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Case Report

Lethargy In an Infant: Unfolded as Methyl Malonic Aciduria

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ABSTRACT

Methyl malonic aciduria (MMA) is a rare inherited metabolic disorder characterized by the inability of the body to process certain proteins and fats properly and is primarily caused by mutations in genes involved in the metabolism of vitamin B12. Patients often exhibit symptoms such as failure to thrive, developmental delays, lethargy, dehydration, vomiting, and metabolic acidosis which can lead to severe complications, including neurological damage, kidney dysfunction, and even death. Diagnosis of methyl malonic aciduria involves measuring levels of methyl malonic acid in the blood and urine, along with genetic testing to identify the specific gene mutations responsible. Management requires dietary interventions aimed at restricting protein intake and supplementing with vitamin B12, however, in some cases, patients may require additional treatments, such as the administration of carnitine or medications that lower the levels of toxic metabolites.

Keywords: Metabolic disorders, Organic aciduria

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INTRODUCTION

Organic aciduria, belongs to a class of inborn metabolic disorders characterized by accumulation of toxic acid metabolites and increased excretion through urine, caused by deficiency of certain enzymes used for metabolism.[1] Methyl malonic aciduria (MMA) or aciduria is caused by elevation of MMA in the body, and it usually presents with homocystinuria and low methionine as it is an autosomal recessive disorder in the metabolism of methylmalonyl coenzyme or cobalamin (cbl) vitamin B12, where it represents a defect in conversion of methyl malonic acid to succinyl acid where toxins become accumulated in the body.[2] The disease occurs in 1/50000 to 1/100,000 live births, manifesting in the first few days of life, later in childhood or, rarely, in adulthood. There are many subtypes of MMA depending upon the mutation, with common mutations being MMUT, MMAA, MMAB and MCEE genes.[3] The long-term effects and compliance to management are dependent upon type of gene involved with the most common mutation being MMUT gene as it provides information for making methyl malonyl mutase, which is required for metabolism of protein building blocks, lipids and cholesterol.[4] The current case report purpose is to describe a pediatrics case of MMA which highlights the major contribution of early diagnosis and modification of diet which can improve quality of life and play an important role in improved clinical outcome.

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CASE REPORT

A 22-day-old baby boy presented to hospital with decreased oral intake, lethargy, vomiting and weak neonatal reflexes. He was delivered via Lower Segment Caesarean Section with immediate cry at 33 weeks gestational age. Baby was admitted in Intensive Care Unit with complaints of weakened suckling reflex, tachypnoea, dehydration and respiratory distress. General physical examination revealed lethargic, severely dehydrated, deeply comatose child with subcostal recession, absent neonatal reflexes, and feed intolerance with heart rate of 120/minutes and respiratory rate of 65/minute. At birth, weight of baby was 2.4 kg, Occipital Frontal Circumference (OFC) of 35 cm and length 51 cm. He was managed with intravenous fluids, antibiotics and bubble Continuous Positive Airway Pressure (CPAP) for respiratory distress. Bedside investigations revealed blood glucose of 2.0 mmol/L, positive urine for ketones and Arterial Blood Gas (ABGs) showing pH of 7.3, HCO3 12 mmol/L. On systemic examinations, there was hypotonia with deep tendon reflexes elicited. Keeping in view the feed intolerance symptoms, metabolic acidosis with high anion gap and hyperammonaemia, differential diagnosis of meningitis and inherited metabolic disease was made. Baseline investigations revealed hypochromic microcytic anaemia with haemoglobin 9.1 g/dl, platelets 10 x 109/L, and total leucocyte count (TLC) 2.7 x 109/L; negative Coombs

test, ALT 35 U/L, ALP 140 U/L, ammonia 476 mg/dl, total bilirubin was 229 umol/L, urea was 6.1 mmol/L and creatinine was 80 umol/L, respectively. Serum electrolytes sodium and potassium were 137 mmol/L and 2.1 mmol/L, respectively. Serum vitamin B12 was 1867 pg/ml, which was in normal range. To rule out septicaemia, cerebrospinal fluid (CSF) culture and blood culture were checked. CSF culture revealed no growth, while blood culture showed growth of gram negative and staphylococcus. Plasma amino acid level showed raised glycine level while urine organic acid report revealed elevation of methyl malonaic acid and moderate elevation of lactic acid. Magnetic Resonance Imaging (MRI) showed cerebral atrophy. Urine for organic acid report findings revealed methyl malonaic aciduria as shown in Figure-1,2 and 3).

Whole genomic sequencing showed homozygous genetic variant in the MMUT gene (c.1531 C>T, *p*.(Arg511*), present in gnomAD (all frequency 0.000004000), which is classified as pathogenic (Class I) based on American College of Medical Genetics and Genomics (ACMG) criteria (PVS1, PS3, PM2_SUP). Child was advised to start basic P formula and followed up after feed revealed decreased ammonia level and further managed with protein restricted diet, vitamin B12 and oral carnitine. Detailed parental counselling was done regarding the diagnosis and danger signs of the disease were explained in depth.

Figure-1: Urine Organic Acid Report

DISCUSSION

Methylmalonic aciduria (MMA) is a rare inherited metabolic disorder characterized by defective metabolism of certain proteins and lipids, leading to the pathological accumulation of methylmalonic acid in blood and urine. This heterogeneous group of disorders encompasses multiple subtypes, each resulting from mutations in distinct genes involved in the methylmalonic acid metabolic pathway. The most prevalent form is isolated methylmalonic aciduria caused by mutations in the methylmalonyl-CoA mutase gene (MUT), which includes two variants: mut0 (complete enzyme deficiency) and mut- (partial enzyme deficiency). Additional subtypes include combined methylmalonic aciduria and homocystinuria, which result from defects in cobalamin (vitamin B12) metabolism and are classified as cblC, cblD, cblF, and cblJ types based on the specific complementation group affected.

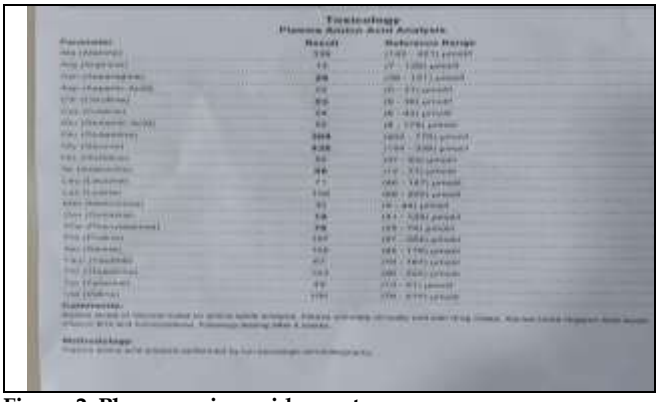

Figure 2: Plasma amino acid report

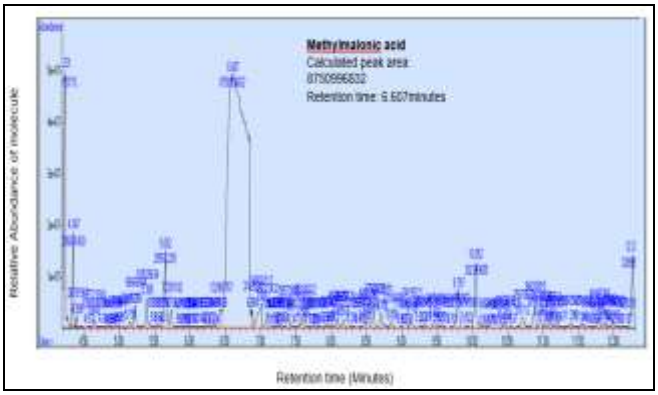

Figure-3: Urine organic acid chromatogram with its mass spectrum analysed by Gas Chromatography-Mass Spectrometry (GC-MS) showing a peak of Methyl malonic acid at 6.6070min with peak area 8750996832.

Each subtype presents distinct biochemical profiles and clinical manifestations, reflecting the underlying enzymatic deficiencies in the propionate catabolic pathway.[5] The symptoms and severity of MMA can vary depending on the specific type and individual but common symptoms include poor feeding, vomiting, low muscle tone, failure to thrive, developmental delays, intellectual disability, seizures, and anemia which if left untreated, can lead to life-threatening complications such as metabolic crisis, coma, and even death.[6] Currently, there is no cure for

MMA, but management focuses on preventing metabolic crises and reducing symptoms.[7] While treatment involves a strict low-protein diet, special medical formulas, and sometimes supplementation of certain vitamins and minerals, severe cases may require organ transplantation or gene therapy. Advancements in molecular genetics and newborn screening have improved early detection and diagnosis of MMA, allowing for prompt initiation of treatment, however, challenges still remain in terms of providing accurate and timely diagnosis, as well as ensuring access to specialized care and treatments for affected individuals.[8] As MMA is a complex disorder that requires multidisciplinary management involving metabolic specialists, geneticists, dieticians, and other healthcare professionals, support from patient organizations and advocacy groups can also greatly help affected individuals and their families in managing the condition. More focus should be placed on raising awareness about this rare genetic disorder, promoting early detection and diagnosis, and advocating for improved access to specialized care and treatment options. It is through these efforts that we can hope to improve the outcomes and quality of life for individuals living with this disease.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MUM & QUA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MQAK: Conception, data analysis, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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