

Leukoencephalopathy associated with cobalamin deficiency

Article abstract—Patients with cobalamin deficiency may experience cognitive impairment or neuropsychiatric symptoms. Although abnormalities of central myelin are the presumed cause of these manifestations, there is a paucity of reports of white matter lesions as shown on neuroimaging studies, and the effects of cobalamin replacement on these lesions are not known. We report a man with subacute cognitive impairment associated with cobalamin deficiency and remarkable confluent white matter abnormalities on MRI, confirmed by biopsy. With cobalamin replacement, both his cognitive deficits and imaging abnormalities partially resolved. This case indicates that leukoencephalopathy, in the absence of anemia or myelopathy, should be added to the spectrum of disorders associated with cobalamin deficiency. Early detection and treatment may be associated with a greater potential for recovery.

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Cobalamin (vitamin B₁₂) deficiency may produce cognitive and neuropsychiatric manifestations.^{1,2} The symptoms, which may be subtle and arise from atypical causes of cobalamin deficiency,³ are assumed to be reversible and produced by white matter abnormalities. Despite the presumed central myelin etiopathogenesis of cognitive impairment in this disorder,³ white matter abnormalities on brain imaging are rarely reported,⁴ and the effects of cobalamin replacement therapy on such structural abnormalities are not known. We describe a patient with cobalamin deficiency who presented with subacute onset of cognitive impairment and marked white matter abnormalities on brain MRI and report the changes in both his cognitive abilities and MRI in response to therapy.

Case report. A 76-year-old right-handed man with a history of hypertension, atrial fibrillation, hypothyroidism, and remote colon cancer was admitted because of a 6-month history of increasing forgetfulness, reading difficulty, and problems balancing his checkbook. He also complained of headaches, fatigue, weight loss, visual impairment, and gait abnormalities. His medications included enalapril, digoxin, warfarin, levothyroxine, and allopurinol. He had no history of tobacco or alcohol use.

An initial mental status examination revealed a forward span of six digits and an inability to count backwards or state the days of the week backwards. He was unable to remember any of three words or any of 10 items in a short story after a delay. Spontaneous speech, naming, and repetition were normal. He could not count identical dots arrayed randomly in front of him or copy intersecting pentagons or a cube. Visually guided limb movements were slow but accurate, and his praxis performance of transitive limb gestures to command was normal. He had bilateral plantar extensor reflexes and a cautious gait that appeared to be due to his visual disturbance. He was spatially disoriented and unable to find the door of his room from his bed. Of note, his visual acuity was 20/25 on the right and 20/20 on the left, and his tongue, muscle tone and strength, reflex, sensory, and coordination examinations were normal. Ini-

tial neuropsychological testing⁵ was notable for mild general cognitive impairment (Mattis dementia rating scale, 124), severe nonlateralized deficits in visual attention (Mesulam cancellation tasks), attention and concentration (4%) and visual memory deficits (<1%) on the Wechsler memory scale-revised (WMS-R), and visual form perception deficits on the Benton visual form discrimination (BVFD) test (<1%). He had moderate impairment of the abilities to acquire verbal material and to recall these after a delay (California verbal learning test). Naming (Boston naming test) was normal. He endorsed symptoms of mild depression on the Beck depression inventory.

Laboratory evaluation revealed a low vitamin B₁₂ (78 pg/ml; normal, 205–700 pg/ml) level. The following tests were normal: serum chemistries (SMA-18), complete blood count (hemoglobin, 15.9 gm/dl; hematocrit, 46%; mean corpuscular volume, 91 fl), thyroid function tests, sedimentation rate, C-reactive protein, rapid plasma reagin, human immunodeficiency virus, antinuclear antibodies (homogenous, 1:20; speckled, 1:80), and Sjögren antibodies. CSF analysis was only notable for a protein level of 111 mg/dl. CSF cytology, stains, and cultures (bacterial, fungal, acid-fast bacilli) were negative. Brain MRI revealed predominantly bilateral temporo-occipital and parieto-occipital high-intensity changes on T₂-weighted images that did not enhance with gadolinium contrast (figure 1). The Schilling test, EEG, and four-vessel cerebral angiogram were normal. Stereotactic brain biopsy revealed gliosis and edema with vacuolization of axonal sheath myelin (figure 2). Immunocytochemistry did not reveal evidence of progressive multifocal leukoencephalopathy. Cyanocobalamin supplementation (1000 µg IM every month) was the only treatment begun.

On followup examinations at 9 weeks and 10 months after discharge, he reported feeling better. His mood, appetite, and energy levels had improved. He no longer had headaches and was now able to read, although his wife noted persistent memory difficulties. He had a digit span of six digits forward, was able to repeat and remember 9 of 10 items on a short story, and was able to draw intersecting pentagons and a cube. His spatial scanning had improved, as evidenced by normal dot counting. He was no longer spatially disoriented. With the exception of a mildly

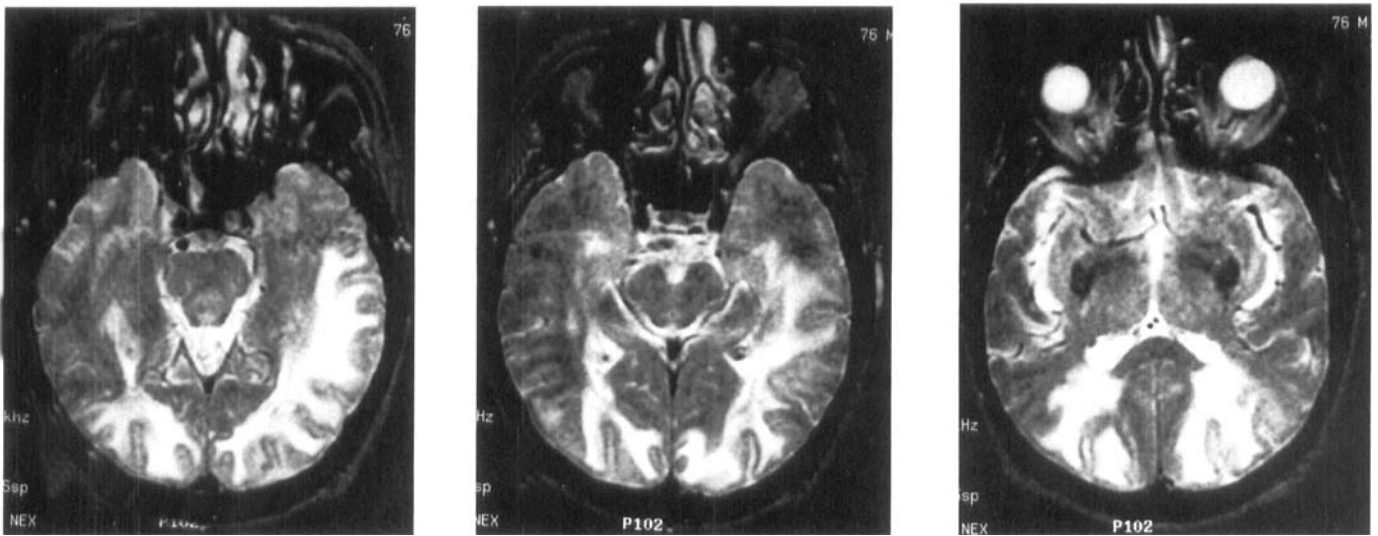


Figure 1. T₂-weighted MRI showing significant leukoencephalopathy involving right more than left posterior white matter regions.

cautious gait and a left plantar extensor response, his neurologic examination, including optokinetic nystagmus response, was normal. Neuropsychological testing⁵ 10 months after discharge revealed a Mattis dementia rating scale of 127. His WAIS-R verbal IQ was estimated at 106. He showed improvement in measures of attention and concentration (61%), verbal acquisition, visual memory (13%) on WMS-R, and visual form perception (12%) on the BVFD test. Verbal memory continued to be significantly impaired. His vitamin B₁₂ level 9 weeks after discharge was 1167 pg/ml. A followup brain MRI scan revealed considerable resolution of white matter changes in the inferoposterior aspect of both hemispheres (figure 3).

Discussion. Cognitive impairment associated with cobalamin deficiency, in the absence of the more typical myelopathy or macrocytic anemia, is becoming increasingly recognized.¹ The normal Schilling test

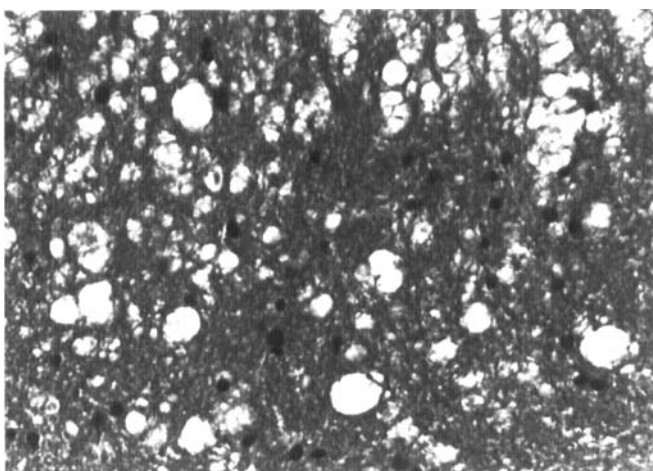


Figure 2. Diffuse white matter vacuolization with gliosis and myelin sheath swelling (hematoxylin and eosin, $\times 4600$, before 51% reduction).

in our patient suggests a food cobalamin absorption defect, and places him in the unusual category of patients with a subtle expression and an atypical etiology of cobalamin deficiency.³ He had partial resolution of cognitive impairment and MRI abnormalities after cobalamin replacement. His cognitive impairments were most notable for problems with attention and working memory, verbal memory, and visuospatial processing. With cobalamin replacement, his attention and working memory improved, as did some aspects of visuospatial processing. His verbal memory remained significantly impaired.

The pathogenesis of the neurologic abnormalities associated with cobalamin deficiency is not well understood. However, abnormalities of myelin are thought to be causative. Because myelin replacement is heavily dependent on fatty acid synthesis, the integrity of two cobalamin-dependent enzymes involved in fatty acid metabolism is implicated.¹ Impairment of methylmalonyl-coenzyme A (CoA) mutase results in accumulation of propionyl CoA, which is thought to replace succinyl CoA and acetyl CoA as substrates in the synthesis of fatty acids leading to the formation of anomalous fatty acids. Impairment of methionine synthase activity affects essential methylation reactions and may cause cerebral myelination defects in patients with inherited disorders selectively affecting activity of this enzyme.³ These effects on methylation reactions may reduce the supply of adenosylmethionine and interfere with protein and neurotransmitter synthesis, although the specific clinical consequences of such defects are unclear.³ Older reports describe scattered areas of vacuolization within the central myelin of patients with cobalamin deficiency.^{6,7} Similar pathologic changes are present in primate models⁸ and were seen in the brain biopsy of our patient. The

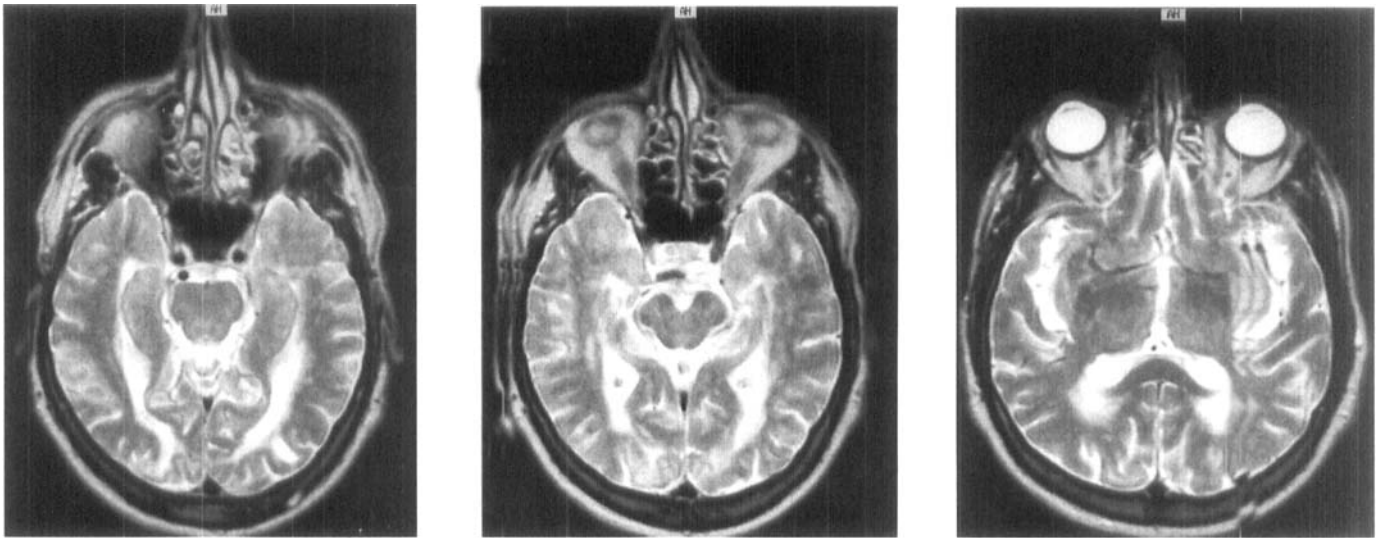


Figure 3. T_2 -weighted MRI showing partial resolution of leukoencephalopathy after cobalamin replacement therapy.

single other MRI report of cobalamin deficiency demonstrated only nonspecific periventricular hyperintensities.¹ We are unaware of any cases reported with confluent white matter changes that were followed by partial resolution of cognitive impairment and imaging abnormalities after treatment.

Our observations extend the spectrum of cobalamin deficiency-associated neurologic abnormalities (in the absence of macrocytic anemia or clinical myelopathy¹) to include significant leukoencephalopathy. The partial resolution of symptoms in our case, similar to other reports,^{2,9} suggests that early detection and treatment of such patients with white matter abnormalities may critically affect their response to treatment. Clinicians should consider subtle and atypical cobalamin deficiency states in evaluating a wide range of cognitive and neuropsychiatric symptoms.

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