



# Vitamins are Indeed Vital Amines: A Discussion of 3 Deficiencies With Neurologic Manifestations

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## Abstract

Optimal functioning of the human nervous system depends on a constant supply of nutrients, vitamins, and minerals. In the developed world, nutritional deficiencies are relatively rare and infrequently present with neurologic manifestations. These neurologic disorders can be mistaken for inflammatory and/or autoimmune phenomena. This manuscript describes 2 pediatric cases with neurologic signs/symptoms arising from vitamin deficiencies—(1) optic neuropathy and (2) Wernicke encephalopathy associated with a Guillain-Barre-like pattern of weakness. The 2 cases and the subsequent discussion of vitamin A, B1, and B12 deficiencies underscore the value of taking a thorough dietary history and emphasize risk factors for these 3 nutritional deficiencies.

## Keywords

pediatric neurology, neuroimmunology, nutrition, neuroophthalmology, neuroimaging

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## Introduction

Nutrition plays an important role in the development and function of the human nervous system. Optimal functioning of the central and peripheral nervous systems depends on a constant supply of nutrients, vitamins, and minerals. In the developing world, physicians are quite familiar with the effects of vitamin deficiencies. Vitamin A deficiency, for example, afflicts almost half the children in Sub-Saharan Africa and is also the leading cause of treatable blindness globally. Likewise, thiamine deficiency is seen in 10% of adolescents in some Asian countries, where rice is heavily utilized for food and modern industrial techniques remove thiamine and lead to a deficiency. In developed countries, vitamin deficiencies are less common, though in specific circumstances they occur: thiamine deficiency in adults with heavy alcohol use and vitamin B12 deficiency in adults with pernicious anemia. In children of the developed world, however, vitamin deficiencies are less likely. This report describes the presentation in 2 pediatric patients—(1) optic neuropathy and (2) Wernicke encephalopathy associated with a Guillain-Barre-like pattern of weakness—who underscore the value of taking a dietary history and emphasize risk factors for select vitamin deficiencies.

## Case I

A 12-year-old Caucasian female, with a history of narcolepsy and duodenal stenosis repaired in infancy, presented with 2 months of progressive painless vision loss in the left eye. The patient initially noticed central vision loss in her left eye that extended into the ipsilateral temporal visual field. She also reported intermittent vision loss of the upper visual field of her right eye. Other complaints included recurrent urinary tract infections, conjunctivitis and dry skin. Progressive, worsening vision loss prompted referral to an ophthalmologist, who discovered bilateral keratinized conjunctivae, Bitot spots, severe xerophthalmia, and bilateral disc edema on examination. The ophthalmologist referred the patient to our facility for further evaluation and management.

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Nutritional history revealed a body mass index (BMI) of 19.5 kg/m<sup>2</sup>. She had lost 22 pounds over the preceding 3 months due to loss of appetite in the setting of modafinil therapy for narcolepsy. When her BMI was 23.4 kg/m<sup>2</sup>, she typically ate 2 to 3 small meals per day, as well as additional snacks (eg, pretzels, chips). Her typical breakfast was limited to donuts and her usual lunch and dinner were mainly chicken and French fries. She did not eat any other meats, fish, dairy products or fruits and vegetables regularly, but occasionally consumed ice cream. She exclusively drank water or sweet tea. Given her selective eating habits, the patient was previously started on a daily multivitamin (MVI), iron, and vitamin D by her primary care physician.

The patient was later admitted for further investigation of worsening vision. Other than ocular exam findings previously described, her physical exam revealed clear breath sounds bilaterally, normal heart sounds with 2+ pulses, soft and nontender abdomen, intact cranial nerves III-XII bilaterally, 5/5 strength in all major muscle groups bilaterally, normal sensation in all modalities, 2+ symmetric reflexes, normal coordination, and normal gait and station. She underwent extensive infectious, inflammatory, and nutritional investigations, including magnetic resonance imaging (MRI) of the brain and orbits. She was found to have significantly low serum levels of vitamins B12, B9 (folic acid), A, B1 (thiamine), C, and E as well as low zinc and borderline copper levels (Table 1). She was immediately started on replacement therapy with folate, zinc, B12, thiamine, vitamins E and A. Nutrition was consulted, and the patient was started on a balanced diet with select parameters below.

Calories: 1970 to 2215 kcal/day (40-45 kcal/kg) [DRI 40]

Protein: 59 to 74 g/day (1.2-1.5 g/kg)

Fluid: 2050 to 2100 mL for maintenance

After initiation of vitamin replacement, the patient's vision improved in both eyes. In the left eye, her vision changed, from near total loss to an ability to see and discern color. A

comprehensive neurologic exam did not reveal any additional deficits aside from the visual changes described above. MRI brain and cervical spine did not detect any pathologic findings other than nonspecific subcortical white matter signal changes in the left temporal tip (Figure 1). MRI of the orbits revealed borderline increased signal in both optic nerves (Figure 2). Given signs of optic neuritis by imaging as well as papilledema (Figure 3) on exam, the possibility of autoimmune optic neuritis was considered. Due to slow improvement with vitamin supplementation, the outside ophthalmologist and family strongly advocated for corticosteroid therapy out of concern for missing the window to treat an autoimmune process. She received 3 doses of methylprednisolone 1 g, with a taper over 5 weeks. During her hospital stay, she regained the ability to see shapes and numbers on the left; vision remained stable in the right eye following corticosteroid therapy. Her initial investigations also revealed significant pancytopenia and macrocytic anemia (Table 2), which markedly improved with vitamin replacement.

## Case 2

A 17-year-old African American male had a history of obesity and 30 lb weight loss in the setting of poor oral intake and vomiting from cholelithiasis and recent laparoscopic cholecystectomy. In the first 10 days following surgery, he developed generalized weakness as well as progressive lower extremity weakness along with multimodality sensory deficits. An initial neurologic exam revealed 2/5 lower extremity strength, areflexia, loss of proprioception and vibration senses, as well as reduced sensation to light touch. Given the motor and sensory exam findings, there was initial concern for Guillain Barre syndrome (GBS), prompting treatment with intravenous immunoglobulin (IVIG) 2 g/kg over 5 days. Nutrition was also consulted on admission, with resultant diet recommendations:

Calories: 3110 to 3530 kcal/day (37-42 kcal/kg IBW) [DRI 37]

Protein: 101 to 126 g/day (1.2-1.5 g/kg IBW)

Fluid: D5NS + KCl 20 mEq/L 200 mL/h

On the third day of admission, the patient was noted to have bilateral horizontal nystagmus and ophthalmoparesis most noticeable on extreme lateral gaze in the left eye. He also developed upper extremity ataxia, including dysmetria and tremor more noticeable on the left side as well as mild left-sided ptosis. His mental status exam revealed some difficulties with attention. He demonstrated normal spelling of short words and naming of months, but he had difficulty with spelling words backward as well as digit span. With the additional cranial nerve findings and some degree of encephalopathy, Miller Fisher syndrome and Bickerstaff encephalitis were also considered.

The patient had a normal brain MRI 1 month prior to this hospitalization. An MRI of the entire spine was performed to rule out myelopathy and nerve root enhancement. Serum B12 and copper levels were normal. Repeat brain MRI and lumbar puncture (LP) were performed to rule out autoimmune etiologies. Cerebrospinal fluid (CSF) revealed albuminocytologic dissociation (CSF protein 110 mg/dL), which supported the

**Table 1.** Laboratory test results for case 1.

Vitamins	Range and units	Presentation	2 months	6 months
Vitamin B12	180-914 pg/mL	84	650	1363
Vitamin A	0.20-0.50 mg/L	<0.06	0.7	0.71
Retinyl Palmitate	0.00-0.10 mg/L	<0.02	0.04	<0.02
Vitamin B1	70-180 nmol/L	47	-	122
Vitamin C	23-114 µmol/L	<5	-	-
Zinc	60-120 µg/dL	47.8	68.6	-
Folate	>5.8 ng/mL	5.1	>20	>20
Vitamin E (gamma tocopherol)	0.0-6.0 mg/L	1.2	-	-
Vitamin E (alpha Tocopherol)	5.5-9 mg/L	4.7	-	-
Vitamin D 25 Hydroxy	20-120 ng/mL	46.60	-	25.78
Copper	64-1332 µg/dL	55.4	-	-



**Figure 1.** MR brain FLAIR weighted imaging sagittal view demonstrating solitary focus of subcortical white matter signal change in the left temporal tip.

diagnosis of GBS. However, MR brain was characteristic of Wernicke encephalopathy (Figure 4). His vitamin B1 level was also very low (value 23; normal 70-180 nmol/L). He was started on replacement therapy (vitamin B1 250 mg IV TID  $\times$ 3 days, then 250 mg IV daily  $\times$ 5 days). Following B1 replacement, the patient's ophthalmoparesis, sensory ataxia, and lower extremity sensory changes significantly improved. He showed improvement in lower extremity strength as well.

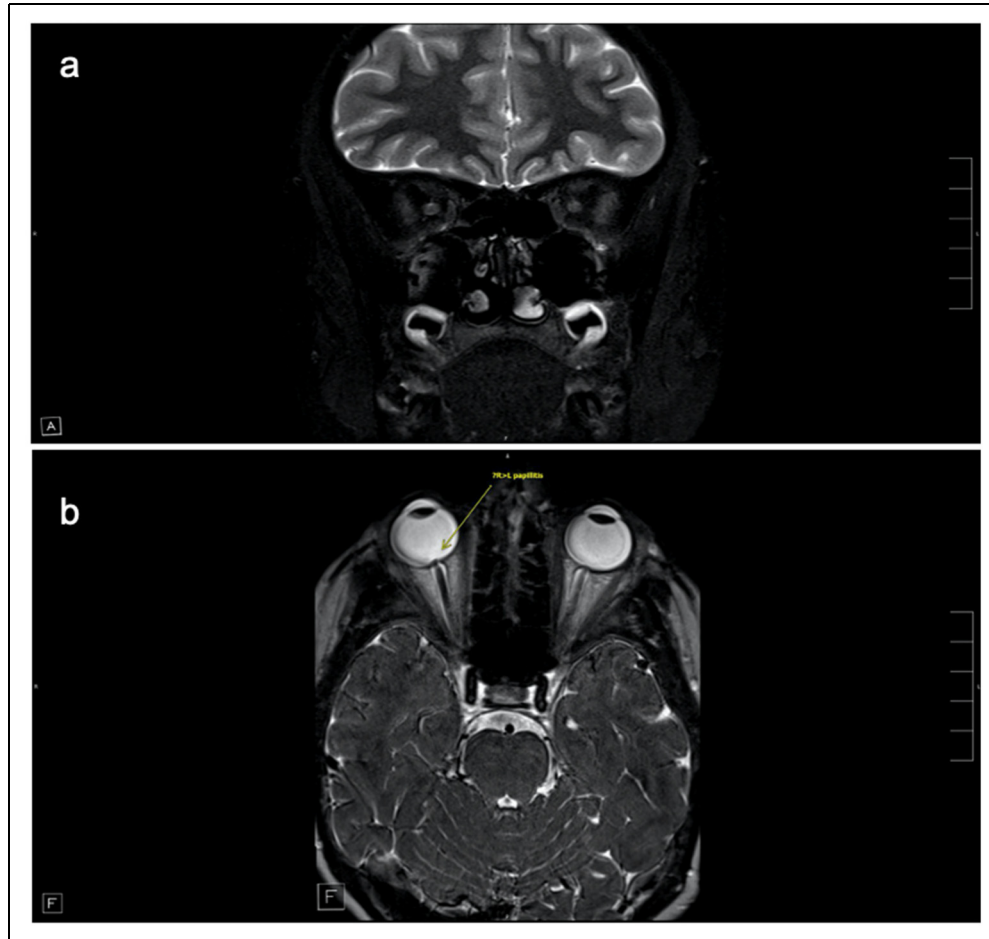
## Discussion

These 2 cases emphasize the importance of knowing the risk factors and presentations of vitamin deficiencies in neurology. In particular, the signs and symptoms of vitamin A, thiamine, and B12 deficiencies are illustrated by the 2 patients above. As a preface to the discussion below, clinicians who suspect nutritional deficiency may consult the NIH Dietary Supplement Fact Sheets (<https://ods.od.nih.gov/factsheets/list-all/>).

## Vitamin A Deficiency

Vitamin A is a fat-soluble vitamin involved in many biochemical processes. It is best known for its role in vision, with one of the earliest symptoms of vitamin A deficiency being night blindness given its role in the regeneration of rhodopsin. It is critical for differentiation of the stratified squamous epithelium of the ocular surfaces. Thus, deficiency of vitamin A can lead to xerophthalmia as well. Night blindness is often the first symptom, but it progresses to atrophy of the mucosal ocular surface with appearance of glistening white plaques of desquamated epithelium (Bitot spots) then keratinization of the cornea. Vitamin A also functions in epithelial integrity in other organs, preservation of immune competence, hematopoiesis, and bone growth.<sup>1</sup>

Because of its role in maintaining epithelial integrity, vitamin A deficiency can result in disruption of the lining of the urinary, gastrointestinal, and respiratory tracts in addition to the surface of the eye.<sup>2</sup> These impairments in epithelial



**Figure 2.** Coronal (a) and axial (b) T2 weighted imaging of optic nerve demonstrating increased T2 signal in the optic nerves and prominent right greater than left optic disk (marked with arrow), respectively.

integrity as well as immune dysfunction often led to frequent urinary and respiratory tract infections. Interestingly, in developing countries when vitamin A deficiency in children and pregnant females was treated, all-cause mortality decreased

by roughly one-third, illustrating the importance of vitamin A *beyond* vision.<sup>3</sup>

Other pathologies that occur with vitamin A deficiency include anemia<sup>4</sup> and bony overgrowth.<sup>5</sup> In developed countries,



**Figure 3.** Dilated fundus color photos of the patient depicting bilateral optic disc edema with faint retinal pigment epithelium changes.

**Table 2.** Laboratory test results for case 1.

CBC/ Differentials	Ref range and units	Presentation	2 months	6 months
WBC	4.5-13.5 THOU/CUMM	2.5	6.4	4.5
RBC	4.00-5.20 X10E6/UL	2.15	3.98	4.77
Hb	11.5-15.5 G/DL	7.5	12.7	14.2
Hct	35.0-45.0%	18.6	37.1	42.2
MCV	77.0-95.0 FL	99.8	93.1	88.3
MCH	25.0-33.0 PG	34.8	31.9	29.7
MCHC	31.0-37.0 G/DL	34.9	34.3	33.6
RDW	11.0-14.0%	18	13.7	13.2
Platelet count	150-450 THOU/CUMM	142	290	251

vitamin A deficiency and malnutrition from lack of food are rarer. Other risk factors must be considered. Liver disease and/or malabsorption from celiac disease, inflammatory bowel disease, and pancreatic disorders (eg, cystic fibrosis) can result in an inability to absorb fat-soluble vitamins, like vitamin A.<sup>6</sup> Risk factors for vitamin A deficiency include pregnancy,<sup>7</sup> alcoholism,<sup>8</sup> intestinal surgery,<sup>9-11</sup> cystic fibrosis,<sup>12</sup> liver disease,<sup>13</sup> and malnutrition from any cause.<sup>6</sup> Vitamin A deficiency in the developed world is uncommon, unless associated with significant malnutrition or weight loss in the settings of strict diet or bariatric surgery, among other contexts. All fat-soluble vitamins should be measured in patients who have undergone gastric bypass surgery, and deficiency should be suspected in those with evidence of protein-calorie malnutrition.<sup>14</sup>

Foods rich in Vitamin A include liver, egg yolk, whole milk, and dairy products (particularly butter). Historically, the substitution of butter in place of margarine by the Danes in War World I caused the incidence of xerophthalmia to plummet, leading to the discovery that vitamin A supplementation could treat this disorder. Butter was used as the primary source of fat due to blockade by German U-boats (preventing its export for sale) and served as a good source of vitamin A where the previously used margarine was not.<sup>3</sup>

There are multiple cases of vitamin A deficiency presenting with vision loss in adolescents—similar to our patient who had highly selective eating habits—often associated with anorexia, anxiety over food allergies, autism, and extreme diets. Such diets are often comprised of mostly carbohydrates, such as potatoes (fries, chips), pretzels, and large amounts of vegetable lipids. These have been called “cafeteria diets.” The literature shows that selective eating habits have also been deemed a cause of vitamin A deficiency in children and adolescents.<sup>15</sup>

Simkin et al reported the case of a 16-year-old male who had restricted his diet to white bread and French fries, driven by his anxiety over his peanut and dairy allergies. He developed progressive nonpainful vision loss, recurrent infections (perirectal abscess, urinary tract infection (UTI)), and xerophthalmia. His deficiency was not recognized for 2 years; he suffered nutritional optic neuropathy (NON) as well as bilateral facial palsies. He underwent an extensive neurologic evaluation, similar to our patient above. Later he was documented to have multiple vitamin deficiencies and responded to vitamin supplementation.<sup>16</sup>

Kinlin et al reported a 10-year-old male with autism spectrum disorder whose diet consisted of popcorn, French fries, soft drinks, and chocolate bars. He presented for drastic sudden loss of visual acuity requiring him to hold the wall during ambulation as a compensatory behavior. He was later found to have deficiencies of both A and D vitamins. His signs and symptoms improved with vitamin A supplementation.<sup>17</sup>

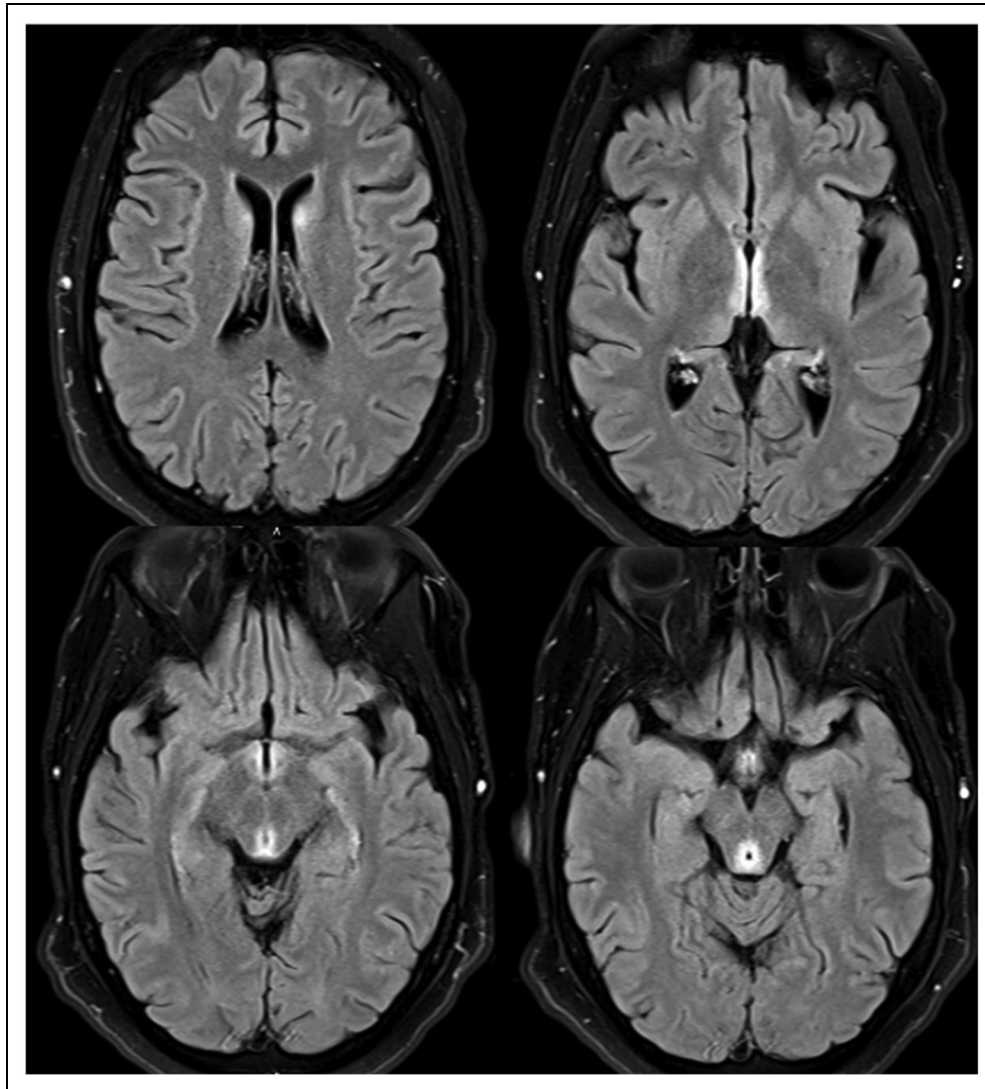
Chiu and Watson reported the case of a 12-year-old male with autism who developed a right-sided optic neuropathy at the age of 9 years, attributed initially to “Epstein Barr infection.” His diet consisted only of “hot chips and nuggets.” Examination revealed severe visual loss, bilateral corneal, and conjunctival keratinization and marked pallor of his optic nerves. He was found to have a vitamin A deficiency and supplementation reversed the corneal and conjunctival keratinization. However, visual acuity was not recovered. The authors attributed the optic neuropathy to bony overgrowth from Vitamin A deficiency. Unfortunately, serum levels of B-complex vitamins were not reported. Chiu and Watson also reviewed 5 other cases of children with autism and vitamin A deficiency, with similar findings of restricted diet—usually some combination of potatoes, rice, pretzels, snack mix, cookies, and muffins.<sup>18</sup>

Martini et al reported the case of a 5-year-old girl who presented with fever and severe keratoconjunctivitis as well as a history of photophobia and epiphora. Physical exam revealed bilateral conjunctivitis and purulent discharge, thin scalp hair, dystrophic skin covered with lanugo and diffuse muscle atrophy. Her weight and height were less than the third percentile for age. Laboratory evaluation revealed moderate anemia as well as pyuria, bacteriuria, and squamous cells in the urine. Her diet consisted mainly of oat milk for the preceding 2 years, which is relatively low in protein, low in vitamin A, and high in carbohydrate. She was ultimately diagnosed with vitamin A deficiency. Supplementation with vitamin A and a more balanced diet led to resolution of many of her symptoms, albeit her vision remained impaired due to a combination of *irreversible* retinal atrophy and ocular infection complicated by corneal thinning.<sup>19</sup>

We must emphasize that the common features of the diets above are high amounts of simple carbohydrates (sugars) and low amounts of protein (energy-rich, nutrient-poor diets). Micronutrient deficiencies are rare in developed countries but prevalent in developing countries. Individuals in developed countries may not meet micronutrient intake requirements from food alone, presumably due to consumption of energy-rich, nutrient poor diets. For example, dietary surveys indicate that 43% of the US population does not consume the recommended daily amount of vitamin A.<sup>20</sup>

Even when accounting for vitamin A from fortified foods, which is significant, 51% of adults fall short of the estimated average requirement. In contrast, more than 94% of children and adolescents (ages 2-18 years) receive vitamin A at or above the required amount daily. Fortified, ready-to-eat cereal and fortified milk are important sources of vitamin A in pediatric patients.<sup>21</sup>

Patient 1 presented with symptoms of vitamin A deficiency, including recurrent urinary tract infections, conjunctivitis, and



**Figure 4.** MRI brain FLAIR-weighted imaging axial view demonstrating abnormal signal changes in the caudate nucleus bilaterally, mesial/posterior thalamus bilaterally, periventricular region around the third ventricle, and periaqueductal gray matter.

dry skin with exam findings that supported poor epithelial function, like bilateral keratinized conjunctivae, severely dry eyes, and Bitot spots on the cornea. She was also found to have megaloblastic anemia and pancytopenia, suggestive of concurrent vitamin B12 deficiency. She also presented with progressive painless unilateral central vision loss and bilateral papilledema with radiologic findings consistent with bilateral optic neuritis. This finding is difficult to attribute directly to vitamin A deficiency. The etiologies of optic neuropathy are manifold; they include inflammatory, infectious, toxic/metabolic, and hereditary causes.

When caused by infectious or inflammatory disease, optic neuropathy characteristically presents as subacute, unilateral, *painful* vision loss. However, one should also consider dietary, toxic, and metabolic etiologies when there is a subacute progressive painless vision loss.<sup>22</sup> There is a small percentage (8% in the Optic Neuritis Treatment Trial) of inflammatory

optic neuritis that has presented with painless vision loss in the literature.

Nutritional optic neuropathies are characterized by slowly progressive, *painless*, bilateral vision loss without an afferent pupillary defect because of the symmetric nature of optic nerve involvement.<sup>22,23</sup> This condition should be considered especially when a central or cecentral visual field defect (defect extends from central vision to the natural blind spot) and disturbances of color vision are present. Unilateral vision loss is unusual for a strictly NON. Early in the disease, optic nerves usually appear normal or, on occasion, only slightly hyperemic. Continued nutrient deficiency can cause the gradual development of bilateral temporal optic disc pallor due to injury of ganglion cell axons specifically in the papillo-macular nerve fiber bundle. This damage eventually leads to diffuse pallor of the optic disc.<sup>22,24</sup> The vision impairment in nutritional optic neuropathies, when treated, gradually recovers

over several weeks to months with the risk of permanent residual deficit. Although full recovery is expected in nutritional optic neuropathies, the overall outcome depends on the etiology and comorbidities as well as duration of nutrient deficiency and residual neuronal integrity. Full recovery is unlikely after temporal optic disc pallor is observed on exam, reflecting injury of the papillomacular bundle. Early intervention with dietary supplementation can reverse existing visual loss and prevent further progression.<sup>25,26</sup>

Our patient had signs of optic neuropathy as manifested by increased signal in the optic nerves and decreased visual acuity and color vision. These findings led the referring ophthalmologist to consider autoimmune optic neuritis and suggest corticosteroid therapy. Certainly, female sex and age put the patient in a higher risk category for autoimmune disease, but the associated vitamin deficiencies suggested that she had NON. Corticosteroids are the treatment of choice for inflammatory optic neuropathies, given their anti-inflammatory properties. In nutritional optic neuropathies as well as other neuropathies, the use of steroids is more controversial. Studies have shown that despite the initial noninflammatory mechanism of injury, the course of disease may be compounded by secondary injury due to *resultant* inflammation. Corticosteroid therapy has been studied in other noninflammatory optic neuropathies, such as ischemic neuropathy, with inconclusive results.<sup>27</sup> Given current knowledge, there has been no study investigating steroid therapy for nutritional optic neuropathies. The treatment is usually limited to nutritional repletion and supplementation.

### Vitamin B12

Vitamin B12 is an essential, water-soluble vitamin and an important cofactor for many biochemical reactions. It is found naturally in meat and foods of animal origin but not in fruits and vegetables. Vitamin B12 derivatives are also called cobalamins. An acidic environment in the stomach is required for the release of cobalamin from food protein.<sup>28</sup>

Physiologically, vitamin B12 functions in the regulation of homocysteine, hematologic development, and the nervous system; specific processes that require B12 are erythropoiesis, synthesis and maintenance of the myelin sheath, and the synthesis of deoxyribonucleic acid (DNA). B12 deficiency clinically presents with hematologic, gastrointestinal, and neuropsychiatric manifestations.<sup>28</sup>

Hematologic disease from vitamin B12 deficiency results from asynchrony between cytoplasmic and nuclear maturation. Manifestations include macrocytosis, immature nuclei, and hypersegmented neutrophils.<sup>20</sup> Anemia, leukopenia, thrombocytopenia, or pancytopenia may be observed as well.<sup>25,29</sup> Neurologic manifestations may be the earliest and only manifestation of vitamin B12 deficiency.<sup>30</sup> The commonly recognized neurologic findings may include a myelopathy with or without an associated neuropathy, optic neuropathy (impaired vision, optic atrophy, centrocecal scotomas), paresthesias without abnormal signs, and neuropsychiatric disturbances.

The best characterized neurologic manifestation of vitamin B12 deficiency is a myelopathy that has commonly been called subacute combined degeneration.<sup>25</sup>

Clues to possible vitamin B12 deficiency in a patient with polyneuropathy include a relatively sudden onset of symmetric sensory and motor symptoms, concomitant involvement of upper and lower extremities, and the presence of risk factors for vitamin B12 deficiency or laboratory evidence of B12 deficiency.

Neuroimaging studies, including T2-weighted MRI of the spine, reveal lesions classically involving the posterior and lateral columns, predominantly in the upper thoracic and mid-thoracic regions. These lesions result in concomitant upper and lower extremity involvement and less commonly subcortical white matter.<sup>25</sup>

Neuropsychiatric manifestations of vitamin B12 deficiency include impaired memory, personality changes, emotional lability, psychosis, and rarely delirium or coma. These neuropsychiatric manifestations may be seen in patients *without* hematologic manifestations or low B12 levels.<sup>31</sup>

Another rare complication of vitamin B12 deficiency is optic neuropathy which occurs in <1% of B12-deficient patients.<sup>32</sup> The optic neuropathy presents as progressive, bilateral, painless vision loss that is often associated with reduced color vision and central or cecentral scotomas. The optic nerve may appear normal in the early stages of disease until optic atrophy develops.<sup>22</sup> Optic neuropathy as a presenting symptom of B12 deficiency has been described in a few cases where supplementation partially reversed these manifestations.<sup>33–35</sup> In NON, experts believe that malnutrition reduces the threshold of the optic nerve to resist otherwise tolerable exposure to toxins such as alcohol and tobacco. It is often associated with a peripheral neuropathy. The most commonly cited micronutrients are B12, thiamine, and copper, but others appear to contribute as well. Vitamin B12 is particularly important in the detoxification of cyanide, which is present in tobacco smoke. The Cuban epidemic of optic neuropathy in the 1990s was thought to be partially due to the continued access to alcohol and tobacco during the sudden cessation of trade with Eastern Europe, following the collapse of the Soviet Union, which led to lack of access to animal protein, fruits, and vegetables. This epidemic of optic neuropathy resolved once MVIs were distributed. B12 is thought to be particularly important in optic neuropathy and B12 supplementation is suggested even in those cases with normal serum B12 levels.<sup>36</sup>

Chavala et al reported that deficiency of vitamin B12 can cause impaired color vision and centrocecal scotomas as part of an optic neuropathy.<sup>37</sup> Areekul et al reported similar manifestations in a patient with vitamin B12 deficiency due to massive, small bowel resection, and significant weight loss.<sup>38</sup> Pineles et al reported 3 children with autism whose diets were quite restrictive, without meat or dairy products, resulting in B12 deficiency and optic neuropathy.<sup>34</sup>

Dietary B12 is obtained primarily from animal protein, such as meat and dairy. Any diet or condition that restricts these products elevates the risk of B12 deficiency (eg, veganism, autism). Other factors include gastritis, achlorhydria, antacids,

gastric surgery (eg, bariatric surgery), previous small bowel surgery (eg, ileum resection), inflammatory bowel disease, and pernicious anemia.<sup>36</sup>

B12 is rarely the only vitamin that is deficient in NON. It is thought that B1 (thiamine), B2 (riboflavin), B3 (niacin), B6 (pyridoxine), B9 (folic acid), and B12 (cobalamin) all play a role in NON, with B1, B9, and B12 playing major roles.<sup>26</sup> In our patient, we made the diagnosis of NON, as there were *multiple* micronutrient deficiencies; we did not suspect that a single vitamin deficiency was the *sole* reason for the patient's optic atrophy.

### Vitamin B1 Deficiency

Thiamine serves as a cofactor for many enzymes. Several of these enzymes are involved in energy metabolism and housed within the mitochondrion. Other B1 enzymes are involved in the biosynthesis of nucleic acids. The brain is *highly* vulnerable to thiamine deficiency because it has high energy demands; the brain relies heavily on ATP generation through mitochondrial pathways.<sup>39</sup>

After thiamine is absorbed, it is phosphorylated into thiamine diphosphate (TDP). TDP is the active form of thiamine which is mostly present in erythrocytes; it is not detectable in plasma or serum. Thiamine status was previously assessed indirectly by measuring the transketolase activity. The decreased enzyme activity was presumed a consequence of decreased thiamine. However, transketolase activity was found to be nonspecific, as other factors may decrease the enzyme activity as well. The current, most sensitive method to assess thiamine status is whole blood thiamine testing in which TDP is measured with liquid chromatography-tandem mass spectrometry.<sup>40</sup>

Thiamine is readily available in many foods, including whole grains, meats, and fish. Dairy products, green vegetables, and most fruits contain little thiamine, but with the advent of industrial food processing, thiamine is often depleted by heat and/or sulfur dioxide during processing. In developing countries, the reliance on rice, which is depleted of thiamine, leads to thiamine deficiency in an estimated 15% of adolescents.<sup>39,41,42</sup> Thiamine deficiency is also exacerbated by excessive caffeine and chocolate consumption (both inactivate thiamine), gastrointestinal surgery (eg, bariatric surgery), and gastrointestinal diseases like chronic diarrhea and inflammatory bowel disease. Thiamine stores can be depleted in as little as 4 weeks. Lactation also increases the need for thiamine and breastfeeding infants are at risk of deficiency if their mothers are thiamine deficient.<sup>25,42</sup>

Thiamine deficiency is thought to be much more common than recognized. Disease in patients *without* alcoholism may be especially underrecognized. Cases have been reported in the settings of nutritional deficiency such as excessive vomiting (eg, hyperemesis gravidarum),<sup>43</sup> malignancy, intestinal obstruction, and TPN without thiamine supplementation.<sup>44</sup> Many of these cases, like ours, were associated with characteristic radiologic lesions in structures around the third ventricle, cerebral aqueduct, and fourth ventricle, including the dorsomedial thalamus, ocular motor nuclei, vestibular nuclei, locus ceruleus, and periaqueductal gray.<sup>44</sup>

Clinical signs include ocular findings (classically ophthalmoplegia), mental status changes, and gait ataxia. These findings are not unexpected given the involvement of structures in the midbrain and brainstem. Reliance on recognizing the classic triad of ophthalmoplegia, gait ataxia, and mental status changes may easily delay diagnosis, and more subtle signs—ptosis, horizontal nystagmus, and abducens palsy in the setting of mild confusion—should raise suspicion of possible thiamine deficiency.<sup>25</sup>

“Dry beriberi” has been previously described as a manifestation of thiamine deficiency, characterized by rapidly progressive sensorimotor neuropathy with predominantly large-fiber sensory loss. Dry beriberi is often associated with Wernicke encephalopathy and Korsakoff syndrome.<sup>45</sup> The central nervous system is more likely to be affected when the thiamine deficiency is severe and abrupt, whereas the peripheral nerves are usually impaired by an insidious, longer term thiamine deficiency. Cardiac muscle, which also has high energy demands, is affected by thiamine deficiency as well. “Wet beriberi” classically presents as high-output heart failure with concomitant peripheral edema.

A high suspicion for thiamine deficiency is necessary before the provision of carbohydrate, as thiamine is a necessary vitamin for carbohydrate metabolism. Consequently, thiamine is often given prophylactically prior to dextrose-containing IV fluids in high-risk populations.<sup>25</sup> Patients with alcohol use disorder constitute a well-known group at risk of thiamine deficiency. Patients with significant recent weight loss or inadequate nutrient intake should be considered high-risk as well.

Patient 2 initially presented with ascending lower extremity weakness and paresthesias, then later developed ophthalmoparesis and encephalopathy. CSF findings suggestive of GBS prompted initial treatment with IVIG. However, additional neurologic exam findings expanded the differential diagnosis and prompted further imaging, which led to the final diagnosis of thiamine deficiency.

We suspect that our patient developed acute peripheral neuropathy and Wernicke encephalopathy simultaneously due to underlying thiamine deficiency, worsened by administration of dextrose after prolonged starvation associated with a 30 lb weight loss in 1 month. Although the patient was not evaluated for thiamine deficiency in prior hospitalizations, we suspect subacute thiamine deficiency given involvement of *both* central and peripheral nervous systems. One's thiamine requirement is related to total caloric intake, especially the proportion of carbohydrate relative to protein and fat. High carbohydrate diets can precipitate symptoms of thiamine deficiency. Given the short half-life of thiamine and lack of significant body stores, a continuous dietary supply of thiamine is necessary.

Signs and symptoms of dry beriberi can mimic those of autoimmune neurologic diseases, like GBS and its variants. The distinction between dry beriberi and GBS can be difficult, as there is often overlap in the presenting symptoms and diagnostic features. Both GBS and dry beriberi can lead to peripheral sensorimotor polyneuropathy as well as albuminocytologic dissociation in the CSF.<sup>45</sup>

Wernicke encephalopathy is characterized by subacute onset of the classic triad of ophthalmoplegia, gait ataxia, and mental status



changes. However, the triad is frequently incomplete. Ocular abnormalities include nystagmus (more often horizontal than vertical), ophthalmoparesis (commonly lateral rectus involvement), and conjugate gaze palsies (usually horizontal). The gait and truncal ataxia are due to cerebellar and vestibular dysfunction and may be compounded by a coexisting peripheral neuropathy. Mental status changes include poor concentration, apathy, delirium, and frank psychosis (eg, delusions, hallucinations).<sup>25</sup>

Wernicke encephalopathy is largely a clinical diagnosis. However, MR features may support thiamine deficiency, including increased T2 or FLAIR signal in the paraventricular regions: thalamus, hypothalamus, mammillary body, periaqueductal midbrain, tectum, pons, fourth ventricle floor, medulla, midline cerebellum, and (rarely) splenium of the corpus callosum or basal ganglia.<sup>46,47</sup> The pathologic changes on MRI require time to develop, as demonstrated by our patient who had a normal brain MRI prior to his recent cholecystectomy.

Relatively rapid clinical improvement with thiamine supplementation also supports the diagnosis of thiamine deficiency in our patient. Ocular signs can improve promptly, but fine horizontal nystagmus may persist. Improvement in gait ataxia and memory is often delayed. Mental status improves over weeks. Recovery of consciousness may be observed even in patients in a deep coma.

## Conclusion

The central and peripheral nervous systems are both vulnerable to nutritional deficiencies. Multiple nutrient deficiencies often coexist and exhibit myriad clinical symptoms. Moreover, the clinical features of nutritional deficiencies can overlap with other neurologic diseases, confounding their recognition. Early detection, prompt and adequate provision of vitamin replacement as well as appropriate proportions of dietary carbohydrate/fat/protein are crucial to prevent irreversible neurologic damage.

Neurologic symptoms occur late in malnutrition and can be insidious. Likewise, the initial signs of nutritional deficiencies may go unnoticed or lead to misdiagnosis. The 2 patients above exhibit the common neurologic presentations of visual loss and lower extremity weakness which have been associated with underlying nutritional deficiencies. Attention to the dietary history, an awareness of the risk factors, and clinical significance of nutrient deficiencies can result in more timely diagnoses and effective treatment.

## Author Contributions

Bedirhan Tarhan, Sydur Rahman: Conceptualization, Investigation, Writing - original draft. Nancy Joseph, Douglas Hyder, Carla Zingariello, John Sladky: Writing - review & editing. S. Parrish Winesett: Conceptualization, Investigation, Writing - review & editing.

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## Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

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