Early onset familial Alzheimer disease

Genetics

-PSEN1 (Presenelin-1, 14q24.3), APP (Amyloid beta A4, 21q21), PSEN2 (Presenilin-2, 1q31-q42)

-AD

Clinical findings/Dysmorphic features

-Dementia, confusion, poor judgment, language disturbance, agitation, withdrawal, hallucinations

-Early onset: <age 60

Pathogenesis

-Enhanced production of the 42 amino acid APP C-terminal degradation product (Aβ42) at the expense of the 40 amino acid C-terminal APP C-terminal degradation product (Aβ40) --> Aβ42 is toxic to cells in culture, prone to aggregation, and found in plaques

-Triple dose of APP may explain Alzheimer’s in Trisomy 21

Genetic testing/diagnosis

-Gross cerebral cortical atrophy

-Post mortem: beta-amyloid plaques, intraneuronal neurofibrillary tangles, amyloid angiopathy

-Sequencing: PSEN1 (20-70%), APP (10-15%), PSEN2 (rare)

Others

-EOFAD: 1-6% of all Alzheimer’s, 60% of which is familial, and 13% inherited in an AD manner

-LOFAD: might be associated with APOE e4, but not sensitive or specific --> supports diagnosis

-APOE e2 may be protective