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A case of cyanocobalamine responsive methylmalanoic acidemia presenting with metabolic stroke

Nimanthika M.W.A.[1], Kankananarachchi C.P.I [2], Wackwella H.C. [1], Silva K. D. N. [1] , Deshapriya U.D.S. [1], Gamage P. [1], Liyanarachchi M. S. [1] , Jasinge E. [3], Fernando M. [1], Kodikara S.K.Y.I [2], Liyanarachchi N.D. [1], Hewawitharana G.P. [1]

[1] Teaching Hospital, Karapitiya, Sri Lanka
[2] Faculty of Medicine, University of Ruhuna, Sri Lanka
[3] Lady Ridgeway Hospital, Colombo, Sri Lanka

Correspondence email: imalke462@gmail.com

https://orcid.org/0000-0002-9351-2966

Introduction

Methylmalonic academia (MMA) is a rare autosomal recessive disorder of propionate catabolism. It has two subtypes, isolated MMA and MMA with Homocystinuria [1]. MMA is secondary to the defect of the conversion of L-Methylmalonoic-CoA to Succinyl-CoA. The enzyme responsible for converting L-Methylmalonoic CoA to Succinyl CoA is methyl malonyl CoA mutase (MUT). Adenocyanocobalamine, derived from Cyanocobalamine (B12), is an essential coenzyme of the MUT enzyme. Deficiency of either MUT or B12 results in the accumulation of Methylmalonic acid in body fluids causing MMA. The onset of clinical manifestation of MMA can range from the early neonatal period to adulthood.

Moreover, vitamin B12 responsive phenotype can present in the neonatal period or late infancy. Metabolic stroke is a known manifestation of MMA [2]. Here, we present a case of a 13-month old baby with vitamin B12 responsive MMA presents with a metabolic stroke.

Case Presentation

A 13-month-old baby boy presents with rapid breathing, vomiting, fever and altered level of consciousness of 2-day duration. (Figure 1) He was the 3rd child born to consanguineous parents following an uneventful antenatal and perinatal period. His birth weight was 3.1 kg. He was thriving well along the birth centile. There was no developmental delay. The child was, on average, Sri Lankan diet, which elder brother, and there is a history of the sudden death of the second child of the family at the age of 5 months. The diagnosis of the deceased sibling was not evident, but the parents claimed that he also had a similar presentation to this child.

This child was admitted initially to a district general hospital. On admission, he was dehydrated and was having acidotic breathing. His Glasgow Coma Scale (GCS) was 13/15. There were no focal neurological signs. Initial venous blood gas showed severe metabolic acidosis with a high anion gap. (PH-7.1, HCO3-3.0 mmol/L, Lactate- 3.2, PCO2- 12 mmHg). Blood glucose on admission was 34 mg/dL with positive urine ketone bodies. The rest of his biochemical investigations showed mildly elevated serum creatinine, urea and uric acids. Full blood count showed no abnormality, and the blood picture was normal. He was transferred to the paediatric intensive care unit (PICU) of the Teaching Hospital Karapitiya for further management. On arrival, the child was haemodynamically stable but continued to have an altered level of consciousness. During the PICU stay, he developed severe dystonia with quadriparesis. However, he did not have any seizures.

He had an elevated plasma ammonia level of 292 µmol/L (40-80). Urine organic acid profile showed marked elevation in methylmalonic acid, moderate elevation in 3-OH propionic acid and mild elevation of methylcitric acid and tiglylglycine. Plasma homocysteine levels were within the normal range. Acylcarnitine profile revealed slightly elevated propionyl carnitine (C3) and other indices such as C3/C2 and C3/C16 levels. His serum B12 level was normal. MRI scan of the brain showed high signal

T2W and FLAIR sequence in bilateral global palladium suggestive of a metabolic stroke secondary to organic academia.(Figure 2) The Electroencephalogram (EEG) showed mild cerebral dysfunction without any evidence of epilepsy. There was no evidence of cardiomyopathy or arrhythmias.

He was kept nil by mouth and started on intravenous Dextrose and bicarbonate. Furthermore, he was empirically commenced on Thiamine, Biotine, Carnitine and B12 until the definitive diagnosis was confirmed. Benzexol, Levedopa and Clonazepam were started to manage dystonia. Once the acute stage is settled, he was started on low protein diet. Special branch chain amino acid depleted formula was not started because of the unavailability. The genetic sequencing found a pathogenic mutation in the MMAA gene (variant c.433 C>T P(Arg.145) confirming the diagnosis of Cobalamine A (cblA) type methyl malonic acidemia.

The child was discharged home after a five weeks of stay. He was continued with weekly B12 injections, low protein diet, Carnitine, Lactulose and Metronidazole prophylaxis. The child remained severely dystonic despite being on number of medications. On discharge, he required nasogastric tube feeding.

Discussion

The incidence of MMA varies in different parts of the world. The detection rate of MMA in newborn screening is 0.79, 1.2 and 6.4 per 100000 newborns in the Asia-Pacific region, Middle East and North Africa, respectively [3]. The exact prevalence of MMA in Sri Lanka is unknown, and no MMA cases have been published in Sri Lanka. MMA was first reported by Lindblad et al. in 1967, and the condition usually presents in the early neonatal period with a severe life-threatening form [4]. Vomiting, dehydration, shock, metabolic acidosis and hypoglycemia are characteristic features of acute presentations of MMA. However, some individuals with MMA have a more insidious onset of presentation. Infections, prolonged fasting and stressful events can precipitate acute decompensation episodes [3]. In this case, the child had a febrile illness at the outset. Therefore, it is likely that the acute decompensation secondary to an intercurrent infection.

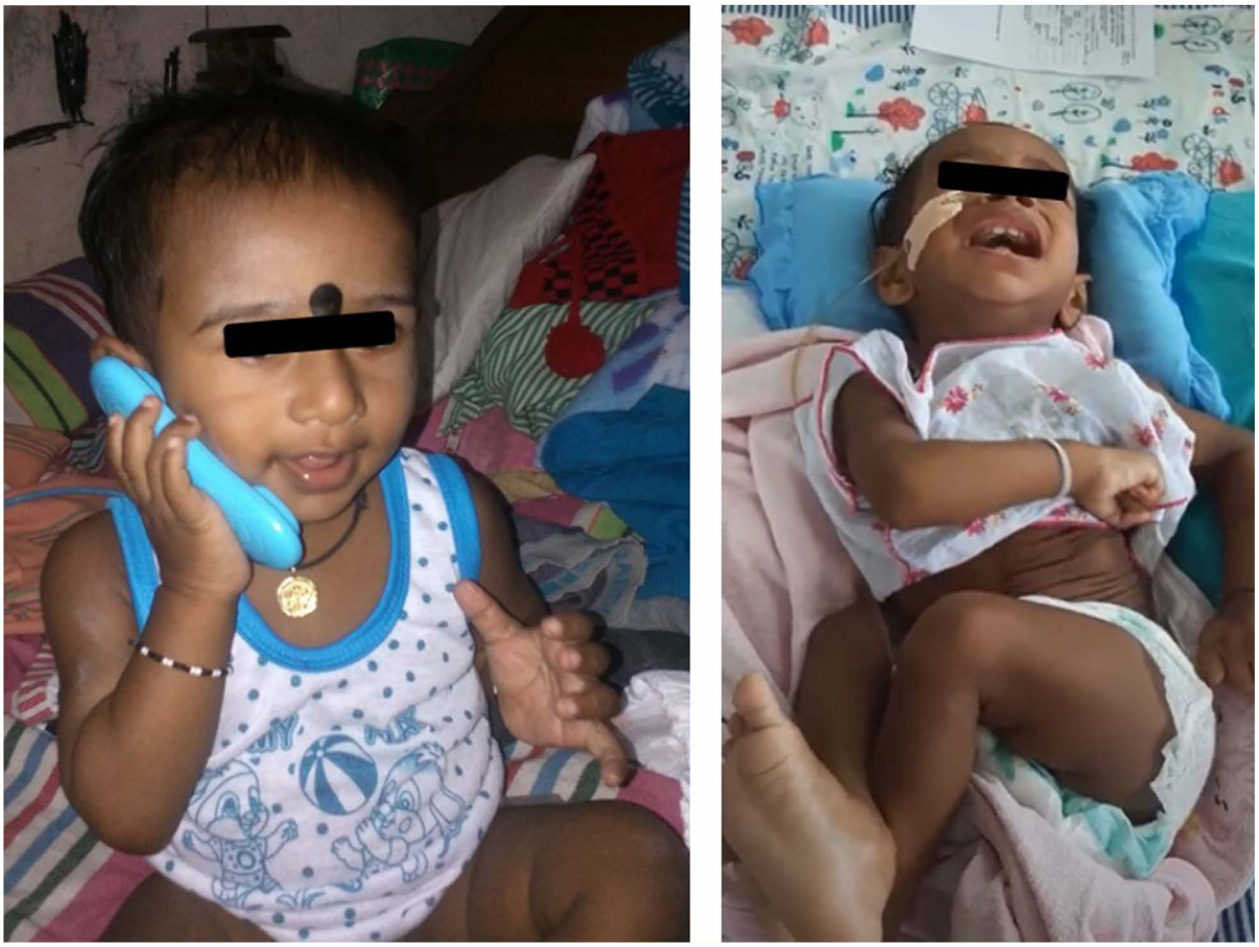

Figure 1 : The child before the acute metabolic crisis (Right) and after developing dystonia (Left)

A study done by Amira et al. in Egypt revealed that 50% of children with MMA had a late onset of presentations. The same survey showed that 80% of patients with MMA were born to consanguineous parents, and 10% had a history of sudden infant death [5]. Similarly, this child's parents were first cousins before their marriage, and the sudden infant death of the previous sibling is highly likely to be secondary to a similar condition.

MMA has a polygenic inheritance with identified mutations in MUT, MMAA, MMAB, MCEE, and MMADHC genes. In this case, the abnormality was identified in the MMAA gene with p.Arg145*. The same mutation was identified as a cause of MMA in several studies previously [6, 7,8]. Devi et al. assessed exome sequencing of 22 children with MMA and revealed that the prevalence of mutations in MUT, MMAB and MMAA is 40%, 33% and 20%, respectively. The identified mutation of this child (p.Arg 145*) is the most commonly reported mutation in European ancestry [8].

Dystonia, choreoathetosis and quadriparesis are known complications of an acute metabolic stroke. Children with MMA have different types of MRI findings. Periventricular white matter changes, ventricular dilatation, basal ganglia calcifications, cerebellar atrophy and corpus callosum thinning are recognized MRI findings of MMA [9, 10]. In this child, marked changes were seen in the Globus pallidus region.

The long term neurological outcome of children with MMA depends on the duration of the coma and the highest peak ammonia concentration. Therefore, it is essential to start prompt treatment early. Cessation of protein in the diet, intravenous dextrose, ammonia scavengers, L carnitine and B12 supplementations should be done pending the confirmatory diagnosis. Though there is a unique formula available in the world, these are not available in Sri Lanka. This child was mainly started on a rice-based diet with added fruits and vegetables. Both kidney and liver transplantation have been recognized therapeutic modalities of MMA [11].

Conclusions

Organic acidemias such as MMA are rare but essential to diagnose early to minimize the long term neurological damage. In resource limiting settings, suspected organic acidemias should be managed with empirical Carnitine, B12, Thiamine, Bicarbonate and Biotin supplements. To prevent the delayed diagnosis, it's Important the establish an expanded newborn screening in Sri Lanka to identity treatable IEMs early.

Acknowledgement

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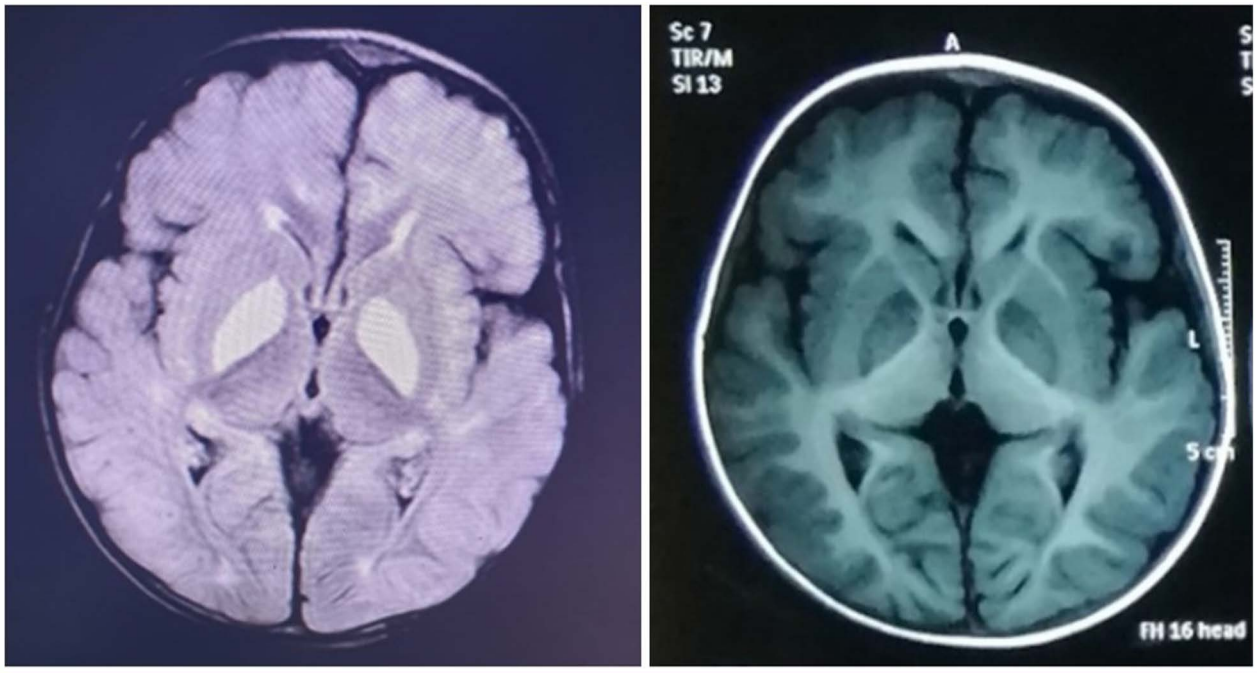

Figure 2 : MRI brain images showing bilateral symmetrical T2 FLAIR high signal intensity (black arrow) and T1 low signal intensity (white arrow) involving the globus pallidi

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