Wernicke Encephalopathy Associated with Crohn's Disease

Marco Vidor[1], Wirdasari[1], Virly Nanda Muzellina[2], Simon Salim[3]*

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2]Division of Gastroenterology - Pancreatobilliary, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[3]Division of Cardiovascular, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia.

Corresponding Author:
Marco Vidor, MD. Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo National General Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: vidor.marco@gmail.com.

ABSTRACT

Poorly controlled Crohn's disease is associated with several complications, including malabsorption of vitamins and minerals such as vitamin D, vitamin B12, and vitamin B1 (thiamine). Thiamine, among other vitamins, plays a crucial role in Adenosine Triphosphate formation as well as nerve propagation. Thiamine deficiency initially manifests as wet or dry beriberi but may lead to the devastating Wernicke–Korsakoff syndrome. In this report, we present a case of full-blown Wernicke encephalopathy associated with uncontrolled Crohn's disease.

An 18-year-old young man was admitted with a chief complaint of hematemesis for 2 weeks before admission. He was previously diagnosed with Crohn's disease in the past year, with constipation as the predominant symptom, and has been taking mesalazine 500 mg twice daily. Esophagogastroduodenoscopy and colonoscopy re-evaluation showed a worsening picture of Crohn's disease pangastritis. The patient experienced swelling in both legs, the scrotum, and the upper extremities during hospital admission. On day 14 of hospitalization, the patient fell into a state of confusion with visual and auditory hallucinations, ophthalmoplegia, and ataxia. A Brain MRI showed a typical picture of Wernicke encephalopathy. Intravenous thiamine was administered, and the patient regained consciousness. His clinical symptoms improved every day until he was discharged.

Uncontrolled Crohn's disease may have several complications that clinicians need to be aware of, including thiamine deficiency. Wernicke encephalopathy shows a devastating clinical picture, but with thiamine therapy, it may resolve before further deterioration leads to irreversible Korsakoff syndrome.

Keywords**:** *Crohn's disease, thiamine deficiency, Wernicke encephalopathy, Korsakoff syndrome*

INTRODUCTION

The prevalence of Crohn's disease in Asia has been increasing significantly in the past 3 decades, with Lebanon, Japan, and South Korea as the highest-ranking countries.[1] In 2011, the prevalence of Crohn's disease in Indonesia was 2.1%, showing a similar number compared to other Asian countries.[2] Clinical risk factors involved, including smoking, lack of physical activity, low dietary fiber intake, and vitamin D deficiency, have been associated with an increased risk of developing Crohn's disease but

not ulcerative colitis.[3–6]

Wernicke encephalopathy is an acute neurologic complication of thiamine (vitamin B1) deficiency which characterized by mental confusion, ophthalmoplegia, and gait ataxia, as first described by Carl Wernicke in 1881.[7] The prevalence of Wernicke encephalopathy in the general population ranges from 0.4% to 2.8%.[8] Korsakoff syndrome is a chronic neurological complication as a consequence of Wernicke encephalopathy.[7] Several conditions have been associated with Wernicke encephalopathy, including chronic alcoholism, anorexia nervosa or other psychiatric illness leading to poor intake, hyperemesis in pregnancy, prolonged parenteral nutrition feeding without proper supplementation, prolonged fasting or starvation, gastrointestinal disease or surgery, hemodialysis, or peritoneal dialysis[9]. The diagnosis of Wernicke encephalopathy is challenging since only 10% of cases show the full-blown triad of confusion, ophthalmoplegia, and gait ataxia. Meanwhile, emergent treatment is required to prevent death and neurological morbidity.[10]

CASE ILLUSTRATION

An 18-year-old young man visited the emergency unit with a chief complaint of hematemesis that started spontaneously 2 weeks before admission. Bloody vomitus occurred 2–3 times a day, usually induced when food or drink was introduced. He also noticed bloody diarrhea and complained of swelling in both legs. He was diagnosed with Crohn's disease 1 year before admission, with constipation as the predominant symptom. He routinely complied with his medication, mesalazine 500 mg twice daily, for 1 month before hospital admission. The previous dose of 1,000 mg twice daily had been adjusted due to an improvement in symptoms (decreasing abdominal pain). He denied any alcohol or steroid consumption before hospital admission.

From the initial physical examination, the patient was alert and hemodynamically stable and had a slight pitting edema in both ankles. His laboratory results were hemoglobin 15.2 g/dL, thrombocytes 115,000/µL, urea 81.3 mg/dL, creatinine 1.7 mg/dL, eGFR 57.6 mL/min/1.73 m^2, sodium 133 mEq/L, potassium 3 mEq/L, albumin 4 g/dL, C-reactive protein 1.5 mg/dL, aspartate aminotransferase 17 U/L, and alanine aminotransferase 17 U/L.

Esophagogastroduodenoscopy and colonoscopy found a worsening picture of Crohn's disease and severe pangastritis (**Figure 1**). Corticosteroid therapy started immediately with methylprednisolone 3 × 16 mg, mesalazine at 1,000 mg twice daily, and omeprazole 2 × 20 mg. Hematemesis and bloody feces never recurred on admission.

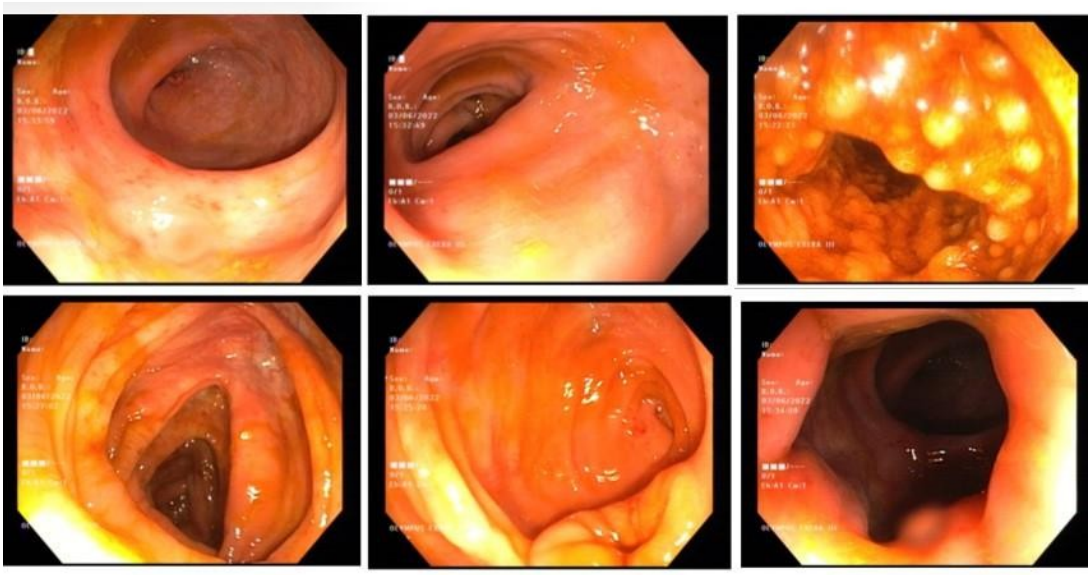

Figure 1. A colonoscopy evaluation shows a worsening picture of Crohn's disease.

On day 7, the patient noticed swelling in both legs; his arms got worse (**Figure 2**); and his scrotum became swollen. His vital signs showed normal blood pressure (120/80 mmHg), tachycardia (120 bpm), and normal respiratory and temperature functions. On day 14 of hospitalization, he was delirious and had auditory and visual hallucinations, bilateral paresis of the abducens nerve with binocular diplopia, and unidirectional nystagmus (**Figure 3**). No pathologic reflexes or meningeal signs were found. His vital signs showed normal findings except for mild tachycardia. Echocardiography was performed on day 15, which showed normal systolic function with high cardiac output (9.8 L/min).

On day 15, brain magnetic resonance imaging (MRI) revealed a symmetrical hyperintense lesion in the periaqueductal, third ventricle, medial thalamus, and inferior part of the fourth ventricle (**Figure 4**), which was typical for Wernicke encephalopathy. A blood sample for thiamine level was collected, and intravenous (IV) thiamine was immediately administered (200 mg initially, then 200 mg/day for 14 days). His pretreatment blood sample was not evaluated due to hemolysis, and post-treatment with initial thiamine administration showed a normal value of 70.4 ng/mL (29.6–76.2 ng/mL).

The patient regained consciousness after 1 day of IV thiamine; ophthalmoplegia resolved after 5 days of treatment; leg and arm edema resolved after 10 days of treatment; and scrotal edema resolved after 14 days of treatment. He was discharged after 14 days of IV thiamine, was fully alert with no sequelae, and continues to have oral thiamine 100 mg three times a day. His plans include the use of biologic agents for his Crohn's disease.

DISCUSSION

Poorly controlled inflammatory bowel disease has several complications, including vitamin and mineral deficiencies, which are due to malabsorption and low intake. Deficiencies in vitamins A, D, E, and B12 and zinc have been associated with Crohn's disease, and the prevalence of this disease is higher in patients with active disease.[7] Crohn's disease has also been associated with thiamine deficiency that leads to Wernicke encephalopathy.[11] Our patient had been diagnosed with Crohn's disease 1 year before admission, and he was treated with mesalazine 500 mg twice daily for the last month. Thiamine, or vitamin B1, plays multiple

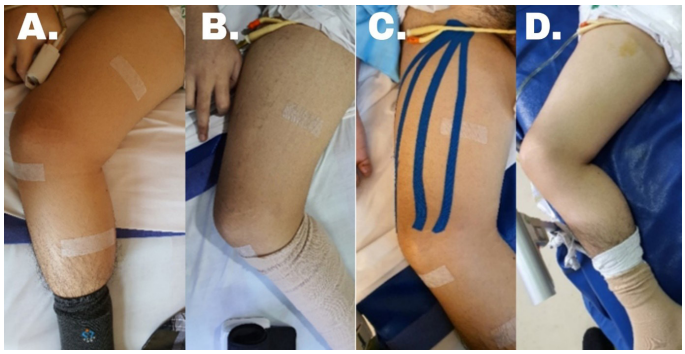

Figure 2. A. Initial leg swelling. B–D. Leg swelling improvement with thiamine therapy on days 10, 16, and 28 of hospital admission.

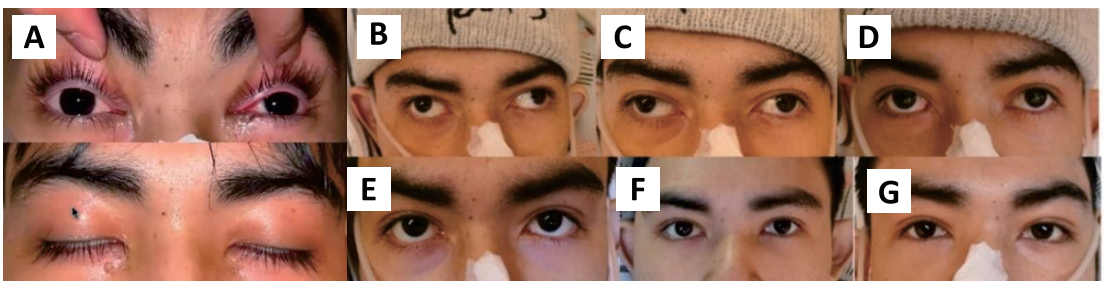

Figure 3. A. Eye examination when ophthalmoplegia was first discovered. B–G. Ophthalmoplegia improvement with thiamine therapy on days 1–5 after initial thiamine administration.

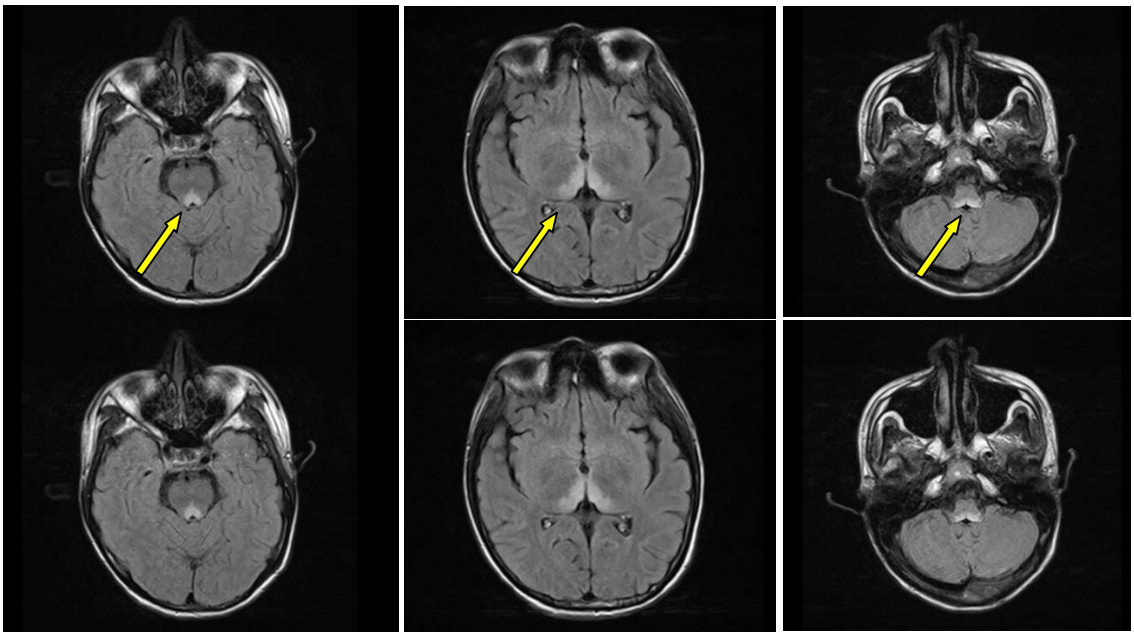

Figure 4. Brain MRI result for Wernicke encephalopathy

important roles in human metabolism. The phosphorylated form is a cofactor of enzymes involved in carbohydrate and branched-chain amino acid metabolism; it also initiates nerve impulse propagation. Thiamine absorption occurs in the small intestine; its peak absorption occurs in the jejunum and ileum.[12,13] Thiamine deficiency is manifested as beriberi and Wernicke–Korsakoff syndrome.[13] There are two beriberi phenotypes in adults: dry and wet beriberi. Sensory and motor impairments in the distal extremities manifesting as symmetrical polyneuropathy are the main features of dry beriberi, whereas cardiac involvement (cardiomegaly, cardiomyopathy, tachycardia, heart failure) and peripheral edema are the main features of wet beriberi.[13]

Our patient aligns well with the wet beriberi signs and symptoms. He had swelling on his extremities, which combined with a normal serum albumin level and high cardiac output made the presentation confusing to the physician. A further development of neurologic complications also coincides with thiamine deficiency, with nystagmus, ophthalmoplegia, and impaired consciousness. Genetic predisposition might be involved in the development of Wernicke encephalopathy; this explains why not all patients with thiamine deficiency progress to this complication.[14]Wernicke encephalopathy has chronic neurological consequences that manifest as short-term memory loss and confabulation; this condition is called Korsakoff syndrome.[13] Our patient was found to have thiamine deficiency in the later stage of the disease, which he might not have had if we had noticed earlier that his complaint of leg swelling was a clinical sign of wet beriberi. There was a 7-day window after he first complained of leg swelling before he developed a full-blown triad of Wernicke encephalopathy. Owing to his brain MRI, we

diagnosed with Wernicke encephalopathy and proceeded to thiamine therapy immediately. The majority of hospitals in Indonesia do not have the luxury of ordering an MRI as a diagnostic tool. We learn that we should be able to diagnose thiamine deficiency clinically.

Currently, there is no standardized dosing for thiamine therapy in patients with Wernicke–Korsakoff syndrome. Various studies agree on administering thiamine 200–500 mg three times a day for 5–7 days, followed by oral thiamine 100 mg three times a day for 1–2 weeks, and then 100 mg daily thereafter.[15] Earlier research initially recommended a thiamine dosage of 50–100 mg intravenously, but later on suggested a higher dosage of thiamine due to its lack of toxicity.[16] High-dose thiamine administration is defined as thiamine administration ≥200 mg intravenously. Eleven patients with Wernicke–Korsakoff syndrome were administered high-dose thiamine

(500 mg intravenously three times a day for 2–3 days), then decreased to 250 mg three times daily, and finally continued with an oral regimen of thiamine for a lifetime. Of these 11 patients, 73% showed symptom resolution. The study concluded that there is no significant association between the timing of thiamine administration and symptom resolution.[17] The latest clinical trial comparing thiamine administration of 100 mg IV once daily, 100 mg IV three times daily, and 300 mg IV three times daily found no significant difference between high- or low-dose thiamine administrations to improve symptoms of Wernicke–Korsakoff syndrome.[18] Besides administering thiamine, it is recommended to replace magnesium if disturbances are present. Magnesium deficiency will impair thiamine replenishment.[17]

The patient was administered thiamine 200 mg intravenously daily for 14 consecutive days. As soon as the patient regains consciousness, we also give oral thiamine supplementation of 100 mg three times daily. A sudden improvement in our patient's consciousness after thiamine administration confirms the diagnosis of thiamine deficiency. Unfortunately, his pretreatment blood sample cannot be evaluated, but this does not exclude the diagnosis of thiamine deficiency. Diagnosis and initiation of treatment with thiamine supplementation can be made with a clinical approach.

CONCLUSION

Although rare, thiamine deficiency is a severe, life-threatening complication of uncontrolled Crohn's disease. An atypical presentation of leg swelling and the further development of neurological pathology can help draw inferences about this condition. Immediate treatment with thiamine supplementation is important not only to reverse the process but also to prevent permanent damage. Clinicians need to raise awareness about the clinical manifestations of thiamine deficiency since early recognition and therapy are needed for a better outcome, and misrecognition may lead to the devastating consequences of irreversible Korsakoff syndrome.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest in this study.

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