Propionic Acidemia

Genetics

-Genes: PCCA (Propionyl-CoA carboxylase alpha chain, mitochondrial; 13q32.3); PCCB (Propionyl-CoA carboxylase beta chain, mitochondrial; 3q22.3)

-AR

Clinical findings/Dysmorphic features

-Spectrum: neonatal-onset to late-onset disease

-Neonatal-onset (most common): healthy newborn with poor feeding and decreased arousal --> progressive encephalopathy --> w/o prompt diagnosis and management --> lethargy, seizures, coma, death; frequently accompanied by metabolic acidosis with anion gap, lactic acidosis, ketonuria, hypoglycemia, hyperammonemia, cytopenias

-Late-onset: can be asymptomatic; metabolic crisis under catabolic stress (ill, surgery, fasting)

-Isolated cardiomyopathy in absence of metabolic decompensation or neurocognitive deficits

-Manifestations over time: FTT, ID, seizures, basal ganglia lesions, pancreatitis, cardiomyopathy

-Other reported complications: optic atrophy, HL, ovarian insufficiency, chronic renal failure

Etiology

-Live-birth incidence is 1:105,000-1:130,000 in the US

Pathogenesis

-Organic acidemia caused by deficiency of propionyl-CoA carboxylase (PCC), a biotin-dependent carboxylase located in mitochondrial inner space

-PCC converts propionyl-CoA to D-methylmalonyl-CoA --> enters Krebs cycle as succinyl-CoA

-Propionyl-CoA is common to pathway for degradation of some amino acids (VOMIT: valine, odd-chain fatty acids, methionine, isoleucine, threonine) and cholesterol

-Gut bacteria (i.e., Propionibacterium sp.) also produce propionate metabolized through PCC

-Deficiency of PCC: --> toxic effects of free organic acids and ammonia; --> accumulation of propionyl-CoA (inhibits enzymes including oxidative phosphorylation --> decreased energy production); --> decreased production of Krebs cycle intermediates

Genetic testing/diagnosis

-Plasma acylcarnitine profile: elevated propionylcarnitine (C3)

-UOA: elevated 3-hydroxypropionate; presence of: methylcitrate, propionylglycine, lactic acid

-Plasma amino acids: elevated glycine

-PCCA 50% of cases (Seq 78%; Del/Dup 18%); PCCB 50% of cases (Seq 97%; Del/Dup 3%)

Others

-NBS: acylcarnitine analysis by MS/MS on dried blood spots --> elevated propionylcarnitine (C3); secondary markers: methionine, C3/C2, and C3/C16 ratios

-Elevated C3 on NBS can be caused by methylmalonic acidemias resulting from methylmalonyl-CoA mutase deficiency/disorders of intracellular cobalamin metabolism/maternal B12 def.