ABSTRACT

Thiamine, also known as vitamin B1, is an essential nutrient required for all living tissues. It can be found in high concentration inside the heart, kidneys, brain and skeletal muscles. A severe depletion is not commonly seen, except in cases of inadequate nutrition and/or chronic alcoholism. Thiamine deficiency has 4 clinical forms: Dry Beriberi, Wet Beriberi (chronic and acute), Wernicke encephalopathy and Korsakoff syndrome. Wernicke-Korsakoff syndrome is a neuropsychiatric disorder resulting from Thiamine deficiency and commonly associated with chronic alcoholism, but we describe the first case report on Wernicke-korsakoff syndrome which is a complication of Beriberi syndrome. The prevalence of Wernicke’s encephalopathy ranges from 0.5 to 2.8 percent. Early recognition and adequate thiamine replacement can lead to a full recovery. This report details the case of a 38 years old male patient presented with Beriberi syndrome progressed to Wernicke-korsakoff syndrome (severe Thiamine deficiency) caused by severe malnutrition, starvation and chronic alcoholism.

KEYWORDS: Thiamine, Beriberi, Peripheral neuropathy, Ataxia, Wernicke's encephalopathy and Korsakoff's syndrome

INTRODUCTION

Thiamine, also known as vitamin B1, is a water-soluble nutrient that is absorbed in the jejunum of the small intestine, where Thiamine phosphorylated and converted into Thiamine pyrophosphate (TPP). TPP is the biologically active form of thiamine and serves as a cofactor for several enzymes important in the biosynthesis of essential neurotransmitters and
carbohydrate catabolism. Thiamine is involved in numerous body functions, including the nervous and musculoskeletal systems. It is essential for the transport of electrolytes in and out of nerve and muscle cells. The amount of the nutrient stored is limited due to the short half-life of 9 - 18 days and continuous excretion through the kidneys.\textsuperscript{[1]}

In its initial stage, Thiamine deficiency induces anorexia, irritability, apathy and generalized weakness. As it continues, it leads to Beriberi, classically divided in Dry and Wet, showing in both forms pain and paresthesia. Patients with Dry beriberi present with symmetrical peripheral sensory-motor neuropathy and hyporeflexia, mainly in the lower limbs.\textsuperscript{[2]} Another presentation of neurologic involvement Wernicke-Korsakoff syndrome.\textsuperscript{[1]}

Wernicke-Korsakoff syndrome (WKS) is a disorder of the brain resulting from Thiamine deficiency, and it is commonly associated with chronic alcoholism. WKS is a neuropathological term which encompasses two separate conditions - Wernicke encephalopathy (WE) and Korsakoff syndrome (KS).\textsuperscript{[3]} Carl Wernicke (1881) was the first to describe Wernicke’s encephalopathy (WE). Wernicke’s encephalopathy is a neurological disorder due to deficiency of Thiamine. WE consists of a classical triad of symptoms that include vomiting, nystagmus, palsies of eye movement, fever, ataxia, global confusion, and ophthalmoplegia.\textsuperscript{[4]} Korsakoff’s syndrome (KS) on the other hand is a memory disorder that presents with amnesia, confabulations, attention deficits, and disorientations. Here we discuss the case of a 38-year-old male who developed beriberi syndrome 6 months back and now progressed to Wernicke-Korsakoff syndrome (WKS).

CASE REPORT
A 38-years-old man was brought to the hospital with chief complaints of altered behavior since one day and eye pain since 2 days. His history of present illness states that the patient was apparently normal till 3 days back, when he consumed alcohol continuously for past 3 days without food. On 4th day he had complaints of altered behavior, not able to answer the general questions about his family, eye pain associated with blurred vision and also difficulty in moving eyes, vomiting, ataxia, nystagmus and loss of appetite. Past history reveals that the patient had Beriberi (dry beriberi) syndrome 6 months back and taken treatment. A full recovery was achieved after thiamine replacement for 3 weeks without fail. He is a known alcoholic and smoker for the past 15 years.
At the time of admission, he was conscious and incoherent. Laboratory data included Routine haemogram revealed hemoglobin 13.8 gm%, platelets 1.08 lakhs/cumm, packed cell volume 39%, total leukocyte count 11,200 cells/cumm. Serum creatinine 1.4mg/dl, blood urea 47mg/dl, serum electrolytes - sodium 142mmol/l; potassium 4.9mmol/l; chloride 104mmol/l. Based on the physical examination, past history and laboratory examinations, the patient was diagnosed as WERNICKE-KORSAKOFF’S SYNDROME and was on treatment with Inj. Thiamine 500mg in 5% Dextrose IV STAT, Inj.Pantop 80mg IV BD, Inj.Ondansetron 2CC IV SOS, Inj.Optineuron 1amp IM OD, Tab.Benfothiamine 100mg PO BD, Tab.Pantop (Pantoprazole) 40mg PO OD, Tab.B-Complex 1 tablet PO OD and Tab.Librum (Chlordiazepoxide) 25mg PO BD. The patient was discharged after 11 days of therapy and advised to continue Tab. Benfothiamine 100mg and Tab. B-Complex.

DISCUSSION
Thiamine deficiency involves multiple systems, it can be easily misdiagnosed. Early recognition and appropriate treatment is critical and can lead to a full recovery of the illness. Early stages of Thiamine deficiency manifest as anorexia and nonspecific symptoms including irritability and decreased short-term memory. When Thiamine deficiency persists, patients will progress to a condition called Beriberi, which is classified as Wet or Dry with frequent overlap between the two. The major manifestations of Thiamine deficiency involve the cardiovascular system (Wet Beriberi) and nervous system (Dry Beriberi).[1]

Symptoms of Wet and Dry Beriberi are pain and paresthesia. Dry Beriberi presents with peripheral neuropathy of the motor and sensory systems with diminished reflexes, especially in the lower extremities.[5] In this case, the patient had a history of Dry Beriberi and experienced loss of reflexes in knees and feet, foot drooping and peripheral neuropathy. He was fully recovered after thiamine replacement for 3 weeks without fail. Without thiamine supplementation, its deficiency can lead to Wernicke encephalopathy (WE) and eventually can lead to permanent condition of Korsakoff’s syndrome. Another presentation of neurologic involvement is Wernicke-Korsakoff syndrome.

Wernicke-Korsakoff syndrome (WKS) is a disorder of the brain resulting from Thiamine deficiency, and it is commonly associated with chronic alcoholism. WKS is a neuropathological term which encompasses two separate conditions-Wernicke encephalopathy (WE) and Korsakoff syndrome (KS).[3] WE is a neurological disorder due to deficiency of Thiamine which consists of a classical triad of symptoms that include vomiting,
nystagmus, palsies of eye movement, fever, ataxia, global confusion, and ophthalmoplegia. Korsakoff’s syndrome (KS) on the other hand is a memory disorder that presents with amnesia, confabulations, attention deficits, and disorientations. The key features in Korsakoff’s syndrome include the inability to learn new information or form new memories and the inability to retrieve old memories. Korsakoff’s syndrome is the late manifestation of the condition, where Wernicke's encephalopathy has not been adequately treated.^[4]\]

Although the abnormal eye movements, ataxia, and global confusion appear to improve relatively rapidly, impairments in memory and learning respond more slowly or incompletely, suggesting that they may be due to a different mechanism(s), which may involve interactions between the metabolic effects of Thiamine deficiency and the neurotoxic contribution from alcohol. Patients who develop WE in association with alcohol misuse require much larger parenteral doses of Thiamine, up to 1 g in 24 h, if they are to be treated successfully.^[6]\]

As the patient was chronic alcoholic in this case, at first alcohol affects the forebrain and assaults motor coordination and decision making. Then alcohol knocks out the midbrain, and patient may lose control over emotions and increase chances of blackout. Finally, alcohol batters the brainstem as it affects heart rate, body temperature, appetite and consciousness, a dangerous and potentially fatal condition.

In these patients inhibition of the a-ketoglutarate dehydrogenase complex (a-KGDH) takes place which causes a change in mitochondrial function, and sets in motion a cascade of abnormalities, leading to oxidative stress. This leads to the production of nitric oxide from vascular endothelial cells that may be responsible for the distribution of brain lesions in WE. Low circulating levels of Thiamine have been reported in 30–80% of alcoholic patients. The metabolism of alcohol raises the demand for Thiamine, at the same time alcohol decreases the amount of Thiamine transported across the intestinal mucosa and impairs the conversion of Thiamine to Thiamine pyrophosphate. Ethanol can cause damage to the intestinal mucosa, in that case thiamine absorption can be reduced by up to 90%. It was subsequently demonstrated that both alcohol and malnutrition may interfere with the absorption of Thiamine hydrochloride in man.^[6]\]

The various causes of Wernicke-Korsakoff syndrome include alcohol misuse, thyrotoxicosis, haemodialysis, severe malnutrition because of gastric carcinoma and pyloric obstruction,
hyperemesis gravidarum, prolonged parenteral feeding, and hunger strike.\textsuperscript{4} But in this case, self-imposed long-lasting nutritional deprivation, anorexia, chronic alcohol consumption and also a history of beriberi syndrome is thought to be the main cause of Thiamine deficiency and WKS.

The diagnosis of Wernicke-Korsakoff syndrome was established based on the history, clinical findings, and MRI findings. The radiological findings on MRI brain in patients with Wernicke’s encephalopathy include lesions in mammillary bodies, thalamus, tectal plate, and periaqueductal area. These radiological findings represent typical lesions characteristic of WE.\textsuperscript{[2]} WE remains largely a clinical diagnosis. No specific diagnostic abnormalities have been found in cerebrospinal fluid, brain imaging or electroencephalograms.\textsuperscript{[7]}

Complete blood count particularly looking at the MCV, Urine & Electrolytes (to exclude hypernatraemia, hypercalcaemia, and uraemia), liver function tests, glucose, blood arterial gases (to rule out hypercarbia and hypoxia) and cholesterol. Serum Thiamine levels (vitamin B1) levels may be low, pyruvate is elevated, Red cell transketolase activity is decreased in Thiamine deficiency, but not usually necessary to diagnose the condition and Lumbar puncture may be needed to exclude non-focal CNS infections. Electroencephalography (EEG) may be required to rule out convulsive or non-convulsive status epilepticus.\textsuperscript{[8]}

Total Thiamine in blood sample should be measured immediately before its administration. MRI should be used to support the diagnosis of acute WE both in alcoholics and non alcoholics.\textsuperscript{[5]} Diagnosis is mainly based on the history and physical examination of the patient, and if the condition is suspected, treatment should not be delayed whilst waiting for test results.

The patient was treated by conventional doses of Thiamine 100mg/day intravenously and orally. However it is said that these patients require 500mg/day of Thiamine intravenous administration should be by infusion over 30 minutes.

The treatment of Dry Beriberi (Thiamine deficiency) consists of parenteral administration of Thiamine in the dose of 50 to 100mg, to reestablish the cellular and hepatic deposits, and reversal of symptomatology often occurs after 24 hours. In the Wernicke-Korsakoff syndrome, literature data suggest an intravenous administration of 100mg of Thiamine, followed by intramuscular 100mg daily for 5 days, plus permanent Thiamine
supplementation is required for long term. There are still reports that some patients may not respond to this supplementation due to magnesium deficiency. Magnesium acts as a transketolase cofactor via pentose phosphate pathway, making it necessary to supplement it as well so there can be a response.\[^2\]

Offer oral Thiamine to harmful or dependent drinkers if either of the following applies: (1) They are malnourished (or have a poor diet); prescribe oral Thiamine 50 mg per day (as a single dose) for as long as malnutrition may be present. (2) They are chronic alcoholics. (3) They have decompensated liver disease.\[^8\]

As the unwanted side-effects to B vitamins are most commonly seen after multiple administrations, and the necessary dose of Thiamine amounts to a rather painful volume when given intramuscularly, an intravenous infusion of Thiamine diluted with 100 ml of normal saline or 5% glucose, given over 30 min can be suggested. It is also important to give Thiamine before any carbohydrate diet, because it is well known that glucose infusion precipitates WE in Thiamine deficiency and a normal diet should be instituted immediately after Thiamine. Treatment should be continued until there is no further improvement in signs and symptoms.\[^5\]

More intake of vitamin B1 supplements are advised. The primary sources of this vitamin are pork, beef, vegetables, all grains, dried milk, nuts, oats, oranges, eggs, seeds, legumes, peas and yeast. Foods are also fortified with Thiamine. Some foods that are often fortified with B1 are rice, pasta, breads, cereals and flour.\[^2\]

In this case, four days of intravenous Thiamine treatment quickly reversed the patient’s confusion and ataxic symptoms, but after treatment was stopped, patient developed apathy and short-term memory deficits (anterograde amnesia) typical of Korsakoff’s syndrome. This patient did not show significant improvement in cognitive function, and craving for alcohol and cigarette was increased even with sufficient thiamine administration. Failure of Thiamine treatment is thought to be possibly due to irreversibly damaged cells by lack of Thiamine, deficiencies of other nutrients or alcohol-induced neurotoxicity.

**CONCLUSION**

There is a significant co-morbidity between eating disorders and substance related disorders and the subgroup of patients with anorexia who also misuse alcohol is probably at a
particularly high risk of developing Wernicke-Korsakoff syndrome. Highlighting this issue, we presented a clinical case in which anorexia, combined with magnesium depletion and chronic alcohol misuse, had led to the presentation of the complete Wernicke-Korsakoff syndrome.

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation technique which modulates cortical excitability and it is proven to have therapeutic effects in various neuropsychiatric disorders. rTMS would be a useful treatment tool for enhancing cognitive function and suppressing co-occurring alcohol cravings in WKS. High-frequency rTMS over the left DLPFC (Dorsolateral Prefrontal Cortex) has a positive effect on cognition. Thiamine deficiency involves multiple systems, it can be easily misdiagnosed. Early recognition and appropriate treatment is critical and can lead to a full recovery of the illness.

REFERENCES