Clinical Reasoning: A 61-year-old man with conjugate gaze deviation, hemiparesis, and asymmetric reflexes

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SECTION 1

A 61-year-old man with a history of alcoholic cirrhosis was transferred from an outside hospital for spontaneous bacterial peritonitis, septic shock, and respiratory failure after intubation. The patient was initially on sedation; however, more than 48 hours after the sedative was discontinued, his mental status remained depressed and he also developed new onset of conjugate rightward gaze deviation. On neurologic examination, the patient was unresponsive to verbal stimuli and sternal rub. He could not follow any command, including closing or opening eyes and squeezing hands. He had remarkable conjugate, forced eye deviation that could not be corrected to cross the midline using the vestibulo-ocular reflex. Corneal and gag

reflexes were preserved. He blinked to visual threat less on the left side, had no clear facial asymmetry, and withdrew on his right arm and knees but had a flaccid left arm. His reflexes were brisker on the left biceps and brachioradialis, and the other deep tendon reflexes were absent. His plantar reflex was up-going on the left side and downgoing on the right side. CT of the head had no significant findings.

Questions for consideration:

1. Based on the clinical presentation and neurologic examination, what are the differential diagnoses?
2. What would be the most important test to order for the next step?
3. What would be the second test considered to order if the first test result is negative?

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SECTION 2

MRI of the brain and magnetic resonance angiography of the head and neck revealed no acute or subacute infarct or significant stenosis (figure 1, A–E; figure e-1, A–H at Neurology.org). Continuous EEG was then recorded, which showed diffuse background slowing without epileptiform discharges (figure 1F) while the patient's gaze remained forcefully deviated to the right side

and other neurologic examinations were also unchanged.

Questions for consideration:

1. What are the differential diagnoses now?
2. What would you do next in terms of managing the top differential diagnosis, while the treatment can also yield a diagnostic value?

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Figure 1 Brain MRI and EEG

Axial FLAIR brain MRI shows hyperintense signal within the bilateral mammillary bodies and periaqueductal gray matter (A). There are no signal changes within the right MCA territory on axial FLAIR (B–E) to suggest acute hemorrhage or infarction. Continuous EEG (F) shows diffuse background slowing. There is no focal slowing or attenuation of fast frequencies, epileptiform discharges, or ongoing seizures, while the patient's neurologic examination remains unchanged, including continuous right gaze deviation. FLAIR = fluid-attenuated inversion recovery; MCA = middle cerebral artery.

SECTION 3

Because of the unrevealing findings of neuroimaging and EEG, Wernicke encephalopathy (WE) was then suspected in this critically ill patient with a highly consumptive state in the setting of active infection and alcoholic cirrhosis. Thiamine 500 mg IV 3 times a day was then started. After 2 days of repletion, the patient became awake, started to track examiners' face around the room, nodded when his name was called, and moved his upper extremities spontaneously, although still not able to verbalize and follow commands. Additional review of brain MRI demonstrates hyperintense signal within the periaqueductal gray matter and bilateral mammillary bodies on fluid-attenuated inversion recovery (FLAIR) images. The whole-blood thiamine level tested before the initiation of repletion was 80 nmol/L (normal range: 70–180 nmol/L). Continuous EEG still showed generalized slowing without seizures. Thiamine replacement was then changed to 250 mg daily on the third day. However, despite improvement of neurologic symptoms and signs, the patient developed upper gastrointestinal tract bleeding on the fourth day of thiamine repletion. Repetitive blood transfusion was required. The patient eventually died 2 days after the bleeding event.

DISCUSSION Sustained conjugate deviation of the eyes can be caused by an ipsilateral destructive or a contralateral irritative lesion involving prefrontal eye field of the cortex. It could also be a result of a destructive lesion involving contralateral paramedian pontine reticular formation. Lesion involving the middle cerebral artery territory, including temporal and parietal lobes, usually leads to contralateral, partial, or complete hemianopia, depending on the size of the lesion. Our patient presented with persistent conjugate rightward gaze deviation, left partial hemianopia, left arm weakness, and increased deep tendon reflex as well as positive Babinski reflex on the left side. If ischemic stroke, hemorrhagic stroke, and seizure disorder could be ruled out, diseases that would lead to abnormal extraocular movement (EOM) should be broadly considered as the differential diagnoses, including WE.

The classic triad of WE contains altered mental status, cerebellar ataxia, and ophthalmoplegia. Neuroimaging can be helpful in the confirmation or diagnosis of WE. Brain MRI is more sensitive than CT in the evaluation of neuroradiologic changes related to WE. The typical MRI findings include FLAIR and T2 hyperintensity of the bilateral medial thalami, periaqueductal gray, mammillary bodies, inferior colliculi, and pontine tegmentum.¹ Other lesion sites, including the frontal cortex, lentiform nucleus, cerebellar cortex, and superior vermis of the cerebellum, were also reported in a study retrospectively reviewing

autopsy-proven WE.² Because the sensitivity of head CT and brain MRI in diagnosing WE is only approximately 10% and 50%, respectively,² negative or atypical neuroimaging findings should not exclude the diagnosis of WE.

It is not uncommon for patients with WE to demonstrate part of the classic triad—only less than one-third of patients with WE would have full presentation.^{1,2} Although altered mental status commonly occurred in at least 92% of the autopsy-proven WE, abnormal EOM was observed in only 50% of WE.² The deranged EOM varies from typical bilateral cranial nerve VI palsies to conjugate gaze paresis, horizontal, or vertical nystagmus.¹ Less common ocular findings include anisocoria, diminished pupillary reflex, papilledema, and visual field defect such as central scotoma.^{1,3} As WE lesions could exist in atypical sites, histopathologic changes of the visual pathway, including optic nerve, chiasm, radiation, and the occipital cortex, could possibly serve as the explanation of the visual field defects. The visual field defect in WE is typically more acute than other toxic-metabolic optic neuropathy and could be rapidly reversed after thiamine repletion.³ Right hemiparesis in the upper motor neuron pattern was previously reported in a patient with WE whose MRI showed a left precentral gyrus lesion.⁴ Hemiparesis and change of deep tendon reflex, including hyperreflexia and hyporeflexia, are the neurologic signs to be expected according to the findings of a clinicopathologic study comprising 28 autopsy-proven WE cases.⁵

Thiamine deficiency has been claimed as the contributing factor of WE.¹ However, WE is a clinical diagnosis; the whole-blood thiamine level measured by high-performance liquid chromatography should be considered as a supportive evidence to diagnose instead of a laboratory test to exclude WE. The sensitivity and specificity of these blood tests remain unclear in symptomatic patients with WE because blood level might not accurately represent the thiamine level of the brain.⁶ The whole-blood thiamine level of our patient was low normal. As normal neuroimaging, a normal blood thiamine level does not exclude the possibility of WE. Parenteral thiamine 500 mg is recommended to be given IV over 30 minutes, 3 times daily for 2 days consecutively and 250 mg IV or IM once daily for 5 days.⁷ Of interest, change of EOM, including conjugate⁸ and reversible periodic alternating gaze deviation,⁹ was reported in hepatic encephalopathy. The toxic-metabolic state that alternates the brainstem tegmental function and the hemispheric structure were taken as the presumable etiology. Our patient had been on rifaximin and lactulose before the onset of neurologic symptoms, which makes the culprit of neurologic findings as hepatic encephalopathy less likely.

AUTHOR CONTRIBUTIONS

Dr. Chi-Ying Lin: study concept, acquisition of data, analysis and interpretation, and revision of the manuscript. Dr. Ji Yeoun Yoo and Dr. Amish Doshi: acquisition of data, analysis and interpretation, and critical revision of the manuscript. Dr. Rachel Colman: study concept, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content, and study supervision.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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