

**LETTER TO THE EDITOR**

Refractory Myoclonus as a Presentation of Metabolic Stroke in A Child With Cobalamin B Methylmalonic Acidemia After Liver and Kidney Transplant

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Dear Editor,

Methylmalonic acidemia (MMA) is a group of inherited metabolic disorders affecting methylmalonate and cobalamin (Cbl) metabolism that lead to the accumulation of methylmalonic acid, ketoacidosis, hyperammonemia, and death in severe cases. MMA is caused by mutations in the *MMAA*, *MMAB*, and *MUT* genes. Cobalamin B methylmalonic acidemia (Cbl B-MMA) is a type of MMA caused by mutations in the *MMAB* gene. Treatment of Cbl B-MMA includes cobalamin supplementation and diet modification. Liver and/or kidney transplantation may be considered in severe cases to prevent recurrent episodes of metabolic decompensation and kidney failure.

We describe a novel case of metabolic stroke after liver and kidney transplant in a patient with Cbl B-MMA who presented with acute onset refractory myoclonus that was subsequently responsive to clonazepam and carbidopa-levodopa. The patient was an 8-year-old twin girl born at 33 weeks of gestation who developed metabolic acidosis and hyperammonemia at 6 days old and required peritoneal dialysis. The biochemical workup was consistent with MMA. *MMAB* gene sequencing identified two pathogenic mutations in *MMAB* (c.349-1G>C, intronic, and c.556C>T [p.Arg186Trp]), which confirmed the diagnosis of Cbl B-MMA. She was treated with intramuscular hydroxoco-

balamin, oral levocarnitine, and a mitochondrial vitamin cocktail. At age 5, she developed chronic kidney disease. At age 6, she was diagnosed with generalized epilepsy, which was well controlled with levetiracetam. At age 8, she was scheduled for a combined kidney and liver transplant. Five days prior to the transplant, she developed occasional shoulder and abdominal twitching. Her electroencephalogram (EEG) demonstrated myoclonic seizures during eye fluttering and shoulder twitching, which improved after levetiracetam titration and clobazam initiation. After the transplant, she was tapered off clobazam, dietary modification, levocarnitine and hydroxocobalamin.

One month after the transplant, she was re-hospitalized due to several days of persistent left shoulder and truncal twitching concerning refractory myoclonus. Her neurological examination showed myoclonus in her left shoulder, trunk, leg and cervical dystonia while awake and asleep. Her medications included aspirin, levetiracetam, tacrolimus, mycophenolate mofetil, dapsone, valganciclovir, carvedilol, and ranitidine. The repeated EEG captured shoulder and truncal twitching without EEG changes. Laboratory studies showed normal white blood cell, C-reactive protein, electrolytes, aspartate transaminase, alanine transaminase, creatine kinase, thyroid stimulating hormone, ammonia, and lactate levels. Serum MMA was 106 nmol/mL (normal < 0.4

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nmol/mL), which improved from pre-transplant levels of > 2,500 nmol/mL. The tacrolimus level was 5.8 ng/mL (normal 2–20 ng/mL). The mycophenolic acid level was subtherapeutic. Blood culture, serum Epstein-Barr virus and cytomegalovirus polymerase chain reaction (PCR) were negative. Cerebrospinal fluid (CSF) showed normal cell count, protein, and glucose. CSF bacterial and viral PCR were negative. Urgent magnetic resonance imaging (MRI) of the brain demonstrated restricted diffusion in the bilateral globus pallidus interna (GPi), suggestive of acute metabolic stroke (Figure 1A-C). Magnetic resonance spectroscopy (MRS) showed elevated lactate in the GPi (Figure 1D). Levocarnitine, hydroxocobalamin and mitochondrial cocktail were re-initiated. The patient's refractory myoclonus was treated with clonazepam, and the dose was titrated to 0.4 mg every 8 hours with minimal improvement after 2 weeks (Supplementary Video 1 in the online-only Data Supplement). Carbidopa-levodopa was added and titrated to 5 mg/kg/day of levodopa with further improvement of myoclonus and cervical dystonia. A follow-up brain MRI after one month revealed the evolution of bilateral globus pallidus infarcts suggestive of encephalomalacia with new foci of restricted diffusion in the cerebral peduncles, representing pre-Wallerian degeneration (Figure 1E-H). Two months af-

ter hospital discharge, the dose of carbidopa-levodopa was reduced for a few weeks with a worsening of myoclonus. The dose was increased to the previous dose with improvement in movements. Seven months after her metabolic stroke, there was no observable myoclonus while she remained on the same doses of clonazepam and carbidopa-levodopa (Supplementary Video 2 in the online-only Data Supplement).

Refractory myoclonus was previously described in acute post-hypoxic myoclonic epilepsy and subacute-chronic post-anoxic myoclonus (Lance Adams Syndrome).^{1,2} The mechanism of post-hypoxic myoclonus may arise from cortical and/or subcortical structures. Metabolic stroke in patients with MMA may occur in the setting of metabolic decompensation. Patients typically present with decreased mental status, irritability, diffuse or focal dystonia, tremor, generalized hypertonicity, and hyperreflexia in the lower extremities.³ Neuroimaging commonly demonstrates bilateral globus pallidus infarction, and this area may be particularly susceptible to hypoxia or metabolic derangement.⁴ Liver transplantation may prevent further episodes of metabolic decompensation, but it may not preclude metabolic stroke. There was one previous case report of metabolic stroke after transplant in a patient with MMA.⁵ A previous study suggested that enzyme

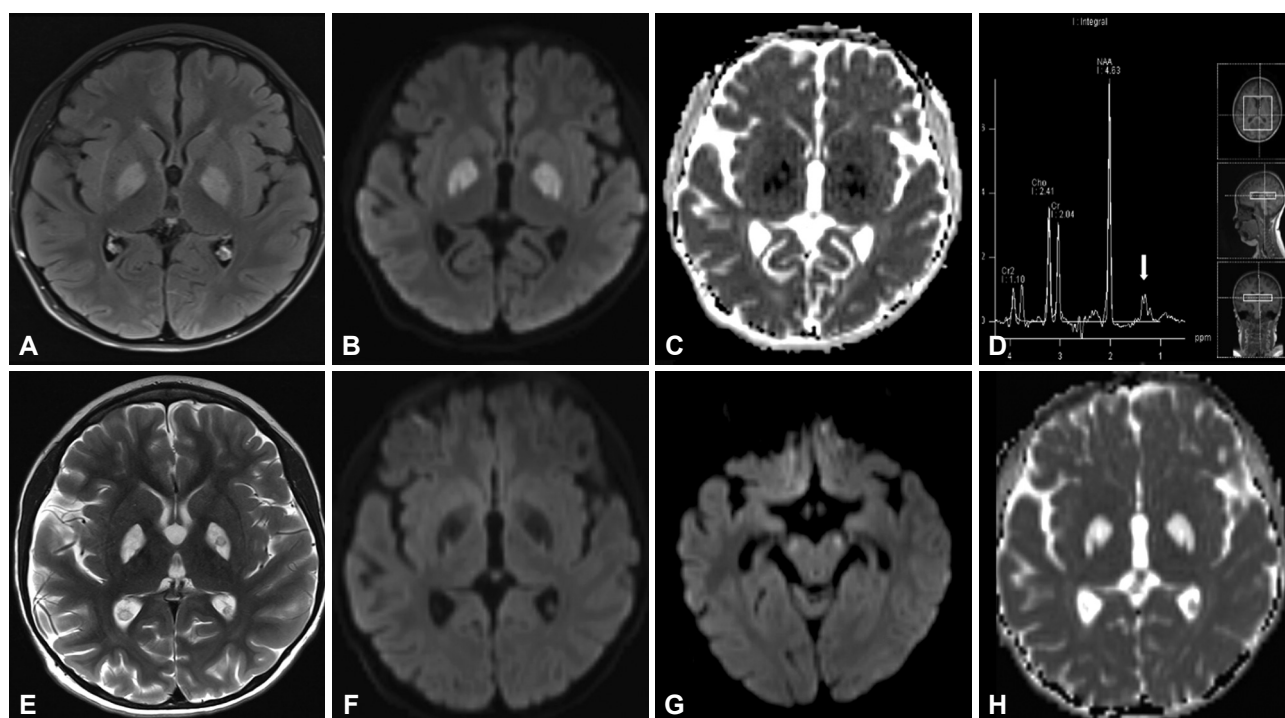


Figure 1. Initial brain magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS). T2-weighted fluid attenuated inversion recovery (FLAIR) axial image (A), diffusion-weighted (DWI) image (B), and apparent diffusion coefficient (ADC) image (C) show increased T2/FLAIR signal in the bilateral globus pallidus with associated diffusion restriction, which raised concern for globus pallidus infarcts. (D) MRS image shows lactate doublet resonating at 1.3 ppm in the cerebrospinal fluid, with more markedly elevated lactate within the voxels corresponding to the areas of the globus pallidus, which is consistent with impaired metabolism related to methylmalonic acidemia neurotoxicity. One-month follow-up brain MRI: T2-weighted axial image (E), DWI image at the level of the basal ganglia (F), DWI image at the level of the cerebral peduncles (G), and ADC image (H) show the evolution of bilateral globus pallidus infarcts suggestive of encephalomalacia with new foci of restricted diffusion in the cerebral peduncles, which represent pre-Wallerian degeneration.

deficiency in the brain was not changed following liver transplantation because the concentration of MMA in the CSF remained high. Although our patient did not have CSF MMA measurements, MMA accumulation in her brain may have contributed to the neurological deterioration and metabolic stroke despite significantly reduced serum MMA levels following liver transplantation. This pathogenesis remains to be fully elucidated.

Our patient is the first report of refractory myoclonus as a presentation of acute metabolic stroke involving bilateral globus pallidus in a child with MMA. The patient's bilateral globus pallidus infarcts likely disrupted normal inhibition from the internal globus pallidus on the thalamus, which allowed thalamic outputs to excite the cortex and led to the involuntary production of movement in the form of myoclonus. Toxic metabolite accumulation in other parts of her brain during acute metabolic stroke may have potentiated her refractory myoclonus.

This report suggests that metabolic stroke should be included in the differential diagnosis in addition to acute/chronic post-hypoxic injury, epilepsy, infectious or inflammatory neurological disease and other toxic encephalopathies when clinicians encounter patients with refractory myoclonus.^{6,7} Our patient's refractory myoclonus responded well to clonazepam and carbidopa-levodopa. Her movements worsened when the dose of carbidopa-levodopa was reduced. To the best of our knowledge, there are no previous data to support the use of carbidopa-levodopa in myoclonus after metabolic stroke. We propose that refractory myoclonus after metabolic stroke may be responsive to carbidopa-levodopa, and this medication may be considered an adjunct to conventional therapies. Our report also emphasizes the importance of continuation of dietary modification and supplementation following liver transplantation to avoid neurological complications in patients with MMA.

Ethics Statement

The written informed consent has been obtained from the patient's legal guardian.

Supplementary Video Legends

Video 1. Video of abnormal movements approximately two weeks after discovery of bilateral basal ganglia metabolic stroke. Movements started as twitches in the left abdominal and shoulder muscles and progressed to involve the left abdomen, shoulder, neck, and at times the left leg.

Videos 2. Video of abnormal movements 7 months after discharge from hospitalization from metabolic stroke. At this time, the patient was being treated with clonazepam and carbidopa-levodopa. The patient displayed significant improvement of myoclonus in the left shoulder and trunk.

Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.14802/jmd.21196>.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

Conceptualization: Valerie Olson, Dararat Mingbunjerdsuk. Data curation: Valerie Olson, Dararat Mingbunjerdsuk. Formal analysis: all authors. Investigation: Valerie Olson, Dararat Mingbunjerdsuk. Methodology: Valerie Olson, Dararat Mingbunjerdsuk. Project administration: Valerie Olson, Dararat Mingbunjerdsuk. Supervision: Dararat Mingbunjerdsuk. Validation: all authors. Writing—original draft: Valerie Olson, Dararat Mingbunjerdsuk. Writing—review & editing: all authors.

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