Thyrotoxicosis Associated Wernicke's Encephalopathy

James Bonucchi, DO¹, Ihab Hassan, MD¹, Bruno Policeni, MD², and Peter Kaboli, MD, MS^{1,3}

¹Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA, USA; ²Department of Radiology, University of Iowa Carver College of Medicine, Iowa City, IA, USA; ³The Center for Research in the Implementation of Innovative Strategies in Practice (CRIISP) at the Iowa City VA Healthcare System, Iowa City, IA, USA.

BACKGROUND: Wernicke's encephalopathy is a rare disorder resulting from nutrition deficiency in thiamine (vitamin B1). It is most often associated with chronic alcohol abuse. It can accompany other disorders such as hyperemesis gravidarum and hyperthyroidism.

CASE: We present a case of severe Wernicke's encephalopathy that developed in a male non-alcoholic inpatient that was precipitated by poor nutritional intake and development of thyrotoxicosis. It is likely that the hypermetabolic state from thyrotoxicosis contributed to the development of Wernicke's encephalopathy, which was extremely debilitating.

CONCLUSION: Wernicke's encephalopathy is a severe, life-threatening illness that can be a consequence of hyperthyroidism in addition to alcohol abuse and can be easily prevented with appropriate supplementation of thiamine.

KEY WORDS: Wernicke's encephalopathy; thyrotoxicosis; thiamine; hyperthyroidism.

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INTRODUCTION

Wernicke's encephalopathy is a rare neurological disorder initially described in malnourished, alcoholic patients. It is characterized by confusion, ataxia, and nystagmus and is caused by thiamine deficiency. Although early recognition and treatment with thiamine can reverse the symptoms, the mortality rate remains 10–20% due to underdiagnosis. It is frequently not identified until autopsy. The classic triad of confusion, ataxia, and nystagmus are not always presenting symptoms, and it may not be considered in non-alcoholics. Thiamine deficiency can be caused by other medical conditions producing malnourishment including hyperemesis gravidarum, peptic ulcer disease, stomach cancer, gastric bypass, anorexia nervosa, re-feeding after starvation, chronic hemodialysis, and prolonged intravenous feeding. The literature reports 4 cases associated with hyperthyroidism. We present a case of Wernicke's encephalopathy precipitated in a non-

alcoholic, non-pregnant patient by thyrotoxicosis after a period of prolonged starvation. This case emphasizes the need for vitamin supplementation in hypermetabolic patients with prolonged starvation.

CASE PRESENTATION

A 39-year-old man presented to the hospital with a 2-week history of nausea, vomiting, poor oral intake, and 30-lb weight loss but was able to maintain fluid intake despite the nausea and vomiting. He denied abdominal pain, fever, chills, constipation, or diarrhea. He had no chronic medical conditions, and he took no medications. His family history revealed an unspecified gastrointestinal cancer in his father. He was a prison inmate at the time of admission and had been incarcerated for the 2 years prior and denied alcohol intake, illicit drug use, or tobacco use.

On admission he appeared fatigued, but was in no acute distress and appeared to be well-nourished with a weight of 85 kg. His heart rate was 120 with a blood pressure of 129/74 without orthostatic changes. Head and neck exam was normal including no lid lag, orbitopathy, thyromegaly, or thyroid nodules. His lungs were clear, and heart sounds were normal without murmurs. His abdominal exam was remarkable only for being moderately obese. He had no peripheral edema, and his neurological exam was normal.

Laboratory evaluation revealed elevated hepatic transaminase levels with an aspartate aminotransferase (AST) of 100 U/l (0–37 U/l), alanine aminotransferase (ALT) of 107 U/l (0–35 U/l), total bilirubin of 1.4 mg/dl (0.2–1.0 mg/dl), alkaline phosphatase of 124 U/l (40–129 U/l), and gamma-glutamyl transferase (GGT) of 57 U/l (8–61 U/l). Complete blood count was within normal limits with the exception of total white blood cell count elevated to 11,100/mm³ (3,700–10,500/mm³). Electrolytes and renal function tests were within normal limits. Ultrasound of the abdomen was performed and showed stones within the gallbladder and thickening of the gallbladder wall with edema. There was no hepatic duct dilatation, although the gall bladder neck and cystic duct could not be visualized due to shadowing from the gallbladder stones. He was noted to have a positive sonographic Murphy's sign. Computer tomography (CT) scan with contrast of the abdomen was unremarkable.

He was diagnosed with cholecystitis and underwent laparoscopic cholecystectomy with subsequent improvement in his liver test abnormalities. His symptoms, however, persisted, and the AST, ALT, and total bilirubin began to increase over 6 days. Due to concern for a retained gallstone, endoscopic retrograde cholangio-pancreatography (ERCP) was performed with sphincterotomy and drainage of debris. Examination of

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the gastric mucosa revealed mild gastritis which was treated with a proton-pump inhibitor. The patient's symptoms improved very slowly. He had minimal oral intake for the first 2 weeks of his hospital stay and developed intermittent orthostatic symptoms, which were treated with intravenous hydration. He did not receive parental nutrition or oral vitamins.

His liver tests again began to normalize, and no objective cause of his nausea was found. The neurology and psychiatry services were consulted due to suspicion of malingering to avoid returning to prison. Magnetic resonance imaging (MRI) was performed of his brain and was normal (Fig. 1). Although the patient denied any secondary gain from remaining in the hospital, the primary team and consultants concluded that his symptoms could be explained by malingering as no organic etiology could be found.

After 21 days of hospitalization, the patient and the physician team concluded he could return to the prison infirmary to continue his convalescence. The afternoon he returned to prison, he developed acute confusion and somnolence. He was transferred back to the hospital and was found to have a heart rate of 150. His neurological exam was significant for delirium and nystagmus. CT scan of his brain and lumbar puncture were both normal. The thyroid-stimulating hormone was found to be 0.01 IU/ml (0.27–4.20 IU/ml) with a free thyroxine of 7.62 ng/dl (0.93–1.70 ng/dl) and free triiodothyronine of 17.47 pg/ml (2.57–4.43 pg/ml).

He was treated with propylthiouracil, prednisone, iodine, and propranolol. His tachycardia and free thyroxine normalized over the course of several days, but his mental status continued to deteriorate. Repeat brain MRI (8 days after the previous brain MRI) showed bilateral abnormal symmetric hyperintensity of the mammillary bodies, fornix, medial thalami, peri-aqueductal midbrain, superior vermis, and bilateral pre-central gyri, consistent with Wernicke's encephalopathy (Fig. 2a–c). Measured serum thiamine was 0.7 µg/dl (1.6–4.0 µg/dl), which supported thiamine deficiency. The patient

Figure 1. Baseline MRI performed before initial discharge back to prison showing no evidence of signal abnormality.

Figure 2. a Follow-up study 8 days after normal MRI (Fig. 1) demonstrates abnormal signal intensity in the thalamus and fornix and is enlarged in the axial FLAIR. b Signal abnormality is demonstrated in the pre-central gyri bilaterally. c Restricted diffusion is identified in the areas of abnormal FLAIR signal.

was started on thiamine and folate supplementation, but he had minimal improvement in his mental status. He remained hospitalized for an additional 11 weeks, and at the time of discharge, required skilled nursing care and suffered significant neurological deficits. Six months later, he continues to be unable to communicate or care for himself.

DISCUSSION

Thiamine is a water soluble vitamin that has a minimal storage pool. Theoretically, it could easily be depleted as its biological half-life is 9–18 days. Its active metabolite is thiamine pyrophosphate, an important coenzyme for carbohydrate metabolism, and energy generation. Prolonged starvation is the common denominator of all conditions associated with Wernicke's encephalopathy in the literature.^{1–5} The encephalopathy is usually precipitated by a carbohydrate load, whether with nasogastric feeding, intravenous administration of dextrose, or total parenteral nutrition. Although our patient did not receive parental nutrition, he did receive dextrose containing intravenous fluids during his hospitalization.

The higher incidence of Wernicke's encephalopathy in alcoholics is due to alcohol interfering with active gastrointestinal transport of thiamine. In chronic liver disease, activation of thiamine pyrophosphate from thiamine is decreased, and the capacity of the liver to store thiamine is diminished.¹

Alcohol, however, is not the only risk factor associated with Wernicke's encephalopathy. In 1 series, 50% of patients who were diagnosed with Wernicke's encephalopathy either clinically on autopsy had no history of alcohol abuse.⁶ The non-alcoholic patients all had a history of malnutrition with low serum albumin.⁶ Hyperemesis gravidarum and diabetic ketoacidosis with administration of intravenous glucose has also been associated with the development of Wernicke's encephalopathy.⁷

Our patient presented with a history of only 2 weeks of vomiting and weight loss, followed by a 21-day hospital stay with minimal oral intake leading to depletion of his thiamine stores. At the time of hospitalization, he likely had subclinical hyperthyroidism, which developed into thyrotoxicosis during hospitalization as a result of iodinated intravenous contrast, referred to as the Jod-Basedow phenomenon. This hypermetabolic state likely accelerated the depletion of his thiamine stores and precipitated the encephalopathy. This has been reported 4 previous times in the published literature.^{8–11} Neither malnourishment nor thyrotoxicosis alone should cause Wernicke's encephalopathy; however, together, they augmented the depletion of thiamine.

It is known that thyroid hormone stimulates oxidative metabolism and ATP utilization which induces the upregulation of the Krebs cycle.¹² Thiamine is an important coenzyme for pyruvate dehydrogenase, the enzyme converting pyruvate to acetyl CoA in the mitochondria for use in the Krebs cycle, and it is also required by α -ketoglutarate dehydrogenase which is a Krebs cycle enzyme. Without thiamine, the Krebs cycle is ineffective in carbohydrate metabolism. It has been shown in rats that there is an increase in mitochondrial mass in the hyperthyroid state.¹³ Therefore, it is postulated that hyperthyroidism is a hypermetabolic state in which there is increased utilization of thiamine. The hypermetabolic state may precipitate Wernicke's encephalopathy in a patient whose thiamine stores are depleted secondary to prolonged starvation.

The exact mechanism that causes neuron cell death is not well understood. It is postulated that the deficiency in thiamine results in failure of cellular energy generation, focal lactic acidosis, breakdown of the blood brain barrier, and excitotoxic effects from *N*-methyl-D-aspartate receptor activation.¹⁴ It is thought that these cellular effects result in neuron cell death, proliferation of astrocytes, and activation of microglia resulting in the typical symmetric damage in the thalamus, mammillary bodies, cerebellum, and pons seen in Wernicke's encephalopathy.¹⁴

Imaging plays an important role in the diagnosis of Wernicke's encephalopathy, as patients do not always present with the classic clinical findings. MRI is the modality of choice because it has a better contrast resolution than CT and because diffusion-weighted imaging (DWI) may facilitate the diagnosis. MRI has been reported to have a sensitivity of 53% and a specificity of 93%.¹⁵ The absence of imaging abnormalities does not exclude the diagnosis. MRI findings have been correlated with postmortem pathology, where areas of abnormal signal intensity corresponded to edematous change-induced spongy disintegration of the neuropil.¹⁶

The classic imaging findings of Wernicke's encephalopathy are symmetrically abnormal increased fluid attenuation inversion recovery (FLAIR) signal located in the midline around the third ventricle, cerebral aqueduct, floor of the fourth ventricle, and cerebral cortex. The exact mechanism underlying the pathogenesis of the lesions in Wernicke's encephalopathy is incompletely understood, although thiamine is associated with glucose and oxidation metabolism, which is abundant in the peri-ventricular and peri-aqueductal area. Imaging findings are similar for Wernicke's encephalopathy in alcoholic and non-alcoholic patients.

Zhong et al.¹⁷ demonstrated in his article the relationship between imaging findings and the patient clinical outcome. He reported all patients presented with abnormal signal in the peri-aqueductal gray matter. Patients with coma also exhibited abnormal signal in the regions of the medial thalami, the head of the caudate, floor of the fourth ventricle and surrounding the third ventricle. Of the patients with coma, the ones with poorer outcomes also presented with cerebral cortex signal abnormality. DWI abnormalities can also be present, representing cytotoxic edema. This finding does not always represent irreversible lesions.^{18–19}

Our patient demonstrated impressive interval changes in between the studies performed 8 days apart. The first MRI was unremarkable (Fig. 1); however, the follow-up study demonstrated FLAIR hyperintensity in the thalamus, peri-aqueductal gray matter, and floor of the fourth ventricle (Fig. 2a). High FLAIR signal was also identified symmetrically and bilaterally in the pre-central gyri; this finding was described as unusual in the past; however, the current literature considers this a usual finding seen in patients with poor outcomes (Fig. 2b). DWI demonstrated restricted diffusion in all the mentioned regions (Fig. 2c). Enlargement of the fornix associated with abnormal signal was present; this finding is unusual and has not been described in the literature.

This case adds to the existing 4 cases of thyrotoxicosis-induced Wernicke's encephalopathy. Although a rare phenomenon, the consequences to the patient of delayed recognition and treatment can be catastrophic, as in this case. Severe disability can be easily avoided with prompt administration of thiamine, an inexpensive and safe vitamin. Wernicke's en-

cephalopathy can develop suddenly, as was the case with our patient. In this case, the continued tachycardia should have been a clue to another condition needing further evaluation, specifically hyperthyroidism. When patients experience relative malnourishment, thiamine supplementation should be administered, or appropriate use of parenteral and/or enteral nutrition supplements should be initiated. Finally, this case is unique because of the baseline MRI scan only 8 days before the worsening of his symptoms that was normal, with significant abnormality observed in a short period of follow-up.

Thiamine deficiency should be considered in any patient with prolonged starvation regardless of previous history of alcohol intake, especially in patients with untreated hyperthyroidism. In these situations, thiamine supplementation will prevent Wernicke's encephalopathy. One area of particular relevance is in the surgical treatment of obesity, namely, gastric bypass. As more patients undergo these procedures, the incidence of thiamine deficiency will likely increase, as patients are prone to malnourishment and favor diets high in simple sugars due to the malabsorption of protein and fat. Close monitoring in the first few weeks and months postoperatively is advised.⁵

This case underscores the need for supplementation with vitamins before caloric replacement in hospitalized patients with prolonged malnutrition or increased metabolic demands.

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Corresponding Author: James Bonucchi, DO, Department of Internal Medicine, University of Iowa Carver College of Medicine, 200 Hawkins Drive, Iowa City, IA 52242, USA (e-mail: james-bonucchi@uiowa.edu).

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