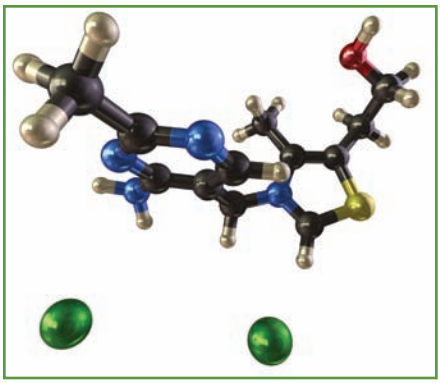

[REVIEW]

Thiamine Deficiency and Delirium

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ABSTRACT

Thiamine is an essential vitamin that plays an important role in cellular production of energy from ingested food and enhances normal neuronal actives. Deficiency of this vitamin leads to a very serious clinical condition known as delirium. Studies performed in the United States and other parts of the world have established the link between thiamine deficiency and delirium. This literature review examines the physiology, pathophysiology, predisposing factors, clinical manifestations (e.g., Wernicke's encephalopathy, Wernicke-Korsakoff syndrome, structural and functional brain injuries) and diagnosis of thiamine deficiency and delirium. Current treatment practices are also discussed that may improve patient outcome, which ultimately may result in a reduction in healthcare costs.

INTRODUCTION

Vitamin B1, also known as thiamine, is one of the eight essential B vitamins that help the body convert food (carbohydrates, fat, and protein) into energy. These vitamins are vital for proper functioning of the central and peripheral nervous system. The human body does not produce endogenous thiamine; therefore, it must be ingested. Various dietary sources of thiamine include meat (e.g., pork, poultry), whole grain cereals (e.g., brown rice and bran), nuts, dried beans, peas, and soybeans. Breads and cereals are commonly fortified with thiamine. The human body requires a minimum of 0.33 milligrams (mg) of thiamine for every 1,000 kilocalories (kcal) it consumes, so an individual who consumes an average 2,000kcal diet per day should ingest a minimum of 0.66mg of thiamine daily.[1] A daily intake of 1.1mg of thiamine is currently recommended for adult women and 1.2mg for adult men. Children require lower levels of thiamine (0.5–1.2mg depending on age and gender), and slightly higher levels of thiamine are recommended for pregnant and breast-feeding women (1.4mg thiamine per day). Studies have found that most healthy people typically consume 0.4 to 2.0mg thiamine daily.[2] See Table 1 for a list of the daily recommended allowances for different age groups.

PHYSIOLOGY OF THIAMINE

Thiamine is a water-soluble vitamin stored primarily in the liver; however, storage only lasts up to 18 days.[3-6] The absorption of thiamine occurs in the duodenum by an active process and is converted to its active form thiamine pyrophosphate.[7,8] This conversion process of thiamine to its active form requires magnesium as a cofactor, and hence hypomagnesaemia can mimic thiamine deficiency.[6,9,10] The absorption process of thiamine is a carrier-mediated, rate-limiting process,[11] and alcohol inhibits this rate-limiting step by interfering with intestinal ATPase

TABLE 1. Daily recommendations for thiamine intake for different age groups

DEMOGRAPHICS	DAILY RECOMMENDED INTAKE (milligrams)	
	UNITED STATES	CANADA
0–3 year(s)	0.3–0.6	0.3–0.6
4–6 years	0.9	0.7
7–10 years	1	0.8-1.0
>10 years (male)	1.2–1.5	0.8–1.3
>10 years (female)	1–1.1	0.8–0.9
Pregnant women	1.5	0.9–1.0
Breast-feeding women	1.6	1–1.2

involved in the absorption of thiamine.[12,13] At the blood brain barrier (BBB), its transport occurs through both passive and active mechanisms[14] depending on the concentration of thiamine in the blood. When the concentration of thiamine in the blood is high, transportation of thiamine through the BBB occurs via passive diffusion. However when the concentration of thiamine in the blood is low, thiamine crosses over via active transport (Figure1).

PATHOPHYSIOLOGY

A deficiency in thiamine leads to decreased activity of thiamine-dependent enzymes that triggers a sequence of metabolic events leading to energy compromise. Neuronal death often occurs in certain neuronal populations that have high metabolic requirements and high thiamine turnover.[15] Areas commonly affected by thiamine deficiency are the mediodorsal thalamic nucleus, mammillary bodies, the periaqueductal gray matter, and the floor of the fourth ventricle, which includes the ocular motor, vestibular nuclei, and the cerebellar vermis.[16] Lesions also may involve the fornices, the hippocampus, the area round the third ventricle, the quadrigeminal bodies, and the cortex.[17] The predilection to affect memory circuits is responsible for the most important sequela of Wernicke's encephalopathy— Korsakoff's psychosis.[18]

Thiamine and enzymes in need of thiamine as a co-factor are present in all body cells. Deficiency of thiamine affects all organ systems, particularly the cells of the nervous system (e.g., neurons and glia cells, which are supporting cells in the nervous system).[19]

Thiamine pyrophosphate (TPP), the active form of thiamine, is a required cofactor in two enzyme-mediated carbohydrate metabolism pathways, which are the Kreb's cycle (also known as the citric acid cycle) and Pentose phosphate pathway. The Kreb's cycle is a central metabolic pathway that completes the oxidative degradation of monosaccharide (carbohydrate) and other nutrients, such as fatty acids and amino acids, and occurs in the mitochondria of every cell that utilizes oxygen. The diagram in Figure 2 shows the utilization of thiamine (TPP) in the Kreb's cycle.

There are two main enzymes, pyruvate dehydrogenase complex (PDH) and alpha-ketoglutarate dehydrogenase (alpha-KGDH) that require thiamine as a cofactor in the Kreb's cycle. The main function of the pathway is the generation of a molecule called adenosine triphosphate (ATP), which provides energy for numerous cellular processes and reactions.[20] A decrease in ATP production in the brain leads to an increase in production of toxic metabolites of dopamine and inhibition of catechol-O-methyl transferase (COMT) activities, which is a vital enzyme for synthesis and breakdown of dopamine in the prefrontal cortex.[21,22] Thus, an increase in the level of dopamine may lead to delirium, including hallucinations and delusions.[22] In addition, proper functioning of PDH is essential for the production of the neurotransmitter acetylcholine as well as for the synthesis of myelin.[20] Low levels of acetylcholine have been linked to delirium as well as the severity of cognitive impairment associated with delirium.[14,23] The citric acid cycle and alpha-KGDH play a role in maintaining the levels of the glutamate, gamma aminobutyric acid (GABA), and

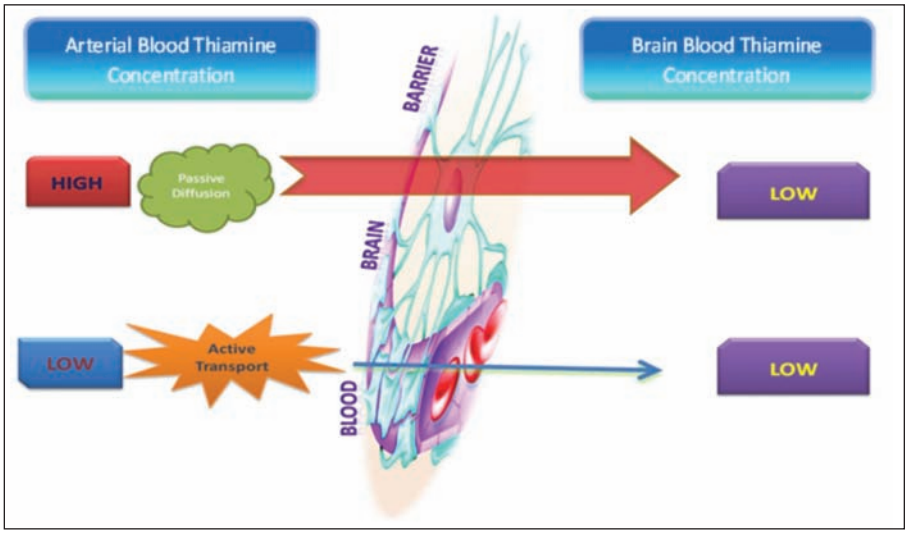

FIGURE 1. Transportation of thiamine through the blood brain barrier

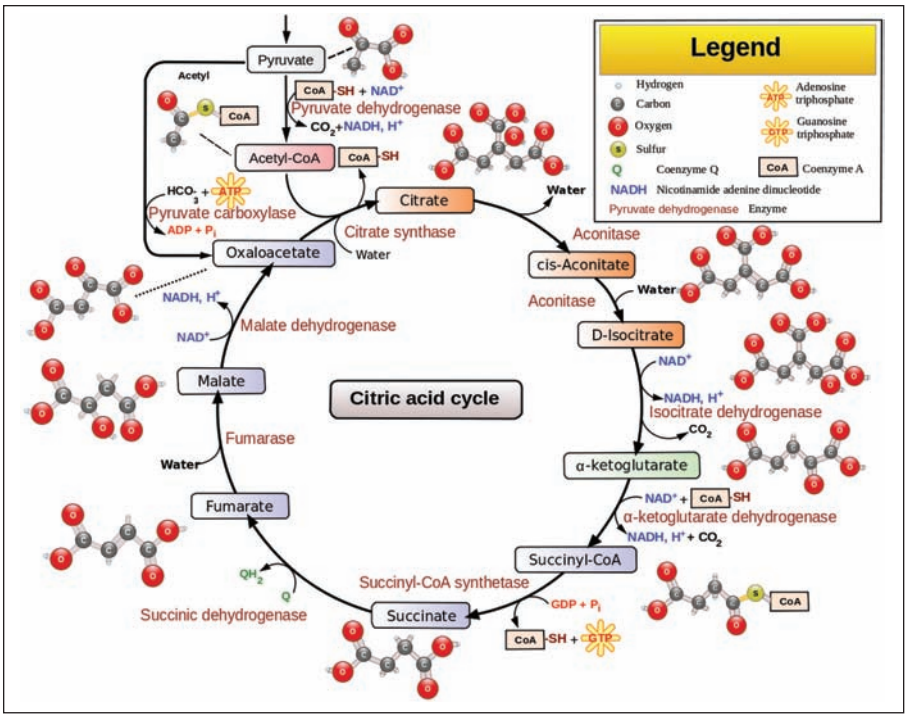

Figure 2. Thiamine (TPP) in the Kreb's cycle

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aspartate.[24,25] GABA is a major inhibitory neurotransmitter in the brain, and a decrease in the levels of this neurotransmitter and an increase in its amino acid precursor, glutamine, leads to neuronal excitation and hence delirium.[14]

Pentose phosphate pathway (PPP) is a very important pathway that occurs in the cytosol of human cells, including the brain, and serves as an alternative pathway to glycolysis.[26] Transketolase is an important enzyme in the pentose phosphate pathway that requires thiamine as a cofactor, modifying a molecule called glucose-6-phosphate, which is derived from glucose. This leads to the production of compounds; ribose-5-phosphate and reduced nicotinamide adenine dinucleotide phosphate (NADPH). Both of these molecules are essential for the production of numerous other important molecules in the cell. Ribose-5-phosphate is needed for the synthesis of nucleic acids, complex sugar molecules, and other compounds. NADPH provides hydrogen atoms for chemical reactions that result in the production of steroids, fatty acids, amino acids, certain neurotransmitters, and other molecules. In addition, NADPH plays an important role in the synthesis of glutathione, a compound that is essential in the body's defense against oxidative stress. Glutathione converts reactive H_2O_2 into H_2O. Impairment of this process leads to conversion of H_2O_2 to hydroxyl free radicals, which causes cellular injuries in neuronal cells, which presents as delirium.[27]

PREDISPOSING FACTORS TO THIAMINE DEFICIENCY

Thiamine deficiency can result from conditions that restrict eating, such as orofacial cancers, or limit adequate vitamin absorption, such as gastric bypass surgery,[28] gastric and colon cancer, hyperemesis gravidarum, or starvation by choice or associated with sepsis, surgical complications, and coma.[27,29,30] By far the most common cause of thiamine deficiency throughout the world is alcoholism,[31] as described in landmark studies of alcoholic Wernicke-Korsakoff syndrome (WKS).[32,33] Individuals with alcoholism are at special risk for thiamine deficiency because of poor diet associated with their lifestyle and because chronic alcoholism compromises thiamine absorption from the gastrointestinal tract, impairs thiamine storage, and may reduce thiamine phosphorylation essential for cellular function.[31,34-37] Table 2 outlines the predisposing factors for thiamine deficiency.

DIAGNOSIS

Wernicke's encephalopathy (WE) remains a clinical diagnosis; however, the best aid for a correct diagnosis is having a high index of clinical suspicion. Diagnosis includes taking a good history, looking out for causes of thiamine deficiency, and physical examination for expected signs (e.g., edema, problems with balance). Laboratory testing, although not specific for thiamine deficiency, include measurements of some carbohydrate metabolites that accumulate in the body due to impairment of carbohydrate metabolism. These metabolites include blood levels of lactate and pyruvate.[38] Blood levels of magnesium should also be checked because magnesium is required for the conversion of thiamine into its active form, thiamine pyrophosphate.[39]

A presumptive diagnosis of WE can be confirmed by determining blood thiamine concentrations or by measuring the erythrocyte transketolase activity.[40,41] This test is limited by its lack of specificity.[42] Recently, an isocratic high performance liquid chromatography method for the assessment of thiamine, thiamine monophosphate, and thiamine diphosphate in human erythrocytes has been described.[43] This procedure has improved reproducibility, practicability, and performance compared with previous methods, and is suitable for both clinical and research purposes.

Other routine diagnostic studies include lumbar puncture, electroencephalography, and neuroimaging studies. Cerebrospinal

fluid is normal in most patients, although raised protein concentrations can occur in late stages. Results of electroencephalography are within normal limits at an early stage, but show nonspecific slowing of the dominant rhythm in a late stage. Among paraclinical studies, magnetic resonance imaging (MRI) is currently considered the most valuable method to confirm a diagnosis of WE. MRI has a sensitivity of only 53 percent, but its high specificity of 93 pecent means that it can be used to rule out the disorder.[8,44] MRI studies typically show an increased T2 signal, bilaterally symmetrical, in the paraventricular regions of the thalamus, the hypothalamus, mamillary bodies, the periaqueductal region, the floor of the fourth ventricle, and midline cerebellum.[8,45] Disruption of the BBB has been seen in these regions in 6 of the 12 patients studied with contrast-enhanced computed tomography (CT) or MRI scans.[45] Importantly, the typical pattern of lesions on an MRI is observed in only 58 percent of patients.[46] Unusual sites of lesions include cortical regions and the splenium of the corpus callosum. Valuable adjuncts for an early diagnosis of Wernicke's encephalopathy are diffusion weighted MRI and proton MR spectroscopy,[47] which also may provide information on the pathophysiology of this encephalopathy. Ultimately, the diagnosis in a living patient is mainly supported by the response of neurological signs to parenteral thiamine.[38]

Clinically, early detection of thiamine deficiency is a difficult task because symptoms can be vague and nonspecific such as frequent headaches, fatigue, irritability, abdominal discomfort, and in children, decline in the growth rate.[6] However, thiamine deficiency presents acutely with the life-threatening condition WE. WE has an estimated mortality rate of about 20 percent.[11,48] This condition is marked by lesions of periventricular nuclei, hypothalamic nuclei, tectal plate and thalamus. Involvement of these organs resulting in WE's cardinal signs of ophthalmoplegia, nystagmus, ataxia, and delirium with significant spatial (the inability of a person to determine his true body position, motion, and altitude relative to the earth or his surroundings) and temporal (a state in which an individual has no bearing of time) disorientation.[33,49] Infarction of the mammillothalamic tracts is another antecedent of WE. About 82 percent of patients with WE present with delirium according to autopsy-based series.[32] This constellation of symptoms is largely due to involvement of thalamic or mamillary bodies and range from a confusional state to mental sluggishness, apathy, impaired awareness of the immediate situation, inability to concentrate and, if left untreated, coma and death.[32,50] Some patients may present with confusion or agitation, hallucinations, and behavioral disturbances that mimic an acute psychotic disorder.[51,52] Ocular abnormalities occur in approximately 29 pecent of patients, and include nystagmus, symmetrical or asymmetrical palsy of either lateral recti or other ocular muscles, and conjugate-gaze palsies, which result from lesions of the pontine tegmentum and of the abducens and oculomotor nuclei.[53] Acute WE, if left untreated, leads to the more profound, debilitating, global amnesic condition of Korsakoff's psychosis (KS),[54] although WE does not necessarily evolve into KS if adequately treated.[11,33] It remains controversial whether KS can develop without WE and whether mild forms of neuropsychological sequelae arise from repeated bouts of thiamine deficiency or inadequate treatment of such episodes.

About 80 percent of cases of WE-KS diagnosis are made during autopsy.[55] This might be caused by either a relatively nonspecific clinical presentation of the disease in some cases or poor clinical recognition of the neurological signs by clinicians. Studies

TABLE 2. Predisposing factors of and conditions associated with thiamine deficiency

PREDISPOSING FACTORS
• Staple diet of polished rice/malnutrition • Gastrointestinal surgical procedures: gastrostomy, gastrojejunostomy, partial or subtotal colectomy, gastric bypass surgery, vertical banded gastroplasty, therapy with an intragastric balloon
PSYCHIATRIC CONDITIONS
• Chronic alcohol abuse • Anorexia nervosa • Anorexia bulimia • Binge-eating disorder
MEDICAL DISORDERS
• Peptic ulcer, gastric cancer, colon cancer, ulcerative colitis with megacolon • Severe obesity • Recurrent vomiting or chronic diarrhea • Pyloric stenosis, peptic ulcer, drug-induced gastritis, biliary colics, Crohn's disease • Intestinal obstruction or perforation, lithium-induced diarrhea • Pancreatitis, hyperemesis gravidarum • Cancer and related conditions: gastric carcinoma, non-Hodgkin's lymphoma, myelomonocyitic leukemia, large B-cell lymphoma, myeloid leukemia, allogenic bone marrow transplantation/chemotherapeutics (e.g., erbulozole, ifosfamide)
SYSTEMIC DISEASES
• Renal diseases • Aquired immunodeficiency disease • Chronic infectious febrile diseases • Thyrotoxicosis

have shown that the possibility of an incorrect diagnosis is high in alcohol-dependent patients presenting to accident and emergency departments.[11] The common signs of WE are difficult, if not impossible, to differentiate from intoxication with alcohol, and such problems need to be addressed with emergency medicine doctors and nurses as part of their training.[25] The lack of an adequate training and preparation may result in misdiagnosis and treatment.[29,56] There are no specific routine laboratory tests available, and no specific diagnostic abnormalities have been revealed in cerebrospinal fluid, brain imaging, electroencephalogram, or evoked potentials.

TREATMENT

Thiamine deficiency is the established cause of WKS. WKS usually occurs in individuals with chronic alcoholism and affects the central nervous system (brain and spinal cord). WKS is the foremost neurological complication of thiamine (vitamin B1) deficiency,[50] and the term WKS refers to two different syndromes, each representing a different stage of the disease: WE is an acute syndrome requiring emergent treatment to prevent death and neurological morbidity; and Korsakoff syndrome (KS) refers to a chronic neurological condition that usually occurs as a consequence of WE.[50,57]

The treatment of clinical manifestations of thiamine deficiency, especially WE is a medical emergency, and in patients in whom the disorder is suspected thiamine should be initiated immediately, either intravenously or intramuscularly, to ensure adequate absorption.[58] Studies[11,31,48] support several different regimens for patients with the disorder and those at risk of developing it. Specifically, patients who have signs indicative of WE should be treated empirically with a minimum of 500mg thiamine hydrochloride per 100mL of normal saline, given by infusion over a period of 30 minutes, three times per day for 2 to 3 days. In cases where there is no response, supplementation may be discontinued after 2 to 3 days. In cases where an effective response is observed, 250mg thiamine should be given intravenously or intramuscularly daily for 3 to 5 days, or until clinical improvement ceases, and should be continued. Doses of thiamine below 250mg per day apparently may not restore vitamin status,[59,60] improve clinical signs,[61] or prevent death.[62] In particular, when patients with WE are inappropriately treated with low doses of thiamine, the biochemical abnormalities caused by thiamine deficiency can lead to irreversible brain damage and death.[11,48] Recent data from a controlled study into the therapeutic benefits of thiamine in alcohol-dependent patients without clinically apparent WE indicate that at least 200mg of parenteral thiamine may be required to improve neurological symptoms.[63] Prophylactic treatment with intravenous or intramuscular administration of 100mg per day (in the United States[64]) or 250mg once daily in for 3 to 5 consecutive days should be used in all patients with severe alcohol withdrawal and poor diet with signs of malnutrition.[11,48,62] It is mandatory that thiamine is given before or concomitantly with intravenous administration of glucose so as not to precipitate WE. The changes in mental status have shown to improve after 2 to 3 weeks of therapy. Deficiency in other vitamins and electrolytes, especially niacin and magnesium, also should be corrected. Thiamine supplementation by mouth should be continued for several months at a dose of 30mg twice daily, since it is not toxic to the body in excess amounts.[59]

Typical brain lesions of WE are observed at autopsy in 0.8 to 2.8 percent of the general population in the Western world, and the vast majority of affected patients are alcoholic.[50,65] The prevalence of WE lesions seen on autopsy in alcohol abusers is generally higher than in those individuals who do not abuse alcohol.[66] Among those with alcohol-related deaths, it has been reported to be even higher: 29 to 59 percent.[67,68] Cases of WE in men generally outnumber cases in women; yet women appear more susceptible to developing WE than men.[50,69]

CONCLUSION

Thiamine is an essential requirement for normal cerebral energy metabolism. Deficiency of thiamine leads to mitochondria dysfunction, which manifests as WE/KS. The underlying pathophysiology of thiamine deficiency is multifactorial in nature and involves a wide-ranging cascade of events that involves impairment of glucose metabolism, ultimately resulting in neuronal cell death. Additional studies are required to explain the predilection of selective brain structures due to thiamine deficiency. Also, randomized, controlled trials are needed to define the optimum dose and duration of thiamine treatment for prophylaxis or treatment of clinical manifestations of thiamine deficiency. Clinicians and other ancillary health workers should be properly trained to have a high index of suspicion of thiamine deficiency in situations of unbalanced nutrition that has lasted for 2 to 3 weeks to avoid misdiagnosis of the life threatening WE or irreversible brain damage caused by KS. Finally, while thiamine deficiency involves a variety of functional impairments at several different levels, understanding the mechanisms that underlie the characteristic focal vulnerability associated with this disorder remains the primary goal and is expected to continue to yield important new insight into how derangement in the metabolic process leads to life-threatening neuropsychiatric conditions.

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