Isolated Methylmalonic Acidemia

Genetics

-Genes: MMUT (methylmalonyl CoA mutase; 60%), MMAA (methylmalonic aciduria type A protein; 25%), MMAB (methylmalonic aciduria type B; 12%, MCEE (Methylmalonyl-CoA epimerase; unknown), MMADHC

Clinical findings/Dysmorphic features

-Complete or partial deficiency of:

1) Methylmalonyl-CoA mutase

2) Methylmalonyl-CoA epimerase

3) Defect in transport/synthesis of its cofactor adenosyl-cobalamin (cblA, cblB, or cblD-MMA)

-Onset: neonatal period to adulthood; periods of relative health and intermittent metabolic decompensation (associated with intercurrent infections and stress)

-Secondary complications: ID (variable); tubulointerstitial nephritis with progressive renal failure; "metabolic stroke" (acute and chronic basal ganglia injury); pancreatitis; growth failure; functional immune impairment; optic nerve atrophy

1) Neonatal period: lethargy, vomiting, hypotonia, hypothermia, respiratory distress, severe ketoacidosis, hyperammonemia, neutropenia, thrombocytopenia; untreated: death < 4weeks

2) Infantile/non-B12-responsive: normal at birth, but develop lethargy, vomiting, dehydration, FTT, hepatomegaly, hypotonia, encephalopathy within a few weeks to months of age

3) Intermediate/B12-responsive: usually in first months or years of life; anorexia, FTT, hypotonia, DD; protein aversion and/or vomiting/lethargy after protein intake

4) Atypical and "benign"/adult: increased, albeit mild, urinary excretion of methylmalonate

Etiology

-Approximately 1:80,000 newborns

Pathogenesis

-Failure to convert methylmalonyl-CoA into succinyl-CoA during propionyl-CoA metabolism in mt-matrix --> elevated MMA in blood/urine, hypomethioninemia, or variations in other metabolites, such as malonic acid

-Suggestive findings: normal B12; elevated propionylcarnitine (C3); hyperammonemia; hyperglycinemia; lactic acidosis; CBC showing neutropenia, thrombocytopenia, anemia

Genetic testing/diagnosis

-Diagnosis: organic acids in plasma and/or urine by gas-liquid chromatography and MS

-Establishing the specific subtype: cellular biochemical studies (14C propionate incorporation, B12 responsiveness, complementation analysis, cobalamin distribution) and genetic testing

-Biallelic pathogenic variants in one of the five genes (MMUT, MMAA, MMAB, MCEE, MMADHC) – with confirmation of carrier status in the parents – can establish the diagnosis

Others

-MUT form of MMA is unresponsive to vitamin B12 therapy

-Elevated homocysteine in cbl C,D,F