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Wernicke's Encephalopathy in Colon Cancer

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Key Words

Wernicke's encephalopathy · Thiamine · 5-fluorouracil

Abstract

Wernicke's syndrome, caused by thiamine deficiency, is most commonly associated with alcoholism but can also occur in patients who are malnourished or have malabsorption of nutrients for other reasons. Since the classic triad of encephalopathy, nystagmus and ataxia occurs simultaneously in only 10–33% of cases, a high index of suspicion is needed in any patient with confusion and memory loss. In this case report, we present a 56-year-old female patient with metastatic colon cancer complicated with enterocutaneous fistula. She developed Wernicke's encephalopathy precipitated by 5-fluorouracil infusion. Replacement with thiamine rapidly reversed her neurologic symptoms and signs.

Background

Wernicke's encephalopathy is an acute or subacute neurological disorder characterised by ocular abnormalities leading to ophthalmoplegia, ataxia and altered mentation due to thiamine (vitamin B1) deficiency. It was first described by the German neurologist Karl Wernicke in 1881. The patients he described suffered from mental confusion, eye movement disorders, and ataxia. In 1887, the Russian psychiatrist Sergei Korsakoff published reports describing a syndrome of anterograde amnesia and confabulation. Alcoholism was soon found to be associated with these two conditions. Excessive alcohol intake interferes with thiamine absorption and hepatic storage. Other conditions associated with undernutrition such as recurrent dialysis, hyperemesis, starvation, gastric plication and cancer may also cause Wernicke's encephalopathy.

Presentation of the Case

A 56-year-old woman with colon cancer was admitted to the hospital with fecaloid discharge from a laparotomy incision during the previous 3 weeks.

The patient had been in excellent health until about 2 months earlier when she had been diagnosed with a left-sided colon cancer. She had been categorised as having stage III adenocarcinoma of the colon, and adjuvant calcium folinate and 5-fluorouracil (5-FU) had been planned for 6 months. The first cycle of her chemotherapy was administered.

Two weeks after the first cycle she was admitted to the hospital due to a discharge from an abdominal incision scar. On the day of admission her temperature was 37°C, the pulse was 92 bpm, and respirations were 16 per minute. The blood pressure was 120/60 mm Hg. On physical examination, the patient appeared well. Head and neck were normal. Breath sounds were clear. Heart sounds were normal. Abdominal examination revealed a left lower quadrant fecaloid discharge located on the laparotomy incision of a previous surgery. Neurologic examination showed no abnormality. A fistulography was consistent with an enterocutaneous fistula formation.

She was ordered nil by mouth and parenteral fluids including dextrose in water were started. Eight hours after starting parenteral nutrition, she suddenly developed epilepsy and loss of consciousness. Upon neurological examination, the patient was found to be disoriented and to have difficulty in cooperation. Cranial nerve examination showed ophthalmoplegia. She had horizontal nystagmus. Deep tendon reflexes were hyperreactive. Complete blood count revealed WBC 9,760 per microliter, Hb 9.8 g/dl, Hct 31.1%, PLT 280,000 per microliter. Clinical chemistry showed a glucose level of 123 mg/dl, urea 27 mg/dl, creatinin 0.5 mg/dl, AST 38 IU, ALT 41 IU, ALP 128 IU, total bilirubin 0.41 mg/dl, Na 138 mEq/l, K 4.1 mEq/l, Ca 9.6 mg/dl and albumin 3.5 g/dl.

Cranial MRI scan was ordered. Bilateral, increased thalamic and periaquaeductal signal intensities suggested Wernicke's encephalopathy in light of the relevant history and physical findings of the patient ([fig. 1](#)). Serum thiamine level was measured and reported as 19.8 pg/l (normal: 25–75). This constellation of findings was consistent with Wernicke's encephalopathy precipitated by 5-FU infusion for metastatic colon cancer. Rapid institution of thiamine treatment 100 mg per day reversed her symptoms gradually in about 10 days. Her level of consciousness and cooperation improved and orientation in time and location was restored. Her cycloplegia and nystagmus were no longer detectable after 10 days of treatment although ataxic gait persisted somewhat. Subsequent MRI scan of the brain showed complete resolution of the abnormalities detected one month previously ([fig. 2](#)).

Discussion

Thiamine is a water-soluble vitamin supplied by diet. It possesses a critical role in energy metabolism serving as a cofactor for key enzymes such as alpha-ketoglutarate dehydrogenase, pyruvate dehydrogenase, and transketolase in Krebs cycle and pentose phosphate pathway of the cells. Since thiamine is used in the final metabolism of carbohydrates and many amino acids, deficiency of this vitamin causes many disorders related to cardiovascular, neuromuscular, and gastrointestinal systems. Diet deficient in thiamine for 2–3 weeks results in symptoms [1]. Since thiamine-dependent enzymes play a major role in cerebral energy utilization, thiamine deficiency results in necrosis in the medial thalamus and periaquaeductal gray matter and irreversible brain damage due to derangements in the blood-brain barrier. Common causes include alcoholism, eating disorders, malnutrition, gastric bypass surgery, magnesium deficiency, hyperemesis gravidarum, disorders associated with prolonged vomiting, prolonged parenteral nutrition, HIV infection, chronic dialysis, and finally cancer.

Confusion in a patient with cancer is almost always pathological. Infections, electrolyte imbalances, cerebral metastasis, chemotherapeutics, and opioid overdose are common causes. As the incidence of Wernicke's encephalopathy in cancer patients is not known, a

high index of suspicion is needed for diagnosis to prevent the morbidity and mortality associated with this condition. Chronic malnutrition contributes to thiamine deficiency in cancer patients especially after prolonged nausea and vomiting associated with chemotherapy. Tumors with a high proliferation index such as leukemias and sarcomas deplete thiamine rapidly especially after parenteral hyperalimentation or glucose load.

In the present case, the presence of an enterocutaneous fistula may have exacerbated nutritional loss including thiamine, although there has been no report in the literature which associates Wernicke's encephalopathy with enteral fistulae.

Another interesting association is that the patient's symptoms and signs were precipitated by 5-FU infusion, although we cannot differentiate it confidently from Wernicke's encephalopathy precipitated by glucose infusion. However, Wernicke's encephalopathy associated with glucose infusion usually occurs after an average of 14 days after the start of glucose infusion [2]. A literature search suggests that high-dose doxifluridine, ifosfamide, and 5-FU can cause encephalopathy resembling a Wernicke-Korsakoff syndrome. Basu and Dickerson [3] concluded that cancer patients were unable to convert thiamine pyrophosphate, the active form of the vitamin, since the excretory level of thiamine was high, making a deficient state unlikely. We also detected a near-normal thiamine level in the blood of our patient. However, the gold standard test to detect thiamine deficiency is to measure red cell transketolase activity [4]. This test is expensive and not widely available. Basu et al. also showed in rats that treatment with 5-FU resulted in decreased liver and spleen concentrations of thiamine without affecting the urinary excretory levels supplemented with large doses of the vitamin [5].

In conclusion, this case illustrates how thiamine can rapidly reverse neurologic signs and symptoms if recognized early even though the association with 5-FU is a rather rare entity in a patient with colon cancer.

Fig. 1. Typical MR imaging features of Wernicke's encephalopathy. Axial T2-weighted (**a**, **e**), FLAIR (**b**, **f**), and DWI (**c**, **g**) images show symmetrical increased signal intensity in the medial thalami (**a–c**), as well as in the tectum of the midbrain and the periaqueductal area (**e–g**). Contrasting images (**d**, **h**) show enhancement of the tectum of the midbrain and the periaqueductal area by gadolinium contrast medium (**h**).

Fig. 2. MR imaging findings one month after thiamine treatment. Axial T2-weighted (**a**, **e**), FLAIR (**b**, **f**), and DWI (**c**, **g**) images show normal signal intensity in the medial thalami (**a–c**), as well as in the tectum of the midbrain and the periaquaeductal area (**e–g**). Contrasting images (**d**, **h**) show no enhancement in these areas.

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