Brain Magnetic Resonance Imaging with Bilateral Hyperintensities in the Globus Pallidi

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An MRI of the brain and spine of an 11-year-old male revealed the following abnormality which is consistent with his chronic condition:

Figure 1. (A) Axial fast-recovery fast-spin-echo T2-weighted and (B) Axial fluid attenuated inversion recovery T2-weighted magnetic resonance images of the brain.

Figure 2. Coronal fast spin-echo T2-weighted magnetic resonance images of the brain.

What is your diagnosis?
**RADIOLoGIC DIAGNOSIS:** Metabolic infarcts of the globus pallidi consistent with methylmalonic acidemia (MMA). T2 MRI revealed bilateral linear hyperintensities in the globus pallidi, identified by white arrows in Figures 1 and 2. The presence of these lesions is unique to MMA, an inborn error of metabolism. These lesions were best visualized in the T2-weighted MRI sequences.

**CASE REPORT**

An 11-year-old male with a past medical history of mut0 (mutase absent) MMA, chronic constipation, poor feeding (requiring a gastrostomy tube), and stage III chronic kidney disease (CKD) presented to a neurologist with weekly throbbing headaches that coincided with nausea, vomiting, and photophobia. He was short in stature and underweight (<3rd percentile height and weight, height 123.1 cm, weight 24.49 kg) for his age. The patient is previously and currently receiving medical and dietary treatment for his MMA – effectively preventing frequent episodes of acidosis, with none occurring in the preceding four years. Upon physical examination of the lower extremities, spasticity, clonus, and 3+ reflexes were observed bilaterally. Lab work reveals elevated methylmalonate (1702 nmol/L) as well as mild normocytic anemia (hemoglobin 10.1, hematocrit 32.0%, mean corpuscular volume 72.1), CKD stage III (eGFR 55 ml/min), hyperuricemia (uric acid 7 mg/dl), and hyperphosphatemia (phosphorus 5.8 mg/dl) – complications consistent with MMA. No other complications of MMA are evident at present. The patient shows no intellectual impairment and grade-appropriate academic performance. He does not experience seizures, has no signs of cardiovascular disease, and echocardiography has excluded cardiomegaly. Brain and spine MRIs were ordered to investigate possible neurological sequelae of MMA. Notably, imaging of the brain revealed bilateral abnormal intensities in the inferior basal ganglia/globus pallidi most clearly visible in the axial (Figure 1A) and coronal (Figure 2) T2-weighted MRI sections. The diminished intensity of the lesions in the T2 FLAIR sequence (Figure 1B) indicates fluid accumulation consistent with gliosis. These symmetric hyperintensities limited to the globus pallidus are hallmark findings of MMA.

**DISCUSSION**

Methylmalonic acidemia (MMA) is one member of a heterogeneous group of autosomal recessive inborn errors of metabolism known as organic acidemias/acidurias. These disorders are associated with the massive accumulation of organic acids in the blood stream, body tissue, and urine. The excess organic acids are toxic to the function of multiple organ systems, with the central nervous system, kidneys, and bone marrow being the most effected. As the name suggests, MMA’s specific complications are triggered by high levels of methylmalonic acid and metabolites of methylmalonic acid’s precursors. This organic acid build-up is caused by one of three mechanisms: genetic defect or absence of the enzyme methylmalonic acid coenzyme A mutase (mut), defect in the synthesis and transport of mut’s cofactor 5’-deoxyadenosylcobalamin, and defect in the mitochondrial transport of cobalamin. Functional mut converts methylmalonic acid-CoA to succinyl-CoA. This reaction is a critical part of the catabolic pathway for all odd-chain fatty acids as well as the amino acids isoleucine, valine, methionine, and threonine. Inability to utilize this pathway is theorized to lead to an energy deficit, causing “metabolic infarction” in sensitive tissues. This is the proposed mechanism behind bilateral symmetrical infarction of the globus pallidi, a hallmark feature of chronic MMA. MMA also produces a number of more clinically apparent symptoms, including failure to thrive, anorexia, seizures, psychomotor developmental delay, dysmorphic facies, lethargy, vomiting, hypotonia, and agitation with inevitable metabolic decompensation during times of physiologic stress. Infection, prolonged fasting, or trauma induce a catabolic state that, in these disorders, results in severe metabolic acidosis with increased anion gap, hyperammonemia, hypoglycemia, and electrolyte imbalances that may lead to coma or death. The mut0 form of MMA, observed in this case, typically presents with one of these episodes of compensation within two weeks of birth. If the initial episode of decompensation is survived, the long-term complications of MMA may include chronic renal failure, anemia, neurological deficits, leukopenia, pancreatitis, and cardiomegaly. The mortality rate of MMA can be high (a 1990s study described it as 80%). Diagnosis is often significantly delayed due to MMA’s low prevalence (1 in 48,000) and non-specific presentation, further increasing the risk of death. Health care professionals in areas where consanguinity is prominent should be vigilant for MMA and other organic acidemias, as there is a higher prevalence of the disorders in such areas. No other demographic factors are helpful in screening. No race or sex predilection has been noted. When MMA is suspected, prompt diagnosis should be made with gas chromatography-mass spectroscopy analysis of urine. This test reveals markedly elevated methylmalonic acid and elevated methylcitrate, propionic acid, and 3-hydroxypropionic acid in patients with MMA. Definitive diagnosis requires genetic mutation or mutase activity analysis, which can identify the complementation group subtype of MMA.

Post-diagnostic neuroimaging of patients with MMA may reveal several nonspecific abnormalities such as enlarged ventricles and sulci, cortical and cerebellar atrophy, white matter abnormalities (subcortical, periventricular, and internal capsule), thinning of the corpus callosum, and basal ganglia. Symmetrical lesions confined within the anatomic boundary of the globus pallidi are unique to MMA. In contrast, infarction of the globus pallidus due to stroke is typically unilateral and follows a vascular distribution rather than being contained by the neuroanatomic boundary. Other diseases which may cause metabolic damage to the globus pallidi include Leigh Disease, propionic acidemia, and poisoning from cyanide or carbon monoxide. Although these diseases may involve other structures, isolated symmetrical globus pallidi infarcts have only been reported in MMA. In one study of brain MRIs from 64 MMA patients, 48% of the MMA patients (all types) and 45% of the mut0 patients had metabolic infarction of the...
globus pallidi. A staging system has been proposed based on sequential involvement of five different segments of the globus pallidi. Correlations between lesion staging and neurologic symptoms have not been clearly established in humans. Studies in non-human primates, however, suggest that selective lesions of the globus pallidi would lead to dyskinesia, attention deficit disorder, and stereotypical behaviors.¹

The symptoms, neurological impairment, and risk of potentially lethal metabolic exacerbations have been shown to be reduced in MMA patients through broad, aggressive therapy. Current treatments include protein-restricted high-energy diets, hydroxycobalamin injections, oral L-carnitine administration, and peritoneal dialysis. Additionally, use of antibiotics, such as metronidazole, may reduce the production of propionate, a precursor to methylmalonic acid, by gut bacteria. Modern management techniques are believed to significantly improve long-term outcomes. Both survival rates and average IQ of MMA patients have increased in the last two decades.¹,⁴,⁸,⁹ Renal damage may require kidney transplantation. Liver transplantation, alone or in combination with kidney transplantation, has also been utilized in the management of MMA with unclear efficacy.⁵

REFERENCES


Mr. Burkett is a Tulane University medical student. Ms. Bennett is a Tulane University medical student. Dr. Castillo-Jorge is Chief Resident in the Tulane University Department of Radiology. Dr. Garza-Garcia is a PGY-3 Resident in Tulane University Department of Radiology. Dr. Palacios is Professor of Neuroradiology at Tulane University Health Sciences Center in New Orleans, LA. Dr. Nguyen is Associate Professor at Tulane University Health Sciences Center in New Orleans, LA. Dr. Neitzschman is Professor of Radiology and Chairman of the Department of Radiology at Tulane University Health Sciences Center in New Orleans, LA.