Non–Alcohol-Related Wernicke's Encephalopathy: Diagnosis and Treatment

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LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. During their twice-weekly rounds, Dr Stern and other members of the Consultation Service discuss diagnosis and management of hospitalized patients with complex medical or surgical problems who also demonstrate psychiatric symptoms or conditions. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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Have you ever wondered whether, and why, Wernicke's encephalopathy (WE) can develop in someone who does not have an alcohol use disorder? Have you been uncertain about how best to treat WE? If you have, the following case vignette and discussion should prove useful.

Case Vignette

Ms A, a 56-year-old woman with a history of major depressive disorder, posttraumatic stress disorder, alcohol use disorder in early remission, and opioid use disorder in sustained remission, was being treated with sertraline (250 mg oral/d), topiramate (75 mg oral/d), disulfiram (250 mg oral as needed for periods of increased risk of drinking), and intramuscular (IM) naltrexone (380 mg monthly). After 2 weeks of disorganized thinking, mood lability, and anxiety, she had a witnessed generalized tonic-clonic seizure and was treated at a local emergency department (ED) for postictal confusion. A computerized tomography (CT) scan of her head (without contrast) and a magnetic resonance imaging (MRI) scan of her brain (without contrast) were unremarkable. She was confused, complained of double vision, and had tangential speech marked by seemingly illogical speech that did not return to the topic of the initial question being asked. Her body mass index (BMI) was noted to be 17.4 kg/m^2 at that time, which is underweight in adults.[1] Her only abnormal laboratory studies were a positive urine drug screen for marijuana and an elevated serum ethanol level of 73 mg/dL. A CT/angiogram of her head was also unremarkable. Ms A said that she had an alcoholic beverage earlier that day to relax but had not otherwise used alcohol in more than 1 year. She was diagnosed as having a partial right third cranial nerve palsy, WE (due to symptoms of confusion, a cranial nerve III palsy), and hypomania (with distractibility and pressured speech). The ED team mistakenly believed that Ms A had been taking oral thiamine and gave her an additional 100 mg of oral thiamine before discharging her to outpatient follow-up in her primary care clinic to monitor her symptoms. However, due to limited medical capabilities of her rural outpatient clinic, a plan was made for admission to the regional tertiary care hospital to provide intravenous (IV) thiamine, as neither IV nor IM thiamine could be administered in the clinic.

On admission to the hospital, Ms A described that she had not been feeling or behaving like her usual self for several weeks, but could not elaborate, and she abruptly ceased to cooperate with the evaluation. She reported

Clinical Points

- Wernicke's encephalopathy (WE) is an acute neuropsychiatric syndrome that arises from thiamine deficiency; while traditionally thought of as a complication of a chronic alcohol use disorder, it can also occur for a variety of reasons unrelated to alcohol use.
- A WE diagnosis must meet 2 of the following 4 criteria: dietary deficiency, oculomotor abnormalities (with either ophthalmoplegia or nystagmus), cerebellar dysfunction/ataxia, and either an altered mental status (eg, disorientation) or a mild short-term memory impairment.
- WE is treated by administration of parenteral thiamine, as intestinal absorption of thiamine may be impaired; a suggested treatment regimen is 500 mg IV thiamine 3 times daily for 2 consecutive days, followed by 250 mg IV thiamine once daily for 5 consecutive days.

Table 1. Differential Diagnosis for Wernicke's Encephalopathy and the Classic Triad of Symptoms

General	Neurocognitive disorder
	Epileptic disorders
	Malignancy
	Concussion
	Infectious etiologies
	Paraneoplastic syndromes
Confusion	Delirium
	Medication interactions
	Stroke
	Hepatic encephalopathy
Ataxia	Normal pressure hydrocephalus
	Progressive supranuclear palsy
	Cerebellar pathology
Oculomotor	Multiple sclerosis
Dysfunction	Migraine headache
	Myasthenia gravis

double vision (that resolved when covering 1 eye) but was without nystagmus or other ocular findings; no ataxia was observed during the physical examination. Although she was malnourished (weighing less than 100 lb, with a BMI of 16.2 kg/m^2), she denied recent daily alcohol use. Despite lack of ataxia and recent alcohol use, IV thiamine was prescribed due to suspicion of WE. The Psychiatry Department was consulted to rule out a psychiatric cause for her presentation and to manage her psychiatric medications.

On examination, Ms A was agitated and restless; her speech was pressured with loose associations. She was euthymic and denied other symptoms of mania (including promiscuity, hyper-religiosity, grandiosity, and increased spending). She was orientated in all spheres. Her immediate and long-term recall was intact, although her recall of recent personal events was poor. The Neurology Department was consulted and noted a dramatic decrease in weight over the past year since topiramate was added. Topiramate was then tapered and discontinued due to concern about its contribution to her weight loss and thiamine deficiency. She was switched to levetiracetam for seizure prophylaxis. The consulting neurologist attributed her symptoms to WE, a toxic metabolic etiology, or an infectious encephalopathy.

Given an unremarkable MRI scan, the internal medicine team thought that "her overall picture with pressured speech and positive drug screens was one of an underlying mental health issue complicated by intermittent illicit drug use," vaguely pointing to Ms A's history of depression and recent marijuana use as potential etiologies of her symptoms. They concluded that Ms A did not have WE; instead, they attributed her symptoms to a combination of a mood disorder and substance use. As a result, the primary team discharged Ms A and gave her a prescription for oral thiamine (after receiving 2,500 mg IV of thiamine divided into 5 doses). On the day of discharge, the consultation-liaison psychiatry team felt that her mental status had improved in terms of agitation and pressured speech, perhaps due to treatment of WE.

What Is WE?

WE is an acute neuropsychiatric syndrome that arises from thiamine deficiency.[2–6] It is often characterized by a triad of symptoms (oculomotor dysfunction, ataxia, and confusion).[2,3,5,6] WE is potentially life-threatening, with infectious etiologies[5] being the most common cause of death in patients with WE. However, since WE may present without all 3 classic symptoms, it frequently is underrecognized and underdiagnosed.[7] Consulting psychiatrists often play a key role in preventing morbidity and mortality associated with WE by assisting in its early recognition and treatment.[6]

What Is the Differential Diagnosis of WE?

A differential diagnosis (Table 1[2,6,8,9]) for patients who present with symptoms of WE is broad, as each component of the classic triad of WE can be nonspecific.

How Often Does Non–Alcohol-Related WE Occur?

WE, while traditionally thought of as a complication of a chronic alcohol use disorder, can also occur for a variety of reasons unrelated to alcohol use. WE can arise as a sequelae of any etiology leading to thiamine deficiency.[9] Without consumption of foods rich in thiamine (such as whole grain foods, meat, fish, eggs, vegetables, legumes, or milk[10]), thiamine depletion can occur after approximately 4 weeks.[8] Autopsy studies have found that brain lesions characteristic of WE (including neuronal loss most prominent in the medial thalamus and atrophy of the mammillary bodies, a highly specific finding[11–13]) were present in up to 12.5% of those who abuse alcohol[14,15] and in as many as 2.8% of the general population.[14,16,17] This finding suggests that WE may be more frequent and occur within a broader patient population than what might have been thought.

What Are the Diagnostic Criteria for WE?

The diagnostic criteria for WE have included a triad of symptoms (confusion, ataxia, and oculomotor dysfunction).[5,9] However, overreliance on the need for the entire clinical triad contributes to underdiagnosis.[7] Roughly one-third[7] of inpatients diagnosed with WE have

all 3 features of the syndrome, while autopsy studies have estimated that it may be less common, as only 16% of patients had all 3 symptoms, while 19% demonstrated none of the 3 symptoms.[16] Furthermore, while 82% of patients with WE identified on autopsy had presented for care with confusion (including disorientation and poor memory), only 29% and 23% of these patients presented with oculomotor abnormalities (such as ophthalmoplegia or nystagmus) and ataxia, respectively.[16]

As a result of underdiagnosis, Caine et al[18] suggested that making a WE diagnosis must rely on meeting 2 of the following 4 criteria: dietary deficiency, oculomotor abnormalities with either ophthalmoplegia or nystagmus, cerebellar dysfunction/ataxia, and either an altered mental status (eg, disorientation) or a mild short-term memory impairment. Their addition of dietary deficiency is impactful, as the diagnostic sensitivity increased from 22% (with diagnosis based on the classic clinical triad of symptoms) to 85%.[18] Although WE is commonly thought of as a consequence of an alcohol use disorder, it should also be considered in the context of a nutritional deficiency.

How Should Suspected Cases of WE Be Evaluated?

Evaluation of suspected WE has proved to be difficult, as brain imaging may not be especially useful and there continues to be no expeditious or reliable laboratory test for WE.[6,19] Brain imaging studies with CT have lacked utility,[20] while MRI may demonstrate lesions with symmetrically increased signal intensity associated with WE in the mammillary bodies, medial thalami, periaqueductal region, and the tectum of the midbrain, with a specificity of 93%.[20] Due, however, to a sensitivity of only 53%,[20] MRI scans can only reliably rule-in suspected cases of WE. In terms of laboratory studies, serum thiamine levels can be obtained in emergency settings,[21] but serum thiamine levels may not accurately reflect brain levels, leaving the utility of serum thiamine levels unclear (as a normal serum thiamine level does not rule-out WE).[22] Furthermore, low levels of erythrocyte thiamine transketolase activity can help to establish a diagnosis of WE, but this test can be difficult to obtain, and it is often unavailable in emergency settings.[23]

What Are the Complications of WE?

Timely recognition and treatment of WE is essential to prevent the development of neurologic deficits.[5] Without prompt treatment, ocular palsies, vestibular dysfunction, gait dysfunction, and encephalopathy (with confusion and disorientation) can persist.[5] With treatment early in the disease course, ophthalmoplegia, gait dysfunction, and the confusion and disorientation of encephalopathy may resolve within hours.[24] It should be noted that even with treatment, residual neurologic deficits are still quite frequent. Approximately 60% of patients continue to display horizontal nystagmus after treatment; another 60% have gait difficulties (including a slow and wide-based shuffling gait).[5] Cognitive deficits also persist, with as few as 20% recovering completely from WE and the rest having ongoing learning deficits or recent memory deficits.[5,25] When WE is left untreated, it can progress to Korsakoff syndrome, which is marked by confabulation (a phenomenon in which patients may answer questions by generating false memories to compensate for memory deficits without an intention to deceive their examiner[26]) as well as both retrograde and anterograde amnesia.[5,25] Confabulation is typically observable during the course of the clinical interview, but screening tests, such as the Confabulation Screen,[27] have recently been developed to assist in discerning the presence of this symptom.

Due to misdiagnosis and variable presentations, the mortality rate is difficult to estimate.[5,6,28] Regarding deaths due to WE, the cause of death is typically attributed to a comorbid condition,[6] most commonly an infectious etiology for which the mortality rate may be as high as 10%–15%.[5] Among infectious etiologies, bronchopneumonia accounted for 52%[28] of deaths in 1 cohort of WE patients, while "unspecified infections" were responsible for up to 77% of patients in another cohort.[5]

How Should WE Be Treated?

Despite unreliable brain imaging techniques and laboratory testing to evaluate WE, treatment with thiamine repletion has proved to be safe and effective, and it should be started as soon as WE is suspected.[17] WE is treated by administration of parenteral thiamine, as intestinal absorption of thiamine may be impaired.[29] While IM thiamine is also effective, IV thiamine is preferred, as the high volume of thiamine given is often painful in the IM formulation.[17] A suggested treatment regimen is 500 mg IV thiamine 3 times daily for 2 consecutive days,[30] followed by 250 mg IV thiamine once daily for 5 consecutive days.[17,30,31] Another guideline[31] suggested that 500 mg IV thiamine 3 times daily should be given for 3 consecutive days (instead of 2 with older guidelines) before transitioning to 250 mg IV thiamine once daily for 5 consecutive days. Although different dosing regimens can be found in different sets of guidelines, a systematic review found that evidence from randomized controlled clinical trials is not sufficient to favor one suggested regimen over another.[32] IV thiamine should be diluted in 50–100 mL of normal saline and administered slowly (over a 30-minute period) to reduce the risk of anaphylaxis.[17] Patients with possible thiamine deficiency should receive IV thiamine prior to IV fluids that contain glucose, as administration of glucose without thiamine could precipitate or exacerbate WE.[33] This could potentially occur, as thiamine plays an important role in the metabolism of glucose, and administering glucose prior to thiamine could accelerate utilization of physiologic thiamine stores.[33,34] Specifically, thiamine deficiency can inhibit anaerobic glycolysis, which allows glucose to be converted to adenosine triphosphate, which can be a usable form of energy.[34] Toxic intermediates of glucose metabolism without thiamine, such as lactate, may also accumulate and cause damage to the brain.[33] Administration of magnesium is also an important consideration, as patients with WE may not respond to treatment with thiamine in the context of hypomagnesemia.[32]

Case Vignette Follow-Up

Three days after discharge, Ms A was evaluated by her outpatient psychiatrist. Some improvement was noted, as her speech was more linear and her behavior was less disorganized. Olanzapine, which had been started at 2.5 mg daily for disorganized behavior prior to admission, was increased to 5 mg daily. One week after discharge, the outpatient psychiatrist noted that Ms A was less confused, less tangential, and no longer demonstrating pressured speech. This was perhaps due to the combination of thiamine that had been administered as well as the olanzapine. After 3 weeks, Ms A's thinking and behavior continued to improve (although she still felt "scattered" with distractibility that had not completely remitted). Although diplopia persisted, it also began to improve. Additionally, she gained weight (3 lb 10 days after discharge and 7 lb after 20 days when her BMI returned to 17.4 kg/m^2). After 10 weeks, olanzapine was tapered and discontinued. Six months later, Ms A asked for olanzapine to be restarted again, as she noticed that her weight was declining, although her thinking and behavior continued to improve with her mood remaining stable.

Conclusion

Ms A, a woman with altered mental status, diplopia, and weight loss as well as a remote history of alcohol use disorder, with only mild use prior to presentation, was treated for WE despite having fewer than the 3 classic symptoms. Iatrogenic low body weight and poor nutritional status were likely contributors to her WE. Furthermore, inadequate knowledge about WE, as well as stigma associated with mental health and substance use disorders, may have contributed to an initial delay in diagnosis and to further delays in accessing appropriate care. Providers without adequate knowledge of WE were not initially able to recognize the nonclassic presentation in this case. After WE was considered among other differential diagnoses, the attribution of her symptoms to primary mental health or substance use disorders, despite psychiatric consultation recommending treatment for WE, potentially contributed to the difficulty in obtaining definitive treatment.

This case reinforces the need for consideration of broader diagnostic criteria for WE that could enhance early recognition and treatment. The criteria proposed by Caine could have correctly identified Ms A as a potential WE case and facilitated both shared clinical decision-making and more expeditious treatment, thereby reducing the risk of more significant morbidity or mortality.

A key consideration that assisted in our care of Ms A was collaboration between her outpatient providers. The patient's outpatient psychiatrist and mental health therapists had all been working with Ms A as a team for 3 years. As her symptoms worsened, discussions between her mental health care team and primary care provider became frequent. While there was some contact between the team and community informants such as a friend and her landlady, collaboration between primary care and mental health providers appears to have been the most important facet of her care, ensuring that despite the challenges of her complex and nontraditional presentation, the possibility of this dangerous diagnosis was recognized and appropriate treatment was eventually rendered.

WE is a dangerous condition that can lead to long-term neurologic deficits and even death; wider recognition of nonclassic symptoms of WE could assist in earlier diagnosis and more prompt treatment of WE.

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