Gastroesophageal Reflux Disease Presenting with Intractable Nausea

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Background: Typical symptoms of gastroesophageal reflux disease are heartburn and regurgitation. A subset of patients present with atypical symptoms, such as chest pain, cough, wheezing, and hoarseness.

Objective: To review the clinical presentation and treatment of patients who presented with nausea as the primary symptom of gastroesophageal reflux disease.

Design: Case series.

Setting: Outpatient department of a university hospital.

Patients: 10 outpatients who had chronic, intractable nausea and had not responded to empirical therapies.

Measurements: Patients were evaluated by esophagogastroduodenoscopy, 24-hour esophageal pH studies, gastric-emptying tests, electrogastrography, or a Bernstein test.

Results: Abnormal acid reflux was found to be the cause of intractable nausea in all 10 patients. In 5 of the 10 patients, esophagitis was documented by esophagogastroduodenoscopy. Six patients had abnormal results on the 24-hour esophageal pH study. In these 6 patients, 32 of 33 episodes of nausea were accompanied by an episode of acid reflux. One patient had positive results on the Bernstein test. Nausea resolved after treatment with omeprazole in 7 patients, after treatment with cisapride or ranitidine in 2 patients, and after Nissen fundoplication in 1 patient.

Conclusions: Intractable nausea is an atypical symptom that can occur in a subset of patients with gastroesophageal reflux disease. A 24-hour esophageal pH study should be considered in patients who have unexplained nausea but normal findings on esophagogastroduodenoscopy, a gastric-emptying test, and electrogastrography. Nausea related to gastroesophageal reflux disease resolves or is markedly reduced with proton-pump inhibitors or promotility drugs.

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In patients who have typical symptoms of gastroesophageal reflux disease, such as heartburn and acid regurgitation, the diagnosis is usually obvious (1). A subset of patients, however, can present with atypical symptoms, including angina-like chest pain, cough, wheezing, shortness of breath, and hoarseness, that hinder immediate diagnosis of gastroesophageal reflux disease. In addition to being a symptom of gastroesophageal reflux disease, chronic nausea can be a symptom of chronic peptic ulcer disease, gastroparesis, occult gastrointestinal cancer, intestinal pseudo-obstruction, and increased intracranial pressure secondary to a tumor.

Methods

Patients

We reviewed the charts of patients who had been referred to the gastroenterology division of the Milton S. Hershey Medical Center from September 1991 to August 1995 for evaluation of chronic idiopathic nausea. Three men and seven women (age range, 27 to 67 years) who had received a diagnosis of gastroesophageal reflux disease presented with chronic nausea. The average duration of nausea was 2.1 years (range, 3 months to 6 years).

None of the 10 patients had responded to empirical medical therapies for chronic nausea. In some instances, the patients had not responded to more than one treatment regimen: Nine did not respond to standard histamine-2 (H_2) blockers (400 mg of cimetidine, 150 mg of ranitidine, 20 mg of famotidine, or 150 mg of nizatidine twice daily); 6 did not respond to metoclopramide; 6 did not respond to antiemetic agents; 3 did not respond to cisapride; 2 did not respond to omeprazole (20 mg once daily); 1 did not respond to high-dose H_2 blockers (300 mg of ranitidine twice daily); 1 did not respond to bethanechol; and 1 did not respond to sucralfate.

Six of 10 patients had intermittent vomiting in addition to nausea. In most patients, the vomiting did not occur after meals. Each patient had episodes of nocturnal vomiting. Patients reported two to eight episodes of vomiting per week. One patient had insulin-dependent diabetes mellitus, a comorbid condition that can contribute to nausea; however,

Table 1. Results of Gastrointestinal and Central Nervous System Studies in Patients with Nausea and Gastroesophageal Reflux Disease*

Patient	Gastric Emptying†	Electrogastrography	Abdominal Ultrasonography	Upper Gastrointestinal Series	Computed Tomography or Magnetic Resonance Imaging
1	ND	ND	ND	ND	ND
2	Normal (70%)	Normal (3 cpm)	ND	Normal	Normal
3	Normal (82%)	Normal (3 cpm)	Normal	Normal	Normal
4	Normal (92%)	ND	Normal	ND	ND
5	Normal (76%)	Normal (3 cpm)	Normal	Normal	ND
6	ND	ND	Normal	Normal	ND
7	Normal (50%)	ND	Normal	ND	Normal
8	Normal (77%)	Normal (3 cpm)	Normal	Normal	Normal
9	Normal (72%)	Normal (3 cpm)	Normal	Normal	Normal
10	Normal (84%)	Normal (3 cpm)	Normal	Normal	Normal

* cpm = cycles per minute; ND = not determined.
† Values given in parentheses are the percentages emptied at 120 minutes.

this patient was subsequently found to have normal gastric emptying.

After carefully reviewing the medications of all patients, we did not believe that any medication was causing the nausea. Dietary modifications had not been prescribed for any patient before our discovery of gastroesophageal reflux disease.

One patient smoked cigarettes, and three infrequently drank alcoholic beverages. The referring physicians and investigators did not believe that any of the patients had neuropsychiatric conditions.

Evaluation

All patients had esophageal and gastric evaluations: Ten had esophagogastroduodenoscopy, 6 had 24-hour esophageal pH studies, and 1 had a Bernstein test for determination of acid perfusion. An ambulatory pH monitoring system (Synectics, Inc. Houston, Texas) with dual monocrystalline antimony pH catheters was used for the esophageal pH studies as described elsewhere (2).

Solid-phase gastric-emptying scans were done in eight patients, and electrogastrography was done in six patients as part of the evaluation. The solid-phase gastric-emptying scans were done by the nuclear medicine division as described elsewhere (3). Electrogastrography measures gastric myoelectrical activity. Gastric dysrhythmias that alter upper gastrointestinal motility may elude diagnosis if tests other than electrogastrography are used. Electrogastrography has shown altered gastric myoelectrical activity in patients who have unexplained nausea and vomiting (4).

Electrogastrograms were recorded by using four standard silver-chloride electrodes positioned on the epigastrium as described elsewhere (5). The electrodes were connected to a rectilinear recorder through a direct nystagmus coupler (Model 9859, Sensormedics, Inc., Anaheim, California), and a hard copy of the electrogastrographic signal was obtained. The signal was also analyzed by computer (5), and frequencies from 2.4 to 3.6 cycles per minute were considered normal (5). Frequencies of 0 to 2.4 cycles per minute were considered to be bradygastric; frequencies of 3.6 to 9.9 cycles per minute were considered to be tachygastric.

All patients had normal liver function test results; complete blood cell counts; and levels of amylase, lipase, electrolytes, blood urea nitrogen, and creatinine. Normal results on other studies are listed in **Table 1.**

Results

Either endoscopic studies or 24-hour esophageal pH studies showed gastroesophageal acid reflux in all 10 patients (**Table 2**). Esophagitis was documented in 5 of the 10 patients by esophagogastroduodenoscopy and was graded according to a published endoscopic grading system (6). Three patients had grade 4 esophagitis (ulceration, diffuse erythema, mucosal friability), 1 patient had grade 3 esophagitis (erosions, diffuse erythema, mucosal friability), and 1 patient had grade 1 esophagitis (localized erythema of the gastroesophageal junction). Six patients had 24-hour esophageal pH studies, and each study showed abnormally increased acid reflux.

Table 2. Confirmation of Gastroesophageal Reflux Disease in Patients with Intractable Nausea*

Patient	Esophogastroduodenoscopy and Esophagitis	24-Hour pH Study†	Bernstein Test
1	Yes	ND	ND
2	Yes	ND	ND
3	No	Yes (19%)	ND
4	No	Yes (41%)	ND
5	No	ND	Yes
6	No	Yes (9%)	ND
7	Yes	ND	ND
8	Yes	Yes (NA)	ND
9	Yes	Yes (75%)	ND
10	No	Yes (20%)	ND

* NA = not available; ND = not determined.
† Values given in parentheses are the percentages of time that esophageal pH was less than 4.0.

During the 24-hour period, the esophageal pH was less than 4.0 between 9% to 75% of the time (average, 33%). The normal range in our laboratory is less than 6%. Diaries of symptoms indicated that 32 of 33 reported episodes of nausea correlated with episodes of acid reflux. One patient was believed to have gastroesophageal reflux disease on the basis of positive results on the Bernstein test.

Gastric emptying and gastric myoelectrical activity were found to be normal according to a solid-phase gastric-emptying test and electrogastrography (**Table 1**).

After gastroesophageal reflux disease was shown to cause chronic nausea, treatment was directed toward reducing acid reflux. In 7 of the 10 patients, nausea was effectively treated with the following dosages of omeprazole: 20 mg twice daily (5 patients), 20 mg once daily (1 patient), and 40 mg twice daily (1 patient). Nausea was markedly reduced in 1 patient who received 300 mg of ranitidine twice daily and in 1 patient who received 10 mg of cisapride four times daily. Finally, 1 patient did not respond to 300 mg of ranitidine twice daily or to 60 mg of omeprazole once daily and thus had open Nissen fundoplication. Nausea resolved after the antireflux surgery. Time to resolution of nausea ranged from 1 to 16 weeks (mean, 7.3 weeks). All 10 patients were considered to have responded to these therapies for gastroesophageal reflux disease.

Acid suppression was objectively measured in several patients. During treatment, three patients had follow-up studies to confirm effective acid suppression. Patients 2 and 7 (**Table 2**) initially had macroscopic esophagitis on esophagogastroduodenoscopy; repeated esophagogastroduodenoscopy confirmed that the esophagitis had healed. Patient 4, who initially had an esophageal pH less than 4.0 during 41% of the 24-hour esophageal pH study, had normal results on follow-up while receiving therapy (esophageal pH < 4.0 for 1.3% of the time). The total follow-up period ranged from 2 to 14 months (mean, 6.4 months), and all patients reported continued relief of nausea.

Discussion

Patients who present with atypical symptoms of gastroesophageal reflux disease can present a diagnostic challenge (7–10). After we extensively evaluated a group of patients with chronic intractable nausea, gastroesophageal reflux disease was the only abnormality we could find. Gastroesophageal reflux disease was diagnosed by esophagogastroduodenoscopy, a 24-hour esophageal pH study, and a Bernstein test.

Our study is limited by the small number of patients, retrospective analysis, and short-term follow-up. However, gastroesophageal reflux disease should be considered in the differential diagnosis of chronic nausea, especially in troublesome cases in which gallbladder, pancreatic, neurologic, or peptic ulcer disease has been excluded.

Because chronic nausea is not typically attributed to gastroesophageal reflux disease, abnormal acid reflux was not considered in our patients before referral. Even when esophagitis was seen on endoscopy, the association with nausea was not appreciated and standard-dose H_2-blocker therapy was frequently unhelpful. Gastroesophageal reflux disease cannot be excluded on the basis of normal endoscopic findings because endoscopy lacks sufficient sensitivity (11–13). Endoscopic evidence of esophagitis is present in only 50% to 60% of symptomatic patients (14, 15).

If esophagitis is found on esophagogastroduodenoscopy, a course of high-dosage H_2-blocker therapy (for example, 300 mg of ranitidine twice daily or 40 mg of famotidine twice daily) or a proton-pump inhibitor can be started. In patients who have chronic unexplained nausea and normal findings on esophagogastroduodenoscopy, a 24-hour esophageal pH study is recommended because it is the most sensitive test for diagnosing gastroesophageal reflux disease (16). Because about 40% of patients with gastroesophageal reflux disease have gastroparesis, an assessment of gastric emptying may be helpful. Electrogastrography can have a role in evaluating a patient with chronic unexplained nausea because gastric dysrhythmias have been associated with nausea (4).

We found it unusual for a patient with gastroesophageal reflux disease to respond to standard-dose H_2 blockers. The one patient whose nausea was relieved by an H_2 blocker needed high-dosage ranitidine (300 mg twice daily). We and other researchers (17, 18) have observed that a high level of acid suppression may be required to heal esophagitis in some patients. In our study, the most common dosage of omeprazole needed to relieve nausea was 20 mg twice daily.

In conclusion, chronic nausea can be caused by gastroesophageal reflux disease. In patients with unexplained nausea, gastroesophageal reflux disease should therefore be considered if results on standard tests are normal. A 24-hour esophageal pH study may confirm that gastroesophageal reflux is associated with nausea in patients who have normal findings on esophagogastroduodenoscopy and gastric-emptying tests. In our experience, nausea related to gastroesophageal reflux disease was effectively treated with proton-pump inhibitors and promotility agents.

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Risk Factors for Deep Venous Thrombosis of the Upper Extremities

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Background: Hypercoagulable states and triggering factors (surgery, trauma, immobilization, pregnancy, and use of oral contraceptives) are associated with an increased risk for deep venous thrombosis of the lower extremities. In contrast, risk factors for deep venous thrombosis of the upper extremities have not been identified.

Objective: To evaluate the prevalence of hypercoagulable states and triggering factors in patients with primary deep venous thrombosis of the upper extremities.

Design: Frequency-matched case–control study.

Setting: Hemophilia and thrombosis center at a university hospital.

Patients: 36 patients who had primary deep venous thrombosis of the upper extremities, 121 patients who had primary deep venous thrombosis of the lower extremities, and 108 healthy controls. Patients who had deep venous thrombosis of the lower extremities and study controls were frequency-matched by age, sex, geographic origin, and social status with patients who had deep venous thrombosis of the upper extremities.

Measurements: Resistance to activated protein C was evaluated by a clotting method based on the activated partial thromboplastin time. If test results were abnormal or borderline, DNA analysis for substitution in coagulation factor V gene was done. Antithrombin, protein C, protein S, antiphospholipid antibodies, and total plasma homocysteine levels were also measured.

Results: Prevalences of abnormalities of the natural anticoagulant system (9%) and hyperhomocysteinemia (6%) in patients who had deep venous thrombosis of the upper extremities were similar to prevalences of both factors in controls (6% and 7%, respectively) but lower than in patients who had deep venous thrombosis of the lower extremities (31% and 14%, respectively). Antiphospholipid antibodies were found only in patients who had venous thrombosis of the lower extremities (7%). The overall prevalence of hypercoagulable states in patients who had thrombosis of the upper extremities (15%) was similar to that in controls (12%) but was significantly lower than that in patients who had thrombosis of the lower extremities (56%). A recent history of strenuous exercise of muscles in the affected extremity was the most frequent triggering factor for patients who had deep venous thrombosis in the upper extremities (33%).

Conclusions: This preliminary study indicates that the prevalence of hypercoagulable states is low in patients who have primary deep venous thrombosis of the upper extremities.

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