Hexosaminidase A deficiency (Tay Sachs Disease)

Genetics

-Gene: HEXA (Hexosaminidase A; 15q23-q24); HEXA encodes alpha chain of the heterodimeric protein β-hexosaminidase A (HEX A) (also called GM2 gangliosidase)

-AR

Clinical findings/Dysmorphic features

1) Infantile (Tay-Sachs): progressive weakness, loss of motor skills, decreased attentiveness, increased startle response beginning at 3-6 months --> progressive neurodegeneration (seizures, blindness, spasticity, eventual total incapacitation) --> death usually < 4 years

2) Juvenile (subacute): muscle coordination problems, seizures, vision problems starting as young children

3) Chronic and adult-onset: later onset, rarer, some with bipolar form of psychosis

-Cherry red spot on eye exam (accumulation of GM2 gangliosides in the surrounding area)

Etiology

-Incidence approximately 1:3600 in AJ births

-Carrier rate: 1:27, (c.1274\_1277dupTATC, p.Tyr427IlefsTer5 accounts for ~ 80%)

Pathogenesis

-β-hexosaminidase A cleaves terminal β-linked N-acetylgalactosamine from GM2 ganglioside

-Excessive and ubiquitous neuronal glycolipid storage (≤12% of the brain dry weight)

-Enormous predominance is the specific glycolipid GM2 ganglioside

Genetic testing/diagnosis

-Diagnosis relies on absent/near-absent β-hexosaminidase A activity in serum/white blood cells/other tissues from symptomatic individual (in presence of normal/elevated activity of the β-hexosaminidase B) --> 0-5% infantile TSD vs. <15% juvenile or chronic and adult-onset type

-more than 130 HEXA pathogenic variants have been detected to date

-Panel of six most common pathogenic variants:

--> 3 x LOF (p.Tyr427IlefsTer5, c.1421+1G>C, c.1073+G>A)

--> p.Gly269Ser (associated with adult-onset form in hom or in comhet state with a null allele)

--> 2 x pseudodeficiency alleles (p.Arg247Trp and p.Arg249Trp; not associated with neurologic disease but with reduced degradation of synthetic substrate during HEX A enzymatic testing)

Others

-Normal-sized liver and spleen (vs. Gaucher)

-HEX A is composed of 1 alpha and 1 beta subunit; HEX B is composed of 2 beta subunits