

Vitamin B₁₂ Deficiency With Bilateral Globus Pallidus Abnormalities

Anjail Z. Sharrief, MD; Joel Raffel, MD; David S. Zee, MD

Objective: To describe a case of vitamin B₁₂ deficiency with classic and rare clinical features and novel radiographic features.

Design: Case report.

Setting: Johns Hopkins Hospital neurology service.

Patient: Middle-aged man with neuropathy, myelopathy, impaired cognition, and extrapyramidal signs.

Results: The patient had neurologic and hematologic signs of vitamin B₁₂ deficiency, with elevated methylma-

lonic acid and homocysteine levels. Brain magnetic resonance imaging showed signal abnormality in the globi pallidi, as can be seen in inherited methylmalonic acidemia. The clinical and radiographic findings reversed with vitamin B₁₂ administration.

Conclusion: Vitamin B₁₂ deficiency can present with extrapyramidal symptoms and reversible bilateral globus pallidus abnormalities.

Arch Neurol. 2012;69(6):769-772. Published online February 13, 2012. doi:10.1001/archneurol.2011.1084

COBALAMIN (VITAMIN B₁₂) deficiency is one of the most easily treated neurologic disorders, yet its protean manifestations make its diagnosis sometimes difficult. Causes of vitamin B₁₂ deficiency include absence of intrinsic factor, bacterial overgrowth, and other factors affecting absorption.¹ Treatment with vitamin B₁₂ can reverse the symptoms, so its recognition is essential. Herein, we present a patient with several classic neurologic symptoms associated with vitamin B₁₂ deficiency. The brain magnetic resonance imaging (MRI) showed abnormalities that have not, to our knowledge, been associated with acquired vitamin B₁₂ deficiency but with inherited methylmalonic acidemia.

REPORT OF A CASE

A 43-year-old right-handed medical technologist presented with progressively worsening symptoms. He began stumbling 3 months prior to hospital admission and falling beginning 2 weeks before hospitalization. In the week preceding admission, he developed numbness and tingling in his hands and feet and difficulty manipulating needles at work. His

unsteadiness worsened and he went to the local emergency department where he also described 2 weeks of difficulty with memory, sustaining attention, and completing sentences. He did not have headaches, change in vision, or other neurologic symptoms.

Medical history included cleft palate repair in infancy. He was single and lived alone. He did not smoke or use illicit drugs or alcohol, and there were no toxic exposures. He had no dietary restrictions. A brother died in infancy of an undiagnosed illness associated with liver dysfunction.

Results of initial laboratory studies revealed a white blood cell count of 2100/μL (to convert to × 10⁹/L, multiply by 0.001) and a hemoglobin level of 34 g/dL (to convert to grams per liter, multiply by 10) with a normal comprehensive metabolic panel. Brain computed tomography and MRI revealed lesions in the globi pallidi (**Figure 1**). He was transferred to our hospital for further management.

His vital signs were normal and the general examination showed widespread eyes and evidence of cleft palate repair. He appeared timid with hypomimia. He had impaired recall but normal orientation, attention, and language. There was delayed

Author Affiliations:
Department of Neurology,
The Johns Hopkins Hospital,
Baltimore, Maryland
(Drs Sharrief and Zee); and
Royal Hospital of London,
London, England (Dr Raffel).

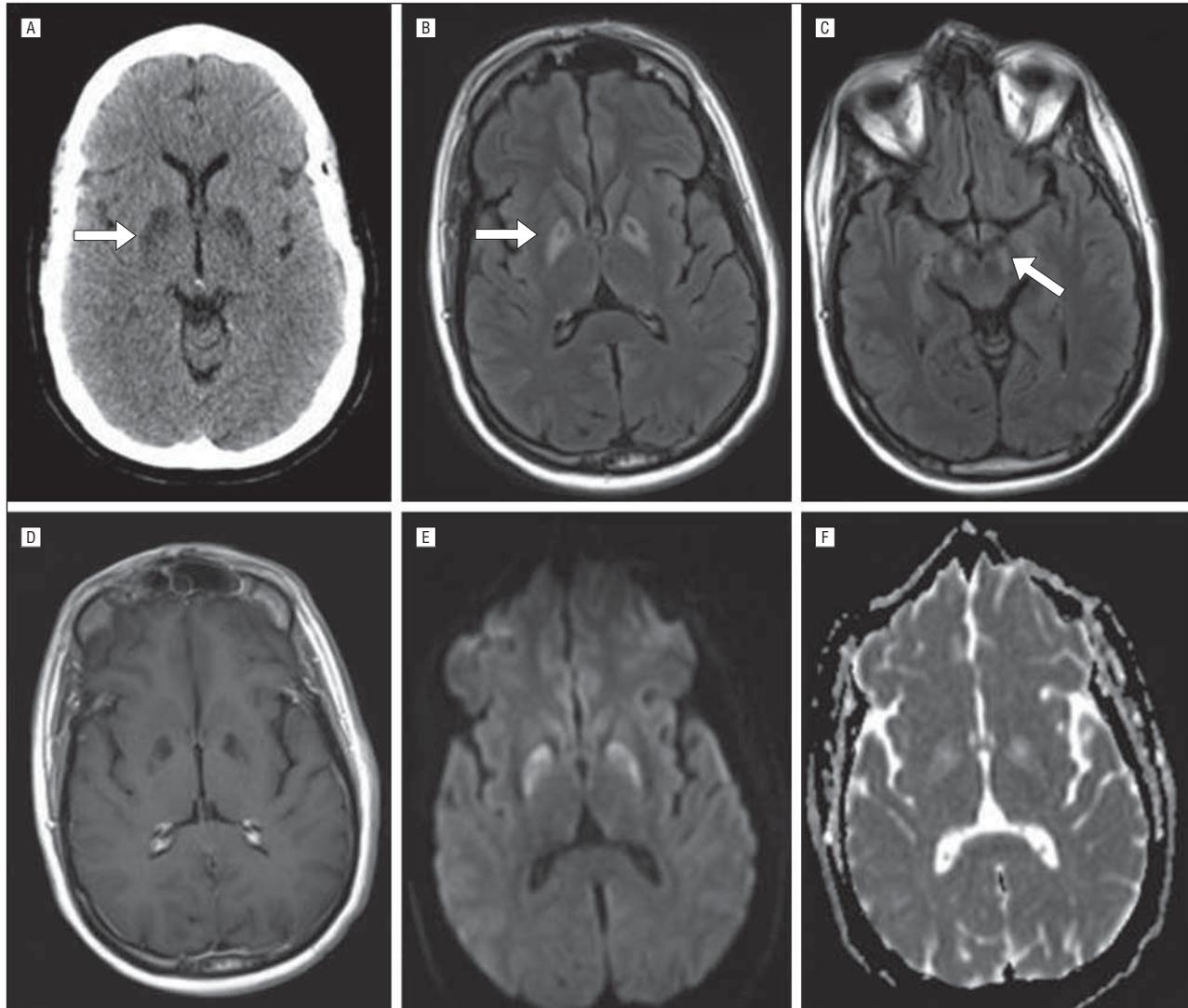


Figure 1. Brain computed tomography and magnetic resonance imaging. A, Hypoattenuation in the globi pallidi (GP) (arrow). B and C, Fluid-attenuated inversion recovery image with increased signal in the GP (B) and midbrain (C) (arrows). D, T1 image with decreased GP signal. E and F, Magnetic resonance imaging diffusion (E) and apparent diffusion coefficient (F) with increased GP signal.

initiation of saccades on command. Motor system examination showed normal tone but a lack of spontaneous movement and mild weakness of ankle dorsiflexion. There was no tremor and coordination was normal. Brachioradialis, patellar, and Achilles reflexes were absent, and biceps and triceps reflexes were elicited with reinforcement. Plantar responses were downgoing. Vibratory sensation and proprioception were impaired. His gait was wide based and he was unable to walk in tandem. Romberg sign was present.

Laboratory studies confirmed leukopenia and macrocytic anemia (mean corpuscular volume, $109 \mu\text{m}^3$ [to convert to femtoliters, multiply by 1]). Serum vitamin B₁₂ level was 254 pg/mL (to convert to picomoles per liter, multiply by 0.7378), which is close to the lower limit of the reference range (200-900 pg/mL). Homocysteine and methylmalonic acid (MMA) levels were markedly elevated at 89.1 $\mu\text{mol/L}$ (to convert to milligrams per liter, multiply by 7.397) (reference range, 4.0-15.2 $\mu\text{mol/L}$) and 36 000 nmol/L (reference range, 87-318 nmol/L), re-

spectively. These confirmed the diagnosis of vitamin B₁₂ deficiency. Red blood cell folate level, thyroid function, hemoglobin A_{1c} level, and results of autoimmune screen and cerebrospinal fluid studies were normal.

Sensory nerve conduction studies revealed absent sural responses and diminished ulnar and median amplitudes and velocities. Motor nerve conduction studies revealed decreased amplitudes of the left peroneal and right tibial responses. Electromyography was normal. These findings were consistent with a length-dependent mixed sensory and motor neuropathy with axonal and demyelinating features.

Brain MRI showed hyperintense signal in the globi pallidi on the fluid-attenuated inversion recovery image and hypointense signal on T1 images (Figure 1). The fluid-attenuated inversion recovery signal abnormality extended to the midbrain. Magnetic resonance spectroscopy for the left globus pallidus showed an increased lactate peak and slightly decreased *N*-acetylaspartate peak. Cervical spine MRI showed signal change in the poste-

rior cord consistent with subacute combined degeneration (**Figure 2**). The patient received parenteral vitamin B₁₂ therapy and his numbness, gait, and memory improved within 1 week. He resumed working within 2 months.

Further evaluation revealed absence of antibodies to intrinsic factor and parietal cells. Within 1 month, his vitamin B₁₂, MMA, and homocysteine levels were normal and his anemia and leukopenia resolved. Subsequent endoscopy with biopsy of the stomach revealed marked intestinal metaplasia and inactive chronic gastritis, consistent with autoimmune gastritis. Results of antibody testing remained negative. One year later, MRI showed nearly complete resolution of the brain lesions (**Figure 3**) and nerve conduction study findings were improved.

COMMENT

We have described a case of vitamin B₁₂ deficiency with classic neurologic features of subacute combined degeneration of the spinal cord, peripheral neuropathy, and impaired cognition, as well as hematologic findings of macrocytic anemia and leukopenia. Atypical features included extrapyramidal signs and bilateral globus pallidus abnormalities. While the vitamin B₁₂ level was normal, serum MMA and homocysteine levels were markedly elevated and the symptoms, severe. The features of this presentation may shed light on the etiology and pathogenesis of acquired vitamin B₁₂ deficiency and its relationship to inherited methylmalonic acidemia.

Methylmalonic acidemia is an autosomal recessive disorder caused by complete or partial deficiencies of methylmalonyl coenzyme A mutase or defects in the genes important for its cofactor, adenosylcobalamin. Clinical presentation includes developmental delay, seizures, and extrapyramidal signs. Bilateral globus pallidus degeneration can be seen in this disorder.²⁻⁴ Acute infarction of the globi pallidi has been described during metabolic crises.^{2,3,5,6} Magnetic resonance spectroscopy findings have varied, but when associated with acute infarction, decreased *N*-acetylaspartate and increased lactate levels have been found in the globus pallidus.^{2,4}

The proposed mechanism for globus pallidus degeneration in methylmalonic acidemia is through effects of MMA on succinate-supported mitochondrial oxygen consumption.⁷ The globus pallidus is thought to be a target of injury because of its high energy requirements and resultant sensitivity to mitochondrial dysfunction. This idea is supported by its propensity to injury in other conditions affecting cerebral metabolism and mitochondrial function.^{8,9}

The MRI findings in methylmalonic acidemia are consistent with the proposed biochemical mechanism for injury. Magnetic resonance imaging during acute metabolic crisis or infection has shown restricted diffusion in the bilateral globus pallidus with associated low intensity on the apparent diffusion coefficient map, suggesting acute ischemic injury. This could result from impaired oxygen consumption. Follow-up imaging after the acute episode has been reported for 2 cases in the litera-

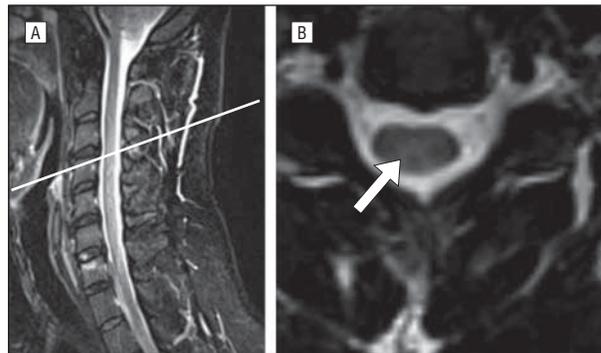


Figure 2. Cervical spine magnetic resonance imaging. A, Sagittal short T1 inversion recovery image demonstrating increased signal primarily in the posterior aspect of the cord. B, Axial image.

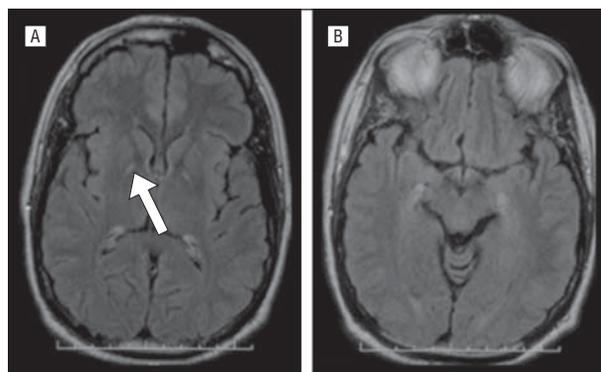


Figure 3. Follow-up magnetic resonance imaging. Axial fluid-attenuated inversion recovery image with near complete resolution of signal abnormality in the globi pallidi and midbrain after 1 year of treatment. There is slight residual increased signal in the globi pallidi, consistent with gliosis.

ture^{5,6}; both showed resolution of the abnormal diffusion and apparent diffusion coefficient signal with less remaining T2 abnormality than would be expected after infarction. In our case, there was increased signal in the globi pallidi on the apparent diffusion coefficient map, suggesting that at the time of imaging, there was increased diffusion of water, as would be observed with vasogenic edema. This might have been related to subacute ischemia or a metabolic cause of vasogenic edema.

The magnetic resonance spectroscopy finding of decreased NAA in the globus pallidus supports a role of neuronal injury in the pathologic process in our case. The follow-up imaging showed resolution of the abnormal diffusion and apparent diffusion coefficient findings and little remaining abnormality on fluid-attenuated inversion recovery imaging. This suggests that treatment reversed the biochemical process reflected in the diffusion and fluid-attenuated inversion recovery abnormalities.

Injury to the globi pallidi may explain the extrapyramidal symptoms of our patient. These included bradykinesia, hypomimia, and impaired saccade initiation. There are reports of extrapyramidal findings in vitamin B₁₂ deficiency.¹⁰⁻¹² Kumar¹⁰ described a patient with vitamin B₁₂ deficiency who presented with bradykinesia, tremor, and decreased blink rate that resolved with vitamin B₁₂ administration. The proposed mechanism of the reversible parkinsonism was through MMA's effects on the basal ganglia. Pacchetti et al¹² described a patient

with a normal brain MRI who had chorea and dystonia that resolved with vitamin B₁₂ administration. Although no structural changes were reported, magnetic resonance spectroscopy might have helped elucidate the metabolic abnormality in both cases.

Evaluation for causes of vitamin B₁₂ deficiency in our patient revealed evidence of autoimmune gastritis. Results of antibody testing were negative on 2 occasions, as can be seen in up to approximately 30% of cases.¹³ There was no evidence of insufficient dietary intake, *Helicobacter pylori* infection, or disease of the terminal ileum. The severity of his symptoms, despite normal vitamin B₁₂ levels, and the unique clinical and radiographic presentations raise the question of an underlying genetic predisposition for developing vitamin B₁₂ deficiency.

The hematologic and neurologic abnormalities of our patient reversed with vitamin B₁₂ administration. This suggests that any possible predisposition was insufficient to cause systemic manifestations with abundant vitamin B₁₂. Screening for known mutations that cause these inherited syndromes might be helpful in understanding this patient's problem. However, such screening would be costly and is not clearly indicated given his full recovery with vitamin B₁₂ administration.

This case has demonstrated the complexity of the symptoms, diagnosis, and pathophysiology underlying vitamin B₁₂ deficiency. To our knowledge, this is the first reported case of reversible bilateral globus pallidus abnormalities in vitamin B₁₂ deficiency. These abnormalities are similar to those reported in methylmalonic acidemia and support the role of MMA in the pathogenesis of this disease. Finally, this case underscores the roles of MMA and homocysteine in the diagnosis of vitamin B₁₂ deficiency.

Accepted for Publication: July 27, 2011.

Published Online: February 13, 2012. doi:10.1001/archneurol.2011.1084

Correspondence: Anjail Z. Sharrief, MD, Department of Neurology, The Johns Hopkins Hospital, 600 N Wolfe St, Meyer 8, 154, Baltimore, MD 21287 (asharri1@jhmi.edu).

Author Contributions: Study concept and design: Sharrief and Raffel. Acquisition of data: Sharrief and Raffel. Analysis and interpretation of data: Sharrief and Zee. Drafting of the manuscript: Sharrief and Raffel. Critical revision of the manuscript for important intellectual content: Sharrief, Raffel, and Zee. Administrative, technical, and material support: Sharrief. Study supervision: Zee.

Financial Disclosure: None reported.

REFERENCES

1. Dali-Youcef N, Andr s E. An update on cobalamin deficiency in adults. *QJM*. 2009; 102(1):17-28.
2. Trinh BC, Melhem ER, Barker PB. Multi-slice proton MR spectroscopy and diffusion-weighted imaging in methylmalonic acidemia: report of two cases and review of the literature. *AJNR Am J Neuroradiol*. 2001;22(5):831-833.
3. Yeşiladağ A, Ayata A, Baykal B, et al. Magnetic resonance imaging and diffusion-weighted imaging in methylmalonic acidemia. *Acta Radiol*. 2005;46(1):101-103.
4. Radmanesh A, Zaman T, Ghanaati H, Molaei S, Robertson RL, Zamani AA. Methylmalonic acidemia: brain imaging findings in 52 children and a review of the literature. *Pediatr Radiol*. 2008;38(10):1054-1061.
5. Michel SJ, Given CA II, Robertson WC Jr. Imaging of the brain, including diffusion-weighted imaging in methylmalonic acidemia. *Pediatr Radiol*. 2004;34(7):580-582.
6. Takeuchi M, Harada M, Matsuzaki K, Hisaoka S, Nishitani H, Mori K. Magnetic resonance imaging and spectroscopy in a patient with treated methylmalonic acidemia. *J Comput Assist Tomogr*. 2003;27(4):547-551.
7. Wajner M, Coelho JC. Neurological dysfunction in methylmalonic acidemia is probably related to the inhibitory effect of methylmalonate on brain energy production. *J Inherit Metab Dis*. 1997;20(6):761-768.
8. Lim CC. Magnetic resonance imaging findings in bilateral basal ganglia lesions. *Ann Acad Med Singapore*. 2009;38(9):795-798.
9. Subhaschandra S, Jatishwor W, Suraj T. Isolated symmetrical bilateral basal ganglia T2 hyperintensity in carbon monoxide poisoning. *Ann Indian Acad Neurol*. 2008;11(4):251-253.
10. Kumar S. Vitamin B12 deficiency presenting with an acute reversible extrapyramidal syndrome. *Neurol India*. 2004;52(4):507-509.
11. Celik M, Barkut IK, Oncel C, Forta H. Involuntary movements associated with vitamin B12 deficiency. *Parkinsonism Relat Disord*. 2003;10(1):55-57.
12. Pacchetti C, Cristina S, Nappi G. Reversible chorea and focal dystonia in vitamin B12 deficiency. *N Engl J Med*. 2002;347(4):295.
13. Lahner E, Norman GL, Severi C, et al. Reassessment of intrinsic factor and parietal cell autoantibodies in atrophic gastritis with respect to cobalamin deficiency. *Am J Gastroenterol*. 2009;104(8):2071-2079.