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Wernicke's Encephalopathy: Under Our Radar More Than it Should Be?

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Thiamine (Vitamin B1) is a vital cofactor in the metabolism of glucose. Thiamine deficiency leads to a specific constellation of central and peripheral nervous system dysfunction. Historically, thiamine deficiency has been associated with alcoholism, but there are several other populations that are at risk including post-operative gastrointestinal surgery patients and those on parenteral nutrition. The clinical manifestation of thiamine deficiency is often classified as Wernicke's Encephalopathy. It is identified as a triad of mental status changes, eye movement abnormalities and unsteadiness of gait with poor balance. This article describes the clinical features of thiamine deficiency, its manifestations, and the use of thiamine supplementation as treatment for this condition.

CLINICAL CASE

A 30 year old woman presented with abdominal sepsis due to choledocholithiasis to an outside hospital. Her hospitalization was complicated by post-endoscopic retrograde cholangiopancreatography (ERCP)-induced pancreatitis with infected peri-pancreatic fluid collections. As a consequence of poor oral intake due to persistent nausea, vomiting and abdominal pain, parenteral nutrition (PN) was initiated. Several attempts were made to restart oral nutrition, but were unsuccessful. Despite appropriate antimicrobial coverage and drainage of her complex intra-abdominal infections, her mental status deteriorated. On the day of transfer to our center she was not oriented to person, place or time. Her pupils were miotic and she had roving eye movements. She was intubated and underwent an MRI of the brain that showed T2/FLAIR hyperintensities along the medial thalami and periaqueductal region (see Figure 1). A lumbar puncture performed was unremarkable for infection. CSF Herpes Simplex PCR was negative. Serum copper, TSH, B12, Zinc and pyridoxine were within normal limits. Thiamine was found to be low. The neurology consult service reviewed the PN formulation she received at the outside hospital with the nutrition support service and found thiamine had not been included for unclear reasons. She was treated with intravenous thiamine 500

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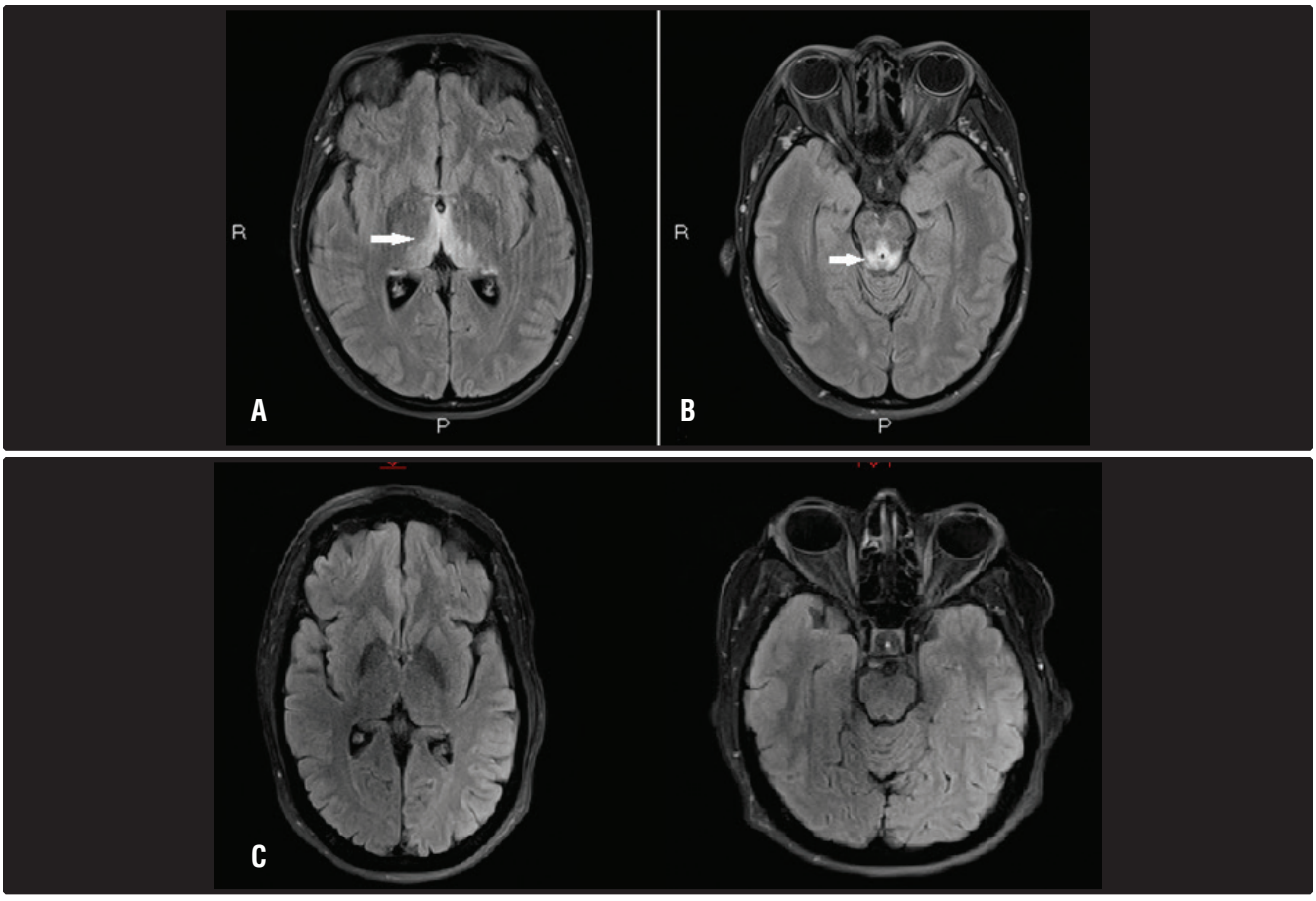

Figure 1. A. MRI brain image of a Fluid Attenuation Inversion Recovery (FLAIR) sequence from the case presented demonstrating bilateral medial thalamic hyper-intensities as demarcated by the solid white arrow. These are typical findings seen in Wernicke's encephalopathy. **B.** This again is a FLAIR sequence from the same patient. In this image, the solid arrow points to hyperintensities in the periaqueductal gray matter. **C.** Normal MRI of an age matched patient for comparison.

mg three times daily for three days and then switched to oral replacement 50 mg daily. She slowly improved to the point of independence for her activities of daily living, although ataxia and memory issues persisted 2 months later.

INTRODUCTION

Wernicke's Encephalopathy (WE) is a severe neurological syndrome due to deficiency of thiamine (vitamin B1). It was first described by Carl Wernicke in 1881 in a paper depicting three patients presenting with eye movement abnormalities, ataxia and mental status changes, in addition to retinal hemorrhages and optic disk swelling.[1] Since that first report, WE has been associated with alcohol misuse. However, only two of the three patients described by Wernicke fell into that category. The first case described is of a young woman with persistent vomiting due to pyloric stenosis following sulphuric acid ingestion.[1]

Untreated WE is fatal. The three patients initially described by Wernicke died within weeks of onset of the syndrome.[1] In subsequent publications there have been case reports and case series devoted to the clinical manifestations and treatment for WE. Despite over a century of reports about this condition, diagnosis is not uncommonly delayed, if not missed altogether. It is important to note that there are no large scale, class I studies on WE, so we are left to rely mostly on Class IV evidence for management and diagnosis. The purpose of this report is to give the general practitioner a review of the protean manifestations of this condition, identifying those at risk, its diagnosis, and treatment.

Epidemiology

The specific prevalence or incidence of WE is not accurately known. Our knowledge of the prevalence

of this condition comes from autopsy reports. The prevalence ranges from 0.8-2.8% of autopsy cases.[2] Based on one review, the predicted clinical prevalence was of 0.04-0.13%.[3] From other case series, the incidence is reported as high as 1.9% of autopsies.[4] Autopsy confirmed WE was missed by clinical examination in 75-80% of cases in one series.[3] WE is more common in the setting of alcohol misuse or abuse. However, other conditions have been associated with its onset (Table 1).

Table 1. Susceptible Populations (Other Than Chronic Alcohol Users)

- Anorexia Nervosa or dieting
- Hyperemesis Gravidarum
- Parenteral nutrition without or with inadequate supplementation
- Refeeding syndrome
- Gastrointestinal surgery (e.g. bariatric surgery, gastrectomy, etc.) with excessive diarrhea/vomiting or weight loss/failure to thrive
- Cancer patients
- Transplant patients
- Dialysis patients (hemodialysis or peritoneal dialysis)
- AIDS
- Chronic congestive heart failure on diuretics
- Psychiatric illness with weight loss
- Thyroid Diseases

Clinical Manifestations of Thiamine Deficiency in Non-Alcoholic Patients

In susceptible patients, like the case in question where persistent vomiting and diarrhea led to the use of PN, consideration of the triad of Wernicke's disease (eye movement abnormalities, ataxia, and mental status changes) is a useful diagnostic tool. Unfortunately, the likelihood of each symptom varies. Thirty-to-forty percent of patients with thiamine deficiency will have only one of the symptoms or signs of the triad.[5] The complete triad is only present somewhere between 5-16% of patients with thiamine deficiency.[2,3,5] Interestingly, in some reports the triad has been noted to be more common in alcoholics than in non-alcoholics with WE,[2] while other reports do not see a difference between alcohol related and non-alcohol related WE.[5] In non-alcoholics, dietary deficiency and a history of vomiting were more frequent than in alcoholics with WE.[2]

Given the seemingly rare presentation of the "classic" triad, it is of utmost importance to identify the various presentations of this condition and discuss them separately. Additionally, in the post-surgical or PN-related WE, it might be useful to discuss the timeline in which it may develop. Thiamine deficiency leads to brain lesions in susceptible regions with high thiamine turnover in 2-3 weeks.[3] Therefore, it stands to reason that in a patient with malnutrition, or improper thiamine intake, symptoms would emerge in this timeframe. Case reports support this concept where patients on PN (without thiamine or with inadequate thiamine along with poor endogenous stores) complain of double vision, vertigo unsteady gait and postural tremors within 11 days to two weeks following the initiation of PN.[6-8]

Additional signs of thiamine deficiency that may present with encephalopathy include heart failure (wet beriberi) leading to peripheral and pulmonary edema and orthopnea.[3] A rarer manifestation is hypotension and lactic acidosis without edema.[3] Seizures have also been reported, but are also rare.[3]

Clinical Features of the Wernicke's Encephalopathy Triad

Alteration in Mental Status

Alteration in mental status is the most common feature of thiamine deficiency present in 70-80% of patients according to one autopsy series.[2] Specific manifestations can include apathy towards the examination, an inability to answer questions of orientation, or to follow multiple step commands. Poor concentration as manifested by a diminishing ability to remember and repeat a series

(continued on page 34)

(continued from page 32)

of numbers (an individual should be able to recite 5 to 7 digits within a minute of being presented with such a series) is also seen.[2] At its most severe form an alteration in mental status can manifest as coma.[2] As patients recover with treatment (discussed below), they may describe a distorted account of the events. This confabulation can occur in the acute phase of WE, but also in a more delayed fashion in Wernicke-Korsakoff syndrome. Progression to coma is gradual. Although patients appear somnolent during the examination they can be easily aroused. Coincident toxicities or alternative causes should be considered concomitantly. Given the relatively common finding of delirium in the inpatient setting, consideration for WE should be included in the differential and workup of a delirious or encephalopathic patient.

Abnormal Eye Movements

In thiamine deficiency, nystagmus is the most common eye movement abnormality (at least in alcoholic-related disease),[4] and it can be present in the horizontal or vertical planes. Patients may also complain of double vision. This is a consequence of two abnormalities:

1. The first is weakness of the lateral rectus muscles that are responsible for eye abduction. This can affect either side and vary in intensity.
2. There may also be difficulty with conjugate gaze (coordination of both eyes to simultaneously focus on a target). Ophthalmoplegia (a lack of any eye movement) is also possible.

Ocular abnormalities occur in about a third of patients,[3] but others note that non-alcohol related disease has a greater proportion of eye abnormalities.[5] More rare ocular abnormalities include unequal pupillary size and "light-near dissociation".[3] In light-near dissociation, the pupil constricts when focusing on a nearby object, but does not constrict in response to direct light. As in the initial reports, visual disturbances due to optic disc edema or retinal hemorrhages can occur.[3]

Gait Ataxia

Thiamine deficient patients may be non-ambulatory. If they can walk, they take short steps and display gait unsteadiness. They maintain a broad stance to support themselves. In milder cases, the only way to provoke this ataxia is by having the patient walk with one foot in front of the other or to rub one heel along the front of the opposite leg's shin from the knee down to the ankle in one swift movement. Ataxia is present in anywhere from 23-60% of patients.[3,5] Careful consideration of a superimposed polyneuropathy should be investigated. Thiamine deficiency leads to a large fiber peripheral neuropathy manifesting with preferential weakness of the lower extremities and an inability to sense the position of limbs in space (proprioception) that is most notable when the eyes are closed. This loss of position sense tends to be more pronounced than pain.[9]

Korsakoff's Syndrome

Once the acute encephalopathy of thiamine deficiency resolves, the enduring problem with learning and memory is classified as Wernicke-Korsakoff syndrome. The defining feature of Korsakoff Syndrome is memory impairment out of proportion to other aspects of cognition in an otherwise alert patient. The timeline of development of Korsakoff's psychosis after Wernicke's encephalopathy is not always clear.

Diagnosis

A clinical history and neurological examination are sufficient to make the diagnosis of WE as it remains a clinical diagnosis. Measurement of serum thiamine via high-performance liquid chromatography can help in the *diagnosis* of thiamin deficiency; however, it often takes over a week for the results to return.[3] Given the potential for long term neurological harm and even death, waiting for lab results is not practical and is unsafe; *treatment should begin after the lab draw*. Additional ancillary testing can also include magnetic resonance imaging (as was done in the case discussed above). MRI brain findings of WE include abnormalities in and around the cerebral aqueduct, third ventricles and in the mamillary bodies, tectal plate, dorsal medulla and medical thalamus.[10] In our case, the MRI was significant for signal abnormalities along the medial thalami (which can appear within a week of symptom onset) (Figure 1). The sensitivity of MRI is reported as 53% with a specificity of 93% and a positive predictive value of 89%.[11] Therefore, imaging can help in excluding the diagnosis, but as noted earlier, clinical suspicion is most important.

Treatment

Treatment of WE, or suspected WE, once identified, consists of intravenous (IV) thiamine replacement (see

Table 2. Suggested Thiamine Replacement Found in the Literature

- 200 mg IV in 100 ml of normal saline or 5% glucose over 30 minutes three times a day until symptoms resolve [2]
- 500 mg IV three times a day for three days followed by 250 mg IV daily for 5 days or until clinical improvement is no longer noted [12*]

** In the patient with alcohol misuse*

Table 2). The exact dose of thiamine needed to effectively treat this condition has not been extensively studied; doses as low as 50 mg IV have been successfully used to treat WE.[7] Other treatment paradigms suggest 200 mg IV in 100 ml of normal saline or 5% glucose over 30 minutes three times a day until symptoms resolve.[2] It is ideal to give IV thiamine over 30 minutes as the infusion can be very painful at the site. Alternatively, the Royal College of Physicians recommends using 500 mg IV three times a day for three days followed by 250 mg IV daily for 5 days or until clinical improvement is no longer noted.[12] This recommendation is based on patients with evidence of alcohol misuse. It is advisable to draw a thiamine level *prior* to the first dose, but once the level is drawn, BEGIN TREATMENT. Additionally, thiamine infusion should precede or be given along with intravenous glucose, as glucose can precipitate WE in thiamine-deficient individuals.[3] Intravenous thiamine has rare adverse side effects, but anaphylaxis is possible.[3] For WE, risk of the medication is low. The benefit can be argued to be rather high as will be discussed in the next section. At our institution and based on the pharmacy purchasing information, a day's worth of therapy costs approximately $120 (personal communication). Following the completion of a course of parenteral administration of thiamine, oral thiamine at 30 mg twice a day is recommended for as long as the nutritional risk factor is present. The prophylactic course may be indefinite for the most vulnerable patients.[3]

Expected Clinical Course

Based on case series of alcohol-related Wernicke's Encephalopathy, the first symptoms that respond to thiamine are the eye movement abnormalities, which resolve within hours-to-days.[4] Confusion may persist despite treatment for days-to-weeks, but should gradually improve.[4] As mental status clears, however, long-term deficits in memory may become more obvious. Korsakoff Syndrome, a condition of persistent impaired memory (loss of recent memories and inability to form new memories) can occur as a sequela of WE.[4] In WE not related to alcohol, 25% of patients were noted to have Korsakoff's Syndrome.[5] Interestingly, in a large case series of patients with alcohol abuse, 84% were felt to have Korsakoff's Syndrome, 21% of them had complete resolution in time, while 26% had no recovery.[4] According to a large case series, ataxia improves in 2-4 weeks.[4] In those that had resolution (38%), it occurred in days; however, approximately one-third of the patients had no improvement in their ataxia.

CONCLUSION

WE is a rare, but treatable, condition that often goes underdiagnosed. It has been associated with alcohol use and abuse, but there are other patient populations at risk. Patients with recent GI surgery, malnutrition or in need of parenteral nutrition are at higher risk. Symptoms can start within 10 to 20 days of parenteral nutrition and can progress rapidly in this population if thiamine is not included. The triad of eye movement abnormalities, ataxia and alteration in mental status is not present in all patients with WE. In vulnerable patients, a screening examination of mental status with focus on attention span and concentration, along with a thorough assessment of ocular motility is useful. Evaluation for truncal and limb ataxia is also key, but clinicians must be aware of the possibility of a superimposed peripheral neuropathy. Neuroimaging can be useful in the diagnosis, but clinicians should rely on the patient's clinical presentation/history and their own clinical acumen. Clinicians should be vigilant in vulnerable populations and, given the relatively low cost and risk of parenteral thiamine, should highly consider empiric treatment at one of the doses described above.

In our experience, we opt for the higher 500 mg IV TID for three days given the low risk profile. Outcomes can vary and, despite treatment, irreversible disability is not uncommon. Appropriate counseling to patients and their families about the course of the disease is warranted. ■

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Answers to this month's crossword puzzle:

1 O	V	2 E	R	3 S	T	4 I	T	5 C	H	■	6 S	7 W	A	8 B
L	■	G	■	A	■	S	■	E	■	9 R	A	Y	■	L
10 I	L	E	O	C	O	L	I	C	■	■	G	■	11 N	O
V	■	S	■	■	■	E	■	U	■	12 P	■	13 L	■	A
14 E	A	T	■	15 D	A	T	U	M	■	16 Y	17 E	A	S	T
■	■	E	■	O	■	S	■	■	18 P	L	A	N	■	I
19 E	N	D	O	S	T	O	M	20 A	■	21 O	R	G	A	N
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22 R	A	23 V	24 A	G	E	■	25 A	D	J	O	U	R	N	■
O	■	26 A	S	E	■	27 A	■	O	■	P	■	H	■	28 K
29 B	A	C	K	■	30 I	S	O	M	31 A	L	T	A	S	E
O	■	C	■	32 O	■	T	■	33 I	R	A	■	N	■	L
34 T	H	I	O	P	U	R	I	N	E	S	■	35 S	F	O
I	■	N	■	E	■	A	■	36 A	N	T	37 I	■	■	I
38 C	U	E	■	39 N	I	L	■	40 L	A	Y	E	R	E	D