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A Newborn with Propionic Acidemia Mimicking Urea Cycle Defect

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Abstract

Neonatal-onset propionic acidemia is the most common form of disorder. A 9-days old new born admitted to our hospital with lethargy suggested urea cycle defect at first look due to lack of metabolic acidosis, normal ketone and anion gap in laboratory evaluations. The case mimicking urea cycle defect, which was diagnosed as neonatal-onset propionic acidemia by specific tests, was presented because of its unusual manifestation.

Keywords

Propionic Academia, Mimicking, Urea Cycle Defect, Lack of Metabolic Acidosis

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1. Introduction

Propionic acidemia is a disorder associated with propionyl CoA accumulation resulted from defects in synthesis and structure of mitochondrial enzyme propionyl CoA carboxylase [1]. It is inherited in autosomal recessive manner and has a prevalence of 1:35,000-75,000 [2, 3].

The main features of this disorder are based on recurrent vomiting, ketosis, hypotonia, difficulty in feeding, lethargy, hyperglycemia, episodes of seizure and hyperammonemia during the acute episodes of this disorder [4, 5]. Some patients have late-onset disease (manifested any time after three months of age), show milder symptoms, and long survival rate. PA is usually associated with long-term neurological complications and is characterized by recurrent episodes of metabolic crises [6]. Propionic acidemia has 3 forms, namely neonatal-onset, late-onset [7] and isolated cardiomyopathy [8]. Neonatal form is the most common type, having 2 distinct presentations. It can be diagnosed either with elevated propionyl carnitine (C3) before onset of symptoms by neonatal screening programs or clinical deterioration in the first days of life which advances to encephalopathy, coma, seizure and cardiovascular failure if not treated [9]. In this form of PA, acute decompensation can develop in case of catabolic stress such as infection, injury or surgery. There are a broad spectrum of neurological symptoms and signs, including structural abnormalities, neurodevelopmental delay, metabolic stroke-like episodes, cranial nerve abnormalities, and seizures [10]. When the metabolic demand is increased, patients' deterioration occurs [11]. Isolated cardiomyopathy is a novel form which is first described by Lee et al. in 2009 [12].

In newborns, hyperammonemia is usually due to severe deficiency or even absence of activity of any of the five enzymes of the urea cycle or the N-acetyl glutamate synthase NAGS cofactor. Under normal physiological conditions, ammonia is converted to urea in the liver by five enzymes: carbamoyl phosphate synthase 1 (CPS1), ornithine transcarbamylase (OTC), argininosuccinic acid synthetase (ASS1), argininosuccinic acid lyase (ASL), and arginase (ARG) [13]. In addition, hyperammonemia can be seen in organic acidemias and fat acid oxidation defects. Common laboratory findings in propionic acidemia and other organic

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acidemias include metabolic acidosis with increased anion gap, elevated ketones in blood and urine, normal or decreased blood glucose and neutropenia as well as thrombocytopenia in rare cases. In the patients with propionic academia, acute episode of hyperammonemia is always an emergency and a life-threatening episode [14].

Here, we presented an interesting case which was thought to have urea cycle defect initially by metabolic acidosis, increased ketones and high ammonia concentration without increased anion gap but diagnosed as propionic acidemia by specific tests.

Table 1. Blood electrolytes, liver function and coagulation tests.

Parameters	Result	Normal Values
Glucose	100 mg/ dL	40-80 mg/ dL
BUN	4.7 mg/dL	5.1-16.8 mg/ dL
Urea	10 mg/dL	10.9-35.95 mg/dl
Creatinine	0.7 mg/dL	<0.85 mg/dl (for newborns)
Na	136 mmol/L	136-145 mmol/L
K	5 mmol/L	3.5-5.1 mmol/L
Cl	102 mmol/L	98-107 mmol/L
AST	79 U/L	0-31 U/L
ALT	24 U/L	0-41 U/L
LDH	3099 U/L	125-220 U/L
GGT	180 U/L	12-64 U/L
ALP	492 U/L	<500 U/L
CK	1O19 U/L	30-200 U/L
Ca	9.6 mg/dL	7.6-10.4 mg/ dL
P	6.1 mg/dL	2.7-4.5 mg/ dL
CRP	44 mg/ dL	0-5 mg/dl
PT	16,5 s	12-14 s
APTT	46 s	26.5-40 s
INR	1.3	0.5-1.5
Fibrinogen	408 mg/dL	200-400 mg/ dL
D-Dimer	6.1 µg/ dL	0-0.7 ug/ dL

2. Case Report

A new born boy was admitted to neonatal intensive care unit on the postnatal day 9 due to impaired general health status and high blood ammonia levels. He was born at term via spontaneous vaginal delivery with birth weight of 3,869 g and height of 50 cm. Ventilation support was provided due to high respiration rate and irritability in another facility and breastfeeding was initiated on the postnatal day 6. There was no history of maternal drug use with uneventful prenatal period. She was born as a first child of a mother aged 20 years and a father aged 25 years with consanguinity (first degree cousins). There were lethargy and hypotonicity during the physical examination and there were no suction, searching, catching and Moro reflexes. The other system examinations were normal. Ketone was found negative while ammonia level was found high. Laboratory results are shown in Table 1. It was found that there was no acidosis and the lactate was moderately high (Table 2). There was no finding of cytopenia on complete blood count. No acidosis developed and lactate levels returned normal range during follow-up. On urinary organic acid analysis, it was found that 3-OH propionic acid, methyl citrate and propionyl glycine excretions were increased. The patient was diagnosed as propionic acidemia with these findings and Tandem mass spectrophotometer (Table 2). No abnormal finding was detected on echocardiography and brain magnetic resonance imaging.

Table 2. Blood gases, TANDEM, urine organic analysis tests.

Parameters	Results	Normal Values
pH	7.4	
HCO3	14 mmol/L	<15 mmol/L
Anion gap	14,2	<15
pCO2	33	<45
Lactate	4,4	<3
Ammonia	2272 umol/L	
Free carnitine	4,5 umol/L	3.80-50 umol/L
C3/C16 (propionyl/palmitoyl)	5.1 High	C3:<6.92 umol/L C16:<8.70 umol/L
C3/C2 (propionyl/acetyl)	0.71 High	C3:<6.92 umol/L C2:5-80 umol/L
C3/C0 (propionyl/ free carnitine)	1.23 High	C3:<6.92 umol/L C0: 3.80-50 umol/L
C3/methionine (propionyl/methionine)	1.21 High	C3:<6.92 umol/L Methionin:10-53 mmol/L
C16:1-OH (3-OH palmitoleyl)	0.2 µM High	<0.12 umol/L

3. Discussion

Neonatal-onset propionic acidemia is characterized by feeding problems and vomiting within first days of life followed by lethargy, seizure, coma and death. The most common laboratory findings include metabolic acidosis with anion gap, ketonuria, hypoglycemia, hyperammonemia and cytopenia. There are case reports of patients presented with findings of severe hyperammonemia or severe neurological symptoms [15-16]. The primary genetic reasons include organic acidemia, fatty acid oxidation defects and disorders of pyruvate metabolism. Metabolic acidosis and/or ketotic hypoglycemia are typical for organic acidemias and fatty acid oxidation defect can cause hyperammonemia but it is associated with non-ketotic hypoglycemia and generally manifests at late infantile period. Generally, there is lactic acidemia with high ammonia concentrations in disorders of pyruvate metabolism. In other causes of hyperammonemia, ammonia concentration rarely exceed 200-300 µmol/L. Extremely high ammonium levels exceeding 1000 µmol/L is a distinguishing feature for urea cycle defects [17]. Other findings suggesting a urea cycle defect include normal blood glucose, normal anion gap and respiratory alkalosis. In our case, there was feeding difficulty with initiation of breastfeeding and lethargy but presence of high ammonia

concentrations (2272 μmol/L) and lack of acidosis, ketosis and hypoglycemia initially suggested a urea cycle defect rather than organic acidemia or fatty acid oxidation defect. However, propionic acidemia can also cause high ammonium levels mimicking urea cycle defects by inhibition of N-acetyl glutamate synthesis through accumulation of propionyl-CoA [18].

In our patient, hypotonia and lethargy were developed on the day 9 of life. When compared to urea cycle defect and fatty acid oxidation defects, it is more likely to present symptoms in neonatal period in organic acidemias. Organic acidemias are potential diagnoses when considering age at presentation, while urea cycle defect was potential diagnosis when considering laboratory findings. In a large cohort of patients with urea cycle defect from multiple centers (n = 260), only 34% presented during the neonatal period (<30 days of age) [17]. Of the remaining patients, the first episode of hyperammonemia was reported at 31 days to 2 years of age in 18 percent, >2 to 12 years of age in 28 percent, and over 12 years of age in 20 percent [19]. The treatment should be initiated as soon as possible when a urea cycle defect is suspected and diagnostic work-up should be performed simultaneously [20-23]. Initially, the treatment include rehydration, maintaining urinary output without causing over-hydration, removal of ammonia by drugs and/or hemodialysis, stopping protein intake, minimizing catabolic process by inducing anabolism and providing nitrogen uptake of muscle tissue. Main principles include protein-free high-energy dietary supplementation with intravenous glucose, treatment of hyperammonemia and supplementation with multivitamins and calcium in the initial treatment in organic acidemia. In addition, low-dose metronidazole to reduce propiogenic gut flora, carnitine to promote propionate renal clearance, and alternative-pathway ammonia-lowering drugs for secondary hyperammonemia. Plasma carnitine levels are usually low in patients with organic acidemia; thus, 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. L-carnitine conjugates with propionate and promotes transfer out of the mitochondria, so it can be excreted in the urine. It is helpful to eliminate the use of sodium bicarbonate for metabolic correction, and to correct its deficiency, which is a common finding in PA [24].

Multivitamins and calcium supplements also are provided to avoid deficiencies that may result from the low-protein diet. Carglumic acid may be considered in cases of methyl malonic aciduria (MMA) and propionic acidemia (PA) when significant hyperammonemia (e.g. >400 micromole/L) is present [25]. Accumulation of propionyl-CoA in these disorders leads to reduced synthesis of N-acetyl-glutamate, the physiologic activator of carbamoyl phosphate synthetase. Carglumic acid, a molecular analogue, may reduce hyperammonemia through direct activation of carbamoyl phosphate synthetase-1. In the acute phase of a not yet diagnosed metabolic patient with hyperammonemia, it is useful to start a nitrogen scavenger, sodium benzoate [26]. Protein-free, high-calorie intravenous fluid therapy was initiated in the patient while waiting for tandem mass spectrophotometer, urine-blood amino acid and urine organic acid analyses. In addition, enteral sodium benzoate and intravenous metronidazole were given due to hyperammonemia and peritoneal dialysis was initiated. Biotin, carnitine, vitamin B12, vitamin B2 and redoxon were prescribed. As sepsis couldn't be excluded, intravenous antibiotic therapy was initiated after taking samples for culture tests. The ammonia concentration was decreased to 1002 μmol/L after loading dose and to 326 μmol/L after second dose of sodium benzoate.

As was in our patient, acute metabolic crises with hyperammonemia are common in PA individuals. For their management, patients should be stabilized with IV fluid, glucose, restriction of proteins, vasopressors (if hypotension persists), and mechanical ventilation (if oxygen saturation is not maintained by alternative measures) [26].

The patient was diagnosed as propionic acidemia as there was elevated C3 (propionyl) in acylcarnitine profile and increased 3-OH propionic acid, methyl citrate, propionyl glycine and excretion of methyl citrate in urine organic acid analysis. The presence of consanguinity between parents (first degree cousins) was consistent with autosomal recessive inheritance pattern of PA. Specific laboratory findings for propionic acidemia include C3 elevation in acylcarnitine profile, increased glycine in plasma amino acid analysis, and elevation in propionyl CoA metabolites (3-hydroxia propionate [normal range: 3-10 mmol/mol CR], propionic acid, propionyl glycine, triglycine, tiglic acid methyl citrate). Increased glycine concentration in urine and blood results from reduced glycine oxidation due to inhibition of glycine cleavage enzyme by propionyl CoA. The patient was treated with low-protein diet free from isoleucine, valine, threonine and methionine, carnitine and biotin during follow-up. The patient is 5-months now and still attending to follow-up visits.

In spite of being very rare, isolated dilate cardiomyopathy can be the leading and/or sole symptom of late-onset PA [27]. Echocardiography was found normal in our patient during the diagnosis and follow-ups.

The presence of hyperammonemia without ketoacidosis and hypoglycemia doesn't exclude organic acidemia in newborns

presented with sepsis and clinical findings (hypotonia, lethargia, and impaired sucking after initiation of nutrition) suggesting metabolic disease. Rehydration, treatments targeting catabolic processes and treatment of hyperammonemia as well as carnitine, biotin and B12 supplementation should be implemented until specific tests are available. Appropriate management should be maintained after completion of specific tests.

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