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X-Linked Adrenoleukodystrophy: Diagnostic and Therapeutic Approach

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Abstract

X-Linked adrenoleukodystrophy (ALD) is a rare neurodegenerative disorder with a wide clinical spectrum. It is characterized by progressive cerebral demyelination, spinal cord axonal degeneration and adrenal and testicular insufficiency. ALD is caused by mutations in the ABCD1 gene, involved in the metabolism of fatty acids. The main biochemical feature is elevated plasma and tissue levels of very long-chain fatty acids and the diagnosis relies on their measurement in plasma along with MRI studies. Allogeneic bone marrow transplantation is the preferred treatment in patients with the severe, cerebral form of ALD, offering a halt in disease progression, but only when instituted in the early stages of cerebral demyelization. The aim of this review is to summarize the present understanding of ALD, as well as to overview the advances in the diagnostics and treatment.

Keywords: Adrenoleukodystrophy, X-linked, Hematopoietic stem cell transplantation, ABCD1

Abbreviations: ABC: Adenosine Triphosphate - Binding Cassette; ALD: Adrenoleukodystrophy; ALDP: Adrenoleukodystrophy Protein; ALDRP: Adrenoleukodystrophy Related Protein; AMN: Adrenomyeloneuropathy; Cr: Creatine; Ch: Choline; HSCT: Hematopoietic Stem Cell Therapy; MR: Magnetic Resonance; MRI: Magnetic Resonance Imaging; NAA: N-Acetylaspartate; VLCFA: Very Long Chain Fatty Acids

Introduction

Adrenoleukodystrophy (ALD) is an X-linked inherited disorder that affects the central nervous system, peripheral nerves, adrenal cortex and testes. Also known as Schilder's disease and sudanophillic leukodystrophy, ALD is a peroxisomal metabolic storage disease caused by mutations in the ABCD1 gene, involved in the degradation of very long-chain fatty acids (VLCFA). The consequent accumulation of VLCFA leads to progressive central demyelination and adrenal insufficiency.

The first case of X-linked ALD (X-ALD) was likely described in 1910 [1]. Siemerling and Creutzfeldt in 1923 described it as "bronzed sclerosing encephalomyelitis" [2]; another synonym for ALD is Siemerling-Creutzfeldt disease. Biaw [3] in 1970 assigned the term adrenoleukodystrophy [3]. Since then, significant advances have been made in elucidating the pathophysiological mechanisms of the disease, as well as in the diagnostic and therapeutic approaches.

X-ALD is a rare disease, with an overall estimated incidence of 1:17,000, including symptomatic female heterozygotecarriers [4]. This makes it the most common of the leukodystrophies. The clinical presentation of ALD is strikingly diverse, from rapidly progressive, fatal neurological involvement in young children, to slowly progressive adrenomyeloneuropathy in older children or adults. The symptoms of ALD overlap with the other numerous leukodystrophies which makes the diagnosis of ALD challenging.

Genetics and Pathophysiology

The breakthrough in the ALD field came in 1993 when mutations in the ABCD1 gene were identified in patients with ALD [5]. The gene is mapped to Xq28 and encodes the adrenoleukodystrophy protein (ALDP), one of four members of the peroxisomal subfamily of ATP-binding cassette (ABC) proteins. ALDP is involved in the transport of very long-chain fatty acids (VLCFA) from the cytoplasm into the peroxisomes, where the oxidation and degradation of VLCFA takes place.

A gene that is closely related to ABCD1 has been mapped to chromosome 12q11. This gene is referred to as ALDR or ABC2. Its gene product, referred to as ALDRP, has 66% homology to ALDP [6], is also localized to the peroxisomal membrane and can correct the defect in very long chain fatty acid metabolism in cultured fibroblasts of X-ALD patients. The relationship between ALDP and ALDRP is still unclear, but it has been proposed that variations in the expression of ALDRP may account for the wide range of phenotypic expression that is a specific feature of

X-ALD. Also, these similarities between ALDP and ALDRP have led to the hypothesis that over expression of ALDRP might be used as a therapeutic strategy.

The inactivating mutations in the adrenoleukodystrophy gene, most of which are unique to particular families, have been defined in more than 400 families. In general, there is no correlation between the nature of the mutation and the phenotype. In one family the same mutation was associated with 5 widely different phenotypes [7]. De novo mutation of ABCD1 occurs in less than 8% of ALD patients [8].

The defect in the ALDP results in accumulation of VLCFA, which in turn produces an intense inflammatory response in the white matter of the central and peripheral nervous system. The VLCFA accumulation itself is thought to be responsible for the adrenal and testicular involvement. The inflammatory mechanism that leads to demyelination is not completely understood, but thought to result from activation of brain macrophages and astrocytes bearing CD1 molecules that recognize lipid antigens which are abnormally acylated by the excessive VLCFA. The precise mechanism by which the accumulation of VLCFA leads to the inflammatory demyelination that is the cause of the neurologic disability is still unclear.

Clinical Presentation

Most male X-ALD patients develop adrenocortical insufficiency in childhood and progressive myelopathy and peripheral neuropathy in adulthood. A subset of male patients, however, develops a fatal cerebral demyelinating disease, cerebral ALD. Female carriers can also develop progressive myelopathy and peripheral neuropathy, but generally at a later age than males. They only very rarely develop adrenocortical insufficiency or cerebral ALD. The three major disease categories are:

A. The severe, cerebral demyelinating form (cerebral childhood form) - appearing in mid-childhood (4-8 years);

B. Spinal cord demyelination and axonal degeneration (adrenomyelopathy, AMN) - occurring in men in their 20s or later and older women.

C. Impaired adrenal gland function (Addison's disease or Addison-like phenotype). AMN is the most frequent form, affecting 60% of affected males and 50% of female carriers [4].

The cerebral childhood form occurs in approximately 35% of ALD patients. The mean age of onset is 7 years, with the earliest onset noted at around 3 years. It develops in three phases:

A.An asymptomatic latent phase, when there are no clinical signs, but MRI changes of demyelination are present (the first lesions can be evident at around 4 years of age);

B.A phase with clinical signs which are the result of demyelination and start rapidly progressing (the first symptoms appear mostly at an age of 6-7 years);

C.A terminal phase with significant motor, sensory and cognitive sequellae, which leads to coma and death.

The symptoms depend on the topography of the demyelienation. The parieto-occipital forms are the most frequent [4], the initial symptoms consisting of cognitive visuomotor and visuospatial abnormalities and immediate memory deficits. Behavioral changes ensue, such as hyperactivity or attention deficit and emotional troubles, along with sensory disorders (visual field amputation, diminishing visual acuity, impaired auditory discrimination) and motor disorders (pyramidal syndrome of the lower extremities, gait abnormalities, hemiparesis, cerebellar ataxia). Sometimes seizures also occur. Once the symptoms appear, they progress rapidly and lead to an almost absolute loss of all cognitive functions, tetraplegy and blindness, and a vegetative state ensues usually within 3 years.

The frontal form presents with a frontal syndrome and hemiparesis. Sometimes adrenal insufficiency is the first sign of the disease, appearing well in advance of the neurological symptoms. The cerebral demyelinating form of ALD can also occur at a later age or in adulthood, when it assumes a progressive course similar to the childhood form.

Adrenomyeloneuropathy (AMN) is the more frequent form of ALD. The symptoms appear at an age of 20-30 in men and 40-50 in half of the female carriers and typically consist of spastic paraparesis with disturbed gait as a result of posterior spinal cord degeneration and urinary problems such as dysuria and urgency. Sometimes clinical signs of peripheral neuropathy (demyelinating, axonal, or both) can be seen. The symptoms are progressive and lead to a significant motor disability, but the progression varies and can extend over 20 years, without remission.

Adrenal insufficiency may be diagnosed after the appearance of neurological symptoms or decades in advance. Testicular dysfunction usually occurs late in the course of the disease. AMN in female carriers assumes a less severe form; the peripheral neuropathy is rarer, but neurogenic pain is a more frequent and severe feature. A certain percentage of men diagnosed with AMN will later develop the cerebral form. There is no biological marker that can be used for predicting the evolution of the disease on an individual level, but in general the earlier the onset, the faster the progression [4].

A significant proportion of the patients with ALD will develop adrenal insufficiency at some point [9], which affects primarily the glucocorticoid, followed by the mineralocorticoid function. ALD is the most frequent cause of adrenal insufficiency in males over the age of 4, and the second most frequent cause of

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adrenal insufficiency in adults [9]. It assumes the usual clinical presentation - melanodermy, followed by adrenal crisis with its usual clinical presentation. It can be the only sign of ALD for decades before the appearance of neurological signs.

Diagnostic Workup

The diagnosis of ALD is primarily based on biochemical and MRI studies. The biochemical signature of ALD is elevated plasma VLCFA levels, present in all affected males. Three parameters are analyzed: the concentration of C26:0, the ratio of C24:0 to C22:0 and the ratio of C26:0 to C22:0. All three parameters are usually elevated. With methodological advances, false positives and false negatives in males are exceptionally rare. The abnormality is present at birth and remains relatively constant throughout life. In contrast, only a proportion of female carriers have elevated plasma VLCFA; therefore targeted mutation analysis is the most effective means for carrier detection. MRI diagnostics are of great value, most frequently showing signs of symmetrical demyelination, with contrast accumulation at the edge of the lesions.

In the childhood cerebral form, MRI of the brain shows signs of demyelination with hyposignal in the T1 sequence and hypersignal in the T2 and FLAIR sequence, which allows for localization of the lesions and evaluation of the inflammatory character of the lesions based on the gadolinium uptake. Cortical atrophy can be seen in the later stages [4]. Studies have shown that the degree of MRI abnormality as assessed by the Loes scoring system [10], when coupled with age, aids in predicting the future course and in selecting patients who are candidates for bone marrow transplantation [11].

Newer modalities like MRI spectroscopy have provided new inputs into the disease.Proton MR spectroscopy is useful for determining the early signs of disease in patients even when MRI is still normal. MR spectroscopy shows abnormal metabolite ratios in the areas of abnormal T2 signal, but also in normal-appearing brain regions, including a decrease in N-acetylaspartate (NAA)/Creatine (Cr) and NAA/Choline (Ch) and an increase in Ch/Cr [12]. Lipids-lactate peaks are also valuable markers for the demonstration of the presence and progression of lesions. The metabolic ratio alterations seem to be proportionate to the severity of the ALD phenotype. Interestingly, higher VLCFA levels are associated with a lower NAA/Cr ratio [13].

The spectroscopic changes are not disease-specific, but are a sensitive indicator of disease progression [14] and can be useful in the evaluation of therapeutic interventions [15]. In AMN, cerebral and spinal MRI shows no changes in the early stages of the disease. The lesions, namely progressive atrophy of the spinal cord, appear in the later stages, but never show gadolinium uptake. Spectroscopy reveals axonopathy in the morphologically normal cerebral white matter, with reduced NAA/Cr and NAA/Ch, most prominent in the internal capsule and parieto-occipital white matter [16].

Although MR abnormalities are rare in heterozygous women, even when symptomatic [17], the spectroscopy shows axonal abnormalities, which may be indicative of the distal axonopathy that represents the principal neuropathological change in AMN [18]. Wilken and colleagues examined the prognostic significance of MR spectroscopy for patients who received bone marrow transplants [15]. They found an association between outcome and the N-acetylaspartate levels in affected brain white matter. A high level was associated with a positive outcome, whereas low levels had a negative predictive value, as did increased levels of choline-containing compounds. Abnormal NAA/Ch ratios in the regions adjacent to the MRI lesions are a negative predictor for progression [14].

Genetic testing for ABCD1 mutations is useful in the identification of female carriers, as they may have normal VLCFA levels. This investigation should be performed in all females who are at risk of being a carrier for ALD, but is only possible when the mutation in the family is known. Prenatal diagnosis is important for the prevention of the disease, and is performed by measuring VLCFA levels in cultured amniocytes and ABCD1 mutational analysis in chorionic villus samples.

Therapeutic Options

The application of immunomodulatory and immunosuppressive drugs has failed to prevent progression of cerebral neuroinflammation. Initially proposed treatments were Lorenzo's oil and statin therapy as well as VLCFA intake restriction, but clinically relevant benefit from such treatments has not been proven and they remain controversial. The preferred treatment option for preadolescent patients in the early stages of childhood cerebral ALD is allogeneic hematopoietic stem cell transplantation (HSCT).

This therapy was first described in 1990 [19] and several studies have shown promising results, when the treatment is performed early in the course of cerebral involvement and a human antigen-matched donor is available. The procedure can stop the progression of demyelination and stabilize the neurological symptoms. The outcome is significantly better when there are no neurological deficits and the MRI Loes severity score is less than 9 at the time of treatment. Despite the success of HSCT reports, numerous factors complicate the widespread usage of this treatment for ALD patients. The procedure should not be performed in patients with advanced disease, as the treatment is unable to stabilize neurological involvement in patients with advanced ALD.

It has been shown that MR spectroscopy might be predictive of clinical outcome after HSCT and may be further substantiated by using additional new imaging approaches, such as diffusion tensor imaging and magnetization transfer

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MRI [20]. While disease progression of patients before HSCT is mainly characterized by a further increase of elevated choline-containing compounds as an indicator of active demyelination, a positive outcome after HSCT is found to be correlated with high NAA levels in affected white matter before HSCT.

The positive effects of HSCT when instituted at an early stage of the disease may validate the efforts to institute newborn screening programs [21]. The benefit of HSCT was also shown for the first time in a patient with adult-onset ALD, with only mild symptoms remaining 2 years post-treatment [22]. The overall transplant-related mortality in HSCT patients is relatively high and non-myeloablative HSCT is being introduced as an alternative to myeloablative HSCT, with promising outcomes. For patients where a matched donor is unavalaible, umbilical cord blood stem cells are an alternative.

4-Phenylbutyrate (4-PB) has attracted interest as a potential therapeutic option for ALD. It has shown to improve the capacity of cultured ALD-cells to metabolize VLCFA. In the mouse model, it was shown that 4-PB reduces VLCFA levels in the brain and adrenal gland. 4-PB has the effect of increasing the expression of ALDRP, which, as noted previously, may be able to substitute for the function of ALDP. Its clinical effects have not yet been evaluated. ABCD2, the gene encoding ALDRP, when over expressed in cultured human fibroblast cell lines from ALD patients can normalize peroxisomal β-oxidation and prevent accumulation of VLCFA. Thus, the pharmacological induction of ABCD2 should be able to compensate for the lack of functional ABCD1 and is a potential attractive therapeutic target. Pujol and coworkers have shown that valproic acid induces expression of ABCD2 in human ALD fibroblasts. Other potential therapeutic strategies such as antioxidant therapy and neuroprotective therapy with insulin-like growth factor and neurotrophin-3 are being experimented upon. Preliminary work using lentiviral-based gene therapy in two young ALD patients shows short-term neurological benefits similar to HSCT [23].

It is now clear that early diagnosis is perhaps the single most important factor in treating ALD patients as there is no effective treatment for patients experiencing severe neurological symptoms. Efforts to add newborn screening for ALD and other peroxisomal disorders are moving forward; ALD screening has been initialized in the Netherlands as of 2015 and the USA since 2016. As in many fields, advances in gene therapy have the potential to revolutionize the treatment of ALD.

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