Gaucher Disease

Genetics

-GBA (Lysosomal acid glucosylceramidase; 1q22)

-AR

Clinical findings/Dysmorphic features

-Continuum: perinatal lethal - asymptomatic type

-Type 1: clinical/radiographic evidence of bone disease (osteopenia, focal lytic or sclerotic lesions, osteonecrosis, “Erlenmeyer flask bone”), hepatosplenomegaly, anemia/thrombocytopenia, lung disease, absence of primary CNS disease

-Types 2 and 3: presence of primary neurologic disease

--> 2: onset <2y; limited psychomotor development; rapidly progressive course; death by 2-4y

--> 3: onset ~2y; more slowly progressive course; survival into 3rd or 4th decade

Etiology

-GD type1: with prevalence of 1:855 and carrier frequency of 1:18 in AJ

Pathogenesis

-Defective lysosomal enzyme glucocerebrosidase --> accumulation of glucosylceramide (GL1) and other glycolipids --> GL1 is stored in cells of monocyte/macrophage lineage

-CNS: GL1 originates from turnover of membrane gangliosides, although neuronal cell death may be the basis of neuropathic involvement

Genetic testing/diagnosis

-Diagnosis: deficient glucocerebrosidase activity in peripheral blood leukocytes or identification of biallelic variants in GBA

-Targeted first in AJ: c.84dupG + c.115+1G>A + p.Asn409Ser + Leu483Pro account for 90%

-GBA: Seq >99%, InDel <1%

Others

-Most common lysosomal storage disorder

-Severe horizontal gaze palsy (fixed esotropia) and preserved vertical gaze movement

-Carriers are at an increased risk for developing Parkinsonism