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Case Report:

Wernicke encephalopathy following splenectomy in a patient with liver cirrhosis: a case report and review of the literature

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Abstract: Objective: To report a case of Wernicke encephalopathy in the early stage after surgery. Methods: A nonalcoholic female patient with hepatitis B-related cirrhosis and hypersplenism underwent splenectomy in a local hospital. No surgical complications occurred and the patient recovered well. However, on the eighth postoperative day she developed psychiatric and neurological disturbance without an obvious cause. She was then admitted to our hospital. Brain magnetic resonance imaging (MRI) with FLAIR T2 showed symmetric high-signal intensities in the periaqueductal area of the midbrain, which were consistent with Wernicke encephalopathy. She was thus given intramuscular thiamine immediately. Results: After the administration of thiamine, the patient's confused mental state resolved within 3 d, and her dystaxia gradually improved over the next 5 d. The brain MRI with FLAIR T2 was re-examined one month after the episode, and showed nearly complete resolution of the previously abnormal signal intensities in the periaqueductal area of the midbrain. Conclusion: Physicians should be aware of the possibility of acute Wernicke encephalopathy, especially in patients with liver dysfunction.

Key words: Wernicke encephalopathy, Liver cirrhosis, Thiamine, Splenectomy
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1 Introduction

Wernicke encephalopathy, first described in the 1880s, is a rare neurological disorder resulting from thiamine (vitamin B_1) deficiency (Reuler *et al*., 1985). It is characterized by confusion, dystaxia, and nystagmus. These symptoms usually have an acute onset and occur more often in combination. The encephalopathy is most often associated with severe alcohol abuse, but thiamine deficiency can be caused by other medical conditions producing malnourishment, including unbalanced nutrition, recurrent vomiting, chronic diarrhea, hyperthyroidism, systemic illness, or magnesium depletion (Attard *et al*., 2006; Merkin-Zaborsky *et al*., 2001; Chiossi *et al*., 2006; Harrison *et al*., 2006; Bonucchi *et al*., 2008). Although early recognition and treatment with thiamine can readily reverse the symptoms, the mortality rate of Wernicke encephalopathy remains 10%–20% due to misdiagnosis (Bonucchi *et al*., 2008). It is frequently identified at autopsy, and in case series, only 20% of patients with Wernicke encephalopathy were diagnosed before death in nonalcoholic patients (Ogershok *et al*., 2002).

Here, we present a nonalcoholic female patient with hepatic cirrhosis and hypersplenism who developed Wernicke encephalopathy following splenectomy. This case emphasizes the need for early diagnosis and thiamine supplementation.

2 Case report

A 50-year-old woman was diagnosed with hepatitis B-related cirrhosis and hypersplenism, and

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had a splenectomy in a local hospital 9 d before being admitted to our hospital. In the local hospital, supportive treatments, including antibiotics, transfusion, and liver-protection, were performed after the operation, with continuous intravenous administration of vitamin C and B_6 (vitamin B_1 excluded). She recovered well with good incision healing and clear consciousness. Review of system was negative for abdominal pain, fever, or jaundice. She started oral food intake (low) 5 d after the operation and complained of nausea and vomiting occasionally. On the 8th postoperative day, she developed psychiatric and neurological disorders without an obvious cause, symptoms including illusion, acousma, babbling, non-purposeful movements, and dystaxia. She was admitted to our hospital. She had no history of chronic alcohol consumption, psychosis, diabetes mellitus, hypertensive disease, coronary artery disease, or tuberculosis.

On admission, she weighed 46 kg and had a temperature of 37.1 °C, heart rate of 80 min^{-1}, respiration of 18 min^{-1}, and blood pressure of 111/85 mmHg. She was emaciated, drowsy, dysphoric at times, incoherent, and not cooperative with the examination. Pupils were equal (3 mm) and reactive to light. No obvious nystagmus, oculomotor dysfunction, jaundice, or enlarged superficial lymph nodes were observed. Harsh breath sounds without any rales were heard in both lungs. Cardiac rhythm was normal and no murmurs were heard. The abdomen was soft and symmetrical, without tenderness, rebound tenderness, or guarding. There was a well-healed scar (12 cm) in her upper abdomen. She had abnormal involuntary movements in the extremities. Babinski reflex and Kernig sign were negative.

In terms of laboratory examination, white blood cell (WBC) count was 7000 cells/μl with 84.1% neutrophils and 14.3% lymphocytes, hemoglobin (HB) concentration 12.7 g/dl, platelet count 16000 μl^{-1}, C reactive protein (CRP) level 16.1 mg/L (reference range, 0 to 8.0 mg/L), and erythrocyte sedimentation rate (ESR) level 48 mm/h (reference range, 0 to 15 mm/h). The levels of serum blood urea nitrogen (BUN) and creatinine were 4.9 mmol/L and 38 μmol/L, respectively. The serum sodium and potassium were 148 and 3.63 mmol/L, respectively. The urine dipstick, blood culture, prothrombin time (by international normalized ratio (INR)), partial thromboplastin time, fibrinogen, troponin, thyroid hormones, and arterial blood gas were all normal, and cerebral spinal fluid (CSF) examination was unrevealing. The total protein was 69.4 g/L, serum albumin 35.2 g/L, triglyceride 1.18 mmol/L, cholesterol 4.10 mmol/L, alanine aminotransaminase (ALT) 54 U/L (reference range, 3 to 50 U/L), aspartate aminotransaminase (AST) 98 U/L (reference range, 3 to 50 U/L), alkaline phosphatase (AKP) 286 U/L (reference range, 35 to 130 U/L), total bilirubin 25.8 μmol/L (reference range, 1.0 to 22.0 μmol/L), and magnesium 0.79 mmol/L. The blood ammonia concentration was 12 μmol/L. The plasma D-dimer concentration was 796 μg/L (reference range, 0 to 500 μg/L). In brief, laboratory studies only revealed that she had a mildly elevated CRP, ESR, ALT, AST, AKP, total bilirubin, and D-dimer.

On admission, brain magnetic resonance imaging (MRI) with FLAIR T2 showed symmetrical high-signal intensities in the periaqueductal area of the midbrain, which were consistent with Wernicke encephalopathy (Fig. 1a). The electrocardiogram (ECG) and chest radiograph of the patient revealed no abnormal findings, and the electroencephalogram (EEG) showed mild generalized slowing. A non-contrast head computed tomography (CT) showed no evidence of intracranial bleeding or trauma.

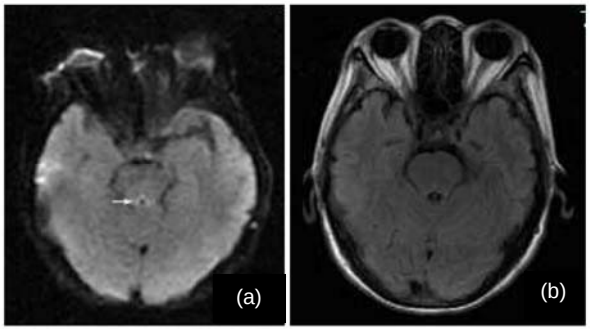

Fig. 1 (a) The initial MRI with FLAIR T2 on admission demonstrates symmetrical high-signal intensities in the periaqueductal area of the midbrain; (b) Follow-up MRI with FLAIR T2 one month later shows nearly complete resolution of the previously abnormal signal intensities in the periaqueductal area of the midbrain

On the basis of symptomatic and supportive treatments, the patient was given intramuscular thiamine immediately and the dose was maintained at 200 mg/d throughout hospitalization, even though the serum thiamine concentration was not tested. Her confused mental state resolved within 3 d, and her

dizziness and dystaxia gradually improved over the next 5 d. On Day 15, she was discharged with a good mental status and given oral thiamine of 60 mg/d. The brain MRI with FLAIR T2 was reexamined in the outpatient clinic one month after the episode. The MRI showed nearly complete resolution of the previously abnormal signal intensities in the periaqueductal area of the midbrain (Fig. 1b).

3 Review of the literature

Wernicke encephalopathy is characterized by an acute onset of symptoms that may include changes in psychological status and the development of nystagmus and motor problems, such as uncoordinated gait and ataxia. This triad of symptoms is seen, however, in only 16% of patients (Sechi and Serra, 2007; Cho *et al*., 2009), and considerable discrepancy exists between pathologic features and presenting signs (Doherty *et al*., 2002; Loh *et al*., 2004).

Wernicke encephalopathy can be diagnosed primarily from the clinical features, and it should be confirmed by symptomatic improvement with thiamine treatment. MRI is currently considered the most valuable method to establish a diagnosis of Wernicke encephalopathy, with a sensitivity of 53% and specificity of 93% (Antunez *et al*., 1998). The MRI characteristically shows an increased T2 signal that is bilaterally symmetrical in the paraventricular regions of the thalamus, the hypothalamus, mammillary bodies, the periaqueductal region, the floor of the fourth ventricle, and the midline cerebellum (Sechi and Serra, 2007). However, the absence of imaging abnormalities does not exclude the diagnosis of Wernicke encephalopathy.

To date, there are few relevant reports of Wernicke encephalopathy in the early stage after operation. In this case, the main MRI feature only included the symmetrical high T2 signal intensities in the periaqueductal region of the midbrain, which were in accord with the manifestations of Wernicke encephalopathy, but not very typical. Additionally, the patient had mildly elevated CRP, ESR, ALT, AST, AKP, total bilirubin, and D-dimer, values not considered to be in the range to explain her clinical presentations (i.e., this was not hepatic encephalopathy). Given the course of the patient's presentation with dystaxia and mental confusion, which all improved rapidly with administration of thiamine, we feel that this is most supportive of a diagnosis of Wernicke encephalopathy.

In this study, the patient developed Wernicke encephalopathy on the 8th postoperative day, and the physiopathologic mechanism might relate to the following factors: (1) Decreased ability to store thiamine due to liver cirrhosis might lead to depletion of thiamine faster than expected. In chronic liver disease, activation of thiamine pyrophosphate from thiamine is decreased, and the capacity of the liver to store thiamine is diminished (Reuler *et al*., 1985; Bonucchi *et al*., 2008); (2) Low level of hepatic glycogen storage and administration of a large dose of intravenous glucose after operation in patients with liver cirrhosis could accelerate thiamine consumption, further exacerbating the tricarboxylic acid cycle obstruction and thereby worsening the condition (Koguchi *et al*., 2004; Hack and Hoffman, 1998); and (3) Low food intake, accompanied with occasionally nausea and vomiting, might induce insufficient thiamine uptake and utilization. Onishi *et al*. (2005) also reported a patient of hepatocellular carcinoma with liver cirrhosis who developed Wernicke encephalopathy, presenting as postoperative delirium.

Wernicke encephalopathy is a medical emergency, and if not recognized and treated promptly is associated with progression to irreversible Korsakoff psychosis, consisting of confabulation and anterograde memory deficits (Harrison *et al*., 2006). Thiamine is a pivotal cofactor in the tricarboxylic acid cycle. Its deficiency impairs cerebral metabolism of glutamate, and eventually the generation of proteins, DNA, and neurotransmitters. The central nervous system (cerebellar vermis and the midline mesencephalon structures) is particularly sensitive to thiamine deficiency due to cellular dependence on oxidative metabolism. Cell death occurs via necrosis and apoptosis (Hack and Hoffman, 1998). Even with early recognition and aggressive therapy, permanent disability often occurs due to the irreversible cytotoxic effects on specific regions of the brain. Because of a theoretical concern of preventing Wernicke encephalopathy, thiamine is usually given before glucose (Koguchi *et al*., 2004; Hack and Hoffman, 1998). However, this preventative measure is not always undertaken in the clinical practice; therefore a high

index of suspicion must be maintained for thiamine deficiency in at-risk patients.

In conclusion, physicians should be aware of the possibility of acute Wernicke encephalopathy especially in patients with liver dysfunction. Early diagnosis and intervention may alleviate or prevent irreversible brain damage.

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