A Unusual Presentation of Propionic Acidemia with Thrombocytosis- A Case Report

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Abstract

Propionic acidemia is an inborn error of metabolism due to defective enzyme, propionyl-coenzyme A (CoA) carboxylase, which results in an accumulation of propionic acid. In this report we describe a term male neonate who presented with metabolic acidosis, seizures, hypoglycemia, ketosis, hyperglycinemia, thrombocytosis, and hepatomegaly. The diagnosis was established on the basis of tandem mass spectrometry, arterial blood gas analysis, serum lactate, serum ammonia and urine organic acid analysis. We report this unusual presentation with thrombocytosis which has never been reported in literature.

Introduction

Propionic acidemia is the most common acidemia due to defective enzyme, propionyl-coenzyme A (CoA) carboxylase, which results in an accumulation of propionic acid. Metabolism of isoleucine, valine, threonine, and methionine results in production of propionyl-CoA. The enzyme propionyl-CoA carboxylase catalyzes conversion of propionyl-CoA to methylmalonyl-CoA. This enzyme has 2 subunits and defects in genes encoding these units (PCCA and PCCB) result in insufficiency of the enzyme and accumulation of toxic metabolites. The clinical picture varies from patients presenting with mild psychomotor retardation to those with severe metabolic decompensation with vomiting, dehydration, encephalopathy and in rare instances fatal outcome. We report this unusual presentation of propionic acidemia with thrombocytosis in term male neonate. This association has never been reported in literature.

Case Report

A term male neonate weighing 2500 g was born to 26 year old primigravida by normal vaginal route after an uneventful antenatal period. He was the product of a non-consanguineous marriage. The baby cried immediately after birth and was started on breast feeding within 1 hour of birth. There was no history of unexplained neonatal death in the family. At 15 hours of life baby developed poor feeding, lethargy, and seizures, he was immediately shifted to neonatal intensive care unit. On examination the baby was normothermic, pink with a heart rate of 146/min, respiratory rate of 48/min and normal peripheral perfusion. There were no gross congenital anomalies. The sensorium was depressed with minimal spontaneous eye opening and limb movements. Response to painful stimuli was decreased. Neonatal reflexes were sluggish. There were no focal neurological deficits. The blood sugar by glucometer was 25 mg%, he was given 10% dextrose bolus @ 2ml/kg and injection calcium gluconate (10%) 2ml/kg was given slowly and blood sample was sent for sepsis screen and electrolytes. The baby was started on antibiotics and dextrose infusion @ GIR 8mg/kg/min which was gradually increased to 10. The seizure was partially controlled and he was started on phenobarbitone loading(total of 40mg/kg) then to phenytoin loading (40mg/kg), midazolam bolus 0.1 mg/kg but seizure was not controlled and baby was started on midazolam infusion and started on mechanical ventilation. On the basis of clinical features and partial response to anticonvulsant, inborn error of metabolism was kept as possibility and arterial blood gas analysis, serum lactate, ammonia tandem mass spectrometry and urine for organic acid. Hematological investigations revealed: Hb 15gm% TLC 9800 /cummm (polymorphonuclears 70%, lymphocytes 30%, immature to total neutrophil ratio 0.07) platelet count 7 lacs/cumm and µESR 1 mm fall in 1st hour. Initial and subsequent blood sugars ranged between 25 to 50 mg/dl. The C-reactive protein was normal. Arterial blood gas analysis yielded pH 7.30, bicarbonate 18.2 mmol/L, base excess 3.4 mmol/L, paO2 90 mmHg paCO2 32 mmHg and lactate 5.0 mmol/l. Blood ammonia was 56 mcg/dl (normal: 90-150 mg/dl) and lactate was 46 mcg/dl (normal 7-20 mcg/dl) and serum creatinine 0.5 mg/dl and urine ketones was positive. The electrolytes, liver function test, renal function test and T3,T4,TSH was normal. The tandem mass spectrometry revealed hyperglycinemia and urine for organic acid established the diagnosis of propionic academia with typical metabolites screened by chromatography with urinary propionylglycine 20.7mmol/creatinine, 3hydroxypropionate 240mmol/creatinine and 2...
Propionic acidemia has a heterogeneous clinical presentation(1-5). Two-thirds of the patients manifest within the first week of life and almost 80% by two weeks. Propionic acidemia is an autosomal recessive disorder in which there is accumulation of propionic acid due to a deficiency in Propionyl CoA Carboxylase, a biotin dependent enzyme involved in amino acid catabolism. Abnormal levels of organic acids in the blood (organic acidemia), urine (organic aciduria), and tissues can be toxic and can cause serious health problems. In most cases, the features of propionic acidemia become apparent within a few days after birth. The initial symptoms include poor feeding, vomiting, loss of appetite, seizure, weak muscle tone (hypotonia), and lack of energy (lethargy) and metabolic acidosis with increased lactate. These symptoms sometimes progress to more serious medical problems, including heart abnormalities, seizures, coma, and possibly death. The present case too presented within the first week with poor feeding, lethargy, metabolic acidosis and seizures. It has been suggested that propionic acidemia must be considered in all newborn infants with unexplained neurological deterioration even in the absence of a metabolic acidosis. Neutropenia, thrombocytopenia and anemia are frequently encountered during the acute crisis(probably a result of propionate mediated marrow suppression) however in the present case there was thrombocytosis instead of thrombocytopenia. The late onset form, however, poses a challenge in diagnosis. The midfacial and nipple anomalies suggest that propionic acid acts as a teratogen in the fetus(5).

In the present case the dysmorphic features were absent. The clinical course is variable. Death is reported in 30% during the initial presentation, in 40% during subsequent crisis. The rest have either frequent crisis or a mild course. The diagnosis is best confirmed by screening urine samples for propionic add metabolites by GC-MS(6). The most valuable diagnostic metabolites excreted include 3-OH propionate, 2-methyl citrate, 2-methyl-3-oxovalerate, 3-OH butyrate. Propionic acidemia needs to be differentiated from methylmalonic acidemia, multiple carboxylase deficiency and isovaleric acidemia. The clinical presentation of methylmalonic acidemia is very similar to propionic acidemia, but can be differentiated from the latter by the presence of methylmalonic acid in the urine. Multiple carboxylase deficiency is differentiated from propionic acidemia by skin manifestations, which include generalized erythematous rash with exfoliation and alopecia totalis. Isovaleric acidemia is differentiated by its sweaty feet odor (characteristic odour is absent in propionic acidemia) and absence of propionic acid in the urine. Therapy of propionic acidemia has to begin during the acute metabolic crisis when the diagnosis is still uncertain. The main principles of management during this phase include prevention of toxic metabolite accumulation by restricting protein intake, adequate caloric intake- glucose (25-30 g/kg/day) and lipids (2-4 g/kg/day), and metronidazole therapy (10-20mg/kg/day) which has been found to reduce urinary excretion of propionate metabolites by 40%; elimination of toxic metabolites by exchange transfusion, peritoneal or hemodialysis; and supportive measures such as assisted ventilation, correction of fluid and pH imbalances, L carnitine (100mg/kg/day) and therapeutic trial with oral biotin (10 mg/day) (7).

High protein or low caloric in take, or catabolic states such as infections, trauma or surgery can lead to serious life threatening crises. A protein intake of 0.7-1.5 g/kg/day with non-propiogenic amino acids, adequate caloric intake and L-Carnitine (100mg/kg/day, orally) form the mainstay of therapy. Special amino add mixtures are available for patients with propionic acidemia (Milupa’s OS1, OS2,Weyth Byla’s S14, and Maxamaid). Prenatal diagnosis of propionic acidemia is possible by determining propionyl CoA carboxylase (PCC) enzyme activity in chorionic villous biopsies, cultured amniotic fluid cells or by measuring methylcitrate concentration in amniotic fluid (8). Most survivors have been documented to have poor psychomotor outcome, probably a result of delayed diagnosis and inability to prevent and treat intermittent crisis. There is a need for early selective screening of patients with
non-specific clinical symptoms and laboratory findings and initiate emergency non-specific treatment as outlined above if mortality and long term neurodevelopment morbidity are to be improved. The present case highlights unusual association propionic academia with thrombocytosis which has never been reported in literature.

References

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