



X-Linked Adrenoleukodystrophy

Background

X-Linked Adrenoleukodystrophy (X-ALD) is a peroxisomal fatty acid beta oxidation disorder defined by the accumulation of very long chain fatty acids (VLCFA). This is due to a mutation in the ABCD1 gene for X-ALD. The accumulation of VLCFA is present in all tissues, but primarily in the adrenal cortex, the myelin of the central nervous system, and the Leydig cells of the testes. It is characterized by progressive neurologic deterioration, behavioral changes and adrenocortical insufficiency. The combined incidence of X-ALD in heterozygotes and hemizygoters is 1 in 17,000; the United States population has a frequency for affected males of 1 in 20,000. X-ALD is panethnic.

Clinical

The accumulation of VLCFA causes the deterioration of the myelin sheath, which leads to neurological decline and adrenal insufficiency. There are three categories of X-ALD, however, there is no genotype-phenotype correlation and confirmatory testing results cannot predict the phenotype. It has been documented that within the same families, brothers who inherit the same ABCD1 allele for X-ALD can have different forms of the disorder (childhood versus adult-onset), thus supporting the suggestion that epigenetic factors have a strong impact on phenotypic variation.

Neurologic degradation occurs quickly in Childhood Cerebral Demyelinating ALD (ALD) due to increasingly progressive demyelination of cerebral white matter. Neurologic deficits begin before 10 years of age, usually between ages 4-8 in males. Initial symptoms include difficulty concentrating and hyperactivity, visual problems (strabismus), and difficulty with verbal and written communication, most of which are often first noticed in academic settings. These boys may be labeled with ADD/ADHD, but are unresponsive to the usual intervention therapies. Other symptoms include seizures, dementia, incoordination, learning difficulties, visual and auditory impairment, progressive behavioral issues, changes in muscle tone (stiffness and contractures), difficulty in swallowing, and adrenal insufficiency. Once neurologic deficits occur, patients regress to a vegetative state within 2 years, and death usually within 5 years of diagnosis.

The adult-onset form of X-ALD is known as Adrenomyeloneuropathy (AMN). Clinical symptoms develop in the 20s and 30s and progress more slowly than the childhood form, over decades versus within a few years. While intellect is usually kept intact and cerebral involvement is limited, the progressive demyelination causes spastic paraparesis, peripheral neuropathy, and sphincter issues. There is almost always adrenal insufficiency. Treatment options for AMN are very limited and usually are only administered to provide palliative care.

Addison Disease, or adrenocortical insufficiency, can occur in males with an ABCD1 mutation as the primary manifestation of X-ALD, while neurologic manifestations are usually absent. In 10% of X-ALD cases, this is the only clinical sign of X-ALD. Most males with ALD or AMN also have Addison's Disease. Males diagnosed with Addison Disease should also be evaluated for X-ALD.

Female carriers can manifest symptoms, including spastic paraparesis and sphincter issues, but maintain normal adrenal function. As an X-linked recessive disorder, females who carry one copy of the ABCD1 gene for X-ALD may develop mild symptoms, though usually after age 35.

Testing

Newborn screening measures C26:0 lysophosphatidylcholine (C26:0 LPC) in dried blood spots. Confirmatory plasma and skin fibroblasts analysis are performed for VLCFA levels in both males and females. Almost all males (99%) will have abnormal concentrations of VLCFA in plasma, while 85% of affected females will have abnormal VLCFA in plasma/fibroblasts. Of the known female carriers, 15-20% will have a normal VLCFA concentration, and will need further testing to verify carrier status. Analyzing both VLCFA and lignoceric acid oxidation in females may help in determining carrier status. Molecular analysis is helpful in detecting carrier females and asymptomatic males within families. Brain MRI is performed to measure the disease progression once cerebral involvement begins.

In newborns, it is important to evaluate for Zellweger Spectrum Disorder when X-ALD is suspected. In children, behavioral changes that are consistent with ADD/ADHD could also indicate X-ALD. Male patients with Addison's Disease should also be evaluated for X-ALD as most cases of X-ALD have Addison's Disease.

Treatment

Under the supervision of an endocrinologist, adrenocorticoid insufficiency is treated with steroid supplementation. To limit neurological decline, dietary changes may include limiting fat intake. Hematopoietic Stem Cell Transplantation (HSCT) is the most effective treatment for X-ALD, and also used as a precursor to gene therapy. For either treatment pathway, it is vital that HSCT is administered before any cerebral demyelination or neurological symptoms occur. Otherwise, this has been found to accelerate the neurological decline in patients.

Because the diagnosis and treatment of X-ALD is complex, the pediatrician is advised to manage the patient in close collaboration with a metabolic geneticist and endocrinologist.

Inheritance

The ABCD1 gene for X-ALD is found at chromosome Xq28. It is an X-linked recessive disorder, which means that affected men cannot pass the X-ALD gene on to their sons, but will pass the X-ALD gene on to their daughters. Women who have one X-ALD gene (heterozygous) have a 50% chance of passing that affected gene on to their children (male or female). Women who are homozygous for X-ALD gene pass an affected gene to all of their children; all sons will be affected and daughters will be at risk for disease manifestations. The range of severity of X-ALD can be affected by large deletions within the ABCD1 gene, versus missense mutations within that gene.

Genetic counseling is vital in determining other family members who may be at risk for having X-ALD, especially asymptomatic males and females as they can develop symptoms later in life. Once someone is diagnosed with X-ALD within a family, it is imperative that all family members are tested as asymptomatic males may be detected before symptoms occur thus allowing for the best chance for effective interventions. As with all genetic diseases, genetic counseling is also appropriate to help families understand recurrence risks and ensure that they receive proper evaluation and care.

References

GeneReviews <https://www.ncbi.nlm.nih.gov/books/NBK1315/>

Genetics Home Reference <http://ghr.nlm.nih.gov/condition/x-linked-adrenoleukodystrophy>

Online Mendelian Inheritance in Man <http://omim.org/entry/300100>