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Case Report
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A Methylmalonic Acidemia Patient Mimicking Diabetic Ketoacidosis and Long-Term Follow-Up

Atasoy Kutri and Kılıç Yıldırım. Long-Term Follow-Up of a Methylmalonic Acidemia Patient

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ABSTRACT
Objectives: Methylmalonic acidemia (MMA) is the most common inherited type of organic acidemia. It has a diverse presentation in older infants without any initial apparent symptoms. MMA sometimes presents with sudden metabolic decompensation, which may mimic common emergencies like diabetic ketoacidosis (DKA); without early recognition, it can be fatal. In this case, we aimed to emphasize that less common diagnoses such as organic acidemia should be kept in mind in infants with severe acidosis and metabolic decompensation, or in patients with an atypical clinical course to prevent serious morbidities and even death.
Materials and Methods: We report a case of MMA in an infant who presented acutely mimicking DKA and underwent long-term surveillance.
Results: An 8.5-month-old girl, the first child of an unrelated family, was admitted with complaints of vomiting and hyperglycemia and metabolic acidosis were detected. In her history, complementary feeding started at 7 months, and she had one hospital admission at 7 months due to vomiting, which improved with intravenous fluid therapy. A diagnosis of DKA was made, and appropriate fluid therapy and insulin infusion were started. However, despite achieving normoglycemia, the anion gap (AG) remained high, and metabolic acidosis persisted. Due to ongoing drowsiness and high serum ammonia levels (215 µg/dL), a metabolic disorder was suspected, and peritoneal dialysis was initiated. Tandem mass spectrometry analysis showed markedly elevated C3 propionylcarnitine levels and increased C3/C2 and C3/free carnitine ratios, while urinary organic acid analysis revealed a significant increase in methylmalonic acid excretion, along with a marked rise in 3-hydroxypropionate and methylcitrate. *MUT* gene analysis revealed a homozygous mutation c.360_361insT (p.K121*), confirming the diagnosis of MMA. Long-term follow-up has shown a progressive decline in her estimated glomerular filtration rate (eGFR), with even lower levels observed during acidosis attacks.
Conclusion: Inborn errors of metabolism, especially organic acidemia, should be suspected in any infant presenting with severe high AG metabolic acidosis. MMA is also associated with chronic tubulointerstitial nephritis and a progressive decline in GFR.
Keywords: Methylmalonic Acidemia, Hyperglycemia, Diabetic Ketoacidosis, Glomerular Filtration Rate

INTRODUCTION

Methylmalonic acidemia (MMA), a form of organic acidemia, occurs due to a defect in the methylmalonyl-CoA mutase (MCM) enzyme, which is responsible for converting methylmalonyl-CoA to succinyl-CoA.[1] A partial or complete deficiency of the cobalamin-dependent MCM enzyme leads to the accumulation of methylmalonyl-CoA, resulting in a significant increase in the excretion of methylmalonic acid (MMA) in both blood and urine.[2]

MMA affects around 1 in every 50,000 to 80,000 babies. It is more prevalent in nations with high levels of consanguinity and lack of newborn screening, such as economically disadvantaged countries.[1] Patients often present between 1 month and 1 year old with symptoms such as poor feeding, vomiting, dehydration, shock, hypoglycemia, hyperammonemia, and high anion gap (AG) metabolic acidosis, which can progress to coma or death if not treated. The mild form of the disease may occur in infancy and childhood.[3] MMA can occur unexpectedly in older infants, mimicking septic shock or diabetic ketoacidosis (DKA) and be potentially lethal if not detected early.[4] We reported a case of MMA in a newborn with severe high AG metabolic acidosis that mimicked DKA, despite no early symptoms.

CASE REPORT

An 8.5-month-old female patient, with no prior medical history, presented with a complaint of projectile vomiting including the contents of her meals, for the past four days. There was no associated fever, diarrhea, or abdominal pain. About two days later, respiratory distress developed, her feeding gradually worsened, and she had frequent urination, without a foul odor. There was no history of drug or substance intake. The patient's family history revealed that the parents, who are not related but are from the same village, had their first child with a term birth. She had a history of meconium aspiration and was followed in the neonatal intensive care unit for 1 week. Complementary feeding started at 7 months, and she had one hospital admission at 7 months due to vomiting, which improved with intravenous fluid therapy. Upon examination, she was found to be dehydrated. Laboratory tests showed a blood glucose level of 234 mg/dL, and +2 ketones in the urinalysis, and metabolic acidosis (pH: 7.01, HCO_3: 6.4 mmol/L). A diagnosis of DKA was made, and appropriate fluid therapy and insulin infusion were started. However, despite achieving normoglycemia, the AG remained high (28), and metabolic acidosis (pH: 7.18, pCO2: 20 mmHg, HCO_3: 10.4 mmol/L) persisted. In addition, insulin, and C-peptide values were also normal. Due to ongoing drowsiness and high serum ammonia levels (215 µg/dL), a metabolic disorder was suspected, and peritoneal dialysis was initiated, which led to the correction of both the acidosis and hyperammonemia. To clarify the etiology before starting peritoneal dialysis, blood and urine samples were taken for Tandem mass spectrometry (MS), and urinary organic acid analysis, and the patient was referred to our Pediatric Metabolism and Nutrition Department for further investigation and management. On physical examination at the time of admission, body temperature was 36.7 °C; pulse was 118 beats per minute; respiratory rate was 40/min; blood pressure was 95/55 mmHg; body weight was 7400 grams [<3 p, -1.12 standard deviation (SD)]; height was 64 cm (<3 p, -1,96 SD); oxygen saturation was 97%, with no significant findings on systemic examination and no specific odor. Initial laboratory results included hemoglobin: 9.2 g/dL, total leukocyte count: 8240/cmm with 68% neutrophils, platelet count:
251,000/nL, C-reactive protein: 8 mg/dL, venous blood gas: pH 7.35, HCO_3: 20.3 mmol/L, AG: 24.5 mmol/L, lactate: 1.2 mmol/L, blood glucose: 75 mg/dL, serum electrolytes: normal, blood urea nitrogen: 7.93 mg/dL, creatinine: 0.4 mg/dL, serum calcium: 7.6 mg/dL, and glomerular filtration rate: 72. Urine analysis showed pH: 5.5; density: 1022; glucose 2+; protein 1+; and ketones 2+. Serum ammonia was 68 µg/dL, lactate was 13 mg/dL, and pyruvate was 0.7 mg/dL; all were normal. Amino acid levels in both urine and blood were normal. In pre-dialysis tests at the external facility, Tandem MS analysis showed markedly elevated C3 propionylcarnitine levels and increased C3/C2 and C3/free carnitine ratios. Urinary organic acid analysis revealed a significant increase in methylmalonic acid excretion, along with a marked rise in 3-hydroxypropionate and methylcitrate. Based on these findings, the patient was diagnosed with MMA, and treatment with 100 mg/kg levocarnitine and 1 mg hydroxocobalamin was initiated.

Her feeding was adjusted to a branched-chain amino acid-deficient special formula, and isoleucine powder supplementation was provided upon identifying a low isoleucine level in her blood amino acids. *MUT* gene analysis revealed a homozygous mutation c.360_361insT (p.K121*), confirming the diagnosis of MMA. Genetic testing showed that both parents were heterozygous for the same mutation.

After diagnosis, the patient had four episodes of metabolic acidosis, two of which were resistant. At the age of 3, she developed metabolic acidosis, hyperuricemia, and hyperkalemia. In addition to her existing treatment, scholl solution, anti-potassium therapy, and allopurinol were started. At the age of 5, the patient experienced a refractory metabolic acidosis and hyperammonemia attack accompanied by delirium, during which antihypertensive medications were added to her treatment. Long-term follow-up has shown a progressive decline in her eGFR, with even lower levels observed during acidosis attacks. The informed consent of the patient was obtained from her family.

DISCUSSION

We present a case of an infant with MMA who experienced unexpected decompensation associated with high AG and severe metabolic acidosis without any preceding signs or symptoms. In this report, the infant presented with hyperglycemic DKA with a weak insulin response. Due to the persistence of DKA, an underlying metabolic issue was investigated. Hyperglycemia is a rare but fatal MMA symptom that resembles DKA.[5,6] Although hyperglycemia is an infrequent MMA manifestation.[7] There have been described cases of severe and prolonged metabolic acidosis and hyperglycemia despite substantial insulin doses. DKA is the most prevalent cause of

DKA, but it responds well to standard treatment; thus, additional causes of acidosis/hyperglycemia should be examined in poor responders.[8]
Organic acidurias (OAs) should be included in the differential diagnosis, especially in countries where national newborn screening is not implemented. Determining the etiology of hyperglycemic DKA is important and can lead to a good outcome.[9] The unusual presentation of our patient, mimicking DKA, reminds us of the wide spectrum of clinical signs of organic acidemia. In infants with severe acidosis and metabolic decompensation, or with atypical clinical course, there should be a suspicion of a less common diagnosis, such as organic acidemia, to prevent severe morbidities and even death.[10]
Despite significant advancements in treatment, long-term complications such as developmental delay, neurological disorders due to degeneration of the basal ganglia, interstitial nephritis, progressive renal failure, pancreatitis attacks, and cardiomyopathy are commonly observed.[11-13] Impaired kidney function is a well-documented long-term complication of MMA and occurs more frequently than in other organic acidemias. The onset of kidney dysfunction in MMA is related to the molecular subtype. Mut[0] patients are typically affected at an earlier age compared to CblB patients, while CblA and mut- patients may experience kidney issues in later stages of life.[2,14,15] The pathogenesis of kidney damage associated with MMA is not well understood.
Kidney involvement in MMA patients can be both tubular; [proximal renal tubular acidosis (RTAs), impaired urine acidification and concentration ability, and hyporeninemic hypoaldosteronism] and glomerular (chronic interstitial nephritis).[16] Mitochondrial dysfunction appears to play a key role in the pathomechanisms of kidney damage in MMA. In a metabolic acidosis environment, increased ammonia production in the proximal tubule has been suggested as a potential mechanism contributing to the worsening of kidney function.[17] In a rat model, it has been observed that nitrogen nucleophiles, such as ammonia, cause kidney damage and induce chronic tubulointerstitial inflammation through the activation of an alternative complement pathway. Additionally, the activation of the renin-angiotensin system (RAS) plays a role in the pathogenesis of kidney dysfunction associated with metabolic acidosis. This suggests that both toxic metabolites like ammonia, and systemic pathways like RAS, contribute to the kidney damage seen in conditions such as MMA, where metabolic derangements lead to renal complications.[18]
In a study conducted by Şeker Yılmaz et al.[19] from our country, 12 out of 37 isolated MMA patients (32%), were found to have kidney involvement. One patient, despite good metabolic control, exhibited early-onset and rapidly progressing kidney complications, particularly RTA type 4 and stage 3 chronic kidney disease.
In MMA patients, monitoring kidney function is strongly recommended. Serum creatinine, as a surrogate marker of kidney function, may be misleading, because in MMA patients with protein deficiency, a reduction in muscle mass likely results in an overestimation of GFR. Other kidney function markers, such as serum cystatin C, may better reflect the true eGFR and provide a more accurate assessment of renal function in these patients.[20]
During the follow-up of our patient, we observed that the serum creatinine levels began to rise around the age of one, peaked at the age of five, and then stabilized. During the long-term follow-up, the eGFR, calculated using the Schwartz formula, progressively decreasedto a value of 65.66 mL/min/1.73 m^2 at the age of eight. Additionally, during episodes of acidosis, the eGFR was found to be even lower (Table 1).
Blood pressure monitoring should be an integral part of kidney function assessments in patients with conditions like MMA. Hypertension can be a significant complication in these patients and may contribute to the progression of kidney dysfunction, making its early detection and management crucial for preserving renal health.[2] In the case of our patient, during a resistant metabolic acidosis and hyperammonemia episode at the age of five accompanied by a delirium episode, antihypertensive medication was added to the existing treatment.
Combined liver and kidney transplantation appears to be an effective treatment for renal failure in MMA, and it can result in normal kidney function even 10 years after transplantation.[21,22] Kidney transplantation improves kidney function shortly after the transplant, and, in some cases, even years after the procedure (ranging from 1.5 to 14 years). However, it has also been reported that nephropathy and renal failure can recur after kidney transplantation.[23,24] While a few patients show normal kidney function even 15 years after transplantation, some patients develop progressive kidney failure after transplantation. Liver transplantation does not appear to correct a non-functional kidney.[22,25,26]
In countries like Türkiye, where national newborn screening is not implemented, OAs should be included in the differential diagnosis when high AG metabolic acidosis is accompanied by hypo/hyperglycemia,. It is especially important to remember that all patients with MMA are at risk of developing kidney failure during the long-term course of the disease.

Ethics
Informed Consent: The informed consent of the patient was obtained from her family.

Footnotes
Authorship Contributions

Surgical and Medical Practices: G.K.Y., Concept: G.K.Y., Design: M.A.K., G.K.Y., Data Collection or Processing: M.A.K., Analysis or Interpretation: M.A.K., G.K.Y., Literature Search: M.A.K., Writing: G.K.Y.
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Table 1. Summary of the patient's laboratory values in follow-up

Age (Year)	BUN (5-18 mg/dL)	Creatinin (0,4-0,6mg/dL)	eGFR* (mL/min/1.73 m^2)	Cloride (98-107 mEq/L)	Uric acid (3,4-7 mg/dL)	Urine keton	Urine MMA
1	**34**	0.25	143	**111**	3.09	+	-
2	**26.85**	**0.61**	**76.63**	**106**	**9.39**	-	
3	13	0.51	91.66	98	5.3	-	-
4	14	0.53	88.20	104	3.7	-	-
5	**45**	**0.97**	**54.43**	**107**	**8.1**	++	
6	17	**0.77**	**76.071**	96	5	-	-
7	19	**0.89**	**72.30**	92	4	-	-
8	9,2	**0.98**	**65.66**	105	3.4	-	-

BUN: Blood urea nitroge, eGFR: Estimated glomerular filtration rate, MMA: Methylmalonic acid