Diabetic Gastroparesis Presenting with a Cyclic Vomiting Pattern

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Gastroparesis is a syndrome characterized by delayed gastric emptying in the absence of mechanical obstruction of the stomach. Approximately 20~40% of patients with a long course of diabetes mellitus and/or other complications, especially neurologic dysfunction, develop diabetic gastroparesis. Diabetic gastroparesis has been thoroughly investigated; however, few reports have considered an associated episodic cyclic vomiting pattern. We present a literature review and report the case of our recent experience with a 29-year-old male patient who presented with a cyclic vomiting pattern associated with diabetic gastroparesis. (**Korean J Helicobacter Up Gastrointest Res 2017;17:148-153**)

Key Words: Cyclic vomiting syndrome; Diabetes mellitus; Gastroparesis

INTRODUCTION

Cyclic vomiting syndrome (CVS) is a disorder characterized by recurrent episodes of severe nausea and vomiting interspersed with symptom-free periods. Rome IV criteria defines it in more detail, CVS must include all of the following 3 criteria: 1) CVS is stereotypical episodes of vomiting concerning acute onset and duration with less than 1 week, 2) the symptoms are at least discrete episodes in the last year and 2 episodes in the past 6 months, occurring at least 1 week apart, 3) there was no vomiting between episodes, but other milder symptoms can occur between cycles.¹ This syndrome was initially described in literature in 1882 by Gee,² who reported a series of 4- to 8-year-old children experiencing recurrent emetic episodes. While CVS has been studied in pediatric populations, it can occur in all age groups, including young and middle-aged adults. Prevalence of CVS in adults is increasing, but the lack of awareness of CVS in adults has led to delay in diagnosis or misdiagnosis. Some evidence suggests that there are differences in terms of symptom profiles, pathogenesis, and comorbidities between adults and children.³ In contrast to most childhood cases, CVS in adults is associated with a number of un-

derlying chronic systemic diseases including diabetes mellitus (DM).⁴

Gastroparesis is a syndrome characterized by delayed gastric emptying in absence of mechanical obstruction of the stomach. Its actual prevalence is unknown. However, it is estimated that 20% to 40% of patients with diabetes, primarily those with a long duration of type 1 DM with other complications, develop gastroparesis.⁵ Diabetic gastroparesis has been thoroughly investigated, but few reports have considered episodic CVS. A recent article initially dealt with a subset of patients with a cyclic vomiting pattern in a population of patients with diabetic gastroparesis.³ We describe a case of severe diabetic gastroparesis presenting with a cyclic vomiting pattern.

CASE REPORT

A 29-year-old male was admitted for evaluation of recurrent episodes of severe nausea and vomiting for 2 years. He had been diagnosed with type 1 DM at another hospital 7 years previous. He received insulin injection 3 times daily (mixture of 50% rapid-acting and 50% intermediate-acting insulin, and the dose of insulin was 30 unit-20 unit-20 unit) without an oral hypoglycemia agent. However, he had overeating behaviors and his blood glucose levels showed unstable. At the current presentation, he denied other underlying diseases including hypertension, tuberculosis, and hepatitis. He also denied history

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of substance abuse including marijuana or opioid. He had no siblings and no family history of DM or genetic disease. He complained of periodic severe nausea and vomiting symptoms that lasted 3 or 4 days. He was not able to eat during these periods due to persistent nausea, repeated vomiting, and abdominal pain. After such an emetic phase, the symptoms resolved, and the patient

showed good health for several weeks to months. These symptoms tended to occur when the patient was in a postprandial state, but there was no specific trigger or aggravating factor. He had previously been admitted to another hospital with these symptoms 1 month prior to the visit to our hospital and underwent esophagogastro-duodenoscopy. The endoscopic findings were compatible

Fig. 1. Esophagogastroduodenoscopy shows reflux esophagitis (A) and diffuse mild hyperemic gastric mucosa at the mid-body of the greater curvature, compatible with erythematous gastritis (B).

Fig. 2. The esophagogram shows normal course, good distensibility, and smooth passage of contrast media with good peristaltic movement (A). Upper gastrointestinal series also shows normal mucosal folds with no filling defect or narrowing (B).

with reflux esophagitis and erythematous gastritis, for which he was prescribed ranitidine, mosapride, and trimbutine maleate for 5 days, resulting in symptom resolution. He was free of nausea and vomiting for about 1 month, but then the symptoms relapsed. He revisited the previous hospital and again underwent esophago-gastroduodenoscopy. The endoscopic findings showed no significant interval change. Therefore, abdominal computed tomography was performed and showed no evidence of mechanical obstructive lesion. He was then transferred to our hospital and admitted.

His height was 171 cm, and body weight was 75 kg. Blood pressure was 131/77 mmHg, heart rate 72/min, respiratory rate 18/min, and body temperature 36.4°C, and there were no abnormal findings on physical examination. Laboratory findings revealed elevated fasting blood sugar of 226 mg/dL and glycosylated hemoglobin (HbA1c) of 7.9%. In addition, his blood hemoglobin was 14.4 g/dL, white blood cell count 11,400/mm³ (neutrophils 81.5%, lymphocytes 12.3%, monocytes 4.3%, eosinophils 0.2%, and basophil 1.7%), platelet count 355,000/mm³, blood urea nitrogen 9.0 mg/dL, creatinine 0.7 mg/dL, total pro-

tein 6.7 g/dL, albumin 4.5 g/dL, AST 13 IU/L, ALT 8 IU/L, total bilirubin 1.0 mg/dL, direct bilirubin 0.3 mg/dL, GGT 12 IU/L, ALP 48 IU/L, total amylase 79 mg/dL, lipase 31 mg/dL, CEA 2.08 µg/L, CA 19-9 24.87 U/mL, ACTH 15.7 pg/mL, and cortisol 9.88 µg/dL. Serologic markers for HBV, HCV, human immunodeficiency virus, and venereal disease research laboratory test were normal. Esophagogastroduodenoscopy showed reflux esophagitis and erythematous gastritis without significant interval change (Fig. 1). Esophagogram and upper gastrointestinal series showed normal anatomic findings without filling defect or narrowing (Fig. 2). With high suspicion of gastrointestinal motility disorder, we performed a gastric emptying time scan at the emetic phase, and gastric emptying half-time was 325.21 minutes (Fig. 3). In addition, we conducted an autonomic function test, nerve conduction study, and ophthalmoscopy. The findings were compatible with parasympathetic cardiovagal dysfunction, peripheral polyneuropathy, and severe non-proliferative diabetic retinopathy.

We controlled his blood sugar with insulin injection 4 times daily by using multiple subcutaneous insulin in-

Fig. 3. The scintiscanning of gastric emptying time shows a severe delayed half-time of gastric emptying (T1/2=325.21 min). *Geometric mean.

fection protocol (24 unit long-acting insulin once every morning and 10 unit three times injections of every pre-prandial rapid-acting insulin). In addition, we prescribed metoclopramide 5 mg tid, domperidone 10 mg tid, mosapride 5 mg tid, and amitriptyline 10 mg qd for diabetic gastroparesis with a cyclic vomiting pattern. When he was discharged, his clinical symptoms were improved after proper diagnosis and management based on careful history taking. He visited our outpatient department twice after discharge during 1 month and there was no symptoms recurrence in the interim. Unfortunately, he was lost to follow-up in our hospital.

DISCUSSION

Gastroparesis is a syndrome characterized by delayed gastric emptying without gastric mechanical obstruction.⁶ This syndrome typically shows clinical symptoms of early satiety, nausea, vomiting, and bloating.⁷ The pathophysiology of gastroparesis is complex and poorly understood. However, diabetes accounted for almost one-third of cases of gastroparesis, and other causes include previous gastric surgery, neurologic disorder, rheumatologic disorder, and viral infection. Development of diabetic gastroparesis is associated with duration of diabetes and it can cause severe symptoms and result in nutritional compromise, impaired glucose control, and a poor quality of life.⁸ About 5% to 12% of patients with diabetes in previous studies complained of symptoms associated with diabetic gastroparesis.⁹⁻¹² In patients with diabetic gastroparesis, mechanisms of gastrointestinal motility are altered, mainly due to vagal neuropathy, reductions in the number of intrinsic inhibitory neurons that coordinate motor function¹³ and the number of the interstitial cells of Cajal as pacemaker cells,¹⁴ and hormonal changes like increased glucagon level. Chronic exposure to high blood glucose increases the risk of diabetic neuropathy including gastrointestinal symptoms. Furthermore, acute hyperglycemia can affect motor dysfunction in patients with diabetes.¹⁵ Neurohormonal dysfunction and hyperglycemia also reduce the frequency of antral contractions for churning food. In contrast, the emptying of liquids is usually normal in patients with hyperglycemia.¹⁶

Christensen et al.³ reported that a sizeable percentage of diabetic gastroparesis patients demonstrate cyclic vomiting symptoms. Their study included 67 patients with diabetic gastroparesis, and 38 (56.7%) showed a cyclic vomiting pattern. The group showing cyclic vomiting associated with diabetic gastroparesis had a female predominance (28 patients, 73.7%), a mean age of 43.7 ± 1.5 years, mean duration of diabetes of 17.8 ± 1.8 years, mean duration of diabetic gastroparesis of 4.7 ± 0.6 years, and HbA1c of $8.4 \pm 0.3\%$. Comparing these data with that of our patient, he was diagnosed at a younger than average age, with short durations of diabetes and diabetic gastroparesis, and had low HbA1c. Nevertheless, he developed gastroparesis with a cyclic vomiting pattern.

The main strategy in the management of diabetic gastroparesis is the correction of exacerbating factors such as glucose and electrolyte abnormalities, optimal nutritional support, and the use of prokinetic agents and symptomatic therapies. Moreover, previous medications can delay gastric emptying time, such as antihypertensive agents as calcium-channel blockers or clonidine, anticholinergic agents, and antidiabetic glucagon-like peptide-1 analogues as exenatide or pramlintide. Typically, severity of diabetic gastroparesis is determined according to gastric retention at 4 hours. When gastric retention is more than 35 percent at 4 hours, the condition is considered severe gastroparesis.¹⁷ The current case showed a severe delayed half-time of gastric emptying ($T_{1/2} = 325.21$ minutes). According to the severity of the condition, we prescribed prokinetics and a parenteral nutritional agent with additional liquid nutrient supplements.

Cyclic vomiting, although classically associated with migraine, has also been linked to food allergy and mitochondrial, metabolic, and endocrine disorders, such as overreaction of the hypothalamic pituitary-adrenal (HPA) axis.¹⁸⁻²¹ In terms of the HPA axis, corticotropin releasing factor (CRF) is considered as an importance trigger for the vomiting phase starts, and it stimulates of the hypersecretion of ACTH and cortisol.²¹⁻²³ The current patient did not show features of migraine and abnormal ACTH and cortisol level. Another study also reported that absence of migraine was more common in male cyclic vomiting patients associated with diabetic gastroparesis than

in their female counterparts.³ Previous studies have postulated that autonomic dysfunction and vagal cholinergic dysfunction can occur in CVS and migraine.^{24,25} Autonomic nervous system dysfunction could explain the increased gastric emptying time, and previous studies have shown that sympathetic adrenergic function, assessed as vasoconstriction to cold and postural adjustment ratio, was abnormal in patients with cyclic vomiting and migraine. In addition, vagal cholinergic function, assessed as valsalva ratio and electrocardiogram R-R interval interval, was also lower in both cyclic vomiting and migraine patients.²⁴ In our case, electrophysiological findings of the autonomic function test showed parasympathetic cardiovascular dysfunction. These findings suggest that treatment should focus on the autonomic and enteric nervous systems in diabetic gastroparesis patients with cyclic vomiting symptoms.

Although several empiric treatments have been effective in case series, there has been no controlled trial demonstrating a specific therapy proven to be effective for CVS. Generally, avoidance of predisposing factors; antiemetics, prokinetics, and analgesics; and nutritional support with intravenous fluids are recommended for such patients. Tricyclic antidepressants are the most commonly using drug class for prevention of cyclic vomiting episodes in adults, and it also has CRF inhibitory action.²⁶ A recent study reported that antidepressants may be related with CRF haplotype 1 gene,²⁷ and it might influence the central control of nausea and vomiting. These agents also play a prophylactic role in migraine, depression, anxiety and the abdominal pain associated with irritable bowel syndrome and presumably act centrally to modulate the vomiting process.²⁸

The existence of this CVS-like subset of diabetic gastroparesis raises the question of whether these findings are a manifestation of or a response to underlying diabetic gastroparesis. Unfortunately, there has been little research on this cyclic vomiting manifestation associated with diabetic gastroparesis. Nonetheless, when physicians meet the DM patients with recurrent nausea and vomiting, they should suspect the possibility of CVS as well as diabetic gastroparesis and immediate proper management should be administered. A cyclic vomiting pattern can oc-

cur even in young diabetic gastroparesis patients presenting with the associated symptoms.

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