Thiamine deficiency and wernicke encephalopathy: Are we doing enough?

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Abstract

Wernicke encephalopathy is a neuropsychiatric disorder characterized by a triad of symptoms including: altered mental status, ataxia, and ocular signs. Manifested as petechial hemorrhage and demyelination in the brain due to thiamine deficiency, the current treatment involves repletion of thiamine. There are currently no published guidelines for the treatment of this disease despite its high morbidity and mortality.

We present a case of a 43-year-old Caucasian male with a history significant for chronic alcohol use who presented with altered mental status. His exam revealed nystagmus, a positive Romberg test, and an ataxic gait. He was unable to perform the heal to shin or the finger to nose test. A MRI revealed a positive reversible pulvinar sign, consistent with Wernicke encephalopathy. He was started on Thiamine IM and transitioned to oral therapy. Improvement was initially noted in patient's gait and nystagmus, with eventual improvement in insight and judgement.

Our patient improved with administration of thiamine. Currently, little research exists to suggest an optimal dosage or frequency for the improvement of symptoms, with suggested doses between 200 mg and 500 mg per day. Due to the lack of consensus for dosing, there is a need for large-scale prospective clinical trials to further establish the correct dosage, frequency, and duration of treatment.

Keywords: Wernicke encephalopathy, Thiamine deficiency, Reversible pulvinar sign, Nystagmus, Ataxia, Alcoholism.

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Introduction

Wernicke encephalopathy is a neuropsychiatric disorder first characterized by Carl Wernicke in 1881. He characterized it as a triad of symptoms including: altered mental status, ataxia, and ocular signs (nystagmus and ophthalmoplegia), although this triad is only present in 16-38% of patients [1]. This triad of symptoms is due to the petechial hemorrhage and demyelination within periventricular structures [2]. This damage is a result of thiamine deficiency, as thiamine dependent systems are necessary to prevent cellular damage. Thiamine deficiency may be detected by measuring the erythrocyte thiamine transketolase (ETKA) before and after the administration of thiamine pyrophosphate. The diagnosis of thiamine deficiency is confirmed with a low ETKA and more than 25 percent stimulation after thiamine pyrophosphate administration. However, lacking clear sensitivity and specificity, the level of ETKA may be normal in symptomatic patients, and does not exclude the diagnosis of Wernicke encephalopathy [1]. Current treatment involves thiamine replacement on a clinical rather than laboratory basis as deficiency leads to the disorder.

As death has been reported in 17-20% of patients, determining the optimum treatment regimen for patients exhibiting features of Wernicke encephalopathy is paramount. Among those who survive, 85% will progress to Korsakoff psychosis (a form of memory impairment characterized by anterograde amnesia). Of those with Korsakoff psychosis, 25% will require placement in long-term care [1].

Despite the serious morbidity and mortality of this condition, as well as added healthcare costs due to the need for long term care, there are currently no guidelines for thiamine dosing in the United States.

Case

The patient was a 43-year-old Caucasian male with a past medical history significant for a seizure disorder and noncompliance with therapy who presented to the Emergency Department (ED) due to altered mental status. Patient was unable to provide a history, but per family, the patient had a 1-2-week history of progressive confusion and talking about past events as if they were in the present. He had also been having more seizure episodes, as many as 1-2 per week. Patient had no past surgical history. He was a current every day smoker of ½ a pack a day and a current daily user of alcohol, both beer and liquor. Although his family was unable to quantify the exact amount of alcohol consumed, his family noted him to be inebriated daily for more than one year. He also was a daily user of Marijuana of unknown quantity.

On physical exam, the patient was cachectic and frail appearing. Vitals were within normal limits. He was unable to track objects with his eyes and had to move his entire head. He was alert and oriented to person and place, but not to time. He was unable to perform heel to shin and was unable to complete the finger to nose test. His Romberg test was positive, and he had an ataxic gait. Otherwise, the physical exam was unremarkable.

Laboratory studies revealed a potassium of 3.3, glucose of 154, albumin of 3.3 and a creatine kinase total of 31. Patient was positive for Cannabis on urine drug screen. Labs were otherwise unremarkable. Computed Tomography (CT) scan was performed which showed no acute intracranial abnormality.

After initial evaluation, the patient's mental status change was felt to be related to alcohol abuse and uncontrolled seizures. The patient was admitted for further evaluation. Human Immunodeficiency Virus (HIV) serology, Lyme titer, Rocky Mountain Spotted Fever (RMSF), and Rapid Plasma Reagin (RPR) were negative, and he was restarted on carbamazepine for the seizures. He was placed on a Clinical Institute Withdrawal Assessment (CIWA) protocol with oral thiamine, and his electrolytes were repleted.

On hospital day 2 the patient developed acute psychosis with both visual and auditory hallucinations. Psychiatry was consulted, and he was placed on 1:1 observation. A Magnetic Resonance Imaging (MRI) of the brain revealed an abnormal signal with T2 signal adjacent to the third ventricle in the region of the right and left thalamus extending caudally into the periaqueductal gray matter (Figure 1). The MRI findings, oculomotor abnormalities, cerebellar dysfunction, and altered mental status supported the diagnosis of Wernicke encephalopathy. His thiamine was changed to intramuscular (IM) 100 mg for 7 days before being transitioned to oral (500 mg once and then 100 mg daily), vitamins with folacin, cyanocobalamin, and pyridoxine. Haloperidol was used as needed for agitation.

Approximately one week later, the patient's nystagmus and agitation improved. He became more cooperative and no longer required 1:1 supervision. His mental status improved after several weeks, and he was more oriented. The patient's mobility improved after several weeks and he was able to ambulate ad lib, although he would then wander into other patient's rooms. Despite improvements in mentation, the patient still struggled with insight and judgement which ultimately returned to baseline at his 6 month follow up (he was lost to follow up prior to the 6-month visit). A repeat MRI was not performed due to his clinical improvement, and no residual memory disorder was apparent.

Discussion

Our patient exhibited the classic findings of Wernicke encephalopathy, including dietary deficiency, oculomotor abnormalities, cerebellar dysfunction, and altered mental status.

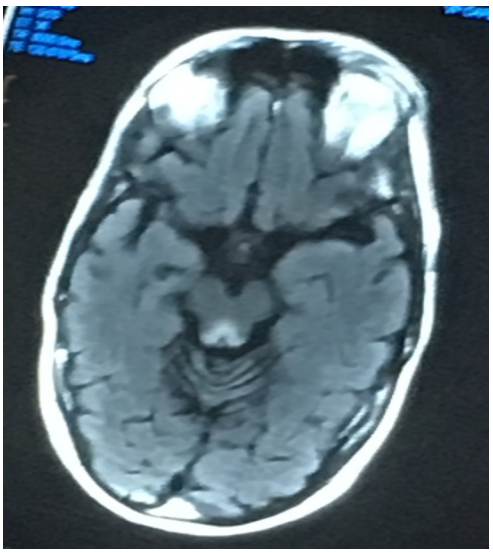

Figure 1. *Reversible Pulvinar Sign.*

We found our patient responded well to the dosing of thiamine administered and ultimately had a complete resolution of the symptoms, arguing against the development of Korsakoff syndrome An ETKA level was not ordered to evaluate for thiamine deficiency, as it was not felt that the result would contribute much to this case.

In reviewing the literature, a wide range of thiamine dosing has been deployed for suspected Wernicke encephalopathy, including doses ranging from 100 mg to 500 mg IM daily. However, there are currently no published guidelines defining thiamine dosing in the setting of alcohol use disorders and prevention/treatment of Wernicke encephalopathy. Based on our experience and review of the literature, it is most important to administer parenteral thiamine as soon as the diagnosis is suspected.

The nutritional requirement for thiamine has been defined as a single 100 mg oral dose daily. However, in healthy individuals, only 4.5 mg of thiamine is absorbed from this dose. In those with alcohol use, the absorption is reduced to one third or less of this; therefore, intravenous (IV) or IM dosing of thiamine is preferred [2].

Due to the lack of guidelines and consensus, dosing is often inadequate. Isenber-Greda et al. performed a retrospective study in the Bronx to look at how well we are doing in the United States at prescribing thiamine in those with alcohol use disorders. They reviewed all adult patients admitted to medicine or surgery who were referred to the addiction psychiatry service for consultations related to alcohol use disorders. Of the 217 patients included, they found that a substantial percentage was not prescribed thiamine and of those who were, 71.5% received the traditional oral dose of 100 mg daily [3].

Even though thiamine is better absorbed parenterally in this situation, very little research exists to suggest an IV or IM dosage or frequency necessary for the improvement of symptoms. In 2013, the Cochrane group performed a systematic review of the literature for randomized control trials. They found two studies, but only one with sufficient data for a quantitative analysis [4]. The Ambrose trial in 2001 assigned 107 participates to one of five different doses of intramuscular thiamine and measured outcomes after 2 days. The trial did find a significant difference favoring a dose of 200 mg/day over a dose of 5 mg/day, but no difference was found between the other doses [5].

Nishimoto et al., in a case series, followed 11 patients from 2010-2013 treated with high dose thiamine (>500 mg IV). They found that 73% of patients displayed symptom resolution or improvement; however, the power of this study was limited due to small sample size [1].

Alim et al. performed a retrospective study in Canada studying adult patients between 2014-2015, who received at least one dose of IV thiamine and whose admission lasted at least 3 days [2]. The study included 141 patients and compared those who received low dose thiamine (less than 100 mg IV daily) and those who received high dose (greater than 100 mg IV daily). They found that patients who received higher dose were more likely to be considered for a diagnosis of Wernicke encephalopathy (46.2% *vs*. 4.3%). However, there was no statistical significant

difference in the time to resolution of symptoms between the high dose and the low dose groups.

While there are currently no guidelines for prescribing in the United States, the Royal College of Physicians in the United Kingdom has published recommendations of 500 mg IV three times daily for 2-3 days. If improvement in symptoms is noted, then the initial dose is to be followed by 250 mg IV daily for the next five days or until no further improvement is observed. After parenteral replacement, the patient should be placed on an oral regimen of 100 mg three times daily for the rest of the hospital stay [6]. These guidelines have been based on clinical practice as randomized control studies have not been conducted to establish dosing.

The various prescribing patterns seen throughout these studies signify the lack of consensus on how to appropriately treat Wernicke encephalopathy and highlight the need for large-scale prospective clinical trials to further establish the correct dosage, frequency, and duration of treatment with IV thiamine [7-11]. Furthermore, based on the likelihood that patients at risk for Wernicke encephalopathy would be placed on an CIWA protocol, it may be beneficial to standardize the CIWA protocol to include daily parenteral treatment with thiamine.

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