

**Disease Name:**

**PROPIONIC ACIDEMIA**

(PROPIONYL-CoA CARBOXYLASE DEFICIENCY; KETOTIC HYPERGLYCINEMIA)

**Classification:**

Organic aciduria

**Genetic Information:**

**Inheritance:**

Autosomal recessive

**Population Incidence:**

In US the incidence is estimated to be 1:100,000

**Ethnic Incidence:**

Saudi Arabia the frequency is 1:2000 to 1:5000; Greenland Inuit population incidence about 1:1000

**Gene & Location:**

PCCA gene- 13q32  
PCCB gene- 3q21-q22

**Common Mutation:**

PCCB gene has several common mutations in different populations

**OMIM #**

\*232050; #606054; \*232000

**Disease Information:**

**Symptom Onset:**

Most patients present in newborn period, others have presented later in life.

**Symptoms:**

In the newborn period, symptoms include severe metabolic acidosis manifested by refusal to feed, vomiting, lethargy, hypotonia and seizures. Another neonatal presentation may be hyperammonemia similar to a urea cycle defect with less metabolic acidosis. A few patients have presented later in life with acute encephalopathy, episodic ketoacidosis or with developmental retardation without ketosis or acidosis. Immune deficiency with signs mimicking sepsis can be another presenting feature.

**Physical Findings:**

Short stature and failure to thrive are common in these children as are osteoporosis and skin lesions. Pancreatitis is a complication seen in this and other organic acidurias. May have dystonia or seizures as well as central hypotonia and abnormal EEGs.

**Treatment:** Treatment regimens are complicated with a diet restricted in protein, and use of a special formula deficient in the amino acids that feed into propionate metabolism. L-carnitine may be a useful therapeutic adjunct to replete intracellular and extracellular stores of free carnitine. Oral antibiotic therapy may be useful as well to decrease gut production of propionate, or use of a laxative to increase gut motility. Continuous overnight feedings may be helpful in decreasing beta-oxidation and the release of odd-chain fatty acids since it theoretically will inhibit lipolysis. Liver transplant protects against acute metabolic decompensation but does not completely prevent, and the biochemical correction is incomplete with continuously elevated metabolites.

**Natural History without treatment:** The usual course is severe neurological damage to coma and death, although a few asymptomatic adults have been reported. Some have progressed to cardiomyopathy similar to seen with beriberi. This incidence is unknown as is the etiology.

**Natural History with treatment:** Even with treatment, developmental delay, seizures, dystonia, cerebral atrophy, and EEG abnormalities are common in survivors. Increased protein intake, intercurrent illness or other stress precipitates repeated episodes of decompensation. Necrosis of the basal ganglia and/or metabolic stroke can result from these crises. Bone marrow suppression occurs frequently and may be secondary to build-up of toxic metabolites. Common laboratory findings are neutropenia, thrombocytopenia, and hypogammagobulinemia. Pancytopenia usually manifests 2-3 days after the acute metabolic presentation. There is a high frequency of infections among affected children.

**Metabolic Information:**

**Missing Enzyme & Location:** Propionyl-coenzyme A carboxylase. The problem is during the conversion of propionyl CoA to D-methylmalonyl CoA.

**MS/MS profile:** C3 (propionyl carnitine)- elevated  
C3/C2 ratio >0.4

**Prenatal testing:** Prenatal diagnosis is possible by measuring propionyl CoA carboxylase activity in amniocytes or by DNA analysis if a mutation has been identified in the family or there is a common mutation in the family's ethnic group.

**Miscellaneous Information:**

Thrombocytopenia is frequent during acute illnesses and resolves when the patient is doing well. Elevation of C3 acylcarnitine on newborn screening does not differentiate between propionic or methylmalonic aciduria. Anecdotally patients are treated with thiamine are purported to have less problems with lactic acidosis and cardiomyopathy.

Prepared for the NW Regional Newborn Screening Program by Sara Copeland MD, Judith Tuerck RN MS and Lorinda Paradise at OHSU in Portland, OR.

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