Glutaric acidemia Type I

Genetics

-Gene: GCDH (glutaryl-CoA dehydrogenase; 19p13.13)

-AR

Clinical findings/Dysmorphic features

-Macrocephaly at birth (75%); acute encephalopathic episodes (i.e. illness); sudden onset of hypotonia and severe movement disorders (choreoathetotic movements) following an acute episode of dystonia

-Relatively normal development if treated

Etiology

-Prevalence: 1 in 100,000

-Prevalence in Amish: 1 in 300

Pathogenesis

-Deficiency in glutaryl-CoA dehydrogenase: lysine/tryptophan metabolism (in mt matrix)

-Converts glutaryl-CoA to crotonyl-CoA --> impaired break down of amino acids lysine, hydroxylysine, tryptophan

-Accumulating glutaryl-CoA is metabolized to 3-hydroxyglutaric acid and glutaconic acid

-Excessive levels of these amino acids/intermediates cause damage to brain (basal ganglia)

Genetic testing/diagnosis

-Elevated glutaric acid, 3-hydroxyglutaric acid, glutaconic acid, glutarylcarnitine --> detected by gas chromatography/MS (organic acids) or tandem MS (acylcarnitines)

-C5DC level is increased

Others

-Sarah’s painting Ruthie’s prayer

-Bleeding in brain or eyes --> mimics non-accidental trauma/child abuse

-Treatment:

During crisis: prevent or reverse catabolic state --> high-energy intake (plus insulin in case of hyperglycemia); reduce production of neurotoxic GA and 3-OH-GA by decrease/omitting natural protein for 24 −48h; prevent secondary carnitine depletion by carnitine suppl.

Long-Term: reduce accumulation of toxic agent glutaric acid; low protein diet which specifically restricts lysine and tryptophan; alternatively, they can be put on a lysine free diet with tryptophan supplements for protein biosynthesis; patients are also given carnitine