Galactocerebrosidase deficiency (Krabbe Disease)

Genetics

-Gene: GALC (Galactocerebrocidase, 14q31)

-AR

Clinical findings/Dysmorphic features

1) Infantile-onset (onset <12 months): progressive neurologic deterioration in infancy and death before age two years (85%-90%) --> excessive crying to extreme irritability, feeding difficulties, gastroesophageal reflux disease, spasticity of lower extremities and fisting, loss of acquired milestones (smiling, head control), staring episodes, peripheral neuropathy; average age of death is 13 months (infections or respiratory failure)

2) Later-onset (onset >12 months, to 5th decade): slower disease progression (10%-15%) --> slow development of motor milestones or loss of milestones (e.g. sitting without support, walking), slurred speech, spasticity of extremities with truncal hypotonia, vision loss, esotropia (both eyes turns inward), seizures, peripheral neuropathy

Etiology

-1:250,000 in US; 1:100,000 in Europe

Pathogenesis

-Galactocerebrosidase: liposomal hydrolysis of galactolipids formed during white matter myelination

-Pathologic changes in the peripheral and central nervous system (globoid cell formation and decreased myelin) may result from toxic nature of accumulated psychosine (galactosylsphingosine) --> cannot be degraded due to galactocerebrosidase deficiency

Genetic testing/diagnosis

-More than 200 pathogenic variants, 30-kb deletion (from large intron 10, extends beyond the end of gene) accounts for ~45% of pathogenic variants in persons of European ancestry

-CT: nonspecific - diffuse cerebral atrophy of grey and white matter; MRI: demyelination of the brainstem and cerebellum; abnormal EEG, low nerve conduction velocity

-Low GALC enzyme activity (0-5% of normal activity)

-GALC targeted mutation analysis: GALC 30-kb deletion (45% of Europeans, 35% of Mexicans); c.809G>A mutation (50% of late onset Krabbe); GALC sequencing (virtually 100%)

Others

-On NBS --> HSCT decreases morbidity and mortality when given to infants before symptoms

-Supportive care to control irritability and spasticity if diagnosed when symptomatic