MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)

Genetics

-Genes: MT-TL1 (>80%); MT-ND5 (<10%)

-Maternal inheritance

Clinical findings/Dysmorphic features

-Multisystem disorder; onset between 2 and 40y

-Manifestations: stroke-like episodes; encephalopathy with seizures/dementia; muscle weakness; exercise intolerance; headaches; vomiting; hearing impairment; peripheral neuropathy; LD; short stature

-During stroke-like episodes: increased T2-weighted signal areas that do not correspond to the classic vascular distribution (hence: "stroke-like")

-Lactic acidemia is very common and muscle biopsies typically show ragged red fibers

Etiology

-Prevalence estimated to be 0.2:100,000 in Japan

-Prevalence of m.3243A>G estimated to be 16:100,000–18:100,000 in Finland

Pathogenesis

-11 mt-tRNAs (mainly MT-TL1) involved in MELAS --> impaired mitochondrial protein synthesis

-6 protein-encoding genes also involved in MELAS (i.e. MT-ND1, NADH dehydrogenase subunit 1 and MT-ND5, NADH dehydrogenase subunit 5) --> pathogenic variants in ETC structural subunits result in impaired ATP synthesis via oxidative phosphorylation

Genetic testing/diagnosis

-Diagnosis based on clinical diagnostic criteria and identifying a pathogenic variant

-Blood leukocyte DNA is initially tested for m.3243A>G in MT-TL1 (present in ~ 80% of individuals with typical clinical findings) --> if normal, targeted testing for pathogenic variants m.3271T>C and m.3252A>G in MT-TL1 and m.13513G>A in MT-ND5

Others

-mtDNA encodes 22 tRNAs

-During acute stroke-like episode --> intravenous arginine within three hours, followed by intravenous arginine as a continuous infusion over 24 hours for the next three to five days