Although intractable nausea and emesis often are associated with disorders that affect the gastrointestinal (GI) tract, they can be symptoms of central nervous system pathology. Brainstem pathology should be considered in the differential diagnosis of any patient who presents with persistent nausea and emesis.

Persistent nausea and emesis can be a symptom of neurologic conditions that increase intracranial pressure such as hydrocephalus, intracranial hemorrhage, and tumors. Lesions within the posterior fossa can induce emesis without increasing intracranial pressure if they damage vestibular pathways or the dorsomedial portion of the medulla.1 This article presents the case of a 39-year-old woman with 8 weeks of nausea and emesis due to brainstem herpes simplex encephalitis. The etiologies of intractable nausea and vomiting are discussed. The clinical manifestations, diagnosis and treatment of herpes encephalitis, and the brainstem anatomy mediating vomiting also are discussed.

CASE PRESENTATION

Initial Presentation and History

A 39-year-old woman presented to our facility with the chief complaint of nausea and emesis that had become progressively more frequent over a 2-month period. The patient’s nausea was now persistent, and she was having approximately 9 episodes of emesis daily. She also complained of loss of appetite, weight loss, dull epigastric pain, and malaise. Three weeks earlier, she had undergone an extensive evaluation at another facility. Physical examination at that facility revealed no abnormalities. Normal diagnostic studies included an abdominal radiograph, esophagogastro-duodenoscopy, upper GI series with small bowel follow-through, hepatobiliary iminodiacetic acid scan, computed tomography (CT) of the abdomen, urine pregnancy test, and brain magnetic resonance imaging (MRI). Additional endocrine and psychiatric evaluations were performed and found to be normal. The patient was discharged with a diagnosis of gastroparesis of unknown origin and was medically treated with oral erythromycin, phenergan, and ativan.

Physical Examination

On admission to our hospital, the patient had a temperature of 99.4°F (37.4°C), pulse was 96 bpm, and blood pressure was 110/68 mm Hg. Findings from a general medical examination were normal. Bowel sounds were present, and there was no abdominal tenderness or distension. Stool was negative for occult blood. Neurologic examination showed normal mental status, cranial nerves, motor function, sensation, and coordination. Reflexes were 2+ in all four limbs, and toes were downgoing bilaterally.

Diagnostic Evaluation

Admission blood work was notable for normal complete blood count, chemistry, and coagulation studies, except for a potassium level of 2.6 mEq/L and a bicarbonate level of 31.4 mEq/L. Serum amylase and lipase levels were normal. Urinalysis showed more than 80 mg/dL ketones but was otherwise normal.

Herpes Brainstem Encephalitis: A Cause of Intractable Emesis

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Electrocardiogram showed normal sinus rhythm, and chest radiograph was normal. A repeat esophagastroduodenoscopy was performed at our facility and demonstrated grade 3 reflux esophagitis, erosive gastropathy at the level of the fundus, gastritis, bilious gastric fluid, and duodenitis.

During the first 3 hospital days, the patient developed new symptoms. She complained of difficulty swallowing and gait imbalance. Several episodes of hypoxia occurred with oxygen saturation levels dropping into the low 80s. Because of further respiratory decompensation and the development of hypotension on hospital day 3, the patient was admitted to the medical intensive care unit, where she was intubated and placed on mechanical ventilation. Her neurologic examination in the intensive care unit was notable for periods of agitation alternating with stupor, oculomotor bobbing (eg, intermittent, brisk, conjugate, bilateral downward movement of the eyes with slow return to midposition), difficulty moving both eyes leftward, an absent gag reflex, right hemiparesis, and a Babinski sign on the right side.

Due to the patient’s neurologic changes, brain CT, electroencephalography (EEG), and lumbar puncture were performed. Brain CT scan was normal. The EEG revealed an abnormal record characterized by diffuse 8-Hz activity mixed with generalized, polymorphic theta and delta activity. These findings were interpreted as indicative of diffuse brain dysfunction. There were no lateralizing or epileptiform discharges. Cerebrospinal fluid (CSF) analysis showed 18 erythrocytes/mm³, 15 leukocytes/mm³ (93% lymphocytes), a protein level of 26 mg/dL, and a glucose level of 75 mg/dL. In addition, results of a VDRL test and acid-fast bacilli stain were negative, as were cultures for bacteria and fungi. Polymerase chain reaction (PCR) for herpes simplex virus-type 1 (HSV-1) from the CSF was positive. Re-evaluation of her brain MRI scan that was conducted 3 weeks earlier revealed the presence of a 0.75 cm gadolinium-enhancing lesion in the medulla (Figure). No mass effect was noted. Testing for HIV was negative. A repeat brain MRI scan was not performed.

**Treatment**

The patient was treated with acyclovir intravenously for 2 weeks. Her clinical condition improved, and nausea and vomiting dissipated. She became alert but required tracheostomy to control oral secretions. She was able to communicate verbally. At the time of hospital discharge, the patient had residual neurologic deficits that included severe imbalance and dysphagia necessitating a gastrostomy tube for enteral feeding. She was discharged to a rehabilitation facility.

**DISCUSSION**

**Differential Diagnosis of Nausea and Emesis**

The differential diagnosis of nausea and emesis is extensive.2 Besides primary GI disorders, intractable emesis can be associated with medications and chemotherapy, pregnancy, psychiatric disorders, endocrine disturbances, and central nervous system disorders. Adverse reactions to medication are among the most common etiologies. Chemotherapeutic, analgesic, cardiovascular, antibiotic, anti-Parkinsonian, and anticonvulsant drugs can produce nausea with or without emesis.

GI and systemic infections are another frequent cause. Acute enteric illness resulting in emesis is most prevalent in children less than age 3 years but can occur at any age.2 Bacterial infections with *Staphylococcus aureus*, *Salmonella* species, *Bacillus cereus*, and *Clostridium perfringens* also produce nausea and emesis, in many cases via toxins that act on the brainstem.2

Disorders of the gut and peritoneum constitute a common group of conditions that are associated with nausea and emesis. Examples of these disorders include obstruction of the small intestine, gastric outlet...
obstruction, gastroparesis, chronic intestinal pseudo-
obstruction, pancreatitis, cholecystitis, and appendicitis.

Endocrinologic and metabolic causes of nausea and
emesis include uremia, diabetic ketoacidosis, hyper-
parathyroidism, hyperthyroidism, and Addison disease. 
Activation of the area postrema in the medulla has 
been postulated as an underlying pathogenetic mecha-
nism for emesis in patients with uremia or diabetic 
ketoadacidosis. In thyroid and parathyroid diseases, di-
ruption of normal GI motor activity is thought to in-
duce nausea and emesis.2

Emesis is common during the first trimester of preg-
nancy, with 70% of women experiencing this symp-
tom.2 These symptoms peak in the ninth week of preg-
nancy, with a mean onset of symptoms at 39 days after 
the last menses and a mean cessation at 84 days after 
the last menses.3 Emesis usually is not harmful to the
fetus or the mother. Intractable emesis during preg-
nancy, hyperemesis gravidarum, occurs in 1% to 5% of 
pregnancies2 and can produce dangerous fluid and 
electrolyte disturbances.

Psychiatric disorders associated with emesis include 
psychogenic vomiting, depression, anorexia nervosa, 
and bulimia nervosa. Central nervous system conditions 
that increase intracranial pressure can produce vomiting 
with or without nausea. These include intracerebral 
hemorrhage, subarachnoid hemorrhage, subdural and 
epidural hematomas, meningitis, hydrocephalus, brain 
neoplasms, and large infarctions. Labyrinthine disorders 
and lesions affecting the brainstem can stimulate activa-
tion of emesis pathways in the brainstem.

**Herpes Simplex Encephalitis**

HSV is the most common etiology of sporadic en-
cephalitis in immunocompetent adults in the United 
States,4,5 with an estimated incidence of between 1 in 
250,000 and 1 in 1 million persons per year.5 Most 
cases of HSV encephalitis in adults are caused by 
HSV-1. Only 6% to 15% of encephalitis cases in adults 
are caused by HSV-2.6 Early in the course of HSV 
encephalitis, the symptoms most often reported consist 
of fever, malaise, and headache.2 If untreated, these 
symptoms progress to personality change, depressed 
level of consciousness, generalized or focal seizures, 
and focal neurologic deficits such as aphasia and hemi-
paresis. In untreated patients, symptoms often take 2 to 
3 weeks to reach maximal severity.7

Diagnostic tests that aid in the diagnosis of HSV-1 
encephalitis are brain neuroimaging, EEG, and exami-
nation of CSF. MRI scan is the imaging test of choice. 
The classic abnormalities seen on MRI are high-signal 
lesions on T2-weighted images in the medial and the 
inferior temporal lobes.9 Infrequently, the MRI scan is 
shows no abnormalities.

A distinctive EEG pattern is seen in two thirds of 
pathologically proven cases.9 This pattern consists of 
unilateral or bilateral complexes of sharp waves or 
sharply contoured slow waves that repeat at regular 
1 to 5 second intervals. These discharges usually are 
seen over the temporal areas.

Although there are no CSF characteristics that are 
considered pathognomonic, the fluid is abnormal in 
most cases. CSF examination often reveals a lymphocy-
tic pleocytosis of 5 to 500 cells/mm³, a slight to moder-
ate elevation of the protein concentration, and a nor-
mal or slightly decreased glucose level.8 Erythrocytes or 
xanthochromia may be present, and the presence of 
either helps to distinguish HSV encephalitis from 
other forms of encephalitis. In approximately 10% of 
cases, the CSF is normal.9 Viral cultures for HSV are 
positive in only a small number of patients.9,10

The application of the PCR technique to detect 
nucleic acid in CSF has facilitated the diagnosis of HSV 
encephalitis. Compared with brain biopsy, the sensitiv-
ity of HSV-1 PCR is more than 95% and the specificity 
approaches 100%;11,12 however, the sensitivity declines 
if antiviral treatment has been given for longer than 
1 week.13

**HSV brainstem encephalitis.** HSV encephalitis typi-
cally involves cerebral tissue, particularly the temporal 
lobes and the inferior portion of the frontal lobes.8 How-
ever, the infection sometimes can involve the brainstem 
exclusively or predominantly.14–18 HSV brainstem en-
cephalitis is caused mainly by HSV-1; although, HSV-2 
also has been reported as a cause.18,19

In brainstem HSV encephalitis, the neurologic 
examination reveals findings consistent with brainstem 
dysfunction. The case patient had clinical evidence of 
multifocal brainstem involvement. Specifically, signs of 
left pontine injury were demonstrated by left peripher-
al cranial nerve VII involvement, impaired ability to 
look left, right hemiparesis, and ocular bobbing. Med-
dullary dysfunction was suggested by a loss of gag 
reflex and intractable nausea and vomiting.

**Treatment of HSV encephalitis.** The recommended 
treatment for herpes simplex encephalitis is intra-
venous acyclovir, given at a dosage of 10 mg/kg body 
weight every 8 hours for 2 to 3 weeks.8 Because untreat-
ed HSV encephalitis is associated with a mortality rate 
higher than 70%,20 intravenous acyclovir should be 
started when there is clinical suspicion of encephalitis. 
Clinicians should not delay treatment until the PCR 
result is available.

Acyclovir generally is safe, but rarely it can cause
renal dysfunction or skin rash. In patients with renal impairment, the dosing interval must be lengthened.

**Neural Circuitry of Emesis**

The neural circuitry underlying emesis resides in the medulla. The afferent component of the circuitry is located in the dorsomedial medulla. Chemosensitive receptors are located in the area postrema. Capillaries within the area postrema are fenestrated, placing these chemoreceptors outside of the blood-brain barrier. The chemoreceptors detect emetic agents in circulating blood. These receptors relay their information to the adjacent nucleus tractus solitarius (NTS). The NTS also receives abdominal vagal afferent nerves that detect intestinal luminal contents and gastric tone. Neurons from the NTS project rostrally within the medulla to the central pattern generator, which coordinates the sequence of motor and autonomic behaviors during emesis through its connections with motor and autonomic nuclei in the medulla. The case patient’s MRI scan, conducted at the time when her symptoms were primarily nausea and vomiting, demonstrated encephalitic involvement of the dorsomedial medulla. The NTS is located in this portion of the medulla. Presumably, the case patient’s intractable nausea and emesis was produced by dysfunction of this nucleus.

**CONCLUSION**

In the case patient, protracted nausea and emesis were a symptom of lower brainstem dysfunction. The isolated, protracted nature of these symptoms prompted an extensive GI evaluation and contributed to the delay in making the diagnosis of HSV brainstem encephalitis. Abnormalities found on esophageal-gastro-duodenoscopy conducted at our facility were likely secondary to repetitive vomiting and were not the primary cause of her nausea and emesis. Clinicians must remember that nausea and emesis may be the initial symptoms of conditions unrelated to the GI tract. Neurologic causes, including brainstem HSV encephalitis, should be included in the differential diagnosis of intractable nausea and emesis.

**REFERENCES**