Biochemical Basis of Heterogeneity in Acute Presentations of Propionic Acidemia

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Abstract Propionic acidemia (PA), an uncommon organic acidemia has varied clinical and metabolic presentation causing difficulty and delay in the diagnosis. We report a case of PA in an infant who presented with failure to thrive, acute encephalopathy due to severe hyperammonemia without acidosis and fungal sepsis. The biochemical basis of severe hyperammonemia is discussed.

Keywords Acute encephalopathy · Candida sepsis · Hyperammonemia · Ketoacidosis · Neutropenia

Introduction

Organic acidemias (OAs) are inherited metabolic disorders characterized by excretion of non-amino organic acids in the urine and classically present in the neonatal period with acute life-threatening ketoacidosis. However, propionic acidemia (PA) caused by deficiency of biotin dependent propionyl-CoA carboxylase (PCC) has variable clinical and metabolic presentations with formidable challenge in diagnosis. This heterogeneity in metabolic presentation occurs due to inhibition of enzymes of tricarboxylic acid

(TCA), urea cycle and other pathways by intra-mitochondrial accumulation of propionyl-CoA and metabolites [1]. In addition, immune suppression with predisposition to sepsis with unusual organisms is also seen in PA with misdiagnosis as immunodeficiency disorder [2, 3]. We report on an infant with PA who presented with failure to thrive, acute encephalopathy due to severe hyperammonemia without acidosis and fungal sepsis and discuss the biochemical basis for this heterogeneity.

Case Report

A 32-days-old male infant, second born of a non-consanguineous parentage was referred with poor suck and lethargy since 10 days and multifocal clonic convulsions since 3 days. Pregnancy and delivery were uncomplicated; he was born term with birth weight of 2,450 g. At admission he was non-responsive with periodic breathing and prolonged capillary filling time requiring ventilation and inotropes. His weight was 2,550 g, length 52 cm and head circumference 34 cm suggestive of failure to thrive. There was oral thrush, firm hepatomegaly, depressed tone and reflexes. Investigations showed leucopenia (3.71×10^9 cells/L), neutropenia (460×10^6 cells/L), and thrombocytopenia (109×10^9 cells/L), C reactive protein 69 mg/L, blood glucose 2.11 mmol/L, serum calcium 3.75 mmol/L, sodium 126 mmol/L, bicarbonate 20.4 mmol/L, and anion gap 16.4 mmol/L, with no hepatic or renal dysfunction. There was no acidosis in arterial blood gas (pH 7.41 and base excess -3.4). Neuroimaging showed hypodensity of white matter consistent with age. CSF analysis was normal; urine showed ketosis and yeast like budding cells. With diagnosis of sepsis, pending culture reports child was started on broad spectrum antibiotics and loading doses of anticonvulsants. Blood and urine cultures grew *Candida albicans* and CSF was

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initiated as the ammonia levels were very high. Sodium benzoate (250 mg/kg), carnitine (100 mg/kg), and biotin (10 mg/day) along with metronidazole were added but the infant succumbed to the illness.

Several clinical and metabolic presentations have been reported with PA in various age groups [4]. Most common and typical is acute neonatal-infantile onset with failure to thrive, vomiting, seizures, encephalopathy, severe ketoacidosis, moderate hyperammonemia, and hyperglycinemia. Encephalopathy due to severe hyperammonemia without ketoacidosis is an uncommon acute presentation [5]. This mimics urea cycle disorder (UCD), non-ketotic hyperglycinemia (NKH), and transient hyperammonemia of newborn (THAN) with delay in diagnosis and initiation of treatment. Elevated glycine levels in the blood and CSF and high CSF: plasma glycine ratio is diagnostic of NKH. Ketonuria is rare in newborns and its presence should alert the possibility of OA. A diagnosis of THAN is usually considered in a preterm with onset of respiratory distress syndrome in the first day life. In both NKH and THAN urine organic acids are normal. PA may also present like an immune disorder with neutropenia and pancytopenia due to bone marrow suppression. The probable biochemical basis is not established; however, chronic neutropenia and pancytopenia beyond neonatal period is not reported [6]. Considerable delay in diagnosis in our case was due to evaluation for immunodeficiency in view of fungal sepsis.

Fig. 1 Urine gas chromatography mass spectrometry showing peaks of 3-OH propionate, propionylglycine and methylcitrate consistent with diagnosis of propionic acidemia

dehydrogenase, *NAG* N-acetyl glutamate, *NAGs* N-Acetyl glutamate synthase, *PCC* propionyl CoA carboxylase, *PDG* phosphate dependent glutaminase. Metabolites and alternate metabolic pathways in propionic acidemia (*dotted line*)

Propionyl-CoA is formed from the catabolism of branched chain amino acids (isoleucine, threonine, methionine, and valine), odd-chain fatty acids and three-carbon side chain of cholesterol. Leucine stimulates oxidation of isoleucine and can also increase endogenous propionate formation. The accumulation of organic acid metabolites namely propionyl-CoA, 3-OH propionate, 3-OH butyrate, and methyl citrate in liver mitochondria in PA interfere with other metabolic pathways including TCA cycle, electron transport chain, urea cycle, and glycine synthase complex resulting in lactic acidosis, hyperammonemia, and ketotic hyperglycinemia. The integration of these pathways is shown in Fig. 2. Severe hyperammonemia in PA is explained by several complex mechanisms [1, 7]. Propionyl-CoA competitively inhibits *N*-acetyl glutamate synthase, the allosteric activator of carbamoyl phosphate synthase, the rate limiting enzyme of urea cycle resulting in hyperammonemia. In addition a dysfunctional TCA cycle also contributes to hyperammonemia. In UCD hyperammonemia is associated with increased glutamine which contributes to the nitrogen molecule for ammonia formation. In contrast hyperammonemia in PA correlates with increased urine methylcitrate and decreased serum glutamine and urine citrate. The functional lack of α -ketoglutarate due to interaction of TCA cycle shifts the equilibrium of the reactions catalyzed by mitochondrial glutamate dehydrogenase and phosphate-dependent glutaminase, with net production of ammonia and decreased levels of glutamine and glutamate in the muscle and liver. The high ammonia levels stimulate the respiratory center causing hyperventilation and respiratory alkalosis.

Treatment of acute decompensation includes management of dehydration, infection and metabolic abnormalities with appropriate fluids, broad spectrum antibiotics and dialysis to remove the toxic substances. However, the mortality remains high in cases of early presentations of encephalopathy with severe hyperammonemia with or without acidosis.

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