Case Series

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Six Patients with Methylmalonic Acidemia and Their Outcome: Literature Review and Case Series

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ABSTRACT

Background: Methylmalonic acidemia (MMA) is a congenital disorder due to the defects in the propionate pathway. It results from a deficiency in methylmalonyl coenzyme A mutase or one of the steps of the synthesis of the cobalamin (B12) cofactors for the enzyme. There is deficiency of methylmalonyl coA mutase (MCM) in the classic MMA. It presents with severe metabolic acidosis in the first month of life, progressive failure to thrive, feeding problems, recurrent vomiting, dehydration, hepatomegaly, lethargy, seizures, and developmental delay. Quantitative analysis of urinary organic acid patterns by GC-MS is used in MMA diagnosis. Treatment with large doses of hydroxocobalamin is helpful in some cases of MMA.

Case Presentation: We Reported 6 patients with MMA with a variety of clinical manifestations and outcomes.

Conclusion: The overall prognosis of classic MMA remains doubtful, whereas vitamin B12 responsive MMA has a reasonable outcome.

Introduction

Methylmalonic acidemia (MMA) is an autosomal recessive genetic disease that affects organic acid metabolism.[1] It is a rare disorder with an overall incidence of approximately 1: 50,000 for isolated MMA[2] and is mainly caused by a defective methylmalonyl-CoA mutase or abnormal metabolism of cobalamin coenzyme.[1] This cobalamin-dependent mitochondrial enzyme catalyzes the isomerization of l-methylmalonyl-CoA to succinyl CoA and uses adenosylcobalamin (Adocbl) as a cofactor.[3] MMA is characterized by the accumulation of methylmalonic acids due to the inactivation of the MCM. MCM is present in the metabolic

pathway of four types of amino acids (valine, isoleucine, methionine, and threonine), cholesterol, and odd chain fatty acids.[4]

Clinical features of organic acidopathies are due to the accumulation of toxic metabolites, altered mitochondrial energy metabolism, carnitine depletion, and CoA sequestration. Acute illness may be associated with metabolic acidosis, acute alterations of consciousness or encephalopathy, anorexia, and nausea and vomiting. Chronic complications include poor growth, movement disorders, progressive spastic quadraparesis, epilepsy, cardiac dysfunction, progressive renal disease, pancreatitis, osteopenia, osteoporosis, vision loss and functional immunodeficiency.[5] The treatment for MMA includes dietary protein restriction, L-carnitine supplementation, and oral antibiotics administration to reduce the production of propionate by intestinal bacteria. Supplementation of hydroxycobalamine or cyanocobalamin is used for cobalamin responsive patients.[6]

Case Presentation

Case 1: A 6-month-old infant presented with lethargy, vomiting, and progressive respiratory distress due to respiratory viral infection. The parents had consanguinity marriage. He had a history of 3 days admission 2 weeks ago with pneumonia diagnosis with similar symptoms, neck dystonia, and gaze palsy. Laboratory tests were as below: Blood Gas: PH: 7.05, HCO3: 3mEq/L, PCO2: 10mmHg, Anion gap: 27mEq/L, urine ketone: positive, uric acid = 9.6 mg/dL, cholesterol = 168 mg/dL, triglyceride = 485 mg/dL. MRI showed ischemia of basal ganglion. The patient was treated with the probable diagnosis of organic acidemia. Dextrose Water 10% (1.5*maintenance fluid) and intravenous bicarbonate were administrated. The diagnosis of methylmalonic acidemia was established with acylcarnitine plasma profile and urine organic acid. Serum homocysteine was normal. To differentiate between defects in the mutase enzyme and impaired cobalamin metabolism, hydroxocobalamin test was done. The defect of the enzyme was diagnosed. The patient was treated with diet (special milk) according to a nutritionist, carnitine, and metronidazole (ten days per month). He rarely had acidosis attacks in his follow-up and his IQ was acceptable but his growth was not normal. Unfortunately, he expired in 4 years and 9 months due to severe acidosis crises, gastrointestinal bleeding, septicemia, disseminated intravascular coagulopathy, hemorrhagic pancreatitis, gangrenous fingers, renal failure and acute respiratory distress syndrome (multi-organ damage). Laboratory tests of recent admission were as below: INR > 6, PTT > 120, PT > 60, CRP: 2 positive, Urea: 192 mmol/L, Creatinine: 1.8 mg/dL, Blood sugar: 44mg/dL, Lipase: 1397 U/L, Amylase: 1442 U/L.

Case 2: The patient was a 15-month infant that presented with lethargy, frequent vomiting, and progressive respiratory distress, and a history of 2 times admission in recent two weeks due to similar symptoms. The parents had no consanguinity marriage. His development was normal. Laboratory tests were as below: VBG: PH:7.07, HCO3<3 mEq/L, PCO2:8 mmHg, urine ketone: positive, uric acid=9 mg/dL. The patient was managed with probable diagnose of organic acidemia. In acylcarnitine plasma profile: propionyl carnitine: 16.7 (normal is below 5), propionyl carnitine/Acetyl carnitine: 0.81 (normal is below < 0.28), methylmalonic acid: 55.1mmol/mol creatinine (normal is below <18.6). The diagnosis of methylmalonic acidemia was established. Serum homocysteine was normal. Due to the patient's lack of response to the hydroxycobalamine test, the enzyme MUT disorder was considered. The patient was treated with diet, l-carnitine and metronidazole (ten days per month). He was well at a 2-year follow-up. His development was normal but he had growth disorder.

Case 3: The patient was a 2-year-old child with lethargy, frequent vomiting, and

respiratory distress. He had a history of similar symptoms with upper and lower limb paresis and aphasia 2 months ago. The paresis of the upper limbs and aphasia had improved but the paresis of the lower limbs had relative improvement and the patient was unable to walk. Ischemia of basal ganglion and the internal capsule was reported in the brain MRI. In recent admission, the patient had diabetic ketoacidosis with blood sugar of 700 mg/dL, severe metabolic acidosis and positive urine ketone. The patient was treated with dextrose water 10% (1.5*maintenance) and intravenous insulin and bicarbonate. The diagnosis of methylmalonic acidemia was established due to the acylcarnitine plasma profile and urine organic acidemia. Serum homocysteine was normal. An optimal response was observed in the hydroxocobalamin test. The diagnosis of a defect in cobalamin A or B was established but the genetic study was not done. The patient was treated with hydroxycobalamine 1 mg/daily intramuscularly 2 times a week and L-carnitine. The patient was well in 2-year old follow up but still had paresis of lower limbs and was unable to walk.

Case 4: A ten-year child was admitted due to frequent vomiting, abdominal pain, and mild metabolic acidosis. He had a history of frequent similar attacks from neonatal period that had been treated with oral bicarbonate, B12 vitamin and L-carnitine. He underwent chemotherapy for 6 months because of Hodgkin's lymphoma at the age of 5 years old. He had complete improvement. He also had a history of renal failure from 8 months ago but he had no follow up. During this hospitalization, he suffered from coffee ground vomiting, and melena. In laboratory tests normal amylase and lipase serum levels, urea=85mg/dL, creatinine =4.3 mg/dL were reported. Ultrasound showed a decrease in kidney sizes. Serum homocysteine was normal. High glycine and normal methionine were reported in amino acid chromatography. Due to the lack of improvement in symptoms and severe acidosis, he underwent peritoneal dialysis, but the desired response was not observed and unfortunately he expired.

Case 5: A 6 months infant was referred due to developmental delay and megaloblastic anemia. The parents had consanguinity marriage. In chromatographic studies, low levels of methionine and high homocysteine serum amino acids were reported and methylmalonic acid was increased in urine organic acids. The cobalamin C (cblC) deficiency was reported in the genetic study. The patient was treated with hydroxocobalamin 1mg intramuscularly 2 times a week and Betaine powder (250mg per kg per day). She had a seizure in her follow-up that was treated with anticonvulsant drugs. During follow up, although the patient's biochemical parameters were relatively normalized, she still had delayed development, microcephaly, and seizures.

Case 6: A one-year-old infant presented with lethargy, vomiting, respiratory distress, history of similar symptoms in neonatal period with normal development. She had severe metabolic acidosis in laboratory tests. The diagnosis of methylmalonic acidemia was established with acylcarnitine plasma profile and urine organic acidemia. Due to unresponsiveness to hydroxycobalamine test, deficiency of MUT enzyme was suggested and the patient was treated with a low protein diet, alkaline therapy, carnitine, and metronidazole for 10 days. She was well at follow-up.

Discussion

MMA is a rare inborn error of metabolism, belonging to the organic acidemias. It leads to increased levels of methylmalonic acid in body fluids.[7] These patients usually present shortly after birth with acute metabolic acidosis and hyperammonemia. Infants who survive the first attack might develop similar acute metabolic episodes during a catabolic state such as infection or prolonged fasting or after ingestion of a high protein diet.[8]In our setting genetic studies were expensive so it was not routine for all suspected patients. The diagnosis was just made by urine organic

acid and acylcarnitine profile in clinically suspected patients. However genetic study was done for the fifth case and confirmed the cobalamin C deficiency.Permanent neurologic damages may occur during these episodes, resulting in extrapyramidal signs such as hypertonicity, loss of speech, dystonic posturing, and dysphagia.[9] While survival of MMA patients has greatly improved over the past decades with conventional management strategies, patients continue to develop serious long term neurological complications including developmental delay, seizures, metabolic stroke, and also renal insufficiency and pancreatitis.[7]The first case in our report expired due to pancreatitis following metabolic crisis as a rare complication.

Dietary and pharmacological interventions should be started as soon as diagnosis of MMA.[10]

The multisystemic complications of MMA cause additional challenges to medical management and increase the mortality and morbidity rates.[11]

Conclusion

The overall prognosis of classic MMA remains doubtful, whereas vitamin B12 responsive MMA has a reasonable outcome.

Conflict of Interests

Authors have no conflict of interests.

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