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Wernicke encephalopathy presented in the form of postoperative delirium in a patient with hepatocellular carcinoma and liver cirrhosis: A case report and review of the literature

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ABSTRACT

Objective: Although Wernicke encephalopathy has been reported in the oncological literature, it has not previously been reported in postoperative cancer patients.

Methods: In this communication, we report a patient of hepatocellular carcinoma with liver cirrhosis who developed Wernicke encephalopathy in the form of postoperative delirium. Preoperatively, the patient had a very good appetite and had eaten all the food of an 1800 cal/day diet until 1 day before operation. The operation was done without any complications. The patient developed delirium 2 days after the lobectomy of the liver. The level of delirium remained unchanged until administration of thiamine starting on day 7 postoperatively, which resulted in palliation of delirium without brain damage. Laboratory data demonstrated that the serum thiamine level at day 6 postoperatively was below the lower limit of normal. As the mechanism of Wernicke encephalopathy, we thought that decreased ability to store thiamine due to liver cirrhosis led to depletion of thiamine faster than had been expected.

Results and significance of the research: In cancer patients, clinicians must always remain aware of the possibility of Wernicke encephalopathy, especially in patients with liver dysfunction, which decreases the ability to store thiamine in the liver. Early detection and intervention may alleviate the symptoms of delirium and prevent irreversible brain damage.

KEYWORDS: Vitamin B1 deficiency, Cancer, Delirium

INTRODUCTION

Delirium is one of the most common neuropsychiatric complications in patients with cancer and is associated with higher mortality and longer hospital stay and causes severe distress for families and caregivers (Stiefel et al., 1992). Therefore, it is important to identify the underlying pathologies and alleviate the symptoms of delirium. Postoperative delirium is observed in about 37% of patients and is defined as an acute change in cognitive status characterized by fluctuating consciousness and inattention occurring within 30 days postoperatively (Dyer et al., 1995). However, the etiology is not well understood.

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Thiamine is an essential coenzyme in intermediate carbohydrate metabolism (Davis & Icke, 1983; Reuler et al., 1985), and its deficiency is known as one of the causative factor of delirium (Wernicke encephalopathy). It is a potentially reversible condition; however, if untreated, it causes severe and irreversible damage to the brain (Korsakoff syndrome), leading to death. The mortality rate is about 10%–20%.

Although it is recognized in 0.8%–2.8% of autopsied samples, only 0.06%–0.13% of patients are clinically diagnosed in the general population (Harper et al., 1989; Pereira et al. 1997; Munir et al. 2001). This disorder often remains unrecognized. Clinical diagnoses of "undiagnosed" cases often involve misdiagnoses of liver failure or dementia (Harper et al., 1986). Wernicke encephalopathy has been reported in the oncological literature (van Zaanen & van der Lelie, 1992; Kondo et al., 1996; Onishi et al., 2004); however, there was no case of Wernicke encephalopathy reported in postoperative cancer patients. Wernicke encephalopathy may be unrecognized and overlooked in postoperative cancer patients.

In this communication, we report a case of Wernicke encephalopathy developed in the form of postoperative delirium. Early recognition and subsequent treatment resulted in successful palliation of delirium.

To determine the etiology of delirium, Francis' criteria (Francis et al., 1990) were used to standardize judgments. Based on clinical assessment and medical chart review, a potential cause was categorized as (1) definite, if it was temporally related, there was laboratory confirmation, the patient improved with treatment or cessation of the offending agent, and there was no other cause present; (2) probable, if all the previous criteria were met but another main cause was present or laboratory confirmation was not obtained.

CASE REPORT

A 72-year-old man was referred by his surgeon for psychiatric consultation because of sleep–wake cycle disturbance, disorientation, and bizarre behaviors after resection of hepatocellular carcinoma.

The patient was diagnosed with chronic hepatitis due to type C hepatitis virus 15 years ago, diagnosed as hepatocellular carcinoma 3 months ago, and received lobectomy of the liver. Before surgery, the patient had a very good appetite and had eaten all the food of an 1800 cal/day diet until 1 day preoperatively. This was confirmed by the statements of family members and nursing charts. Surgery was performed without any complications. Surgical duration was about 9 h.

On day 2 postoperatively, the patient presented with insomnia, disorientation in time and place, poor attention, and poor concentration.

At psychiatric referral on day 2 postoperatively, he showed short-term memory disturbance, disorientation in time and place, poor attention, and poor concentration. His mood fluctuated, but there was no delusional thought recognized. On the delirium rating scale (DRS) (Trzepacz et al., 1988), he scored 19 points (delirium level). His psychiatric features fulfilled the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria (American Psychiatric Association, 1994) for delirium and also fulfilled Dyer's criteria for postoperative delirium. He had no medical history of psychiatric illness or alcohol or drug abuse. Laboratory examinations demonstrated that serum transaminase (GOT = 96 IU/ml, normal range: 10–40 IU/ml, GPT = 164 IU/ml, normal range: 5–40 IU/ml) and bilirubin levels (32 μmol/l, normal range: 5–12 μmol/l) were above the normal range following surgery and that the serum albumin level was low (2.3 g/dl, normal range: 3.8–5.3 g/dl). However, these data were not severe enough to cause delirium based on validated diagnostic criteria for delirium (total bilirubin level $\geq$ 43 μmol/l) (Lawlor et al., 2000; Morita et al., 2001).

On day 6 postoperatively, the delirium level was unchanged. There was no nystagmus on neurological examinations. Ataxia was not investigated because the patient was bedridden and could not respond to the instructions of the psychiatrist because of delirium. The serum thiamine level was checked on day 6 for the differential diagnosis of delirium. Starting from day 7, intravenous hyperalimentation together with thiamine administration (1.5 mg/day) was started. Thereafter, the psychiatric features changed. On day 8 postoperatively, he could maintain concentration and talk with the staff and family members. He scored 2 points on DRS on day 10 postoperatively. There was no memory deficit suggesting Korsakoff syndrome or signs of vascular dementia on psychiatric examination.

Laboratory examination later demonstrated that the level of thiamine on day 6 postoperatively was below the normal range (18 ng/ml; normal range 20–50 ng/ml).

The clinical findings, effective alleviation of delirious symptoms after thiamine administration, and low level of thiamine in the serum fulfilled Francis' criteria for delirium induced by thiamine deficiency. We thought that clinical findings from day 6 at least were induced by thiamine deficiency; however, at day 2 postoperatively, we could not diagnose the patient with delirium induced by

thiamine deficiency because we did not test the serum thiamine level on day 2 postoperatively.

We asked the patient whether he had developed appetite loss before admission to the hospital, but the patient reported that he had good appetite until admission to the hospital but said that he was always careful not to eat too much in order to control his blood glucose level.

The patient showed complete recovery and was discharged from hospital 28 days postoperatively.

MEDICAL HISTORY

The patient had undergone partial gastrectomy and blood transfusion 40 years earlier and was diagnosed as having chronic hepatitis 15 years earlier. He was also diagnosed as having diabetes mellitus 15 years earlier and was receiving insulin therapy.

He worked as a company president. He was very kind to others and had no medical history of psychiatric illness or alcohol or drug abuse.

DISCUSSION

This study illustrated the clinical manifestations and treatments of Wernicke encephalopathy that developed as postoperative delirium in a cancer patient.

The classical triad of Wernicke encephalopathy is acute onset of ocular abnormalities, ataxia, and global confusional state (delirium). However, it has been shown that patients with Wernicke encephalopathy may develop a variety of symptoms in addition to or in place of the classical triad. Clinical and pathological studies indicated that ocular signs were present in 29%–93%, ataxia in 23%–70%, and delirium in 82%–90% (Harper et al., 1986). It has also been indicated that only 16% of patients showed the classical triad, whereas 19% had no clinical signs (Ogershok et al., 2002).

There are several factors that make the proper diagnosis of Wernicke encephalopathy difficult in this patient. First, as described above, ocular signs were lacking and ataxia was not investigated; second, delirium developed 2 days postoperatively; third, although poor nutritional state is the only prerequisite for the development of Wernicke encephalopathy (Ebels, 1978; Drenick et al., 1966), this patient never showed appetite loss before or after admission to the hospital and the patient had eaten all the hospital food. The clues to diagnosis in this patient were low albumin level and delirium. At day 2 postoperatively, we initially thought that clinical pictures of the patient were that of postoperative delirium of unknown origin. Clinical diagnosis might be right at this stage; Wernicke encephalopathy might develop later.

Causes of thiamine deficiency in cancer patients include deficiency, malabsorption, increased thiamine consumption, elevated thiamine requirements, and decreased storage of thiamine (Drenick et al., 1966).

The main organ functioning as the principal storage depot for thiamine is the liver. Patients placed on a strict thiamine-free diet will develop a state of total body depletion within 18 days (MacLean et al., 1983). However, the thiamine content may be reduced in liver disease (Hoyumpa, 1980).

The patient took an adequate amount of thiamine preoperatively because he had no previous episode of delirium suggesting Wernicke encephalopathy. However, the ability to store thiamine might have been decreased because of liver dysfunction due to liver cirrhosis. We speculated that marginal thiamine storage due to liver cirrhosis led to consumption and depletion of thiamine faster than had been expected.

In this case, we are not certain whether the patient developed Wernicke encephalopathy on day 2 postoperatively. Postoperative delirium develops in about 17% of patients, and advanced age, preoperative cognitive impairment, and the use of anticholinergic drugs are independent risk factors for delirium (Dyer et al., 1995). It may be speculated that this patient first developed postoperative delirium and then developed Wernicke encephalopathy.

Treatment of Wernicke encephalopathy should be started immediately with 50–100 mg of intravenously administered thiamine, as its use prevents disease progression. Intravenous administration should be continued for several days followed by maintenance therapy with oral administration of thiamine (Zubaran et al., 1997).

In our case, cognitive impairment improved after intravenous administration of thiamine of 1.5 mg/day, which is similar to the amount of thiamine required for the adult and is much less than the amount of thiamine required for initial treatment of Wernicke encephalopathy. At that time, we could not diagnose the patient as having thiamine deficiency and we could not administer a large amount of thiamine. It is known that a small amount (2–3 mg) of thiamine may be sufficient to reverse ocular symptoms (Cole et al., 1969); however a small amount (1.5 mg/day) of intravenous thiamine administration compared to the large amount (100 mg intravenous injection) required for the initial treatment of Wernicke encephalopathy was effective for successful palliation of delirium and for preventing irreversible brain damage in this patient.

Our case suggests that thiamine deficiency should be considered in the differential diagnosis in patients developing postoperative delirium, especially in patients with liver disease even though the patient has consumed adequate amounts of food. Our findings also indicate that even the administration of a small amount of thiamine may be effective in preventing Wernicke encephalopathy. Therefore, if there is any doubt, intravenous thiamine administration even before a definitive diagnosis is established is recommended to prevent the progression of this otherwise fatal disorder. Early intervention may correct the symptoms and prevent irreversible brain damage in the patient.

The limitation of this study is that this is a single case study and is not representative of all cases.

If thiamine deficiency is considered as the underlying cause of postoperative delirium, some patients that were diagnosed as having therapy-resistant delirium of unknown origin may recover from this reversible delirious state. Further prospective study will clarify the prevalence and treatment outcome of Werincke encephalopathy among cancer patients with postoperative delirium.

REFERENCES

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Press.

Cole, M., Turner, A., & Frank, O. (1969). Extraocular palsy and thiamine therapy in Wernicke's encephalopathy. *American Journal of Clinical Nutrition*, *22*, 44–51.

Davis, R.E. & Icke, G.C. (1983). Clinical chemistry of thiamin. *Advances in Clinical Chemistry*, *23*, 93–140.

Drenick, E.J., Joven, C.B., & Swendseid, M.E. (1966). Occurrence of acute Wernicke's encephalopathy during prolonged starvation for the treatment of obesity. *New England Journal of Medicine*, *274*, 937–939.

Dyer, C.B., Ashtom, C.M., & Teasdale, T.A. (1995). Postoperative delirium. A review of 80 primary data-collection studies. *Archives of Internal Medicine*, *155*, 461–465.

Ebels, E.J. (1978). How common is Wernicke–Korsakoff syndrome? *Lancet*, *2*, 781–782.

Francis, J., Martin, D., & Kapoor, W.N. (1990). A prospective study of delirium in hospitalized elderly. *JAMA*, *263*, 1097–1101.

Harper, C.G., Giles, M., & Finlay-Jones. R. (1986). Clinical signs in the Wernicke–Korsakoff complex: A retrospective analysis of 131 cases diagnosed at necropsy. *Journal of Neurology Neurosurgery and Psychiatry*, *49*, 341–345.

Harper, C., Gold, J., Rodriguez, M., et al. (1989). The prevalence of the Wernicke–Korsakoff syndrome in Sydney, Australia: A prospective necropsy study. *Journal of Neurology Neurosurgery and Psychiatry*, *52*, 282–285.

Hoyumpa, A.M., Jr. (1980). Mechanisms of thiamin deficiency in chronic alcoholism. *American Journal of Clinical Nutrition*, *33*, 2750–2761.

Kondo, K., Fujiwara, M., Murase, M., et al. (1996). Severe acute metabolic acidosis and Wernicke's encephalopathy following chemotherapy with 5-fluorouracil and cisplatin: Case report and review of the literature. *Japanese Journal of Clinical Oncology*, *26*, 234–236.

Lawlor, P.G., Gagnon, B., Mancini, I.L., et al. (2000). Occurrence, causes, and outcome of delirium in patients with advanced cancer: A prospective study. *Archives of Internal Medicine*, *160*, 786–794.

MacLean, L.D., Rhode, B.M., & Shizgal, H.M. (1983). Nutrition following gastric operations for morbid obesity. *Annals of Surgery*, *198*, 3473–3455.

Morita, T., Tei, Y., Tsunoda, J., et al. (2001). Underlying pathologies and their associations with clinical features in terminal delirium of cancer patients. *Journal of Pain and Symptom Management*, *22*, 997–1006.

Munir, A., Hussain, S.A., Damanpaul, S., et al. (2001). Wernicke's encephalopathy in a non-alcoholic man. Case report and brief review. *Mount Sinai Journal of Medicine*, *68*, 216–217.

Ogershok, P.R., Rahman, A., Nestor, S., et al. (2002). Wernicke encephalopathy in nonalcoholic patients. *American Journal of the Medical Sciences*, *323*, 107–111.

Onishi, H., Kawanishi, C., Onose, M., et al. (2004). Successful treatment of Wernicke encephalopathy in terminally ill cancer patients: Report of 3 cases and review of the literature. *Supportive Care in Cancer*, *12*, 604–608.

Pereira, J., Hanson, J. & Bruera, E. (1997). The frequency and clinical course of cognitive impairment in patients with terminal cancer. *Cancer*, *79*, 835–842.

Reuler, J.B., Girard, D.E., & Cooney, T.G. (1985). Current concepts. Wernicke's encephalopathy. *New England Journal of Medicine*, *312*, 1035–1039.

Stiefel, F., Fainsinger, R., & Bruera, E. (1992). Acute confusional states in patients with advanced cancer. *Journal of Pain and Symptom Management*, *7*, 94–98.

Trzepacz, P.T., Baker, R.W. & Greenhouse, J. (1988). A symptom rating scale for delirium. *Psychiatry Research*, *23*, 89–97.

van Zaanen, H.C. & van der Lelie, J. (1992). Thiamine deficiency in hematologic malignant tumors. *Cancer*, *69*, 1710–1713.

Zubaran, C., Fernandes, J.G., & Rondnight, R. (1997). Wernicke–Korsakoff syndrome. *Postgraduate Medical Journal*, *73*, 27–31.