IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Wernicke's Encephalopathy: What You Need To Know.

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ABSTRACT

Acute brain disorders such as Wernicke's encephalopathy, which result from a thiamine (vitamin B1) deficiency, are often associated with chronic alcoholism, malnutrition or gastrointestinal disorders that impair nutrient absorption. This review provides a comprehensive overview of Wernicke's encephalopathy, focusing on its pathogenesis, clinical presentation, diagnostic criteria and management strategies. The classical triad of symptoms -ataxia, ophthalmoplegia and confusion – characterises this condition. However, early diagnosis is challenging due to the variability in clinical symptoms. Prompt intravenous thiamine administration is crucial to prevent Wernicke-Korsakoff syndrome, a more severe and chronic progression of the disease. This review emphasizes the importance of awareness and education in the prevention, diagnosis and treatment of Wernicke's encephalopathy, summarizing current research and research guidelines.

KEYWORDS: Wernicke's encephalopathy (WE), thiamine, beriberi, ataxia, ophthalmoplegia, alcohol use disorder, vitamin B1, Wernicke's triad.

INTRODUCTION

Thiamine, also known as vitamin B1, is a crucial water-soluble vitamin necessary for energy metabolism, as it helps convert carbohydrate into energy. It is essential for the proper functioning of the heart, muscles and nervous system. Thiamine can be found in various foods such as whole grains, legumes, nuts, seeds, pork, fortified bread and cereals. Symptoms of thiamine deficiency include fatigue, irritability, impaired memory, loss of appetite, and muscle weakness. Severe deficiencies can lead to diseases like Wernicke's encephalopathy (WE) and beriberi [(1)].

Wernicke's encephalopathy is a severe neurological condition caused by a deficiency of thiamine (vitamin B1). Typically, a thiamine deficit lasting 4-6 weeks leads to Wernicke's encephalopathy [(2)], primarily affecting the central and peripheral nervous systems. First identified in 1881 by Carl Wernicke [(3)], WE brain lesions are found in 0.4%-2.8% of the general population, mainly in individuals with moderate to severe alcoholism [(4)].

Chronic alcohol use is the primary cause of WE because alcohol impairs thiamine absorption and storage. Malnutrition due to inadequate food intake also significantly contributes to this condition. Thiamine deficiency can result from prolonged vomiting, as seen in hyperemesis gravidarum and other diseases. Additionally, certain medical conditions, such as gastrointestinal diseases and eating disorders like anorexia nervosa, may hinder the body's ability to absorb nutrients. Three symptoms are characteristic of WE: disorientation, ataxia (lack of coordination), and ophthalmoplegia (abnormalities in eye movement). For a diagnosis of WE, at least two of these symptoms must be present. Early detection and thiamine supplementation are crucial to prevent the progression to Korsakoff syndrome, a persistent and debilitating condition. Korsakoff syndrome involves significant deficits in both anterograde and retrograde memory, while immediate memory remains intact. Patients with the syndrome may confabulate, creating stories when they are conscious and coherent. Confabulations can be spontaneous, typically seen in the acute stage of Wernicke's, or provoked, often observed in chronic Korsakoff syndrome [(5)(6)].

EPIDEMIOLOGY

The prevalence of Wernicke's encephalopathy (WE) is estimated to range from 1% to 3%, based primarily on autopsy studies. These studies provide most of the prevalence data, as the diagnosis is often missed or overlooked. Several studies have shown lower prevalence rates when using clinical records compared to necropsy investigations, indicating that WE is frequently underdiagnosed. Malnutrition and vitamin deficiencies are considered the primary causes of WE's higher prevalence in developing countries. There is no evidence to suggest that any particular race is more susceptible to WE, and the female-to-male ratio for the condition is approximately 1:1.7 [(7)].

ETIOLOGY

Thiamine, or vitamin B1, is essential for brain health and glucose metabolism. A severe thiamine deficiency is the primary cause of Wernicke's encephalopathy. Because alcohol interferes with thiamine absorption and storage, WE is often associated with chronic alcohol use disorder. Additionally, many individuals with this disorder consume insufficient nutrients, exacerbating thiamine deficiency. Other causes of thiamine deficiency include persistent vomiting, eating disorders, and gastrointestinal conditions that impair nutrient absorption. If thiamine intake is not adequately increased, conditions such as severe infections, hyperthyroidism, or increased thiamine requirements during pregnancy can also precipitate this disease. Furthermore, thiamine deficiency can result from other medical conditions like AIDS and cancer, due to higher metabolic demands or malabsorption issues [(8)(9)].

PATHOPHYSIOLOGY

For every 1000 kcal of energy expended, approximately 0.5 mg of vitamin B1 (thiamine) is required, translating to roughly 1.4 mg per day for a healthy adult. However, this recommended intake is often insufficient when alcohol is regularly consumed, as alcohol inhibits thiamine absorption. Whole grain cereals, lentils, brown rice, and yeast are primary dietary sources of thiamine [(10)]. The jejunum, a part of the small

intestine, is the primary site for thiamine absorption, where it is taken up through both active transport and passive diffusion [11]. The human body can store about 30 to 50 mg of thiamine, which is typically sufficient for 3 to 4 weeks with a daily intake of 2 mg. Once absorbed, thiamine crosses the blood-brain barrier and is converted into thiamine diphosphate (TDP), which acts as a coenzyme for critical enzymes in the pentose phosphate pathway (PPP) and the Krebs cycle (KC) [11]. Thiamine is essential for maintaining cellular integrity and osmotic balance. It is stored in various tissues as thiamine diphosphate and serves as a necessary cofactor for several enzymes involved in the Krebs cycle and PPP. The Krebs cycle is vital for the metabolism of carbohydrates and ATP production, while the PPP is essential for the synthesis of pentoses in cells lacking mitochondria. NADPH formation and nucleic acid synthesis, both of which are dependent on pentoses, play significant roles in scavenging free radicals during oxidative stress and are critical for metabolic processes. Consequently, thiamine deficiency reduces intracellular TDP levels, inhibiting both the Krebs cycle and PPP, and increasing cellular susceptibility to oxidative stress. Thiamine deficiency leads to reduced ATP, DNA/RNA, and NADPH production, along with the accumulation of toxic intermediates. This toxic buildup can cause cytotoxic and vasogenic edema. Vasogenic edema is characterized by the accumulation of extracellular fluid due to blood-brain barrier breakdown and serum protein leakage, while cytotoxic edema results from intracellular fluid accumulation. Magnetic resonance imaging (MRI) can often detect the brain regions most commonly affected by thiamine deficiency, including the putamen, caudate, pons, splenium of the corpus callosum, red nucleus, dorsal medulla, substantia nigra of the midbrain, cranial nerve nuclei, dentate nucleus, vermis, paravermian region of the cerebellum, fornix, and pre- and postcentral gyri. Thiamine also plays a crucial role in maintaining the blood-brain barrier, and metabolic acidosis resulting from thiamine deficiency can cause a drop in pH, leading to conditions such as Wernicke encephalopathy [12]. The enzyme thiamine Di phosphokinase is deactivated following acute alcohol ingestion, which further impairs thiamine absorption. Chronic alcohol consumption, particularly in those with moderate to severe alcohol use disorder, often leads to magnesium deficiency, a common electrolyte imbalance. Magnesium is necessary for the formation of phosphorylated thiamine complexes, and its deficiency can exacerbate symptoms that mimic thiamine deficiency [13].

CLINICAL FEATURES

The classical clinical triad of Wernicke's encephalopathy (WE) includes gait ataxia, ophthalmoplegia, and mental status abnormalities. The most prominent feature of the syndrome is a change in mental state, which can range from mild neurocognitive symptoms and apathy to severe conditions, including, in rare cases, coma. Cognitive abnormalities vary significantly, with the second most common symptom being ophthalmoplegia, which may be accompanied by other visual disturbances. The most frequently observed ocular abnormalities are horizontal nystagmus and complete ophthalmoplegia, although these occur infrequently. Additional eye symptoms may include axial bleeding, papilledema, anisocoria, miosis, ptosis, and sixth nerve palsy. Gait ataxia, the third characteristic of WE, may present as a slight irregularity in gait or as a complete inability to stand or walk. The presence of hypotension, unconsciousness, and hypothermia should also raise suspicion for the disease [12]. According to reports, the sensitivity of Caine's criteria for diagnosing WE is 85% [13]. A

complete physical examination, combined with a thorough clinical and social history, is essential for diagnosis. When WE is suspected, the immediate priority is to administer thiamine, even before waiting for laboratory test results. While basic laboratory workup and brain imaging support a provisional clinical diagnosis, there is no specific laboratory test to confirm WE. For detecting acute encephalopathy, MRI is more sensitive than CT, particularly in identifying periventricular lesions, which are frequently observed but not always present. Brain MRI is a valuable tool in confirming WE or diagnosing Korsakoff syndrome. To exclude other potential causes of neurological abnormalities, a comprehensive metabolic panel and blood count are also necessary [12].

DIFFERENTIAL DIAGNOSIS

It is crucial to rule out other conditions that may mimic WE, such as hepatic encephalopathy, normal pressure hydrocephalus, delirium tremens, alcohol withdrawal syndrome, stroke, and persistent hypoxia. A brain MRI can assist in validating the clinical diagnosis of WE and in excluding other conditions such as stroke; however, neither test should delay the administration of thiamine if WE is suspected. Despite the widespread nature of delirium and its potential connection to WE, studies have shown little evidence of a significant link between these two disorders. Nevertheless, in patients who present with delirium, especially those at risk for thiamine deficiency, WE should be considered as part of the differential diagnosis. Frequent causes of delirium should also be thoroughly evaluated [12].

TREATMENT/MANAGEMENT

Wernicke encephalopathy (WE) is a reversible medical emergency that can manifest in both acute and chronic forms. The main goal of WE therapy is to prevent brain injury by promptly and effectively correcting the deficiency of certain vitamins. Treatment for WE involve administering parenteral thiamine once the clinical diagnosis is made, especially in individuals suspected of having a thiamine deficiency due to a poor diet. It is important to check the plasma thiamine level before starting intravenous thiamine; however, treatment should not be delayed while awaiting results. Patients who have undergone bariatric surgery should have their plasma thiamine levels monitored for six months and receive sufficient thiamine supplementation. Most patients experience improvement in neurological symptoms with parenteral vitamin B1, especially those who are highly malnourished. Oral thiamine is not recommended as the first line of treatment for acute and subacute WE due to limited thiamine absorption in chronic alcoholics and undernourished patients. The aim of treatment is the immediate correction of thiamine deficiency in the brain. WE is a reversible condition and requires immediate emergent attention as it can manifest as an acute or chronic condition. Thiamine is most effectively administered rapidly through parenteral means; however, in some cases, persistent neurological deficits can occur, and the acute condition can progress to chronic Korsakoff syndrome For Wernicke's encephalopathy, thiamine should be administered parenterally at a dose of up to 500 mg once or three times a day. All malnourished patients may require higher doses of thiamine. Oral dosing is not reliable and is not recommended. Thiamine is generally administered before or together with glucose solutions because glucose oxidation can decrease thiamine levels and worsen the neurological symptoms of Wernicke’s encephalopathy.

Patients with magnesium deficiency should also be treated, as this can hinder recovery from Wernicke's encephalopathy, especially in patients with alcoholism. In comatose patients with WE, intravenous thiamine administration should be prolonged, although no recommended duration has been established yet. Once the patient responds stably to thiamine, oral vitamin B1 (50–100 mg) should be continued, particularly in individuals with alcohol dependence and those who have undergone bariatric surgery. More robust recommendations for the management of Wernicke encephalopathy–Korsakoff syndrome require additional studies. In cases of vitamin B1 deficiency, it is recommended to replace vitamin B1 first before starting a high-carbohydrate diet, which can increase thiamine metabolism enzyme activity and exacerbate neurological symptoms. Magnesium deficiency is common, particularly in chronic Wernicke's encephalopathy, so magnesium supplementation should be initiated without waiting for laboratory results of magnesium levels in the serum, as it is critical for, WE recovery, especially in patients with alcohol dependence. In cases of persistent cognitive impairment (e.g., Korsakoff dementia), cognitive promoters such as acetylcholinesterase inhibitors and memantine drugs have shown some benefits. However, a case report comparing the use of rivastigmine in five patients with controls who received conventional treatment found no significant differences in improvements between the two groups. The management of WE is complex and often requires a multidisciplinary collaborative effort. Medical intensive care and neurology teams are primarily involved in the care of severe WE cases, which are generally treated in intensive care units. It is essential for other specialties, particularly psychiatric teams, to be appropriately involved. Social workers, nurses, dietitians, and pharmacists are also essential in the treatment due to the support requirements of WE patients. To minimize the recurrence of WE, encouraging alcohol abstinence and ensuring patient compliance are crucial. Adequate vitamin supplementation is essential for WE patients, especially those who have undergone weight reduction interventions such as gastrectomy. Additionally, patients and their families should be thoroughly educated about the prognosis and outcomes. If long-term care for WE is required, it should be carefully established. All teams involved in the treatment of WE patients must maintain close communication to provide standard treatment, improve the quality of life, and reduce the burden on patients' families [(8)(12)].

OUTCOME

Wernicke's encephalopathy (WE) is a dangerous illness with elevated rates of morbidity and death. General disorientation usually resolves quickly even with thiamine therapy, but ophthalmoplegia and ataxia may not go away. The best results with thiamine supplements are typically seen in patients with little to no neurological symptoms. Nonetheless, Korsakoff psychosis may emerge in survivors of WE, necessitating long-term hospitalization. Fewer than ten percent of these patients will make enough progress to be released from extended care. Long-term neurological impairments such as ataxia, nystagmus, and Korsakoff syndrome are common in patients, greatly impairing their quality of life. Although long-term follow-up studies are sadly lacking, anecdotal accounts indicate that a significant number of these patients pass away too soon. Nystagmus and Korsakoff syndrome are conditions that significantly reduce the quality of life [(12)].

CONCLUSION

In summary, Wernicke's encephalopathy is a serious and urgent disorder that emphasizes the significance of prompt diagnosis and treatment. Its symptoms—which range from ataxia and confusion to ophthalmoplegia—are indicative of thiamine deficiency and should be identified as soon as possible to avoid the condition worsening and leading to Wernicke-Korsakoff syndrome. The timely delivery of thiamine and the resolution of the underlying causes of deficiency are critical to effective therapy. We can improve patient outcomes and quality of life by raising awareness among healthcare practitioners and ensuring that thiamine supplementation is accessible. To address this avoidable but possibly deadly neurological condition, further study and education in this field are still necessary.

ACKNOWLEDGEMENT

I am thankful to JDT Islamic College of Pharmacy, Vellimadukunnu, Kozhikode for providing me with the facilities and resources necessary to complete my review.

CONFLICT OF INTEREST

There is no conflict of interest

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