic syncope was defined as a drop in systolic blood pressure > 25mmHg from baseline sustained > 2 minutes without an associated increase in heart rate. Orthostatic hypotension as per Consensus Committee of the American Autonomic Society and the American Academy of Neurology is defined as drop in systolic blood pressure ≥ 20 mmHg or diastolic blood pressure ≥ 10 mmHg within three minutes of standing from a supine position [18].

Electrogastrogram with water load satiety test

Patients fasted after midnight. Three EKG-like electrodes were placed on the epigastrium in the standard locations to record gastric myoelectrical activity and a respiratory sensor belt was placed around the chest to measure respiratory rate and detects body movements. The myoelectrical signal was filtered with a 0.016 Hz high pass filter and 0.25 low pass filter to record frequencies from approximately 1cpm to 15cpm which are the frequencies of interest in the electrogastrogram (EGG).A 10-minute baseline EGG was recorded. Patients then ingested water over a 5-minute period until they were "completely" full [5]. The volume ingested was recorded. Ingested volumes < 300mL in 5 minutes was considered abnormal [19]. An additional 30 minutes of EGG signal was recorded after the WLST. The clinical EGG diagnosis was based on these results and defined as bradygastria (1-2.5cpm), normal (2.5-3.75cpm), tachygastria (3.75-10cpm) and duodenal or respiratory frequencies (10-15cpm). Gastric myoelectrical activity was reported as normal or abnormal (bradygastria, tachygastria or mixed dysrhythmia). Nausea and stomach fullness were recorded before and 10, 20 and 30 minutes after ingestion of water on a 100mm visual analog scale.

Statistical analysis

Results of these tests from patients with gastroparesis were compared to those with CUNV using SAS Statistical Analysis Software. Categorical data were compared using the Fisher's exact procedure and continuous data were compared using the Wilcoxon-rank sum test. *P* values < 0.05 were considered significant.

Results

Table 1 lists demographics, tilt table, water load satiety and EGG results for the patients with gastroparesis and CUNV. Twenty of the 44 patients (45%) had delayed gastric emptying (GP group) and 24 (55%) had normal gastric emptying (CUNV group).The two groups did not differ in age, sex, presence of diabetes, thyroid disease, GERD or chief complaint. The cause of gastroparesis was diabetes in 30% of patients and idiopathic in 70% of patients. No patients had post-surgical GP. The prevalence of OI, based on positive tilt test, in the GP and CUNV patients was 55% vs. 46% respectively, (*P* = 0.763). Twenty percent of GP patients (n=4) and 17% of CUNV patients (n=4) had POTS (*P* = 1.000).

Electrogastrogram tests were obtained in 36 of the 44 patients. Gastric dysrhythmias were recorded in 69% of GP patients and 31% had normal 3cpm GMA. In the GP patients with dysrhythmias, 36% had bradygastria, 36% had tachygastria and 28% had mixed dysrhythmias. On the other hand, 70% of CUNV patients had dysrhythmias and 30% had normal GMA. In the CUNV patients with dysrhythmias, 7% had bradygastria, 36% had tachygastria and 57% had mixed dysrhythmias. The prevalence of bradygastria, tachygastria or mixed dysrhythmia between these two groups was not statistically significant (*P* = 0.133, *P* = 1.000 and *P* = 0.227 respectively).Additionally, prevalence of gastric dysrhythmia in patients with positive tilt vs. negative tilt was also similar (56% vs 80%, *P* = 0.159).

Forty-four percent of GP and 20% of CUNV patients ingested abnormally low water volume of < 300mL, *P* = 0.159 during the five-minute timed test. The GP group ingested less average volume of water (363.8 ml±208.2) than CUNV group (457 ml±218.7), but the difference was not statistically different (*P* = 0.191).The volume of water ingested in patients with positive tilt (429.4 ml±205.9) and negative tilt test (405 ml±228.9) was also similar (*P* = 0.719).

Table 2 shows gastric emptying test results at 2 and 4 hours in the two patient groups. Gastric emptying results are also compared in patients with positive and negative tilt table tests. Patients with GP had significantly higher percentage of meal retained at 2 and 4 hours as expected, when compared with the CUNV group (*P* < 0.001 and *P* < 0.001, respectively). There was no significant difference in the percentage of meal retained at 2 and 4 hours between the positive tilt and negative tilt test patients (*P* = 0.688 and *P* = 0.809, respectively).

Table 1: Patient demographics and results of tilt table test, electrogastrogram (EGG) and water load satiety test (WLST) in patients with gastroparesis and chronic unexplained nausea and vomiting (CUNV).

	Gastroparesis (n = 20)	CUNV (n = 24)	*P*-value
Age, mean ± SD (years)	43±14	37±16	0.177
Female (%)	17 (85)	18 (75)	0.447
Diabetic (%)	6 (30)	4 (17)	0.472
Hypothyroid (%)	2 (10)	3 (13)	1
GERD (%)	15 (75)	13 (54)	0.213
Chief complaint nausea (%)	14 (70)	17 (71)	
Chief complaint vomiting (%)	6 (30)	7 (29)	
Positive Tilt Test (%)[a]	11 (55)	11 (46)	0.763
POTS	4 (20%)	4 (17%)	1
Normal EGG (%)[b]	5 (31)	6 (30)	1
Abnormal EGG (%)[b]	11 (69)	14 (70)	1
· Bradygastria (%)	4 (36)	1 (7)	0.133
· Tachygastria (%)	4 (36)	5 (36)	1
· Mixed dysrhythmia (%)	3 (28)	8 (57)	0.227
Water Load < 300mL (%)	7 (44)	4 (20)	0.159
Water Load (mL)[c]	363.8±208.2	457±218.7	0.191
	312.5	412.5	

[a]Positive tilt test indicates evidence of orthostatic intolerance which includes postural orthostatic tachycardia (POTS), neurocardiogenic syncope (NCS) and orthostatic hypotension (OH).
[b]Missing EGG data on 4 patients in gastroparesis group and 4 patients in CUNV group.
[c]Values are % mean ± SD, median. Water load data missing in the following groups: 4 in the gastroparesis group, 4 in the CUNV group.

Figures 1 and 2 compare the symptoms of fullness and nausea before and after WLST in patients with GP and CUNV. Patients with GP reported more fullness at baseline (*P* = 0.016) and 30 mins after water load test (*P* = 0.029) compared with CUNV patients. Nausea reported at baseline, 10 mins, 20 mins and 30 mins after WLST was similar in GP and CUNV patients (*P* = 0.117, *P* = 0.558, *P* = 0.512 and *P* = 0.634, respectively).

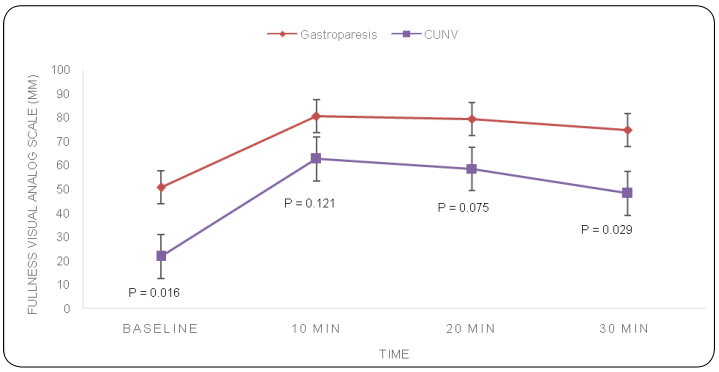

Figure 1: Fullness intensity (mean ±SEM) reported at baseline and 10, 20 and 30 minutes after water load test in the GP and CUNV patients. *P*-value compares the fullness intensity at baseline, 10, 20 and 30 minutes between the two groups.

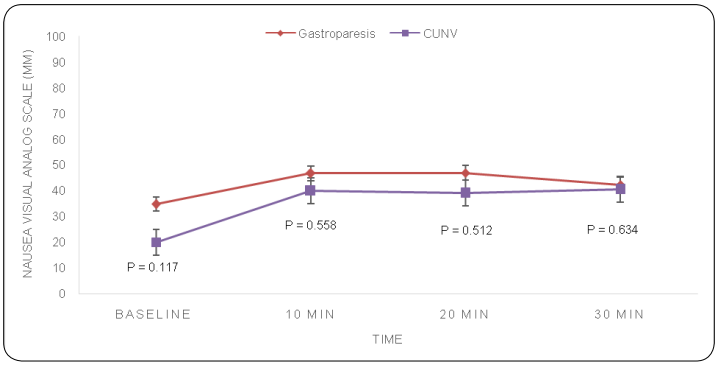

Figure 2: Nausea intensity (mean ± SEM) reported at baseline and 10, 20 and 30 minutes after water load test in the GP and CUNV patients. P-value compares the nausea intensity at baseline, 10, 20 and 30 minutes between the two groups.

Table 3 shows the changes in intensity of fullness and nausea after the water load compared to baseline in the GP and CUNV groups. Within each group, fullness was significantly higher at 10, 20 and 30 minutes after water load compared with baseline. When the two groups were compared to each other the increase in fullness at the different time points was not statistically significant (*P* = 0.209, *P* = 0.366 and *P* = 0.757 respectively). Nausea increased significantly at 10, 20 and 30 minutes after

Table 2: Comparison ofpercent meal retained at 2 and 4 hours in patients with gastroparesis (GP) vs chronic unexplained nausea and vomiting (CUNV) and patients with positive tilt table vs negative tilt table tests.

	GP (n = 20)	CUNV (n = 24)	*P*-value	Positive Tilt (n = 22)	Negative Tilt (n = 22)	P- value
Meal retained at 2 hours[a]	61±14 64	24±14 24	< 0.001	42±25 40	39±21 38	0.688
Meal retained at 4 hours[a]	21±15 18	3.7±3.9 3	< 0.001	12±12 8.9	11±15 5.1	0.809

[a]Values are % mean ± SD, median

Table 3: Changes in intensity of fullness and nausea after the water load test compared to baseline in GP and CUNV patients.

Symptom	Gastroparesis (n = 16)			CUNV (n = 19)[c]			
	Mean ± SD (mm)	Mean change from baseline (95% CI)	*P*-value[a]	Mean ± SD (mm)	Mean change from baseline (95%CI)	*P*-value[a]	P-comparison[b]
Fullness							
Baseline	71.2 ± 54.0	-		30.6 ± 41.5	-	-	-
10 min	112.8 ± 30.9	41.6 (17.9, 65.4)	0.002	90.3 ± 49.2	59.7 (33.4, 86.0)	<0.001	0.209
20 min	111.2 ± 32.4	40.0 (15.3, 64.7)	0.004	83.4 ± 44.9	52.8 (28.5, 77.2)	<0.001	0.336
30 min	104.7 ± 41.9	33.5 (6.2. 60.8)	0.02	69.0 ± 50.2	38.4 (12.6, 64.2)	0.006	0.757
Nausea							
Baseline	48.8 ± 44.8	-		27.9 ± 32.8	-	-	-
10 min	65.7 ± 52.3	16.9 (0.77, 33.1)	0.041	55.8 ± 47.1	27.9 (9.7, 46.2)	0.005	0.376
20 min	65.6 ± 46.2	16.9 (-4.5, 38.3)	0.113	54.8 ± 51.0	26.9 (6.5, 47.4)	0.013	0.543
30 min	59.3 ± 47.7	10.6 (-10.7, 31.9)	0.31	51.7 ± 46.1	23.8 (6.7, 40.9)	0.009	0.401

[a]*P*-value represents the change in fullness and nausea at 10, 20 and 30 minutes from baseline within each group.
[b]*P*-comparison is comparing the mean change in fullness and nausea at 10, 20 and 30 minutes from baseline between GP and CUNV groups.
[a,c]Missing data on fullness and nausea in 1 CUNV patient

water load compared with baseline in the CUNV group ($P = 0.005$, $P = 0.013$ and $P = 0.009$, respectively) but only at 10 mins for the GP group ($P = 0.041$). When the two groups were compared to each other the increase in nausea at the time points after the water load test was not statistically significant.

Discussion

The prevalence of gastric dysrhythmias, decreased water load volumes and POTS was similar in our patients with CUNV and GP. Gastric dysrhythmias were found in 70% of CUNV patients and 69% of GP patients. Gastric dysrhythmias occur in patients with diabetic and idiopathic GP and decreased ICCs [9, 20-23].The CUNV patients had lesser depletion of ICCs and normal rates of gastric emptying compared with GP patients [10]. The variable loss of ICCs and gastric dysrhythmias in patients with CUNV and GP represents a pathophysiological abnormality common to both groups of patients with chronic nausea [8-10]. Gastric dysrhythmias are associated with symptoms of nausea and vomiting [21-23] and may be considered a gastric biomarker for nausea [24]. For example, pregnant women with nausea in the first trimester have gastric dysrhythmias [25] and nausea and gastric dysrhythmias are common in motion sickness [26,27], chronic renal failure [28], anorexia nervosa [29] and functional dyspepsia, dysmotility type [5]. A recent double-blind placebo-controlled trial showed aprepitant decreased nausea and tachygastria when compared with placebo in patients with and without GP [30]. Taken together these studies suggest gastric dysrhythmias are shared pathophysiological abnormalities that may account, in part, for nausea in CUNV and GP.

The volume ingested during satiety testing with liquid caloric or noncaloric test meal reflects gastric capacity or accommodation [31-33]. Ingestion of abnormally low

volume is associated with poor gastric accommodation, early satiety and abdominal fullness [31-33]. Forty-four percent of patients in GP group and 20% of patients in CUNV group ingested less than 300ml of water, indicating poor gastric accommodation or capacity. Thus, abnormalities of gastric accommodation are shared pathophysiological events that may contribute to symptoms in both groups. Eighty percent of the CUNV patients ingested > 300mL of water; the source of symptoms in these patients may also include gastric dysrhythmias and hypersensitivity to distention.

The CUNV and GP patients also reported similar increases in nausea after ingesting the water load. In patients with functional dyspepsia (post-prandial distress syndrome) nausea and fullness increased immediately and significantly after the WLST compared with healthy volunteers [5]. In that study gastric dysrhythmias were elicited after ingestion of the water load in 67% of patients [5], a finding consistent with the 69-70% of gastric dysrhythmias in our patients with GP and CUNV. Thus, impaired gastric accommodation and gastric dysrhythmias frequently occur together in patients with CUNV and GP and may represent pathophysiological events underlying postprandial symptoms. These gastric abnormalities are objective targets for the development of drugs or devices or diets to address these symptoms.

Most patients with GP have severe depletion of ICCs [7,8,20] and gastric dysrhythmias [34,35]. Sixty-nine percent of our patients with GP had gastric dysrhythmias. However, 31% had normal 3cpm GMA. In patients with GP secondary to pyloric stenosis, normal 3cpm GMA was preserved indicating normal numbers of ICCs in the corpus/antrum were present and that GP was due to pyloric obstruction from fibrosis [36]. In the current study endoscopy excluded pyloric stenosis in patients with GP and 3cpm GMA. Thus, these patients have a GP subtype termed idiopathic gastric outflow obstruction due to pyloric neuromuscular dysfunction [37]. Abnormalities in pyloric distensibility have been reported in 36% of patients with severe GP [38]. Endoscopic pyloric therapy with botulinum toxin injection or balloon dilation improved symptoms in this idiopathic obstructive subtype GP [37].

Patients presenting to gastroenterologist for evaluation of nausea and vomiting may have OI disorders (i.e. POTS) that may be underappreciated [13]. POTS was identified by upright tilt table test in 20% of our GP and 17% of CUNV patients. Our patients were seen in GI clinic that specializes in the diagnosis and treatment of patients with chronic nausea and vomiting. ANS dysfunction is associated with a variety of gastric neuromuscular abnormalities including GP, rapid emptying, and gastric dysrhythmias [14-16,39,40]. In a study of 22 patients with POTS and GI symptoms identified from retrospective review of medical records at Mayo Clinic, 9% had delayed and 27% had rapid gastric emptying [14]. In another retrospective study, 66% of patients with POTS had abnormal gastric emptying (18% delayed and 48% rapid gastric emptying) [15]. Our results suggest a certain percentage of patients with chronic nausea and vomiting evaluated by gastroenterologists may have POTS in addition to gastric dysrhythmias, GP or rapid gastric emptying.

POTS was diagnosed in 17% of our subjects with CUNV. To our knowledge no studies of POTS in adult CUNV patients specifically have been published. Wagoner et al found 35% of children with nausea and vomiting evaluated in pediatric gastroenterology clinic had POTS [41]. Camilleri and Faley reported poor coordination of gastric contractions or post-prandial gastric hypomotility in 6 out of 8 patients with functional dyspepsia and IBS all of whom had evidence of sympathetic denervation [42]. Fludrocortisone treatment of OI in children with chronic nausea and vomiting reduced nausea by > 26% in 71% of patients [43]. Chelimsky et al reported that abdominal pain and nausea may be presenting symptoms of ANS dysfunction in children [44,45]. High instability coefficient of the GMA dominant frequency was significantly elevated in patients with POTS compared with healthy subjects ($p < 0.05$) [39]. It is possible that ANS dysfunction may also contribute, in part, to dysfunctions in GMA and accommodation in adult patients with CUNV and GP. More studies of OI and POTS in adults with CUNV are needed to understand the contributions of ANS dysfunctions to symptoms and gastric neuromuscular dysfunction in these patients.

Our results suggest several novel approaches to treatment of patients with GP and CUNV may be considered. First, the WLST results indicated limited gastric accommodation or gastric capacity in both GP and CUNV patients and drugs that relax the fundus such as buspirone should be considered in these patients. Second, almost one third of patients with GP had normal 3 cpm GMA, the combination that indicates functional gastric outlet obstruction. These patients may be treated with endoscopic pyloric therapies as discussed above [37]. Third, if POTS is identified then increase in fluid and salt intake is recommended along with use of medications such as fludrocortisone, midodrine, pyridostigmine

and/or SSRI in more severe cases [13]. Fourth, almost 60% of these patients have gastric dysrhythmias and development of gastric antiarrhythmic agents is needed. Ideally controlled trials of drugs would lead to best practices in treatment choices for these abnormalities and symptoms.

In summary, the incidence of gastric dysrhythmias, abnormal gastric accommodation, WLST-induced symptoms of nausea and POTS were similar in patients with GP and CUNV. These findings support the concept that CUNV and GP are part of a spectrum of related gastric neuromuscular disorders. Gastricdysrhythmias and gastric accommodation dysfunction nare shared pathophysiological abnormalities relevant to nausea and vomiting commonly reported by patients with either CUNV or GP. A subset of patients with CUNV and GP also has POTS that may affect both gastric neuromuscular function and symptoms of nausea and vomiting. New drug therapies are needed to address these pathophysiological findings and improve relief of symptoms in patients with GP and CUNV.

Declarations

The authors hereby warrant that this article is an original work, has not been published before and is not being considered for publications elsewhere in its final form either in printed or electronic form.

Each author warrants that his or her institution has approved the protocol for any investigation involving humans and that all experiments were conducted in conformity with ethical and humane principles of research.

The authors grant the Integrative Gastroenterology and Hepatology Journal the right to access the original data and material, and publication of this article once it is accepted.

Each author warrants that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the article. Dr. Koch is a shareholder of the 3CPM ® company.

Authors' contributions

Erinda Stefi, DO-first author, data collection, study design, analysis, critical revisions, intellectual content.

Hossam Shaltout, PhD-study design, analysis, critical revisions, intellectual content.

Anya Brown-data collection.

Kenneth Koch, MD-study design, critical revisions, intellectual content

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