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CASE SERIES

Isolated Methylmalonic Acidemia in Pediatric Population: A Case Report

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Abstract

Methylmalonic acidemia is an autosomal recessive heredity disorder resulting from an inborn defect of organic acid metabolism. It can manifest either in the early days of life or can have a late onset in childhood.

The treatment mainly involves protein restriction, carnitine, and vitamin B12 supplementation. Here, we report a case of methylmalonic acidemia that presented with complaints of multiple episodes of vomiting, hypotonia, and lethargy, followed by regression of achieved milestones. Through the laboratory tests, he was diagnosed with methylmalonic acidemia and confirmed with a genetic report. The child is showing improvement with protein restriction and supplements.

The study aims to highlight the significance of early metabolic disease diagnosis and identification as well as the necessity of early treatment and improved results.

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Introduction

Propionic acid and/or methylmalonic acid build up occurs as a result of methylmalonic acidemia, an inherited metabolic defect. It is brought on by insufficient activity of the propionyl-CoA catabolic pathway's enzymes, PCC and/or methylmalonyl-CoA mutase (MCM).[1]

The onset and severity of isolated methylmalonic acidaemia (MMA) exhibit significant variation in their characteristics. The most prevalent kind, known as the acute/neonatal type, appears in the first few days of life. At birth, babies with the infantile/B12-unresponsive phenotype are normal; nevertheless, symptoms appear a few weeks to months later. The symptoms are usually triggered by protein load or infection.[2]

Neurocognitive impairment and developmental delay are the long-term symptoms of methylmalonic acidemia.

Case Report

We had a case of an 11-month-old boy, 2nd by birth order born of non-consanguineous marriage, with a normal birth history and a delayed development history. He presented with a complaint of multiple episodes of vomiting at 9 months of age, followed by regression of achieved milestones like losing rollover, eye contact,

fixation, and the following. On examination, the child had a head circumference of 44 cm with anterior fontanelle open at the level. He was lethargic with intermittent irritability. The tone was decreased in all four limbs, and antigravity movement was present with normoreflexia**.** After admission into the hospital, investigations showed increased SGOT/SGPT, an acidic pH of 7.315, and increased lactate and low bicarbonate levels. MRI brain s/o bilateral parieto-occipital white matter hyperintense signals with mild cerebral (fronto-parietal predominance) and cerebellar atrophy. TMS (tandem mass spectrometry) and GCMS (gas chromatography mass spectrometry) showed increased levels of propionylcarnitine, methylmalonic acid, methylcitric acid, and hydroxyisovaleric acid, suggesting methylmalonic acidemia.

Next-generation sequencing (NGS) was done to confirm the findings showed MMA, c.433C>T, Exon 2, Homozygous, Methylmalonic aciduria, Vitamin B12 responsive, cblA type, Autosomal recessive, pathogenic.

A low-protein diet along with carnitine and vitamin B12 supplements were used to manage the child. On treatment, the child is showing improvement in terms of weight gain and achieving the milestones. Currently, the child, walking with support at 20 months, has bisyllable speech with meaning, and has good cognition.

Discussion

Methylpropionic acidemia also called as methylmalonic aciduria is an amino acid metablolism disorder. The primary cause of it is methylmalonyl-coenzyme deficiency. A mutation in adenosylcobalamin metabolism, or MCM, leads to an increase in the synthesis of methylmalonic acid and propionic acid, which is the precursor to methylmalonic acid.[3]

The disorder is mainly inherited as autosomal recessive disorder. The onset of disease can be seen in the early days of life (neonatal) or late onset in childhood.

The clinical presentation of the disease is age-related as follows (Table 1):[4]

If the laboratory investigations show metabolic acidosis, increased lactate, increased plasma ammonia, anemia, leucopenia, a diagnosis of metabolic disorder should be suspected. In the presence these findings, the patient requires further investigations like plasma amino acid chromatography, urinary organic acids and serum or plasma acylcarnitine. Elevations in urine methylmalonic, methylcitric acid, and 3-hydroxy-propionic acid, as well as high plasma levels of propionylcarnitine, alanine, and glycine, may confirm the diagnosis.[5]

Table 1: Onset age and symptoms

Age of onset	Symptoms
Neonates (0-28 days)	Lethargy, seizures, hypotonia, poor feeding, vomiting
Infants (1-12 months)	Developmental delay, acute encephalopathy, visual and cognitive impairment, hypotonia, seizures, visual inattention and nystagmus
Children (1-12 years)	Acute encephalopathy, movement disorders, seizures, lethargy, ataxia, muscular weakness, visual impairment, neuropsychiatric disturbance.

However, next-generation sequencing (NGS) is required to confirm the diagnosis and to further classify the phenotypes like vitamin B12 responsive and non-vitamin B12 responsive.

Neuroimaging has little effect on the clinical diagnosis of MMA. Nonetheless, imaging can provide insight into brain damage and direct medical diagnosis and treatment.[4]

During an acute crisis, the patient should be stabilized with supportive measures like decreased protein intake (up to 0.8 g/kg of protein per day for maintenance), parenteral nutrition therapy and intravenous glucose infusion. Extended fasting should also be avoided. The associated infection should be treated aggressively.[5]

L-carnitine, antibiotics to lower intestinal flora, vitamin B12 in responsive MMA patients, low-protein diet, vitamin and mineral supplementation are all standard therapies for long-term management.[6]

Secondary complications include growth failure, pancreatitis, intellectual disability, arrhythmias and/or cardiomyopathy, bone marrow failure, optic nerve atrophy, renal cancer, liver steatosis/fibrosis/cancer, and metabolic stroke (bilateral lacunar infarction

of the basal ganglia during acute metabolic decompensation).[7]

Genetic Counselling

Methylmalonic acidemia is an autosomal recessive disease. An isolated MMA-causing variation that both parents are known to be heterozygous for gives offspring a 25% probability of being affected and a 50% chance of being an asymptomatic carrier. Molecular genetic carrier screening and prenatal/ preimplantation genetic testing are options if isolated MMA-causing pathogenic mutations have been found. [7]

Conclusion

The gold standard for diagnosing MMA is mutation analysis, which can also be used to determine if a treatment plan is B12 responsive or not.[1] As soon as MMA is diagnosed, dietary and pharmacological intervention should be initiated. While the general prognosis for classic MMA is still uncertain, but vitamin B12-responsive MMA has a reasonable outcome.

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