Cobalamin C Deficiency: An Uncommon Cause of Hemolytic Uremic Syndrome

Thrombotic microangiopathies (TMA) refers to a group of disorders characterized by microangiopathic hemolytic anemia (MAHA) and thrombocytopenia leading to microthrombi formation and tissue injury leading to acute kidney injury. Previously used terminology, typical hemolytic uremic syndrome (HUS) was used for an infective etiology (Shiga toxin mediated) and atypical HUS for disorders in the alternate complement pathway regulation. Understanding the etiology is crucial as it directs the management [1, 2]. We report a child presenting with an uncommon etiiology of HUS.

A 3-year-old developmentally normal boy, born to non-consanguineous parents, presented with fever, pain abdomen, and decreased urine output for 8 days' duration. He had also developed fast breathing over the preceding 12 hours. There was no history of rash, loose stools, ear discharge, joint pain or swelling, red urine, bleeding from any site or any significant past history. On examination, child was pale, had generalized anasarca, heart rate 160 beats/min, respiratory rate 70 breaths/min, and blood pressure 193/118 mmHg (>99th centile), with saturation of 60% on room air and 85% on oxygen by non-rebreathing mask. Auscultation of the chest revealed bilateral crepitations, other systemic examination was unremarkable. The child was drowsy with a score of 13 on the Glasgow Coma Scale (E3, V5, M5), had bilaterally equal normally reacting pupils with normal fundoscopy. Rest of the neurological examination was unremarkable.

Investigations revealed anemia, leucocytosis, thrombocytopenia and high reticulocyte count (Hb - 6.7 g/dL, total counts – 16,750/µL, platelets – 1,00,000/mm^3, Reticulocyte count – 11.9%, Table I). Peripheral smear examination revealed normocytic normochromic red blood cells with presence of schistocytes (5.6%). There was evidence of acute kidney injury (AKI), KDIGO stage III associated with hyperkalemia and ECG changes as depicted in **Table I**. Blood gas analysis revealed mixed metabolic and respiratory acidosis; with hyperkalemia and hypoxia; pH 6.8, bicarbonate 6.7 mmol/L, lactate- 8.2 mmol/L, potassium 7 mEq/L, sodium – 135 mEq/L, Chloride – 103 mmol/L, pO_2 52.8 mmHg, pCO_2 48.2 mmHg, with raised anion gap of 32 mEq/L. Point-of-Care ultrasound was suggestive of pulmonary edema with systolic cardiac dysfunction (left ventricular ejection fraction 40%). Urgent treatment measures were taken for hyperkalemia (intravenous calcium gluconate, sodium bicarbonate followed by dextrose-insulin infusion), blood pressure control (intravenous labetalol), along with other supportive care in the form of invasive mechanical ventilation in the pediatric intensive care unit. In view of AKI and anuria, child underwent hemodialysis; and labetalol and sodium nitroprusside infusion were continued. As markers for sepsis were missed (C-reactive protein 47mg/L, serum procalcitonin 19ng/mL), possibility of sepsis associated TMA or atypical HUS due to complement pathway defect triggered by sepsis were considered. The child was started on broad spectrum intravenous antibiotics and underwent plasmapheresis (daily for 7 days followed by alternate day for 2 weeks and twice a week for another 2 weeks) with partial improvement in haematological parameters (**Table I**). During the course of illness (day 28 of admission), child developed acute pain in abdomen; laboratory work-up revealed pancreatitis which was managed conservatively. In view of refractory hypertension, child was started on multiple antihypertensives. A 2-dimensional echocardiography showed concentric left ventricular hypertrophy and normal right ventricular pressures, and renal doppler suggested poor flow in the segmental vessels.

Work up for other etiological factors of TMA was done simultaneously which showed normal serum complement levels (C3 80mg/dL, C4 43mg/dL, negative antifactor H antibody) and normal ADAMTS13 activity (60.1%). Tandem mass spectrometry revealed low methionine levels and normal acyl-carnitines and urinary gas chromatography suggested methylmalonic aciduria, with hyperhomocysteinemia (**Table I)**. Whole exome sequencing revealed a homozygous pathogenic variant (NM_015506.3, c.347T>C,p.Leu116Pro) in the *MMACHC* gene which established a diagnosis of methylmalonic aciduria and homocystinuria, cobalamin 1C type (MMACHC).

In view of cobalamin C deficiency, child was started on injectable hydroxocobalamin (1000 µg intramuscularly daily), oral trimethylglycine (250 mg/kg/day), pyridoxine (10 mg/day), folic acid (5 mg/day) and carnitine (100 mg/kg/day) [3]. Subsequently, the child showed improvement and became dialysis free over the next 2 months and the blood pressure was well controlled on antihypertensive

Table I Baseline laboratory characteristics over the course of treatment

Investigation	*At admission*	*Interval (after 1 mo)*	*Discharge (at 2 mo)*
Hemoglobin (g/dL)	6.7	7.3	8.8
Total leucocyte count (cells/μL)	16,750	5,950	8,860
Platelet count (cells/mm^3)	1,00,000	1,15,000	2,72,000
Peripheral smear	Normocytic normochromic cells Schistocytes (5.6%)	Schistocytes (1%)	
Reticulocyte count (%)	11.9	2.6	
Blood urea (mg/dL)	250	35	131
Serum creatinine (mg/dL)	11.4	1.1	1.5
Serum sodium (mmol/L)	138	133	141
Serum potassium (mmol/L)	6.5	3.2	4.8
Serum homocysteine (μmol/L)		99.4 (Normal < 20)	12.8
Serum methionine (μmol/L)		4.27 (Normal <75)	
Propionylcarnitine (C3) (μmol/L)		4.00 (Normal <5.65)	
Methylmalonic acid (μmol/L)		26.53 (Normal < 5.34)	
Serum vitamin B12 (pg/mL)		433	2000
Serum folate (ng/mL)		18	20
Serum amylase (U/L)		192	96
Serum lipase (U/L)		1762	641

drugs. The parents were trained and advised to continue daily hydroxocobalamin injections intramuscularly along with other supportive care [3]. The family was counseled regarding the nature of the illness, and the risk of further episodes of decompensation. His asymptomatic elder sibling was also advised regarding screening for targeted *MMACHC* variant gene testing with serum total homocysteine and vitamin B12 levels.

While awaiting investigations the initial management focused on plasmapheresis along with intravenous antibiotics considering a possible diagnosis of a sepsis triggered TMA or atypical complement mediated HUS. Since there was no history of developmental delay or failure to thrive, an inborn error of metabolism was kept as a lower possibility. With specific management of Cobalamin C deficiency, the serum total homocysteine levels showed marked improvement in a week, while clinical improvement in terms of dialysis free period and control of blood pressure was more gradual. An important aspect of cobalamin C deficiency is the combined defect of hyperhomocystinemia which leads to the vascular manifestations of this disease and the organic acidemia due to methyl malonic aciduria which contributes to the encephalopathy in these patients during a crisis. It is important to understand that in the absence of adequate nutrition, prolonged starvation or catabolic state in the critically ill state, the organic acidemias are likely to worsen. In our patient, pancreatitis complicated the situation with inability to increase the calorie intake per orally or via intralipid infusion. Due to a primary distal remethylation defect in the methionine pathway, protein restriction is not recommended for these patients [3], and in some cases low dose methionine may have to be supplemented to allow availability of methionine for remethylation to occur.

This report highlights the need to suspect uncommon etiologies in parallel with more common etiologies when a patient presents with a clinical picture of TMA. Serum/plasma total homocysteine levels and urine methyl malonic acid levels along with serum vitamin B12 levels can help guide underlying diagnosis. Treatment with cobalamin should be initiated while awaiting urine organic acid levels and genetic studies, if cobalamin C deficiency is suspected. Early and specific treatment leads to improved outcomes [3, 4]. Studies from India, quote a high prevalence of the p.Arg132Ter variant in the *MMACHC* gene in India, with a neurological presentation without kidney disease [5]. While some studies suggest genotype-phenotype correlation, it is not fully understood why certain variants have a renal phenotype without overt signs of neurodevelopmental delay [6,7]. In addition to monitoring of renal functions, these patients require multidisciplinary care for growth and development monitoring, regular screening for eye manifestations. The

neurocognitive and eye manifestations are believed to be less responsive to treatment [3,4].

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***Published online**: April 05, 2024; **PII**:S097475591600626*

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