ATP7A-Related Copper Transport Disorders

Genetics

-Gene: ATP7A (Copper transporting ATPase1, Xq21.1)

-XLR (1/3 de novo)

Clinical findings/Dysmorphic features

1) Menkes disease: healthy until 2-3 mths; then loss of developmental milestones, hypotonia, seizures, FTT; infants exhibit typical neurologic and hair changes (short, sparse, coarse, twisted, light; steel wool cleaning pads; pili torti); temp. instability; hypoglycemia; death by age 3y

2) Occipital horn syndrome (OHS)/X-linked cutis laxa: "occipital horns" (distinctive wedge-shaped calcifications at occipital bone); lax skin and joints; bladder diverticula; inguinal hernias; vascular tortuosity; intellect is normal or slightly reduced

3) ATP7A-related distal motor neuropathy: adult-onset disorder; resembling Charcot-Marie-Tooth disease; no clinical or biochemical abnormalities characteristic of Menkes disease or OHS

Etiology

-Incidence 1:100,000 births

Pathogenesis

-ATP7A is transmembrane protein that functions in copper transport across membranes --> copper accumulates in some tissues (small intestine and kidney), low in brain and other tissues

-Reduced activity of numerous copper-containing enzymes (i.e. structure and function of bone, skin, hair, blood vessels, nervous system)

Genetic testing/diagnosis

-Plasma and CSF catecholamine analysis: catechol concentrations abnl in males with Menkes disease and OHS (normal in ATP7A-related DMN) (abnl levels reflect partial deficiency of the copper-dependent dopamine beta hydroxylase critical for catecholamine biosynthesis

-Serum copper concentration and serum ceruloplasmin concentration low in Menkes disease and OHS (normal in ATP7A-related DMN)

-ATP7A: Seq 80%, InDel 20%

Others

-ATP7A-related DMN: unique variants within or near the luminal surface of the protein