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## **DEFICIENCY OF THIAMINE AND WERNICKE-KORSAKOFF SYNDROME – REVIEW OF PATHOPHYSIOLOGY, CLINICAL PRESENTATION, DIAGNOSTICS AND TREATMENT**

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## **Abstract**

**Introduction and aim of the study:** Thiamine is a water-soluble vitamin, which bioactive form is necessary for energy metabolism in all cells. Deficiency of thiamine may be caused by malnutrition, alcoholism and certain diseases and it leads to an acute neuropsychiatric disorder called Wernicke encephalopathy. Untreated patients can develop a residual syndrome called Korsakoff syndrome. The aim of our study is to present current knowledge of history, pathophysiology, causes, symptoms and treatment of vitamin B1 depletion and Wernicke-Korsakoff's syndrome.

**Material and methods:** Our review is based on the analysis of materials collected in „Pubmed”, „Google Scholar” and other scientific articles using keywords: „thiamine”, „thiamine deficiency”, „Wernicke encephalopathy”, „Korsakoff syndrome”.

**Conclusions:** Despite numerous studies, Wernicke encephalopathy is still difficult to diagnose. Attention should be paid to the possibility of vitamin B1 deficiency in people who are at risk of it like alcoholics, malnourished or psychiatric patients. Wernicke encephalopathy is an acute neuropsychiatric disorder so the treatment should be started as soon as possible to reduce the risk of developing Korsakoff syndrome.

**Key words:** „thiamine”, „thiamine deficiency”, „Wernicke encephalopathy”, „Korsakoff syndrome”, „WE”, „KS”

## **Introduction**

Thiamine deficiency leads to a group of diseases called „beriberi”. It is a condition that can manifest with peripheral cardiac failure, neuropathy, and encephalopathy. [1]

The term „beriberi” is divided into two forms: „wet” characterized by life-threatening heart failure, frequently with pulmonary edema (wet lungs) and peripheral edema and „dry” with dominant symptoms from the nervous system like peripheral polyneuropathy and paralysis. The encephalopathic manifestation of beriberi is referred to as Wernicke-Korsakoff syndrome. [2]

### **The history of thiamine**

The first researcher which connected lack of nitrogenous food with beriberi was Takaki, a Japanese naval surgeon. In 1882 he observed that 61% of of the crew of a Japanese naval vessel suffered from beriberi after 272 days of cruising. In 1884 he equipped a ship with dried milk and meat, giving a carbon to nitrogen ratio of 16:1 and it turned out that only 14 members of the crew had succumbed to beriberi. [3,4]

Towards the end of the 19th century, Eijkman observed that pigeons that were given polished rice would exhibit neurological damage resembling the symptoms observed in humans suffering from beriberi. He discovered that rice polishing contains something which was called „antiberiberi factor”. [3] Gerrit Grijns demonstrated that every type of food loses this factor at 110-120°C. Grijns also initiated the initial efforts to extract this substance through a water-based process from the outer layer of the rice, known as silverskin.

He obtained concentrated substances with high activity, but it was not pure. Ten years later Casimir Funk isolated a crystalline substance from rice polishing. He believed that he had successfully identified the active component responsible for preventing beriberi and he thought that it was amine so in 1911 it was called vitamine like a vital amine crucial for sustaining life. [4] Unfortunately, the crystals discovered by Funk were found to lack any anti-neuritic activity. In 1936 thiamin was synthesized by Williams. In 1936 Peters discovered the role of thiamin with glucose metabolism. When he added glucose to cells with thiamin sufficiency, they immediately began to respire. When he added it to cells with thiamin deficiency, they did not respond. He additionally discovered that this effect was more pronounced in cells originating from the lower brain.

This research resulted in linking thiamine to the emerging field of oxidative metabolism. [3]

## What do we know about thiamine now?

Thiamine, also known as vitamin B1, is a water-soluble vitamin, stored in body tissues, especially in the liver. People are unable to synthesize thiamine. Its main source is pork, but we can also find it in other meats, eggs, fish, liver, vegetables, sunflower seeds, legumes and whole or enriched grain products. [5, 6]

Thiamine consists of a pyrimidine ring (2,5- dimethyl-6-aminopyrimidine) and a thiazolium ring (4-methyl-5-hydroxy ethyl thiazole) joined by a methylene bridge.

A healthy adult requires approximately 0.5 mg per 1,000 kcal. The body contains only 30–50 mg of thiamine reserves, meaning any malnutrition lasting over 3-4 weeks can exhaust these stores entirely.

It is destroyed with high temperatures and in an alkaline environment with a pH >8. [5]

Coffee and tea contain polyphenolic compounds which can inactivate thiamine. Its absorption is most efficient in the upper jejunum, by an active, carrier-mediated process.

Thiamin Pyrophosphate (TPP) is the bioactive form of thiamine. TPP is necessary for energy metabolism in all cells. [7,8] It functions as a co-enzyme in important intracellular pathways:

- as a cofactor for transketolase in the pentose phosphate pathway, a process occurring in the cytosol that produces pentoses, which are vital for nucleic acid synthesis. They are also a primary source of NADPH for fatty acid synthesis [13];

- as a cofactor for pyruvate dehydrogenase in the transition from glycolysis to the tricarboxylic acid cycle (Krebs cycle), which comprises a sequence of chemical reactions taking place in the mitochondrion, where acetate derived from carbohydrates, fatty acids, and amino acids undergoes oxidation to carbon dioxide, thereby generating chemical energy in the form of adenosine triphosphate (ATP). [7, 8, 1];

- and as a cofactor for  $\alpha$ -ketoglutarate dehydrogenase within the TCA cycle [7, 8]

When thiamine is deficient, intracellular TPP becomes depleted, triggering a cascade of metabolic changes in the central nervous system.

Deficiency of thiamine leads to a reduction of pentose phosphate pathway and tricarboxylic acid cycle efficiency. As a result, cellular energy depletion occurs, leading to a reduction in DNA, RNA and NADPH synthesis. [10]

A deficit of cellular energy leads to the accumulation of toxic metabolic products like lactate, alanine and glutamate, pH reduction and cerebral lactic acidosis. Excess glutamate causes excitotoxic damage of neurons. An overabundance of extracellular glutamate can attach to NMDA (N-methyl-D-aspartate) receptors, elevating calcium (Ca<sup>2+</sup>) levels inside cells, ultimately resulting in necrosis or apoptosis. [12] Thiamine deficiency also causes vasogenic edema by inducing blood-brain barrier (BBB) dysfunctions. [10,12]

### **Wernicke encephalopathy**

Deficiency of thiamine causes neuropsychiatric disorder called Wernicke encephalopathy (WE). [12] Carl Wernicke described it for the first time in 1881. He observed a woman with pyloric stenosis due to sulfuric acid ingestion and two alcoholics. They presented a triad of symptoms: mental confusion, ataxia and ophthalmoplegia. After their death, on histologic examination he notices hemorrhagic lesions around the periaqueductal region so the disease was named „polioencephalitis hemorrhagica superioris”. [9]

Nowadays it is known that WE is neurologic disorder resulting from thiamine deficiency.

It is characterized by the previously mentioned clinical triad: mental confusion, oculomotor abnormalities and ataxia. [10]

About 75-80% of cases of Wernicke encephalopathy is missed because the classical triad of symptoms occurs in only 16-20% of patients [11]. Roughly 19% of patients exhibit none of the classic triad symptoms upon initial presentation of Wernicke's encephalopathy.

Around 82% of patients exhibit alterations in mental status, as indicated by autopsy-based studies.

Initial signs of thiamine depletion comprise fatigue, weakness, and emotional disturbances, often preceding other physical manifestations. Some patients might display symptoms such as confusion, agitation, hallucinations, and behavioral disruptions, resembling those seen in an acute psychotic disorder. Oculomotor abnormalities include nystagmus, asymmetrical or symmetrical palsy of ocular muscles or conjugate-gaze palsies. Patients can also present anisocoria, sluggish reaction of the pupils to light or light-near dissociation. [14]

Signs and symptoms of thiamine deficiency also encompass nausea, vomiting, loss of appetite, fatigue, apathy, insomnia, anxiety, difficulties in concentration, stupor, signs of decompensation like disorientation, hallucinations or confabulation and eventually coma. [15]

There can be also seen hypotension and tachycardia, hypothermia, epileptic seizures and progressive hearing loss. [14]

### **Korsakoff syndrome**

Patients who suffered from Wernicke encephalopathy, but they were not promptly administered with sufficient thiamine replacement therapy, can develop a residual syndrome called Korsakoff syndrome (KS). [16]

Sergei Korsakoff's series of reports from 1891 to 1897 delineated "psychosis polyneuretica" as an independent disease from WE marked by severe memory impairment stemming from chronic alcohol abuse. [9] He noticed that the syndrome could be connected with peripheral nerve inflammation. Korsakoff defined this memory disorder as manifesting in a setting of clear consciousness. He observed that patients during conversation gave impressions of full cognitive function, but presented significant deficits in current and recent memory. [16,17]

The fundamental symptom of Korsakoff syndrome is a profound deficit in declarative memory, impacting the ability to learn and retain new information.

In Korsakoff syndrome, there is also a temporally-graded decline in memory for past events (retrograde amnesia), typically spanning many years or decades.

Executive deficits like problems with inhibition or behavior can be present in KS. Symptoms such as poor judgment, poor planning abilities, problem solving inabilities can be also observed. [18]

Sometimes, individuals with the disorder engage in inventing "fictions" (confabulations) during their discourse. Confabulation is sometimes divided into „spontaneous” and „momentary”. The first one is a continuous, spontaneous emission of incorrect memories without any external prompting. In the second one brief episodes of erroneous memories or distortions arise in response to memory challenges. [17]

### **The reasons**

The main reason of WE and KS is alcohol abuse. Firstly, it is because people dependent on alcohol tend to give up vitamin-rich food. Secondly, thiamine absorption decreases after acute alcohol consumption. [19] In chronic alcoholic liver disease, the liver's capacity to store

thiamine is diminished by 73%, which is the next reason [20] Additionally alcohol affects renal epithelial cells, resulting in elevated thiamine loss from the kidneys. [21]

Availability of TPP (thiamine pyrophosphate) for utilization is reduced by alcohol consumption because it diminishes the enzymatic activity of thiamine pyrophosphokinase (TPK).

Alcohol is the most common, but not the only cause of WE. Examples of other reasons are:

- Crohn's disease (CD) and colitis ulcerosa (CU).

CD and CU are inflammatory bowel diseases. It is defined by persistent and recurring inflammation within the intestines [21] There are a lot of factors contributing to thiamine depletion in CD and CU. WE can develop after total or partial bowel resection, which is a surgical form of treatment of this disease. There are thirteen described cases, where nausea and vomiting in IBD resulted in WE. Diarrhea, which is a crucial symptom of IBD contributes to thiamin deficiency too. [24];

- Bariatric surgery.

The number of performed bariatric surgery procedures grows every year. The most common procedures of surgical obesity treatment is laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy. For all patients before the surgery it is recommended by guidelines to supplement thiamin in multivitamine treatment.

As research show, all of these surgeries carry the risk of thiamine depletion [25]

Additionally, bariatric patients are more likely for hyperemesis and infection, which favors the development of WE. [26];

- Hyperemesis gravidarum

Hyperemesis gravidarum is an extreme manifestation of nausea experienced during pregnancy. Although it affects only 0.5% to 3%, it can lead to serious nutritional depletion like thiamin deficiency and WE. There was even a case described of a woman with hyperemesis gravidarum, who was diagnosed to have Korsakoff psychosis. [27];

- Acute and chronic kidney disease

Malnutrition is prevalent among patients with chronic kidney disease (CKD), particularly those undergoing dialysis. Diminished clearance in kidney disease results in the buildup of



metabolic waste products. High concentration of these products is toxic. As an uremic toxin, the antimetabolite of thiamine (oxythiamine) isn't eliminated by the kidneys, causing the inhibition of transketolase. Consequently, it results in difficulties with the conversion of thiamine to thiamine pyrophosphate. What is more, accumulation of oxythiamine may cause functional thiamine depletion. [28];

#### - Cancer

In a group at risk of thiamine deficiency are patients with cancer. There are several reasons for this: reduced availability of thiamine because of malnutrition, vomiting, anorexia; thiamine is consumed at an accelerated rate by rapidly proliferating tumors; the breakdown products of chemotherapy can deactivate thiamine-dependent enzymes. [29]

#### - Depression

Depression increases the risk of developing malnutrition. [30]

It's relatively obscure that malnutrition resulting from depression can lead to Wernicke's encephalopathy but depression may be accompanied by vomiting and diarrhea which is associated with the loss of vitamins. There are known and described cases of 9 patients with depression who developed WE due to vomiting or diarrhea, and 7 patients with decreased food intake which was identified as the primary cause of WE in cases of depression. [31]

#### - Anorexia nervosa

Anorexia nervosa (AN) is a severe psychiatric condition marked by the inability to maintain a healthy body weight. Thiamine deficiency is present in 38% of individuals diagnosed with AN. Wernicke's encephalopathy (WE) subsequent to anorexia nervosa (AN) remains a relatively uncommon neuropsychiatric condition. Patients with AN often suffer from other diseases that increase the risk of developing encephalopathy, such as alcoholism or depression. [32]

### **Diagnostics**

The lack of specific clinical features in patients with Wernicke's encephalopathy (WE) makes diagnosis exceedingly challenging. It is often undiagnosed until death. The classic triad is notably more prevalent among alcoholics compared to non-alcoholics. [33] Among 97 alcoholics diagnosed with Wernicke-Korsakoff syndrome (WKS) upon autopsy, chart reviews indicated that only 16% had documented evidence of all three 'classical signs.' [19]

The recommendations state is the clinical diagnosis of Wernicke's encephalopathy (WE) in alcoholics necessitates the presence of at least two of the following four signs: dietary deficiencies, eye signs, cerebellar dysfunction, and an altered mental state or mild memory impairment. [34]

Nowadays in many countries there is performed a high-performance liquid chromatography (HPLC) which measures level of thiamine and its phosphate esters in human blood to identify patients with thiamine deficiency [32] A less frequently employed approach involves the detection of monophosphorylated and diphosphorylated forms of thiamine in whole red blood cells. [33]

Computer tomography is not considered a reliable diagnostic test for Wernicke's encephalopathy. [31] Sensivity of MRI is 53% so it can only confirm a clinical suspicion of WE. [19]

## **Treatment**

There is no consensus on the optimal dose of thiamine, its preparation form, duration of treatment, or the number of daily doses. As per numerous case reports, administering either 100 or 200 mg of thiamine intravenously has been successful in curing the disease in non-alcoholics.

Alcoholic patients with WE may require higher daily doses and a recommendation of 500 mg three times daily has been proposed. [34]

Currently, the standard treatment in the acute phase of the disease is intravenous thiamine at a dose of 50-100 mg per day. Thiamine pyrophosphate may be administered instead of thiamine. Treatment should be carried out for 5-7 days. During this time, the consumption of carbohydrates is limited. After 5-7 days, thiamine is administered orally at a dose of 150 mg per day.

Maintenance treatment typically entails oral administration of thiamine at a dose ranging from 25 to 50 mg per day for several months. It is important to supplement magnesium as well, because magnesium acts as a cofactor for thiamine's activity [33, 35]

To prevent the onset of Korsakoff syndrome and to address symptoms of Wernicke's encephalopathy, immediate parenteral thiamine treatment should be initiated in all patients

displaying any indications of chronic alcohol misuse and poor dietary habits, even while they are still inebriated. [14]

## **Conclusion**

Wernicke encephalopathy is an acute neuropsychiatric disorder. Despite many studies, this disease is still very difficult to diagnose. Treatment started early enough would reduce the occurrence of Korsakoff syndrome. It is important to remember that WE should be considered in patients with cerebellar disorders or mental status changes. Especially in those who we know may be at risk of thiamine deficiency.

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All authors have read and agreed with the published version of the manuscript.

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The authors report no conflict of interest.

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