

## Methylmalonic acidemia with hypocalcaemia in a newborn

\*Heena Sudhir Bhandekar<sup>1</sup>, Ishani Arora<sup>1</sup>, Smruti Ingole<sup>1</sup>, Ashwini Lakra<sup>1</sup>

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### Introduction

Methylmalonic acidemia (MMA) is caused by deficiency in the enzyme methylmalonyl-CoA mutase or a defect in the transport or synthesis of its cofactor, adenosyl-cobalamin<sup>1</sup>. Patients with severe MMA have features like hypothermia, vomiting, lethargy, respiratory distress, hyperammonaemia and severe ketoacidosis<sup>1</sup>. The incidence of MMA is 1 in 50,000–80,000 newborns<sup>2</sup>. However, it is more frequently detected in developing countries with no systemic newborn screening programme and with a higher rate of consanguineous marriages. Here we report an unusual case of MMA with persistent hypocalcaemia.

### Case report

A baby was born to a primigravida mother at 36 gestational weeks, with a birth weight of 2.3 kg, a length of 52cm and a head circumference of 34cm. There were no antenatal complications and no abnormality was detected on antenatal scans. Baby was delivered by lower segment caesarean section in view of breech presentation. Baby cried immediately after birth. Cry, tone and activity were normal at birth. The skull and spine were normal and there were no dysmorphic features. No abnormality was detected on systemic examination and the genitals were that of a normal male. Baby was with mother in the postnatal ward till day 2 of life, when he developed refusal to feed and lethargy and was transferred to the neonatal intensive care unit (NICU). On admission to the NICU, baby had a heart rate of 128/min, respiratory rate of 58/min, a temperature of 96°F, an oxygen saturation of 96%, depressed sensorium and ankle clonus. Detailed investigations carried out in the patient are given in Table 1.

<sup>1</sup>Datta Meghe Medical College and Shalinitai Meghe Hospital and Research Centre, Wanadongri, Nagpur, Maharashtra, India

\*Correspondence: [hnbhandekar3@yahoo.com](mailto:hnbhandekar3@yahoo.com)




<https://orcid.org/0000-0002-4980-6713>

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Baby was started on intravenous (IV) 10% dextrose 100 ml/kg/day on day 2 of life which was changed to 0.45% dextrose saline plus inj KCL 120ml/kg/day on day 3 of life. Antibiotics used were inj piperacillin and tazobactam 100 mg/kg/dose intravenously twice a day. Baby developed multifocal tonic clonic movements of limbs and inj. phenobarbitone was added. As the serum calcium was 5.84mg/dl, inj calcium gluconate was started in a dose of 200 mg/kg/day. The metabolic acidosis and hypocalcaemia persisted despite treatment with inj sodium bicarbonate and inj calcium gluconate. Further investigations revealed worsening kidney function tests and persistent hypocalcaemia (5.2mg/dl), positive urine ketones (+++) and elevated plasma ammonia (910µmol/L). We put baby on respiratory support with bubble continuous positive airway pressure (CPAP) in view of worsening neurological status and tachypnea. Inotrope inj Adrenaline infusion was started for the features of shock. Baby developed cardiorespiratory failure on day 5 of life and was put on mechanical ventilation. However, despite all resuscitative efforts baby succumbed in the next three hours and could not be revived.

Metabolic screening of the baby, sent on day 3 of life, revealed MMA after the death of the patient. Gas chromatography mass spectrometry (GCMS) screening revealed increased excretion of 3-hydroxypropionic acid, methyl-citric acid, methylmalonic acid, 2-methyl-3-hydroxyisovaleric acid, 4-hydroxy-phenyl-lactic acid, glutaric acid and adipic acid. Tandem mass spectrometry (TMS) screening revealed increased propionyl-carnitine/acetyl-carnitine ratio suggestive of MMA.

### Discussion

MMA is a lethal disease. It is a heterogeneous disorder of methylmalonate and cobalamin metabolism and its severe form has a poor prognosis. Isolated methylmalonic acidurias and combined methylmalonic aciduria and homocystinuria are the two main clinical variants of the disease, which are respectively caused due to different gene mutations<sup>2</sup>. Complete or partial deficiency of the enzyme methylmalonyl-coenzyme A (CoA) mutase and a defect in the transport or synthesis of its cofactor, adenosyl-cobalamin or deficiency of the enzyme methylmalonyl-CoA epimerase causes the isolated form of the disease. Combined MMA presents with homocystinaemia or

homocystinuria and methylmalonic aciduria or MMA. MMA is an autosomal recessive disorder. Table 2 gives the spectrum of its clinical presentation<sup>3</sup>:

Most common form of the disease is a benign variant, which manifests in older children. More common laboratory findings of MMA are hyperammonaemia, acidosis, hypoglycaemia, ketosis and neutropenia. Major long-term complications of MMA include delayed development, 'metabolic stroke' (mainly involving basal ganglia), paraparesis or quadriparesis, progressive renal failure, movement disorders like dystonia and choreoathetosis, optic nerve atrophy, pancreatitis, growth failure or functional immune impairment.

Our patient presented with all the clinical features of severe neonatal-onset form of MMA with hypocalcaemia. Though hypocalcaemia is a known metabolic abnormality in MMA<sup>4</sup>, no case reports have been documented in literature so far. Most of the causes of early onset hypocalcaemia were ruled out in our case on maternal history like history of gestational diabetes, intake of anticonvulsants or antacids in mother or birth asphyxia in baby<sup>5</sup>. Further, there was no history of toxemia of pregnancy in the mother. However, serum vitamin D or parathyroid hormone level of mother and detailed evaluation for hypocalcaemia in baby could not be done as baby succumbed very early. Regardless, this association needs further research.

**Table 1: Detailed investigations of patient according to day of life**

Investigation	Day of life -2	Day of life - 3	Day of life - 4	Day of life - 5
Haemoglobin	14.1 g/dl			
Total leucocyte count	5800/cu mm			
Platelet count	256,000/cu mm			
C-reactive protein	Negative			
Serum calcium	5.84 mg/dl		5.2mg/dl	
Serum magnesium	3.03 mg/dl			
Serum creatinine	0.93 mg/dl	1.07mg/dl	1.38mg/dl	
Blood urea	77.69 mg/dl	88.5mg/dl	86.98mg /dl	
Serum sodium	148meq/L	156meq/L	150mEq/L	
Serum potassium	5.8mEq/L	4.39mEq/L	3.75mEq/L	
pH	7.244	7.194	7.127	
pCO <sub>2</sub>	15 mmHg	12.4mmHg	19.1mmHg	
pO <sub>2</sub>	88 mmHg	132mmHg	85 mmHg	
Serum chloride	123 mmol/L	128 mmol/L	128 mmol/L	
Serum bicarbonate		8.9 mmol/L		
Base		-22.6 mmol/L	-21.6 mmol/L	
Aspartate transaminase	429 IU/L			
Alanine transaminase	20.9 IU/L			
Total serum bilirubin	7.61 mg/dl			
Indirect serum bilirubin	6.9 mg / dl			
Serum albumin	2.9 mg/dl			
Ammonia			910 ug/dl	
Lactate				16 mg/dl
Gas chromatography mass spectrometry (GCMS)			Positive for Methylmalonic acidaemia	
Tandem mass spectrometry screening (TMS)			Positive for Methylmalonic acidaemia	
Neurosonogram				No abnormality detected

**Table 2: Spectrum of clinical presentation of methylmalonic acidaemia<sup>3</sup>**

Clinical Variant	Clinical features
<i>Neonatal Onset (severe)</i>	Feeding difficulty, respiratory distress, vomiting, lethargy, dehydration, encephalopathy, progressive coma
<i>Late-onset (acute and intermittent)</i>	Frequent episodes of lethargy, altered sensorium or coma, ataxia, sometimes with focal neurological deficits
<i>Progressive (chronic)</i>	Delayed development, failure to thrive, movement disorders, hypotonia

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