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Case report

Wernicke encephalopathy induced by glucose infusion: A case report and literature review

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ABSTRACT

Introduction: Wernicke encephalopathy (WE) is a potentially fatal condition caused by thiamine (vitamin B1) deficiency. Chronic alcoholism is the most common cause of WE; however, other conditions responsible for thiamine deficiency should also be considered.

Case Report: We report the case of a 64-year-old woman with a history of diabetes who presented with confusion and apathy. Magnetic resonance imaging of the brain showed T2 hyperintensities involving dorsolateral medulla oblongata, tegmentum of the pons, vermis of the cerebellum, periaqueductal region, and the bilateral mammillary bodies. She had a history of intravenous glucose administration before her mental symptoms developed. On suspicion of WE, she was treated with a high dose of thiamine empirically. Her clinical condition improved rapidly in 2 weeks.

Conclusion: Endogenous thiamine stores can be rapidly depleted in the case of enhanced glucose oxidation. Patients who receive glucose should also be prescribed thiamine to avoid inducing or exacerbating WE.

1. Introduction

Wernicke encephalopathy (WE) is a potentially fatal but reversible neurological disorder caused by thiamine deficiency. The triad of ophthalmoplegia, mental status changes, and ataxia classically characterizes WE. However, this triad is seen in only 16 % of patients [1], most patients have a broad spectrum of nonspecific clinical features, making this disease often misdiagnosed. The prevalence of WE based on autopsy studies varied throughout the world from 0.8 % to 2.8 %, with a higher prevalence in developing countries due to vitamin deficiencies and malnutrition [2].

Abbreviations: WE, Wernicke encephalopathy; MRI, Magnetic resonance imaging.

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WE occurs predominantly in alcoholics. Other susceptible populations include patients with malnutrition, gastrointestinal surgery including bariatric surgery [3], and those with increased thiamine requirement (e.g., children, in critically ill conditions, and during pregnancy) [4]. In addition, prolonged or excessive intake of carbohydrates or glucose increases the requirement of thiamine and may result in relative thiamine deficiency. Here, we report a case of iatrogenic WE after intravenous glucose administration.

2. Case presentation

A 64-year-old woman with a 14-year history of diabetes developed 2 months of confusion and apathy. She could not recall recent events, got lost in her residence, and had difficulty in recognizing her family members. She had insomnia, delusion, intermittent paraphasia, and difficulty in word comprehension. Her activities of daily living declined, but without urinary or fecal incontinence. She denied alcohol abuse or any form of malnutrition.

On admission, the patient's initial vitals were within normal parameters, temperature of 36.6 °C, heart rate of 65 beats per minute, respiratory rate of 19 breaths per minute, blood pressure of 141/58 mmHg. On neurologic examinations, she was alert but apathetic, with hypomimia and mild bradyphrenia. Her spontaneous word count decreased, and she had difficulty in communicating. She was disorientated to time and place and her family members. She had distractibility but could follow commands to complete simple actions such as closing her eyes or raising her limbs. She had difficulty in the oculomotor examination and could not complete the head impulse test, visual gaze, and visual pursuit. She showed non-persistent horizontal gaze-evoked nystagmus without obvious ophthalmoplegia and asymmetric eye position. Her bilateral faces were symmetrical, and she did not show hearing or swallowing disorder. She could walk independently but slowly and showed no apparent ataxia or gait unsteadiness. She had almost normal strength and tone in her extremities, normal reflexes, and plantar flexor responses. Her sensation was intact. Examinations identified no involuntary movement or obvious dysmetria. Her serum tests including complete blood count, serum chemistry and lipids profile, liver function tests, hypercoagulability studies, D-dimer levels were normal. She had a slightly elevated blood glucose level (7.2 mmol/L, reference range 2.5–4.5 mmol/L). Her chest X-ray and electrocardiogram examination were normal.

Based on these manifestations, metabolic or toxic encephalopathy and immune-mediated encephalitis were initially considered.

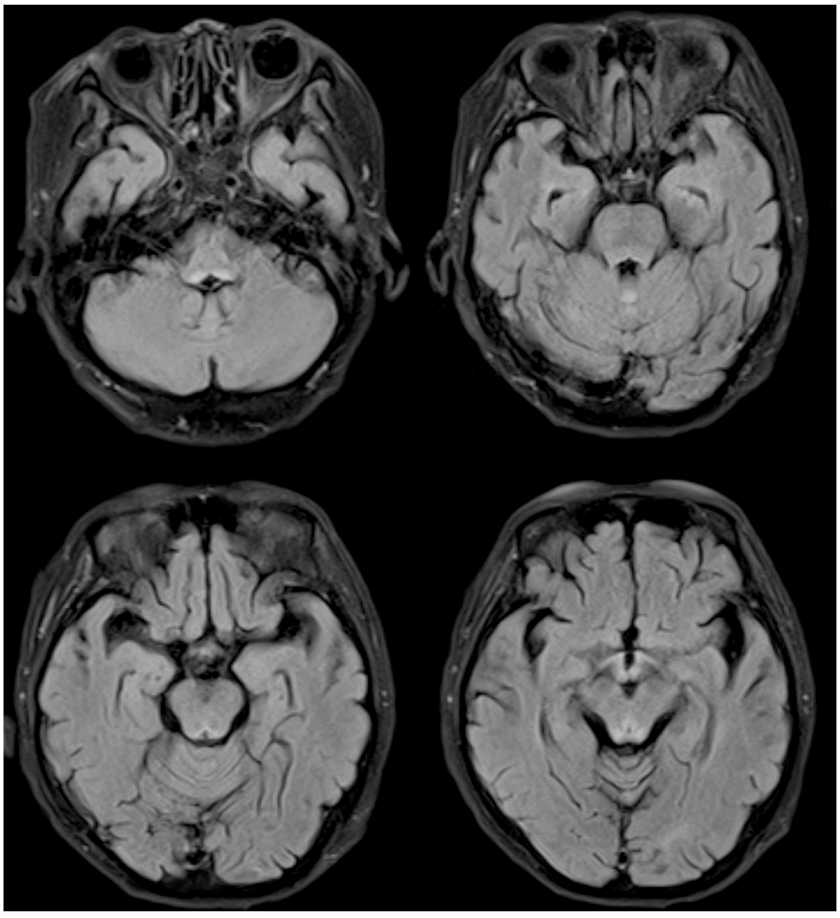

Fig. 1. Brain Magnetic resonance imaging scans showed T2 hyperintensities involving the dorsolateral medulla oblongata, tegmentum of the pons, vermis of the cerebellum, periaqueductal region, and the bilateral mammillary bodies.

Neuromyelitis optica spectrum disorders and autoimmune encephalitis were preferentially suspected. Magnetic resonance imaging (MRI) of the brain was then conducted. MRI showed T2 hyperintensities involving the dorsolateral medulla oblongata, tegmentum of the pons, vermis of the cerebellum, periaqueductal region, and the bilateral mammillary bodies (Fig. 1). There was no contrast enhancement lesions. These imaging findings raised the suspicion of WE. Further probing of the patient's history revealed that she had experienced transient hypoglycemia due to insulin overdose 2 months earlier. She was then treated with glucose intravenously in a local hospital. Her hypoglycemia improved rapidly; however, several days after glucose treatment, she developed altered mental status. Considering that excessive glucose intake increases the demand for thiamine, this treatment might lead to thiamine deficiency, a presumptive clinical diagnosis of WE was made. A high dose of thiamine was administered empirically. Thiamine hydrochloride (500 mg) dissolved in 100 mL of saline was administered intravenously every 8 h for 3 consecutive days, followed by 250 mg for 5 days and 100 mg for 5 days. Her clinical condition improved rapidly. The gaze-evoked nystagmus was diminished 3 days after treatment. About one week later, the apathy and confusion improved. She could identify her family members and communicate using simple language. Her memory improved gradually. There was no side-effect or unexpected event during the thiamine treatment. She got an almost complete recovery after 2 weeks of treatment, and was discharged home with a slow tapering regimen of oral thiamine, starting at a dosage of 60 mg per day. Last follow-up 9 months after the onset revealed no clinical manifestations.

3. Discussion

WE is caused by thiamine (vitamin B1) deficiency, which, in its biologically active form, thiamine pyrophosphate, is an essential cofactor for several enzymes in the tricarboxylic acid cycle and pentose phosphate pathways and thus participates in cellular energy metabolism. Thiamine is mainly obtained from food. The daily thiamine requirement for a healthy adult is 1.4 mg per day or 0.5 mg per 1000 kcal consumed. The body's reserves of thiamine are 30–50 mg, which would be completely depleted in 4–6 weeks in the absence of thiamine intake [5]. Thiamine deficiency causes depletion of cellular energy (adenosine triphosphate) and reduction of the reduced form of nicotinamide adenine dinucleotide phosphate synthesis, leading to the accumulation of toxic intermediate metabolic products such as lactate, alanine, and glutamate. Reduced cellular pH in cells and disruption of the homeostasis of cellular electrolytes further cause cytotoxic edema and cell damage [6–8]. Brain regions with high metabolic requirement, including structures around the third ventricle, medial thalami, periaqueductal region, mammillary bodies, and the tectal plate of the midbrain, are vulnerable to thiamine deficiency. The less commonly involved areas are the cerebellum, the dentate nuclei, the cranial nerve nuclei, the red nuclei, the caudate nuclei, the splenium, and cerebral cortex [5,9]. The damages are initially reversible after thiamine supplementation; however, delayed thiamine administration may lead to structural, irreversible lesions in the brain with possible permanent neurological sequelae or a fatal outcome [10,11].

Patients with WE show a broad spectrum of clinical manifestations. The classical triad of clinical symptoms (abnormal mental state, ataxia, and ophthalmoplegia) is found in only 16 % of patients. The most common symptom is altered mental status, which occurs in 76–80 % of patients [1,12,13]. Patients often present with disorientation, confusion, sluggishness, apathy, and memory impairment. Some patients experience agitation, hallucinations, and behavioral disturbances mimicking psychotic disorder. Decreased consciousness levels are not common in the early stage but can be seen in untreated patients. Mental changes mainly result from the involvement of the midline thalamic nuclei or mammillary bodies [6]. Agitation and delirium may also be related to alcohol withdrawal in some alcoholics. Trunk ataxia and loss of equilibrium occur in 25 % of patients, mainly caused by the involvement of the cerebellar vermis and vestibular dysfunction. The presentation can range from mild gait abnormality to complete inability to stand. Approximately 29 % of patients exhibit oculomotor abnormality [14]. Complete ophthalmoplegia occurs rarely; the most common sign is nystagmus, usually horizontal. Decreased visual acuity, diplopia, or conjugate-gaze palsies may appear in some patients. Other uncommon manifestations of WE include hypotension and tachycardia, hypothermia, and progressive hearing loss [15].

Previous studies reported that vestibular symptoms manifested by vertigo and oculomotor abnormalities may be the early signs of patients with thiamine deficiency, due to the high vulnerability of nucleus prepositus hypoglossi, the medial vestibular nucleus, the sixth nerve nucleus and the paramedian tract neurons. These neurons are generally damaged prior to the involvement of diencephalic neurons (mammillary bodies and midline thalamus). Encephalopathy is often considered as a late stage of thiamine deficiency [16,17]. This patient mainly presented with altered mental status, without complaining of vertigo, ataxia and gait unsteadiness, although she had horizontal gaze-evoked nystagmus. We postulated that she might have a relative slight damage in vestibular system, or have a partial recovery when she presented to hospital, considering that the recovery from oculomotor abnormalities often occurred early after thiamine supplementation [18,19]. Encephalopathy in patients with thiamine deficiency may potentially associate with poor outcome. Fortunately, this patient got almost complete recovery after thiamine supplementation. The possible explanation is, her thiamine deficiency was induced by transient glucose over-application. She had intact gastrointestinal function and eat food normally, this ensured a basic daily thiamine intake and may compromise the potential deterioration of her condition.

The clinical diagnosis of WE requires two of the following: (1) nutritional deficiency and a history of an alcohol use disorder or any other deficiency states, (2) oculomotor abnormalities, (3) equilibrium disorders, and (4) an altered mental state or mild memory impairment [20]. However, due to the clinical heterogeneity, diagnostic delay and misdiagnosis often occur. Detection of thiamine level and erythrocyte transketolase activity can be helpful. However, these measurements are limited due to the low specificity and technical unavailability [18]. MRI is currently the most valuable method for WE diagnosis. MRI typically shows T2, fluid-attenuated inversion recovery, and diffusion-weighted imaging hyperintensity in the thalamus, mammillary bodies, periaqueductal region, and the floor of the fourth ventricle. This typical pattern of lesions on MRI is observed in 58 % of patients. Other sites, including the cerebellum, cranial nerve nuclei, putamen, caudate, splenium of the corpus callosum, and cerebral cortex, can be involved. Contrast-enhanced lesions may be found, suggesting the destruction of the blood-brain barrier. Although MRI has high specificity (93

%) for the diagnosis, its sensitivity is only 53 % [14,18,21,22]. Normal brain imaging cannot exclude WE diagnosis.

In this regard, a high degree of clinical suspicion and recognition of predisposing conditions is critical to diagnose WE. Alcoholism accounts for only approximately 50 % of WE; other predisposing factors include hyperemesis gravidarum, prolonged parenteral nutrition, malignancies, immunodeficiency syndromes, liver disease, hyperthyroidism, and gastrointestinal surgical procedures [18,23]. Most of the surgical procedures are risk factors for the WE. The patients undergoing bariatric surgery in Western nations has been constantly increasing, as has the number of WE related to these surgical procedures. WE after bariatric surgery usually occurs between 4 and 12 weeks postoperatively, especially in young women with vomiting [24]. In addition, acute infection and prolonged carbohydrate or glucose loading may aggravate thiamine deficiency and trigger WE [8]. Clinicians should consider WE diagnosis in patients with predisposing factors, even if they show only one component of the classic triad or other atypical manifestations.

This patient didn't show classical triad of clinical symptoms, also she denied alcohol abuse or any malnutrition status. This led to the initial misdiagnosis. Based on her specific imaging findings and her history of glucose administration prior to her mental changes, a presumptive clinical diagnosis of WE was made. This is an iatrogenic WE case induced by inappropriate glucose use. Notably, thiamine requirement depends on total caloric intake, especially the proportion of calories provided by carbohydrates. Endogenous thiamine stores can be rapidly depleted in the case of enhanced glucose oxidation, thereby increasing the risk of WE. In general, patients who receive glucose should also be treated with thiamine in advance or at the same time to avoid inducing or exacerbating WE [18].

For the treatment of WE, prompt thiamine supplementation is the foremost method. Parenteral administration, either intravenous or intramuscular, is most effective, while oral administration is not recommended. The initial dose of thiamine is 500 mg every 8 h for 2–3 days, followed by 250 mg for 3–5 days or until complete clinical improvement [18]. Generally, the daily thiamine requirement for a healthy adult is 1.4 mg. However, there are individual differences in thiamine absorption and utilization. For example, mutations in the SLC19A3 gene encoding thiamine transporter 2 can impair the absorption and transport of thiamine and affect individuals' ability to cope with thiamine deficiency or respond to therapy. In this case, biotin therapy, in addition to thiamine, helps to improve their symptoms [25–27]. For people with alcohol withdrawal, poor nourishment, and signs of malnutrition, prophylactic treatment with thiamine is recommended [28,29]. Parenteral thiamine administration is generally safe. In a prospective study, generalized pruritus (0.093 %) and transient local irritation (1.02 %) were observed in patients treated with thiamine intravenously [30].

Thiamine supplementation can improve the symptoms in most patients; however, delayed treatment may lead to irreversible lesions in the brain with possible permanent neurological sequelae. Clinicians should maintain a high level of suspicion for this disease. Considering the possible poor outcome in patients with delayed treatment and the very low incidence of side effects of thiamine, it is recommended that thiamine administration should be started empirically even if the diagnosis has not been confirmed [31].

There are limitations in this case report. Due to technical unavailability, we didn't detect the thiamine level and erythrocyte transketolase activity, and the potential gene mutation that related to thiamine metabolism. These information may be helpful to make an individualized treatment. We failed to follow up the patient's imaging changes. Because the patient's symptoms recovered completely, she refused to review the MRI detection.

4. Conclusions

We report a case of WE due to rare iatrogenic thiamine deficiency. Currently, the diagnosis of WE is often difficult and delayed, therefore, it is important for clinicians to be familiar with the predisposing conditions of WE and have a high degree of clinical suspicion. In addition to those common predisposing conditions, clinicians should realize that thiamine requirement depends on total caloric intake, especially the proportion of calories provided by carbohydrates. Rapid or excessive glucose intake may deplete the endogenous thiamine stores, thereby increase the risk of WE. Patients who receive glucose should be treated with thiamine in advance or at the same time to avoid inducing or exacerbating WE.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

Consent for publication

Written informed consent was obtained from patient.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [Youdong Wei], upon reasonable request.

CRediT authorship contribution statement

Xiangkun Tao, Renjie Qiao, Can Liu conducted the literature review and acquired the data. Lu Guo, Jingcheng Li performed analysis and interpretation of data. Yulai Kang, Youdong Wei drafted the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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