What Goes Around Comes Around? Wernicke Encephalopathy and the Nationwide Shortage of Intravenous Multivitamins Revisited

Introduction

Wernicke encephalopathy (WE) is an acute neurologic disorder caused by thiamine deficiency and characterized by ophthalmoplegia, ataxia, and confusion. WE is usually associated with alcoholism, malnutrition, and GI malabsorptive diseases but has also been reported in patients who received total parenteral nutrition (TPN) without proper thiamine replacement.¹⁻⁶ After the intravenous (IV) multivitamin (MVI) shortage in 1996, several children and adults who received TPN developed WE as a result of thiamine deficiency.⁷⁻¹⁰

We report five cases of WE among patients at St Jude Children's Research Hospital in the setting of IV MVI shortages. Because of the current ongoing drug shortages, our cases highlight the risk of developing WE during MVI shortages and inadequate supplementation. The cases also emphasize the importance of early diagnosis of WE; if untreated, thiamine deficiency can progress to irreversible neurologic and cardiovascular compromise.

Case Report 1

A 5-year-old girl with metastatic medulloblastoma undergoing radiation therapy presented with new onset vertical nystagmus, worsening ataxia, and dysnomia. At the time of presentation, she was receiving TPN without MVIs, which had been discontinued as a result of a national shortage. She was not taking a prescribed oral MVI because of nausea. The patient complained of blurred vision and myopia. Magnetic resonance imaging (MRI) revealed bithalamic (Fig 1A, arrows), tectal (Fig 1B, arrowheads), and periaqueductal gray matter (Fig 1B, arrow) edema; magnetic resonance angiography and venography were normal. MRI 2 days later demonstrated an increase in the previous edema and new foci of thalamic and tectal cytotoxic

edema (Fig 1C, arrows), which were consistent with progressive WE. IV thiamine was given, and the vision of the patient improved after the second dose. The patient continued to receive oral thiamine, and her symptoms completely resolved over the next 2 weeks.

Case Report 2

A 9-year-old girl with osteosarcoma of the right proximal humerus who had recently received IV methotrexate 9 days before admission was admitted for abdominal pain, mucositis, diarrhea, and decreased oral intake. One week after admission, her neurologic status declined. The patient was somnolent with incoherent speech. Her lactate level was increased (8.9 mmol/L; normal range, 0.7 to 2.1 mmol/L). MRI revealed T2 prolongation of the medial thalami, mammillary bodies, and dorsal pons. The thiamine level of the patient was low (43 nmol/L; normal range, 87 to 280 nmol/L). She was treated with IV thiamine and began to receive TPN. MRI performed 7 days after the initiation of thiamine showed a mixed response of decreased T2 prolongation involving the subthalamic nuclei and mammillary bodies but increased T2 prolongation involving the bilateral caudate heads. The patient remained hospitalized for 80 days, and her neurologic status gradually returned to baseline.

Case Report 3

A 19-year-old woman with acute myelogenous leukemia was admitted with severe fatigue, blurred vision, dizziness, and ataxia 105 days after a matched, unrelated donor transplant. Her course was complicated by worsening nausea and vomiting despite receiving antiemetics. Twenty-four hours before admission, the oral intake of the patient improved. However, her speech was notably incoherent, and she was unable to remember the names of her medical providers. The patient had been taking TPN for 2 months without the necessary IV MVIs as a result of an ongoing national shortage. She was prescribed an oral MVI, which she had not been taking and actually did not contain any thiamine. Emergent brain

Fig 1.

MRI before the start of IV thiamine revealed abnormal enhancement and enlargement of the infundibulum and edema of the proximal bilateral optic tracts. After thiamine administration, the vision of the patient improved over the next 12 hours. She was administered oral thiamine and discharged. Within a few weeks, her neurologic status and MRI returned to baseline.

Case Report 4

A 4-year-old girl with parameningeal rhabdomyosarcoma arising from the left ear with intracranial extension was admitted for nausea, vomiting, and mucositis in the setting of fever and neutropenia. The patient had received cranial irradiation to the left infratemporal region, followed by chemotherapy, and had been taking long-term TPN with oral MVI supplementation. During the second week of her hospitalization, her clinical status deteriorated. Her examination was notable for tachypnea, tachycardia, intractable vomiting, and persistent fever. Laboratory data showed metabolic acidosis. Endoscopy revealed gastritis and mucositis. MRI revealed evidence of a leptomeningeal metastatic tumor, with no findings suggestive of metabolic disturbance. IV thiamine was administered empirically for the ongoing metabolic acidosis and worsening somnolence of the patient. Within 24 hours, her clinical status improved and returned to baseline within 3 days, and the metabolic acidosis resolved.

Case Report 5

A 6-year-old boy with medulloblastoma developed nausea and vomiting after completing his second course of high-dose chemotherapy with autologous stem-cell rescue. Emergent head CT revealed no hydrocephalus, and MRI showed no new changes. Persistent nausea and vomiting prompted admission 3 weeks later, at which time the laboratory work-up showed a significant metabolic acidosis in the setting of worsening ataxia, new-onset somnolence, aphasia, restlessness, and poor eye contact. An EEG was consistent with encephalopathy. The cardiac status of the patient deteriorated; he developed ventricular tachycardia, for which he was resuscitated and intubated. The medical history of the patient revealed discontinuation of IV MVIs 4 weeks before admission as a result of an allergic reaction. An oral MVI was prescribed but not taken because of intractable vomiting. Two days after his admission, he was given a trial dose of IV thiamine. The neurologic status and lactic acidosis of the patient improved; however, he developed multiorgan failure and died 3 weeks after admission.

Discussion

WE, which is generally considered a disorder of chronic alcoholics and uncommon in children, usually results from an inadequate intake or absorption of thiamine, is typically precipitated by carbohydrate ingestion, and is characterized by vertical nystagmus, ophthalmoplegia, confusion, and, in rare cases, gait ataxia. The disorder responds rapidly to thiamine.¹¹ In this series, three cases of WE were related to a lack of IV MVIs, and two cases of WE were related to poor oral intake and vomiting. Two patients also presented with lactic acidosis, which has been reported in patients with thiamine deficiency.⁹ In all patients, symptoms improved to some degree with thiamine administration. It takes approximately 2 weeks to 2 months for body stores of thiamine to be depleted, which is consistent with the onset of symptoms in our patients.

MRI is far more sensitive than CT for detecting WE-related brain abnormalities. Classically, MRI of adult alcoholics with WE has shown signal abnormalities in the bilateral dorsomedial thalami, tectal plate, periaqueductal gray matter, and/or mammillary bodies, as was the case in patient 1. However, in children and nonalcoholic patients, MRI findings may vary and include cranial nerve, cerebellar, cortical, white matter, or bilateral basal ganglia (putamen and caudate) involvement.^{12,13} Enhancement may be present; cytotoxic edema and cortical involvement are associated with a poor prognosis.¹³ The involvement of the infundibulum and optic tracts in patient 3 has not been previously reported to our knowledge, and in conjunction with the absence of WE-related MRI findings in the remaining patients, underscores the imaging variability in WE and the necessity for having a high clinical index of suspicion for WE in susceptible pediatric patients.

The early diagnosis of WE is important because many of the acute neurologic changes can be reversed with the administration of thiamine.^{2,11} Ocular symptoms often improve within hours of administering thiamine, although complete resolution may take 2 weeks or longer. Complete recovery occurs in only 20% to 25% of patients once memory deficits, which are termed Korsakoff syndrome, develop.²

No long-term clinical cognitive deficits attributable to thiamine deficiency have been evident in our patients; however, MRI abnormalities persist in two of the patients, for whom the clinical relevance may have not yet been manifested. Small residual bilateral medial thalamic signal abnormalities, which corresponded to the site of previous cytotoxic edema, continued to persist on MRI imaging for patient 1 eight months later. MRI imaging for patient 2 continued to demonstrate minimal residual cortical signal abnormality 11 months later.

The perceived rarity of this disorder in children may preclude clinicians from making a prompt diagnosis. Early recognition may also be more difficult in children because they typically lack the classic symptoms. A lack of a thiamine level should not prevent making the diagnosis and instituting treatment if the clinical suspicion is high, especially because levels may take several days to be reported. Levels were drawn only for patients 1 and 2; however, the level of the former patient was unreportable as a result of a laboratory error.

Our report highlights the importance of ensuring that patients take proper vitamin supplementation to prevent this potentially devastating disorder. Moreover, to our knowledge, this is the first published report of harm to pediatric patients as a result of a drug shortage. It remains unknown whether the deficiency of thiamine may have also interfered with chemotherapy metabolism and potentially affected treatment efficacy. However, it is known that lactic acidosis as a result of thiamine deficiency may be a complication of the administration of certain chemotherapeutic agents.¹⁴⁻¹⁷

In light of recent IV drug shortages, many more children with chronic illnesses who receive TPN with IV MVIs may be at risk of developing WE if an oral equivalent is not prescribed, taken as directed, or absorbed as a result of malabsorption or persistent vomiting. Consistent compliance with oral supplementation is also necessary because oral thiamine is poorly absorbed. It will be important in this era of ongoing drug shortages to find and substitute acceptable alternatives to prevent such complications.¹⁸

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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