Thiamine Deficiency Presenting as Intraventricular Hemorrhage

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Case Description
A 48-year-old man with hypertension, coronary artery disease, and obesity presented with a 6-week history of nausea, vomiting, decreased oral intake with 40-pound weight loss, and lethargy. Laboratory results were significant for low platelet count of 71,000 per mm$^3$, slight elevation of prothrombin time/partial thromboplastin time and international normalized ratio acute kidney injury, and mild elevation of transaminases. Initial computed tomography of the head was unremarkable for acute intracranial findings (Figure [A]). Lumbar puncture revealed elevated opening pressure of 41 mmHg but otherwise normal cerebrospinal fluid studies. After fluid repletion with D5 normal saline, there was a gradual decline in the patient’s mental status requiring endotracheal intubation for airway protection. Repeat computed tomography of the head 3 days after initial presentation showed bilateral thalamic hemorrhage with extension into the third ventricle (Figure [B]). Brain magnetic resonance imaging (MRI) showed increased T2 flair signal at the medial thalami (Figure [C]), peri-aqueductal region of midbrain, and the mammillary bodies (Figure [D]). Initial management included blood pressure control, platelet transfusion, fresh frozen plasma administration, and external ventricular drain placement. Digital subtraction angiography showed no evidence of underlying vascular anomaly. Computed tomography scan of the abdomen showed splenic enlargement and liver cirrhosis likely accounting for the elevated transaminases, mild coagulopathy, and low platelet level. The patient continued to be obtunded, requiring mechanical ventilation and vasopressors. Metabolic workup was notable for a thiamine level of 37 μg/dL (normal reference range: 78–185 μg/dL). Additional management included thiamine repletion and lactulose. Three days later, the patient was able to be weaned off vasopressor support and extubated after 5 days. His platelet count, coagulation studies, and transaminases normalized over time. His mental status and neurological function slowly improved during the course of his hospitalization. The patient was eventually discharged to rehab with short-term memory deficits.

Discussion
Wernicke encephalopathy (WE) is a medical emergency caused by thiamine deficiency. Severe neurological deficits and even death might result if this condition is left untreated. WE was initially reported by Carl Wernicke in 1881 as superior acute hemorrhagic polioencephalitis” in 2 men with alcoholism and in a woman affected by pyloric stenosis, whereas the association of WE with thiamine deficiency was first suspected in the 1940s.1 Alcoholism is the best known WE risk factor. Alcoholics can encounter thiamine deficiency because of a combination of inadequate dietary intake, reduced gastrointestinal absorption, decreased hepatic storage, and impaired utilization. WE is also common in several other malnourished populations, such as patients who undergo cancer chemotherapy or bariatric surgery and have anorexia nervosa, hyperemesis gravidarum, or other severe gastrointestinal illness. Those with nutritional deficiency susceptibility such as elderly patients can also develop thiamine deficiency and subsequent WE. Patients who develop refeeding syndrome, thyrotoxicosis, and hypomagnesemia are reported to be at risk as well.2 It is crucial to recognize and treat this disease early with thiamine. If WE remains untreated, it will result in Korsakoff syndrome, which is a permanent state of amnesia characterized by inability to form new episodic memories with progression to coma and death in extreme cases.3

In a cohort of 43 WE cases, 60% had different types of intracranial hemorrhages; of which, only 16% were grossly identifiable.4 Autopsy studies revealed a higher prevalence of WE lesions (0.8–2.8%) than is predicted by clinical studies (0.04–0.13%).5 Majority of affected population in the western world are men with underlying alcoholism.

Carl Wernicke described the presence of altered consciousness, ocular signs, and ataxia as the classical triad of symptoms in patients presenting with WE.4 WE is often underdiagnosed since only one third of patients carry all features of the clinical triad. The most common symptom is mental status abnormality which is usually found in 82% of patients with WE, other symptoms are less common: ocular...
abnormalities, 29%; ataxia, 23%; and polyneuropathy, 11%.² Ataxia often precedes other symptoms by a few days or weeks. Horizontal gaze-evoked nystagmus is the most common ocular finding. Bilateral lateral rectus palsies and miosis can be present as well. Gait ataxia is predominantly caused by a combination of polyneuropathy, cerebellar involvement, and vestibular dysfunction. Hypothermia has been reported in 1% to 4% with posterior and posterolateral hypothalamic WE lesions.²

Metabolic rate highly influences body requirement of thiamine which is essential in cellular metabolism and cerebral energy utilization due to its role as a cofactor in the oxidation of glucose. Thiamine is converted to thiamine pyrophosphate in neuronal and glial cells. This enzyme is necessary for several biochemical pathways in the brain, such as intermediate carbohydrate and lipid metabolism as well as production of amino acids and glucose-derived neurotransmitter.³ As a result, the greatest times of thiamine need are usually during periods of high metabolic demand and high glucose intake.³ This likely explains the observation that WE is precipitated in susceptible patients by administration of intravenous glucose before thiamine supplementation. Thiamine stores in the body are only sufficient for ≤18 days. Therefore, it has been proposed that in regions with high turnover, thiamine deficiency results in neuronal injury within 2 to 3 weeks.³⁻⁵ In the acute phase, vascular congestion, microglial proliferation, and petechial hemorrhages are demonstrated in WE lesions. Lactate production subsequently increases in both neurons and astrocytes. Consequently, there is focal acidosis and intracellular oxidative stress resulting in increased free radicals, cytokines production, and loss of osmotic gradients across cell membranes with cytotoxic edema.³ Chronically, there is demyelination, gliosis, and loss of neuropil with relative preservation of neurons.² Atrophy of the mammillary bodies is a highly specific finding in chronic WE and Korsakoff syndrome; it is present in up to 80% of cases.³

T2 flair hyperintensities and enhancement of medial thalami, mammillary bodies, and periaqueductal gray matter are typically seen on brain MRI. Atypical MRI findings have been reported in the cerebellum, vermis of cerebellum, cranial nerve nuclei, red nuclei, dentate nuclei, caudate nuclei, splenium, and cerebral cortex.⁷ Petechial periventricular hemorrhages can be found in 20% of WE. Intraventricular hemorrhage (IVH) in the third ventricle and quadrigeminal cisterns has been reported in rare cases.⁸ Rapid thiamine depletion in patients with nutritional deficiency associated WE seems to lead to larger intracerebral hemorrhages often with IVH. Prognosis is often worse.⁸

**Figure.** A, Computed tomography (CT) of the head on admission revealed no acute process (A) but after the patient developed somnolence, a repeat CT head showed bilateral thalamic hemorrhage extending into the third ventricle and toward foramen of Monroe (B). Brain magnetic resonance imaging T2 flair showing hyperintense signal in the medial thalami (C) and midbrain in the periaqueductal region (D).
There may be a correlation with coagulopathy or associated bleeding diatheses such as renal or hepatic disease, but these features are not present in all patients.4

IVH most commonly occurs as a secondary phenomenon when parenchymal or intracerebral hemorrhage ruptures into the ventricular space or when subarachnoid hemorrhage extends into the ventricles. Forty percent of intracerebral hemorrhage and 10% of subarachnoid hemorrhage can be complicated by IVH. Isolated IVH is rarely caused by traumatic brain injury without subarachnoid hemorrhage. Other causes of IVH include: intraventricular tumors (papilloma, neurocytoma, meningioma, metastases, astrocytoma, and ependymoma), intraventricular aneurysms developing within the distal lenticulostrate or choroidal, aneurysms of the anterior communicating artery, posterior inferior cerebellar artery, or basilar tip rupture into the ventricles without other obvious subarachnoid hemorrhage. Coagulopathies, pituitary apoplexy, sympathomimetic abuse, vasculitis, or fibromuscular dysplasia can also be attributed to IVH. Twenty to 50% can remain cryptogenic.9 IVH usually contributes to morbidity in 1 of 2 ways. First, the blood clot itself may block the narrow cerebrospinal fluid flow, which leads to obstructive hydrocephalus and subsequent fatality if not properly treated. Second, break down of blood products initiates an inflammatory response that may occlude the arachnoid granulations resulting in a delayed communicating hydrocephalus.

After confirming the presence of IVH with a noncontrast computed tomography of the head, other neuroimaging tools are essential to define the secondary cause of IVH. These include MRI/magnetic resonance angiogram to rule out ischemic infarct or vascular anomaly. If these studies are unrevealing, other neuroimaging tools like conventional computed tomography of the head, other neuroimaging tools like conventional computed tomography of the head, and magnetic resonance imaging/magnetic resonance angiogram should be obtained and followed up regularly. If the cause remains undetermined, reimaging patients after the reabsorption of blood products in 1 to 2 months using contrast MRI and possibly catheter angiography is recommended.9

Parenteral thiamine administration remains the treatment of choice for WE. Thiamine 500 mg IV should be infused for 30 minutes TID for 2 consecutive days, followed by 250 mg IV daily for 3 to 5 days. It should be administered before any glucose is given to prevent worsening of thiamine deficiency. Oral administration is an unreliable initial treatment method given alcoholic and malnourished patients have variable gastrointestinal absorption. After that, patients should be continued on thiamine 100 mg by mouth daily until they are no longer considered at risk.2 Intravenous multivitamins, 2 mEq/kg magnesium, fluid and electrolyte replacement are also essential in treating WE.2

Disclosures
T.G. Jovin reports ownership interests in Blockade Medical, consulting work with Codman Neurovascular, Neuravi, Silk Road Medical, is an advisory board member with Medtronic, and a Principle Investigator of the Stryker Neurovascular–sponsored Trevo and Medical Management Versus Medical Management Alone in Wake Up and Late Presenting Strokes (DAWN) clinical trial. The other authors report no conflicts.

References

TAKE-HOME POINTS
• Wernicke encephalopathy is a medical emergency; severe neurological deficits including Korsakoff syndrome and even death might result if this condition is left untreated.
• Only one third of patients with Wernicke encephalopathy present with the classical clinical triad (altered consciousness, ocular signs, and ataxia) which likely contributes to delayed recognition.
• Medial thalamus, mammillary bodies, and periaqueductal gray matter T2 hyperintensities are typically seen on brain magnetic resonance imaging. Periventricular and intraventricular hemorrhages are less common.
• Magnetic resonance imaging/magnetic resonance angiogram of the brain and catheter-based angiography should be obtained to exclude secondary etiologies of intraventricular hemorrhage.
• Thiamine administration before glucose correction is critical to prevent precipitation of Wernicke encephalopathy.

Key Words: cerebral hemorrhage ■ cognition disorder ■ diet ■ hospitalization ■ intensive care unit ■ thiamine deficiency
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