

Methylmalonic Acidemia

Shahid Mahmud, Syed Awais Ul Hassan Shah, Kanwal Jehanzeb and Salman Ali

ABSTRACT

Methylmalonic Acidemia (MMA) is an inborn error of metabolism that results in accumulation of methylmalonic acid in blood and increased excretion in urine. The effects of MMA vary from mild to life threatening and it usually presents in early infancy. Affected infants can have vomiting, dehydration, hypotonia, developmental delay and failure to thrive. The emergency treatment of the newborn with MMA mainly comprises rehydration and promotion of anabolism, followed by long-term dietary management by both the restriction of precursor amino acids using a low protein diet and avoidance of prolonged fasting. Prognosis depends on the type of MMA and whether the condition is well controlled in general and during episodes of metabolic decompensation. We report here the presentation and management of a 2-year boy with MMA who failed to achieve expected milestones for age. To the best of our knowledge, only one case of MMA has been reported from Pakistan.

Key Words: *Methylmalonic acidemia. Metabolic acidosis. Inborn error of metabolism. Developmental delay. Methylmalonic aciduria. Methylmalonic acid.*

INTRODUCTION

Methylmalonic Acidemia (MMA) appears to be more common than other organic acidemias. It can present in the neonatal period. Affected infants present in the first few days of life with vomiting, respiratory distress, feeding intolerance, lethargy and severe acidosis, which if not aggressively treated, often progresses rapidly to coma and death.^{1,2} In most children, the disease is diagnosed during an episode of metabolic decompensation. These children present intermittently with severe illness and metabolic acidosis but are otherwise normal during crisis-free periods. Increased levels of organic acids including methylmalonic acid can be toxic to various organs in the body resulting in varied clinical features of the condition.³

This report describes a rare inborn error of metabolism in a 2-year boy.

CASE REPORT

A 2-year boy, resident of Multan, reported on the first of March 2012 with complaints of exacerbation of pre-existing symptoms of recurrent vomiting and lethargy off and on for the last 13 months. The patient had past history of failure to thrive and developmental delay since the 3 months of age. He was product of a consanguineous marriage, delivered at term in a hospital where the antenatal checkups were done regularly by the mother and were reported to be normal. The couple had already lost a 7 days old baby girl who was brought in the hospital with vomiting and dehydration in a serious

condition, but she passed away without any diagnosis. There was no rash or any specific odor from the patient. He was first admitted at 10 days of age due to neonatal jaundice which resolved after 5 days of phototherapy. He was exclusively breast fed and weaning started at 11 months of age. The second admission at 11 months of age was due to vomiting and high grade fever. He was admitted, given antibiotics, intravenous fluids and discharged. His third admission was with lethargy, unable to take feed and persistent vomiting. During this time, he was again rehydrated, managed with intravenous fluids, antibiotics, intravenous sodium bicarbonate, and discharged. His fourth admission was with high grade fever and vomiting. The fifth admission was at 2 years of age with similar complaints and generalized tonic clonic seizures, not associated with fever but associated with frothing from mouth and fixed gaze. During all these admissions patient had hypoglycemia and severe metabolic acidosis.

He had achieved neck holding at 7 months of age, started sitting with support at 9 months and without support at 11 months of age. He had poor speech development. He turned to voice, but he was unable to crawl or pull to stand and pincer grasp was not present. Although the chronological age of the patient was 2 years, his developmental age was 7 - 8 months.

General physical examination revealed a lethargic and dehydrated boy with heart rate of 130/minute, blood pressure of 60/40 mmHg and a respiratory rate of 62/minute. His capillary refill time was 6 seconds. He had deep and sighing breathing and had subcostal and intercostal recessions. He was immediately shifted to PICU where he was given oxygen and normal saline bolus and rehydrated with fluids, started on broad spectrum antibiotics and kept NPO. Bedside, investigations revealed blood glucose of 27 mg/dl, urine for ketones positive and ABGs showing pH of 7.07, HCO 35 mmol/l

Department of Paediatrics, Military Hospital, Rawalpindi.

*Correspondence: Dr. Syed Awais Ul Hassan Shah, House No. 111, Lane No. 6, Askari 12, Near Chaklala Cantt, Rawalpindi.
E-mail: awais_ul_hassan@hotmail.com*

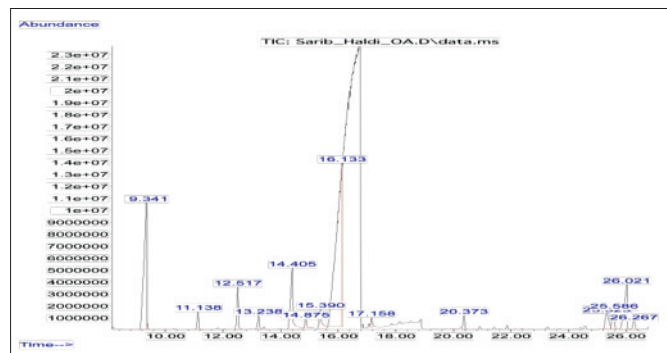
Received: November 26, 2012; Accepted: January 13, 2015.

and PCO_2 of 26 mmHg. His hypoglycemia was corrected with 10% dextrose and he was given sodium bicarbonate replacement to correct acidosis.

Once stabilized, systemic examination revealed GCS of 9/15, hypotonia, elicitable deep tendon reflexes, and intact sensations. Abdominal examination revealed a liver palpable 3 cm below right costal margin which was soft, non-tender, had rounded margins, smooth surface and was non-pulsatile. Total liver span was 8 cm.

Keeping in view the recurrent episodes of vomiting, lethargy, developmental delay, history of an early neonatal death, marked acidosis, hypoglycemia and ketonuria on repeated admissions, a working diagnosis of inborn error of metabolism, possibly organic acidemia was made, which was precipitated due to the sepsis.

Baseline investigations revealed hypochromic microcytic anemia with Hb of 10.1, platelets of 100 and TLC of 4.5. Liver function tests revealed ALT of 234 U/L, serum ammonia of 257 $\mu\text{mol/L}$ and serum lactate of 2.53 mmol/L. Renal function tests, serum calcium, magnesium and CSF were normal. Urine for metabolic screening and urine for reducing sugars other than glucose were negative. His coagulation profile, thyroid profile and X-ray chest were normal. When levels of MMA were investigated in urine and plasma, laboratory tests showed 7100 $\mu\text{mol/L}$ of MMA in urine (normal = less than 5 $\mu\text{mol/L}$) as seen in Figure 1 and 440 $\mu\text{mol/L}$ in plasma (normal = less than 1 $\mu\text{mol/L}$); confirming the diagnosis of methylmalonic acidemia. Acylcarnitine



Name: ABC Age: 2 years Gender: Male Ref Doctor: XYZ
File No: 152/12 Date: 18/03/12 Sample: Urine

RT	Compound
9.341	Lactic acid
11.138	Pyruvic acid
12.517	4- cresol
14.405	Drug metabolite
15.390	3- hydroxyisovaleric acid
16.133	Methylmalonic acid
20.373	Succinic acid
26.021	Int Std
29.214	Adipic acid
34.736	2- oxoglutaric acid
34.924	4- hydroxyphenylacetic acid
40.417	Homovanillic acid
43.027	Hippuric acid
45.596	4- hydroxyphenyllactic acid
47.375	4- hydroxy Phenylpyruvic cid
51.089, 52.159	4- hydroxyhippuric acid

Figure 1: Showing elevated levels of MMA in urine by GAS chromatography mass spectrometry method.

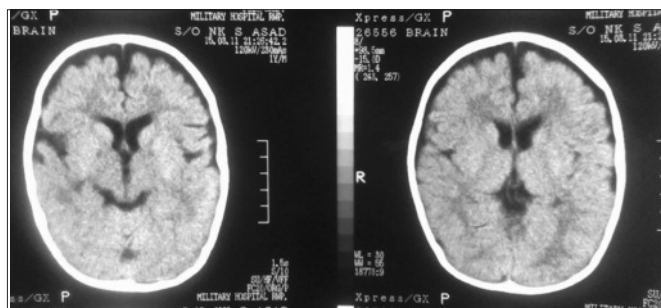


Figure 2: CT scan brain of the patient showing cerebral atrophy and prominence of the ventricles and sulci.

profile was suggestive of a MMA pattern. Serum amino acids and urinary orotic acid was normal. CT scan of brain showed cerebral atrophy and prominence of ventricles and sulci (Figure 2). He was further managed with protein restricted diet, Inj. vitamin B12, oral carnitine and sodium bicarbonate replacement. Detailed parental counselling was done regarding the diagnosis and danger signs of the disease were explained. In case of emergency, the parents were given telephone contact of Paediatric registrars on duty and Consultants and were given open access to PICU.

DISCUSSION

Oberholzer *et al.* and Stoke *et al.* reported the first patients with Methylmalonic Acidemia (MMA).^{4,5} MMA is usually diagnosed in the first year of life. However, in this case, the patient was diagnosed in the 2nd year of life despite repeated admissions in PICU.

It is an autosomal recessive disorder, which means the defective gene must be passed onto the child from both parents. About 1 in 25,000 - 48,000 babies are born with this condition. However, the actual rate may be higher, because a newborn may die before the condition is ever diagnosed. MMA affects boys and girls equally.⁶ The cause of this disease is the mutations in the *MUT*, *MMAA*, *MMAB*, *MMADHC*, and *MCEE* genes. The long-term effects of methylmalonic acidemia depend on which gene is mutated and the severity of the mutation. These mutations generally result in accumulation of methylmalonyl CoA and other potentially toxic compounds to accumulate in the body organs and cause the signs and symptoms of the disease.⁴

Infants may appear normal at birth, but develop symptoms once they started weaning with protein diet, which can worsen the condition. Symptoms include lethargy (84%), failure to thrive (73%), recurrent vomiting (73%), dehydration (71%), respiratory distress (67%), hypotonia (63%), developmental delay (47%), hepatomegaly (41%) and coma (40%). When a child presents with such symptoms, it is called metabolic crisis, which if not addressed at appropriate time can lead to worsening of the condition.² This patient presented with lethargy, failure to thrive, recurrent vomiting, dehydration, respiratory distress, hypotonia,

developmental delay, hepatomegaly and seizures. The patient got admitted five times due to metabolic crisis.

The laboratory findings in different patients are metabolic acidosis (92%), ketonemia/ketonuria (81%), hyperammonemia (71%), hyperglycinemia/glycinuria (68%), leucopenia (60%), anemia (55%), thrombocytopenia (50%) and normal serum cobalamin (100%).² This patient had pancytopenia, metabolic acidosis, ketonuria, hyperammonemia and normal serum cobalamin. Plasma glycine was normal in this patient.

MMA levels in urine range from 10 - 20 umol/L in mild disturbances of MMA metabolism to over 20000 umol/ in severe disturbance of MMA.⁷ In this patient, the levels of MMA in urine were found to be 7100 umol/L.

Brain CT and MR imaging reveal prominence of ventricles and sulci and a delay in white matter myelination. In the largest published series on brain imaging findings in methylmalonic acidemia, 4 of 23 patients had symmetrical globipallidi infarcts.⁹ In this patient, the CT scan showed cerebral atrophy and prominence of ventricles and sulci. No globus pallidus infarct was seen in the CT brain of this patient.

The main treatment for 'vitamin B12 responsive' MMA is parenteral hydroxycobalamin or cyanocobalamin given in the dose of 1 mg/kg/day.⁸ Children with MMA may benefit by taking L-carnitine which conjugates and detoxifies propionyl-CoA and methylmalonyl-CoA. Antibiotics can help lower the amount of methylmalonic acid made in the intestine. Children who are having symptoms of a metabolic crisis should be treated in the hospital. During a metabolic crisis, dextrose infusion is given to correct hypoglycemia and sodium bicarbonate for treating metabolic acidosis. The offending amino acids, i.e. leucine, valine, methionine and threonine should be restricted. A diet low in proteins (milk and dairy products, meat, poultry, fish, eggs, dried beans) and fats, and high in carbohydrates like bread, cereal, pasta, fruit and vegetables should be advised to prevent metabolic crisis. In addition to low protein diet, there are special medical formulas available which contain appropriate amount of proteins required for growth and development but without leucine, valine, threonine and methionine. Infants and young children with MMA need to eat frequently to prevent a metabolic crisis.¹⁰ This patient was managed with all of the above except for the special milk formulas which were not available in our country and thus the child was put on protein restricted diet.

Some children have long-term problems even if they have never had a metabolic crisis. These can include learning disabilities or mental retardation, delays in walking and motor skills, abnormal involuntary movements (dystonia and chorea), spasticity, poor growth with short

stature, skin rashes and infections, osteoporosis, enlarged liver, kidney disease or failure.⁶ This patient had developmental delay, hypotonia, poor growth and recurrent infections.

Genetic testing should be offered to the parents of such patients. Prenatal diagnosis is possible by measuring methylmalonate levels in the amniotic fluid, in maternal urine and by estimating enzyme activity in the fetal white blood cells and cultured fibroblasts. Attempts have been made to give Inj. vitamin B12 to mothers antenatally.⁷ Parents of this patient were advised regular follow-up and antenatal treatment before next pregnancy.

MMA is a rare entity and few cases in children have been reported in literature. The report of rare cases, such as the one in this article, will help improve the knowledge of paediatricians and geneticists about MMA, thus allowing early diagnosis and better therapeutic results.

REFERENCES

1. Bindu PS, Kovoov JM, Christopher R. Teaching neuro-images: MRI in methylmalonic acidemia. *Neurology* 2010; **74**:e14.
2. Marquard J, El Scheich T, Klee D, Schmitt M, Meissner T, Mayatepek E, *et al.* Chronic pancreatitis in branched-chain organic acidurias: a case of methylmalonic aciduria and an overview of the literature. *Eur J Pediatr* 2011; **170**:241-5.
3. Dionisi-Vici C, Deodato F, Röschinger W, Rhead W, Wilcken B. 'Classical' organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. *J Inherit Metab Dis* 2006; **29**:383-9.
4. Oberholzer VG, Levin B, Burgess EA, Young WF. Methylmalonic aciduria. An inborn error of metabolism leading to chronic metabolic acidosis. *Arch Dis Child* 1967; **42**:492-504.
5. Stoke O, Jellum E, Eldjarn L, Schnitler R. The occurrence of beta-hydroxy-n-valeric acid in a patient with propionic and methylmalonic acidemia. *Clin Chim Acta* 1973; **45**:391-401.
6. Rezvani I. Defects in metabolism of amino acids. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, editors. *Nelson textbook of paediatrics*. 18th ed. Philadelphia; Elsevier: 2007; p. 85.
7. Fowler B, Leonard JV, Baumgartener MR. Causes and diagnostic approach to methylmalonic acidurias. *J Inherit Metab Dis* 2008; **31**:350-60.
8. Saudubray JM, Charpentier C, Coude FX, Ogier H, Pham Dinh D, Bartlett K, *et al.* [Prognosis of congenital methyl-malonic aciduria. Correlations between tolerance to proteins, response to vitamin B12 and enzymatic defect]. *Arch Fr Pediatr* 1980; **37**:IX-XIV.
9. Brismar J, Ozand PT. CT and MR of the brain in disorders of the propionate and methylmalonate metabolism. *AJNR Am J Neuroradiol* 1994; **15**:1459-73.
10. Deodato F, Boenzi S, Santorelli FM, Dionisi-Vici C. Methylmalonic and propionic aciduria. *Am J Med Genet C Semin Med Genet* 2006; **142**:104-12.

