CLINICAL VIGNETTE

Diabetic Gastroparesis

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Case Report

A 59-year-old Caucasian female with a past medical history significant for poorly controlled type 2 diabetes complicated by peripheral neuropathy, nephropathy and proliferative retinopathy, coronary artery disease s/p 2 myocardial infarctions, and hypertension, was referred to us for severe diabetic gastroparesis that started 1 year prior to referral. In this time, she reported that she'd had over 20 hospitalizations and an additional 20 emergency room visits for severe nausea, vomiting, and abdominal pain. In addition, she'd lost over 50 lbs. Her initial HBAIC was 8.1% with hemoglobin of 9.1 g/dL. A nuclear medicine gastric emptying scan revealed severe gastroparesis with 4% of the meal emptying at 90 minutes. She had been treated with anti-emetics along with prokinetic agents such as erythromycin and metoclopramide with no success and she received parenteral nutrition. She was subsequently treated successfully with domperidone and she is now free of nausea, vomiting, and abdominal pain. She also gained 85 lbs in 1 year. Her recent HBAIC was 6.6% and her blood sugars are now well controlled.

Gastroparesis

Gastroparesis is defined as delayed gastric emptying when there is no mechanical obstruction of the stomach[1]. The main symptoms are recurrent episodes of early satiety, postprandial nausea, vomiting, epigastric pain, and bloating. Complications of severe gastroparesis include weight loss, malnutrition, poor absorption of oral medications, low quality of life, and the burden of repeated hospitalization/emergency department visits. The most common causes of gastroparesis are diabetes, idiopathic (including viral illness causing delayed gastric emptying), and post surgical (ie, damage to the vagus nerve).

In one tertiary referral series, diabetes mellitus accounted for almost one third of cases of gastroparesis. It is a common condition affecting up to 5 million individuals in the United States. The female to male ratio[2] is 4:1. It is unclear why there is a high female predisposition.

About 5% to 12 % of patients with diabetes report gastroparesis symptoms. It typically does not develop until diabetes has been present for more than 10 years and patients have evidence of retinopathy, neuropathy, and nephropathy. There is increased mortality with diabetic gastroparesis and the major causes of death are cardiac and renal dysfunction.

Physiology of Gastric Emptying

The proximal stomach receives and stores ingested food, while the distal stomach grinds solids into small particles prior to emptying into the small intestine. The rate of gastric emptying varies with the physical texture, particle size, fat, fiber, and energy content of a meal. Non- nutrient liquids empty rapidly and the rate is fastest when there is a large volume. If there are increased calories in the liquid phase of the meal, emptying is relatively constant over time. Solids are initially retained in the stomach and undergo churning while antral contractions propel particles toward the closed pylorus. Food particles are emptied once they have been broken down to approximately 2 mm in diameter. Thus, solids empty during 2 phases over 3 to 4 hours: initial lag period, followed by a phase of relatively constant emptying.

Impaired Gastric Emptying in Patients with Diabetes

Gastroparesis is due to a combination of 1) incoordination of motor activity (the interstitial cells of Cajal) between the different parts of the stomach and 2) vagus nerve autonomic neuropathy (causing reduced gastric tone, antral hypomotility, pylorospasm, decreased antral-duodenal coordination). In individuals with diabetes, dysrhythmias are common. Chronically elevated blood glucose levels increase the risk of diabetic neuropathy. Increased glycated hemoglobin levels are associated with increased rates of gastrointestinal symptoms. Acute hyperglycemia also may contribute to motor dysfunction in patients with diabetes; in experiments, the time at which half of the consumed solids are emptied from the stomach (the half-time) is approximately 15 minutes longer in patients with hyperglycemia (blood glucose levels exceeding 180 mg per deciliter [10 mmol per liter]) than in subjects with euglycemia.[3] Neurohormonal dysfunction and hyperglycemia reduce the frequency of antral contractions (needed to churn food) in patients with diabetes. In contrast, the emptying of liquids is usually normal in patients with hyperglycemia.[3]

Diagnosis

The diagnosis of gastroparesis requires that 1) there is delayed gastric emptying and 2) there is no mechanical obstruction that is contributing to the delayed gastric emptying. Gastric emptying scan (scintigraphy) is the gold standard for diagnosis, although food retained in the stomach after a 12-hour fast is suggestive of gastroparesis. Any medications that affect gastric emptying should be stopped prior to testing: prokinetic medications, proton pump inhibitors (delay emptying, should be stopped for at least 72 hours), and narcotics (delay emptying, should be stopped for at least 12 hours). Either upper endoscopy or upper gastrointestinal series can be used to ensure that there is no mechanical obstruction (peptic ulcer disease, gastric mass, gastric outlet obstruction) that is contributing to the delayed gastric emptying.

Differentiation from other causes of nausea and vomiting is important. Gastroparesis causes chronic symptoms that are worse after meals. Viral gastroenteritis causes acute and self-limited symptoms. Cyclical vomiting syndrome causes episodes of severe nausea and vomiting interspersed with long periods of time that are symptom free. Rumination syndrome causes effortless regurgitation of solids and liquids within 1 to 20 minutes of ingestion, whereas gastroparesis causes nausea and postprandial distress immediately after eating. However, the vomiting associated with gastroparesis typically doesn't occur until 1 to 4 hours after eating, at night when lying supine, or after awakening when the prior day's food consumption is vomited.

Management

Management depends on the severity of the disease.[4] Mild gastroparesis is defined as symptoms that are relatively easily controlled. The patient is able to maintain weight and nutrition with minimal dietary modifications. Compensated gastroparesis is defined as moderate symptoms that are partially controlled with pharmacologic agents without weight loss. Gastroparesis with gastric failure is defined as patients who are refractory to medication, unable to maintain oral nutrition, and undergo frequent emergency room visits and hospitalizations.

The goal of medical therapy should include alleviation of symptoms, correction of malnutrition, and resumption of oral intake. The first step of treatment includes dietary modification. Small frequent meals that are low in fat and low in non-digestible fiber are easiest to digest. Glycemic control (with goal glucose levels < 180mg/dL) is of extreme importance for diabetic patients and patients with type 1 diabetes may be candidate for an insulin pump.

Prokinetic medications may be added to further alleviate symptoms. Metoclopramide is a dopamine receptor antagonist and is given at doses of 10 to 20mg 30 minutes before meals and at bedtime. This is also available in a subcutaneous formulation for patients who have frequent vomiting. There is a Food and Drug Administration mandated black box warning regarding tardive dyskinesia that should be discussed with all patients. If metoclopramide is not effective, domperidone, another dopamine receptor antagonist, is given at doses of 20 to 30mg 4 times a day. This is available through the FDA-approved compassionate use limited access program. It is recommended that serum potassium levels

be normal and that electrocardiogram QTc be less than 475 microseconds prior to starting. These medications, in combination with anti-emetic medications, should be tried for at least 2 to 3 months before being labeled as ineffective for a particular patient.

Erythromycin stimulates the motilin receptors on smooth muscles and neurons in the gastroduodenal area. It does not have an independent anti-emetic effect. Through the studies performed, it is concluded that it improves gastric emptying but it benefits only a minority of patients with regard to symptom amelioration. It is given as erythromycin 125mg 3 times a day. Tolerance can develop with the medication and if it occurs, patients should stop taking this medication for 1 to 2 weeks before resuming.

The above medications can be tried in conjunction with tricyclic antidepressants and anti-emetics including scopolamine patches.

Non-Pharmacologic Therapy

Injection of botulinum toxin into the pyloric sphincter can cause a decrease in pylorospasm and was initially thought to accelerate gastric emptying. However, 2 randomized controlled trials showed that botulinum toxin injection is not superior to placebo.[5,6]

Gastric electrical stimulation can be used in the treatment of refractory gastroparesis. The FDA approved the Enterra device as a Human Use Device under the Humanitarian Device Exemption in 2000 for patients with diabetic and idiopathic gastroparesis. It delivers high frequency/low energy gastric electrical stimulation through 2 electrodes sutured to the muscle layer of the stomach greater curvature and has been shown in a double blind trial that it significantly reduced vomiting and improved quality of life. The mechanism is unclear, as patient response is independent of gastric emptying. Predictors of response include diabetic gastroparesis, patients with predominance of nausea and vomiting in symptomatology (as opposed to abdominal pain), and patients not on narcotic medications. About 10% of patients develop complications such as infection, pain, and dislocation of electrodes, which warrant removal of the device.

Venting gastrostomy and feeding jejunostomy is another option that can reduce hospitalizations if other modalities have failed to give symptomatic relief. In addition, near-total gastrectomy can be considered as a last resort in order to reduce nausea, vomiting, and post-prandial pain.

Conclusion

The prevalence of gastroparesis associated with diabetes is likely to increase given the increasing rates of obesity and diabetes in our population. Uncontrolled hyperglycemia is the most common cause and therefore, tight control of blood sugars is of extreme importance both to prevent gastroparesis and to control its symptoms once it is diagnosed. The pathogenesis of gastroparesis is complex and incompletely understood, and will need futher investigation in order to provide more specific and effective therapy.

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