Maple Syrup Urine Disease

Genetics

-Genes: BCKDHA (BCKA decarboxylase (E1) alpha subunit --> MSUD type 1A; 45%); BCKDHB (BCKA decarboxylase (E1) beta subunit; MSUD type 1B; 35%); DBT (dihydrolipoyl transacylase (E2) subunit; MSUD type 2; 20%)

-AR: not digenic --> no individuals are heterozygous for variants in two different genes

Clinical findings/Dysmorphic features

1) Classic:

-12h after birth: untreated neonates with classic MSUD have maple syrup odor in cerumen

-12-24h: elevated plasma concentrations of BCAAs (leucine, isoleucine, valine) + allo-isoleucine + disturbance of plasma amino acid concentration ratios

-2-3 days: ketonuria (fatty acids are moved from triglyceride stores in the body in response to inadequate intake or availability of carbohydrates); irritability; poor feeding

-4-5 days: deepening encephalopathy --> lethargy, intermittent apnea, opisthotonus (spasm of the muscles), "fencing" and "bicycling"

-7-10 days: coma and central respiratory failure

2) Intermediate:

-Partial BCKAD deficiency --> manifests intermittently/responds to dietary thiamine therapy

-Experience severe metabolic intoxication and encephalopathy during catabolic stress

Etiology

-Rare in most populations, with incidence estimates of 1:185,000 live births

-Founder variant (c.1312T>A, p.Tyr438Asn) in BCKDHA (E1a) in Mennonites (PA, Kentucky, NY, Indiana, Wisconsin, Michigan, Iowa, Missouri) --> carrier 1:10; incidence 1:380 births

Pathogenesis

-Decreased activity of branched-chain alpha-ketoacid dehydrogenase complex (BCKAD) in mitochondria --> catalyzes oxidative decarboxylation of branched-chain keto acids (2nd enzymatic step in the degradative pathway of BCAAs)

-BCKAD with 4 subunits (E1a, E1b, E2, and E3) --> pathogenic variants in both alleles encoding any subunit --> decreased activity of complex --> accumulation of BCAAs and corresponding branched-chain ketoacids (BCKAs) in tissues and plasma

Genetic testing/diagnosis

-Increased plasma conc. of leucine; isoleucine and valine are also typically elevated; decreased concentrations of other essential and non-essential amino acids --> elevated ratios of leucine to alanine, glutamate, glutamine, tryptophan, methionine, histidine, phenylalanine, tyrosine

-Plasma conc. of allo-isoleucine (>5 µmol/L; distinctive metabolite in all forms of MSUD)

-Urinary excretion of branched-chain alpha-hydroxyacids and BCKAs --> gas chromatography-mass spectrometry or dinitrophenylhydrazine (DNPH) test

-BCKAD enzyme activity in a variety of cells including lymphoblasts (< 3%)

Others

-E3 subunit of BCKAD is shared with pyruvate and alpha-ketoglutarate dehydrogenase complexes --> MSUD type 3: increased urinary excretion of BCKAs and alpha-ketoglutarate + elevated plasma concentrations of lactate, pyruvate, and alanine