

A Newborn with Methylmalonic Acidemia Accompanied by Extremely High Ammonia Levels

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Abstract

Most organic acidemias become clinically apparent during neonatal period or early infancy. Infants typically have severe metabolic acidosis with increased anion gap, ketosis and hyperammonemia. Extremely high ammonia levels exceeding 1000 $\mu\text{mol/L}$ is a discriminative feature for urea cycle defect while levels exceeding 200-300 $\mu\text{mol/L}$ are rarely encountered in other reasons of hyperammonemia. Lethargy developed in a boy with extremely high ammonia levels (3693 $\mu\text{mol/L}$) on the post-natal day 3. Higher extremes in ammonia are mainly observed in urea cycle defects. We presented this case which was diagnosed as methylmalonic acidemia by specific tests to emphasize that extremely high ammonia levels can be seen in organic acidemias.

Keywords

Organic Acidemia, Hyperammonemia, Methylmalonic Acidemia, Urea Cycle Defects

1. Introduction

Methylmalonic acidemia (MMA) is a heterogeneous genetic metabolism disorder that is characterized by accumulation of methylmalonic acid and methylmalonyl-CoA in body fluids without hyperhomocysteinemia [1]. According to the studies conducted on the issue, the incidence rate of MMA is 1 in 50,000–80,000 newborns but it is more common in countries where the amount of consanguinity is high and the countries with no systematic newborn screening, similar to developing countries [2, 3]. MMA appears to be more common than the other organic acidemia probably due to its several underlying causes [4-6].

Patients typically presents at the age of 1-month to 1-year with varied presentations of symptoms ranging from poor feeding, vomiting, dehydration, shock, hypoglycemia, hyperammonemia and hyperglycemias with high anion gap (AG) metabolic acidosis if left untreated can lead coma or even death [7-9]. Organs involvement in methylmalonic acidemia includes central nervous system (CNS), bone marrow and kidneys.

It isn't only caused by defective mitochondrial enzyme,

methylmalonyl-CoA mutase but it may also result from abnormalities in synthesis, cellular uptake or transport of 5'-deoxyadenosylcobalamin which is the cofactor of methylmalonyl-CoA mutase [10].

Some of these defects (cb1C, cb1D, cb1F) can cause combined MMA and homocystinuria by disrupting methylcobalamin metabolism as well. Isolated MMA is only seen in MCM enzyme defects (mut 0, mut-, cb1A and cb1B). In mut 0 mutations, there is no enzyme activity while there is residual enzyme activity in mut- mutation [10-12]. cb1C and cb1F lead to combined MMA and homocystinuria in all cases; however, cb1D may result in MMA, homocystinuria or combined MMA and homocystinuria [13].

MMA can present in different clinical forms. Severe form manifest with abdominal distention, lethargy, generalized hypotonia, convulsion, leukopenia, thrombocytopenia, anemia, severe metabolic acidosis and elevated ammonia levels at neonatal period [14]. In mild form, clinical is variable with milder symptoms. Feeding difficulties, recurrent vomiting, hypotonia, metabolic acidosis, elevated

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ammonia levels and neutropenia, intermittent ataxia and behavioral problems can be observed. It is a progressive disorder and metabolic decompensation can be seen during infection in general [14, 15].

The newborn presented with feeding difficulty and lethargy on the postnatal day 3 and had history of consanguinity between parents and 3 deceased siblings. The case which was considered as organic acidemia by history, physical examination and laboratory findings and had extremely high ammonia levels were presented to emphasize the fact that extremely high ammonia levels can be observed in organic acidemias.

2. Case Report

A 3-day old boy was admitted to newborn unite, as it was found that he had hypoglycemia in another facility where he presented with feeding difficulty. In the history, it was found out that the parent were first-degree cousins and the mother had given 8 live births from 9 pregnancies with 3 deceased children (at postnatal day 8 and 6, and one year of age). There was no information about cause of death in 2 siblings; however, data regarding the child died on the postnatal day 6 were found, indicating that the sibling died after presentation to a healthcare facility with feeding difficulty where he/she was diagnosed as hypoglycemia, neonatal convulsion. The parents had 3 healthy girls and one healthy boy. In the physical examination, there was weak sucking, tachypneic breathing and lethargy and cardiovascular examination was normal. Abdomen was free without organomegaly. Genitourinary system examination was also found to be normal. The test and results obtained in laboratory tests were as follows: blood glucose, 45; blood gases (pH, 7.24; PCO₂, 13, HCO₃, 6, ABe, -21); complete blood count (WBC, 7700/mm²; Hb, 18.6 g/dL; Hct, 37%; MCV, 33; PLT, 320.000/mm²); blood biochemistry (BUN, 25 mg/dL; creatinine, 0.6 mg/dL; Na, 147 mmol/L; K, 5.2 mmol/L; Cl, 115; total bilirubin, 9.9 mg/dL; direct bilirubin, 0.35 mg/dL; AST, 89 U/L; ALT, 1389 U/L; LDH, 1143 U/L; CK, 2802 U/L; Ca, 7 mg/dL; P, 9 mg/dL; protein, 5.6 mg/dL; albumin, 3.8 mg/dL). Vitamin B12 level was normal.

After obtaining samples for culture tests, intravenous fluid therapy, ampicillin sulbactam plus cefotaxime therapy was started by initial diagnoses of metabolic disease and sepsis in the patient with consanguinity between parents and deceased sibling who had metabolic acidosis and hypoglycemia. Bicarbonate replacement was given. Blood and urine samples were drawn for amino acid detection by tandem mass spectrophotometer. Peritoneal dialysis, Na benzoate therapy, biotin, carnitine, vitamin B12, B1, B2, redoxane and intravenous metronidazole was initiated to the patient with normal lactate and extremely high ammonia (3093 μmol/L)

levels. As it was failed to feed via oral route, protein-free fluid therapy containing high glucose were maintained. General status of the patient with extremely high ammonia levels was deteriorated rapidly and the patient died. In the tandem mass spectrophotometer, following results were obtained: Propionyl, 10.08 μmol/L (<9) high; palmitoleyl, 225 μmol/L (<8.7), normal; propionyl/palmitoleyl, 4.48 (<2), high; acetyl, 23.09 μmol/L (5-80), normal; propionyl/acetyl, 0,44 (>0,2 abnormal), high; 3-OH palmitoleyl, 0,24 μmol/L (<0,18), high; methylmalonic acid, 429 uM(<3 uM normal); MCA, 10.7 Um (<1 uM normal), normal. In urine organic acid analysis, methylmalonic acid excretion was increased by 84 folds. These findings were compatible to classic methylmalonic acidemia resulted from mutase enzyme defect.

3. Discussion

Newborns with organic acidemia typically present within the first one or two weeks after birth with poor feeding, vomiting, increasing lethargy that progresses to coma, floppiness, and muscular hypotonia. Pregnancy and perinatal history are often uncomplicated. Family history may reveal consanguinity and/or siblings who died during the neonatal period [16, 17]. This presenting episode may be mistaken for sepsis, and if unrecognized, is associated with significant mortality. A benign variant of MMA is a more frequent form of the disease. It occurs in older children who usually have low levels of methyl malonic acid in blood and urine and have normal growth and development. These children present intermittently with acidotic crises and are otherwise normal during crisis-free periods. Increased levels of organic acids including methylmalonic acid can be toxic to various cell types in the body. In our case, our patient, due to being in the newborn period, was consistent with a more progressive form.

The initial management includes intravenous hydration and correction of metabolic acidosis, hyperammonemia, hypoglycemia, and electrolyte abnormalities. Other associated illnesses, such as infections, are also treated. Insulin may be needed to avoid hyperglycemia and to promote protein synthesis. Acidosis is corrected with sodium bicarbonate. Patients with persistent severe acidosis or hyperammonemia may need the dialysis or hemofiltration. Peritoneal dialysis is obsolete [18].

Medications are given to reduce the formation or increase the excretion of toxic metabolites. Plasma carnitine levels are usually low in patients with organic acidemia [19]. L-carnitine [100 to 200 mg/kg per day (IV) or 100 to 300 mg/kg per day divided in three doses (PO)] is given to enhance the formation and excretion of acylcarnitine

conjugates thought to be toxic to the brain, liver, and kidneys. Multivitamins and calcium supplements are also provided to avoid deficiencies that may result from the low-protein diet. According to Guven *et al.*, metabolic disease must always be considered as possible diagnosis when an infant presents with a severe metabolic acidosis accompanied by an increased AG and other causes of increased AG metabolic acidosis with increased osmolar gap, e.g. drug ingestion should be ruled out [20]. Our case presented with feeding difficulty and lethargy on the day 3 of life and had consanguinity between parents and deceased sibling. With these symptoms, urine and blood amino acids and urine organic acid analyses were performed by TANDEM mass spectrophotometer. Due to the metabolic acidosis with increased anionic gap and that there was the metabolic disease history in the family, without losing time, the patient was given biotin, carnitine, vitamin B12, B1, B2 and redoxan as well as intravenous antibiotic therapy since sepsis couldn't be excluded. Protein-free, high-energy intravenous fluid replacement was maintained. Pharmacotherapy was initiated for bicarbonate replacement and hyperammonemia. During follow-up, insulin infusion was given. Acidosis was recovered after bicarbonate replacement but bicytopenia was developed. After 6 hours, ammonia concentration increased to 3693 $\mu\text{mol/L}$. Antibiotics with broader spectrum was initiated. Peritoneal dialysis was initiated as no available hemodialysis option, but the patient died despite respiratory and cardiovascular support. Carglumic acid may be considered in cases of methylmalonic aciduria (MMA) and propionic acidemia (PA) when significant hyperammonemia (eg, >400 micromol/L) is present [21]. However, we couldn't give carglumic acid as it couldn't be supplied. In tandem mass spectrophotometer ad urinary organic acid analysis, it was found that there was increase in methylmalonic acid, methyl citrate, propionic acid and 3-OH propionic acid levels. Homocysteine was normal. These findings indicated methylmalonic acidemia.

Patients with MMA can die in the newborn period or during a later episode of metabolic decompensation. Those who survive often have significant neurodevelopmental handicap, although normal cognitive development can occur [22]. Brain CT and MRI demonstrate widening of sulci and fissures, delayed myelination, and involvement of basal ganglia and white matter [23].

Although it was thought that rapid development of bone marrow suppression and deterioration within hours was precipitated by comorbid septicemia, no bacterial growth was observed in culture tests.

In organic acidemias, propionyl CoA accumulation cause hyperammonemia by decreasing synthesis of N-acetyl glutamate, physiological activator of carbamoyl phosphate synthetase 1. In our case, extremely high ammonia levels

despite lack of sepsis suggested that hyperammonemia was precipitated by excess amounts of propionyl CoA. Higher amounts of pro-substance supports the likelihood of mut 0 mutation in our case.

Primary genetic causes of hyperammonemia include organic acidemias, fatty acid oxidation defect and pyruvate metabolism disorders. Metabolic acidosis and/or ketotic hypoglycemia are typical for organic acidemias while fatty acid oxidation defect can also cause hyperammonemia but it is associated with non-ketotic hypoglycemia and manifests at late infancy. In pyruvate metabolism disorders, there is generally lactic acidemia in addition to high ammonia concentrations. Ammonia levels over 1000 $\mu\text{mol/L}$ is a discriminative feature for urea cycle defects while ammonia levels exceeding 200-300 $\mu\text{mol/L}$ is rarely seen in other hyperammonemias [24].

4. Conclusion

Our case which is diagnosed as methylmalonic acidemia showed that organic acidemias can also cause extremely high ammonia levels beyond 3000 $\mu\text{mol/L}$. Thus, treatment approaches encompassing all metabolic causes associated with hyperammonemia should be given until obtaining results of specific tests in infants considered to have metabolic disease.

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