

Expanding the Spectrum of *Methylmalonic Acid-Induced Pallidal Stroke*: First Reported Case of Metabolic Globus Pallidus Stroke in Transcobalamin II Deficiency

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Abstract A 10-year-old boy with transcobalamin II (TCII) deficiency on oral cyanocobalamin therapy presented with acute right hemiparesis and sensory axonal neuropathy in the context of an intercurrent viral illness. MRI demonstrated unilateral globus pallidus stroke with normal MRA. Echocardiogram was normal. Methylmalonic acid in serum was mildly elevated at 10.29 $\mu\text{mol/L}$ (normal < 0.37 $\mu\text{mol/L}$), which was an 18-fold increase from his previous baseline. The patient was switched to IM cyanocobalamin and serum methylmalonic acid levels normalized over 6 months to 0.01 $\mu\text{mol/L}$. After 4 months of IM cyanocobalamin therapy, the neuropathy had resolved. Repeat MRI 4 months after the sentinel stroke demonstrated a chronic-appearing contralateral globus pallidus stroke of uncertain timing.

Conclusions: We are describing the first case of metabolic stroke and peripheral neuropathy in TCII

deficiency. The neuropathy was responsive to parenteral hydroxycobalamin. Unilateral globus pallidus stroke in the appropriate clinical context should not exclude a metabolic etiology as it may herald contralateral involvement and may provide an opportunity for early recognition and treatment. IM hydroxycobalamin should be strongly considered in all patients with TCII, particularly when they reach later childhood. This case highlights the selective vulnerability of the globus pallidus to increased levels of methylmalonic acid of various causes, which is important for both diagnosis and ultimately understanding the mechanisms of neurological injury in this group of conditions. Metabolic stroke may occur with lower levels of methylmalonic acid than previously reported in the context of an intercurrent bioenergetic stressor.

Introduction

The globus pallidus is an area of the brain that shows a selective vulnerability in a number of conditions associated with methylmalonic aciduria (MMA), including methylmalonyl-CoA mutase deficiency, cobalamin complementation group disorders, and severe pernicious anemia (Heidenreich et al. 1988; Trinh et al. 2001; Sharrief et al. 2012). The pathophysiology behind this selective vulnerability is currently unknown, although it has been postulated to result from respiratory chain dysfunction that preferentially affects the highly metabolically active globus pallidi (Heidenreich et al. 1988). Here we present the first reported case of globus pallidus stroke associated with methylmalonic aciduria in a patient with transcobalamin II (TCII) deficiency (OMIM #275350), thereby expanding the spectrum of *MMA-induced pallidal stroke*.

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Case Report

The index patient is a 10-year-old, left-handed boy who was diagnosed with TCII deficiency at the age of 10 weeks when he presented with failure to thrive, lethargy, myoclonus, pancytopenia, and megaloblasts in his bone marrow. He had elevated methylmalonic acid and plasma homocysteine with normal serum B12 and folic acid. Enzymatic testing confirmed a defect of TCII. He was initially treated with IM hydroxycobalamin, with rapid normalization of homocysteine and methylmalonic acid levels. At 1 year of age, he was transitioned to oral cyanocobalamin (2,500 µg daily) with sustained normalization of laboratory parameters. The genetic diagnosis was later established as a homozygous sequence variant in the *TCN2* gene (c.497_498de/tc). He remained systemically well following the early infantile period, with no history of metabolic decompensations. He did preferentially toe walk and on serial neurological assessments had decreased reflexes in his lower extremities; two prior nerve conduction studies were normal. Serum methylmalonic acid level performed at the age of 9 years was 0.58 µmol/L (normal < 0.37 µmol/L).

At the age of 10 years, the patient presented with a 2-day history of gradually progressive right hemiparesis (arm and leg) 2 weeks following a viral exanthem. The family had not noticed any additional weakness, encephalopathy, or seizures. Other than a moderate right hemiparesis, the examination was significant for bilateral lower extremity areflexia, with preserved reflexes in the upper extremities.

MR brain with spectroscopy (Fig. 1) demonstrated a well-defined area of restricted diffusion involving the left globus pallidus. MR angiography was normal. MRS with voxel placed in the left basal ganglia demonstrated a small lactate doublet at 1.33 ppm. Echocardiogram with bubble study was normal.

On first presentation, serum methylmalonic acid was elevated at 8.57 µmol/L, which rose to 10.29 µmol/L over the following 4 days (normal < 0.37 µmol/L). The latter represented an 18-fold increase from his previous level at 9 years of age. Urine methylmalonic acid was also elevated at 184 mmol/mol creatinine. Quantitative acylcarnitines demonstrated only a borderline elevation of C3 at 1.11 µmol/L (normal < 1.08) with normal total and free carnitine. Serum amino acids, homocysteine, hemoglobin, mean corpuscular volume (MCV), WBC count, venous blood gas, and serum immunoglobulins were normal.

Nerve conduction studies in the lower extremities were abnormal with decreased sensory nerve action potential (SNAP) amplitude of the sural nerve (with normal conduction velocity and distal latency) and absent superficial peroneal nerve SNAPs. Motor studies in the lower extremities and sensory/motor studies in the upper extremities were

normal. These findings were in keeping with a length-dependent sensory axonal polyneuropathy.

The etiology of stroke in our patient at this point was not entirely clear, and both primary metabolic and vascular etiologies were entertained. The patient was switched from his oral cyanocobalamin formulation to 1 mg IM hydroxycobalamin daily. He was also started on 3 mg/kg ASA.

On repeat bloodwork at approximately 2, 3, and 6 months' follow-up, the serum methylmalonic acid gradually normalized from 2.70 µmol/L to 1.99 µmol/L, and finally to 0.01 µmol/L, respectively. On clinical assessment at 4 months, the patient's right hemiparesis was mildly improved. Reflexes were 1+ in the lower extremities. There was no evidence of dystonia or chorea. Repeat MR brain (Fig. 2) at 4 months demonstrated interval development of a new, chronic-appearing right globus pallidus stroke as well as gliotic changes of the original left globus pallidus stroke. Spectroscopy was normal. Repeat nerve conduction studies of sural and superficial peroneal nerves were normal.

Discussion

Transcobalamin II (TCII) is one of the three human transporters of cobalamin (vitamin B12). It binds and transports cobalamin absorbed in the terminal ileum to tissue cells throughout the body, where it ultimately participates in cell surface adhesion and internalization of the cobalamin (Quadros 2009). TCII is also synthesized by astrocytes and is the primary enzyme involved in the neuronal uptake of cobalamin in the central nervous system (Begley et al. 1994). Cobalamin ultimately has an important role in the metabolism of both homocysteine and methylmalonic acid as a cofactor for methionine synthase and methylmalonyl-CoA mutase, respectively (Takahashi-Iñiguez et al. 2012; Banerjee and Ragsdale 2003). Methylmalonyl-CoA mutase isomerizes mitochondrial methylmalonyl-CoA to succinyl-CoA, a crucial substrate in energy provision via the citric acid cycle and complex II of the respiratory chain (Dutra et al. 1993; Okun et al. 2002). Inherited deficiency of TCII has been described in over 40 patients (Watkins and Rosenblatt 2011). TCII deficiency is an autosomal recessive condition resulting from mutations in the *TCN2* gene on chromosome 22q12 (Watkins and Rosenblatt 2011; Regec et al. 1995). It typically presents in the first 2 months of life with pancytopenia, failure to thrive, and gastrointestinal symptoms (Kaikov et al. 1991; Gimpert et al. 1975). Laboratory markers typically include increased homocysteine, reduced methionine, increased methylmalonic acid, metabolic acidosis, and megaloblastic anemia (Kaikov et al. 1991). Stroke and peripheral neuropathy have not previously been reported in association with TCII deficiency.

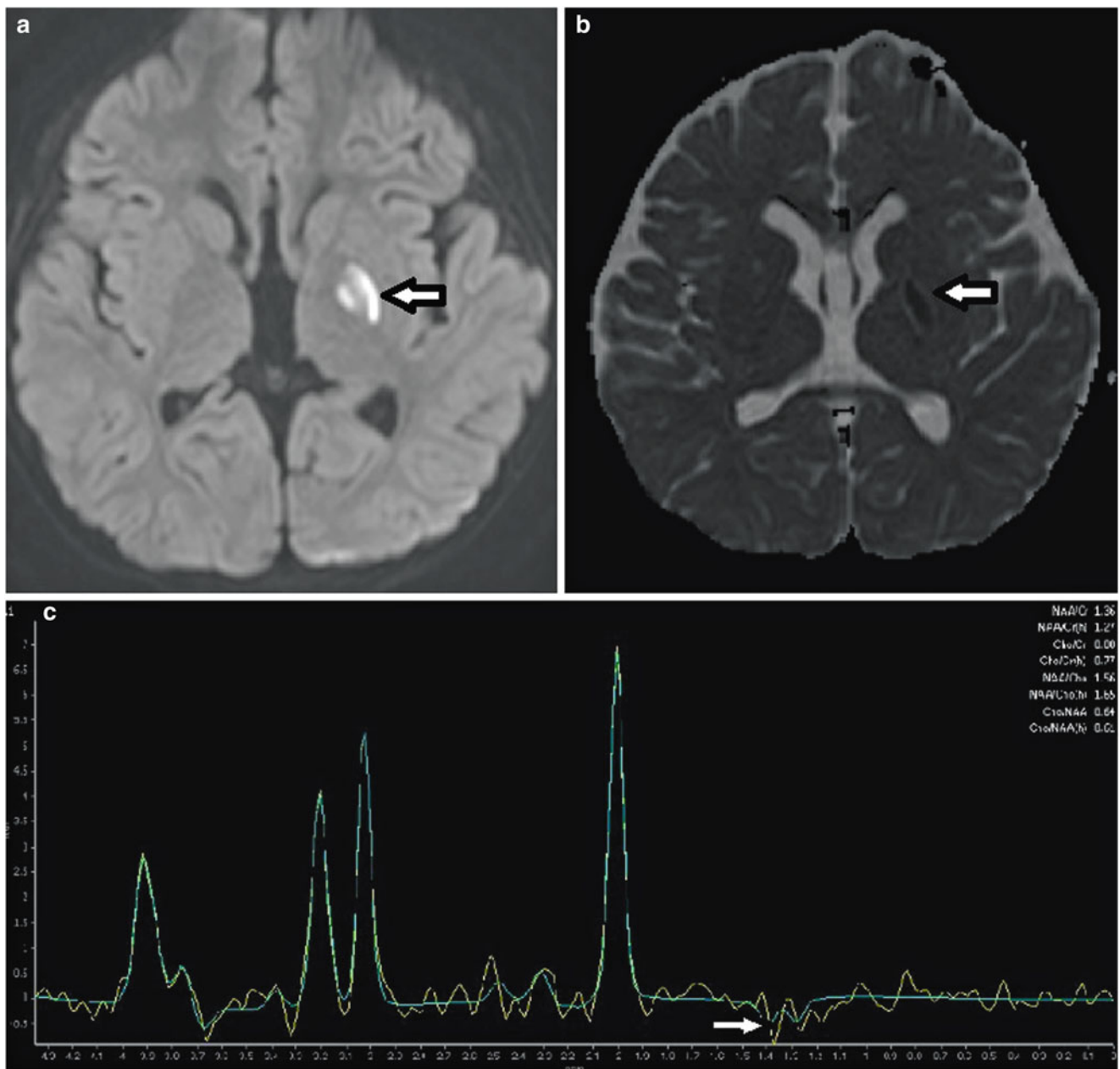


Fig. 1 MR brain with spectroscopy at time of sentinel stroke. Diffusion-weighted imaging (a) with apparent diffusion coefficient (b) demonstrates restricted diffusion in the left globus pallidus

(arrows). Proton spectroscopy (c) with voxel placed in the left globus pallidus demonstrates a small lactate doublet at 1.33 ppm (arrows)

We presume that the mechanism of stroke in our patient was MMA-induced pallidal stroke for the following reasons. Firstly, our patient presented with staggered, bilateral globus pallidus strokes, without any additional parenchymal involvement in the lateral lenticulostriate or anterior choroidal vascular territories bilaterally. The latter vessels supply the globus pallidus, as well as the putamen, caudate, and internal capsule. *It would be highly implausible for a vaso-occlusive stroke to selectively affect*

bilateral pallidi in isolation (the identical portion of the vascular territory bilaterally), sparing the remainder of the vascular territory. This is especially the case with normal vascular imaging. *The selective bilateral pallidal involvement is, therefore, more consistent with a “metabolic” stroke in a vulnerable region of the basal ganglia, as previously described in MMA of various etiologies.* While globus pallidus stroke has not been specifically described in patients with TCII deficiency, it is a logical extension given

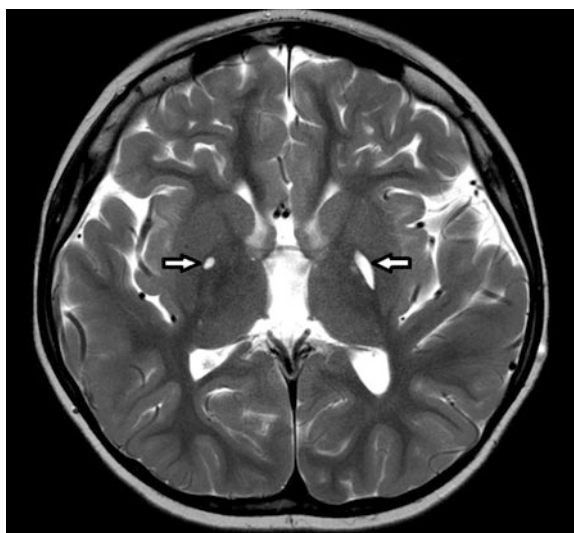


Fig. 2 MR brain at 4-month follow-up. Axial T2-weighted sequence demonstrates bilateral hyperintensities in the globus pallidi (arrows)

the role of TCII in the metabolism of methylmalonic acid. It is admittedly unusual that our patient presented initially with unilateral globus pallidus involvement, as asymmetries have not been previously described with MMA. Repeat neuroimaging was done 4 months after the incident stroke, making it difficult to determine the precise timing of the chronic-appearing contralateral globus pallidus stroke. The asymmetry in the initial presentation may suggest subtle differences in the pallidal neuronal microenvironment in this patient. In addition, although our patient's peak level of MMA was lower than that previously reported in association with MMA-associated metabolic stroke (lowest reported level is 89 $\mu\text{mol/L}$ as per Sharrief et al. 2012), our patient's stroke did occur in the context of an almost 20-fold elevation of MMA from his previous baseline. The threshold for metabolic stroke in our patient may have been lowered in part by the bioenergetic stress of his intercurrent viral illness.

In addition to stroke, our patient presented with a new, electrophysiologically confirmed peripheral neuropathy. A predominantly demyelinating peripheral neuropathy has been previously described in both early-onset and late-onset forms of cobalamin C deficiency and methylene tetrahydrofolate reductase deficiency (Frattini et al. 2010; Nishimura et al. 1985). In addition, sensory neuropathy has been described in patients with other forms of homocystinuria, although this has been attributed to toxicity from supplementation with pyridoxine (Ludolph et al. 1991). Dietary B12 deficiency is also associated with a reversible sensorimotor demyelinating polyneuropathy (Sakly et al. 2005). The presumed pathophysiology relates to deficient methylation of myelin basic protein, an important component of myelin that influences myelin compaction (Frattini et al. 2010). To our knowledge, this is the first report of sensory axonal peripheral neuropathy

in a patient with TCII deficiency. Importantly, abnormalities on nerve conduction studies reversed with IM hydroxycobalamin.

Previous authors have suggested aggressive treatment of TCII deficiency with IM hydroxycobalamin and have cited reports of treatment failure in late childhood and adolescence in patients transitioned from IM treatment to oral cyanocobalamin. The patients with treatment failure presented with cognitive decline, visual dysfunction from maculopathy, and proprioceptive difficulties from presumed dorsal column involvement of the spinal cord. Symptoms improved when IM therapy was resumed (Schiff et al. 2010).

In conclusion, we are describing the first case of metabolic stroke and peripheral neuropathy in TCII deficiency. The neuropathy was responsive to parenteral hydroxycobalamin. This case highlights a number of important issues. Firstly, unilateral globus pallidus stroke in the appropriate clinical context should not exclude a metabolic etiology as it may herald contralateral involvement; in fact, it may provide an opportunity for early recognition and treatment. Secondly, this case suggests that IM hydroxycobalamin should be strongly considered in all patients with TCII, particularly when they reach later childhood. Finally, this case highlights the selective vulnerability of the globus pallidus to increased levels of methylmalonic acid of various causes, which is important for both diagnosis and ultimately understanding the mechanisms of neurological injury in this group of conditions. It appears that metabolic stroke may occur with lower levels of MMA than previously reported in the context of an intercurrent bioenergetic stressor.

Synopsis

Transcobalamin II deficiency may present with metabolic pallidal stroke and peripheral neuropathy, reversible with IM cyanocobalamin.

Contributions

Lance H Rodan – reviewed patient, concept, manuscript preparation, literature review, discussion, manuscript writing, guarantor

Navin Mishra – reviewed patient, manuscript editing, literature review, discussion

Ivanna Yau – reviewed patient, manuscript editing, discussion

Andrea Andrade – reviewed patient, manuscript editing, discussion

Komudi Siriwardena – contributed patient and patient data and reviewed patient, manuscript editing, discussion

Ingrid Tein – reviewed patient, concept, manuscript editing, discussion, supervisor

Conflict of Interest

No authors report a conflict of interest related to the publication of this manuscript.

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