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【 CASE REPORT 】

Hyperemesis-induced Wernicke-Korsakoff Syndrome due to Hypergastrinemia during Long-term Treatment with Proton Pump Inhibitors

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Abstract:
We herein report a patient with Wernicke-Korsakoff syndrome (WKS) who had neither a history of alcoholism or of history of gastric surgery. A 56-year-old woman was transferred to our hospital because of the loss of consciousness and she was diagnosed to have Wernicke encephalopathy. She showed proton pump inhibitor-induced refractory hypergastrinemia with the subsequent development of hyperemesis and a vitamin B1 deficiency.

Key words: Wernicke-Korsakoff syndrome (WKS), hypergastrinemia, proton pump inhibitor (PPI), hyperemesis, vitamin B1

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Introduction

The major cause of Wernicke-Korsakoff syndrome (WKS) is alcoholism. However, this neurological syndrome is also known to be a heterogeneous disorder with a wide range of precipitating illnesses including gastrointestinal disease (including surgery) and hyperemesis gravidarum (1). Thiamine storage is depleted due to persistent vomiting, poor food intake, and increased metabolic demand (2). According to a previous report, 17% cases of WKS not related to alcoholism were caused by dietary insufficiency, starvation or recurrent vomiting (1). It is also important to emphasize that the long-term treatment of the suppression of the secretion of gastric acid with proton pump inhibitors (PPIs) may result in hypergastrinemia and persistent vomiting (3).

Case Report

A-56-year-old woman with a refractory gastric ulcer was admitted to our hospital because of an altered level of consciousness, and an abnormal sensation in her limb. One month before presentation, she showed mild drowsiness during the day. She was admitted to a previous hospital because she was unable to walk due to lower limb weakness ten days before she was admitted to our hospital. Her drowsiness worsened four days before admission to our hospital.

She had no history of alcohol consumption and an umbalanced diet, and no family history of intractable gastrointestinal diseases. About ten years before admission to our hospital, she presented with progressively worsening dyspepsia. She was diagnosed with *Helicobacter pylori* infection and a peptic ulcer, and was treated with a PPI, 30 mg/day of lansoprazole, and an antiemesis. *Helicobacter pylori* eradication therapy was successful, however, her occasional epigastric

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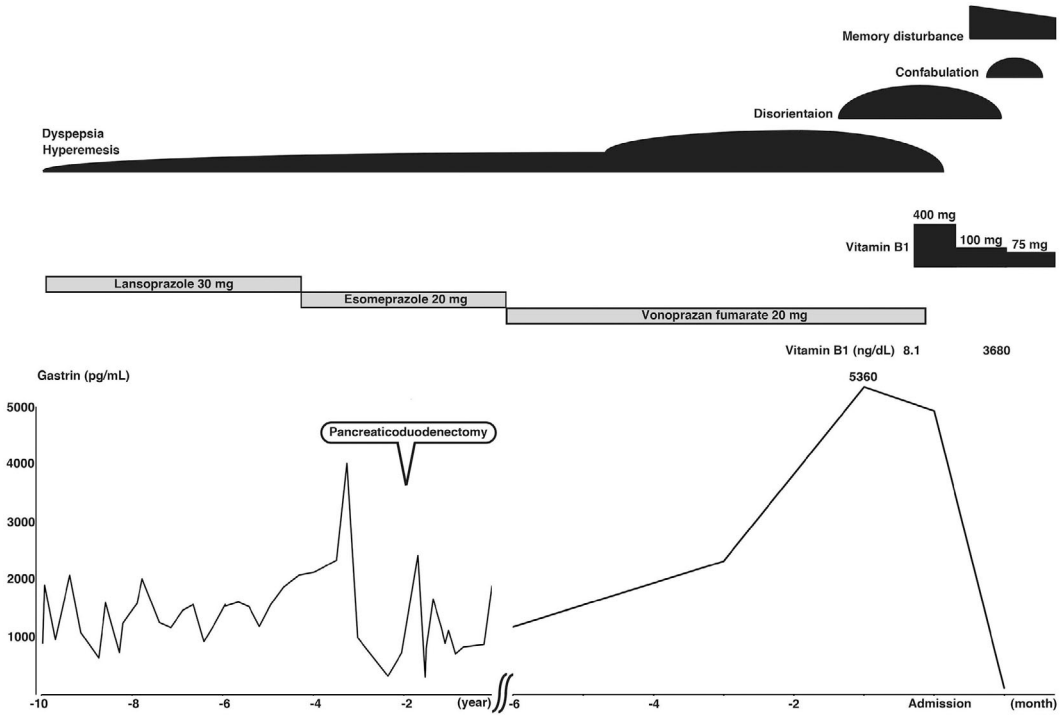

Figure 1. The clinical course. Note that hyperemesis tended to occur more often after PPI was changed from lansoprazole and esomeprazole to vonaprazan fumarate at six months before admission. Plasma gastrin promptly decreased to a normal level after discontinuing vonoprazan.

pain and nausea remained. She did not have repetitive diarrhea. Further investigation revealed a refractory gastric ulcer due to hypergastrinemia. Gastroenterologists performed more than one upper gastrointestinal endoscopy, computed tomography (CT), and positron emission tomography (PET) scan due to a suspicion of gastrinoma, but no tumors other than gastric ulcers were detected. Four years before admission, the gastric mucosa protective agent was changed to esomeprazole 20 mg/day, but dyspepsia and hyperemesis did not improve. At the age of 54, she had a genetic test for a direct sequence analysis of exon2-10 of *multiple endocrine neoplasia (MEN) I* gene, and no significant abnormalities were found. She also underwent pancreaticoduodenectomy, which also showed no significant pathological findings including microtumors. Frequent vomiting and hypergastrinemia persisted despite treatment with esomeprazole. Six months before admission, esomeprazole was replaced by 20 mg/day of vonoprazan fumarate, resulting in an elevated gastrin level (peak level; 5,360 pg/mL) and worsening of dyspepsia and hyperemesis. One month before admission, she complained of an abnormal sensation and gradually developed disorientation and somnolence (Fig. 1), thereafter she was transferred to our university hospital from previous neighborhood hospital.

On admission, the patient's height was 155 cm and weighted 40.4 kg. Her body temperature was 36.6°C, blood pressure was 114/76 mmHg, and heart rate was 61 beats per minute. Her respiratory rate was 11 breaths per minute, and percutaneous oxygen saturation (SpO_2) was 97% in supine position on room air. No enlarged lymph nodes in neck, axilla, or groin were detected. No edema or purpura were seen in the limbs. A neurological examination showed mild clouding of consciousness with score 14 (E4V4M6) on Glasgow Coma Scale, suppression of ocular movement in the upward direction, and lateral gaze evoked nystagmus. Manual muscle testing was grade 3 at both the upper limb and lower limb, but it was difficult to evaluate because of her drowsiness. She also complained of dysesthesia in her fingertips. The biceps, triceps, patellar reflexes were diminished bilaterally. A blood gas analysis indicated respiratory compensation for metabolic acidosis. The results of her blood examination are shown in Table. Her electrolytes, blood sugar, and thyroid hormone levels were normal. However, hypergastrinemia and significantly low level of vitamin B1 (8.1 ng/dL) (normal range: 20-50 ng/dL) were observed. The high level of vitamin B12 was presumed to be due to methylcobalamin prescribed by a physician who had been consulted before transfer. A chest X-ray revealed no significant cardiac enlargement (cardiothoracic ratio: 55%). An electrocardiogram showed a normal sinus rhythm at a rate of 64 bpm and nonspecific ST-T changes in V3-V6. An echocardiogram revealed mild segmental asynergy of the left ventricle (EF: 55.2%). No findings indicating beriberi heart such as high out-put heart failure, pericardial effusion, or pulmonary hypertension were observed. A nerve conduction study revealed sensory polyneuropathy. A cerebrospinal fluid analysis showed normal findings including cytology. Brain MRI, fluid-attenuated inversion recovery (FLAIR) images showed abnormal bilaterally symmetrical hyperintense signals in the mammillary bodies, a periaqueduct area of gray

Table. **Laboratory Data on Admission.**

Complete Blood Count		Biochemistry Test		Immunoserological Test	
WBC	6,800 /μL	TP	5.2 g/dL	CRP	0.14 mg/dL
Hb	8.8 g/dL	Alb	2.4 g/dL	IgG	1,020 mg/dL
Plt	358,000 /μL	CK	68 U/L	IgA	183 mg/dL
Coagulation		AST	21 U/L	IgM	130 mg/dL
PT-INR	1.00	ALT	14 U/L	Anti-TG-Ab	<10.0 IU/mL
APTT	26.2 sec	γ-GTP	10 U/L	Anti-TPO-Ab	3.8 IU/mL
D-dimer	1.1 μg/mL	Cr	1.43 mg/dL	Intact-PTH	580.8 pg/mL
Infectious Disease Test		BUN	26 mg/dL	PTH-RP	<1.1 pmol/L
HBsAb	negative	Na	141 mEq/L	Vitamin	
HBcAb	negative	K	4.7 mEq/L	B1	8.1 ng/mL
Anti-HIV-Ab	negative	Cl	112 mEq/L	B12	5,270 pg/mL
				Folic acid	5.2 ng/mL
RPR	negative	Amylase	65 U/L		
TPHA	negative	Lipase	19.8 U/L		
		Gastrine	4,950 pg/mL		

WBC: white blood cell count, Hb: hemoglobin, Plt: platelet, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, Ab: antibody, TP: total protein, Alb: albumin, CK: creatine kinase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyl transpeptidase, Cr: creatinine, CRP: C-reactive protein, Ig: immunoglobulin, TG: thyroglobulin, TPO: thyroid peroxidase, PTH: parathyroid hormone, RPR: rapid plasma regain, TPHA: treponema pallidum hemagglutination

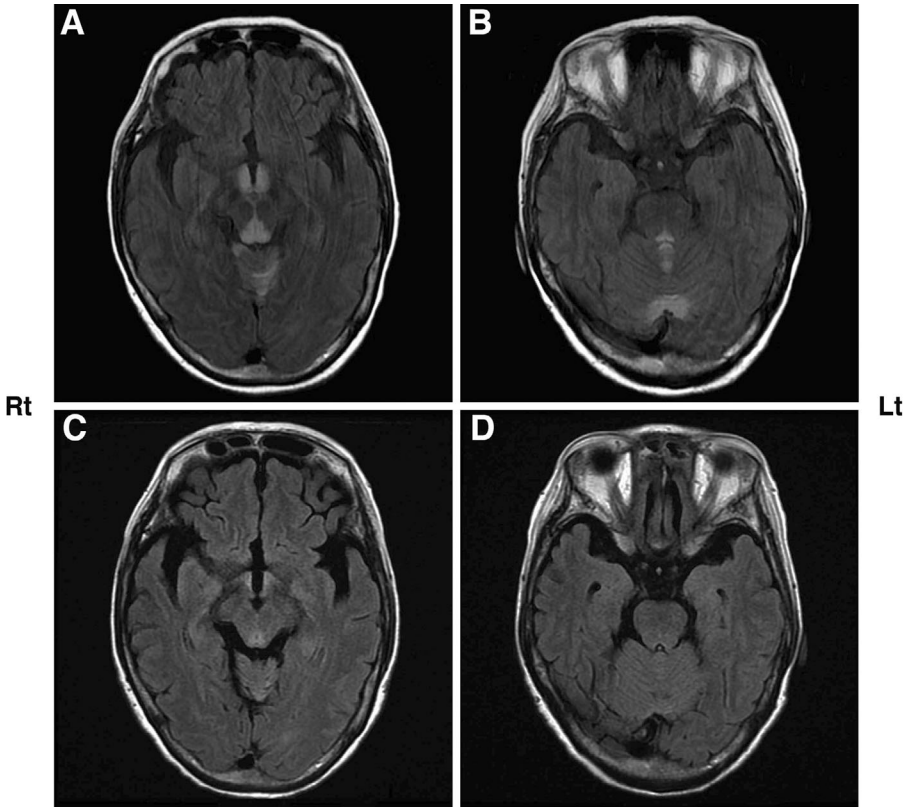

Figure 2. **Fluid-attenuated inversion-recovery (FLAIR) images of brain MRI just before admission (A, B) and 35 days after thiamine treatment (C, D). Hyperintense signals were observed in the bilateral gray matter around the third ventricle, aqueduct, and vermis. These abnormalities have partially subsided after thiamine administration.**

matter in the cerebrum, medial thalami, and vermis, indicating Wernicke encephalopathy (Fig. 2). Vitamin B1 at 400 mg/day was administered intravenously for 18 days followed by tapering in a phased manner. Her consciousness status gradually improved, although she experienced some episodes of confabulation. During reinvestigation to determine

the cause of hypergastrinemia by gastroenterologists, plasma gastrin promptly decreased to a normal level by discontinuing vonoprazan fumarate. Dyspepsia, hyperemesis, and MRI images also significantly improved (Fig. 2). Two months later, the patient was transferred to a rehabilitation hospital with memory disturbance and walking difficulty but no confabulation. Immediately before the patient was transferred to our hospital, an examination of upper gastrointestinal endoscopy revealed only some linear ulcer scars in the lesser curvature of stomach. Two years after admission, she showed gait instability due to peripheral polyneuropathy without dementia including memory disturbance. We concluded that long-term treatment with PPIs comprising lansoprazole, esomeprazole, and vonoprazan fumarate had caused hypergastrinemia and dyspepsia, with the subsequent development of hyperemesis and vitamin B1 deficiency.

Discussion

The major cause of WKS is alcoholism. However, this neurological syndrome is also known to be a heterogeneous disorder with a wide range of precipitating illnesses including gastrointestinal disease (including surgery) and hyperemesis gravidarum (1, 4). Thiamine storage is depleted due to persistent vomiting, a poor food intake, and an increased metabolic demand (2). According to a previous report, 17% cases of WKS not related to alcoholism were caused by dietary insufficiency, starvation or recurrent vomiting (1). Our patient had at least a 10-year history of hypergastrinemia and a 1-year history of hyperemesis prior to hospitalization for onset of WKS. Except for hyperemesis gravidarum, recurrent vomiting-induced WKS may be caused by gastritis, peptic ulcer, pyloric stenosis, biliary colics, Crohn's disease, intestinal obstruction, migraine attacks, and anorexia nervosa (1). In our case, refractory vomiting and hypergastrinemia promptly remitted after discontinuing PPIs, thus indicating that the recurrent vomiting has been induced by hypergastrinemia rather than a direct adverse effect due to any medication. Actually, although several chemical compounds may reduce the thiamine level, only a few drugs including the hypoglycemic agent tolazamide can cause WKS (5, 6).

Several gastrointestinal surgical procedures including gasterectomy, gastrojejunostomy, gastric bypass surgery, gastroplasty, and bariatric surgery may predispose patients to develop WKS (2). Although WKS induced by pancreaticoduodenectomy is considered to be rare, the development of WKS could be explained by a deficiency of vitamin B1 absorption after performing this surgical procedure (7). In a literature review, WKS could be observed within days or weeks after pancreaticoduodenectomy with postoperative complications such as infection and hemorrhage, however, some cases were reported even in few years after surgery (8). It is therefore important to consider the relationship between WKS and a past history of gastric surgery if no specific causation can be identified.

The duration of a precipitating illness prior to presentation of WKS was significantly shorter in the non-alcohol-related WKS (less than 6 months in 83%) than in alcohol-related WKS (more than 1 year in 99%) (1). Many non-alcohol related etiologies were acute illnesses as reflected by a rapid depletion of thiamine storage. However, our patient maintained a thiamine level above the threshold level even after pancreaticoduodenectomy. We suspect that dietary intake and retention of vitamin B1 in nutrients may be relatively preserved during hyperemesis.

Hypergastrinemia is a rare adverse effect of PPIs. However, since gastrin secretion is reduced by gastric acidity, prolonged treatment with PPIs tends to cause hypergastrinemia associated with increased gastric mucosal cell proliferation (3, 9). Generally, PPIs induce a mild elevation of plasma gastrin (ranging from 200-400 pg/mL) and reach a plateau in the first four months of PPI treatment, however, massive elevations has also been reported in the literature (10). Vonaprazon fumarate is a potassium-competitive acid blocker which is a new type of PPI, and it is effective for peptic ulcer and reflux esophagitis refractory to conventional PPIs. However, vonaprazon fumarate caused a greater increase in the plasma gastrin level in a multicenter prospective cross-sectional study (11). Since long-term stimulation by high levels of gastrin may cause chronic hyperplasia of enterochromaffin-like (ECL)-cells and carcinoid formation, long-term treatment with PPIs should be prescribed with caution. Hypergastrinemia-induced hyperemesis has been reported to be caused by not only peptic ulcer and hemorrhagic gastritis but also by continuous stimulation of the vomiting center in the central nervous system via the abdominal vagal pathway and chemoreceptor trigger zone in the area postrema (12).

The authors state that they have no Conflict of Interest (COI).

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