Denouement and Comment

Adrenoleukodystrophy and Adrenomyeloneuropathy

Laboratory evaluation revealed a fasting cortisol level of 3 μg/dL, a 60-minute cosyntropin-stimulated cortisol level of 3.5 μg/dL, an 8 AM corticotropin level of 7240 pg/mL, plasma renin activity of 955 ng/dL/h, a serum aldosterone of 3 ng/dL, a testosterone level of 562 ng/dL, follicle-stimulating hormone of 3.3 mIU/mL, luteinizing hormone 14 mIU/mL, and elevated very-long-chain fatty acid (VLCFA) levels. Magnetic resonance imaging of the brain revealed an enhancing lesion in the left limb of the internal capsule extending into the corticospinal tract and a focus of abnormal signal in the left globus pallidus. Magnetic resonance imaging of the spine revealed diffuse atrophy of the cervical and thoracic cord without any enhancement.

Adrenoleukodystrophy is an X-linked disorder of VLCFA metabolism with an estimated incidence of 1 in 21 000 males.[1] The defective gene (*ABCD1*), located on chromosome Xq28, codes for a peroxisomal membrane protein responsible for forming the channel through which VLCFA moves into peroxisomes. Mutations in this gene impair channel formation, leading to VLCFA accumulation. The adrenal cortex, Leydig cells in the testes, and the central nervous system are the most severely affected. The overabundance of cholesterol-esterified VLCFA is resistant to corticotropin stimulation and can only be weakly converted into steroids, resulting in adrenal insufficiency.

Three types of adrenoleukodystrophy (ALD) can be seen in childhood: childhood cerebral form, adolescent ALD, and adrenomyeloneuropathy (AMN). The childhood cerebral form usually presents between 4 and 8 years of age with hyperactivity, often leading to the misdiagnosis of attention-deficit/hyperactivity disorder. Other neurological findings include difficulty hearing, vision problems, ataxia, poor handwriting, and seizures.[2] Adolescent ALD manifests with neurologic symptoms between the ages of 10 and 21 years. The phenotype is similar to the childhood cerebral form but progresses slower. Adrenomyeloneuropathy typically presents in young adulthood but can present in adolescence[3] with progressive paraparesis secondary to degeneration of the long tracts in the spinal cord. Approximately half of girls who are carriers will develop a mild syndrome similar to AMN but later in life.[4]

The central nervous system can be affected in 2 different ways. In the severe childhood cerebral form and the rapidly progressive adult forms of ALD, there is perivascular lymphocytic infiltration of the parieto-occipital white matter. In AMN—the slow, progressive adult form—there is loss of myelinated axons in the corticospinal tracts, nucleus gracilis, and dorsal spinocerebellar tracts. Sural and peroneal nerves reveal a loss of myelinated fibers.[5]

Diagnosis is made by identifying abnormally high levels of VLCFA in the plasma, red blood cells, or skin fibroblasts and mutation analysis for the defective gene. Elevated baseline corticotropin and abnormal rise in cortisol after corticotropin stimulation are also found in most cases, especially in the childhood form. Any male who presents with Addison disease should have his VLCFA levels tested to rule out ALD as the underlying etiology.[6,7]

Corticosteroid (hydrocortisone) replacement prevents life-threatening complications of adrenal insufficiency; affected children may require stress-dose steroids when ill. Aldosterone deficiency is treated with fludrocortisone acetate, a salt-retaining hormone.

Bone marrow transplant has been used in young boys and adolescents in the early stage of the cerebral form. Lorenzo's oil (a 4:1 mixture of glyceryl trioleate and glyceryl trierucate) received fame in 1992 through a film of the same name, which featured the journey of an affected boy's parents, who discovered their own treatment for the disease. When Hugo Moser, MD, the world expert on ALD, published data in 2005, it became clear that while the oil may not help already sick boys,[8] it is beneficial in delaying or preventing the onset of symptoms in neurologically asymptomatic boys younger than 8 years with normal magnetic resonance imaging results.[9]

It is important to identify all at-risk male family members and possible female carriers and to test them for VLCFA levels and/or with mutational DNA analysis. We counseled the family regarding the X-linked inheritance pattern and 50% risk to future males, prenatal diagnostic options, and at-risk relatives, and tested the at-risk males in our patient's immediate family (males 4 and 5 in Figure 2). They had normal VLCFA levels.

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