Herpes Brainstem Encephalitis: A Cause of Intractable Emesis

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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, esophagogastroduodenoscopy, 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 mEg/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.

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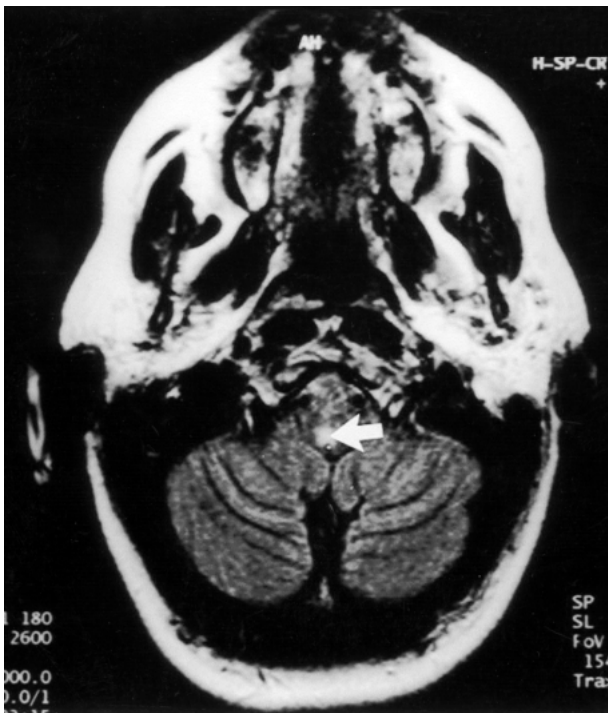

Figure. Magnetic resonance axial image (T1-weighted, gadolinium-enhanced) of the lower brainstem of the case patient demonstrating a small, enhanced region (*arrow*) involving the dorsomedial medulla.

Electrocardiogram showed normal sinus rhythm, and chest radiograph was normal. A repeat esophagogastroduodenoscopy 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, ocular 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/mm^3, 15 leukocytes/mm^3 (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. Reevaluation 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, hyperparathyroidism, hyperthyroidism, and Addison disease. Activation of the area postrema in the medulla has been postulated as an underlying pathogenetic mechanism for emesis in patients with uremia or diabetic ketoacidosis. In thyroid and parathyroid diseases, disruption of normal GI motor activity is thought to induce nausea and emesis.[2]

Emesis is common during the first trimester of pregnancy, with 70% of women experiencing this symptom.[2] These symptoms peak in the ninth week of pregnancy, 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 pregnancy, hyperemesis gravidarum, occurs in 1% to 5% of pregnancies[2] 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 activation of emesis pathways in the brainstem.

Herpes Simplex Encephalitis

HSV is the most common etiology of sporadic encephalitis 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.[5] If untreated, these symptoms progress to personality change, depressed level of consciousness, generalized or focal seizures, and focal neurologic deficits such as aphasia and hemiparesis. 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 examination 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.[8] 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 lymphocytic pleocytosis of 5 to 500 cells/mm^3, a slight to moderate elevation of the protein concentration, and a normal 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.[10] Viral cultures for HSV are positive in only a small number of patients.[8,10]

The application of the PCR technique to detect nucleic acid in CSF has facilitated the diagnosis of HSV encephalitis. Compared with brain biopsy, the sensitivity 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 typically involves cerebral tissue, particularly the temporal lobes and the inferior portion of the frontal lobes.[8] However, the infection sometimes can involve the brainstem exclusively or predominantly.[14–18] HSV brainstem encephalitis 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 peripheral cranial nerve VII involvement, impaired ability to look left, right hemiparesis, and ocular bobbing. Medullary 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 intravenous acyclovir, given at a dosage of 10 mg/kg body weight every 8 hours for 2 to 3 weeks.[8] Because untreated 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.[2] 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 solitarus (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 esophagogastroduodenoscopy 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. **HP**

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