X-linked adrenoleukodystrophy

Genetics

-ABCD1 (ATP-binding cassette sub-family D member 1) --> Adrenoleukodystrophy protein

-95% inherited; ~ 4.1% have de novo variant

Clinical findings/Dysmorphic features

-X-ALD affects the nervous system white matter and the adrenal cortex

-Three main types:

1) Childhood cerebral form (35-40%): between ages 4-8; first ADHD/hyperactivity; progressive impairment of cognition, behavior, vision, hearing, motor function --> total disability within six months to two years; most have impaired adrenocortical function at the time that neurologic disturbances are first noted; symmetric enhanced T2 signal in the parieto-occipital region

2) Adrenomyeloneuropathy (AMN; 40-45%): in 20s or middle age; progressive stiffness and weakness of the legs, sphincter disturbances, sexual dysfunction; often, impaired adrenocortical function; all symptoms are progressive over decades; 60% of heterozygous women (>40 yr-old) manifests AMN; 35% of male with AMN develop cerebral demyelination

3) Addison disease only (10%): between age two years and adulthood (most commonly by age 7.5 years); primary adrenocortical insufficiency, without evidence of neurologic abnormality

Etiology

-Prevalence is estimated at between 1:20,000 and 1:50,000

Pathogenesis

-Peroxisomal disorder, accumulation of saturated VLCFA

-ALDP located in peroxisomal membrane; required for transport of VLCFA into peroxisome

Genetic testing/diagnosis

-Diagnosis of X-ALD: in a male proband with suggestive clinical findings and elevated VLCFA; in a female proband with detection of a heterozygous ABCD1 variant and elevated VLCFA

-MRI always abnormal in boys with cerebral disease (often provides the first diagnostic lead)

-Diagnosis based on elevations in VLCFA in plasma or cultured fibroblasts: concentration of C26:0; Ratio of C26:0/C22:0 and C24:0/C22:0

-ABCD1 seq (92%); ABCD1 del/dup (6%)

Others

-20% of females who are carriers develop neurologic manifestations (AMN) but with later onset (age ≥35 years) and milder disease; carrier females do not have adrenal insufficiency

-Corticosteroid replacement, BMT if diagnosed after changes visible on brain MRI but before significant neuropsychological problems develop

-Lorenzo’s oil