

Neonatal Propionic Acidemia: A Case Report in the Sri Lanka

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Abstract: Propionic acidemia (aciduria) is a rare autosomal recessive inherited metabolic disorder that is caused by a defective form of the propionyl-coenzyme A (COA) carboxylase enzyme, which results in the accumulation of propionic acid. If the patient is having conditions with increased metabolic demand followed by catabolism, they can present as acute deterioration. Clinical features usually start shortly after birth, and rare cases are present in young adulthood. This disorder most commonly is characterized by episodic decompensation with dehydration, lethargy, nausea, and vomiting. Early identification and initial management are crucial to prevent the mortality and morbidity of patients. Our case is the first baby of consanguineous parents, presented with vomiting, Poor feeding, and severe dehydration on day four of life. In developed countries, early detection is done with newborn screening, but in Sri Lanka like third world countries it is not possible due to poor resources. The take-home message is if a newborn who is a product of consanguineous parents presented with non-specific symptoms, always think about the metabolic disorders which need urgent intervention to save the child from acute and long-term complications.

Keywords: Propionic Acidemia, Propionyl-Coenzyme a Carboxylase Deficiency, Autosomal Recessive Metabolic Disorder, Sri Lanka

1. Introduction

Propionic acidemia (PA) is a rare autosomal recessive inborn error of metabolism. The estimated incidence is 1;100,000-150,000. The actual prevalence may be greater because many neonatal deaths may be triggered by undiagnosed acidopathies. It can be early detected by newborn metabolic screening within 72 hours of life. PA is usually presented in early neonatal life with nonspecific symptoms like poor feeding, vomiting, lethargy, and can present with seizures hypotonia and encephalopathy as well. Patients with the milder forms of disease may be present later in life. If a patient has a family history of neonatal deaths or consanguinity, we could suspect metabolic disease and need to investigate it.

Our baby was presented with a history of vomiting, poor

feeding, and severe dehydration on day four of life. we have suspected inborn errors of metabolism Because parents are consanguineous and investigated with urine for organic acid and blood for amino acid profile. Although we diagnosed the baby is having propionic acidemia, the baby died on day fifteen of life.

2. Case Report

A female infant was born at term by emergency cesarean section due to fetal distress with 2730 grams of birth weight and Apgar was nine in one minute and ten in five minutes. This is the first baby of second-degree, consanguineous healthy parents, with an uneventful antenatal period. There was no family history of neonatal deaths. Breastfeeding was started within half an hour of delivery and discharged on day

three following establishment of breast feeding. The next day the baby was admitted with a history of poor feeding, less activity and vomiting. On examination the baby was drowsy, severely dehydrated with acidotic breathing, and hypotonia but she had no dysmorphism, fever, tachycardia or organomegaly.

The investigations revealed capillary blood sugar of 39mg/dl, blood gas evaluation shows a high anion gap severe metabolic acidosis with normal lactate level (pH 6.99, HCO_3^- 3.0, base excess 18.4, lactate level 0.7). White cell count was 15300 with neutrophil 75%, lymphocyte 18.7%, and platelets were 375,000, hemoglobin was 14.5g/dl with PCV 44%. But later he developed pancytopenia. C-reactive protein was <5 (negative) and blood culture was no growth. Urine ketone bodies were positive and urine sugar was negative. Lumbar puncture was normal. Chest x-ray, ultrasound of brain, and abdomen, 2D Echo were normal. EEG shows severe cerebral dysfunction.

Hypoglycemia and dehydration were corrected with 10% dextrose and intravenous fluid. Acidosis was adequately treated with sodium bicarbonate. An antibiotic was started as initial diagnosis was septicemia. As the parents were consanguineous and the baby had not responded to our treatment, a possibility of an inherited metabolic disorder was considered. A dried blood spot test for aminoacidopathies was done. Acylcarnitine Profile (TMS) revealed Propionyl Carnitine (C3) = 6.12 μM (NR, 0.2-4 μM) concentration of C3 and other indices such as C3/C2 and C3/C16 were 'above normal'. These elevations may be associated with propionic acidemias, methylmalonic acidemias, cobalamin synthesis defects or Vitamin B12 deficiency. Urine screening for organic acid by gas chromatography and mass spectrometry and blood for aminoacidopathies was done and confirmed the diagnosis of propionic acidemia.

After initial stabilization and diagnosis, L-carnitine, Biotin and Pyridoxine were started and planned to start PROPIMEX-1 which was an Amino acid modified infant formula with iron, for infant with propionic or methyl malonic acidemia. But unfortunately, the infant died on day twenty of life.

3. Discussion

Propionic acidemia (PA) is an autosomal recessive disorder [1], which is a rare, life-threatening inborn error of metabolism caused by a deficiency of the mitochondrial propionyl-CoA carboxylase (PCC) enzyme. This enzyme is essential for carboxylation of propionyl CoA to D-methyl malonyl-CoA. Due to PCC enzyme deficiency, PA is characterized by the accumulation of propionyl-CoA and toxic metabolites of branched-chain amino acid catabolism, namely 3-hydroxypropionic acid and propionyl carnitine in plasma, urine, and other body fluids [2]. These toxic organic acid metabolites, such as propionate, b-hydroxybutyrate, b-hydroxy propionate and methyl citrate are responsible for the observed hyperammonemia, metabolic acidosis and bone

marrow suppression [3]. In PA, disease onset is determined by several factors, including intake of propiogenic precursors, residual enzyme activities, and presence of catabolic status [4]. The biochemical hallmark of PA is high anion gap metabolic acidosis, hyperammonemia, elevated lactate, and elevated urine ketone bodies [5]. PA is characterized by a relapsing course of severe metabolic ketoacidosis, typically precipitated by excessive protein intake, constipation, and intercurrent infection [6].

Two-thirds of the patients manifest within the first week of life and almost 80% by two weeks of age [7]. They often present with poor feeding, lethargy, vomiting, and they can progress to coma even death if not identified early and not treated appropriately in the neonatal period [8]. The symptoms onset in late infancy and early childhood are usually like those of the neonatal onset disorder [9].

The disease manifestations may also include developmental retardation, hypotonia, seizures, gastroesophageal reflux disease, episodic vomiting, protein intolerance, hypogammaglobulinemia, bone marrow suppression, osteopenia, pancreatitis, cardiomyopathy, and coma [10]. The natural progression of PA with the age is presented as intellectual disabilities and increase risk of neurological complications including stroke-like episodes, gastrointestinal complications, chronic kidney disease, and cardiac complications as well as several other complications [11, 12].

Newborns with PA tested by expanded newborn screening have raised propionyl carnitine (C3). Testing of urine organic acids in persons who are symptomatic or those identified by newborn screening discovered elevated 3-hydroxypropionate and the presence of methyl citrate, tiglylglycine, propionyl glycine, and lactic acid. Testing of plasma amino acids exposes elevated glycine [13]. For the definitive diagnosis of PA needed plasma amino acid profile along with urinary organic acids and genetic analysis results [14]. Diagnosis is confirmed by depending on the detection of biallelic pathogenic variants in *PCCA* or *PCCB* or of deficient PCC enzymatic activity. In individuals with equivocal molecular genetic test results, a combination of enzymatic and molecular diagnostics may be necessary [15].

Acutely decompensated PA is a medical emergency. Treatment for triggering factors such as dehydration, infection, vomiting and reverse catabolism by providing intravenous (IV) lipid and glucose, cessation of protein intake to lessen propiogenic precursors, removal of toxic compounds using nitrogen scavenger medications, extracorporeal detoxifications, IV carnitine and providing of calcium and vitamin D are essential management steps [2].

Long-term management of propionic acidemia is a very challenging risk. natural protein restriction, non-propiogenic amino acids, adequate caloric intake, and L-Carnitine form the mainstay of therapy. Supplementation with a medical formula enriched with leucine, and free of valine, isoleucine methionine and threonine are also helpful [16]. Special amino acid mixtures are available for patients with propionic acidemia named propimex improved growth and nutrition

status in patients with PA in just six months when fed in sufficient amounts that provide energy and protein for patients with failure to thrive at intakes recommended for catchup growth may have resulted in even better growth [17]. A patient with recurrent metabolic decompensations, uncontrollable hyperammonemia, and/or poor growth may need Orthotopic liver transplantation (OLT) [13]. Early stimulation with neurodevelopmental care, occupational therapy, parental education, and genetic counseling are also very important aspects of long-term management.

In the 3rd world country like Sri Lanka, we have very limited facilities to detect metabolic diseases early in life because our neonatal screening has not included it yet.

4. Conclusion

Propionic acidemia is a rare, autosomal recessive metabolic disorder that manifest with nonspecific symptoms in the neonatal period. Most of the developed countries have neonatal screening programmes to detect inborn errors of metabolism, but unfortunately developing countries like Sri Lanka is not doing it yet due to poor resources. So clinical suspicion is very important to diagnose metabolic disorders in early life specially in low resource settings. If the parents are consanguineous, we always have to think about the inborn errors of metabolic diseases as a differential diagnosis although there is no family history. With Regards to our patient, we suspected and did the investigations to diagnosis early. But unfortunately, our baby succumbed due to lack of treatment facilities.

Author Contributors

MP: Data collection, designed and wrote the paper, KW & CA: Contributed to conceptualizing the paper and critically reviewing it. All the authors scrutinized and approved the submitted version of the manuscript.

Ethical Consideration

Anonymity and confidentiality of all data were maintained. Informed written consent was obtained from the parents.

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