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Methylmalonic Acidemia: An Unusual Cause of Chronic Renal Disease in Adults

Kamel El Reshaid[1*], Abdulrahman Al Kanderi[2]

[1]Department of Medicine, Faculty of Medicine, Kuwait University, Kuwait City, Kuwait
[2]Department of Nephrology, Al-Jahra Hospital, Ministry of Health, Kuwait City, Kuwait
Email: *kamel@hsc.edu.kw

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Abstract

Background: Methylmalonic aciduria (MMA) is a genetic disorder of aminoacid metabolism, due to mutations in methylmalonyl-CoA mutase, which leads to the accumulation of methylmalonic acid in body fluids. Patients typically present at the age of 1 month to 1 year with dehydration, renal impairment as well as neurologic manifestations viz. seizure, encephalopathy, strokes and disease in the globus pallidi. **The case:** a 26-year-old man presented with severe acute on top of chronic renal disease with serum creatinine at 590 umol/L and bilateral 8 cm kidneys with thin and echogenic cortex. He had: (a) hypernatremic dehydration, metabolic acidosis and high ammonia level with (b) a history of multiple similar attacks since the age of 8 months. Diagnosis of MMA was confirmed by high serum and urine enzymatic levels as well as genetic testing. His initial management included support with replacements of fluids, electrolytes, and bicarbonates as well as intravenous dextrose, vitamin B12 and broad-spectrum antibiotic (Meropenem) for his chest infection. Subsequently, he received 1) CARBAGLU (carglumic acid) for 7 days to lower his ammonia level to <50 umol/L, 2) special protein-food formula devoid of methionine, threonine, valine and leucine, 3) supportive drugs viz. vitamin B12, sodium bicarbonate and L-carnitine. He improved clinically with a decrease in serum creatinine level to 380 umol/L that remains stable after 3 years of follow-up. **Conclusion**: Untreated homozygous MMA variants, can achieve adulthood with significant renal disease yet their morbidity and mortality can be ameliorated with diet and specific therapy.

Keywords

Methylmalonic Acidemia, Kidney Failure, Metabolic Acidosis, Autosomal Recessive, Amino Acid Disorder, Kreps Cycle, Hyperammonia, Vitamin 12, Carnitine

1. Introduction

Methylmalonic acidemia (MMA) is an autosomal recessive disorder of the branched amino acid metabolism. The defect involves the conversion of methylmalonyl-coenzyme A to succinyl-CoA in Krebs cycle leading to the accumulation of methylmalonic acid in body fluids [1]. Failure of such conversion is due to the low level of mitochondrial methylmalonyl-CoA mutase (MCM) and/or its cofactor (adenosylcobalamin) [2]. Classic MMA is caused by mutations in the MCM gene (6p12–21.1). Alternatively, it can be caused by defects in the biosynthesis of adenosylcobalamin or by deficient cobalamin transport [3]. Residual activity of deficient MCM corresponds to mutations in the MCM gene as well as to the severity of clinical presentation, reflecting a genotype–phenotype correlation in MMA [4]. All these phenotypes are characterized by periods of relative health and intermittent metabolic decompensation, usually associated with infections and stressful events [2]. Patients typically present at the age of 1 month to 1 year with neurologic manifestations, such as seizure, encephalopathy, cognitive disorders, strokes and disease in the Globus pallidi, hypotonia that can lead to disabling movement disorders with choreoathetosis, dystonia, and para/quadriparesis [5]. Other systemic complications include pancreatitis, cardiomyopathy, growth retardation, functional immune impairment, and optic nerve atrophy. Renal manifestations of MMA have been described rarely in children but not in adults [6]. In this case report, we describe a late presentation of the disease, in a previously uncompliant adult patient, and provide details on its diagnosis and its efficacious management.

2. The Case

A 26-years-old man presented with decreased appetite, nausea, vomiting that was associated with weight loss, malaise and muscle weakness. His condition was progressive over months and lately presented with respiratory distress and seizures after a chest infection. Family history was significant for being the 3rd child with 2 neonatal deaths in his previous brothers. The patient had a past history of multiple admissions for acute renal failure secondary to dehydration following repeated vomiting after attacks of upper respiratory tract infections. As early as the age of 8 months, metabolic disorder viz. MMA was suspected yet not confirmed. Unfortunately, since then, the patient has been uncompliant with medications, diet and follow-up. Moreover, he experienced multiple admissions with acute renal failure due to dehydration following infections and stressful events. On admission, he was in distress of shortness of breath and with kussmaul's breathing. His blood pressure was 90/50 mm Hg with postural hypotension and he was febrile. Systemic examination revealed hypotonia and bilateral basal coarse crepitations on chest auscultation. Laboratory tests showed; 1) normal peripheral leucocytic and platelets counts yet hemoglobin was 110 g/L with normal transferrin saturation% and low vitamin B12 at 142 pmol/L. Serum sugar was 3 mmol/L with low HbA1c at 4% (N: 4.8-5.9). Serum urea and creatinine

were elevated at 20 mmol/L and 595 umol/L, respectively. He had metabolic acidosis (pH 7.3 with HCO_3 at 16 mmol/L with normal lactate and ketone levels. Serum electrolytes were normal except for high sodium (150 mmol/L) and high potassium (5.8 mmol/L). Liver functions were normal except for albumin at 30 g/L and a high ammonia level at 112 umol/L. Serum amylase and lipase were normal. Lipid profile was normal. Urine routine and microscopy were normal. Ultrasound as well computerized tomography of the abdomen and pelvis did not show abnormality except for bilateral small (8 cm) kidneys and with thin and echogenic cortex (Figure 1). Since he had metabolic acidosis and high ammonia level out of proportion to his kidney impairment and normal liver function; MMA was suspected and was treated initially as such. Moreover, metabolic screening and genetic testing were done. Metabolic screen showed; 1) high levels of serum glycine, propionic acid, and methylmalonic acid, as well as 2) high urine levels of methylmalonic acid, methylcitrate, propionic acid, and 3-hydroxypropionate. Hence; diagnosis of methylmalonic aciduria was established. Subsequently; genetic testing, by PCR amplification followed by Sanger sequencing, showed that the patient is homozygous for c.2080C>T (p.ARG694Trp) variant in the MUT gene which is associated with MMA via methylmalonyl-CoA Mutase deficiency. His initial management included implementing a protein-restricted diet (0.5 - 1.5 g/kg/d), support with replacements of fluids, electrolytes, bicarbonates, intravenous dextrose as well as daily 1 g of intravenous vitamin B12, daily 1 mg of L-carnitine, and broad-spectrum antibiotic (Meropenem) for his chest infection. Subsequently, he received; 1) CARBAGLU (carglumic acid) 100 mg twice daily for 7 days to lower his ammonia level to < 50 umol/L, 2) a special protein-food formula devoid of methionine, threonine, valine and leucine, 3) supportive drugs viz. vitamin B12 1 mg thrice weekly, sodium bicarbonate 1 g thrice daily, L-carnitine 100 mg thrice daily. He was advised to avoid NSAIDs and radio-contrast studies. The patient improved clinically and had achieved normal fluid status, blood pressure and mental function within a few days. He did not have significant neurological deficits including hypotonia and basal ganglionic disease. His renal function improved with decrease serum creatinine to 380

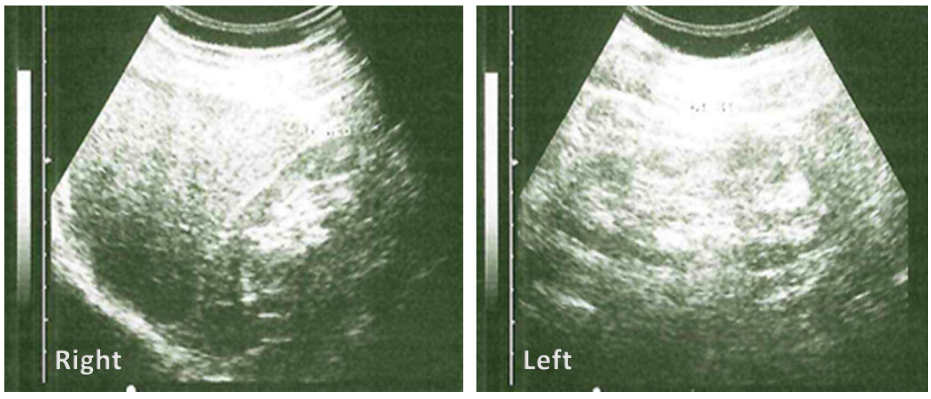

Figure 1. Ultrasonographic scans of the abdomen show bilateral small kidneys (8 cm) with thin and echogenic cortex.

umol/L 2 weeks later. Subsequent to all those measures, awareness of genetic disease milder phenotype, and better future with special-food formula and medications, and availability of life-saving measures with renal replacement therapy; his anxiety and depression improved. He became compliant with his medications and worked as a librarian. Moreover, he married a non-carrier of the gene and had a healthy boy. After 3-years of follow-ups, there were 1) no similar attacks of dehydration, 2) no neurological or psychiatric defects, 3) normal fluid and blood pressure, 4) normal ammonia levels (<50 umol/L), 5) and stable serum creatinine at 390 umol/L.

3. Discussion

In USA, in recent years, every state has a newborn screening program (NSP) that tests newborns for many serious congenital diseases [7]. Many of these conditions are detected by testing a small sample of blood taken from a newborn's heel. The conditions screened for include spinal muscular atrophy, cystic fibrosis, sickle cell disease and other hemoglobinopathies, endocrine diseases, inborn errors of metabolism, lysosomal storage diseases, severe combined immunodeficiencies, critical congenital heart defects, and hearing loss. Since the symptoms of these serious conditions do not always appear at birth, early detection may prove lifesaving and enable children to reach their full potential [8]. The reported cumulative prevalence of MMA is 1:50,000 in Caucasians [9]. However, the true prevalence may be higher because many neonatal deaths may be caused by unrecognized severe phenotypic forms prior to NSP [10]. MMA can be suspected in cases of recurrent attacks of hypernatremic dehydration associated with metabolic acidosis rather than alkalosis with repeated vomiting as well as high ammonia without significant liver disease to account for its metabolism or kidney disease to account for its excretion [11]. Early management entails the exclusion of 1) common causes of metabolic acidosis viz. diabetes, alcoholic ketoacidosis, liver disease, shock, anoxic and/or ischemic injury of tissues, and seizures are often associated with acidosis as well as 2) sepsis especially with candida, and 3) other causes of pediatric strokes viz. cyanotic heart disease, endocarditis and sickling. Treatment of MMA should include: 1) adequate hydration and electrolytes replacement, 2) lower blood ammonia levels by avoidance of high protein diet and especially those rich with methionine, threonine, valine and leucine as well as the use of CARBAGLU and even renal replacement therapy, 3) high doses of Vitamin B12 (co-factor for MCM) and L-carnitine (to remove excess toxic acylcarnitine species from mitochondria), as well as 4) rapid correction of hypoglycemia [12]. In recent years, serum and urine screens for MMA are available as well as its genetic tests [13]. It should be noted that Methylmalonic acid is not elevated in Propionic Acidemia, a disease with a similar presentation [1]. Classically, MMA presents with severe neonatal metabolic crises, progressive failure to thrive, feeding problems, recurrent vomiting, dehydration, hepatomegaly, lethargy, seizures, acute stroke-like events and extrapy-

ramidal and developmental delay [14]. As in our patient, the disease penetrance of MMA is variable with milder phenotypic forms that can survive early deaths yet with progressive lists of complications that include progressive renal disease. Failure to diagnose MMA, presents a massive burden on health services, parents and patient's quality of life [15]. It should be noted that the pathogenesis of MMA-induced renal disease is toxic based on biopsy studies [13]. Moreover, MMA patients with initial low vitamin B12, as in our patient, respond better than those with high ones [16]. Conclusion: untreated milder phenotypic forms of homozygous MMA can achieve adulthood with poor quality of life and significant renal disease yet their morbidity and mortality can be ameliorated with a special diet and specific medications.

Author's Contributions

Prof/Kamel El-Reshaid conceived the study, participated in its design, participated in patient care, and drafted the manuscript. Dr. Abdulrahman Al-Kanderi participated in the study design, and patient care.

Data Availability Statement

The data provided in the current review are available from the references.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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