Adrenoleukodystrophy

Key facts

- X-linked adrenoleukodystrophy (X-ALD) is a disorder characterised by adrenal insufficiency and a progressive loss of physical and mental skills, owing to an abnormality of the white matter of the brain.
- X-ALD is the most common of the peroxisomal disorders: a group of metabolic conditions that occur because of a defect in the peroxisomes, which are essential for the normal breakdown of fatty acids in the cells.
- The clinical features are varied and are because of damage to the adrenal glands, brain cells and myelin sheaths. Broadly speaking, three distinct subtypes are described in affected males (see below).
- The age of onset of symptoms, rate of progression of the disease and life expectancy 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.
- ALD is an X-linked recessive disorder caused by mutations in the *ABCD1* gene. This means it usually affects boys, though in rare cases girls can be affected. 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.

Clinical features

The clinical features of X-linked adrenoleukodystrophy are varied and the diagnosis should be considered in the following circumstances:

1. All boys who have symptoms of attention deficit hyperactivity disorder (ADHD) who shows signs of dementia, behavioural problems, loss of fine motor skills, visual loss or other unexplained neurological symptoms and signs. Early symptoms usually develop between 4 and 10 years of age with rapid progression to total dependence and death within 6 - 24 months of the onset of symptoms.
2. Men with slowly progressive paraparesis, sphincter disturbance, sexual dysfunction, most commonly associated with adrenal insufficiency (adrenomyeloneuropathy). Symptoms most commonly appear in men after their mid-twenties and progress slowly over many decades; rapid progression occurs in 10%-20% of affected males.
3. Unexplained primary adrenocortical insufficiency without neurological abnormalities at any age, but most commonly in childhood. Affected individuals may develop additional features of adrenomyeloneuropathy by middle age.
4. Adult women with clinical features of the condition, but presenting at a much later age.

Diagnosis

- Plasma concentration of very long chain fatty acids (VLCFAs) is increased in >99% of affected males and approximately 85% of 'carrier' females.
- 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

- Adrenoleukodystrophy is an X-linked recessive disorder. The risks to the siblings of an affected individual depend upon the carrier status of the mother; about 93% of mothers are carriers, 7% of affected males with X-ALD have a de novo mutation (gene alteration) in the causative gene.
- For females who are known to be carriers, each son has a 1-in-2 (50%) chance of inheriting the condition, and each daughter a 50% (1-in-2) chance of being a carrier.
- It is not possible to predict the severity of the condition from the type of alteration in the *ABCD1* gene.

Clinical management

- Steroid replacement therapy is essential for patients with adrenal insufficiency, though they will not affect the progressive nature of the condition.
- Receiving optimum care from a multidisciplinary team, with the input of specialists in many different areas, improves the quality of life as symptoms can be treated appropriately as they occur. The different areas of care depend upon the clinical presentation. The family should be actively engaged with the process of individualising care.
- General support for the family is critical.
- Attempts to reduce the levels of VLCFAs in the diet by 'Lorenzo's oil' remain experimental.
- Bone marrow transplantation may be considered in boys in the early stages of disease.

Genetic testing

Genetic testing can be used to:

- confirm the diagnosis in someone with possible adrenoleukodystropy (diagnostic testing) when measurement of VLCFA is not conclusive;
- provide information about the genetic status of female relatives of someone with adrenoleukodystropy through carrier testing; and
- offer prenatal and pre-implantation genetic diagnosis. 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. This ensures that appropriate advice and investigations are undertaken and confirms whether or not prenatal diagnosis is possible. 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.

Genetic testing is available in the UK and usually provided through specialist clinics or regional genetic centres.

This information is intended for educational use and was current in March 2015. For clinical management, it is recommended that local guidelines and protocols are used.