AN UNUSUAL PRESENTATION OF METHYMALONIC ACIDEMIA WITH 3RD STAGE CHRONIC KIDNEY DISEASES

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ABSTRACT

Methylmalonic acid is a substance produced in very small amounts and is necessary for human metabolism and energy production. The measurement of elevated amounts of methylmalonic acid in the blood or urine serves as a sensitive and early indicator of vitamin B12 deficiency. Methylmalonic aciduria is an autosomal recessive metabolic disorder results in inability to digest specific fats and proteins, which in turn leads to a buildup of a toxic level of methylmalonic acid in the blood. It is estimated that this disorder has a frequency of 1 in 48,000 births. Methylmalonic acidemia (MMA) is often complicated by end stage renal disease.

INTRODUCTION

A 8 year-old boy was brought to hospital with the complaints of decreased urine output, initially 6-8 times per day but now got reduced to 3 times per day, increased weight gain, abdominal distension present, reduced appetite, pedal edema puffiness of face, pain in lower limb and unable to walk for past 1 week. The boy was the first child for second degree consanguineous parents. His mother was conceived spontaneously, uneventful obstetric history and morphology scan was normal and term gestation mode of delivery was emergency LSCS (Indication: PROM), cried soon after birth, birth weight of 2.6kg. During infancy, the child was said to have gone through times of difficulty to thrive, irritability and lethargy. Milestone was slightly delayed, neck control was achieved only at 6 months of age and started walking without support after 3 years of age. Now studies in class II suppose to be in class IV and average in studies. Immunized for age according to national immunization schedule. He has 7 years old younger brother with Urogenital sinus and was operated for the same 5 months back.

On examination, the child was alert, active, puffiness of face present, pallor++, vitals are HR -120beat/min, PR-28/min, BP-110/80mmHg, SPO2-98% in RA,CVS S1S2 heard- hemic murmur present, breath sounds – normal vesicular breath sounds, Abdomen – soft bowel sounds present, shiny legs present due to edema and poor muscle coordination. Laboratory investigations showed hemoglobin 9.6gm/dl, blood urea 55mg/dl and serum creatinine 1.8mg/dl, potassium 6.2meq/l, the child was diagnosed as known case of Methylmalonic acidemia, stage 3 chronic kidney diseases, hypertension and stage 1 hypertensive retinopathy, Guillian Barre syndrome- recovery stage. The child was started on kayexalate (1 sachet/day) and salbutamol nebulization was given. Soda bicarb correction was given, onpotassium and salt restricted mixed diet and on nutritional supplement for MMA-Metanutrition. Oral medications of T. Levocarnitine 500mg TDS, T.clonidine 50mg 1-1-1-1,T.methylcobalaminine 1500mcg 1-0-1,inj vit B12 IM on alternate days,T. Amlodipine 5mg 1-0-1,T.sodamint 1-1-1-1. Pediatric neurologist advised to stop Levocarnitine and to continue B12 injection 1500mcg. Child was observed for 48 hours and repeat potassium levels were within normal limits (4.6mEq/l).child had chronic hypertension with hypertensive retinopathy for which he was on Tab. Hydralazine at 40mg/kg before. On day 4, systolic BP of 200mm Hg, he was started on Nitroglycerine infusion at 0.5ml/kg. Subsequently Hydralazine, Clonidine, Prazoin, Enalapril and Amlodipine were restarted. As BP was maintaining in the target levels, Anti hypertensive drugs were gradually tapered. 7th day of admission, child had tachypnea,
fever, multiple episodes of vomiting and aspiration following which he developed severe respiratory distress and acidotic breathing. Blood gas showed high anion gap metabolic acidosis. In view of acute metabolic crisis, child was shifted to PICU, intubated and ventilated and was on PSIMV mode with Fio2 of 50% and PIP/PEEP of 18/6 and was kept in NPO and started on IVF 80% maintenance with 10% dextrose child was on 10 liters of oxygen. Sodium bicarbonate correction was given (1mg/kg). Mega doses of vitamin B12 were given for 2 weeks and alternate doses for next 2 weeks were given. Vomiting subsided and subsequent blood gas analysis showed normal anion gap metabolic acidosis. Tandem Mass Spectrometry and gas chromatography mass spectrometry were repeated as per pediatrician neurologist opinion, as it was not done previously. Reports confirmed methyl malonic academia. Child was noticed to have a progressive limb weakness. Reflexes were not elicitable. Power in all 4 extremities was 3/5 and there was decrease in intensity of voice. Guillain Barre Syndrome was suspected. On day 2 of PICU stay, weakness progressed (power 2/5 in all 4 limbs), there was weak gag reflex which was suggestive of respiratory muscle weakness. Examination also showed weakness of facial muscle on right side. Nerve conduction study was done which revealed pattern of acute motor sensory polyneuropathy of in excitable character confirming Guillain Barre Syndrome. IV Ig 2g was given over 4 days. Gabapentin and Inj tramadol was given for pain management. Air bed was used and limb physiotherapy was started after extubation. On 14th day of PICU stay, child had hyperkalemia (K-7.2), which was managed as per hyperkalemia management protocol. Diet was modified to potassium free diet. After 72 hours K+ became normal. Weakness gradually improved to 3+/5 on the right side and 3-/5 on left and was shifted to ward after 16 days of PICU stay. Child started taking orally well and hence planned for discharge. 

Introduction

Methylmalonic academia (MMA) is an autosomal recessive metabolic disorder. It is a classical type of organic academia. The result of this condition is the inability to properly digest specific fats and proteins, which in turn leads to a buildup of a toxic level of methylmalonic acid in the blood. Methylmalonic academia stems from several genotypes, all forms of the disorder usually diagnosed in the early neonatal period. The disorder can result in death if undiagnosed or left untreated. It is estimated that this disorder has a frequency of 1 in 48,000 births with no increased incidence based on sex or race, though it is estimated that this disorder has a frequency of 1 in 48,000 births with no increased incidence based on sex or race, though the high mortality rate in diagnosed cases make exact determination difficult.

DISCUSSION

Genetic cause

Approximately half of methylmalonic academia cases are caused by mutation of MUT gene. Many mutations in the MUT gene have been identified. Mutations prevent the production of or reduce the activity of methylmalonyl CoA mutase, resulting in impaired catabolism of fatty acids as well as some amino acids. This results in an accumulation of methylmalonyl CoA which causes the symptoms of methylmalonic academia. It is inherited in an autosomal recessive manner. Parents of an individual with an autosomal recessive condition can carry one copy of the mutated gene, but do not show signs and symptoms of the condition. Each pregnancy between carrier parents has 25% chances of producing a child affected with MMA, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

Dietary cause

Vitamin B12 is also needed for the conversion of methylmalonyl-CoA to succinyl-CoA. Mutations leading to defects in vitamin B12 metabolism or in its transport frequently result in the development of methylmalonic acidemia.

Clinical manifestations

Most newborn do not have symptoms at birth, but will soon develop lethargy, vomiting and dehydration. Other findings can include intellectual disabilities, kidney failure, respiratory distress, movement disorders, metabolic stroke, failure to thrive, hepatomegaly, encephalopathy and hypoammonemia. Children may present with chronic renal failure associated with marked hypertension and hypertensive retinopathy.

Diagnostic evaluation

Primary newborn screening for MMA utilizes tandem mass spectrometry to determine the propionylcarnitine (C3) level. Elevated propionylcarnitine and occasionally methylmalonyl carnitine (C4DC), indicates the possibility of MMA. The diagnosis of methylmalonic academia is confirmed through organic acid analysis of urine or plasma revealing elevated methylmalonic acid. Other laboratory findings are urine analysis, blood panel, CT scan, percentage of ammonia and glycine in blood, ketone bodies in blood serum. To establish specific form additional studies must be done. These include vitamin B12 responsiveness, complementation analysis, and C14 propionate tracer assay and cobalamin distribution.

Management

Treatment for all forms of this condition primarily relies on a low protein diet and various dietary supplements like levo isomer of carnitine, cyanocobalmin supplements and rich in vitamin B12. A more extreme treatment includes kidney or liver transplant from a donor without the condition. The foreign organs will produce a functional version of the defective enzymes and digest the methylmalonic acid. Children with renal failure can be maintained on regular hemodialysis or continuous ambulatory peritoneal dialysis.

Genetic counseling should be offered to the parents of such patients. Prenatal diagnosis is possible by measuring methyl malonic acid in amniotic fluid, in maternal urine and by estimating enzyme activity in the fetal blood cells and cultured fibroblasts. Attempts to treat this condition during intra uterine life with vitamin B12 injections.

Nursing management

- Assess skin color and peripheral perfusion, red and broken skin indicates early signs of protein deficiency.
- Assess neurological status using Glasgow Coma Scale to demonstrate altered levels of consciousness, muscle weakness or seizures.
- Assess vital signs of the child every 4th hourly.
- Assess level of MMA in urine of the child.
MMA may prompt reduction of natural protein intake.

✓ Assess blood glucose and lactate of the child as Hypoglycemia and hyperlactatemia are frequently found in patients with MMA.

✓ Nasogastric feeding may be necessary if not taking oral diet. If enteral feeding is not tolerated, intravenous nutrition will be required, i.e. - I.V. Dextrose (carbohydrate) - I.V lipids (fat) - I.V. Vaminolact (natural protein)

✓ Monitor intake and output chart for the child.

✓ Administer medications as per doctors order.

References


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