THIAMINE DEFICIENCY, CLINICAL MANIFESTATIONS AND TREATMENT OF WERNICKE-KORSAKOFF SYNDROME

Abstract. Wernicke-Korsakoff syndrome (WKS) is a severe, debilitating neurodegenerative disorder resulting from thiamine deficiency, which disrupts normal cellular functions within the brain, particularly in regions crucial for memory and cognitive processes. It is characterized by two distinct but often overlapping conditions: Wernicke's encephalopathy (WE) and Korsakoff's psychosis (KP).

Thiamine deficiency impacts various biological processes, including glucose metabolism, neurotransmitter synthesis, myelin sheath integrity, and nerve conduction. In glycolysis, thiamine is a cofactor for pyruvate dehydrogenase (PDH), aiding in the conversion of pyruvate to acetyl-CoA within the tricarboxylic acid (TCA) cycle. Thiamine also serves as a cofactor for α-ketoglutarate dehydrogenase (α-KGDH) in the TCA cycle, contributing to the generation of reducing cofactors
and intermediates necessary for cellular respiration and ATP synthesis. Moreover, thiamine’s involvement in the pentose phosphate pathway (PPP) through its role in transketolase activity influences nucleotide synthesis and antioxidant defense mechanisms. Additionally, thiamine is critical in neurotransmitter and myelin synthesis, both essential for signal transmission along nerves and synaptic plasticity. Thiamine deficiency disrupts these physiological processes, leading to the neurological symptoms characteristic of WKS.

Despite its association with chronic alcoholism, WKS can occur in non-alcoholic populations, including individuals with malnutrition, gastrointestinal disorders, eating disorders, or other medical conditions that impair thiamine absorption and utilization. The diverse etiology and risk factors for WKS highlight the need for comprehensive approaches to its prevention, diagnosis, and management across various clinical settings and populations.

Keywords: Wernicke-Korsakoff syndrome, thiamine deficiency, chronic alcoholism, malnutrition, thiamine-dependent enzymes, cognitive impairments

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DEФІЦИТ ТІАМІНУ, КЛІНІЧНІ ПРОЯВИ ТА ЛІКУВАННЯ СИНДРОМУ ВЕРНІКЕ-КОРСАКОВА

Анотація. Синдром Верніке-Корсакова (СВК) – це важке, виснажливе нейродегенеративне захворювання, яке виникає внаслідок дефіциту тіаміну,
який порушує нормальні клітинні функції в мозку, особливо в областях, важливих для пам'яті та когнітивних процесів. Він характеризується двома різними, але часто подібними станами: енцефалопатією Верніке (EB) і психозом Корсакова.

Дефіцит тіаміну впливає на різні біологічні процеси, включаючи метаболізм глюкози, синтез нейромедіаторів, цілісність мієлінової оболонки та нервову провідність. У гліколізі тіамін є кофактором для піруватдегідрогенази (ПДГ), допомагаючи в перетворенні пірувату в ацетил-КоА у циклі трикарбонових кислот (ЦТК). Тіамін також служить кофактором для α-кетоглутаратдегідрогенази (α-КГДГ) у циклі трикарбонових кислот, сприяючи утворенню відновлюючих кофакторів і проміжних сполук, необхідних для клітинного дихання та синтезу АТФ. Крім того, тіамін має вирішальне значення для синтезу нейромедіаторів і мієліну, які необхідні для передачі сигналу по нервах і синаптичної пластичності. Дефіцит тіаміну порушує ці фізіологічні процеси, що призводить до неврологічних симптомів, характерних для СВК.

Незважаючи на зв’язок із хронічним алкоголізмом, СВК може виникнути в популляціях, які не вживають алкоголь, включаючи осіб з недоїданням, шлунково-кишковими розладами, розладами харчової поведінки або іншими захворюваннями, які погіршують всмоктування та використання тіаміну. Різноманітна етіологія та фактори ризику СВК підкреслюють необхідність комплексних підходів до його профілактики, діагностики та лікування в різних клінічних умовах і популяціях.

Ключові слова: синдром Верніке-Корсакова, дефіцит тіаміну, хронічний алкоголізм, недоїдання, тіамінзалежні ферменти, когнітивні порушення

Introduction. Wernicke-Korsakoff syndrome (WKS) is more widespread than commonly acknowledged and poses a significant health burden that extends beyond individuals with alcoholism. Older studies estimate the prevalence of WKS to be close to 3% in the general population, about 12% to 24% in chronic alcoholics, and even higher rates in individuals with longer durations of heavy alcohol consumption and severe nutritional deficiencies [1, 2, 3]. Interestingly, data indicates that 80% of patients with WKS are undiagnosed during life, and almost 20% present with no clinical signs [4]. A recent investigation revealed that 93% of WE hospitalizations were alcohol-related; these also patients faced a heightened risk of developing KP than non-alcoholic ones [5]. Recovery rates for patients with WE are relatively low – most either die from alcohol-related causes like alcoholic liver disease or develop KP [2, 3].

Analysis of recent research and publications. Recent research and publications on Wernicke-Korsakoff Syndrome (WKS) have focused on various
aspects of the disorder, including its etiology, diagnosis, treatment, and management. Studies have explored the underlying mechanisms of thiamine deficiency and its role in the development of WKS, highlighting the importance of early detection and intervention to prevent irreversible neurological damage (Mrowicka et al., Palm et al., Dingwall et al., Smith et al., etc.). Treatment approaches have also been a focus, with studies evaluating the efficacy of thiamine supplementation, nutritional interventions, and rehabilitation strategies in improving outcomes for individuals with WKS (Rasiah et al., Burile et al., Palmirotta et al.). Although several literature reviews exist, few delve into the precise thiamine-dependent biochemical mechanisms and the defects in these processes that lead to WKS, a gap that this review seeks to address.

**Purpose of the literature review.** To provide a comprehensive overview of existing research and knowledge on the importance of thiamine and the effects of its deficiency that lead to WKS. Thus, by analyzing relevant literature, this review aims to discuss the biochemical underlying causes of the disorder, detail the illness itself, including its etiology, epidemiology, clinical presentation, and inform evidence-based practices for the management and care of individuals affected by WKS.

**Main material.** Thiamine, also known as vitamin B₁, is a water-soluble vitamin and an essential factor for several enzymatic reactions involved in carbohydrate metabolism and neurotransmitter synthesis, both processes that determine the functional status of nerve conduction and synaptic transmission [6, 7]. Its deficit impairs these essential biochemical processes, leading to various physiological and neurological abnormalities. Thiamine regulates carbohydrate metabolic processes like glycolysis, the tricarboxylic acid (TCA) cycle, and the pentose phosphate pathway (PPP) [8]. Pyruvate dehydrogenase (PDH), α-ketoglutarate dehydrogenase (α-KGDH), and transketolase are among the most important thiamine-dependent enzymes [9]. The brain, though accounting for only 2% of body mass, consumes 20% of the body’s glucose due to its elevated metabolic demands. For this reason, the brain is especially sensitive to decreased glucose levels, something exhibited during a deficit of thiamine [10].

In glycolysis, the active form of thiamine serves as a cofactor for PDH to catalyze the conversion of pyruvate to acetyl-CoA in the citric acid cycle [16]. A thiamine deficiency impairs the activity of PDH, disrupting the physiological flow of glucose metabolism and ATP production. In the TCA cycle itself, thiamine is a cofactor for α-KGDH, which structurally resembles PDH and generates reducing cofactors (NADH, FADH₂) and intermediates for cellular respiration and ATP synthesis [6]. The two cofactors transfer electrons from metabolic reactions to the electron transport chain in mitochondria, facilitating the conversion of energy from nutrients into a form usable by cells for various biological processes [11]. Thiamine is also a cofactor for transketolase, an enzyme involved in the PPP that generates ribose-5-phosphate for nucleotide synthesis and NADPH for biosynthetic reactions and antioxidant defense [12]. Reduced transketolase activity due to a thiamine
deficiency disrupts these processes [12]. Decreased cellular antioxidant protection increases susceptibility to oxidative stress-induced damage; reactive oxygen species (ROS) accumulation damages cellular structures, impairs mitochondrial function, and compromises cellular signaling pathways, exacerbating cellular dysfunction and neuronal damage [13]. All of these processes are underlying mechanisms of the pathogenesis of neurodegenerative disorders, including WKS.

Thiamine is also involved in the synthesis of neurotransmitters, chemical messengers that facilitate interneuronal signaling and communication [8]. Brain glucose serves as a source for generating substrates essential for synthesizing acetylcholine (ACh), glutamate (Glu), and gamma-aminobutyric acid (GABA) [10]. Without thiamine, a cofactor for previously mentioned thiamine-dependent enzymes that generate these substrates, neurotransmitters will not be synthesized; without them, proper signal propagation, synaptic plasticity, and the balance between excitation and inhibition will be impaired. As previously mentioned, thiamine is a cofactor for PDH, which helps generate acetyl-CoA. The latter is a substrate for ACh, a neurotransmitter stimulating muscle contraction, autonomic nervous system function, and cognitive processes such as memory and learning. A thiamine deficiency decreases substrate availability for choline acetyltransferase-mediated ACh synthesis, contributing to neurological dysfunction observed in WKS [6, 14].

Furthermore, vitamin B1 helps synthesize glutamate, the primary excitatory neurotransmitter in the central nervous system and GABA precursor [7, 15]. Glutamate synthesis occurs through the conversion of alpha-ketoglutarate (α-KG), an intermediate of the TCA cycle, into glutamate in a reaction catalyzed by the NADH-dependent enzyme glutamate dehydrogenase [6, 10]. For α-KG to be used in glutamate synthesis, its own synthesis is a prerequisite, and without pyruvate dehydrogenase (PDH), this is impossible [10]. Thiamine deficiency impairs α-KG synthesis, leading to decreased glutamate production [6, 14]. NADH, an additional requirement for glutamate synthesis, is generated by α-KGDH, the enzyme that catalyzes the oxidative decarboxylation of α-KG to succinyl-CoA [10]. The activity of α-KGDH is dependent on TPP, highlighting the crucial function of thiamine in facilitating not only ATP production but also glutamate synthesis [16]. Thiamine-dependent enzymes also facilitate the conversion of glutamate into GABA, the primary inhibitory neurotransmitter in the central nervous system that regulates neuronal excitability and maintains neurotransmitter balance [17]. Thiamine deficiency may compromise GABA synthesis by disrupting the metabolism of glutamate and impairing the function of thiamine-dependent enzymes involved in neurotransmitter metabolism and substrate synthesis [7, 18, 19]. α-KGDH, thus, plays a crucial role in maintaining the levels of the neurotransmitters glutamate and GABA and when its activity is reduced, glutamate decarboxylase converts accumulating glutamate into GABA to prevent an excessively excitatory state [20].

On the other hand, thiamine is critical for maintaining the integrity of the myelin sheath, the fatty protective covering of nerve fibers that insulates nerve
fibers, enhancing the efficiency of nerve impulse transmission in the nervous system [6, 7]. The process critical for myelin production is the PPP. Transketolase, a thiamine-dependent enzyme in this path, helps generate NADPH and ribose-5-phosphate, which are essential for lipid and nucleotide synthesis, respectively [12]. NADPH is a reducing agent in the conversion of fatty acyl-CoA to fatty alcohols, a critical step in the synthesis of sphingolipids and cholesterol, major components of the myelin sheath [21, 22]. Ribose-5-phosphate is a precursor for nucleotide synthesis; this process is essential to cell proliferation and protein synthesis, processes crucial for the growth and maintenance of myelin-forming cells like oligodendrocytes and Schwann cells [22]. Disruptions in the PPP as a result of thiamine deficiency will disrupt myelin synthesis or result in demyelination altogether, leading to nerve damage, peripheral neuropathy, muscle weakness, and altered sensation [18, 19]. Thiamine deficiency is thereby implicated in various neurological disorders like WE and Beriberi neuropathy, characterized by disrupted myelin sheath integrity, peripheral neuropathy, and cognitive dysfunction [23].

Adequate ATP levels are essential for maintaining the electrochemical gradients required for nerve conduction and synaptic transmission and a thiamine deficiency can compromise ATP levels (figure 1). ACh, glutamate, and GABA bind to receptors on target cells, triggering changes in membrane potential, and propagating nerve impulses; a lack of myelination impairs nerve conduction velocity, perpetuating disruption of normal neuronal communication [24, 25]. As a result, thiamine deficiency disrupts neurotransmitter balance and impairs synaptic transmission, contributing to neurological dysfunction manifesting as cognitive impairment, memory deficits, muscle weakness, and impaired motor function [18].

**Causes.** The underlying causes of WKS are multifactorial and can include a combination of dietary deficiencies, alcohol abuse, and metabolic disturbances. Thiamine deficiency is the underlying factor in the development of WKS, as it is essential for normal brain function and energy metabolism [6, 26]. Though alcohol abuse remains the primary etiological factor in the majority of cases, nonalcoholic WKS can occur in individuals with conditions that lead to malabsorption or malnutrition, such as gastrointestinal disorders, prolonged fasting, or restricted diets [27]. Alcohol is a substance that interferes with thiamine absorption, storage, and utilization in the body. For one, it stimulates the release of gastrin, a hormone that promotes gastric acid secretion, which, in elevated levels, can damage the stomach lining, impairing thiamine absorption [28]. Alcohol delays gastric emptying, prolonging the exposure of the gastric mucosa to alcohol and its metabolites, irritating and inflaming mucosa [28]. Additionally, alcohol disrupts thiamine-dependent enzymatic pathways involved in energy metabolism. Thiamine deficiency diminishes the availability of TPP, thereby impairing the function of PDH and α-KGDH, critical TPP-dependent enzymes in the citric acid cycle. The resulting damage to these apoenzymes will cause them to later require higher concentrations of thiamine to work normally [26].
The BBB tightly regulates the passage of substances, including thiamine, from the bloodstream into the brain; alcohol-induced alterations in its structure and function can impair thiamine transport, reducing the availability of thiamine in the brain and contributing to neurological dysfunction [26]. Moreover, chronic alcoholism predisposes individuals to other risk factors for WKS, such as malnutrition, gastrointestinal disorders, and liver dysfunction. Alcohol-induced liver damage further compromises thiamine transport by decreasing the synthesis of thiamine-binding proteins and the conversion of thiamine to TPP in the liver [29]. The onset and severity of WKS symptoms in individuals with alcoholism depend on the duration and intensity of alcohol consumption, genetic susceptibility, and coexisting medical conditions. WSK can also be a direct consequence of malnutrition or gastrointestinal disorders, unrelated to alcohol abuse [14].

Malnutrition as a consequence of eating disorders, restricted dieting, extended periods of fasting or starvation, or malabsorption syndromes can lead to thiamine deficiency. Since Mg and Ca are cofactors for the enzyme thiamine pyrophosphokinase, which converts thiamine to TPP, their deficiency indirectly contributes to thiamine deficiency and the development of WKS [30]. Conditions like inflammatory bowel disease, celiac disease, and bariatric surgery can also impair thiamine absorption. Patients undergoing long-term hemodialysis for end-stage renal disease and chemotherapy treatment for cancer may also experience thiamine loss [26, 31]. More rarely, HIV infection and AIDS-related complications, thyrotoxicosis, autoimmune thyroid diseases, and genetic predisposition can disrupt thiamine metabolism [18, 32].

Pathology and pathogenesis. The interplay between the molecular mechanisms and underlying causes of thiamine deficiency contributes to the pathogenesis and pathophysiology of WKS, which comprises two distinct stages: Wernicke's encephalopathy and Korsakoff's psychosis [33]. Carl Wernicke characterized acute encephalopathy by the classical triad – mental confusion, ophthalmoplegia, and gait ataxia [27] and Sergei Korsakoff later included memory loss and confabulation as subsequent neuropsychiatric manifestations of the illness [27]. Most significant pathologies are exhibited in the nervous system. Thiamine deficiency disrupts normal cellular functions in the thalamus, leading to sensory disturbances, including visual and hearing impairments, and mammillary bodies, contributing to memory deficits and other cognitive impairments [18]. Cognitively, WKS manifests in acute confusion, short-term memory loss, disorientation, and confabulation – when individuals fabricate events to fill memory gaps [34]. These cognitive deficits are often accompanied by other neurological symptoms such as ataxia, nystagmus, and peripheral neuropathy. Moreover, alcohol’s neurotoxic effects exacerbate neuronal damage and impair neuroplasticity, contributing to the progression of WKS.

Patients may present with pulmonary hypertension and dilated cardiomyopathy, particularly ventricular dilatation, a condition characterized by the enlargement and weakening of the heart muscle, impairing its ability to pump blood
effectively, resulting in fatigue, shortness of breath, and edema [19]. Severe cases of WKS may result in significant neurological impairment, including autonomic dysfunction, which can affect cardiac and respiratory control [35]. Patients may present with orthostatic hypotension, where blood pressure drops significantly upon standing, and abnormalities in respiratory rhythm [36]. Individuals with WKS may have decreased cough reflexes and reduced respiratory muscle strength, predisposing them to respiratory infections. Individuals also often experience muscle weakness and wasting, which can result from direct neuronal damage, decreased mobility, and physical activity due to neurological impairments, or inadequate protein intake [19]. Gait disturbances and ataxia can increase the risk of falls and subsequent musculoskeletal injuries [19].

**Treatment.** Early recognition and treatment of thiamine deficiency are crucial for preventing the irreversible neurological damage of WKS and improving clinical outcomes in such individuals. Treatment of WKS typically involves a combination of medical interventions and supportive care aimed at addressing alcohol abuse and thiamine deficiency, managing symptoms, and promoting neurological recovery. Thiamine replacement therapy through intravenous, high-dose administration of thiamine helps replenish thiamine stores by bypassing gastrointestinal absorption issues often seen in chronic alcoholics or malnourished individuals, ensuring rapid and reliable delivery of the vitamin to the brain [37]. Administering intravenous fluids helps restore fluid balance and correct electrolyte abnormalities, while nutritional support interventions, including dietary counseling and oral nutritional supplements, help correct malnutrition [31]. Co-occurring conditions like liver disease and psychiatric conditions are managed through pharmacotherapy, psychotherapy, and rehabilitation programs. Benzodiazepines help alleviate agitation and anxiety, antipsychotic medications address hallucinations or delusions, and anticonvulsants help manage seizures [38]. Cognitive rehabilitation programs aim to improve cognitive functioning, enhance memory recall, and promote independent living skills [35]. Regular medical assessments, cognitive evaluations, and nutritional monitoring help track the individual’s health status and adjust treatment as needed. Long-term follow-up and support are essential components of disease management that help prevent the recurrence of symptoms.

**Conclusion.** Through an examination of etiological factors, diagnostic approaches, and treatment modalities, this review underscores the importance of early recognition and intervention to mitigate neurological damage and improve patient outcomes. Moving forward, continued research efforts and interdisciplinary collaboration are essential to further enhance the understanding of WKS and optimize strategies for prevention, diagnosis, and management in clinical practice.

**References:**


Література:


