GBL1-Related Disorders

Genetics

-Gene: GLB1 (β-galactosidase)

-AR

Clinical findings/Dysmorphic features

-2 phenotypically distinct lysosomal storage disorders:

1) GM1 gangliosidosis

-Type I (infantile): onset < 1 yr; progressive CNS dysfunction --> spasticity, deafness, blindness, decerebrate rigidity; life expectancy 2-3 yrs; infants have macular cherry-red spots, DD, regression by 6mths, hepatosplenomegaly, cardiac involvement, coarse facial features, generalized skeletal dysplasia

-Type II (late-infantile): onset 1-3 yrs, life expectancy 5-10 yrs

-Type II (juvenile): onset 3-10 yrs; insidious plateauing of motor and cognitive development followed by slow regression; +/- skeletal dysplasia

-Type III: onset 2nd - 3rddecade --> extrapyramidal signs, gait disturbance, cardiomyopathy; similar to Parkinson; ID is common; short stature, kyphosis, and scoliosis of varying severity

2) Mucopolysaccharidosis type IVB (MPS IVB, Morquio)

-Skeletal changes, including short stature and skeletal dysplasia

-No clinical sx at birth: severe form at 1-3 yrs, attenuated form in childhood or adolescence

-Significant morbidity: respiratory compromise, obstructive sleep apnea, valvular heart disease, hearing impairment, corneal clouding, spinal cord compression

-Intellect is normal unless spinal cord compression leads to CNS compromise

Etiology

-GM1 gangliosidosis: 1 in 100,000 to 200,000 newborns

Pathogenesis

-β-galactosidase activity: Type I ~0%; Type II 1-5%/3-10%; Type III 5-10%; MPS IVB 2-12%

Genetic testing/diagnosis

-Specific GAG pattern in urine is noted in persons with GM1 gangliosidosis

-Keratan sulfate in urine can be diagnostic of MPS IV (does not diff. MPS IVA from MPS IVB)

-GLB1: Seq 99%; InDel <1%

Others

-GM2 gangliosidosis without skeletal changes or other non-CNS findings

-MPS IVA is caused by pathogenic variants in GALNS