

X-linked Adrenoleukodystrophy

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Abstract

X-linked adrenoleukodystrophy (X-ALD) is a rare disorder characterized by progressive demyelination of the central nervous system (CNS) (brain and/or spinal cord) and peripheral adrenal insufficiency (Addison's disease). The minimum frequency of hemizygotes identified in the United States would be 1:42,000 and that of hemizygotes plus heterozygotes 1:16,800. X-ALD is characterized by wide phenotypic variability, with the different clinical forms often being observed within the same family. The two distinct neurological phenotypes are: *adrenomyeloneuropathy*, a non-inflammatory axonopathy which affects spinal cord mostly in adults, and an intensely *inflammatory cerebral myelinopathy* which affects cerebral white matter mostly in children. The cerebral form of juvenile X-ALD (45% of the cases) affects previously healthy boys 5-12 years old. The first manifestations are moderate cognitive deficits, followed by progressive demyelination of the central nervous system, with diminished visual acuity, central deafness, cerebellar ataxia, hemiplegia, convulsions and dementia leading to a neurovegetative state or death within several years. The adult form is characterized by the onset between 20 and 45 years of age of spastic paraparesia, gait disturbances, urinary disorders and sexual dysfunction. The disease progresses towards severe paraplegia complicated by cerebral demyelination in 30% of the cases. The diagnosis is confirmed by the demonstration of high concentrations of very long chain fatty acids (VLCFA) in plasma or fibroblasts. X-ALD is secondary to a mutation in the ABCD1 gene, which is localized to chromosome Xq28. A 34-point scoring system designed specifically for MRI images of X-ALD patients is now used worldwide for therapeutic strategies. Allogeneic bone-marrow transplantation, when performed at an early stage of the disease, can stabilize and even reverse cerebral demyelination in boys with the cerebral form. No other therapy (Lorenzo's oil, immunosuppressors, interferon-beta) has proven to be effective. Screening of heterozygous women is based on the measurement of VLCFA concentrations in plasma (95% reliability), the study of the X-ALD protein in fibroblasts or monocytes/lymphocytes and the search for the X-ALD gene mutation, when it is known. The same techniques are used for prenatal diagnosis (trophoblasts or amniocytes).

Disease name

X-linked adrenoleukodystrophy, X-ALD

Adrenomyeloneuropathy, AMN

Inflammatory cerebral myelinopathy

Excluded diseases

The following diseases will be excluded:

- neonatal adrenoleukodystrophies (a heterogeneous group of neonatally detected

peroxysmal diseases with autosomal recessive inheritance);
 - Schilder's disease.

Definition

X-linked adrenoleukodystrophy (X-ALD) is characterized by the progressive demyelination of the central nervous system (brain and/or spinal cord) and peripheral adrenal insufficiency (Addison's disease). X-ALD has two distinct neurological phenotypes: adrenomyeloneuropathy, a non-inflammatory axonopathy which affects spinal cord mostly in adults, and an intensely inflammatory cerebral myelinopathy which affects cerebral white matter mostly in children. The two forms often co-occur in the same family. Heterozygous women and the X-ALD mouse model often have the adrenomyeloneuropathy phenotype. The gene that is deficient in X-ALD is referred as *ABCD1*.

Diagnostic criteria

The diagnosis is confirmed by the demonstration of high concentrations of very long-chain fatty acids (VLCFA) (saturated cerotic acid C26:0 and the C26:0/C22:0 ratio) in plasma or fibroblasts.

Differential diagnosis

The following must be distinguished:

- the other leukodystrophies (primarily metachromatic leukodystrophy);
- the other causes of Addison's disease (acquired or hereditary);
- the other causes of familial progressive paraplegia;
- multiple sclerosis (MS).

Incidence

It is estimated to be between 1/15,000 and 1/20,000 boys born per year. Bezman *et al*, approximated the minimum frequency of hemizygotes identified in the United States would be 1:42,000 and that of hemizygotes plus heterozygotes 1:16,800

Clinical description

X-ALD is characterized by wide phenotypic variability, with the different clinical forms often being observed within the same family. The cerebral forms (45% of the cases) afflict boys otherwise healthy between age of 5-12 years. The demyelinating lesions (occipital and/or frontal lobes) initially progress slowly for 1-3 years and engender moderate cognitive deficits (visuospatial functions, command execution, immediate memory). Deterioration occurs subsequently with neurological involvement (diminished visual acuity, central deafness, cerebellar ataxia, hemiplegia, convulsions) and dementia leading to a vegetative state or death within 2-5 years. The disease evolves even more rapidly when it starts early (less than 8

years) and the demyelinating lesions affect the occipital lobes. The Adult form, called adrenomyeloneuropathy (AMN, 45% of the cases) is characterized by the appearance, between 20 and 45 years of age, of spastic paraparesis, gait disturbances (spinal cord involvement), urinary disorders and sexual dysfunction. Cerebral MRI is normal. Electrophysiological examinations demonstrate, in 80% of the patients, peripheral sensorimotor neuropathy. The normality of the visual evoked potentials may help to exclude the diagnosis of MS. AMN evolves rapidly (over 1-3 years) in 35% of the cases or slowly (10-15 years) in the remaining 65% of the patients towards severe paraplegia. One-third of AMN patients develop in a second stage demyelinating cerebral involvement identical to that of children. Peripheral adrenal insufficiency (AI) can be the first manifestation of ALD, it is never observed before the age of 3 years and rarely after 40 years. AI can remain the only manifestation of X-ALD for years or decades (8% of the cases), but it is often complicated subsequently by cerebral or spinal cord involvement. AI is seen in 80% of the children with cerebral X-ALD and 65% of the adults with AMN. After 40 years of age, 65% of the female carriers of X-ALD have clinical symptoms resembling those of AMN. In 40% of them, these symptoms are as severe as those in men. Cerebral involvement is very rare and female carriers exhibit no symptoms of AI. Fatemi *et al* demonstrated that MRI abnormalities attributable to X-ALD were present in only 3 of 76 women heterozygous for X-ALD, 65 of whom had AMN. Heterozygous women thus appear to be susceptible to the non-inflammatory axonopathy, but are resistant to the inflammatory brain disease.

Treatment

The development of surrogate markers facilitates the evaluation of therapeutic interventions: A 34-point scoring system designed specifically for X-ALD by Loes *et al*. is now used worldwide. The technique consist on brain neuroimaging studies as predictors of progression in childhood cerebral X-ALD

Corticoid replacement therapy

Adrenal hormone therapy is mandatory for all X-ALD patients who have adrenal insufficiency, and may be life saving even if this therapy has no effect on nervous system involvement.

Bone-marrow transplant

When done at an early stage of the disease, allogeneic bone-marrow transplant (BMT) can stabilize or even reverse the demyelinating lesions of the cerebral form of X-ALD. It is the only treatment whose efficacy has been proven in more than 100 patients with 6-11 years of follow-up (Peters *et al* 2004). However, it

requires a healthy HLA-identical donor and is associated with high morbidity and mortality, especially when the donor is unrelated. Indications for BMT must be carefully considered because the procedure carries a high risk of mortality. It is not recommended for patients with advanced cerebral involvement

Lorenzo's oil

A diet poor in VLCFA, and rich in oleic and erucic acids (Lorenzo's oil) is ineffective against cerebral X-ALD or and AMN, and has no preventive effect. Lorenzo's oil is able to normalize plasma VLCFA concentrations but has no effect on the intracerebral levels of these fatty acids. However, a recent multicenter study (Moser *et al* 2003) that involved 104 boys who were less than 6 years old, were neurologically asymptomatic and had a normal MRI suggested that it could diminish the mean score of MRI and neurological abnormalities during the first 3 years of treatment.

Statins

Statins (lovastatin, simvastatin, etc.) can also lower circulating VLCFA levels, but have no effect on intracerebral concentrations. It is thus unlikely that statins will have a clinical effect.

Immunosuppressive treatments

Other immunosuppressive treatments (cyclophosphamide, ciclosporin, interferon-beta, immunoglobulins, mitoxantrone) are ineffective against the cerebral forms of ALD. A therapeutic trial with riluzole versus placebo is in progress in patients (men and women) with AMN under 60 years of age. http://www.orpha.net/data/eth/FR/MSAPSP_BENSIMON.pdf

Etiology

X-ALD is secondary to a mutation in the ABCD1 gene, which is localized to chromosome Xq28, it codes for a 75-kDa half-transporter protein (called ALDP) located in the peroxisome membrane and it belongs to the family of ATP-binding cassette (ABC) transporters (like CFTR (cystic fibrosis transmembrane-conductance regulator), MDR (multi-drug resistance) and Sulfonyl urea receptor SUR). ALDP can form a homodimer or a heterodimer with 2 hemi-transporters from the same family X-ALD related and PMP70 X-ALD is characterized biochemically by the accumulation of VLCFA (the level is multiplied by a factor of 3-5) due to their defective beta-oxidation in the peroxisomes. in all tissues of the body.. It is possible, but not demonstrated, that ALDP imports VLCFA into the peroxisomes, where they are degraded. ALDP might also participate in the importation of other substrates and thus have other functions. It is generally accepted that the accumulation of VLCFA could have a

toxic effect on the adrenal gland (cortex) and myelin membranes (destabilization leading to demyelination). However, there is no direct proof of this toxicity. Recent findings have suggested that the accumulation of VLCFA could be a secondary phenomenon without great pathophysiological importance. X-ALD mice accumulate VLCFA like ALD patients but do not develop cerebral involvement. Over the age of 2 years, some X-ALD mice develop spinal cord and mild peripheral nerve involvements that resemble AMN. It has been hypothesized that ALDR (ABCD2) and PMP70 (ABCD3) genes might have a redundant effect with the ALD gene: the roles of these genes in the phenotypic expression of the disease are currently being investigated. Pharmacogenetic modulation of the expression of ABCD2 in X-ALD patients is also in progress. ABCD2 overexpression could potentially substitute to some function of ALD (ABCD1) genes.

Methods of biological diagnosis

In homozygotes, the diagnosis is based on the demonstration of elevated VLCFA concentrations in plasma (1 ml, non-hemolysed, at room temperature) or fibroblasts.

Valianpour *et al* used electrospray ionization mass spectrometry, a new and highly sensitive and specific method for VLCFA assay that is suitable for high throughput analyses. This will be valuable for mass screening and searching for new therapeutic agents in in-vitro systems.

This test can also identify 95% of the female carriers. Two recent reports (Aubourg *et al* and Hwu WL *et al*) emphasized the key importance of screening all male patients with Addison's disease with the plasma VLCFA assay.

Study of the X-ALD protein in lymphocytes/monocytes is able to reliably (100%) and rapidly (3 hours) identify female carriers in ALD-affected families in which the ALD gene mutation leads to the absence of ALDP (80% of the cases).

Almost every X-ALD family has its own 'private' mutation of the X-ALD gene (ABCD1) (composed of 21 kb, 10 exons, 2,750 bp of coding sequence). The search for the ABCD1 mutation is thus far from being routinely performed. The website <http://www.x-ald.nl/> updates the ABCD1 mutations that have been identified worldwide.

Genetic counselling

Fewer than 8% of the index cases of X-ALD are attributable to new mutations. It is thus important to enlarge the genetic study to identify women, who are potential carriers, and affected children, adolescents and adults. This analysis is justified because it can permit the identification of X-ALD patients with latent AI (acute AI is often responsible for sudden death of X-ALD-family members), could lead to the

prescription of preventive therapy to neurologically asymptomatic children and can identify children with the early cerebral involvement who can benefit from allogenic bone-marrow transplantation. Thus systematic screening of at-risk family members, including the extended family, is highly recommended.

Prenatal diagnosis

Prenatal diagnosis is systematically offered to female carriers. It is done by trophoblast sampling (11th week of pregnancy) or amniocentesis (15th week of gestation) after sex determination by blood sampling of the mother at 7-8 weeks of gestation. The diagnostic methods used are based on the demonstration of X-ALD protein in cultured cells, the dosage of VLCFA in cultured cells and the direct search for the mutation when it is known.

Unresolved questions

- The function(s) of ALDP

Many studies support that ALDP does play a role in VLCFA metabolism, they showed that the over expression of ALDP increases VLCFA oxidation in cultured skin fibroblasts of X-ALD patients, but the mechanism by which it does so remains unresolved. A current hypothesis continues to be that it is involved in some manner with the transport of VLCFAs into the peroxisome.

- The causes of the clinical phenotype variation;
- The mechanisms of microglial and/or oligodendrocyte dysfunction;
- The potential toxicity of VLCFA on myelin;

The causes of the inflammatory reaction observed in the cerebral demyelinating forms

Despite the fact that a recent study presented by Tagawa *et al* strengthened the hypothesis that VLCFA-containing lipids, such as gangliosides or proteolipids, act as triggers for an autoimmune response that involves CD1 molecules. The findings in this study support the hypothesis that VLCFA-containing gangliosides may act as antigens.

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