Wernicke's Encephalopathy due to Non-Alcoholic Gastrointestinal Tract Disease

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ABSTRACT

Introduction: Wernicke's encephalopathy (WE) is an underdiagnosed neuropsychiatric disorder especially in non-alcoholic groups that causes morbidity-mortality if diagnosis is delayed. Korsakoff syndrome is a chronic consequence of this condition characterized by persistent memory impairment. In this study we present a series of non-alcoholic patients with WE. The purpose of this study was to analyze the predisposing factors in non-alcoholic patients with WE and emphasize the importance of early diagnosis and treatment with thiamine supplementation.

Methods: The clinical records of 6 cases with WE followed by gastrointestinal tract disease and/or surgery who were admitted to our Medical Faculty between 2012 and 2014 were retrospectively reviewed.

Results: The study included 3 men and 3 women in the age range of 24 to 55. All patients had gastrointestinal tract diseases and/or had undergone gastrointestinal surgeries, and were non-alcoholic. Vomiting,

weight loss, and parenteral nutrition were the frequent precipitating factors. The classic triad of mental impairment, oculomotor alterations and gait ataxia was present in 4 of the 6 patients. Magnetic Resonance Imaging showed typical signal alterations in the medial thalami, mammillary bodies and the periaqueductal region of patients in various degrees. Clinical improvement was seen in each patient after thiamine supplementation.

Discussion: Physicians should be aware of the predisposing factors and symptoms to prevent or optimize the management of this potentially devastating disease. Thiamine supplementation should be considered in patients with gastrointestinal tract diseases or those who have undergone surgery.

Keywords: Korsakoff syndrome, thiamine deficiency, thiamine supplementation, Wernicke-Korsakoff syndrome, Wernicke's encephalopathy

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INTRODUCTION

Dietary thiamine is a water-soluble vitamin that is an important co-factor of three key enzymes (pyruvate dehydrogenase complex, alpha-ketoglutarate dehydrogenase complex, and transketolase) in glycolysis, the Krebs cycle, and the pentose-phosphate pathway. In the presence of thiamine, these three enzymes regulate the metabolism of glucose and expression of oxidative stress-fighting compounds, myelin, neurotransmitters, nucleic acids, ATP and ATP-like energy products (1). A minimum of 0.5 mg thiamine is required for every 1000 kcal energy consumed. This requirement is higher in children, in critical conditions and during pregnancy and lactation (2). In addition, there are several factors that lead to the development of thiamine deficiency, which is caused by decreased availability, impaired utilization and accelerated use. These topics will be considered later in this review.

Wernicke encephalopathy (WE), which was first described by Carl Wernicke in 1881, is an acute-subacute neurologic syndrome that occurs

due to thiamine deficiency and is characterized by a triad of mental impairment, ophthalmoplegia and gait ataxia. Nystagmus has also been reported as an important ocular sign (2-4). Korsakoff's syndrome (KS) or Korsakoff's psychosis is a clinical manifestation of WE that is principally characterized by behavioral abnormalities and memory impairments (3, 4). Memory impairment in chronic alcoholics was firstly reported by the Russian psychiatrist Sergei Korsakoff in 1887. Although neither Wernicke nor Korsakoff noticed the relationship between these two entities (5), for today the syndrome is usually referred to under one name, *Wernicke-Korsakoff syndrome* (WKS).

Components of the classic clinical triad may have not seen all together especially in the early phase of the disease. In their clinicopathologic study, Harper and his colleagues showed that only 16% of patients had the classic clinical triad in the early phase which explains why the correct diagnosis is still being missed in patients with WE (3, 6, 7). In addition to

the clinical triad, patients with WE may also present with cardiovascular disturbances, epileptic seizures, progressive hearing loss and peripheral neuropathy (2).

In the diagnosis of WE; history, physical examination, Magnetic Resonance Imaging (MRI) findings should be considered all together. Clinical suspicion is also very important in high-risk groups. Laboratory tests for plasma thiamine level are available but they are not reliable in all circumstances (8). MRI is a valuable technique in the diagnosis of WE with a sensitivity of 53% and a specificity of 93% (9). Symmetric alterations in the medial thalami, mammillary bodies, periaqueductal region and tectal plate are the common typical lesions. Furthermore, atypical MRI findings can be observed in the cerebellum, cranial nerve nuclei, red nuclei, dentate nuclei, caudate nuclei, splenium and cerebral cortex (10). Also, chronic cases can present the atrophy of the mammillary bodies, which is absent in the early stages of WE cases (11, 12).

In this study, we present the clinical and laboratory characteristics of 6 patients with WE who had gastrointestinal (GI) tract diseases and/or had undergone gastrointestinal surgeries we also discuss predisposing factors as well as diagnostic and therapeutic issues related to this entity.

METHODS

This study was done according to Helsinki Declaration. Informed consent was received from all the patients and/or their relatives.

Case-1: A 48-year old woman was admitted to Department of Gastroenterology to confirm an endoscopic biopsy report that compatible with Non-Hodgkin's Lymphoma. She had nausea, vomiting, weight loss, bloating and postprandial symptoms. Therefore, she was given antiemetics and parenteral nutrition due to low oral tolerance and vomiting. Her weight loss was almost 16 kg within two months. Her second endoscopic biopsy showed hyperplastic polyposis with poorly differentiated gastric carcinoma infiltration and atypical cells with signet ring appearance individually distributed in the lamina propria of the corpus mucosectomy material. In the 5th week of admission, she was referred to the Neurology Department because of gait problems and confusion. In her neurologic examination, her reaction time was slow

and she was also partially disoriented, which made taking her medical history quite challenging. In a detailed examination, we found nystagmus in horizontal axis, mild paraparesia, hyporeflexia, disruption in vibration perception, and truncal ataxia. The Romberg test was positive and her mini-mental test score was 20/30.

The MRI scan showed bilateral hyperintense signal alterations in the medial thalami in FLAIR and T2 sequences with a diffusion abnormality in the DWI sequence (Fig. 1 a, b). Electroencephalography (EEG) monitoring revealed slight and widespread disorganization in both hemispheres (irregular slow waves as theta frequency).

First week response to thiamine was total resolution of confusion and partial resolution of nystagmus and ataxia. At the third week following hospital admission for WE, she was referred to Oncology Department for malignancy therapy. But she had a poor prognosis due to her inoperable advanced malignancy and never had a chance to come any follow-up visit.

Case-2: A 24-year-old man who had attempted suicide by ingesting a corrosive substance 3 months ago was admitted to Department of General Surgery. His first endoscopic examination at that time showed ulcerative lesions in the distal esophagus and stomach. This time, he was admitted because of an increase in nausea and a decrease in oral intake that required a second endoscopic examination. His second endoscopic examination showed hyperemia in the stomach and signs of full-occlusive pyloric stenosis. He underwent urgent surgery. Before his surgery, he was given antiemetics and parenteral nutrition. The day after the procedure, he was referred to the Neurology Department because of difficulty in recognizing his family members and trouble with his balance. In his neurologic examination, his reaction time was slow, cooperation was low and he was partially disoriented. In a detailed examination, we found gaze induced nystagmus in all directions, truncal ataxia. His mini-mental test score was 18/30.

The MRI scan showed marked bilateral hyperintense signal alterations in medial thalami, slight changes in the mammillary bodies and periaqueductal region in FLAIR-T2 sequences, with a diffusion abnormality in the DWI sequence (Fig. 2 a-c).

Figure 1. a. Axial T2 sequence MRI, showing the signal alterations in bilateral medial thalami, white arrows. **b.** DWI sequence MRI, showing the signal alterations in bilateral medial thalami, white arrows

Figure 2.

a. Axial T2 sequence MRI; showing the bilateral signal alterations in the medial thalami, white arrows.

b. FLAIR sequence MRI; showing the signal alterations in the mammillary bodies and periaqueductal region, white arrows.

c. DWI sequence MRI; showing the bilateral signal alterations in the medial thalami, white arrows.

Thiamine supplementation provided resolution in the nystagmus and ataxia at the fourth week after hospital admission, but mild amnesic problems persisted even at the end of first year.

Case-3: A-37-year-old man was admitted to Emergency Service with abdominal pain. His clinical and laboratory examination showed mesenteric ischemia and emergency surgery was performed. After undergoing a hemicolectomy and partial small bowel resection, he was given parenteral nutrition. Oral intake was allowed after the first week of his surgery, however his eating performance was low during that period. His weight loss was almost 5 kg within 5 weeks. He could not able to walk without assistance due to his poor general condition. Thirty-three days after his surgery, he was referred to the Neurology Department because of his memory impairment, confusion, and confabulation. In his neurological examination, he was somnolent, uncooperated and disoriented. Beside his mental impairment, he had gaze induced nystagmus in all directions. He was quite mobile in bed but he did not

cooperate with any other physical activities or with the mini-mental test examination.

The MRI revealed marked bilateral hyperintense lesions in medial thalami, and mild hyperintense lesions in the mammillary bodies and periaqueductal region in FLAIR, T2 and DWI sequences (Fig. 3 a-c). EEG monitoring was compatible with a nonspecific paroxysmal anomaly with a slight and diffuse disorganization in both hemispheres.

After thiamine supplementation, his somnolent state resolved. He started walking by the end of first week; however, his cognitive function did not fully restore and he had mild to moderate amnesic problems at discharge. At the end of first year with a follow-up call, we learned his sudden and unexplained death.

Case-4: A-55-year-old woman, who had gastric bypass operation in 7 months ago due to obesity, was admitted to department of General Surgery because of a recurrent surgical wound infection. She was poor general condition, so she was given parenteral nutrition due to low oral intake. She was referred to the Neurology Department because of decreased mobility in her legs and confused state. In her neurological examination, she had disorientation to time and her reaction time was also slow. In her ophthalmic examination, she had lateral gaze palsy in her left eye. We also found quadriparesia and areflexia with an absence of plantar reflex. She complained of numbness in her upper and lower extremities, but there was no objective finding in the sensory examination. Her vibration perception was also decreased. An electromyography (EMG) study was performed to rule out an acute inflammatory demyelinating polyneuropathy (AIDP), there was no evidence of AIDP.

Figure 3.

- a.** FLAIR sequence MRI; showing the marked signal alterations in the medial thalami, white arrows
b. FLAIR sequence MRI; showing the marked signal alterations in slight changes in the mammillary bodies and periaqueductal region, white arrows
c. DWI sequence MRI; showing the marked signal alterations in the medial thalami, white arrows

There were only mild hyperintense lesions in the bilateral medial thalami in the cranial MRI (Fig. 4 a, b). EEG monitoring showed disorganization in the frontotemporal regions.

During the follow-up period, her apathy increased and nystagmus appeared. Thiamine supplementation was subsequently given owing to a suspicion of WE. The outcome was favorable, her symptoms totally resolved and the patient returned to her original state at the end of third month after discharging.

Case-5: A-32-year-old woman with a medical history of sleeve gastrectomy due to obesity 2 months ago was found in her house in an unresponsive state. She was admitted to Emergency Service and referred to the Neurology Department. In her neurological examination,

Figure 4.

- a.** FLAIR sequence MRI; showing the slight bilateral signal alterations in the medial thalami MRI scan, white arrows
b. DWI sequence MRI; showing the slight bilateral signal alterations in the medial thalami MRI scan, white arrows

Figure 5.

a. Axial T2 sequence MRI showing the bilateral signal alterations in the medial thalami

b. Axial T2 sequence MRI showing the signal alterations periaqueductal regions, white arrow.

her eyes were closed, there was no movement or verbal response. Her pupils were isochoric with a weak reaction of pupils to light. Her plantar reflex was absent. Her medical history, which was provided by family members, revealed weight loss of almost 30 kg, nausea and decreased oral tolerance in the last 2 months. These symptoms were related with the cause of hospitalization and parenteral nutrition history one week prior to her last admission.

FLAIR and T2 sequences of the cranial MRI showed marked bilateral hyperintense signal alterations in the medial thalami, mammillary bodies, and periaqueductal region (Fig. 5 a, b). EEG monitoring was compatible with widespread disorganization in both hemispheres.

Twenty-four hours after the first parenteral thiamine administration, the patient became responsive, opened her eyes spontaneously and started to make incomprehensible sounds and moved her extremities. After 3 months of hospital admission she became more alert but nystagmus, ataxia and variable neuropsychiatric problems such as confabulations, paranoid delusions and hallucinations persisted.

Case-6: A-36-year-old man who had nausea, vomiting, weight loss and bloody diarrhea was diagnosed as an ulcerative colitis (UC) 2 months ago; however, in his clinical follow-up, he had not responded to treatment. He was subsequently admitted to Department of Gastroenterology to confirm the UC diagnosis. Mucosal changes compatible with cytomegalovirus (CMV) colitis were seen in his second endoscopic examination, which were also supported with a serologic plasma test of CMV DNA load (2040 copies). He was treated with ganciclovir, but due to his ongoing unresponsiveness to all treatment modalities, he underwent a colectomy in Department of General Surgery with an indication of fulminant colitis. Twenty-five days after being discharged from hospital, he was admitted to the Emergency Department with subacute progressive memory impairment and gait problems. His weight loss was almost 35 kg within 8 weeks. In his neurological examination, his reaction time was slow and he was also disoriented to time. A detailed examination revealed gaze-induced nystagmus in the horizontal axis, paraparesia (muscle strength was 3/5 in the proximal muscle group of lower extremities) and hyporeflexia in lower extremities with a weak flexor plantar reflex. He reported disturbed sensorial feelings with a patchy distribution of paresthesia and hypoesthesia complex. His vibration perception was

Figure 6.

a. FLAIR sequence MRI; showing the bilateral signal alterations in the medial thalami, white arrows.

b. DWI sequence MRI; showing the bilateral signal alterations in the medial thalami, white arrows.

Table 1. Clinical findings and demographic data of patients

	Case-1	Case-2	Case-3	Case-4	Case-5	Case-6
Sex	F	M	M	F	F	M
Age	48	24	37	55	32	36
History	Gastric carcinoma	Gastritis-Pyloric stenosis	Mesenteric ischemia	Bariatric surgery	Bariatric surgery	Fulminant colitis
Vomiting	+	+	-	+	+	+
Weight loss	+	+	+	+	+	+
Parenteral nutrition	+	+	+	+	+	+
Confusion	+	+	+	+	+	+
Ophthalmoparesis	-	-	-	+	-	-
Nystagmus	+	+	+	+	+	+
Ataxia	+	+	NA	NA	+	+
MRI findings	+	+	+	+	+	+
MMT score	20/30	18/30	NA	NA	NA	23/30
Thiamine response	+	+	+	+	+	+
Amnestic syndrome	-	+(mild)	+(moderate)	-	+(moderate)	+(mild)

MRI: Magnetic Resonance Imaging, MMT: Mini-mental test, NA: Not applicable

also decreased. He was not able to walk without the assistance of two family members. Mini-mental test score was 23/30. An EMG study was performed to rule out an AIDP and no compatible findings were found.

MRI showed bilateral hyperintense signal alterations in the medial thalami in FLAIR and T2 sequences with a diffusion abnormality in DWI sequence (Fig. 6 a, b).

After the thiamine supplementation, apathy and nystagmus disappeared in 3 days and he was able to walk at the end of the first week. Muscle strength reached to +4/5 in the proximal muscle groups of lower extremities after two weeks, but subjective sensorial problems did not diminish.

The patient's response to thiamin was quite good in motor functions; however, mild amnestic problems and peripheral neuropathy persisted.

RESULTS

Our patient group included 3 men and 3 women in aged between of 24 and 55 years. All were non-alcoholic patients with a history of GI tract diseases and/or GI surgeries (1 gastric malignancy, 1 gastritis and pyloric stenosis, 1 mesenteric ischemia followed by hemicolectomy and small bowel resection, 1 fulminant colitis followed by colectomy and 2 bariatric surgery) (Table 1). Vomiting was the precipitating factor in 5 patients and weight loss and parenteral nutrition were the precipitating factors in 6. The classic triad of mental impairment, oculomotor alterations and gait ataxia was present in 4 of 6 cases (gait ataxia could not be evaluated in 2 patients because of their limitations in mobilization). Cranial nerve palsy was present in only one patient (case-4), the others were all presented with nystagmus as oculomotor alteration. Other neurologic signs were paraparesis/quadruparesis, sensory deficits and impaired reflexes. The MRI showed typical signal alterations in the medial thalami, mammillary bodies and periaqueductal region in various degrees.

In our cases, we aimed to give at least 500 mg thiamine daily until there is no further improvement in signs and symptoms. And we also carry on the treatment with oral thiamine at discharge in each patient. Clinical improvement was seen in all cases after thiamine supplementation although 4 had residual memory problems in mild to moderate forms and 1 patient (Case 5) had residual nystagmus, mild ataxia and various neuropsychiatric problems.

DISCUSSION

Wernicke's encephalopathy still remains a clinical diagnosis. Knowledge about risk groups, recognition of clinical symptoms and signs are the most important issues in diagnosis of WE.

In 2010, review of the literature that included 625 cases determined the most frequent causes of non-alcoholic WE (13). The most common causes were listed as cancer, gastrointestinal surgery and hyperemesis gravidarum. Other causes were starvation, gastrointestinal tract diseases, AIDS, malnutrition, dialysis and renal diseases, parenteral nutrition, vomiting, psychiatric diseases, stem cell/marrow transplantation, infections, intoxications, thyroid disease, and many other rare conditions (13).

Many case reports have drawn attention to cancer-associated WE. Any type of cancer may cause WE, not only GI tract cancer. Increased thiamine consumption because of rapid growth of cancer cells, inadequate nutrition, nausea-vomiting caused by chemotherapy and parenteral nutrition without sufficient enteral support are the major causes of WE in these patients (14). GI tract cancer needs more attention, because weight loss and nutritional deficiency develop within a shorter time in these patients. A recent study by Zhang et al supports this idea. According to their study, 98% of the patients with GI tract cancer required nutritional intervention and 54% required improved nutrition-related symptom management and/or urgent nutritional support (15). As the median survival time increases, many other factors such as surgical procedures, chemotherapy and chemotherapy-related nausea/vomiting and GI tract obstructions enhance the deficiency of trace elements and vitamins (14, 16, 17). For this reason, the nutritional status of these patients should be followed up and proper nutritional education, support should be given by physicians (15). Our first case was a woman with a recent history of gastric cancer. Her weight loss was almost 16 kg within two months. She presented with nausea and vomiting that was resistant to antiemetic treatments and she was given parenteral nutrition. The cause of WE, in this case was most likely due to decreased oral intake and thiamine consumption, while the thiamine need of body was higher because of increased utilization by cancer cells. In addition, weight loss, vomiting and parenteral nutrition seemed to trigger this situation.

The second one was a man with a history of gastritis and pyloric stenosis after ingesting a corrosive substance. He became severely malnourished in the last three months. His symptoms began with parenteral nutrition after hospitalization. In this case, the mechanism must have been due

to a decreased oral intake and absorption of thiamine while weight loss, vomiting, and parenteral nutrition were triggers. There are individual WE cases associated with pyloric stenosis in the literature (18–20).

As a second most common cause of WE, physicians must take extra care with patients who are candidates for gastrointestinal surgeries. It is challenging to diagnose WE in post surgical patients, especially at the beginning of the disease when the classical symptoms of WE can be missing. In addition, metabolic conditions such as electrolyte imbalances, hypoglycemia, uremia, dehydration, hypoxia, hypercarbia and infectious diseases may be the cause of neurological symptoms in these patients. WE should be considered especially in patients with poor nutritional status and also those with a history of trigger factors such as frequent vomiting and prolonged parenteral nutrition. The patient in the third case was a weak, frail man with a history of mesenteric ischemia, weight loss (5 kg in 5 weeks) and parenteral nutrition. The sixth patient was a man with a history of fulminant colitis, weight loss (35 kg in 8 weeks) and parenteral nutrition. Both of them underwent open GI tract surgeries. The causes of WE in these patients might have been insufficient pre-surgical nutritional status and parenteral nutrition. Consequently, we attach importance to topic interested with preoperative nutritional status for enhancing the outcomes of surgeries (21).

The fourth and fifth patients were two women who underwent bariatric surgeries, gastric bypass and sleeve gastrectomy, respectively. A systematic case series review showed that all types of bariatric surgical procedures can cause nutritional deficiencies (22). According to WE case series in patients who underwent bariatric surgery, the risk is highest in the postoperative period (4 to 12 weeks) depends on duration of thiamine store depletion (23). However, any trigger factor such as alcoholism or malnutrition can cause late-onset WE in these patients (24). Frequent vomiting after surgery is the common predisposing factor that decreases oral intake and provokes depletion (25). In the fifth case, WE occurred 2 months after surgery. She was in an unresponsive state on admission. Weight loss (almost 30 kg in 8 weeks), frequent vomiting and parenteral nutrition history may have caused this serious presentation in this patient. In the fourth case, WE occurred 7 months after surgery while the patient was suffering from a recurrent surgical wound infection with a poor general condition. As such, patients must be closely followed up after bariatric surgeries by the operating center. European Federation of Neurological Societies (EFNS) also recommends follow-up of thiamine status for at least 6 months and parenteral thiamine supplementation after bariatric surgeries (13).

The classic triad of WE was present in 4 of our 6 cases. Gait ataxia could not be evaluated in case 3 and 4, because of their limitations in mobilization. It is important to remember that in most cases the classical symptoms were missing at the beginning and that clinical suspicion and MRI findings were the pathways for diagnosis of WE in these patients. EMG studies were also performed to rule out acute inflammatory demyelinating polyneuropathy (AIDP) in case 4 and 6. Four patients had EEG monitoring, but none showed a specific finding for WE.

As MRI is one of the most important tools to support or rule out WE, it has a vital role especially in patients with altered levels of consciousness because in such cases, the history and neurologic examination can be insufficient. From this perspective, MRI was a powerful tool for supporting WE diagnosis in the case 5 who was totally unresponsive on admission. On the other hand, MRI scans can be totally normal, which emphasizes the importance of clinical suspicion once again.

Outcomes are favorable if thiamine is instituted promptly in patients with WE. Ophthalmoplegia usually improves within hours after thiamine supplementation. Recovery from ataxia occurs in a few days, mental status

improvement takes 2 to 3 weeks. In under-diagnosed or under-treated groups, the estimated mortality rate is 20% and the KS rate among survivors is 85%. Nystagmus and ataxia may have seen as residual defects (2).

Randomized controlled trials are needed to define the optimum dose and duration of thiamine treatment both for prophylaxis and treatment of WE. There is no consensus on the optimal dose, application method (i.v. or i.m.) or duration of treatment. In suspected or manifest cases of WE, EFNS recommends 200 mg intravenously (IV) 3 times a day until there is no further improvement in signs and symptoms. They also recommend follow-up of thiamine status for at least 6 months and parenteral thiamine supplementation after bariatric surgeries (13). On the other hand, the National Institute for Health and Care Excellence (NICE) recommends 500 or 750 mg intravenously (IV) every 8 hours for 5 days. Both EFNS and NICE recommend oral thiamine after parenteral supplementation (13), (<http://www.nice.org.uk/guidance/cg100/chapter/1-guidance#wernickes-encephalopathy>).

Even though thiamine treatment was administered a short time after WE was diagnosed, 4 of our 6 cases had residual memory problems. It is obvious that, if we can increase the knowledge of responsible health providers about WE, we can prevent this neuropsychiatric disorder or at least decrease the ratio of residual defects through earlier intervention.

In conclusion, physicians should be aware of predisposing factors and symptoms in order to prevent or optimize the management of this potentially devastating disease. Thiamine supplementation should be considered in patients with GI tract diseases or history of surgery.

Ethics Committee Approval: This study was done according to Helsinki Declaration.

Informed Consent: Informed consent was received from all the patients and/or their relatives.

Peer-review: Externally peer-reviewed.

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