Review Article

Adrenoleukodystrophy: An overview of a rare genetic disorder.

ABSTRACT

Adrenoleukodystrophy(ALD) is caused by an X-linked inborn error of metabolic disorder due to genetic mutation of the ATP binding cassette subfamily D member 1 (ABDC 1). Three types of ALD cerebral form affect children aged 5-10, while the adrenomyeloneuropathy (AMN) form affects middle-aged men. The latter usually causes adrenal insufficiency, more commonly seen in men. This condition usually presents vast signs and symptoms based on the type one has and gender. Diagnosis of ALD is based on clinical manifestations and laboratory investigations which include blood levels of very long chain fatty Acids (VLCFAs) and abnormal Magnetic resonant image (MRI) findings of white matter, pyramidal tracts in the brain stem, and internal capsules.

Stem cell transplants using hemopoietic stem cells and ex-vivo gene treatment have been used to slow disease progression without a traditional treatment regimen. This review article is partly a teaching session for medical students and other health practitioners, fostering their research skills and integrative learning.

Keywords: Adrenoleukodystrophy, Leukodystrophy, ABCD1 gene, VLCFA, Genetic disorder, Adrenal insufficiency.

INTRODUCTION

Adrenoleukodystrophy is a form of leukodystrophy, an X-linked genetic disorder predominantly affecting males. The word adrenoleukodystrophy (ALD) was coined by Micheal Blaw, but the disease goes far back as 1923 when it was known as Schilder's disease and sudanophilic leukodystrophy. In this disease, there is a loss of expression of the ABCD1 gene, which codes for the ABCD1 protein. [1]

'Adreno' refers to the adrenal glands; 'Leuko' references the brain's white matter, and “dystrophy” means irregular growth. Adrenoleukodystrophy is a peroxisomal disorder distinguished by the accumulation of very long chain fatty acids in tissues, leading to demyelination of white matter and destruction of the adrenal cortex. [1]

Adrenoleukodystrophy is estimated to affect 1 in 10,000-17,000 global population. However, ALD is often undiagnosed or misdiagnosed. Hence, the statistical data may be somewhat inaccurate. ALD is mostly seen in people of Latino or African descent. Being an X-linked disorder, it is more common in males. [2, 3]ALD results from a mutation in one of the genes on the X chromosome, therefore usually called X-linked adrenoleukodystrophy. The mutated gene is called *the ABCD1* gene. [4]

The gene mutation is found on the X chromosome; therefore, females are less likely to be affected because they have two X chromosomes. Usually, the abnormal mutated chromosome will be "switched off," rendering the genes inactive. There are, however, female carriers of this disease who show no symptoms. They can transmit this disease to their male off-springs. [2, 3, 11]

A male, on the other hand, has only a single X chromosome. Therefore, if the X chromosome has the mutation, he will come down with the disease, alongside all the clinical manifestations. [2] Heterozygotes females may exhibit subtle manifestations related to ALD. Heterozygotes females inherit a single copy of the mutated gene on one X chromosome. However, the disease features are not masked by the normal genes on the other unaffected X chromosome. There is almost 100% penetrance in males and about 65% in heterozygotes female [2, 11]

The four main subtypes of the ALD spectrum are identified based on organ affected and age of onset. And are ;

I. The neonatal subtype is a recessive autonomic disorder associated with the Zellweger spectrum.
II. Childhood Cerebral (cALD) form is due to white matter demyelination in the brain. Typically symptomatic from the ages 4-10 with poor prognosis. Patients usually die within 6-24 months after diagnosis.
III. Adrenomyeloneuropathy (AMN) affects mostly men in their mid-20s upwards. It has a slower progression as compared to cALD. The rapidly progressing subtype is only found in 10-20% of males.
IV. Adrenal insufficiency, also called Addison's disease, develops between childhood and adulthood. This part of the spectrum is common in middle age and usually progresses to AMN. [5]

PATHOPHYSIOLOGY

ATP –binding cassette subfamily D member 1 (ABCD 1) gene encodes for the ABCD 1 transporter found on the peroxisomes. This protein transports the very long-chain fatty acids (VLCFA) into the peroxisome to be further metabolized into small fatty Acids. The VLCFA's found in ALD are lignoceric acid (C24:0), hexacosanoic acid (C26:0), and docosahexaenoic acid (C22:0). ALD being mostly an X-linked disorder, has been associated with mutated ABDC 1 gene. This explains the accumulation of VLCFA in the cells and plasma in X-ALD patients. [6]. This accumulation of VLCFA causes the demyelination of neurons in the central nervous system, axonopathy of the spinal cord, and an insufficiency of the adrenal gland. The cell death is due to the accumulation of VLCFA in the cytoplasm, causing a dysfunction in the mitochondria and the endoplasmic reticulum. It has also been shown that VLCFA initiates an inflammation cascade which results in neurodegeneration and demyelination. [7][11] The possible mechanism of development of ALD aside from genetic induced progressive dying-back axonopathy and demyelination are Inflammatory demyelination and fibroblastic defects. [6][10][11]

Molecular Mechanism

There are three phenotypes of ALD with different molecular mechanisms. All these phenotypes are due to a mutation in ABCD 1 gene, but they affect the white matter in different body areas. A study was conducted on an Argentinean Patient to determine the polymorphism of the ABCD 1 gene. In this study, nine mutations were due to: three frameshift, a slicing mutation, a deletion mutation, and three missense mutations. This study showed the spectrum of mutation ABCD 1 allele variant in X-ALD families. [8] ALD has over three thousand mutations discovered at over 900 variant sites. [9][10]

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Splicing

The *ABCD1* gene provides information for making the X-linked adrenoleukodystrophy protein (ALDP). The ALDP is a transport protein that transports fat molecules called very long-chain fatty acids (VLCFAs). The ALDP transports VLCFAs from the cytosol into peroxisomes, where VLCFAs can undergo further metabolism. [2, 4, 11]

ABCD-1 gene in the cortex undergoes mutation, leading to fat accumulation, lipid peroxidation, oxidative stress, and defect in fibroblasts, but ABCD-2 and ABCD-3 overexpression in the medulla can correct the fibroblasts defect found in ABCD-1 associated ALD. [11]

A mutation in *the ABCD1* gene results in a deficiency of ALDP. This will result in interference with the metabolism of VLCFAs. Since VLCFAs are not metabolized, they will accumulate in different body organs and tissues. This accumulation interferes with the normal physiological function of organs and tissues. The major areas affected include the myelin sheath of nerves and the adrenal cortex. [2, 4, 11]

The ABCD-1 protein abnormality in the adrenals, cortex, and hair follicles shows unique pathological findings: the presence of lamellae and lamellar-lipid profiles containing VLCFA esterified to cholesterol. These findings are believed to be responsible for the clinical features pertinent to the structures like gonadal dysfunction, adrenocortical insufficiency, and alopecia. [12][13]

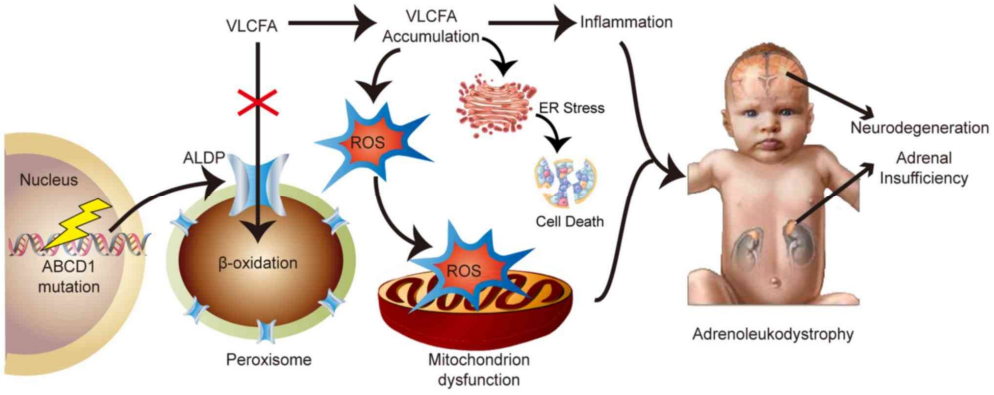

Fig 1: Schematic of the pathogenesis of cALD

Source: https://www.spandidos-publications.com/article_images/etm/18/3/etm-18-03-1945-g00.jpg

Childhood Cerebral (cALD)

Childhood X-linked ALD (cALD) is associated with rapid neurodegeneration, which leads to early death. It mostly affects the brain, unlike adrenomyeloneuropathy (AMN) which has a better prognosis and affects the tracts of the spinal cord. [10]

The mechanism of how the metabolic dysfunction of peroxisome transforms into a neurodegenerative disease has not been thoroughly understood. It has been found that VLCFA is more in cALD than in AMN, which leads to rapid axon degeneration and oxidative stress. These VLFCA have been speculated to affect the blood-brain barrier, making it more permeable for macrophages, which release chemokine and cytokines to continue the inflammatory cascade. These chemicals have been linked to the dysfunction of the peroxisome. Head injuries have been linked to predisposing one to cALD. This was shown in athletes with a brain injury, whose corpus callosum white matter tract showed microvascular endothelial damage, further damaging the blood-brain barrier for macrophages to invade. [11] The demyelination in cALD spreads outwardly from the central corpus callosum to the parietal occipital white matter. The difference in severity and duration may be associated with the gene polymorphism in the pathways leading to VLCFA accumulation. Various factors linked to the etiology of cALD are shown in Figure 1 below. This also shows a T2 weighted image on the left showing demyelination in the parieto-occipital area. On the right, a T1 imaging showing hyperintensity of gadolinium shows a bridge in the blood-brain barrier. [12]

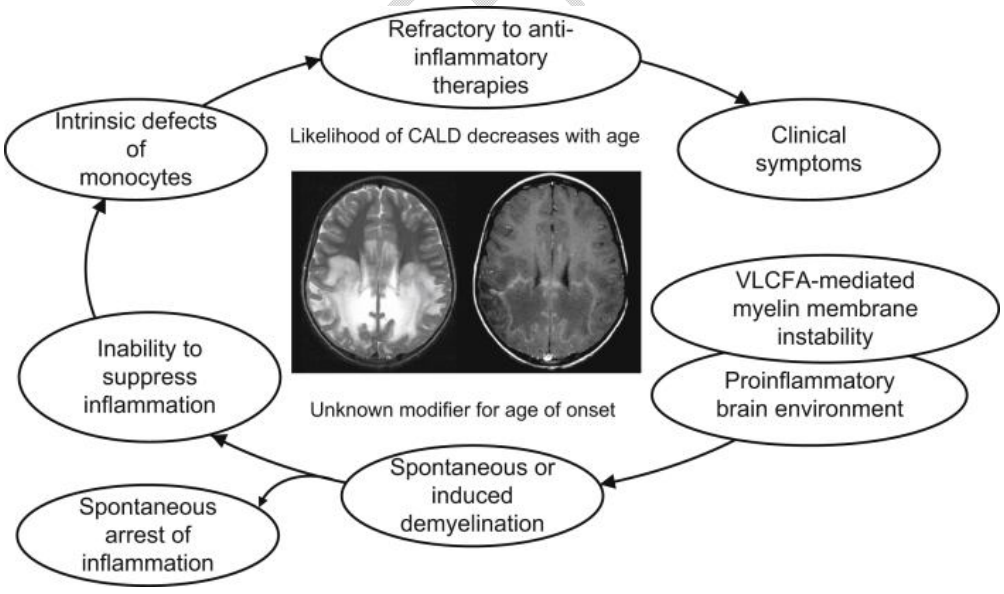

Figure 2: Sequence of factors that may lead to cALD

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3988840/

Adrenomyeloneuropathy (AMN)

In AMN, there is an increase of VLCFA in the spinal cord. This has been associated with distal axonopathy with no change in the myelin. A study found that AMN patients had mitochondrial lipid inclusions that caused the "dying-back" axonal degeneration. This was due to the failure of ATP-dependent transporter in the oligodendrocytes and Schwann cells found in the spinal cord, leading to damage to the axon.[13] Since the severity and duration of AMN did not correlate to the clinical manifestation, an additional non-inflammatory mechanism was proposed. There is an increase in triglyceride in AMN patients, which is protective compared to cALD patients. Triglycerides have been found to reduce acid-induced neuronal necrosis of oligodendrocytes and astrocytes by converting fatty acids into their lipid droplet form. [11]

Adrenal cortex and testis

The Adrenal insufficiency type, also known as Addison's disease, has impaired adrenal function. In the male patient, X-ALD has been associated with Addison's disease. This diagnosis is made when there are no autoantibodies found in the blood. In the adrenal cortex, the glucocorticoid is usually affected first, followed by mineralocorticoids function in X-ALD patients. [14] There is atrophy of the adrenal cortex mainly in the zona reticularis and inner fasciculate this leads to hypocortisolism. The accumulation of VLCFA leads to the adrenal cortex not responding to ACTH, decreasing cortisol secretion.[13] Like in the adrenal cortex, VLCFA accumulation in the testis leads to loss of Leydig cells function since VLFCAs in the cell membrane interfere with the gonadotropin binding to its receptor. This results in an elevated testosterone/LH ratio. [12]

Heterozygous female

There is still ongoing research on X –ALD heterozygous females. Female carriers have been found to have an elevated VLFCA compared to the higher level in men. Some studies had suggested the skewed X-inactivation to account for the difference in severity and course of the disease in females, but to date, no evidence of this has been shown.[15] However, the variation between symptomatic and asymptomatic patients was linked to X-inactivation. [14]This subtype has late onset (30 years or later) and primarily presents with myelopathy. There is no known treatment.

Gene modification

X-ALD is not only associated with ABCD1 gene mutations; environmental and other genetic factors have been proven to play a role. In monozygotic twin studies, these factors have been shown to account for phenotypic differences. A study showed the association of B12 metabolism to ALD, even though causation was not explained. The TCN2 gene mutation has been associated with cALD. ACSBG1 and ABCD4 mRNA have also been associated with cALD. [15] CYP4F2 protein is used to break VLCFA into long-chain dicarboxylic acids; a modification in this gene is found to increase the risk of cALD. So far, eleven microRNAs are associated with the different phenotypic expressions of cALD and AMN. [11]

CLINICAL MANIFESTATIONS

Adrenoleukodystrophy manifestations differ from person to person because it has variable expressivity. Based on the four major types of adrenoleukodystrophy, namely:

Childhood cerebral type (CCALD): The children under this category develop normally for the first few years, but neurologically symptoms begin to sets in the early school years which include; learning disabilities, seizures, new onset behavioral problems, loss of speech, vision loss, deafness and trouble coordinating movement. [16, 17]

Adrenomyeloneuropathy type (AMN): This is the most common form. Adrenal and neurological problems are present. It usually begins in early adulthood, including clumsiness in the limbs, stiffness, weakness, pains in the hands and feet, muscle spasms, urinary problems, and erectile dysfunction. [18]

Adulthood Cerebral type (ACALD): AMN symptoms in men are: slurring speech, behavioral changes, memory, cognitive issues, and inability to take care of themselves. [19]

Adrenal Insufficiency only type: Adrenal deficiency is present, but no neurological problems. Symptoms show between childhood and adulthood: decreased appetite, increased pigmented skin, low blood pressure, muscle weakness, and vomiting. While males can develop all forms of the disease, about half the females with the ABCD1 mutation develop AMN symptoms during middle age. Cerebral forms and Adrenal insufficiency are rare in females. [20]

DIAGNOSTIC FINDINGS

Early diagnosis is crucial to reverse it while it is still possible because once the myelin is lost as the disease progresses, neurological damage occurs.

Blood test: Done to measure the concentration of VLCFs (Very long chain fatty acids), which is usually elevated in males with ALD. Sometimes, the doctor could recommend a complete blood count to monitor one's blood profile [21] [22].

VLCFA	Normal	Males with X-ALD	Obligate Female Carriers
C26:0 µg/mL	0.23+0.09	1.30+0.45	0.68+0.29
C24:0/C22:0	0.84+0.10	1.71+0.23	1.30+0.19
C26:0/C22:0	0.01+0.004	0.07+0.03	0.04+0.02

Table 1: Range of Plasma Very Long Chain Fatty Acid (VLCFA) Values in X-ALD

Source: https://www.ncbi.nlm.nih.gov/books/NBK1315/table/x-ald.T.plasma_very_long_chain_fatty_aci/

Genetic test: Done to identify the ABCD1 genes. Likewise, it helps in accurately identifying other members of the family who might be carriers (females) and do not exhibit symptoms (males). [23]

More than 800 nonrecurrent mutations have been identified, of which 49% missenses, 24% frameshift, 6% deletion/insertion, and 12% nonsense mutation. This can be used in prenatal diagnosis using amniocentesis and newborn screening.

Histological findings: Punch biopsy is commonly used amongst other diagnoses to obtain skin samples in ALD. Fibroblasts are then isolated from the skin sample and grown in the laboratory, where after 2-3 weeks, the concentration of VLCFA is calculated. [24]

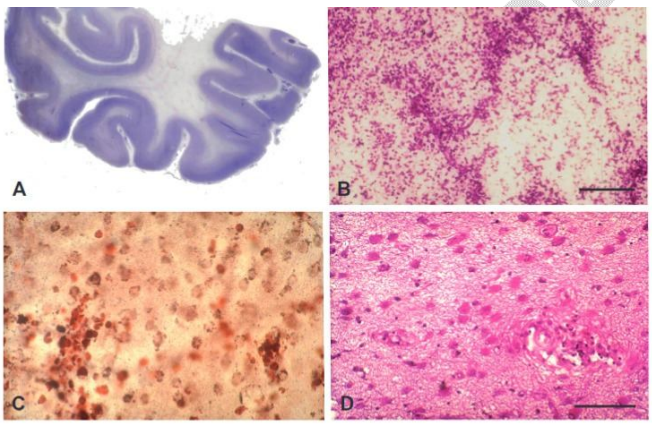

Figure 3: shows the biopsy of cCALD under different staining techniques. Image A shows the loss of myelin and axons in the white matter of the temporal lobe. While inflammatory infiltrates in the white matter at the border of the demyelinating lesion are shown in B. The image for C shows an infiltrating reactive CD68+ cell in the middle zone between the border of demyelination and the demyelinated area. D shows hypertrophic astrocytes in the demyelinated area. [25]

Source: /onlinelibrary.wiley.com/doi/epdf/10.1111/j.1750-3639.2010.00390.x

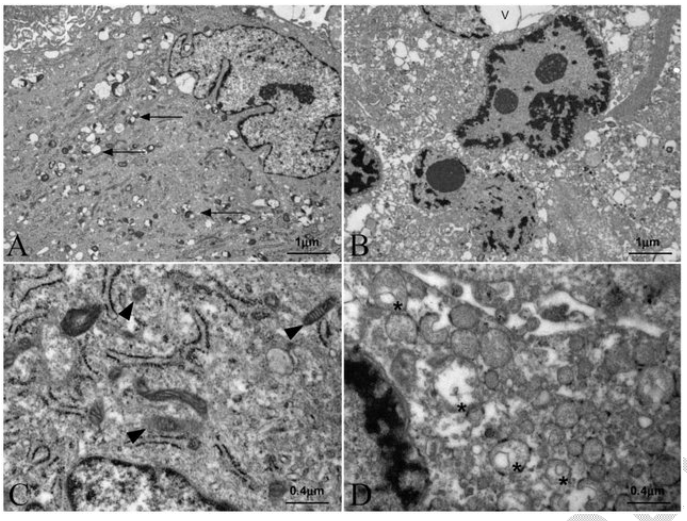

Fig4: Electron microscopy showing X-linked adrenoleukodystrophy fibroblasts show necrotic features during galactose-induced cell death. X-linked adrenoleukodystrophy fibroblasts were cultured in glucose (A) (shown at larger magnification in C); or in glucose-free medium containing galactose (B) (shown at larger magnification in D). V = vacuole; arrows indicate lipid inclusions; arrowheads indicate morphologically normal appearing mitochondria; asterisks indicate swollen mitochondria (n = 4/condition).

Source: https://www.researchgate.net/profile/Cristina-Munoz-Pinedo/publication/233949533/figure/fig1/AS:654050718658584@1532949251319/linked-adrenoleukodystrophy-fibroblasts-show-necrotic-features-during-galactose-induced_W640.jpg

MRI scan (magnetic resonance imaging): This is done to evaluate the extent of the disease. According to Loes et al. [26], five MRI patterns of ALD were described based on anatomic locations and progression of MRI patterns:

1. Deep white matter in the parieto-occipital lobes and splenium of the corpus callosum. About 66% of the cases are mostly children. Lesions may include visual and auditory pathways.
2. Genus of the corpus callosum or frontal lobe found in adolescents.
3. Corticospinal projection fibers are 12% found in adults.
4. Cerebellar white matter is 1% seen in adults.
5. Combined parieto-occipital and frontal white matter 2.5% seen children.

Subcortical U-fiber sparing and cortical tend to be present.

The spinal cord is involved in the disease's adrenomyeloneuropathy form, which affects the thoracic segment. [27]

Signal Intensity: Signal Change varies due to the zonal distribution surrounding the affected white matter.

- T1: Central zone (hypointense), intermediate zone, peripheral zone.
- T1 C+ (Gd): Intensification is seen in around 50% of cases, according to one study, and is assumed to relate to disease progression [6]. With variance infusion, the serpiginous, garland-shaped intensification may be seen in the anterior-most periphery of the lesions

.

- T2: Central zone (Hyperintense), Intermediate zone (isointense to hypointense), Peripheral zone (moderately hyperintense)
- MR Spectroscopy: May present with neuronal loss manifested by a decrease in the NAA peak (N-acetyl aspartate peak) and an increase in the lactate peak. [27][28]

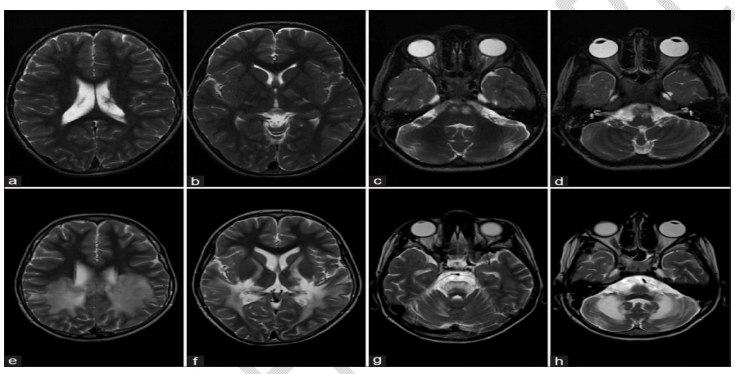

Figure 5: shows the diagnosis of ALD using T 2 weighted imaging. Images a-d are the images done on the initial visit. They show hyperintensity on the internal capsule and corticospinal tract. While images e-h are follow-up imaging, showing more extensive hyperintensity that has spread more bilaterally in the brain. [28]

Source:https://www.neurologyindia.com/viewimage.asp?img=ni_2019_67_6_1559_273651_f1.jpg

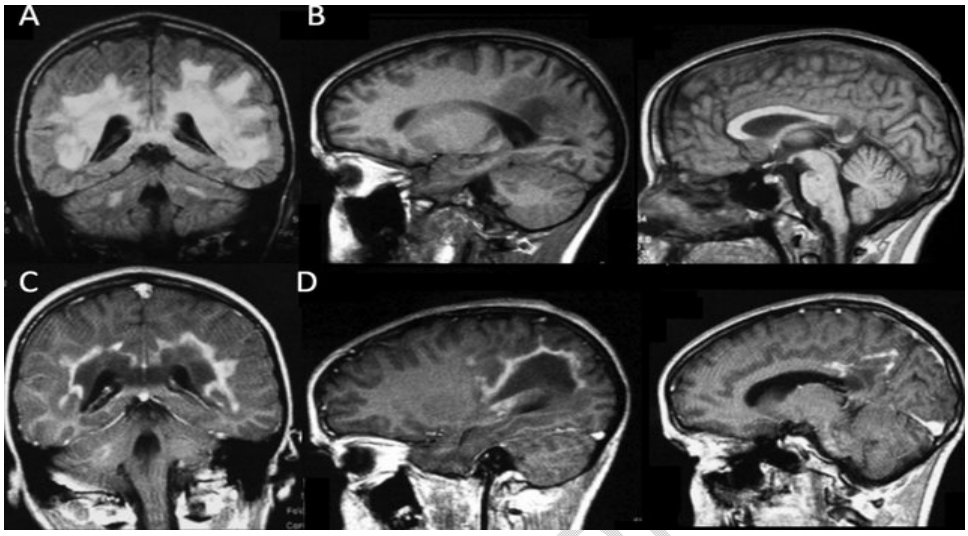

Figure 6: X-linked adrenoleukodystrophy, typical form: A 12 years old boy. MRI shows bilateral involvement of periventricular WM predominantly in the parietal areas, the splenium of the corpus callosum, and cerebellar WM with a peripheral enhancement.

Source: Review of endogenous and exogenous causes of neurotoxicity in children and adults. (researchgate.net)

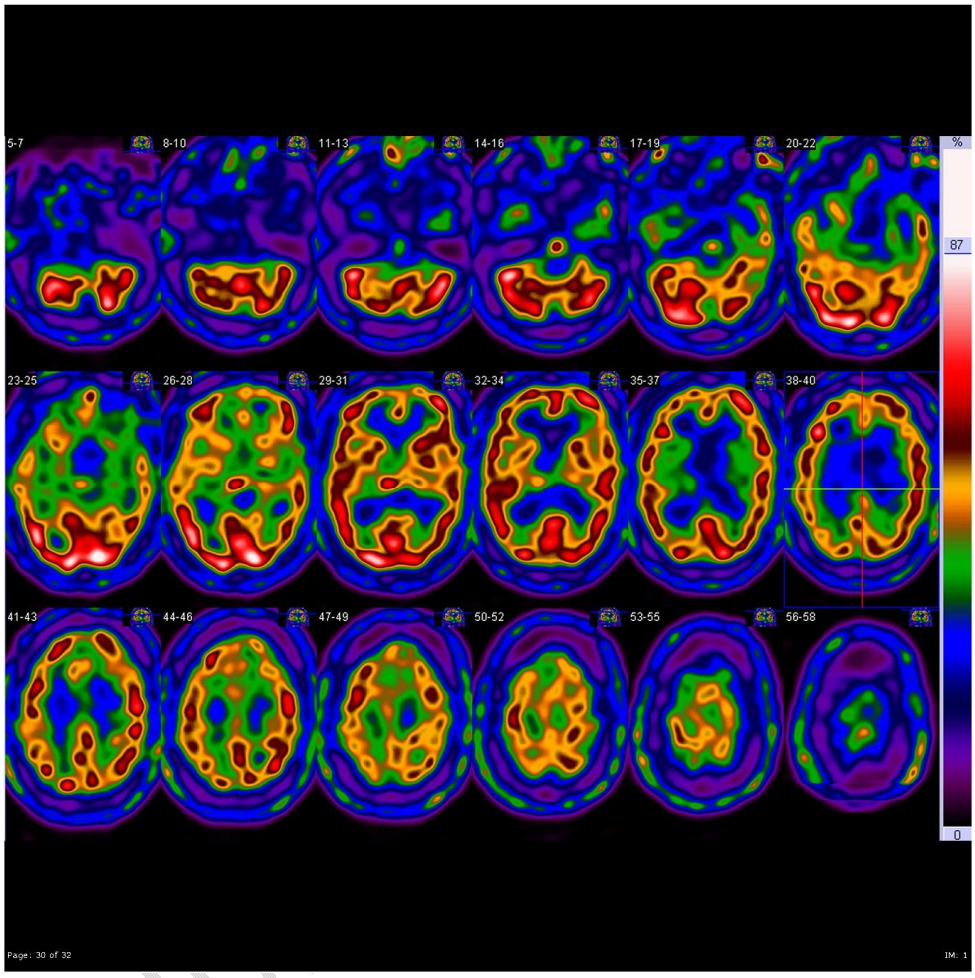

Figure 7: Perfusion scan showing hypoperfusion in metachromatic leukodystrophy

Source: https://prod-images-static.radiopaedia.org/images/1439968/9d1a2ad1b2e9b43f03c3f6618e7f79.jpg

Newborn screening: This was added to the United States recommended uniform newborn screening panel in 2016. With this, boys at risk can be identified and treated early. This is achieved with the use of a machine called a **Tandem mass spectrometer** to measure how much VLCFA is in the dried blood spots. [21][29]

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Metachromatic leukoystrophy is different entitv. Please

MANAGEMENT

Since the disease is caused by gene mutation, there is no overall cure, but there is a treatment for the different forms.

CCALD: Early treatment with allogeneic hematopoietic stem cell transplant (HSCT), also known as bone marrow transplant, can be done, and it is only effective if done in the initial stages of the disease.

ACALD: Supplementation of the missing steroid hormones symptoms of muscle stiffness, pain, and gait problems are treated with medications and physical therapy.

Adrenal Insufficiency: Glucocorticoids are used. [29]

A modality of ex-vivo gene therapy is a possible replacement for stem cell therapy.

The other form of proposed adjuvant therapy used in lowering VLCFA, mitochondrial stabilizer, and reduction of oxidative stress are Lorenzo's oil (erucic and oleic oil), Sirtuin 1(SIRT1), Resveratrol, and pioglitazone. ABCD-2 up regulators like Metformin, working by AMP-activated protein kinase 1 alpha, can lower VLCFA and improve mitochondria's function (anti-inflammatory).[11][12][13][29]

OTHER LEUKODYSTROPHY/DIFFERENTIALS (National Institute of Neurological Disorders and Stroke, NIH 2020)

- adult-onset autosomal dominant leukodystrophy (ADLD)
- adult polyglucosan body disease (APBD)
- Aicardi-Goutieres syndrome
- Alexander disease
- CADASIL
- Canavan disease
- CARASIL
- cerebrotendinous xanthomatosis
- childhood ataxia and cerebral hypomyelination (CACH)/ vanishing white matter disease (VWMD)
- Fabry disease
- fucosidosis
- GM1 gangliosidosis
- Krabbe disease
- L-2-hydroxyglutaric aciduria
- megalencephalic leukoencephalopathy with subcortical cysts
- metachromatic leukodystrophy
- multiple sulfatase deficiency
- Pelizaeus-Merzbacher disease
- Pol III-Related Leukodystrophies
- Refsum disease
- Salla disease (free sialic acid storage disease)
- Sjogren-Larsson syndrome
- Zellweger syndrome spectrum disorders

CONCLUSION

Adrenoleukodystrophy (ALD) is a form of a rare group of a disorder called leukodystrophy. It is an X-linked genetic disorder associated with ABCD gene mutation with a bad prognosis in both males and females. The genetic cause is ABCD 1 gene mutation causing an accumulation of VLCFAs in the brain, spinal cord, adrenal gland, and the testis. The mutation in the ABCD 2 and TCN 2 gene, loss of function mutation in the ACSBG1, ABCD 4, and CYP4F2 protein/gene is recently postulated to be associated with a different form of Adrenoleukodystrophy (ALD). [15]

ALD is primarily at neurodegeneration of the white matter. The clinical diagnosis of this rare disorder is cumbersome and unequivocal; therefore, blood tests and imaging remain the straightforward way of making an accurate diagnosis. There is no cure, but supportive management remains valuable during the disorder. [21]24] [29] More research has to be done to identify the contributory factors to ALD phenotypic differences. Early diagnosis with neonatal screening is extremely important as this may limit the transmission and progress of the disease. Therapy involving early HSCT is proposed to be highly effective in most literature. [21]

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