Review Articles

Wernicke-Korsakoff-Syndrome: Under-Recognized and Under-Treated

Elie Isenberg-Grzeda, M.D., Haley E. Kutner, M.A., Stephen E. Nicolson, M.D.

**Background:** Wernicke-Korsakoff syndrome (WKS) is a well described syndrome of neurological and cognitive problems that comprises both Wernicke’s encephalopathy (WE) and Korsakoff syndrome (KS). WE is an acute neuropsychiatric disorder caused by thiamine deficiency. KS is a chronic consequence of thiamine deficiency with prominent impairment in memory formation. **Method:** The authors review the literature on the pathophysiology, presentation, and treatment of WKS, focusing on the acute identification and treatment of WE. **Results:** Most cases of WE are missed by clinicians, likely because patients do not present with the classic signs associated with the condition. Attaining high serum levels of thiamine during treatment may be important to restore cognitive function as quickly as possible, though the exact dosing and route needed for effective treatment is unknown. Data indicates that the administration of intravenous (IV) thiamine has little risk. **Conclusion:** In order to prevent this potentially devastating disease, physicians should have a high index of suspicion for WKS and dose thiamine accordingly. (Psychosomatics 2012; 53:507–516)

Wernicke’s encephalopathy (WE) is an acute neuropsychiatric disorder caused by thiamine (vitamin B₁) deficiency. It has classically been described by the triad of mental status changes, ophthalmoplegia, and ataxia, though its presentation can vary. The altered cognition of WE can progress to Korsakoff syndrome (KS), an impairment in formation of new memories with relative preservation of other mental functions, characterized by confabulation. Currently, WE and KS are considered to be different manifestations of a common disease, referred to as the Wernicke-Korsakoff syndrome (WKS). In this paper, we will refer to KS as a consequence of untreated or under-treated thiamine deficiency. Thiamine deficiency also causes beriberi, a syndrome of cardiovascular and peripheral nervous system dysfunction. Psychiatrists working in the general hospital may be able to prevent much of the morbidity associated with WKS with early recognition and treatment for those at risk, both in the alcoholic and non-alcoholic populations.

**HISTORIC PERSPECTIVE**

In 1881, Karl Wernicke described features of a new disease entity, first in a 20-year-old seamstress who had attempted suicide by ingesting sulphuric acid, and later in two alcoholic men with delirium. In each case, Wernicke noted the triad of abrupt confusion, ataxia, and ophthalmoplegia. In 1887, Sergei Korsakoff reported on patients with “an extraordinarily peculiar amnesia, in which memory of recent events, those which just happened, is chiefly disturbed. . . .”¹ During their lifetimes, neither Wernicke

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nor Korsakoff knew of the relatedness of their respective disease entities.

Cases of WE and KS reported in the literature in the late-nineteenth and early-twentieth century intimated that dietary deficiency may be the etiological agent, since cases of nonalcoholic patients with persistent vomiting, gastric carcinomas, pernicious anemia, and severe malnutrition were reported. Around the same time, investigations were well underway on beriberi, a disease endemic to populations whose diets were based largely on polished-rice. Reports of beriberi focused on heart failure, edema, loss of sensation, motor dysfunction, and decreased reflexes, but not on cognitive symptoms. In 1911, the first vitamin was isolated from rice-polishing, implicating beriberi as a disease of thiamine deficiency. In 1936, thiamine was synthesized. As more patients survived the acute illness, some began developing permanent memory deficits in the form of KS. A 1947 publication reported on 52 cases of nutritionally deprived prisoners of war who developed beriberi and WE. Support for the idea that WE and KS were related phenomena was bolstered by a 1956 study in which patients who had been diagnosed with KS revealed neuropathologic lesions in the identical brain regions as patients with WE. WE became understood as an acute, potentially reversible illness, and KS as a chronic usually permanent manifestation.

CURRENT PERSPECTIVES

Fortification of flour and bread has been recommended by the United States government since World War II because the milling process to create white flour removes nutrients. With fortification, the prevalence of thiamine deficiency has decreased. Alcoholism now accounts for up to 90% of thiamine deficiency. However, two common misconceptions about WKS persist—that it is a rare disease, and that it is a disease of alcoholics. While the prevalence of WKS in patients with alcoholism is as high as 12.5%, in the general population it is estimated to be 2%. In AIDS patients, the prevalence is 10%, and post-bone marrow transplant (BMT) patients it is 5.5%. 

PATHOPHYSIOLOGY OF WKS

Thiamine Metabolism

Thiamine is a water-soluble B-vitamin essential for glucose metabolism. A minimum of 0.33 mg thiamine is required for every 1000 kcal energy consumed. A daily average dose of 1.1 mg thiamine for adult women and 1.2 mg thiamine for adult men is recommended. In countries where foods are fortified with thiamine, healthy people typically consume 0.4 to 2 mg daily.

Brain stores of thiamine allow a margin of safety. Neuropsychiatric symptoms are apparent only if levels of thiamine are reduced below 20% of normal.

Thiamine pyrophosphate (TPP), which is the major active form of thiamine in the central nervous system (CNS), is a structural component or cofactor of three major enzymes involved in glucose metabolism—transketolase, pyruvate dehydrogenase, and α-ketoglutarate dehy-

### TABLE 1. Thiamine Content of Common Foods*

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving Size</th>
<th>Carbohydrate (g)</th>
<th>Thiamine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbonated cola</td>
<td>12 fl oz</td>
<td>38</td>
<td>0.02</td>
</tr>
<tr>
<td>Coffee, brewed</td>
<td>6 fl oz</td>
<td>1</td>
<td>0.00</td>
</tr>
<tr>
<td>Milk (1% fat)</td>
<td>1 cup</td>
<td>26</td>
<td>0.10</td>
</tr>
<tr>
<td>1 whole raw egg, large</td>
<td>50 g</td>
<td>1</td>
<td>0.03</td>
</tr>
<tr>
<td>Orange</td>
<td>Whole, peeled, seeded</td>
<td>15</td>
<td>0.11</td>
</tr>
<tr>
<td>Bagel, plain</td>
<td>4 in. diameter</td>
<td>48</td>
<td>0.48</td>
</tr>
<tr>
<td>Wheat bread, enriched</td>
<td>One slice</td>
<td>12</td>
<td>0.10</td>
</tr>
<tr>
<td>Beef, sirloin, lean</td>
<td>3 oz</td>
<td>0</td>
<td>0.11</td>
</tr>
<tr>
<td>Chicken breast fried with skin/bone (140 g)</td>
<td>Half breast</td>
<td>13</td>
<td>0.16</td>
</tr>
<tr>
<td>Almonds, whole</td>
<td>1 oz (24 nuts)</td>
<td>6</td>
<td>0.07</td>
</tr>
<tr>
<td>Black beans, cooked</td>
<td>1 cup</td>
<td>41</td>
<td>0.42</td>
</tr>
<tr>
<td>Collard greens, cooked and drained</td>
<td>1 cup</td>
<td>9</td>
<td>0.08</td>
</tr>
<tr>
<td>Potato, baked, with skin</td>
<td>One, 202 g</td>
<td>51</td>
<td>0.22</td>
</tr>
<tr>
<td>Sweet Red or Green Pepper, raw</td>
<td>1 cup, chopped</td>
<td>10</td>
<td>0.10</td>
</tr>
<tr>
<td>Okra, sliced, cooked, drained</td>
<td>1 cup</td>
<td>12</td>
<td>0.21</td>
</tr>
</tbody>
</table>

These enzymes are involved in important metabolic activities, the pentose phosphate pathway, glycolysis, and the citric acid cycle, which yield molecules necessary for biological functions. In neurons and glial cells, these include the synthesis of nucleic acids, neurotransmitters, myelin, and energy-containing compounds like ATP. Because these pathways are involved in creating reducing power in cells, thiamine protects cells from the damaging effects of oxidative stress. In its triphosphorylated form (TTP), thiamine plays a role in nerve membrane function.

Under physiological conditions, in which thiamine concentrations in the gut are low, oral thiamine is absorbed by an energy-dependent active-transport system. The role of nonsaturable process in humans remains unclear, as absorption of thiamine from the gut in humans in vivo has been shown to plateau, such that after a 50 mg oral dose, the amount of thiamine absorbed is 4.5 mg or less.

Once in the blood, thiamine can travel to the site of entry into the CNS extracellular space either by directly crossing the blood brain barrier (BBB) or by indirectly traveling into the cerebrospinal fluid via the choroid plexus. The former method uses a saturable, facilitated-diffusion system, while the latter uses active transport. There is also a non-saturable simple-diffusion mechanism that usually accounts for 10% of thiamine transport into the CNS.

### Thiamine Deficiency

There are several factors leading to the development of thiamine deficiency with chronic alcohol use. First, alcoholics tend to forgo vitamin-rich foods in favor of vitamin-depleted, high-carbohydrate diets. Thiamine stores become depleted within 2 to 3 weeks without supplementation. Second, reduced absorption of thiamine from the gut has been reported under various experimental conditions, including after acute alcohol ingestion. Third, renal epithelial cells are affected by alcohol, leading to increased thiamine loss from the kidneys. Fourth, in chronic alcoholic liver disease, the thiamine storage capacity of the liver is reduced by 73%. Fifth, alcohol reduces the enzymatic activity of thiamine pyrophosphokinase (TPK), effectively diminishing the amount of TPP available for use. Since facilitated diffusion of thiamine into cells is dependent on a concentration gradient, the reduced TPK activity further decreases thiamine uptake into cells. Sixth, alcohol decreases absorption of colonic bacterial thiamine. Finally, hypomagnesemia is common in alcoholics, and magnesium is a necessary cofactor in thiamine utilization. Thus, alcohol has both direct and indirect methods of causing a thiamine-deficient state.

In cases of WKS in which alcohol is not involved, the development of thiamine deficiency can be explained by one of four mechanisms: decreased availability, impaired utilization, accelerated usage, and increased loss of thiamine (see Table 2). Decreased availability of thiamine develops in periods of starvation, malnutrition, malabsorption, excess losses, and vomiting. Impaired utilization occurs when the handling of thiamine is impaired because of low enzyme activity or associated coenzyme deficiencies. Accelerated usage of thiamine develops when there is an

<table>
<thead>
<tr>
<th>Mechanism of Thiamine Deficiency</th>
<th>Etiology</th>
<th>Clinical Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased availability</td>
<td>Starvation</td>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hunger strike</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GI obstruction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic illness</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Anorexia nervosa</td>
<td>Hunger strike</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fad dieting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bariatric surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homebound elderly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TPN (if not supplemented)</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>Bariatric surgery</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Hyperemesis gravidarum</td>
<td>Chemotherapy-induced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Status post-abdominal surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GI obstruction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Impaired utilization</td>
<td>Decreased enzyme activity</td>
<td>Co-factor deficiency</td>
</tr>
<tr>
<td></td>
<td>Malignancy</td>
<td>Chemotherapy-induced</td>
</tr>
<tr>
<td>Accelerated usage</td>
<td>Hypermetabolic state</td>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td></td>
<td>Systemic illness</td>
<td>Infection/sepsis</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
<td>Following rapid infusion of glucose</td>
</tr>
<tr>
<td></td>
<td>Alcohol withdrawal</td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Hematological malignancy</td>
<td>Fast-growing tumor</td>
</tr>
<tr>
<td>Increased losses</td>
<td>Rapid cell turnover/high cell density</td>
<td>Iatrogenic</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis</td>
<td></td>
</tr>
</tbody>
</table>
overall increase in the body’s metabolism of glucose, as in states of increased metabolic rate, conditions of increased carbohydrate metabolism, and conditions involving rapid cell turnover. In such states, thiamine deficiency can develop even with a diet normally considered adequate. Cancer, particularly those involving rapid cell growth (e.g., leukemia and lymphoma), results in accelerated thiamine usage. Cancers often cause poor oral intake of thiamine, whether primarily due to low appetite or direct effects of the disease, or secondary to chemotherapy or vomiting. If TPN is initiated without adequate thiamine supplementation, a state of thiamine deficiency can develop. Increased loss can occur in hemodialysis as thiamine is removed into the dialysate.

For a thorough review of the pathophysiologic consequences of thiamine deficiency, see Sechi and Serra. A deficit of thiamine in the brain leads to cytotoxic edema and astrocyte volume increase within 4 days. After 7 to 10 days, decreased transketolase activity causes endothelial cell dysfunction, nitrous oxide production, and release of intracellular glutamate into the extracellular space. Consequently, loss of osmotic gradients and production of free radicals leads to vasogenic edema and BBB permeability. After 14 days of thiamine deficiency, neuronal DNA fragmentation and lactic acidosis cause irreversible structural damage and neuronal necrosis. During alcohol withdrawal, synergistic neurotoxicity is caused by NMDA-receptor hypersensitivity leading to additional glutamate release. Certain areas of the brain are more vulnerable to damage than others. In one cohort, the mammillary bodies showed histologic damage in 100% of cases. Factors such as embryologic origin of cells, blood supplies, and histologic features do not explain the selective vulnerability of mammillary bodies and other commonly affected areas like the periaqueductal region and the tectum (see Figure 1). Even as research progresses on the biochemical mechanisms of cell damage in thiamine deficiency, the role of such mechanisms in selectively damaging certain areas, including the mammillary bodies, is unknown.

**DIAGNOSING WERNICKE’S ENCEPHALOPATHY**

WE is diagnostically challenging, as autopsies have found that over 80% of true cases of WKS are not diagnosed during life. In a series of patients who had undergone BMT for various reasons, 60% of patients with WKS on autopsy had not been diagnosed during life. Substantial time delays in diagnosing WKS have been reported following bariatric surgery, acute pancreatitis, and malignancy. Other cases of nonalcoholic WKS have been misdiagnosed as primarily psychiatric, subjected to unnecessary invasive tests, and withheld correct treatment while not responding to the incorrect treatments given.
Several factors likely play a role in the difficulties of diagnosing WKS. First, the sensitivity using all three classic signs in diagnosing WE is low. Of 97 alcoholics in whom WKS was first diagnosed at autopsy, chart reviews revealed that only 16% had documentation of all three ‘classical signs.’ Of the remaining cases, 29% had presented with two signs; 37% had presented with one sign; and 19% had none of the classic signs. Mental status changes are the most prevalent sign, and are present in both alcoholics and nonalcoholics with WKS. Among alcoholics with WKS, mental changes were reported in 82% of cases, eye signs were reported in 29% of patients, and ataxia was reported in 23% of patients.

Second, the classic signs of WKS are narrow, and do not depict the true breadth of symptomatology experienced in WKS. “Mental status changes” can mean global confusion, disorientation, drowsiness, apathy, indifference, incoherence in speech, or disorder of memory (mild memory impairment, amnesia). Anxiety, fear, coma, and stupor. “Ophthalmoplegia” is one of several eye signs found in WKS, including nystagmus, lateral rectus palsy, conjugate gaze palsies, papillary abnormalities, retinal hemorrhages, ptosis, scotoma, complete ophthalmoplegia, diplopia, blurred vision, and photophobia. “Ataxia” is an example of various cerebellar signs reported in WKS: unsteadiness of gait, dysdiadochokinesia, impaired heel-shin testing, past-pointing, and dysarthria.

Third, because the signs of WKS are common to many illnesses, the diagnosis of WKS may be overshadowed by other medical conditions. For example, signs and symptoms of WKS overlap those of chronic alcoholism, intoxication, and withdrawal. Also, other medical conditions, including withdrawal or infection can precipitate WKS by increasing both the body’s metabolic rate and its demand for thiamine-related enzymes.

Finally, while there are laboratory assays for measurement of thiamine available, there are currently no quick, reliable, and routine diagnostic tests for WE. Magnetic resonance imaging (MRI) can detect changes most commonly in the medial thalami, mammillary bodies, periaqueductal region, and the tectum of the midbrain with high specificity but with a sensitivity of just 53%, the diagnostic utility of MRI is in only confirming a clinical suspicion of WE. Limited data exist on the usefulness of EEG, evoked potential, and CSF analysis in diagnosing WE. Computed tomography (CT) is not useful for diagnosing WE.

Thus, clinical examination remains the standard in diagnosing WE. Caine proposed operational criteria to improve the sensitivity of diagnosing WE in chronic alcoholics, defined as patients who drank more than 80 g of ethanol daily for most of their adult life. Using the Caine criteria, a diagnosis of WE is made if two out of four signs—eye signs, cerebellar signs, mild memory impairment or confusion, and signs of malnutrition—are present on exam. These criteria are unique in two fundamental ways. First, they use the broadest definition of the clinical signs rather than the narrower classic triad; second, they emphasize importance malnutrition. Thus, a confused chronic alcoholic patient with signs of dietary deficiency should be diagnosed with WE. The proposed criteria were tested by retrospectively applying them to 106 case histories of alcoholic patients who underwent autopsy. In detecting neuropathologically confirmed WE, with or without KS, the criteria had a sensitivity of 85% and a specificity of 100%.

Treatment

As alcohol’s effects on the gut reduce thiamine absorption in an unpredictable way, thiamine must be administered parenterally in order to generate a sufficiently elevated concentration of thiamine in the blood. The rationale for high thiamine blood levels is based on the physiologic processes that deliver thiamine to the CNS. As discussed above, the secondary means of thiamine transport into the CNS, simple diffusion, is not saturable. At high serum concentrations, theoretically, thiamine will cross into the CNS at a higher rate. What constitutes a high dose of thiamine is not yet established. In 1950, Victor and Adams chose 100 mg of thiamine to treat WE, based on their best estimate of what would constitute a high dose. Others recommend treating alcoholics with WE with doses of 500 mg or more, though these are based on limited evidence. The only published randomized controlled trial of thiamine for the treatment of WKS compared five doses of intramuscular thiamine (range 5–200 mg daily) for 2 days in patients being treated for alcohol withdrawal. The patients taking the highest dose performed the best on delayed alternation, a task specific to the cognitive impairment of WKS. However, the results did not show a step-wise dose response. A Cochrane review last updated in 2008 concluded that there is insufficient evidence to guide clinicians in the dose, frequency, route, or duration of thiamine.
administration for either treatment or prophylaxis of WKS in alcoholic patients.\textsuperscript{69}

The Royal College of Physicians (RCP) and European Federation of Neurological Societies each published guidelines with recommendations specific to prevention of WE in alcoholic patients (see Table 3).\textsuperscript{47,70} Despite their differences, both groups recommend a high suspicion for WE and aggressive treatment in order to accommodate the diagnostic uncertainty in the clinical setting and the high benefit to risk ratio of high dose thiamine use.

The safety of IV thiamine has been studied in a prospective trial in which 1070 doses of 100 mg of thiamine hydrochloride were administered to 989 patients by rapid IV push.\textsuperscript{71} The rate of minor reactions was 1.02%, and these consisted of immediate and transient burning in the arm containing the IV lasting seconds to minutes. The only major reaction, generalized pruritus without associated symptoms, was seen in one patient, a rate of 0.093%. While cases of anaphylactic reactions in response to IV thiamine have been highlighted in the literature, the risk is extremely low (one reaction per 5 million ampoules of thiamine-containing solution in the UK).\textsuperscript{47} A retrospective survey by Emergency Department physicians estimated that of thiamine administered parenterally to approximately 300,000 patients, none developed anaphylactic reactions. The authors compared these figures to a 1% to 10% risk of allergic reaction to penicillin, a 2% to 3% chance of a contrast media reaction, and a 1% to 18% chance of an allergic response to streptokinase.\textsuperscript{72} Thiamine is thus generally considered safe when administered parenterally.\textsuperscript{9,47,70–72} It is also important to replete magnesium in alcoholics, as their low magnesium stores can cause thiamine treatment to be refractory.\textsuperscript{73}

The timing of thiamine relative to carbohydrate administration has been debated.\textsuperscript{74} Because thiamine is essential to glucose metabolism, increasing the body’s metabolic rate can cause a relative shortage of thiamine and precipitate WKS. A number of case reports and animal studies have documented such reactions.\textsuperscript{75} A recent review of the emergency management of WKS suggests that a single load of glucose administration will not cause such a state, and glucose administration in emergency situations should not be delayed for thiamine.\textsuperscript{9}

### COURSE OF ILLNESS AND PROGNOSIS

Current understanding of the course of illness is largely based on the 1947 description of 52 prisoners of war who developed WKS during a period of starvation and nutrient deficiency.\textsuperscript{4} The authors divided the syndrome into stages of progression. Mild disease consists of anorexia, appearing first in nearly all cases, followed by nausea, vomiting, nystagmus, and subjective eye symptoms. Moderate disease is marked by insomnia and emotional changes, beginning with anxiety, followed by apathy and apprehension. Progressive loss of recent memory then occurs over 2 to 3 weeks. Severe disease is marked by disorientation, confabulation, and coma. Because this study was conducted during war, the onset, dose, duration, and frequency of thiamine treatment varied. Of those untreated or who received thiamine orally, only 5 of 15 (33%) survived. Of those administered thiamine intramuscularly (average dose of 2 mg), 26 of 37 (70%) survived—a substantial change from the nearly universally fatal case descriptions published prior to this report. Among the 31 soldiers who survived the acute phase of illness, only 1 (3%) developed KS.

 Among alcoholic patients with WE treated with parenteral thiamine, rates of progression to KS range from 56% to 84%.\textsuperscript{1,76} Little consistency exists regarding onset, duration, frequency, and even dose of thiamine treatment. Victor’s case series challenged the notion of irreversibility

| TABLE 3. Comparison of Guidelines for Diagnosis and Treatment of Suspected WE |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Who to Treat | Dose | Route | Frequency | Duration |
| Royal College of Physicians (RCP)\textsuperscript{47} | 500 mg | IV | TID | 3 Days. If response is noted, follow with 250 mg IV or IM daily for 5 days, or until clinical improvement ceases |
| European Federation of Neurological Societies (EFNS)\textsuperscript{70} | 200 mg | IV preferred | TID | Until symptoms resolution |

Wernicke-Korsakoff-Syndrome: Under-Recognized and Under-Treated

\begin{center}

<table>
<thead>
<tr>
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<td>Until symptoms resolution</td>
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\end{center}
of KS. They found that among patients who developed KS, 21% completely recovered (e.g., independent living, employment), 25% significantly recovered (e.g., performed ADLs independently), 28% slightly recovered (e.g., performed simple tasks), and only 26% showed no measurable improvement in memory or learning.1 There are several limitations of existing data on the course of illness and prognosis in WKS.77 First, studies tend to lack documented findings on memory functioning, limiting retrospective diagnoses of KS. Second, typically high mortality rates in the acute phase of illness may represent more severe illness—cases that might have progressed to KS. Third, data from alcoholic patients is not generalizable, and vice versa, because a discrepancy exists between their respective courses of illness in WKS. In nonalcoholic patients, WE tends to appear once and for a short period of time, whereas in alcoholic patients, persistently mild nutrient deficiencies occur over long periods of time, such that neuroanatomical pathology is more severe at the time of clinical presentation.2,57,77

The cause of death associated with patients with WKS is usually related to comorbid disease. Bronchopneumonia accounted for 52% of deaths in one cohort of patients with WKS,53 while in another, unspecified infections accounted for 77%.1 Cirrhosis has also been reported as a cause of death in WKS.1,53 In fact, WKS is not listed as a primary or even secondary cause of death in several cohort studies.1,7,53 In cases where no cause of death has been established, lesions of WKS in the hypothalamus or medulla may have affected thermoregulation, wakefulness, respiratory, and autonomic nervous system functions.53 This is consistent with case reports of WKS presenting with bradycardia, hypotension, hypothermia, and stupor.10,78–80

**RECOMMENDATIONS**

To address the insufficient evidence guiding physicians in the diagnosis and treatment of WKS, we believe consultation psychiatrists can improve the morbidity associated with the syndrome by helping hospitalists maintain a high index of suspicion for WKS and recommending aggressive treatment. Keep in mind:

1. There are misconceptions about WKS. It is not rare; it is not exclusive to alcoholics; and the full classic triad is unlikely.

2. The Caine criteria offer greatly improved sensitivity and specificity in patients with alcohol problems. While these criteria have not been studied in populations without alcohol misuse, clinicians should strongly consider WKS in any patient with alcoholism or medical conditions that are associated with thiamine deficiency and any of the Caine criteria. This would include patients whose illness is associated with decreased availability, impaired utilization, accelerated usage, or increased loss of thiamine (see Table 2).

3. In determining whether to treat a patient with suspected WKS, physicians must consider the likelihood of WKS and weigh the high risk of untreated WKS vs. the low risk of harm in treating with intravenous thiamine. In most cases, the benefit of acutely treating WKS outweighs the potential risk. The clinical priority in treating patients at risk for WKS is not accurate diagnosis, which can delay proper treatment. Rather, the primary goal is delivering thiamine to the brain immediately.

4. There is no place for oral thiamine in the treatment of hospitalized patients with suspected WKS. Rather, administering intravenous thiamine at doses of at least 200 mg, given three times daily or more, as the half-life of intravenous thiamine is 96 minutes.81 It is recommended by RCP to administer thiamine slowly over 30 minutes.47

5. Once thiamine administration is begun, immediate attention should be paid to correct other metabolic abnormalities, especially hypomagnesemia.

6. Some improvement should be noted as early as 6 hours but may take up to 3 days,1 at which point failure to show any response may indicate that other illness is responsible for the symptoms. For those who respond, continue high-dose intravenous thiamine once daily for up to a week or until patient begins oral intake of food. At discharge, patients should be prescribed an oral multivitamin including thiamine.

**CONCLUSIONS**

Over a century after the initial descriptions, WKS remains diagnostically difficult. Evidence points towards underestimates of true prevalence. Thus, consultation psychiatrists are likely to frequently encounter undiagnosed patients. Treatment is a quandary as there are no established guidelines in the United States on how to treat suspected WKS. Indeed, even in countries where national guidelines exist, thiamine is still underdosed.82 Until these issues are resolved, physicians must weigh the potential consequences of untreated WKS with the minimal risk of parenteral thiamine at doses that give the patient optimal chance of
recovery. Future research should focus on creating an evidence base to guide dosing, frequency, route, and timing of thiamine administration.

Disclosure: The authors disclosed no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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