Adrenoleukodystrophy

Key facts

- X-linked adrenoleukodystrophy (X-ALD) is an X-linked recessive disorder caused by a disruption to the transport and breakdown of fatty acids in the peroxisomes.
- X-ALD is the most common of the peroxisomal disorders, with a worldwide prevalence of approximately 1 in 20,000.
- The clinical features are varied, and occur because of damage to the adrenal glands, brain cells and myelin sheaths.
- Broadly speaking, three distinct subtypes are described: a childhood cerebral form, an adrenomyeloneuropathy type and an Addison's disease only form.
- The age of onset of symptoms, rate of progression of the disease and life expectancy of affected individuals vary enormously, even between two affected members of the same family.
- Steroid replacement therapy is important for affected individuals with adrenal insufficiency. No treatment is known to reverse the progression of the neurological symptoms, though several experimental treatments have been tried.

Clinical features

- Children with the cerebral form typically develop symptoms between 4 and 10 years of age. Disease progression is variable but can be rapid, leading to total dependence and death within 6 to 24 months of the onset of symptoms. Children may show signs of dementia, behavioural problems, loss of fine motor skills, visual loss or other unexplained neurological symptoms and signs.
- Symptoms of the adrenomyeloneuropathy subtype most commonly appear in men from their mid-20s onwards. These include progressive paraparesis, sphincter problems, impotence and adrenal insufficiency. Symptoms may progress slowly over many decades, but rapid progression may occur in 10-20% of affected males.
- Adrenal insufficiency may be the only manifestation in individuals affected with the Addison's disease only form. Disease onset can occur at any time between childhood and adulthood. Affected individuals may develop additional features of adrenomyeloneuropathy by middle age.
- About 20% of carrier females develop neurologic manifestations of the condition; these symptoms are much milder than in males and do not usually develop until the fourth decade.

Diagnosis

- Biochemical testing for X-ALD involves the measurement of very long chain fatty acids (VLCFAs) in plasma. Elevated concentrations of hexacosanoic acid (C26:0) with normal concentrations of phytanate and pristanate are the characteristic findings.
- When VLCFA results are equivocal, the diagnosis can usually be confirmed by DNA studies; *ABCD1* is the only gene known to be associated with this condition.
- Brain MRI and adrenal function tests may be used to help establish the extent of the disease in affected individuals.

Genetic basis and genetic testing

- Adrenoleukodystrophy is an X-linked recessive disorder caused by variants in the *ABCD1* gene.
- The *ABCD1* gene encodes the adrenoleukodystrophy protein (ALDP), which is responsible for the transportation of VLCFAs into peroxisomes. Deficiency of functional ALDP results in the characteristic accumulation of VLCFAs in the circulation.
- The risks to family members of an affected individual depend upon the carrier status of the mother: about 93% of mothers with affected children are carriers; 7% of affected males with X-ALD have a de novo mutation in the *ABCD1* gene.
- Genetic testing may be used to confirm the diagnosis where measurement of VLCFAs is not conclusive. It can also provide information about the genetic status of an affected individual's female relatives through carrier testing.
- It is not possible to predict the severity of the condition from the type of variant in the *ABCD1* gene.
- Prenatal diagnosis is usually possible by chorionic villus sampling (CVS) or amniocentesis. If a couple are considering prenatal diagnosis, referral should be made to the local clinical genetics service prior to a pregnancy. All couples considering pre-implantation genetic diagnosis must be referred to their local clinical genetics service. Fetal sex determination by non-invasive prenatal diagnosis is now available, potentially reducing the need for invasive procedures by 50%. It should be discussed with families, but needs to be facilitated by clinical genetics departments or fetal medicine units.

Clinical management

- Steroid replacement therapy is essential for patients with adrenal insufficiency, though they will not affect the progressive nature of the condition.
- Attempts to reduce the levels of VLCFAs in the diet by 'Lorenzo's oil' remain experimental.
- Bone marrow transplantation may be considered in male children during the early stages of disease.

Direction to further reading, guidelines and patient groups

- Orphanet
- Alex – The Leukodystrophy Charity

This information is intended for educational use and was current in November 2019. For clinical management, it is recommended that local guidelines and protocols are used.

Produced in collaboration with Birmingham Women's NHS Foundation Trust's Clinical Genetics department and Imperial College Healthcare NHS Trust.