Review

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Review of thiamine deficiency disorders: Wernicke encephalopathy and Korsakoff psychosis

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Abstract: Wernicke encephalopathy (WE) and Korsakoff psychosis (KP), together termed Wernicke–Korsakoff syndrome (WKS), are distinct yet overlapping neuropsychiatric disorders associated with thiamine deficiency. Thiamine pyrophosphate, the biologically active form of thiamine, is essential for multiple biochemical pathways involved in carbohydrate utilization. Both genetic susceptibilities and acquired deficiencies as a result of alcoholic and non-alcoholic factors are associated with thiamine deficiency or its impaired utilization. WKS is underdiagnosed because of the inconsistent clinical presentation and overlapping of symptoms with other neurological conditions. The identification and individualized treatment of WE based on the etiology is vital to prevent the development of the amnestic state associated with KP in genetically predisposed individuals. Through this review, we bring together the existing data from animal and human models to expound the etiopathogenesis, diagnosis, and therapeutic interventions for WE and KP.

Keywords: alcoholism; alcohol-related brain disorders; memory; neurodegeneration; thiamine.

Introduction

Thiamine, otherwise known as vitamin B1, is a water-soluble vitamin that is a vital component in several biochemical pathways involving glucose metabolism [1]. Wernicke's encephalopathy (WE) is a neuropsychiatric disorder precipitated by the deficiency of thiamine, which was first described by Carl Wernicke in 1881 [2]. Wernicke observed a triad of symptoms in two alcoholics and a woman who had pyloric stenosis due to sulfuric acid ingestion. These symptoms were ophthalmoplegia, ataxia, and mental confusion. Wernicke noticed hemorrhagic lesions around the periaqueductal region on histologic examination of these patients and hence termed the disease "polioencephalitis hemorrhagic superioris." A series of reports written by Sergei Korsakoff from 1891 to 1897 described "psychosis polyneuretica" as a completely independent disease characterized by severe memory loss resulting from chronic alcohol consumption [3]. In 1897, Murawieff proposed that a common etiology may be responsible for the development of both conditions. WE, although mostly precipitated by malnutrition associated with alcoholism, can occur in non-alcoholics as well [4].

WE is an acute condition, which, if left untreated for a prolonged period, can lead to permanent brain damage. Korsakoff syndrome (KS) affects the patient's working memory. Patients are unable to consolidate short-term memories to long-term memories because of lesions in the diencephalon-hippocampal circuit [5]. The acquisition of information and the integration of already stored information are necessary for adapting to new circumstances. Patients with KS are therefore incapable of doing anything outside of their routine habits. Although the older definitions rely on irreversible loss of memory as the cardinal symptom of KS, there are concurrent cognitive and behavioral changes [6]. It is still unclear whether in the absence of alcohol consumption disorder, patients can progress to KS [7, 8]. These neurological manifestation of severe acute thiamine deficiency is also called as dry beriberi. Another variant of the prolonged thiamine deficiency disorder is the "wet beriberi," which presents as cardiovascular manifestations [9]. Although the likelihood of both conditions is somewhat based on genetics, both can occur throughout the world.

WE manifests as a result of insufficient delivery of thiamine to the brain, and this may be caused by inadequate dietary consumption, impairment of intestinal

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absorption of thiamine, or increased thiamine loss from the body. WE takes approximately 4–6 weeks of thiamine deficiency to develop [10]. The delay in thiamine deficiency is because the human body can store 30–50 mg of thiamine, and thiamine consumption is only about 2 mg per day. Dietary thiamine requirement is 0.5 mg for every 1000 kcal consumed. Even though 1.4 mg of thiamine is the recommended daily intake, chronic consumption of alcohol restricts its uptake. In developing nations, WE is mainly due to malnutrition, whereas cases from affluent countries are primarily caused by alcoholism [9]. WE can be broadly divided into alcoholic and non-alcoholic based on the etiologic factor. Acute thiamine deficiency in both alcoholics and non-alcoholics can be corrected by high doses of parenteral thiamine. However, many alcoholics who are diagnosed after significant disease progression due to self-neglect or those who are undertreated in the initial phases of the disease might not respond well to the therapy [11, 12]. During diagnosis, it is essential to differentiate between the two etiological factors because alcoholics require higher doses of thiamine and parenteral route of thiamine administration in contrast to non-alcoholic patients. The reason for this is that alcoholism impairs thiamine absorption and also produces neurotoxicity by itself. Also, therapy needs to be supplemented with non-pharmacologic methods such as individual alcohol cessation counseling and group therapy sessions.

Proper diagnosis of WE is dependent upon clinical judgment. Only 16% of the cases present with the classic triad of symptoms [13]. WE presents a wide range of symptoms, which are not always fully appreciated and correlated clinically with the disease diagnosis. The symptoms often overlap with alcoholic delirium, and this further complicates the diagnostic accuracy. Although not extensively validated in non-alcoholics, the use of Caine's criteria by physicians could improve the diagnostic accuracy for WKS (Wernicke–Korsakoff syndrome), especially when the patient is alcoholic or has a condition that could precipitate thiamine deficiency [14].

Epidemiology

It was indicated in the European Federation of Neurological Societies guidelines that "Wernicke's encephalopathy is not a rare disorder, but rather a rare diagnosis" [11]. Autopsy studies have estimated the prevalence of WE to be between 1% and 3%, which is significantly higher than the percentage of cases detected during clinical examinations. One of the studies had estimated the prevalence of WE lesions to be around 12% during autopsy studies, and this was corroborated by other studies that estimated the prevalence of lesions to be 29%–59% in the autopsy of deaths related to alcohol use [8, 15, 16]. The exact prevalence of WE is often underestimated because of improper diagnosis of the disease. One of the autopsy-based studies has estimated that 30–80% of alcoholic patients have low circulating levels of thiamine and their level of depletion varies depending on factors such as malnutrition, hepatic impairment, and alcoholism [17]. Up to 80% of the cases that are missed during routine diagnosis are confirmed only during an autopsy [18]. This is partly because the symptoms of delirium, which are present in alcoholic WE, are often misdiagnosed as alcoholic delirium. The prevalence of this disease is higher in males than in females with a gender ratio of 1.7:1 [19]. About 75% of the patients with WE who are not diagnosed and not given parenteral therapy develop permanent brain damage, while 20% may culminate in death [20]. Only about 13% of alcoholics go on to develop WKS [21] as compared to the high proportion of alcoholics who develop WE. This implies the involvement of a genetic component. Although WE in pediatrics is hypothesized to be almost identical to that in adults, about one-third go undiagnosed till postmortem examinations [22, 23].

Etiopathogenesis

Thiamine is an essential nutrient required by all tissues for the assembly and efficient functioning of different enzymes involved in the utilization of carbohydrates for cellular function. During thiamine deficiency, critical pathways such as neurotransmitter synthesis, nucleic acid synthesis, and synthesis of steroids and fatty acids are affected. Although thiamine deficiency can affect almost all organs of the body, the impact is most severe in the brain and heart, depending on the population and genetic factors involved. Both the neurons and glial cells in the brain are affected by thiamine deficiency and have been implicated in the development of WE as well as other forms of alcohol-related brain injury [24–26]. Thiamine is metabolized by the liver to its biologically active form thiamine pyrophosphate (TPP, thiamine diphosphate, or carboxylase) by the enzyme thiamine diphosphokinase [27, 28]. Diseases such as liver cirrhosis, which are usually seen in chronic alcoholics, can reduce the body's ability to convert thiamine to its active form. TPP is a vital coenzyme involved in carbohydrate metabolism, and deficiency of thiamine can lead to decreased

functioning of enzymes involved in the tricarboxylic acid cycle (alpha-keto glutamate dehydrogenase and pyruvate dehydrogenase), pentose phosphate pathway (transketolase), and branched-chain amino acid metabolism (branched-chain alpha-ketoacid dehydrogenase). While transketolase is predominantly present in the cytosol, the dehydrogenases are present within mitochondria. Thiamine diphosphate is further converted to thiamine triphosphate (TTP), which is involved in the membrane permeability of chloride ions [28].

Alpha-keto glutamate dehydrogenase, pyruvate dehydrogenase, and transketolase involved in the carbohydrate catabolism are comprised of individual subunits that require thiamine as a cofactor for assembling into a functional enzyme [29]. In the pentose phosphate pathway, transketolase catalyzes the conversion of glucose-6-phosphate (G6P) to ribose-5-phosphate and nicotinamide adenine dinucleotide phosphate (NADPH). Glutathione is a compound that scavenges free radicals during oxidative stress, and NADPH is essential for the formation of glutathione. Additionally, NADPH supplies the hydrogen required for nucleic acid synthesis by ribose-5-phosphate. Pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase are involved in glycolysis and Kreb's/citric acid cycle, the two reactions essential for the creation of adenosine triphosphate (ATP). G6P is ultimately converted to pyruvate at the end of glycolysis, and pyruvate dehydrogenase converts pyruvate into acetyl coenzyme A (CoA), which enters the citric acid cycle. Acetyl CoA is needed for the synthesis of the neurotransmitter acetylcholine and myelin synthesis. Alpha-ketoglutarate dehydrogenase within the Kreb's cycle is vital for the formation of gamma-aminobutyric acid (GABA), glutamate, and aspartate. Transketolase is the most sensitive marker of thiamine deficiency. Its activity can be reduced by up to 90% in areas of the brain that have a high sensitivity to thiamine levels [30].

Thiamine is absorbed in the intestine through both active and passive processes. When the luminal concentration is low, the absorption occurs through active transport, while when the concentration is high, passive mucosal diffusion dominates. Thiamine generally undergoes four stages of transportation before reaching the brain. The first step is the absorption across the luminal brush border membrane of the intestine, and then the second phase involves transportation from the enterocytes into the bloodstream through the basolateral membrane. The third step involves transport of the thiamine from the bloodstream into organs such as the liver, heart, and other storage tissues. Thiamine is stored predominantly in the brain, kidney, heart, liver, and skeletal muscles. Its half-life ranges from 9 to 18 days. Thiamine absorption mainly takes place through an active transport mechanism, which can be saturated. From an approximate dosage of 15 mg of thiamine, only about 4–5 mg may be absorbed. The final step is the transport across the blood-brain barrier into the cerebrospinal fluid (CSF) for neuronal consumption [1, 25, 31, 32]. Several different transported proteins are involved in these processes. Alcohol consumption and malnutrition conditions affect the intestinal absorption process and can potentiate thiamine deficiency in patients who already have lower levels of thiamine due to dietary intake. Alcohol affects the absorption process by interfering with the active transport system in the intestine. This is aggravated by alcohol-induced liver damage, which results in steatorrhea, vomiting, and diarrhea, which further depletes the stored content of thiamine in the body. Alcoholism also interferes with thiamine phosphorylation, while the other cerebral disruptions caused by alcoholism trigger KS in patients with an acute liver injury. Thiamine transport across the blood-brain barrier is altered in conditions of both thiamine deficiency and alcoholism, thus decreasing the amount of thiamine entering the brain through passive diffusion. Chronic alcoholism negatively influences transketolase's stability because of the interaction of the enzyme with acetaldehyde. A decline in cerebral transketolase is correlated with the development of ataxia [33, 34]. In KS, small doses of thiamine may be inadequate in maintaining a concentration gradient to facilitate diffusion into the brain. This differs from WE, which can be corrected with oral doses, as the concentration gradient is sufficient to maintain diffusion. Animal models have demonstrated that the deficiency of other vitamins such as folate and cyanocobalamin can interfere with the active transport process as well.

Even though a person may not be malnourished, his/her dietary practices can still influence the development of thiamine deficiency. For example, a significant proportion of the Asian population consumes polished rice, which, because of the removal of the husk through milling, lacks thiamine [35]. Further, clinical and surgical practices that affect the physiology of the gastrointestinal system or dietary practices may influence thiamine absorption. Surgical procedures involving the resection of part or all of the stomach or intestine for the treatment of conditions such as cancer, peptic ulcer, inflammatory bowel disease, and other similar conditions are common predisposing factors and can frequently be observed in patients who have had a monthly weight loss of more than 7 kg [36, 37]. A recent systematic review found that the risk of WE is not only increased after the first half year

after surgery but persists lifelong, necessitating routine follow-up of thiamine status [38]. Drugs that induce thiamine deficiency include chemotherapeutic agents and high doses of nitroglycerin via intravenous infusion. Cancer has a detrimental impact on the body's thiamine levels as a result of factors such as accelerated thiamine consumption by neoplastic cells, malabsorption, and reduced appetite in patients. This is further aggravated in cancer patients during therapy involving surgery and chemotherapy [39–41].

During thiamine deficiency, alpha-keto glutamate dehydrogenase levels are reduced by the 4th day in astrocytes, and there is an increase in their volume associated with cytotoxic edema. The disrupted glucose oxidation in the mitochondria results in cytotoxicity through necrosis, and the cells exhibit cytotoxic edema. Cell death occurs through both apoptosis and necrosis as a result of the damaged mitochondrial function. The oxidative stress associated with thiamine deficiency is evident in the increased cerebral levels of intercellular adhesion molecule 1 (ICAM-1) and hemeoxygenase-1 in rats. The oxidative stress is considered to increase the expression of endothelial nitric oxide synthase and thereby nitric oxide by the 7–10th day. This nitric oxide forms peroxynitrite when interacting with oxygen free radicals and has been implicated in cytotoxicity, as well as further inhibition of alpha-keto glutamate dehydrogenase, thus initiating a biochemical cycle. The extracellular glutamate level increases, and osmotic gradient disruption occurs as a result of the impairment of astrocyte glutamate transporters (GLT1 and GLAST) and a reduction in complexins, leading to increased presynaptic glutamate transmission [42]. Further protein alterations in astrocyte involve aquaporin-4 and glial fibrillary acid protein (GFAP), which leads to the swelling of cells due to disrupted water balance and cytoskeleton instability. Kreb's cycle impairment affects the de novo synthesis of GABA by affecting its turnover in astrocytes. By the 10th day, there is a breakdown of the blood-brain barrier. Fourteen days after the onset, there is focal acidosis associated with increased lactic acid production in astrocytes due to the disruption of pyruvate dehydrogenase in Kreb's cycle. This leads to the breakdown of genetic material and neuronal necrosis. The changes become progressively irreversible in specific locations of the brain based on their metabolism. Thiamine is converted to TPP in the neuronal and glial cells. Thiamine deficiency can result in impaired energy production and myelin sheath maintenance due to dysfunctional carbohydrate and lipid metabolism, respectively. The carbohydrate metabolism in brain cells is impaired, and they are unable to utilize the supplied carbohydrates. This impact is especially felt in areas of high carbohydrate metabolic consumption, leading to focal lactic acidosis and cerebral energy loss. Because of the impact of carbohydrate deficiency, the symptoms in patients with WE are often aggravated by diets high in carbohydrates, caloric intake, and a glucose load before thiamine supplementation can trigger symptoms [43–47].

The symptoms in patients with WE are a direct outcome of the lesions in specific areas of the brain. The ocular deficits are due to the brainstem lesions affecting pons and the midbrain. However, with thiamine administration, the condition improves, as there is no significant damage to the nerve cells. When damaged, the superior vermis of cerebellum manifests as ataxia, and there is cross-sectional damage to the cerebellar cortex. Vestibular apparatus damage in these patients further worsens the abnormalities with gait and stance. Alcohol is involved in the upregulation of GABA receptors and downregulation of glutamate receptors. The body tries to correct this by a compensatory increase in glutamate and reduction in GABA function. Alcohol withdrawal is an outcome of this compensatory process driven into imbalance and can result in alcohol withdrawal seizures and delirium tremens. However, this state is acute, and withdrawal symptoms persist only for the initial days after stopping the alcohol intake. Glutamate-induced excitability can happen in patients who withdraw and frequently relapse, which, when compounded with the TD-induced glutamate release, results in neurotoxicity [48]. Some patients could, however, redevelop the symptoms of WE even after alcohol cessation if they develop any debilitating condition such as infections, burns, or falls.

Autopsy neuropathology

Many cases of WE remain undiagnosed until the death of the patient because of inconsistent clinical presentation across the patient population. The neuropathological changes involve a symmetrically distributed loss of neurons and myelinated structures from mammillary bodies, superior cerebellar regions, brain stem structures (vestibular and inferior olivary nucleus), and hypothalamic nucleus [49, 50]. The cerebellar lesions are responsible for the ataxic gait, while the brainstem lesions are responsible for the disruption in vital signs characterized by respiratory distress, hypothermia, and hypotension. Macroscopic examination of the brain is less conclusive,

and therefore microscopic examination is required. The overall macroscopy of the brain reveals grayish discoloration of mammillary bodies, dilation across the paraventricular region, and pinpoint hemorrhages around the periaqueductal region. The mammillary body lesions are the classic autopsy sign in WE patients and are present in almost all cases. Similarly, most patients have bilateral histopathological changes in the dorsal thalamic nucleus. On rare occasions, the walls of the third and fourth ventricles become grayish as a result of necrosis. The most apparent feature on microscopic examination is the presence of gliosis due to atrophy, resulting in the packing of cells nearby. Acute lesions are characterized by small, symmetric hemorrhages in the thalamus and brainstem areas that appear as a result of the rapid decline in the thiamine levels. The third ventricle walls undergo gray matter changes because of the necrosis of neurons and other myelinated bodies along with hypertrophic changes in the microvasculature [8, 47].

Genetics and molecules associated with the Wernick–Korsakoff syndrome

Genetic susceptibility in the development of WKS has been hypothesized since the 1970s. However, there have been very few studies specifically aimed at identifying the genetic association in humans. One major epidemiological feature that clearly underlines the genetic factor in the outcome of thiamine deficiency is the difference in races. While the Asian population are more likely to be predisposed to the beriberi syndrome, Europeans have a higher susceptibility to developing WE. WE is considered to evolve as a result of interactions between environmental factors and genetic components, giving rise to a broad spectrum of clinical presentations. The majority of studies have focused on genes that express enzymes dependent on thiamine levels, alcohol-metabolizing enzymes, and GABA receptors. Humans are incapable of de novo synthesis of thiamine and are therefore reliant on dietary thiamine absorption. Genetics associated with the evolution of WKS have been attributed to the *SLC19A2* (solute carrier family 19 member 2) gene and the *SLCA3* (solute carrier family 1 member 3) gene, which translate to SLC19A2 (thiamine transporter 1) and SLCA3 (thiamine transporter 2), respectively. SLC19A2 is a high-affinity, sodium-independent transporter for thiamine driven by transmembrane pH gradient. The SLCA3 protein is involved in thiamine transport at a lower affinity. The genetic susceptibility associated with mutations in these two genes becomes expressed in alcoholics who develop reduced plasma thiamine levels and storage deficiencies. Lieber–DeCarli rat models have demonstrated translational inhibition of the two genes in chronic alcohol consumption. The mutation in *SLC19A2* was initially recognized in a group of Iranian families who developed thiamine-responsive megaloblastic anemia syndrome, an autosomal recessive disorder. There have been two variants of this gene that have been identified in producing different products on transcription. Missense mutations on the *SLC19A3* (solute carrier family 19 member 3) genes were identified in patients with biotin-responsive basal ganglia disease among members of inbred families. Variation in the activity of the gene was responsible for reduced intracellular thiamine transportation due to an alteration in the activity of transporter proteins [34, 51–53].

Although several studies have been conducted on the variation of the three enzymes requiring thiamine cofactor, the results have been inconsistent. Most studies have been conducted in the dermal epithelium and blood cells of patients, and it is unclear whether they are comparable to neuronal cells. Transketolase alteration is also attributed to the development of a genetic predisposition to WE. In the cell culture of patients with WE, the transketolase enzyme had reduced affinity for its cofactor, thiamine pyrophosphate, in contrast to a control group of cells from normal individuals. The abnormality persisted across continuous cell culture passages and was further consolidated by the observations made in monozygotic twins with WKS. Transketolase with such variations in patients with KS can maintain affinity to thiamine at a normal concentration, but the binding capability decreases with thiamine deficiency. The transketolase-like 1 (*TKTL1*) gene, which is found on the X-chromosome, is involved in the synthesis of a transketolase enzyme. This enzyme catalyzes a reaction linking the pentose phosphate pathway with the glycolytic pathway [54–56]. Reports have indicated variations in the alpha-ketoglutarate dehydrogenase complex. However, none of the enzymes involved is thiamine-dependent. Further, patients with such an anomaly have not been shown to demonstrate a therapeutic response to thiamine administration. Another hypothesized yet unconfirmed genetic component is an unidentified “assembly factor” which helps in the formation and stabilization of the transketolase homodimer with thiamine diphosphate and magnesium. It is postulated that the other enzymes might have a similar mechanism of assembly and a variation could alter the turnover of stable enzymes.

Clinical presentation and diagnosis

Wernicke has described the condition as a triad of symptoms characterized by oculomotor dysfunction, cerebellar dysfunction, and delirium. However, the incidence of all three symptoms in patients is rare (≈17%) and the majority of patients present with delirium alone [57]. Only about one-third of the patients have all three symptoms, and delirium is the most prevalent, followed by cerebellar problems and lastly ocular abnormalities. Conversely, younger patients who undergo bariatric surgery present predominantly with sensory motor symptoms of WE and mostly do not develop mental status changes [38]. The initial symptoms of WE are frequent headaches, gastric discomfort, irritability, and fatigue. Certain brain regions are more vulnerable to thiamine deficiency, and the clinical presentation is influenced by the tissue requirements of TPP [44]. Ocular abnormalities remain the hallmark of WE. The clinical symptoms are manifestations of deficits in oculomotor, abducens, and vestibular nuclei. Oculomotor abnormalities involve nystagmus, sluggish reactions to light, lateral gaze palsy, conjugate gaze palsies, and bilateral visual disturbances, which frequently occur together rather than alone [58, 59]. Lesions in the anterior and superior vermis of the cerebellum cause ataxia and dysarthria of the limbs. However, ataxic gait is not just a manifestation of cerebellar pathology; it is the combination of vestibular paralysis and polyneuropathy [60]. The stance of the patients changes from normal to wide with bradykinesia, and patients in the acute stage of the disease have vestibular dysfunction (which mostly does not result in auditory impairment). The posterior hypothalamus is involved in thermoregulation, and lesions can lead to the development of hypothermia. Furthermore, the brainstem involvement causes hypotension, tachycardia, syncope, and respiratory problems. Excessive glutamate release and imbalance between GABA and glutamate levels can result in epileptic seizures [8, 48]. Peripheral neuropathy involving lower extremities can develop over time and is characterized by paresthesia, weakness, and pain toward the distal regions. Memory impairment is usually aggravated with the progression of KP, which is a stable condition due to the irreversible damage to the diencephalon-hippocampal circuit, and the diagnosis of KP can be made several weeks after alcohol cessation. [6, 61].

There are two types of amnesia, retrograde and anterograde. Retrograde amnesia presents in such a way that patients forget events that occurred in the recent past, but their long-term memories are still intact. Because of memory loss, there is the possibility of confabulation, wherein the patient perceives invented memories to be true. These invented memories fill in the missing gaps left by memory loss.

The nonspecific clinical presentation in patients with WE and overlapping clinical presentation with alcohol toxicity makes the diagnosis extremely difficult. The impaired awareness of situations, mental sluggishness, and apathy, if left untreated, can ultimately result in coma and death [25, 62]. Therefore, the best investigative strategy is to be clinically alert toward the presenting symptoms in patients with a nutritional deficiency or other factors that can lead to dietary insufficiency. The major drawback of this strategy is that unless and until the patient presents with the triad of symptoms, the condition tends to be overlooked. Erythrocyte transketolase level and blood thiamine concentration can be used for plausible diagnosis. The method used involves an estimation of the concentration of thiamine, thiamine monophosphate, and thiamine diphosphate in erythrocytes. However, WE cannot be diagnosed solely on the basis of thiamine concentration, as there is no specific critical level below which all individuals develop the condition [34]. Additionally, thiamine is utilized in the form of TPP in the brain, and the development of WE is further dependent on the activity of the enzyme and transporter proteins. Clinically, the response of patients to thiamine therapy is considered a good diagnostic strategy [63]. Even though CSF protein levels tend to be higher in the later stages of the disease, they remain normal during the initial stages. Test reports are not instantaneous, and clinicians should rely on the clinical information available to immediately commence the therapy.

Although imaging studies are not recommended as a diagnostic tool, they could be used to rule out the alternative diagnosis. Magnetic resonance imaging (MRI) remains the relatively superior imaging tool because of its high specificity despite having a midline sensitivity. Increased T2 signals in MRI are correlated with the areas of the brain that have a disrupted blood-brain barrier. MRI evidence of mammillary atrophy and third ventricle enlargement are important hallmarks of the condition. Mammillary body atrophy can usually be found in MRI scans within a week of encephalopathy's onset [64, 65]. A computed tomography (CT) scan is considered insensitive to WE and is not recommended for routine diagnosis [66]. Electroencephalogram (EEG) variations range from diffuse mild to moderate slow waves and are not a good diagnostic option, as the prevalence of abnormalities among patients is inconsistent.

An "operational criterion" put forth by Caine differentiates WE from WE in combination with Korsakoff syndrome and WE with hepatic encephalopathy. The

criterion (2010 European Federation of Neurological Societies guidelines) is comprised of four factors: oculomotor abnormalities, dietary deficiency, cerebellar signs, and either altered mental state or memory impairment [14]. Caine found significant diagnostic specificity in patients who had two out of the fours signs. The diagnosis needs to differentiate between alcoholic WE and non-alcoholic WE because the therapeutic strategies for each group are different and delaying parenteral thiamine administration for alcoholic patients can be detrimental. This emphasizes the importance of obtaining a medical and social history of patients, which includes dietary practices, previous surgeries, diseases, and medications taken by the patient.

Therapeutic options

WE is considered a medical emergency and the patients require immediate intramuscular or intravenous thiamine administration to prevent further progression. The reason for this is that, if left untreated, the biochemical alterations can culminate in permanent neurological impairment. As per a Cochrane review by Day et al., double-blind, randomized, controlled trial (RCT) on thiamine administration in WE identified only two studies of adequate quality [67]. The review also concluded that there was insufficient data from the available clinical studies to recommend an optimal therapeutic regimen that clinicians could use for the treatment or prophylaxis in alcoholic patients. Hence, the conclusions on an optimal thiamine-dosing regimen have mostly been drawn from observations, such as the ineffectiveness of preventing death with a dose below 250 mg and the development of symptoms in patients taking high doses of oral thiamine. The half-life of thiamine is 96 min, and therefore the ideal regimen would involve administration of the drug twice or thrice daily.

Non-alcoholic patients usually respond to intravenous doses of 100 and 200 mg of thiamine. As per the recommendations of the Royal College of Physicians, alcoholic patients who are at risk of developing WE can be treated with a dose of 500 mg of thiamine hydrochloride in 100 mL of normal saline through intravenous infusion over half an hour. This has to be repeated thrice daily for 2–3 days and can be discontinued if the patients do not respond adequately. If the patients show a response, then intramuscular dosing of 250 mg of thiamine daily for 3–5 days is recommended. The higher dose requirement in alcoholics may be attributed to the long-term development of subclinical changes in the brain. If there is no clinical improvement in patients with WE, the next phase of treatment involves preventive strategies involving oral thiamine supplementation regularly and rehabilitation to avoid the development of amnestic state associated with KS. Determination of thiamine levels at different phases of therapy can be used as a guideline to determine whether to continue with the current route of administration and dosage. Thiamine therapy should be supplemented with the administration of electrolytes, especially magnesium and potassium, as they are essential cofactors in the proper functioning of enzymes. Electrolytes, along with other vitamins, tend to be low in alcoholics and supplementation is necessary for preventing treatment failure [11, 19, 39, 68–70].

When a suspected case of WE is administered glucose, especially alcoholics presenting with hypoglycemia, it is recommended that thiamine infusion is given before or along with the glucose load to prevent the exacerbation of symptoms [71]. Patients who have a chronic history of alcoholism can develop symptoms on a withdrawal regimen due to the sudden shift in glutamate and GABA levels. Therefore, the patients should be administered thiamine before the withdrawal regimen is initiated. Further, the treatment should proceed beyond the achievement of sobriety. Ideally, oral supplementation of thiamine should be instituted until the patient is free from any risk factors that can cause the development of thiamine deficiency to reoccur. Therapy involving parenteral thiamine is considered safe except for occasional circumstances of allergic reactions involving pruritus and local irritation. However, rare cases of anaphylactic reactions with multiple intravenous injections can happen, and this can be prevented by infusing thiamine after diluting it with normal saline or dextrose at 5% over half an hour. It is important to note that all of these strategies are inefficient unless the patient ceases alcohol consumption completely. Withdrawal therapy and rehabilitation support are an essential part of alcoholic WE therapy. Therefore, patients should be referred to counseling programs, group therapy sessions, etc., on an individual basis [19, 72, 73]. The recovery rates of mobility problems are comparable to those of mental problems, and hence motor rehabilitation of patients recovering from WE should be considered as a nonpharmacological treatment option [74].

Preventing thiamine deficiency requires initiatives at the government level, which involve thiamine supplementation in a susceptible population. Autopsy studies in Australia have demonstrated a reduction in cases of WE after supplementing flour with thiamine[21]. Although there have been suggestions regarding the supplementation of alcoholic beverages with thiamine, this may not be beneficial as thiamine absorption is inhibited by alcohol. Also,

alcohol metabolism can affect the glucose metabolism by preventing phosphorylation of thiamine and its incorporation into enzymes. Oral multivitamin pills are usually prescribed for patients who have undergone bariatric surgery; however, prescribing multivitamins along with parenteral thiamine supplementation would be more beneficial for these patients. Oral supplementation of thiamine in the form of a capsule that does not require skills to administer (unlike parenteral therapy) makes it an easy, cost-effective alternative. The early therapeutic response to thiamine therapy reflects improvement in biochemical events rather than structural lesions. The recovery of patients with the classic triad of symptoms starts with the improvement of ocular symptoms within a few hours or days. This is followed by an improvement in vestibular function, which is reflected in the ataxic gait improvement. States of delirium may take weeks to recover from, and MRI abnormalities will subside with clinical improvement.

Conclusions

The understanding of WE has advanced with increasing data available from human and animal models. However, the condition remains underdiagnosed, mainly due to the nonspecificity of the symptoms and overlap of clinical presentation with alcoholic delirium. The lack of a highly specific test or diagnostic criterion makes the diagnosis of WE disease complicated, and therefore it is beneficial to initiate thiamine replenishment from a prognostic perspective. In comparison to the oral formulation, parenteral therapy should be immediately initiated in cases where WE is suspected in order to prevent progression to amnestic states associated with KP. The assessment of the history of patients with nonspecific symptoms can not only improve the diagnosis of underlying etiopathogenesis but also help appraise the need for combining nonpharmacological interventions to the parenteral thiamine therapy.

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