

Methylmalonic Acidemia- A Rare Inborn Error of Metabolism

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ABSTRACT

The methylmalonic acidemias (MMA) are a heterogeneous group of autosomal recessive inborn errors of organic acid metabolism. The hallmark of MMA is hyperammonemia, encephalopathy and metabolic acidosis in infancy and especially so in neonatal age group. Management of such cases is often challenging and is associated with variable outcome. We present a nine day old male child who was referred to us with

vomiting, lethargy and myoclonic seizures. Organic acidemia was thought of, because the neonate had metabolic acidosis with increased anion gap along with hyperammonemia, ketonuria and hypoglycemia. Tandem mass spectrometry along with Gas Chromatography-Mass Spectrophotometry helped us to clinch the diagnosis of methylmalonic acidemia in our neonate. Patient was symptomatically managed along with carnitine and multivitamin supplements. He was sent home with advice of regular follow-up.

Keywords: Gas chromatography-mass spectrophotometry, Hyperammonemia, Metabolic acidosis, Organic aciduria, Tandem mass spectrometry

CASE REPORT

A 23 years old second gravida mother with third degree consanguineous marriage delivered a full term 2500 grams male baby who was referred to us from private hospital on 9th day of life with vomiting, lethargy, refusal to feed, breathlessness since twelve hours of birth and repeated myoclonic jerks. On examination, baby was lethargic, hypothermic with acidotic breathing. He had hepatomegaly, jaundice and depressed Moro's reflex with a weak cry and was lying in hypotonic pithed-frog like posture. We suspected an inborn error of metabolism in view of consanguinity, clinical presentation and previous sibling death. The first male child who had similar complaints of vomiting and lethargy, succumbed on 8th day of life before investigations could be done.

Initial investigations revealed severe metabolic acidosis (pH-6.9, bicarbonate-3.2 mmol/L) with high anion gap of 36, serum ammonia (981 μ mol/L), urine reducing substances, ketonuria and normal sepsis screen. All the above reports were in favour of organic acidemia. High glucose infusion rate (GIR 6-10 mg/kg/min) was given to prevent catabolism and metronidazole was added for gut sterilization. Intravenous bicarbonate and vitamin B12 along with carnitine, biotin and Medium chain triglyceride (MCT) oil supplements were added. Serum ammonia reduced drastically from the initial 981 μ mol/L to 79 μ mol/L in 4 days.

Further workup included tandem mass spectrometry (MS/MS) which revealed low free carnitine and free/acyl carnitine ratio with an elevated C3, C3/C0 and C3/

C2 ratios. This was suggestive of either methylmalonic acidemia (MMA) or / propionic acidemia (PA). Plasma aminoacidogram (PAA) showed markedly high levels of precursors (glycine, methionine, valine and lysine). We also found increased levels and high values of serum non-esterified free fattyacid -1141.10 uEq/L (N: 133-455 uEq/L). Subsequently, Gas Chromatography-Mass Spectrophotometry (GCMS) of plasma and urine revealed marked elevated MMA levels [Plasma MMA-13,345.29 μ mol/L (N : <1 μ mol/L), urine MMA-13.524 μ mol/L]; this clinched the diagnosis of isolated methylmalonic acidemia. Serum homocysteine and B12 levels were normal. Hence, we suspected classical *mut* (0) type of MMA. Further, definitive confirmation with molecular studies was planned but could not be done due to financial constraints. Baby improved clinically and was discharged on breast feeds along with the above mentioned supplements. Biochemical profile was planned to be repeated in one month but patient was lost to follow-up and later expired at seven months.

DISCUSSION

Branched chain organic acidurias are a group of inherited metabolic disorders in which organic acids build up in the tissues of affected neonates [1,2]. Methylmalonic acidemia and propionic acidemia are the most frequently encountered organic acidemias in neonates and the rare ones include isovaleric acidemia (IVA) and Maple syrup urine disease (MSUD) [1,2]. Organic acidemias clinically present with multi-systemic involvement with primary involvement of central nervous system [1,2].

MMA is a rare disorder with an overall incidence of approximately 1: 50,000 for isolated MMA [3,4]. MMA is caused either by a genetic defect in the methylmalonyl-CoA mutase [MUT] enzyme itself or in one of the proteins (MMAA, MMAB and MMADHC) involved in the synthesis of its active cofactor adenosylcobalamin (MMA cblA type, MMA cblB type, MMA cblD-variant) [5-10]. There are two distinct subcategories of the *mut* apoenzyme, the *muti* (0) and the *mut* (-). The *mut* (0) apoenzyme has untraceable *mut* activity and *mut* (-) apoenzyme subgroup has low to moderate residual *mut* activity but requires increased concentration of cofactor adenosylcobalamine (AdoCbl) [5-7]. MMA can also be classified into two types; vitamin B12 responsive and vitamin B12 non-responsive [5]. Vitamin B12-responsive included *cblA*, *cblD-var2*, *cblB* and rarely *mut* (-). The Vitamin B12 non responsive are caused by mutations in the MMA-CoA mutase (MUT) gene and are commonly referred as either *mut* (-) and *mut* (0).

In the mitochondria, metabolites from the breakdown of the amino acids (like valine, isoleucine, methionine and threonine), odd-chain fatty acids and the side chain of cholesterol leads to the formation of Propionyl CoA [5]. Mitochondrial propionyl CoA is converted into methyl malonyl CoA by propionyl CoA carboxylase (PCC) along with the cofactor biotin. Methyl malonyl CoA is further converted to succinyl CoA by methyl malonyl CoA mutase (MM CoA mutase) [2,5,8-11]. This reaction requires vitamin B12 (cobalamin) in the form of AdoCbl as the cofactor [5,6,10]. Succinyl CoA is further processed in the tricarboxylic acid (TCA) cycle for energy production [9]. Defects in cobalamin metabolism may also manifest as combined MMA and homocystinuria (*cblC*, *cblD*, *cblF* and *cblJ* defects) as these cobalamin metabolites are used as cofactors in the conversion of homocysteine to methionine [8].

Patients with a complete enzyme deficiency *muti* (0) usually present in the first days to weeks of life with acute deterioration of their general clinical condition. Vomiting, lethargy, hypotonia, seizures, metabolic acidosis and hyperammonemia may progress to coma and death, if untreated [5,12]. Late onset cases of MMA may present at any age ranging from infancy, childhood to adolescence [2,5]. Inadequately treated patients may present with movement disorders, developmental delay, failure to thrive, recurrent vomiting, cardiomyopathy, pancytopenia and renal insufficiency [5].

Diagnosis in MMA neonates involves doing initial metabolic workup including arterial blood gas analysis blood sugar, serum ammonia and lactate, serum/urine ketones and urine reducing substances [1,5]. Tandem mass spectrometric measurement of serum/plasma acylcarnitines with plasma and urine Gas Chromatography-Mass Spectrometry (GCMS) showing grossly elevated MMA levels and its precursors is a vital screening test to detect organic acid disorders [2,5,12,13]. Definitive diagnosis is usually made by

measurement of specific activity of MMCoA mutase enzyme in cultured fibroblasts and molecular genetic testing [5].

Treatment of MMA involves prompt intervention with high glucose infusion rate to prevent catabolism. Other drugs tried include insulin and ammonia-scavenging agents like sodium benzoate, sodium phenyl butyrate and arginine hydrochloride. Affected individuals should be advised a low-protein intake which is beneficial to prevent metabolic crises and irreversible end organ damage [5,12,14]. High carbohydrate diet, L-carnitine, vitamin B12, biotin and special medical formulas / foods that restrict isoleucine, valine, threonine and methionine have been successfully tried [12]. Rarely renal transplantation may be required to restore the renal function in patients of MMA with renal insufficiency [5].

Prognosis is strongly influenced by the duration of coma and peak blood ammonia concentrations especially in neonates [15]. So MMA must be identified at the earliest and prompt therapy should be instituted [3,15]. The patients with *muti* (-) and those with vitamin B12-responsive MMA particularly *cblA* type have better outcome when diagnosed early and treated promptly. Other than these forms the general outcome is still poor. MMA in combination with homocystinuria also has poor prognosis [15].

CONCLUSION

A high index of suspicion for presence of inborn errors of metabolism is necessary in newborns presenting with unexplained lethargy, vomiting, poor feeding, seizures, altered sensorium and failure to gain weight. Additionally in such patients a thorough workup with metabolic screening tests, MS/MS and GCMS along with molecular genetic testing and targeted therapy will go a long way to improve survival with minimal neuro developmental morbidities and decreased mortality.

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