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Case Report

Early neonatal presentation of methylmalonic aciduria: a case report from rural central India

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ABSTRACT

Methylmalonic aciduria (MMA) is an inborn error of metabolism that results in accumulation of methylmalonic acid in blood and increased excretion in urine. They are characterized by impaired conversion of methymalonyl CoA to succinyl CoA by the enzyme methylmalonyl CoA mutase resulting in accumulation of metabolites of branched chain amino acid catabolism. MMA has a wide clinical spectrum, ranging from a benign condition to fatal neonatal disease. Its onset ranges from the neonatal period to adulthood. We report a case of a day 4 old male child who presented with the complaints of respiratory distress, poor feeding, and excessive crying. Mother had a history of previous neonatal loss on day 3 of life. Diagnosis of MMA was made with the help of clinical presentation and laboratory investigations. At present universal newborn screening for metabolic disorders is not done routinely in India. Diagnosing and managing IEM in India and other developing countries is a challenge since most of the classic metabolic test are not routinely available. Many cases are asymptomatic and undetected and hence we report this case to stress the importance of including MMA in newborn screening programme for early detection and intervention.

Keywords: MMA, Metabolic acidosis, Newborn screening, Hypotonia

INTRODUCTION

Methylmalonic aciduria (MMA) is an inherited metabolic disorder that results in increased accumulation of methylmalonic acid in the blood and excretion in the urine.[1] MMA associated with type C homocystinuria cobalamin results from defective biosynthesis of 5'-deoxyadenosyl-cobalamin and methyl-cobalamin, cofactors of the enzymes methylmalonyl-CoA mutase and methionine synthase, respectively.[2]

MMA is a heterogeneous group of autosomal recessive metabolic disorders. They are characterized by impaired conversion of methylmalonyl-CoA to succinyl-CoA by the enzyme methylmalonyl-CoA mutase, resulting in the accumulation of branched-chain amino acid catabolites. This leads to accumulation of methylmalonic acid in plasma, urine and other body fluids.[3]

Isolated MMA is caused by complete or partial deficiency of the enzyme methylmalonyl-CoA mutase, and defects in the transport or synthesis of its cofactors 5-deoxyadenosylcobalamin (cblA, cblB and cblD-MMA), or a deficiency in the enzyme methylmalonyl-CoA epimerase.[4]

MMA has a wide clinical spectrum, ranging from a benign condition to fatal neonatal disease. Its onset ranges from the neonatal period to adulthood. Clinical fetaures include anorexia, failure to thrive, hypotonia, developmental delay, progressive renal failure, functional immune impairment, optic nerve atrophy, and hematologic abnormalities.[5] We present case of a neonate presenting with clinical picture of sepsis, who was diagnosed with MMA. Through this case report, we want to emphasize about high suspicion of metabolic disorders in neonates and their early diagnosis and management in order to reduce long term morbidities.

CASE REPORT

A 2200 gm male child born to G2P2L0 mother, by normal vaginal delivery out of non-consanguineous marriage was admitted to the neonatal intensive care unit with the complaints of respiratory distress, poor feeding, and excessive crying on day 4 of life. Antenatal and postnatal period was uneventful. Child was exclusively on breastmilk for first three days of life. Mother had a history of previous neonatal loss on day 3 of life. There was no history of fever, foul smelling liquor or medication during antenatal period.

Child had length of 52.5 cm (25th centile), head circumference of 34 cm (Percentile), and weight on admission-2000 gm. On general examination, temperature was 37.6^{0} C, heart rate of 150 beats per min, respiratory rate of 74 per min, SpO_2 of 86%. He had icterus but no pallor. He had no dysmorphic features. Anterior fontanel was normal. On respiratory system examination showed subcostal retractions, air entry reduced in right inframammary region and crepitations were present in right infra-axillary region. Abdominal examination revealed firm hepatomegaly of 4 cm, with a liver span of 6.5 cm. cardiovascular system examination was normal. Central nervous system examination showed hypotonia, absent deep tendon reflexes and extensor plantar reflex.

On laboratory investigations complete blood count showed haemoglobin of 12.4 g/dl, white blood cell count of 18,500/mm3, platelet count of 298000/mm^3 with (Lymphocytes-47.5%, mixed-5.7%, and granulocyte-49.6%). His serum electrolytes were sodium=155 mEq/L, potassium=5.14 mEq/liter, chloride=113 mEq/liter, Urea-63 mg/dl, and creatinine-1.22 mg/dl. Blood gas analysis showed pH=7.23, bicarbonate=10.30 mEq/ liter, PCO_2= 25.30, PO_2=76, anion gap=35.70. C-reactive protein was 4.30 mg/l. CSF analysis was done and showed CSF proteins-156 mg/dl, CSF glucose-42 mg/dl. Normal CSF cytology. Considering neonatal sepsis child was started on inj. cefotaxime (100 mg/kg/24 hr/Q12 hr) and inj. amikacin (15 mg/kg/24 hr/Q24 hr) empirically.

Child was intubated and was mechanically ventilated. On day 6 of life, child developed generalised tonic clinic convulsions and central nervous system examination showed pupils were dilated and sluggishly reacting to light, no tone, deep tendon reflex and plantar reflex were absent. Laboratory investigations showed serum calcium of 7.70 mg/dl and serum sodium of 145 mEq/L. Blood gas analysis showed persistent metabolic acidosis. Urine ketones positive. Serum lactate of 3 mmol/L. Blood culture revealed growth of *Klebsiella pneumonia*. Serum ammonia=430 mcg/dL, C-reactive protein=33.70 mg/L. Child was started on Inj.Phenobarbitone (20 mg/kg).

Therefore, metabolic disorder was considered and his metabolic panel (by gas chromatography/Mass spectrometry) showed elevated levels of propionyl carnitine (C3), glycin and other amino acids in blood and increased excretion of methylmalonic acid (MMA), 3-hydroxypropionate (3HP), lactate and methylcitrate in urine. Sample is positive for MMA.

Child had repeated repeated episodes of convulsions not responding to anticonvulsants, child succumbed on day 10 of life. Consent has been taken from parents before publication of case report.

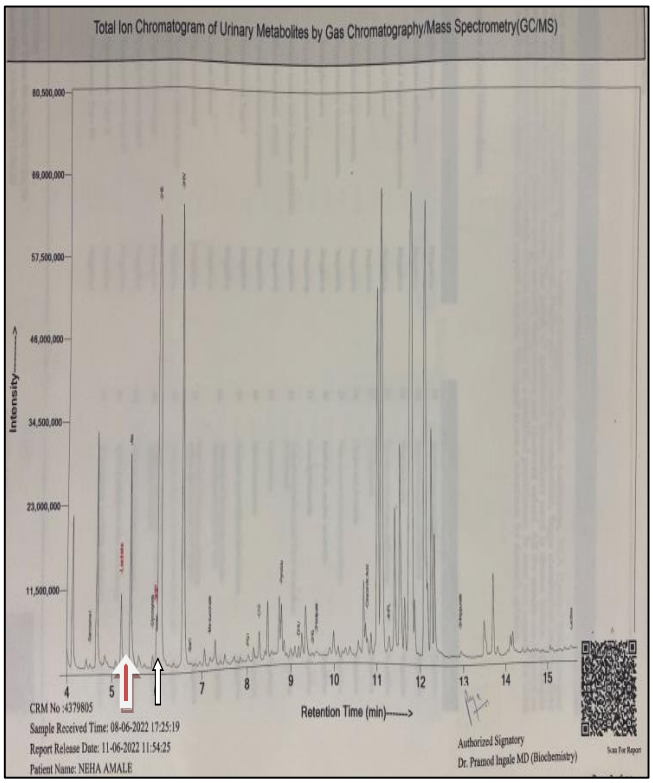

Figure 1: Urine organic acids shows variable degree of elevation of lactate (red arrow) and 3-hydroxypropionate (3 HP) (white arrow).

DISCUSSION

MMA is one of the most common organic acidurias, with an incidence of 1:48000 to 1:250000.[1] MMA is a severe genetic disease with poor prognosis. Methylmalonicaciduria presents early in life with a characteristic picture of vomiting, failure to thrive, hepatomegaly, lethargy, and ketoacidosis. MMA is not apparent at birth as symptoms usually do not present themselves until proteins are added to the infant's diet. Because of this, symptoms typically manifest anytime within the first year of life.[6] Due to the severity and rapidity in which this disorder can cause complications when left undiagnosed, screening for MMA should be included in the newborn screening program. If untreated, these children usually die early in life, Zhou et al found variant responsive to the administration of vitamin B12. Since these latter patients apparently develop normally if treated, an early correct diagnosis becomes especially important.[7]

Newborn screening for MMA is technically feasible using methionine and has been implemented in some countries (e.g., Austria, U.S, Spain, Italy), but not in others (e.g., Germany, France, U.K, Netherlands).[3] Early diagnosis of PA through newborn screening seems to be associated with a lower mortality rate. However, no significant benefit could be shown for surviving patients with regard to their clinical course, including the number of metabolic crises, physical and neurocognitive development, and long-term complications.[8]

In our case, the child presented to us in his neonatal period with respiratory distress and convulsions with persistent metabolic acidosis. He was evaluated with blood investigations and metabolic panel for screening, he was treated symptomatically with anticonvulsant and antibiotics. Child did not survive.

CONCLUSION

At present universal newborn screening for metabolic disorders is not done routinely in India. Diagnosing and managing IEM in India and other developing countries is a challenge since most of the classic metabolic test are not routinely available. Metabolic evaluation is usually done only in very sick neonates or children with metabolic acidosis with hyper-ammonaemia. IEM are also genetic disorder, thus making genetic counselling around recurrence risk imperative for individuals who have had one affected child. Many cases are asymptomatic and undetected and hence we report this case to stress the importance of including methylmelonic aciduria in newborn screening programme for early detection and intervention. Early diagnosis with preventive measures can improve survival and prevent children from developmental and metabolic abnormalities.

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