

Wernicke Encephalopathy and Beriberi During Total Parenteral Nutrition Attributable to Multivitamin Infusion Shortage

ABSTRACT. *Objective.* Wernicke encephalopathy (WE) is an acute neurologic disorder characterized by a triad of ophthalmoplegia, ataxia, and mental confusion. WE is attributable to thiamine (vitamin B1) deficiency. Beriberi is the systemic counterpart of thiamine deficiency and often manifests in cardiovascular collapse. WE is usually associated with alcoholism and malnutrition. It has also been seen in people with gastrointestinal diseases with malabsorption. Patients who have received total parenteral nutrition (TPN) without proper replacement of thiamine have also developed WE. Since November 1996, there has been a shortage of multivitamin infusion (MVI). Many patients who were on chronic TPN with MVI ceased to receive the MVI and were converted to an oral form of the multivitamin. As a result, there have been several reports of children and adults on TPN who have developed WE as a result of thiamine deficiency. With this case report, we bring to attention the association of the MVI shortage and WE. Early diagnosis of WE is important, because if it is treated with thiamine in the acute stages, the neurologic and cardiovascular abnormalities can be reversed.

Case Report. We report a 20-year-old female patient with Crohn's disease who developed WE as a result of thiamine deficiency. She had Crohn's disease since age 9 years and was on chronic TPN. Two months before admission, MVI was discontinued in the TPN because of the shortage of its supply. An oral multivitamin tablet was substituted instead. She was admitted to the hospital for persistent vomiting. In the hospital, she continued to receive TPN without MVI, but continued taking an oral multivitamin preparation. Two weeks after admission, she developed signs of WE including diplopia, ophthalmoplegia, nystagmus, and memory disturbance. She also developed hypotension that was thought to be caused by beriberi. She was treated with 50 mg of intravenous thiamine. Within hours of the intravenous thiamine, her hypotension resolved. The day after the infusion, she no longer complained of diplopia, and her ophthalmoplegia had improved dramatically. Magnetic resonance imaging showed several areas of abnormally high signal on T2-weighted images in the brainstem, thalamus, and mammillary bodies. The topographic distribution of these changes was typical of WE. After 2 months, her mental status and neurologic status had recovered completely.

Conclusion. WE and thiamine deficiency should be considered in all patients with malabsorption, malnutrition, and malignancies. WE from thiamine deficiency can occur as a result of cessation of MVI in the TPN infusion. Even if an oral multivitamin preparation is given instead of MVI, patients with malabsorption may not absorb thiamine adequately. Prompt diagnosis of WE is important because it is potentially fatal and readily treatable with thiamine supplementation. Early recognition of WE

may be more difficult in children, because the classic triad of symptoms may not develop fully. Magnetic resonance imaging may be useful in these cases to confirm the diagnosis of WE. Because the shortage of MVI is expected to be a long-term, there are likely to be more cases of WE in the pediatric population of TPN-dependent children. Because there is no shortage of intravenous thiamine, it should be administered with TPN even if MVI is not available. *Pediatrics* 1998;101(1). URL: <http://www.pediatrics.org/cgi/content/full/101/1/e10>; *Wernicke encephalopathy, thiamine, total parenteral nutrition, multivitamin infusion, ophthalmoplegia.*

ABBREVIATIONS. WE, Wernicke encephalopathy; TPN, total parenteral nutrition; MVI, multivitamin infusion; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; CSF, cerebrospinal fluid.

Wernicke encephalopathy (WE) is an acute disorder characterized by a triad of ophthalmoplegia, ataxia, and mental confusion. Abnormal eye movements may consist of horizontal and vertical nystagmus, weakness or paralysis of lateral rectus muscles, and weakness or paralysis of conjugate gaze. In advanced cases, complete ophthalmoplegia may occur. Altered mental status consists of decreased alertness and attentiveness, perceptual disturbance, and poor memory. Sometimes it may progress to coma. WE is attributable to thiamine (vitamin B1) deficiency.^{1,2} WE is usually associated with alcoholism and malnutrition. It can also be seen in people with gastrointestinal diseases with malabsorption.³ Patients who are dependent on total parenteral nutrition (TPN) without proper replacement of thiamine have also developed WE.^{4,5} It has also been reported in hyperemesis gravidarum⁶ and in children with malignancies.⁷ Importantly, acute WE is treatable with thiamine supplementation.⁸ If treated in the acute stages, many of the neurologic abnormalities can be reversed.²

Recently, there has been a nationwide shortage of pediatric and adult multivitamin infusion (MVI) in the United States.⁹⁻¹¹ Many children who were receiving TPN with MVI had their MVI discontinued and were converted to an oral form of the multivitamin. We report a patient with Crohn's disease who developed WE as a result of thiamine deficiency that presumably was caused by switching from the intravenous to the oral form.

CASE REPORT

A 20-year-old woman with Crohn's disease on chronic TPN was admitted for nausea, vomiting, and dizziness. Her medical history is notable for Crohn's disease, diagnosed at 9 years of age. She had a complicated course with chronic steroid use, including cataracts and osteoporosis attributable to steroids. She had a long history of persistent emesis requiring chronic home TPN.

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Two months before admission, MVI (MVI-12, Astra, USA) was discontinued in the TPN because of the shortage in supply. An oral multivitamin tablet was substituted instead. The patient had frequent daily emesis during the 3 weeks before admission. She took ondansetron and diazepam with mild relief of her nausea and vomiting. She did not take anything by mouth for several weeks except for medications and had been on TPN solely. Two days before admission, she had increasing dizziness and developed shortness of breath. She also complained of palpitations, especially when standing.

On admission, the patient was thought to be dehydrated and was given intravenous fluids. She was found to be anemic, with a hematocrit of 25%, and a packed red cell transfusion transiently improved her dizziness. The transfusion transiently increased the hematocrit to 29%, but throughout the admission, the hematocrit remained in the mid 20s. She continued to receive TPN without MVI, but continued taking an oral multivitamin preparation. Three days after admission, the glucose concentration in her TPN was increased from 10% to 12.5% to give her more calories. Seven days after admission, the dizziness worsened, and she developed vertigo and nystagmus. On examination, she had full extraocular movements with horizontal nystagmus bilaterally on end-gaze (more prominent on leftward gaze). Pupils were normally reactive, and visual acuity was normal. She had a shuffling gait, but there was no tremor or truncal ataxia. She was treated with dimenhydrinate, then meclizine, but neither medication improved her dizziness and they were stopped. Thirteen days after admission, she developed confusion, diplopia, and blurry vision. She kept repeating questions and was disoriented to time. When speaking to the staff, she would often confabulate about recent events. The examination showed mild lateral rectus weakness bilaterally and nystagmus. The glucose concentration in her TPN

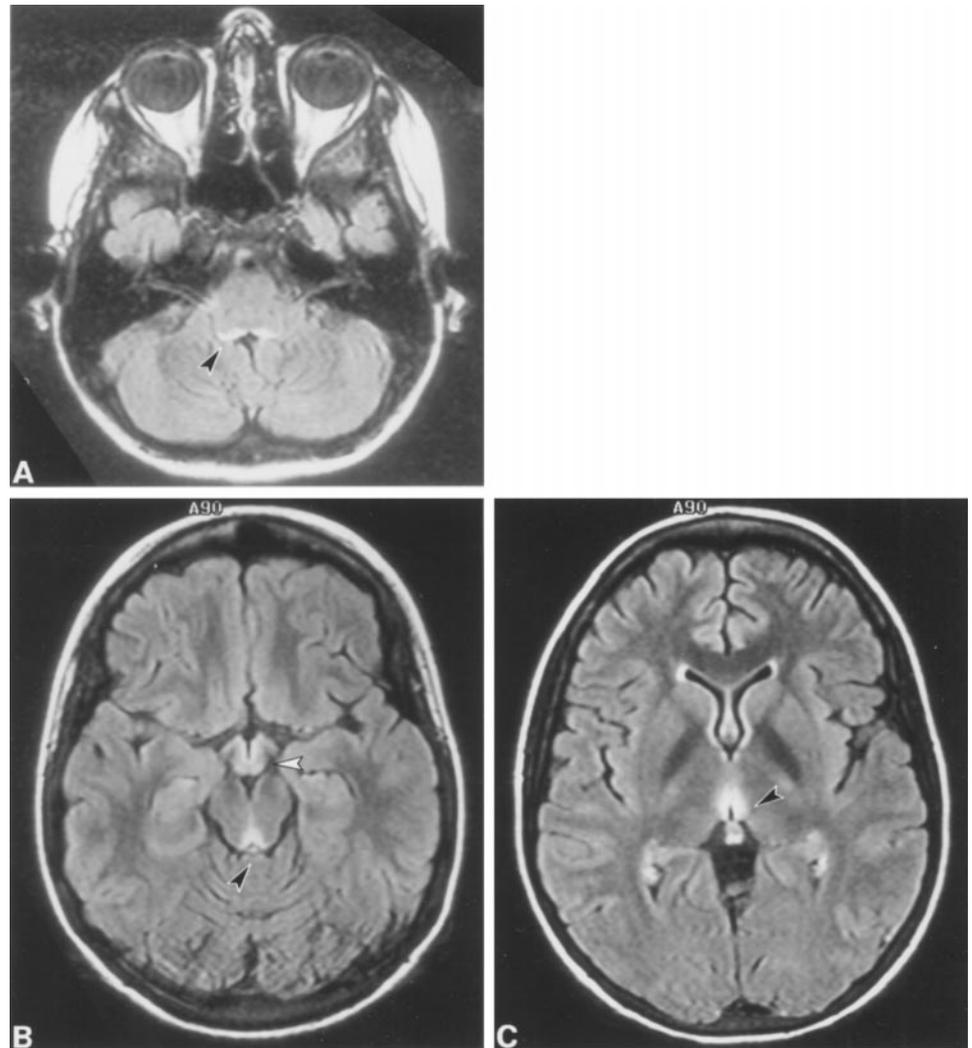
was increased from 12.5% to 15%, but she continued to receive no thiamine or MVI in her TPN.

Fourteen days after admission, she developed complete lateral rectus paresis bilaterally and was unable to abduct the eyes beyond midline. She complained of blurry vision and diplopia. She had difficulty remembering faces and events that had occurred earlier in the day. She developed severe hypotension, with blood pressures as low as 72/34 mm Hg, and tachycardia to 180 beats per minute. The patient was transferred to the intensive care unit for stabilization of her blood pressure. Examination revealed complete loss of abduction bilaterally and vertical and horizontal nystagmus even in primary gaze. She then progressed to nearly complete ophthalmoplegia, including limitation of up- and down-gaze. She had no disk edema. Mild dysmetria was seen. Gait was not tested because of her critical state. Because of the concern for thiamine deficiency, she was treated with 50 mg of intravenous thiamine.

Within 8 hours of the intravenous thiamine, her cardiovascular status had stabilized. By the next day, she no longer complained of diplopia, and her ophthalmoplegia had improved dramatically. She still had bilateral horizontal and vertical nystagmus. Plasma thiamine level was not obtained before the intravenous administration of thiamine. However, a level obtained 3 days later was normal (0.5 $\mu\text{g}/\text{dL}$, with a normal range of 0.2 to 2.0 $\mu\text{g}/\text{dL}$). At that time, MVI-12 was restarted in her TPN at 10 mL per day, giving her 3.0 mg per day of thiamine.

Magnetic resonance imaging (MRI) was performed during this acute phase and showed several areas of abnormally high signal on T2-weighted images and fluid-attenuated inversion recovery (FLAIR) images (Fig 1). These abnormalities were found symmetrically in the medulla around the floor of the fourth ventricle (involving the vestibular nuclei and area postrema), the periaque-

Fig 1. Series of three axial FLAIR sequences of MRI showing abnormalities in at the level of the upper medulla (A), mid-brain (B), and thalamus (C). The major abnormalities are the high signal intensities in the floor of the fourth ventricle near the vestibular nuclei (arrowhead in A), around the aqueduct of Sylvius (arrowhead in B), and the mamillary bodies (open arrowhead in B), and around the third ventricle in the medial thalamus (arrowhead in C). These findings were bilateral and symmetric in these structures and typical of regions of the brain involved with Wernicke encephalopathy. Similar signal changes were noted on T2-weighted images, but the lesions were not as distinct because of the high signal of CSF. The high signal around the optic chiasm (B) and the frontal horns of the lateral ventricles (C) are attributable to a CSF flow artifact. For FLAIR images, repetition time = 10 000 msec, echo time = 135 msec/effective.



ductal gray matter of the midbrain, the mamillary bodies, and the medial thalamus near the third ventricle. These changes were accentuated on FLAIR images. The topographic distribution of these findings was typical of regions of the brain involved with WE. On T1-weighted images, there was increased signal intensity in the basal ganglia bilaterally (data not shown in Fig 1) that was thought to be secondary to chronic TPN use.¹²

One week after treatment with thiamine, the patient had horizontal nystagmus only on end-gaze and mild intention tremor. Her regular gait was normal, but she had difficulty with tandem gait. Romberg sign was absent. Neuropsychologic testing showed slow processing and retrieval difficulty of verbal information. Two months after treatment, she was back to her normal self and had no dizziness or memory problems. She had nystagmus on extreme horizontal gaze, but full ocular movements.

DISCUSSION

Wernicke encephalopathy is an acute disorder characterized by ophthalmoplegia, ataxia, mental confusion, and impairment of memory. The symptoms and signs found in this patient are consistent with WE. We believe she developed WE from thiamine deficiency that occurred as a result of cessation of MVI in the TPN infusion. Although she had been receiving an oral multivitamin preparation instead of MVI, given her chronic bowel disease and emesis, it is likely that she was not absorbing thiamine adequately. The WE was probably exacerbated by the 50% increase in the glucose concentration in her TPN. This additional glucose load likely resulted in additional metabolic need for thiamine. Her ocular signs improved within hours after treatment with intravenous thiamine. She also had improvement of memory and mental confusion, although she still had some processing difficulties during hospitalization. After 2 months, her mental status and neurologic status seem to have recovered completely.

In addition to WE, the patient probably also suffered cardiac dysfunction attributable to beriberi. She had symptoms of hypotension, tachycardia, and dyspnea that were unresponsive to fluid boluses and blood transfusion. The severe hypotension and cardiovascular instability that required intensive care treatment responded dramatically to thiamine. Had she not received the thiamine promptly, she would have most likely suffered irreversible cardiac decompensation.

We believe the patient's neurologic and cardiac symptoms were attributable to a thiamine deficiency, rather than to a broader vitamin deficiency. Her dramatic improvement was seen hours after the intravenous infusion of thiamine. This occurred 2 to 3 days before MVI was reintroduced to the TPN.

The neuropathology of WE consists of neuronal, axonal and myelin loss, prominent blood vessels, and gliosis that affects the midbrain periaqueductal gray matter, floor of fourth ventricle, medial thalamus, hypothalamus, and mamillary bodies.^{2,13} The distribution of lesions found on MRI in our patient is consistent with acute WE.

MRI has become the neuroradiologic study of choice in confirming the diagnosis of WE.^{3,8,14-16} MRI has been reported to demonstrate the typical periventricular lesions in up to 80% of suspected cases.⁸ Furthermore, special FLAIR imaging may improve the ability to detect the abnormalities of WE.¹⁷

FLAIR imaging produces images similar to T2-weighted images, but suppresses the bright signal of the cerebrospinal fluid (CSF) in the ventricles and subarachnoid spaces. Therefore, FLAIR is the ideal MRI sequence for identifying the lesions of WE that are often in the periventricular region of the brainstem and thalamus.

Prompt diagnosis of WE and beriberi is important because it is readily treatable with thiamine supplementation.^{2,8} If treated in the acute stages, many of the neurologic abnormalities can be reversed.² Ocular findings may improve within hours of thiamine administration, although complete resolution may take 1 to 2 weeks. Once memory deficits develop (ie, Korsakoff syndrome), complete or almost complete recovery occurs only in 20% to 25% of patients. Fortunately, our patient seems to have recovered fully. Mortality has been reported to be 17%.²

Because WE occurs primarily in adult alcoholics and is rare in children, pediatricians may not be consider this diagnosis readily. Early recognition of WE may be more difficult in children, because the classic triad of symptoms may not develop fully. WE and thiamine deficiency should be considered in all patients with malabsorption, malnutrition, and malignancies.

Since November 1996, there has been a shortage of MVI.^{9,10} Many children who were on chronic TPN with MVI ceased to receive the MVI and were converted to an oral form of the multivitamin. Recently, there have been several reports of children and adults on TPN who have developed WE or lactic acidosis as a result of thiamine deficiency.^{11,18} As in our patient, these patients received TPN without MVI and developed symptoms between 2 weeks and 2 months. This course is consistent with the time required to deplete body stores of thiamine.

Because the shortage of MVI is expected to be long-term,⁹ there are likely to be more cases of WE in the pediatric population of TPN-dependent children. With this case report, we bring attention to the importance of proper vitamin supplementation during TPN, which is required to prevent these types of neurologic and cardiac disorders. Because there is no shortage of intravenous thiamine, it should be administered with TPN even if MVI is not available.

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