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Non-Alcoholic Wernicke Encephalopathy: A Literature Review

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ABSTRACT

Non-Alcoholic Wernicke Encephalopathy (NAWE) is a severe neurological disorder caused by thiamine (vitamin B1) deficiency due to non-alcoholic ethology such as malnourishment, gastrointestinal disorders, hyperemesis gravidarum, and chronic conditions. Even though Wernicke Encephalopathy (WE) is traditionally associated with chronic alcoholism, the incidence of NAWE is increasing but underdiagnosed due to its nonspecific presentations as compared to other neurological disorders. It is also prone to delayed diagnosis and induces irreversible damage. Although the classical triad of confusion, ataxia, and ophthalmoplegia is common, symptoms are often incomplete in patients who do not have alcoholism, and it may be difficult to diagnose. MRI is beneficial in detecting typical brain lesions. Thiamine deficiency also occurs more commonly in patients undergoing dialysis, bariatric surgery, and psychiatric illnesses, especially schizophrenia, where neglect of self-care and restriction of diet augment the risk. Studies show that giving thiamine intravenously early can greatly reduce the risk of serious problems, but delays may lead to Wernicke-Korsakoff syndrome. Promptness and awareness are of utmost significance in optimizing patient prognosis. This review will elaborate on the analysis of etiologies, clinical presentation, risk factors, and treatment modalities of NAWE to create an overall scenario of this syndrome and optimize the result of early diagnosis

and treatment.

INTRODUCTION

Wernicke Encephalopathy (WE) was first described by Carl Wernicke in 1881 as an acute neuropsychiatric syndrome characterised by a triad of manifestations: confusion, ophthalmoplegia, and gait ataxia. WE is predominantly caused by thiamine (vitamin B1) deficiency, a cofactor for the enzyme transketolase in carbohydrate metabolism. Without sufficient thiamine, the brain's energy metabolism is disrupted, leading to widespread neuronal damage. Carl Wernicke first reported this in alcoholics and in a patient with persistent vomiting, the presence of punctate hemorrhages, particularly over the third and fourth ventricles and the aqueduct of Sylvius [1]. WE in the past has been classically associated with chronic alcoholism, because alcohol disrupts thiamine absorption and metabolism. But WE can also arise without alcohol consumption, causing what is presently known as Non-Alcoholic Wernicke Encephalopathy (NAWE).

NAWE is increasingly being diagnosed in patients with other non-alcoholic conditions that are the cause of thiamine deficiency. They include gastrointestinal disorders, malnutrition, hyperemesis gravidarum, cancers, prolonged fasting, bariatric surgery, dialysis, anorexia nervosa, chronic infections, and AIDS [2]. NAWE remains underdiagnosed due to its atypical presentation and insufficient information on thiamine deficiency in non-alcoholic patients. Although the triad of WE symptoms is familiar, it occurs in only 16-33% of cases, making diagnosis even more difficult [3]. Often, patients present with nonspecific neurological symptoms; therefore, misdiagnosis or a delay in therapy ensues.

Generally, the body cannot synthesize thiamine and must obtain it daily through our diet. The body contains only 30-50 mg of thiamine and uses approximately 2 mg per day. In light of this phenomenon, signs of deficiency may begin to appear after 4-6 weeks of inadequate intake of thiamine-rich food [4]. Untreated acute WE can progress to Wernicke-Korsakoff syndrome (WKS), a chronic and generally irreversible illness of memory deficit, confabulation, and intellectual decline. Early treatment with high-dose parenteral thiamine can reverse WE's acute process and prevent long-term neurological sequelae.

This review was conducted to analyse the current expository knowledge surrounding Non-Alcoholic Wernicke Encephalopathy (NAWE), including its common etiologies, risk factors, clinical presentations, treatment and management strategies. In highlighting these key features,

this review aims to emphasize the importance of early diagnosis and prompt treatment of patients suffering from thiamine deficiency [5].

Method

We conducted a thorough search of different databases, including PubMed, MEDLINE, and Google Scholar, to identify relevant articles. Articles describing NAWE in gastrointestinal illness, psychiatric disorder, malnutrition, and other etiologies of non-alcohol origin were considered. After removing duplicates, three independent reviewers screened titles, abstracts, and full texts for relevance. Data extraction focused on patient demographics, clinical presentation, etiology, diagnostic strategy, treatment, and outcomes. Data were synthesized narratively due to variation in study types. There was no need for ethics approval as only published studies were included in this review.

Result

(A) Prevalence and Incidence

Non-Alcoholic Wernicke Encephalopathy (NAWE) accounts for approximately 50% of the total cases of Wernicke Encephalopathy (WE) [4]. Although the prevalence of WE with autopsy in the general population is 0.4% - 2.8% [2, 3], NAWE can be missed due to nonspecific or subtle symptoms (diagnosed in only 20% of presentations [6]). WE are never diagnosed before autopsy in 80% of cases. The syndrome is not identified by physicians, perhaps with the expectation that the disease is rarer than it is [4, 7].

Patients with GI disease, cancer, and chronic dialysis or bariatric surgery patients are particularly vulnerable due to dysfunctional nutrient absorption or thiamine loss. Nearly 20% of patients with complicated chronic GI diseases and neurological manifestations may present with WE, the majority of whom are not alcoholic [8]. Chemotherapy patients with neoplastic disease are also vulnerable [9], as are dialysis patients, due to thiamine loss during treatment [10].

NAWE is frequently underdiagnosed; about 84% of WE cases go undetected during life, as highlighted by autopsy studies [11]. Nonspecific symptoms of cognitive impairment or ataxia, which are common in this patient group, tend to lead to misdiagnosis.

Diagnosis

Caine Operational Criteria were developed in response to the poor performance of the classic triad of most WE and its elusive nature in diagnosis. A more extensive and structured approach for diagnosing WE using Caine's criteria presents a high diagnostic sensitivity (94%) and specificity (99%).

Diagnosis of Non-Alcoholic Wernicke Encephalopathy (NAWE) is largely clinical and in accordance with European Federation of Neurological Societies (EFNS) guidelines, it takes into account the heterogeneous presentation of signs in alcoholic patients compared to non-alcoholics. However, the Caine's Operational Criteria include four clinical features. At least two out of the four criteria given below must be present to diagnose WE. These are (1) dietary insufficiency typically related to thiamine deficiency, (2) oculomotor abnormalities, (3) cerebellar dysfunction or ataxia, and (4) altered mental status, delirium or memory impairment [12, 13]. Thereby extending the clinical syndrome beyond the scope of its traditional triad of symptoms. Despite the Caine Criteria being initially developed to identify WE in patients with chronic alcoholism, they have since been extended and found to be useful in diagnosing nonalcoholic cases as well.

These criteria allow physicians to diagnose WE even when the classic triad of confusion, ataxia, and ophthalmoplegia is incomplete or not as expected. Hence, it is fitting to apply the same criteria to non-alcoholic patients. In addition to clinical evaluation, standard laboratory work-up may identify the etiology of thiamine deficiency. Complete metabolic panel, complete blood count, and serum erythrocyte transketolase level are useful in assessing nutritional deficits and metabolic disorders that result in NAWE [13]. Measurement of blood thiamine level, although not commonly a part of the emergency setting, can confirm the deficiency, but treatment must not be delayed pending laboratory confirmation.

Magnetic Resonance Imaging (MRI) is useful in the diagnosis of NAWE, as it facilitates the detection of characteristic brain lesions. Though MRI findings in NAWE are similar to those in alcoholic WE, there are fine distinctions. These include lesions in periventricular regions, especially in the thalamus, periaqueductal grey matter, and around the third and fourth ventricles, which are typically seen in NAWE [8]. However, contrast enhancement of the mammillary bodies, which is characteristically seen in alcoholic WE, is less frequently observed in cases of NAWE [8]. All such imaging features are supportive of the diagnosis and can differentiate alcoholic and non-alcoholic WE.

Prompt recognition of NAWE is vital in the prevention of irreversible neurological damage. Symptoms may be atypical or nonspecific, and hence clinicians must be vigilant in vulnerable populations such as patients with prolonged malnutrition, gastrointestinal illness, or chronic medical disease that impinges on thiamine absorption or metabolism.

Table summarizing the diagnosis of Non-Alcoholic Wernicke's Encephalopathy (NAWE) based on the European Federation of Neurological Societies (EFNS) guidelines:

Table 1.0

Diagnostic Criteria	Description
Thiamine Deficiency	Presence of risk factors for thiamine deficiency (e.g., malnutrition, hyperemesis, gastrointestinal surgery)
Clinical Features	Requires two or more of the following signs for diagnosis:
- Oculomotor Dysfunction	Nystagmus, ophthalmoplegia, or gaze palsy
- Ataxia	Unsteady gait or coordination difficulty due to cerebellar dysfunction
- Confusion or Cognitive Impairment	Acute mental status changes, disorientation, memory impairment, or altered consciousness
Neuroimaging (optional but supportive)	MRI findings of symmetrical lesions in the thalamus, mammillary bodies, tectal plate, or periaqueductal grey matter
Laboratory Findings (optional)	Low levels of blood thiamine (although not always necessary for clinical diagnosis)

(B) Causes of Non-alcoholic Wernicke Encephalopathy

Non-alcoholic WE is extensively etiologic, covering the majority of diseases that cause inadequate metabolism, absorption, or intake of thiamine, as further explained below.

- Genetic Variables

Although NAWE is mostly associated with nutritional deficiencies, emerging research suggests that genetic susceptibility is a factor in the pathogenesis of WE. The interaction of genetics and thiamine metabolism, mitochondrial function, and neurodegenerative pathways is increasingly being implicated in determining individual susceptibility to WE [4].

(1) Genes for Thiamine Transport and Metabolism

Although WE is more frequent in adults, some cases have been reported in children. Most of these cases are linked with genetic abnormalities in thiamine metabolism. One such defect is a mutation in the SLC19A3 and SLC19A2 genes, involved in the transport of thiamine [14]. A mutation in the Solute Carrier Family 19 Member 2 (SLC19A2) gene, which encodes the thiamine transporter protein, can lead to a condition known as thiamine-responsive megaloblastic

anemia syndrome (TRMA). Although rare, the mutations can significantly block thiamine absorption and lead to thiamine deficiency and subsequently to neurological conditions like WE [15]. Mutations in the gene SLC19A3 cause biotin-thiamine-responsive basal ganglia disease (BTBGD), which also presents with a few neuropathological features similar to WE, such as focal lesions in sensitive areas of the brain due to a deficiency of thiamine. Even without large genetic mutations, polymorphisms in these genes may modulate individual susceptibility to thiamine deficiency to WE in non-alcoholic patients [14, 15].

(2) Mitochondrial Dysfunction and Oxidative Stress

Thiamine is crucial for mitochondrial function because it acts as a cofactor for those enzymes involved in energy production, such as pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase. Mitochondrial DNA (mtDNA) and nuclear gene variation regulating mitochondrial function may influence the brain's susceptibility to thiamine deficiency. Mitochondrial gene polymorphisms or mutations can increase oxidative stress and neuronal damage, further inducing thiamine -induced energy depletion and an increased risk of WE [16]. Areas of the brain that are most susceptible to WE, such as the mammillary bodies and thalamus, are highly dependent on oxidative metabolism. Genetic mechanisms that undermine mitochondrial efficiency may therefore increase susceptibility to WE in persons with borderline or transient thiamine deficiency, even in non-alcoholic contexts [16].

(3) Neuroinflammatory and Neurodegenerative Pathway

Another area where genetics may affect the pathogenesis of WE is through neuroinflammatory and neurodegenerative mechanisms. Thiamine deficiency has been shown to induce microglial activation, the immune cells of the brain, which may result in neuroinflammation and neuronal loss. Certain genetic polymorphisms associated with inflammatory processes, such as in TNF-α or IL-6 genes can make an individual susceptible to heightened neuroinflammatory insults related to thiamine deficiency. This would further exacerbate the brain injury typical of WE [2]

Besides that, genetic markers for neurodegenerative diseases like APOE gene variants (specifically APOE4) have also been implicated in increased risk of neurodegeneration in other contexts, such as thiamine deficiency. Individuals carrying these genetic predispositions may be more vulnerable to the brain damage induced by even mild thiamine deficiency and are at increased risk of developing WE on minimal alcohol consumption [2].

(4) Genetic Predisposition to Malabsorption Syndromes

In the non-alcoholic patient, WE is often associated with disease affecting nutrient absorption, such as Celiac disease, Crohn's disease, Congenital Tufting Enteropathy, etc.

Genetic predisposition to such malabsorptive conditions has increasingly been recognized to indirectly contribute to a higher risk of WE through a reduced availability of thiamine. For instance, individuals with genetic mutations of HLA-DQ2 and HLA-DQ8 that are susceptible to celiac disease may be at a heightened risk of thiamine deficiency due to malabsorption over a long duration [15]. Further, other genetic determinants of gastrointestinal function, such as NOD2 gene polymorphisms causing Crohn's disease, may disrupt nutrient absorption, and this would make such patients susceptible to WE in case of thiamine deficiency. EPCAM gene mutation would cause structural abnormality in the intestinal epithelium, causing infantile chronic intractable diarrhea, malabsorption and severe micronutrient loss, including thiamine. These genetic determinants show how the nutritional status and genetic susceptibility are intertwined in the etiology of WE in non-alcoholic patients [15].

(5) Epigenetics and Gene-Environment Interactions

Aside from direct genetic influences, epigenetic modifications – heritable variations in gene expression without changes in the DNA sequence — are also a potential influence on non-alcoholic WE. Malnutrition, disease, or drug use are environmental influences that can affect the regulation of genes involved in thiamine transport, metabolism, and neuroprotection. Epigenetic changes caused by chronic stress or malnutrition may reduce the activity of thiamine carriers or mitochondrial enzymes, further increasing the risk of WE in persons who are genetically predisposed [16].

Recent studies have shown that genetic mutations and polymorphisms can predispose individuals to WE, even in the absence of overt nutritional deficiency, especially in patients with NAWE. Clarification of these genetic factors not only contributes to our understanding of WE pathogenesis but also highlights the importance of genetic screening and personalized prevention and treatment measures for WE in high-risk non-alcoholic patients.

- Non-Genetic Variables

(1) Hyperemesis Gravidarum

Wernicke Encephalopathy has been documas a complication of hyperemesis gravidarum during pregnancy. This prolonged vomiting and malnutrition quickly depletes the body's thiamine store. Devi et al. and Kotha et al. documented instances where severe thiamine deficiency and

malnutrition secondary to hyperemesis gravidarum caused WE. This is because the increased nutrition requirements of pregnancy, coupled with failure to maintain an adequate level thereof due to constant vomiting, offer a nidus for thiamine deficiency [17,18]. Two-thirds of the patients had thyroid disease in [18], which may have potentially worsened the condition.

Although WE is uncommon in pregnancy, its presentation may be severe with important implications and necessitate early treatment and thiamine supplementation in pregnant women with suspected WE to prevent permanent neurological damage.

(2) Chronic Malnutrition and Prolonged Parenteral Nutrition

Chronic malnourished patients, particularly with underlying diseases like eating disorders, gastrointestinal disease, or socioeconomic deprivation, are more likely to develop NAWE. Apart from that, patients on long-term parenteral nutrition (PN) are also at risk because thiamine is absorbed via the gut, and its deficiency can occur if not supplemented adequately. In the case of long-term malnutrition, reduced thiamine consumption over a period exhausts the body's limited thiamine stores, ultimately causing damage to the nervous system.

Chandrakumar emphasized the importance of approaching chronic dietary deficiency as a key agent in NAWE, particularly in those with poor nutrition for months or weeks [4]. This long-term insufficiency incapacitates thiamine-dependent processes in the brain to cause the clinical presentation of Wernicke Encephalopathy (WE) - confusion, ataxia, and ocular changes.

Long-term parenteral nutrition (PN) dependent patients are also at risk for thiamine deficiency since their usual avenues of nutrient absorption are bypassed. Unless PN fluids are properly fortified with thiamine, patients can become WE-prone, even if they are being caloric-supplemented adequately. Attard et al. documented one instance where poor thiamine supplementation throughout extensive PN resulted in the appearance of WE, and thereby highlighted the need for proper micronutrient monitoring in such patients 8]. Being a water-soluble vitamin with a low tissue reserve, thiamine must be supplemented in PN patients and must be given regularly in amounts enough not to cause deficiency.

Additionally, chronic undernutrition is usually found in combination with other risk states, such as gastrointestinal disease or cancer that increase the risk of thiamine deficiency. Long-term parenteral nutrition and chronic malnutrition are both significant contributors to NAWE etiology since they lead to persistent thiamine deficiency. Detection of these risks at an early stage and pre-emptive thiamine supplementation are both key to preventing the development of permanent neurological sequelae with NAWE.

(3) Gastrointestinal Disease and Surgery

Gastrointestinal disease and surgery are especially significant in placing patients at risk of thiamine deficiency since these conditions are more likely to lead to malabsorption and increased metabolic demands. GI diseases such as Crohn's disease, ulcerative colitis, irritable bowel syndrome, and other long-term GI diseases tend to impair the absorption of nutrients, including thiamine. Chronic malabsorption, in addition to GI inflammation, can exhaust thiamine stores and result in the development of NAWE. Sechi & Serra have also noted that patients with chronic illness were susceptible to developing thiamine deficiency, especially in cases of prolonged diarrhea, weight loss, or reduced oral intake in the acute exacerbations of the disease [2].

Gastrointestinal surgery, for example, gastrectomy or bariatric procedures, may impair nutrient absorption, particularly in post-operative patients [19]. A case was described of a patient with a background history of total gastrectomy who presented with NAWE, illustrating how vulnerable post-surgical patients are due to the decreased absorptive surface area and impaired digestive process. If the possibility of thiamine deficiency is not taken into consideration in nutrition management after surgery, the development of NAWE is much more likely. EFNS suggests that any bariatric surgery should be followed by at least 6 months' supervision of the thiamine level by parenteral supplementation. Also, individuals with chronic diseases like irritable bowel syndrome (IBS) will not only be malabsorptive but also drastically alter their diet while attempting to manage symptoms, thus reducing their thiamine-containing food intake in the process. With all these factors combined, there is a high-risk environment for NAWE.

The chronic course of such disease, increased metabolic demand and low dietary intake, puts the patient at risk for neurological damage unless managed with thiamine therapy. Galvis et al. recommend having a high degree of suspicion for WE in all clinical conditions that may lead to thiamine deficiency [13].

(4) Chronic Disease and Cancer

Chronic illnesses such as chronic kidney disease (CKD), chronic liver disease, and Acquired Immune Deficiency Syndrome (AIDS) can result in thiamine deficiency due to both impaired absorption and alterations in metabolic requirements [20].

Repeated extraction of body fluids through dialysis can contribute to thiamine loss, placing patients at greater risk of thiamine deficiency. Hung et al. observed that hemodialysis and peritoneal dialysis can both lead to significant loss of water-soluble vitamins [10]. The metabolic

demands of chronic kidney disease further exacerbate this, as the body's micronutrient requirements, including thiamine, may increase due to the stress of disease and treatment. In addition to routine dialysis-related thiamine losses, dialysis patients often experience malnutrition due to dietary restrictions and reduced appetite, compounding the risk of thiamine deficiency [10, 19]. Similarly, Patients with non-alcoholic liver disease, i.e., non-alcoholic steatohepatitis (NASH) or chronic hepatitis as defined by Sechi, are also at high risk of developing NAWE [2]. The liver also performs the vital function of metabolizing thiamine into its active form, thiamine pyrophosphate (TPP), which is necessary for carbohydrate metabolism and energy production for the brain. The authors recommend prophylactic supplementation of thiamine in patients with chronic liver disease to prevent NAWE, especially during hospitalization or acute illness when metabolic demands are high. In cancer patients, especially those undergoing chemotherapy, malnutrition and abnormal metabolism of nutrients are common. Isenberg-Grzeda et al. reported that malnutrition due to cancer; chemotherapy-induced nausea, vomiting, and anorexia all lead to an excessive risk of NAWE [9]. The increased metabolic stress placed on the body by both the malignancy and the treatment can deplete thiamine stores, making the nervous system vulnerable to damage. Also, those with advanced malignancy are in danger of cachexia, a severe wasting and nutritional deficiency syndrome, again exposing the patient to further risk of thiamine deficiency and NAWE.

Thiamine screening regularly, with appropriate supplementation accordingly, should be the norm in all cancer and chronic dialysis patients, particularly high-risk patients due to poor diet or excessive metabolic demands.

(5) Behavioral and Psychotic Disorder

Eating disorders such as anorexia nervosa, bulimia nervosa, and psychotic disorders such as schizophrenia are now known to be significant etiologies of Non-Alcoholic Wernicke Encephalopathy (NAWE). These disorders are typically associated with chronic malnutrition and deficiency of essential micronutrients, including thiamine (vitamin B1). Anorexia and bulimia nervosa, which involve extreme food restriction or food purging, eventually lead to macro and micronutrient deficiencies, including thiamine. The long-term thiamine deficiency in patients with eating disorders disrupts normal neuronal activity and causes permanent damage if left untreated. Chandrakumar stressed the importance of early detection of malnutrition in patients with eating disorders to prevent the onset of WE [4]. In its most chronic state, thiamine

deficiency may be overlooked as early symptoms are subtle and easily attributed to psychiatric symptoms of the eating disorder.

The relationship between schizophrenia and nutritional deficiency is one of several factors, more usually initiated through a sequence of poor diet, self-neglect, and, in some cases, drug treatment side effects of weight gain and restricted dietary habits. Seo et al. reported a case of a patient with schizophrenia who presented with NAWE as a consequence of self-imposed dietary restriction, driven by body image concerns precipitated by weight gain secondary to drug therapy [21]. Psychotic patients are also bound to undergo prolonged hospitalization or institutionalization, the environment of which can facilitate inadequate nutritional care and increase the risk of thiamine deficiency.

McCormick et al. also quoted that schizophrenic patients or those with schizophrenia-related conditions are most likely to be under-monitored for nutritional deficiency despite the reality that their dietary patterns and nutritional deficiencies place them at high risk [22]. In general, psychological and behavioural disorders, schizophrenia, and eating disorders are risk factors for NAWE due to thiamine deficiency and long-term malnutrition.

Early nutritional intervention and thiamine level monitoring of these patient groups are crucial to prevent the occurrence of NAWE and its neurological sequelae. Neuropsychiatric overlap complicates diagnosis because presenting symptoms can closely resemble cognitive or behavioral symptoms of the psychiatric disorder itself.

(C) Treatment of Non-Alcoholic Wernicke Encephalopathy (NAWE)

Treatment for Non-Alcoholic Wernicke Encephalopathy (NAWE) is immediate correction of thiamine deficiency to prevent irreversible neurological damage. Although it is recommended that the evaluation of thiamine levels be done before treatment, it should not be postponed. The Royal College of Physicians advises 500mg of thiamine in 50 - 100 mL of saline intravenously three times daily for 2–3 days; the dose can be altered based on clinical response [6]. Slow infusion of thiamine for 30 minutes must be given to reduce anaphylactic risk. After the initial phase, patients with mild presentation are often given 250 mg IV or IM for an additional 5 days in case of improvement. In those with severe neurological and psychiatric manifestations, such as ataxia, polyneuritis, and impairment of memory, continues the treatment as long as needed until there is improvement [6]. EFNS recommends 200 mg IV every 8 hours until symptom stabilization. An individualized treatment is being prescribed for Korsakoff syndrome, where chronic memory impairments often require extended care and rehabilitation [3, 13].

To avoid aggravation of neurological symptoms, thiamine supplementation is recommended before initiating a high-carbohydrate diet, as carbohydrates improve thiamine metabolism, which results in rapid depletion of thiamine stores in the body, precipitating NAWE. Chronic WE patients may present with magnesium (Mg) deficiency—an essential cofactor in the activation of thiamine into its active form, thiamine pyrophosphate (TPP), especially on the background of chronic alcoholism, severe malnutrition, prolonged diarrhea or vomiting or use of diuretics, which causes renal Mg loss. These same risk factors also predispose to thiamine deficiency; hence, thiamine deficiency and magnesium deficiency often occur together. Thus, magnesium needs to be supplemented without waiting for serum level results [3]. For long-term cognitive impairment, cognitive enhancers such as acetylcholinesterase inhibitors have been attempted but are of limited value [2, 23].

Complications in NAWE, if left untreated, are severe and result in Wernicke-Korsakoff syndrome (WKS): chronic impairment of cognition, memory loss, and confabulation [3,4]. If left untreated, long-term effects may include blindness, gait disturbances, and motor coordination problems, thereby significantly diminishing patients' quality of life [13]. Therefore, early diagnosis and prompt intensive treatment are crucial for high-risk individuals.

Discussion

Non-Alcoholic Wernicke Encephalopathy (NAWE) has become more recognized, yet it’s still an inadequately valued clinical syndrome overshadowed by its association with alcoholism. Wernicke Encephalopathy (WE) classically has been understood to be caused nearly exclusively by chronic alcoholism due to the impact of alcohol on thiamine metabolism and metabolic blockade. Nevertheless, growing evidence demonstrates that WE can happen in patients with no background of alcohol use, particularly with malnutrition or diseases that impair nutrient absorption. NAWE is the consequence of a relative or absolute deficiency of thiamine (vitamin B1), critical to carbohydrate metabolism and to the health of neurons. As the following review of the literature guarantees, NAWE is recognized in a broad range of medical illnesses, and the issue continues to be one of early diagnosis, detection, and treatment of this reversible but potentially disabling state.

(1) Multifarious Clinical Conditions Causing NAWE

One of the most astounding conclusions of this literature is the multifarious range of medical conditions causing NAWE. Non-alcoholic WE is most commonly found in malnourished patients due to GI diseases, psychiatric disease, chronic diseases, or hyperemesis gravidarum, etc. For

instance, Yin, in his research in Anhui, China, found 17 NAWE patients. All were suffering from primary diseases such as gastrointestinal surgery, pancreatitis, psychiatric disease, or chronic vomiting, all of which resulted in inadequate nutrient intake [23]. This etiologic variation highlights the fact that NAWE is not restricted to a single disease or population subgroup but can result from any condition where nutritional status is compromised with specific reference to thiamine deficiency.

Furthermore, this study highlights that patients with psychiatric issues, especially poor feeding or diet-restrictive eating, are vulnerable. Seo et al. described a case where a 37-year-old patient with schizophrenia developed WE following extreme restriction of diet. His weight reduction desire, combined with weight gain due to medication, led to extreme malnutrition and thiamine deficiency [21]. This is a classic example of WE in a non-alcoholic patient. Thus, clinicians managing psychiatric patients, especially those with compromised food intake, must have a high suspicion of NAWE.

(2) Diagnostic Difficulty in NAWE

One of the common themes encountered during this review is that NAWE is difficult to diagnose, primarily because it arises unusually. WE has classically been associated with a triad of symptoms: ophthalmoplegia, confusion, and ataxia. However, as the case series and investigations reviewed here show, in most cases, particularly in non-alcoholics, the classical triad is absent. For instance, less than half of the patients in Yin's series presented with the full clinical trial. In contrast, the majority of patients had more subtle neurological symptoms, including minimal memory impairment, cerebellar impairment, or nonspecifically changed mental status [23]. These are usually readily mimicked by other neurological or psychiatric illnesses and lead to diagnostic delay.

The case presented by He et al. reflects the challenge, as a 56-year-old female patient with schizophrenia presented with a changed mental status, but was initially diagnosed with aspiration pneumonia. It was only after the patient's condition had worsened and an MRI showed symmetrical T2 hyperintense lesions on bilateral basal ganglia and periventricular areas that the diagnosis of WE was established [24]. This lag is typical of the diagnostic uncertainty with which NAWE is otherwise associated; particularly when clinicians appreciate that thiamine deficiency is far from exclusive to alcoholic patients.

Magnetic resonance imaging (MRI) is a primary diagnostic tool exceptionally useful in recognizing NAWE. Neuroimaging produces characteristic findings in the medial thalamus,

mammillary bodies, and periaqueductal grey matter. As evident from case studies by Seo et al. and Nakashima et al., MRI played an important role in the diagnosis of WE when clinical symptoms were still unclear [19,21]. However, the availability of high-tech neuroimaging is not always present, especially in resource-scarce areas, making early detection solely dependent on skilled clinical diagnosis.

(3) The Place of Early Thiamine Supplementation

The most seminal conclusion reached by this literature is the necessity of aggressive and early thiamine supplementation as an adjuvant to NAWE management. Thiamine is a vital cofactor for many enzymes in cell energy metabolism, particularly in the central nervous system. Its lack is preceded by a series of metabolic dysfunctions, culminating in neurologic damage. Yin's work showed the difference in outcome by timing of patient treatment with thiamine: outcome was considerably better in a median of 3.9 days after the onset of symptoms, but patients with delayed treatment (up to 60 days) had a bad prognosis [23]. Such delay characteristically resulted in the development of Wernicke-Korsakoff syndrome, a chronic, irreversible state that is characterised by severe impairments of memory and confabulation. Prompt thiamine therapy is required, not just because it halts the progression of neurological damage but also because the response to thiamine can be dramatic. As in the case of a 31-year-old HIV/AIDS patient reported by Larsen et al., IV thiamine injection led to immediate relief of symptoms, diagnosing WE [25]. This is proof that the condition can be reversed if treated early. Nonetheless, once profound neurological impairment has been attained, as in the case of individuals who develop Korsakoff syndrome, the potential for full recovery is slim.

The evidence-based guidelines now recommend administration of high doses of thiamine, typically 500 mg IV three times daily for at least three days, with continued supplementation according to clinical course. This literature does not recommend waiting until diagnosis is made, since even a brief duration of untreated thiamine deficiency can lead to permanent changes.

(4) Vulnerability of Psychiatric Patients and the Role of Nutritional Support

The literature also indicates how psychiatric patients, particularly those with schizophrenia or other disabling disorders that hinder them from eating sufficiently, are at risk for NAWE. A series of case reports, including Seo et al. and He et al., highlight the manner in which psychiatric illness can predispose to thiamine deficiency, namely, where patients restrict their diet, either due to delusions or as a medication side effect. These findings emphasize the value of continued

nutritional attention and monitoring of psychiatric patients, especially those with eating disorders and dietary changes [21, 24].

Psychiatric illness in NAWE is not just typified by food deprivation. Psychiatric illness patients are often subjected to prolonged hospital stays, abandonment, or neglect, all of which lead to improper nutrition. They thus have a likelihood of developing NAWE and thus need a multidisciplinary group including psychiatrists, dietitians, and neurologists for better management. A balanced diet and healthy lifestyle can be employed to forestall NAWE.

Conclusion

Non-alcoholic Wernicke's Encephalopathy (NAWE) is increasingly accepted as a cause of serious concern among a broad spectrum of illnesses outside the classical association with long-term alcoholism. This review highlights the need for active screening and early treatment of high-risk groups. One of the most significant learning points from this review is the vast range of underlying illnesses that place an individual at risk for thiamine deficiency, such as hyperemesis gravidarum, malignancy, malnourishment, post-gastrointestinal surgery, and chronic diseases such as renal failure and HIV/AIDS. Another significant learning point from this review is the increased need for NAWE awareness in psychiatric illnesses, especially schizophrenia and eating disorders, as key players. Situations in which patients restrict food intake secondary to delusions, medication side effects, or inattention to self-care may increase this risk. Genetic factors are currently emerging as part of the pathophysiology of thiamine metabolism and susceptibility to thiamine deficiency in humans. These paradigm shifts emphasize the point that NAWE is prevalent but remains underdiagnosed due to its atypical presentation and lack of alcohol history. Additionally, more advanced neuroimaging, such as MRI, remains a cornerstone of NAWE diagnosis. Although useful, it's not always accessible; hence, clinical awareness is that much more important. Thus, more emphasis is placed on Caine's Operational Criteria for early clinical suspicion to prevent delay in the administration of thiamine. Thiamine deficiency can emerge over days of low intake, and the timeframe for effective treatment is shorter than was previously estimated. Early diagnosis and prompt intramuscular injection of high-dose thiamine are necessary to prevent permanent neurological injury and Korsakoff syndrome. Most importantly, prompt intervention of nutritional deficiencies among high-risk populations – psychiatric patients and complicated post-surgical patients – is essential in greatly reducing the risk of NAWE and any lasting neurological damage.

This type of attitude shift requires an active, interdisciplinary approach to its management and screening. Future studies strive to develop standardised screening protocols. The potential role of biomarkers in identifying early thiamine deficiency should also be explored. Attention should also be accorded to proper nutritional supplementation, particularly for at-risk groups, such as psychiatric patients, so that prevention of NAWE development could be facilitated. With increasing knowledge of this entity and refinement of diagnostic and treatment strategies, we can significantly reduce morbidity from NAWE and improve health outcomes.

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VEO: Conceptualization and preparation of the original draft of the manuscript and supervision.
VEO, DH, EAO, AO, FOC, SO: performed literature searches and first drafting.
VEO, EAO, DH and FOC: edited and revised the manuscript draft.
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The author(s) declare that it is not applicable.

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