

Methylmalonic Acidemia: A Rare Case Report from Rural India

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Abstract:

Methylmalonic acidemia is an autosomal recessive disorder of amino acid metabolism, involving a defect in the conversion of methylmalonyl-coenzyme A (CoA) to succinyl-CoA. Patients typically present at the age of 1 month to 1 year since symptoms usually do not present themselves until proteins are added to the infant's diet. We report a case of 4.5-month-old male, was brought to the hospital by the relatives with a history of GTCS type of convulsions. Child suspected to have been diagnosed with inborn errors of metabolism so workup for the same done and patient diagnosed with methylmalonic acidemia. Many cases of inborn error of metabolism are asymptomatic and undetected. This case highlights the importance of considering methylmalonic acidemia in newborn screening program for early detection and timely intervention, which help to improve survival and prevent children from developmental and metabolic abnormalities.

Key words: Inborn errors of metabolism, Metabolic acidosis, Acute liver failure, Tandem mass spectrometry, Gas chromatography-mass spectrophotometry, Newborn screening

Introduction:

Methylmalonic acidemia is an autosomal recessive disorder of amino acid metabolism, involving a defect in the conversion of methylmalonyl-coenzyme A (CoA) to succinyl-CoA. Patients typically present at the age of 1 month to 1 year with neurologic manifestations, such as seizure, encephalopathy, and stroke. [1-3] Methylmalonic acidemia 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. There are two forms of methylmalonic acidemia's presentation, the classic, acute onset, with symptoms in the neonatal period, and a later post-neonatal form. Clinical features include anorexia, failure to thrive, hypotonia, developmental delay, progressive renal failure, functional immune optic nerve atrophy, and haematological abnormalities.

It is an inborn error of metabolism that results in accumulation of methylmalonic acid in blood and increased excretion in urine. Inborn errors of metabolism are a heterogeneous group of disorders

that may be inherited or may occur as the result of spontaneous mutation. These diseases involve failure of the metabolic pathways involved in either the break-down or storage of carbohydrates, fatty acids, and proteins. Although any given inborn error of metabolism is very rare, taken as a group, inborn errors occur in 1 in 2500 births, making them quite common. Every newborn with unexplained neurological deterioration, ketosis, metabolic acidosis or hypoglycemia should be suspected of having an inherited error of intermediary metabolism. Patients having neurological deterioration mostly suggests maple syrup urine disease, methylmalonic acidemia, propionic acidemia, isovaleric acidemia and urea cycle disorders. Patients presenting with liver failure suggest galactosaemia, fructosaemia, tyrosinaemia type I (after 3 weeks), phosphomannoisomerase deficiency or bile acid synthesis defects. Cardiac failure should first suggest mitochondrial fatty acid oxidation disorders. Therefore, a working knowledge of these diseases, their presentations, and their evaluation is critical for the emergency provider. [4-7]

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ISSN No. : (p) 2348-523X, (o) 2454-1982

DOI: 10.46858/vimshsj.10204

Date of Published : 30th June 2023

Case report:

A 4.5-month-old male was brought to the hospital by his relatives with a history of Generalised tonic-clonic seizures (GTCS) type convulsions (each lasting 10 minutes, associated with up rolling of the eyes, frothing at the mouth, and involvement of all 4 limbs) presenting intermittently in a span of 1 month. On eliciting his history, he was a 6th-order child, born out of a non-consanguineous marriage, to a G6A3L1D1 mother, of advanced maternal age of 40 years. There is a history of sibling death at 3 months of age (cause unknown).

History of developmental delay was given by the mother with child having partial neck holding and inability to roll over; social smile was absent; and visual fixation was absent.

Upon examination, facial features showed a flat philtrum, frontal bossing, low-set ears, (Pic no.1) and a sacral pit that was found to be non-communicating as noted on the USG (L/S) spine. His investigations revealed anemia (Hb-6.5 g/dl), raised CPK levels (550.30 units/lit), and hyperammonemia (429 ug%).

He was treated with IV fluids, IV anti-epileptics, and IV antibiotics, along with nutritional supplements. He was given blood transfusions, and hepatic drip was started to counter hyperammonemia.

EEG was done which showed sharp spikes and wave complexes in bilateral hemispheres, but MRI brain (plain) showed no significant findings. Otoacoustic emission was found to be normal, and vision was found to be subnormal for age with absent visual fixation. In view of suspected inborn errors of metabolism, blood and urine samples were sent for metabolic screening and found to be positive for methylmalonic acidemia. (Pic no.2 and Pic no.3)

Patient got a repeat episode of convulsion and was loaded with IV anti-epileptics for its management. Repeat blood investigations showed severe thrombocytopenia, elevated CRP levels, deranged LFTs, and dyselectrolytemia (hypokalemia and hypocalcemia). We prescribed carnitine, a vitamin B12 supplement, and a protein-restrictive diet. For further treatment, patient was referred to a higher center.



Pic no. 1: Flat philtrum, frontal bossing, low set ears.

Pic no.2: Increased Propionyl carnitine / Acetyl carnitine ratio and decreased levels of Methionine

Pic no. 3: Increased excretion of Methylcitric acid 1 & 2 and Methylmalonic acid

Discussion:

There are two forms of methylmalonic acidemia, the classic, acute onset, with symptoms in the neonatal period, and a later post-neonatal form. In the neonatal period, clinical signs include symptoms such as vomiting, weight loss, dehydration, temperature instability, hypo or hypertonia, irritability, lethargy, seizures and coma.[8] The differential diagnosis involves sepsis, drug intoxication and ischemic hypoxic encephalopathy.

Post-neonatal crises are usually triggered by protein overload, catabolic events or use of certain medications, the same factors observed in the patient's history in the post-diagnosis period culminating in new hospitalizations.[8,9] The most common clinical features include encephalopathy or unexplained coma, hypotonia, seizures, tachypnea, cardiomyopathy and delayed neuropsychomotor development [8,9]. Some factors are capable of initiating acute decompensation of the disease, despite adequate treatment, such as viral infections, fever or surgical procedures.[10,11]

Clinical features include anorexia, failure to thrive, hypotonia, developmental delay, progressive renal failure, functional immune impairment, optic nerve atrophy, and haematological abnormalities.

Regarding laboratory findings, disease suspicion occurs in the presence of signs of metabolic acidosis, lactate increase, high concentrations of plasma ammonia, leukopenia, thrombocytopenia, anemia and presence of urinary ketone bodies, without other causes. In the presence of hyperammonemia, the patient requires additional tests, such as plasma amino acid chromatography, urinary organic acids and serum or plasma acylcarnitine.

For diagnostic confirmation, one needs molecular genetic examinations and enzymatic studies [8]. High levels of propionylcarnitine, alanine and glycine in the plasma, together with an increase in urinary methylmalonic, methylcitric acid and 3-hydroxypropionic acid prove the diagnosis [10]. Likewise, the diagnosis of the patient under analysis was only possible after an increase in serum propionylcarnitine along with high urinary acids (methylmalonic and 3-hydroxypropionic), which corroborated the diagnosis of MA, leading to better management of

the clinical condition.

Genetic tests have also been requested; however, they are still being carried out. Early diagnosis of Propionyl acidemia 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.[11]

Treatment starts even before the exam results.[8] Strict use of a specific diet is essential to improve the prognosis of patients until new therapeutic options appear.[12] The initial treatment of the decompensation crisis included stabilizing the patient with supportive measures, suspending protein intake (for maintenance, protein intake up to 0.8 g/kg of protein daily) and prevention of prolonged fasting. One should also consider intravenous glucose infusion and parenteral nutrition therapy. Associated infections should be treated quickly. A specialized and multidisciplinary metabolic team should start the evaluation and the specific drug treatment. This should be guided from the level of plasma urea, with L-carnitine, sodium benzoate and vitamin B12 supplementation, when there is a deficiency of the mitochondrial enzyme dependent on cobalamin and N-carbamylglutamate[8,10,12]. In more severe patients, it may be necessary to use extracorporeal detoxification, as in those with ammonia levels higher than 400-500 $\mu\text{mol/L}$. [8,9] In this case, the patient was stabilized and treated for the associated conditions that led to the decompensation, and once diagnosed as MA, drug treatment with vitamin B12 and L-carnitine was initiated, and we instructed the patient concerning the need for a low protein diet and then referred to another higher centre.

Due to the severity and rapidity in which this disorder can cause complications when left undiagnosed, screening for methylmalonic acidemia should be included in the newborn screening program. If untreated, these children usually die early in life, Zhou et al found a variant responsive to the administration of vitamin B12.[13] Since these latter patients apparently develop normally if treated, an early correct diagnosis becomes especially important

Conclusion:

A high index of suspicion for presence of inborn errors of metabolism is necessary and a thorough workup with metabolic screening tests is needed, TMS and GCMS along with molecular genetic testing and targeted therapy will go a long way to improve survival with minimal neurodevelopmental morbidities and decreased mortality. Also, Inborn error of metabolism being a group of genetic disorders, make genetic counseling on its recurrence risk imperative for individuals who have had one affected child.

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