Neonatal onset propionic acidemia without acidosis: a case report

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SUMMARY: Akman İ, İmamoğlu S, Demirkol M, Alpay H, Özek E. Neonatal onset propionic acidemia without acidosis: a case report. Turk J Pediatr 2002; 44: 339-342.

Propionic acidemia is an inherited disorder of organic acid metabolism characterized by a spectrum of clinical and biochemical findings. The usual presentation is life-threatening ketoacidosis and hyperammonemia. In this report we present a neonate with propionic acidemia presenting with prominent neurologic problems without ketoacidosis. The patient had a serum ammonia level of 3,500 µg/dl which was effectively lowered to normal values in 48 hours by peritoneal dialysis, with remarkable improvement in neurologic status. However, she developed Candida albicans peritonitis, and sepsis and died of cardiorespiratory failure. Infants who have an early onset propionic acidemia have a high mortality and morbidity rate. In conclusion, propionic acidemia should be in the differential diagnosis of patients with neurologic symptoms and hyperammonemia with or without acidosis.

Key words: propionic academia, neonate, peritoneal dialysis.

Propionic acidemia is a rare disorder of organic acid metabolism, caused by a deficiency of propionyl-coenzyme A carboxylase[1,2]. The reported incidence in Turkey is approximately 1/50,000-100,000[3,4]. Several clinical patterns of presentation have been described in neonates, older infants and children[3-5]. The disorder is frequently manifested with poor feeding, vomiting, lethargy, hypotonia, metabolic ketoacidosis and hyperammonemia in the neonatal period. Both early-and late-onset disease cause permanent neuroloic problems with markedly delayed development, seizures and cerebral atrophy[5,6]. The plasma ammonia level is related to the severity of the disease[1], and the duration of the hyperammonemic coma is an important prognostic factor for long-term sequelae. Thus, it should be treated immediately and effectively by hemofiltration or peritoneal dialysis[7,8].

We aimed to discuss the clinical and metabolic findings and management of early onset propionic acidemia, and report a patient who presented as a pure neurologic disease without acute episodes of acidosis.

Case Report

The infant, born at term by cesarean section C/S (because of a former C/S) after an uncomplicated pregnancy, was the second child of healthy consanguineous parents (first-degree relatives). Her birth weight was 3,500 g and Apgar scores were 8 and 9 at 1 and 5 minutes. Postnatal course was remarkable for progressive hypoactivity. At 13 days of age she was referred to our institution for feeding difficulties, poor sucking, 500 g weight loss, hypotonia, and hypoactivity.

On examination her vital signs were stable. Neurologic exam revealed a lethargic infant who could be awakened only by stimulation. She had minimal spontaneous activity but did not have any focal deficits. Sucking and rooting reflexes were absent and she had a weak gag reflex. Deep tendon reflexes were hypoactive. She had decreased flexor and extensor head tonus as well as decreased axial tonus. The rest of the physical examination was normal except for oral moniliasis.

On the day of admission to the neonatal intensive care unit she had an apnea and desaturation followed by an irregular respiratory

pattern. She was intubated and put on the respirator. After a few hours she had a left focal seizure and phenobarbital was started. Cranial ultrasonography was normal. EEG revealed a disorganized background activity. Following the sepsis work-up, intravenous antibiotics (ampicillin and netilmicin) were initiated empirically. Cerebrospinal fluid examination was normal. Blood, urine and cerebrospinal fluid cultures were negative.

Laboratory investigations revealed hematocrit of 38.7%, white cell count 3,500/mm^3 with 20% neutrophils and 80% lymphocytes, and platelet count 162,000/mm^3. Serum electrolytes, glucose, kidney function tests, liver enzyme levels, T_3, T_4 and TSH were all within normal limits. Urinalysis revealed moderate ketonuria. Serum ammonia concentration was 3,500 µg/dl (normal: 79-129 µg/dl). Arterial blood gas analysis and serum lactate concentration were normal (Table I). Blood and urine amino acids and urine organic acids were sent to the laboratory. Meanwhile, since serum ammonia level was very high and the clinical condition of the patient was critical, peritoneal dialysis was started to resolve the hyperammonemia. Twenty-four hours after the initiation of peritoneal dialysis, the baby started to improve neurologically.

Table I. Laboratory Findings

Parameter	Results	Normal values
Leukocyte	3,500	5,00-20,000/mm^3
Thrombocyte	40,000	150,000-450,000/mm^3
Glucose	72	50-110 mg/dl
[HCO_3^-]	20	20-25 mEq/L
Anion gap	24	<25
Lactate	1.8	0.5-2.2 mmol/L
NH_3	3,500	79-129 µg/L
Urine ketone	(+)	(–)

On peritoneal dialysis serum ammonia levels decreased to 1,200 µg/dl at the end of the first day and to 175 µg/dl at the end of the third day, but seizures and leukopenia (WBC: 2,200/mm^3) persisted. She developed thrombocytopenia (thrombocyte: 40,000/mm^3) and needed several platelet transfusions and GCSF treatment as well.

Urine organic acid study established the diagnosis of propionic acidemia with characteristic metabolites screened by gas chromatography-mass spectrometry. (Urinary propionylglycine=17.7 mmol/mol creatinine, 3 hydroxypropionate=230 mmol/mol creatinine, 2 hydroxybutyrate=27 mmol/mol creatinine). Carnitine and biotin was started and serum ammonia level was measured daily. Despite the diagnosis of propionic acidemia, metabolic acidosis had never been observed during the hospitalisation period.

On the sixth day of admission, due to malfunctioning of peritoneal dialysis catheter serum ammonia level rose to 385 µg/dl. When the catheter was replaced with a new one and peritoneal dialysis was continued, ammonia level decreased to 87 µg/dl. In the following days, despite neurologic improvement, the clinical condition worsened. The microscopical examination of peritoneal dialysis fluid showed 60 WBC/mm^3 and yeast cells, thus intravenous fluconasole was started. Peritoneal dialysis fluid culture yielded Candida albicans and the clinical condition deteriorated further. The antifungal therapy was changed to amphotericin B. Peritoneal dialysis was continued in the meantime since hemodialysis was not possible for the patient because of hemodynamic instability.

On the 17th day of admission, she was still on respirator when pulmonary hemorrhage occurred and her clinical status deteriorated. The infant died of cardiorespiratory failure the next day in spite of all supportive therapy.

Discussion

Propionic acid is an intermediate metabolite of isoleucine, valine, threonine, methionine, odd-chain fatty acids and cholesterol catabolism[7]. It is normally carboxylated to methylmalonic acid by propionyl-CoA carboxylase (PCC), which requires biotin as a cofactor. Propionic acidemia is an autosomal recessive disease caused by PCC deficiency[7]. Concentrations of propionic acid, methylcitric acid and propionylglycine are markedly elevated in the plasma and urine of infants with propionic acidemia. Definitive diagnosis can be established by measuring PCC activity in cultured fibroblasts or leukocytes. Our patient had significant elevation of characteristic metabolites in her serum and urine but the measurement of PCC activity in cultured fibroblasts was not possible during her hospitalisation.

The clinical manifestations of the disease are variable even within the same family, but generally the earlier the onset, the higher the

mortality and morbidity[5,8,9]. Hyperammonemia, ketoacidosis and thrombocytopenia are the hallmarks of propionic acidemia[7,10]. Less frequently the patient present later in life with mental retardation, choreoathetosis and seizures without acute attacks of ketoacidosis[7,10-12]. While metabolic acidosis is a key feature of early onset propionic acidemia, there are several reports of patients where metabolic acidosis was not a persistent finding[11-14]. Nyhan et al.[11] reported two patients with propionic acidemia presenting with prominent neurologic symptoms suggesting a disease of basal ganglia without episodes of ketoacidosis. These children had spastic quadriparesis, choreoathetosis and seizure disorder. Propionyl-CoA carboxylase activity was 5% of the control in each patient. Similarly, our patient had never had ketoacidosis but exhibited the clinical symptoms of hyperammonemic coma, neutropenia and thrombocytopenia.

Mild-to-moderate mental retardation is common in patients with propionic acidemia even with good compliance to therapy. Neurodevelopmental deficits are usually due to recurrent episodes of hyperammonemia and acidosis as well as long-term exposure of brain to abnormal metabolites[5].

Early diagnosis and treatment are important for better long-term prognosis[5]. Treatment of acute attack includes rehydration, correction of acidosis and prevention of the catabolic state by provision of adequate calories. Very ill patients with severe acidosis and hyperammonemia require peritoneal dialysis to remove ammonia and other toxic compounds[7,15]. Moderate hyperammonemia is common in propionic acidemia due to inhibition of urea cycle enzyme N acetyl glutamate synthetase by propionyl-CoA[16]. In our patient, ,serum ammonia level was extremely high (3,500 μg/dl) at presentation possibly due to the delay in referral of the patient (at 13 days of age) to our hospital. In our patient peritoneal dialysis was very effective in reducing the serum ammonia with concomitant clinical improvement.

Patients with propionic acidemia have frequent infections, as a result of which an acute metabolic decompensation may follow[17,18]. In our patient Candida albicons peritonitis and fungemia progressed to multiorgan failure. The patient did not respond to any therapy and died of cardiorespiratory failure.

We conclude that propionic acidemia should be included in the differential diagnosis of patients with neurologic symptoms and hyperammonemia with or without acidosis. Infants with propionic acidemia should be followed at tertiary care centers with a dialysis unit to treat hyperammonemia. Even with intensive therapy mortality is high during acute attacks.

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