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Wernicke Encephalopathy, A Near Miss, in A Chronic Alcoholic Recently Started on Tizanidine; Could There be A Relationship Between Wernicke Encephalopathy and Tizanidine?

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ABSTRACT

Wernicke encephalopathy (WE) is an acute neurologic condition caused by thiamine deficiency. It is characterized by the triad of eye signs, cerebellar signs and altered mental status, though not all patients with WE manifest all the features of the triad. The most common cause of WE are alcohol use disorder. The diagnosis of WE is mostly made by clinical examination with many cases missed by medical personnel during physical examination. Imaging modality of choice is a brain magnetic resonance imaging. In a person deficient in thiamine, WE can be induced by infection, prolonged consumption of carbohydrate and a glucose load. Medications have rarely been reported as precipitating agents. Our case is that of a 55-year-old female with alcohol use disorder (AUD) who presented with syncope after she was recently started on tizanidine. Patient during the course of admission was diagnosed of WE with no obvious inducing factor, suggesting a possible relationship between the newly prescribed tizanidine and the precipitation of WE. The diagnosis of WE would have been missed if the family did not identify that the patient's mental status had significantly changed from baseline. This case shows that physicians have to actively look for WE in all patients with AUD and they also have to involve family members in patient care. This case also calls for more research to be carried out to ascertain if tizanidine could be a possible trigger for WE.

Keywords: Wernicke encephalopathy; Chronic; Tizanidine

INTRODUCTION

Wernicke encephalopathy (WE) is an acute neurological condition attributed to thiamine deficiency, and it is characterized by the clinical trial of nystagmus, ataxia and confusion. However, this classic triad is usually present in only about 16 - 33% of cases[1]. Untreated WE can progress to Korsakoff syndrome (KS) which is distinctively characterized by significant anterograde and retrograde amnesia and confabulation[2]. KS, though a distinct neuropsychiatric disorder, may have overlapping clinical features to WE hence the terminology Wernicke-Korsakoff syndrome (WKS) which has a mortality rate of up to about 20%[3]. WE mostly occur in thiamine deficiency secondary to alcohol use disorder but can also occur in nonalcohol-related thiamine deficiency conditions like severe malnutrition, gastric bypass surgery, hyperemesis gravidarum, prolonged parenteral nutrition, malignancies, immunodeficiency syndromes, liver disease, hyperthyroidism, severe anorexia nervosa, re-feeding after starvation, and even chronic hemodialysis (HD) due to accelerated loss of water-soluble vitamins during HD[1,4]. Common triggers of WE in persons deficient in thiamine are infection, prolonged carbohydrate intake, glucose loading, with one case report also suggesting withdrawal from anabolic steroid[1,3]. We present a case of a female alcoholic who was in her usual state of health until she was brough to the emergency room for a syncopal episode secondary to profound postural hypotension caused by ingesting tizanidine and alcohol. After treatment for alcohol withdrawal syndrome and postural hypotension, she was found to have Wernicke encephalopathy which improved after treatment with thiamine. This diagnosis would have been missed if it were not for the intervention of the family, seeking for an explanation for the patients altered mental status. Also, because symptoms developed after initiating tizanidine, it raises the question if WE can be induced by tizanidine in a chronic alcoholic. This case shows that WE can easily be missed by physicians if it is not actively looked for during physical examination. It also shows how involving family in patient care is very important in diagnosis and also opens up a potential area of research about possible tizanidine involvement in inducing WE.

CASE PRESENTATION

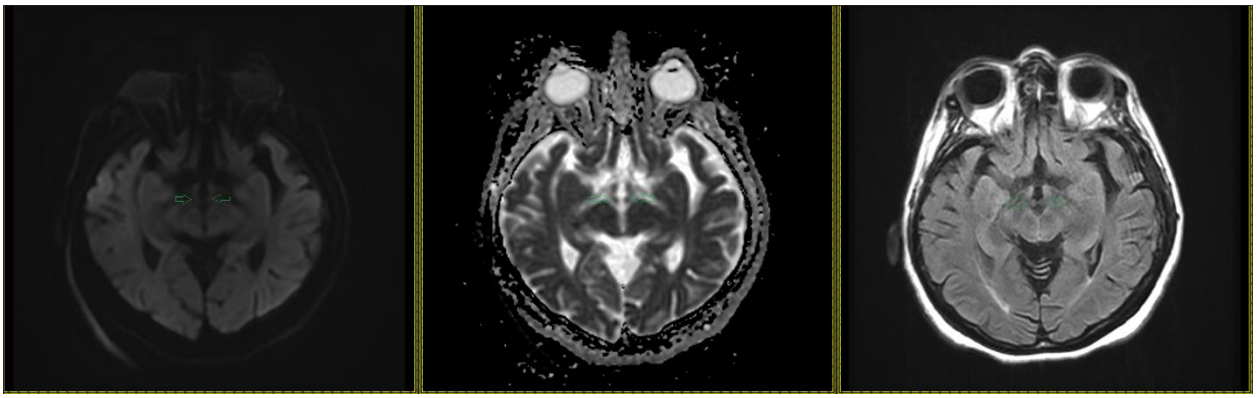
A 55-year-old female was brought to the emergency room after an episode of syncope at a grocery store. Eye witness account confirmed there was no seizure activity. Her daughter reports that patient has not been eating adequately but instead prioritizes drinking alcohol. She drinks alcohol every day and the morning before the syncopal attack, she took her newly prescribed medication with alcohol. Patient has been in her state of health and normal mental status before the present emergency room visit. Patient has a past medical history of alcohol use disorder with many admissions for alcohol withdrawal syndrome. She works as a bartender and was recently diagnosed with sciatica and started on tizanidine 4mg daily. Vital signs on arrival in the emergency room were; blood pressure of 138/76 mmHg, heart rate of 79/minute, respiratory rate of 16 /minute, body mass index of 22.8 Kg/m^2. Physical examination on arriving the emergency room revealed that she was awake, alert and oriented to person, place and time with the rest of the examination being unremarkable.

Relevant laboratory findings revealed a white cell count of 6.5 K/UL, hemoglobin of 10.5 g/dl, mean cell volume of 102.3 fl, sodium of 127 mmol/L, potassium of 3.3 mmol/L, magnesium of 1.21 mg/dl, creatine kinase of 153 U/L, and an alcohol level of 186 mg/dL. The lactic acid was 3.3 mg/dL, ammonia was 30 umol/L, total bilirubin was 0.9 mg/dl, aspartate aminotransferase was 82 U/L, alanine transferase was 36 U/L, folate was >24 ng/ml (after empirical folate supplementation for AUD), vitamin B12 was 703 pg/ml, the urine drug screen was negative and urinalysis was

negative.

Electrocardiogram (EKG) showed normal sinus rhythm with prolonged QTc segment which progressively got shorter during hospitalization. Echocardiogram was normal and chest x-ray showed no acute cardiopulmonary process. Computed tomography showed no acute abnormality and electroencephalography was unremarkable for seizures.
The hospital course was marked by severe alcohol withdrawal requiring initial intensive care unit admission before she was downgraded to the general medical floor. She was treated with chlordiazepoxide which was gradually tapered off with improvement of withdrawal symptoms. She did not receive dextrose infusion during hospitalization. She was placed on a banana bag infusion (contains normal saline, thiamine, folate, magnesium and multivitamins) upon arrival, empirical daily thiamine 100mg for AUD. Five days after admission, patient's withdrawal symptoms had resolved and the medical team had earmarked her for discharge. However, the family remarked and insisted that the patient was confused and forgetful, which has never been the case and they wanted further evaluation for this altered mental status. A neurology consult was obtained and neurological evaluation revealed that the patient was alert and oriented to person and place only. She was cooperative with an intact sensation, muscle tone and power, deep tendon reflexes, speech and language, and she had no focal neurological deficits. However, she had a horizontal bilateral nystagmus and wide-based gait in addition to having periods of confusion and memory deficit. A diagnosis of WE were made and a magnetic resonance imaging of the brain was done but was negative (Figure 1). Thiamine level was not obtained because patient was already on empirical thiamine for many days during the admission and obtaining a level would have not been an accurate representation of the body's thiamine level.

She was treated with intravenous thiamine 500mg daily for 3 days and 250mg for 4 days. Her mental status improved; nystagmus resolved but the wide-based gait persisted before discharge. She was counselled on alcohol cessation and upon discharged, she was to follow up with her neurologist, primary care doctor as well as community alcohol cessation support group.



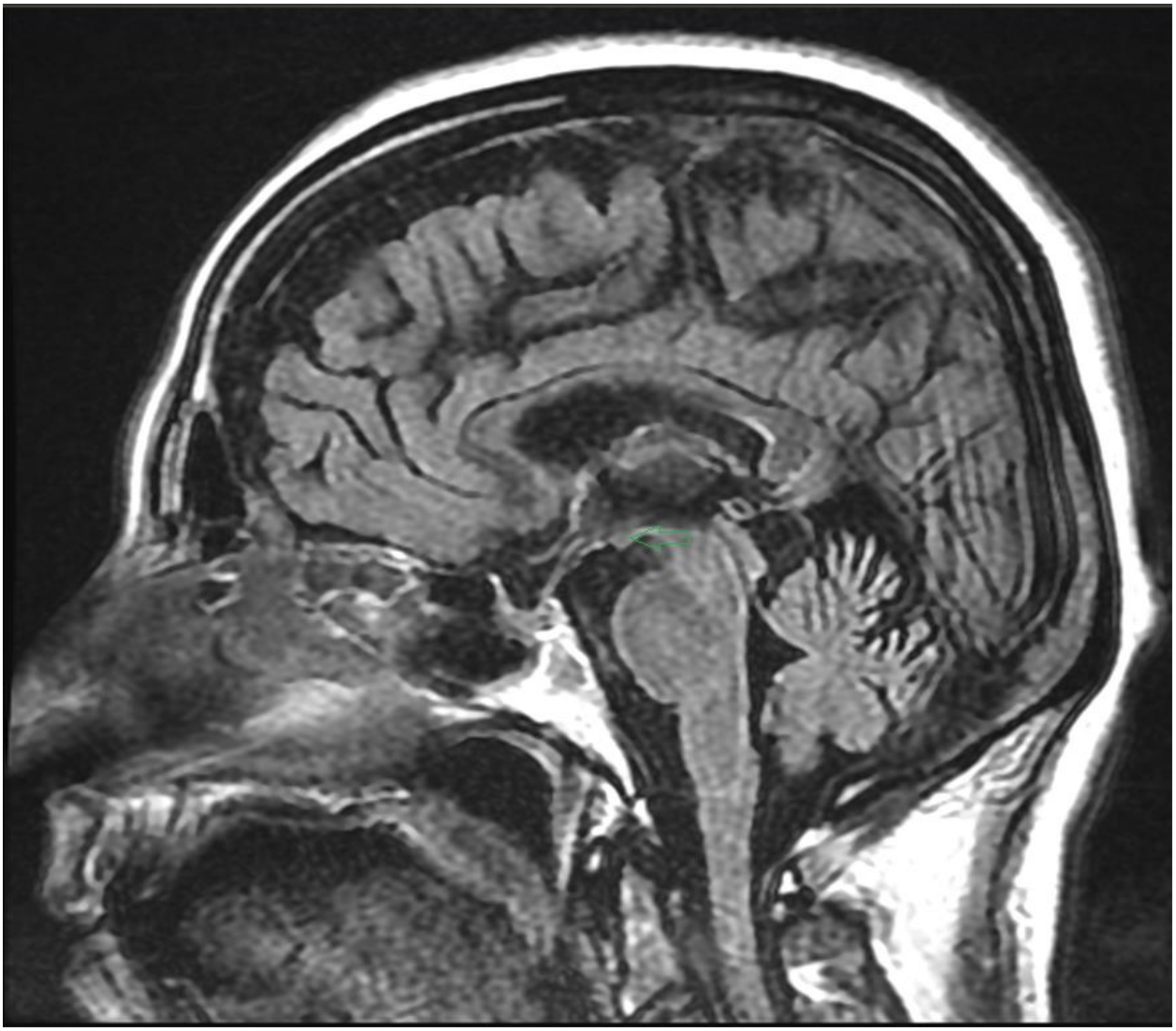


Figure 1: MRI brain showing no diffusion restriction within the mammillary bodies (green arrows). Mild T2 FLAIR hyperintensities noted along the periventricular white matter which may be related to chronic small vessel ischemic disease. No abnormal signal intensity visualized to suggest encephalopathy. Left: Axial Diffuse Weighted Imaging; Middle: Axial Apparent diffusion coefficient; Right: Axial T2 FLAIR, Bottom: T2 FLAIR sagittal.

DISCUSSION

The prevalence of WE according to clinical studies is about 0.04 - 0.13%. This is much lower than the 0·8 - 2·8% on autopsy studies. This gap shows that many WE cases are either overlooked or are missed during physical examination. In fact, about 75 - 80% of autopsy confirmed WE were missed by routine physical examination. Therefore, physicians have to actively look for WE in all patients with AUD presenting to the hospital for whatever reason[5]. Our patient would have also been missed if the family did not insist on obtaining further evaluation for her altered mental status Family member involvement is a very important part of healthcare provision[6]. Family members have good knowledge about the patient's normal habits and behavior and are in a better position to determine when there are changes in their health. This can be exploited by medical personnel to assist in the process of diagnosis and management just like the case of our patient[7]. Family members can also have more than just a role in diagnosis. They are also involved in monitoring their relative's care, sharing of information, advocating for their relatives and supporting them make decisions even when they have capacity to make their own decisions[7,8]. Family members and

close relations play an active role as decision-makers and taking responsibility of patient needs, choices and care especially when patients are in the intensive care unit, when patients lack decision-making capacity or when patients cannot give a thorough history of their illness. Additionally, involvement of family members can lead to a reduction in medical errors, improvement in quality of care and safety of patients and has the potential to reduce patient complications and hospital length of stay[6,8]. They assist in supporting the person emotionally and physically both in the hospital and in the community after discharge. The family of our patient knew her baseline health status and they noted that it was not the same. With their timely intervention, further evaluation of patient disclosed ataxia, nystagmus, confusion and some memory deficits for which a diagnosis of WE were made.

WE are mostly a clinical diagnosis as typical lesions on brain magnetic resonance imaging are found only in 58% of patients[4]. The classic triad is found only in 16 - 33% of cases making clinical diagnosis challenging1. Mental status changes are the most reported symptoms with 34-82% in postmortem-confirmed WE cases. Mental status changes include confusion, inability to concentrate, dizziness, memory disturbances, apathy, drowsiness, and cognitive impairment[1]. Oculomotor dysfunctions are present in about 30% of patients and usually completely resolves with thiamine administration. Persistence of oculomotor symptoms after treatment with thiamine should raise doubts about, WE diagnosis[3]. The diagnostic challenge associated with the WE triad prompted Caine et al[9] in 1997 to establish the new clinical criteria which has been adopted by the European Federation of Neurological Societies (EFNS) in their guidelines on WE[10]. There is an 85% sensitivity with the criteria if a patient suspected of having, WE have at least 2 of the following four features; eye signs, thiamine dietary deficiency, altered mental status or mild memory loss and cerebellar dysfunction. This is especially valid in alcoholics. There is no laboratory test that diagnoses WE. However, a complete metabolic panel and complete blood count can help to rule out differential diagnosis. Erythrocyte transketolase enzyme can be carried out to determine vitamin B1 deficiency. As concerns imaging, MRI is more sensitive that CT scan in identifying WE. Typical MRI findings include a symmetric hyperintensity signal in the paraventricular regions of the thalamus and hypothalamus, mammillary bodies and periaqueductal region[11]. A negative MRI does not exclude WE as it has a sensitivity of only 53% but with a specificity of 93%. An MRI should ideally be performed before treatment with thiamine as treatment quickly reverses brain abnormalities[2,11]. Our patient had all 3 elements of the Caine criteria (thiamine levels were not obtained) making the diagnosis of WE very likely but the MRI of the brain was negative maybe because she had been started on empirical thiamine. Patient was still treated for WE and she improved after treatment.

WE occur secondary to thiamine deficiency whether due to alcohol use disorder or due to nonalcoholic causes. Thiamine is an important coenzyme for the conversion of pyruvate to acetyl CoA by pyruvate dehydrogenase in the mitochondria. It is also required by the Krebs cycle enzyme, α-ketoglutarate dehydrogenase. Hence, the deficiency of thiamine leads to ineffective carbohydrate metabolism and cellular energy generation which then cause lactic acidosis, breakdown of the blood brain barrier, and excitotoxic effects from *N*-methyl-D-aspartate receptor activation[12]. These cellular effects result in neuron cell death and the typical symmetric damage in the thalamus, mammillary bodies, cerebellum, and pons. The cause of this region-selective neuronal loss is not known[13].

In chronic alcoholic use, thiamine deficiency occurs due to impaired absorption of thiamine from the intestine, inadequate nutritional intake, reduced storage of thiamine in the liver and a possible genetic predisposition which affect thiamine utilization[2,4]. Treatment of WE are therefore with intravenous thiamine because oral thiamine might

not be adequately absorbed. Also, to prevent WE occurring in high-risk patients like those with AUD, patient on hemodialysis and malnourished patients, glucose should always be administered either after thiamine administration or with thiamine at the same time but not before[4]. Pharmacologic and lifestyle modification strategies should be used to assist patients with alcohol abstinence[14]. Our patient had not been eating adequately and might have been deficient in thiamine. She was in her usual state of health until she took tizanidine and had the syncopal episode[15]. A literature search did not find a connection between tizanidine and interaction with thiamine or tizanidine as an inducer of WE and therefore could not be excluded as an inciting factor for WE.

Tizanidine is a centrally acting alpha 2 receptor agonist and skeletal muscle relaxant which is used for the symptomatic treatment of painful muscle spasms and spasticity. It also inhibits the release of excitatory amino acids like glutamate and aspartate from spinal interneurons with the resultant effect being the enhancement of the presynaptic inhibition of motor neurons[15,16]. Tizanidine has extensive first-pass metabolism by cytochrome (CYP) 1A2 enzyme. Therefore, using tizanidine with other CYP1A2 inhibitors such as oral contraceptives, cimetidine, and acyclovir should be avoided due to the risk of toxicity[17]. Its side effects include lethargy, bradycardia, hypotension, drowsiness, agitation, and even coma[18]. Tizanidine when taken with alcohol can potentiate the side effects of alcohol leading to postural hypotension, syncope, excessive sedation and myocardial toxicity like bradycardia[15,18]. However, its role of inducing WE in a chronic alcoholic has not been established. This needs further research to ascertain the relationship, if any, between tizanidine and WE.

CONCLUSION

Wernicke encephalopathy is a serious but treatable complication of thiamine deficiency which is more common in people with AUD. It is essentially a clinical diagnosis but unfortunately, many cases are being missed. Treatment is crucial to prevent its progression to the irreversible Korsakoff syndrome. It is an established fact that WE can be induced by infection and glucose load in a patient that is deficient in thiamine but tizanidine has not been reported as an inducer. Therefore, more research needs to be carried out to establish the relationship between tizanidine and WE. This case also shows that patient's relatives are a valuable ally in health care delivery and medical personnel should not hesitate to involve them in patient care. Medical personnel should always look for WE during every patient encounter in patients with AUD to reduce the number of missed cases of WE.

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