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Adrenoleukodystrophy: An Overview of a Rare Genetic Disorder

Adedeji Okikiade [a*], Damisola Ogunesan [b], Franklyn Ndu [a], Jeffery Ndu [a], Peace Njoku [a] and Katlego Ramaphane [a]

[a] All Saints University, College of Medicine, Saints Vincent and the Grenadines.
[b] Lagos University Teaching Hospital, IDI -ARABA, Lagos, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Adrenoleukodystrophy (ALD) is caused by an X-linked inborn error of metabolic disorder due to the mutation of ATP binding cassette subfamily D member 1 (ABDC 1) gene. 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 measurement of very long chain fatty Acids (VLCFAs) blood levels 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.

**Corresponding author: E-mail: okikis@yahoo.com;*

1. INTRODUCTION

Adrenoleukodystrophy is a form of leukodystrophy, the most common peroxisomal disorder characterized by the accumulation of very long chain fatty acids in tissues, leading to demyelination of white matter and destruction of the adrenal cortex. [1] The word adrenoleukodystrophy (ALD) was coined by Micheal Blaw [1] , but the disease goes far back in 1923 when it was known as Schilder's disease and sudanophilic leukodystrophy [1,2]. 'Adreno' refers to the adrenal glands; 'Leuko' references the brain's white matter, and “dystrophy” means irregular growth.

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 [1,3]. ALD results from mutations in the ABCD1 gene located on the X chromosome (Xq28), which codes for the ABCD1 (or ALDP) protein. [1], therefore it is usually called X-linked adrenoleukodystrophy [4].

Being an X-linked disorder, it is more common in males, because they have only a single X chromosome [2,3], if the X chromosome has the mutation, he will come down with the disease, alongside all the clinical manifestations [2].

Females are less likely to be affected because they have two X chromosomes. Females who have the mutated gene on one of their X chromosome are carriers of ALD and they can transmit this disease to their male off-springs [2,3,5]. Usually, carrier females do not display symptoms of the disease, because the abnormal mutated chromosome will be "switched off," rendering the genes inactive. There are, however, female carriers of this disease who may show symptoms and may exhibit subtle manifestations related to ALD. In these cases, 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 females [2,5].

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 autosomal disorder associated with the Zellweger syndrome.
II. Childhood Cerebral (cALD) form is due to white matter demyelination in the brain. Patients are 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. [6].

2. 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. Mutations in the ABCD1 gene result in the accumulation of VLCFA in the cells and plasma in X-ALD patients [7]. The VLCFA's found in ALD are lignoceric acid (C24:0), hexacosanoic acid (C26:0), and docosahexaenoic acid (DHA) [1,7].

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 [8,5]. Other possible mechanisms of ALD development aside from genetic induced progressive dying-back axonopathy and demyelination are Inflammatory demyelination and fibroblastic defects [7,9,5].

2.1 Molecular Mechanism

There are three phenotypes of ALD with different molecular mechanisms [1]. All these phenotypes are due to a mutation in ABCD 1 gene, and they affect the white matter in different body areas. A study was conducted on 10 male patients and 17 female carriers from Argentina to determine the polymorphism of the ABCD 1 gene. In this study, nine mutations were detected: three frameshift, a

slicing mutation, a deletion mutation, and three missense mutations. This study showed the spectrum of mutations of ABCD 1 allele variant in X-ALD families [10]. ALD has over three thousand mutations discovered at over 900 variant sites [11,9].

The *ABCD1* gene provides information for the synthesis of X-linked adrenoleukodystrophy protein (ALDP). The ALDP is a transport protein that transports fat molecules called very long-chain fatty acids (VLCFAs), from the cytosol into peroxisomes, where VLCFAs can undergo further metabolism [2,4,5] (Fig. 1).

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 [5].

A mutation in *the ABCD1* gene results in a deficiency of ALDP and subsequent impairment of VLCFAs metabolism. 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 [2,4,5].

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].

2.2 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 [9].

The exact mechanism by which the metabolic dysfunction of peroxisome transforms into a neurodegenerative disease has not been thoroughly understood. It has been found that VLCFAs are more in cALD than in AMN, which leads to rapid axon degeneration and oxidative stress. These VLFCAs 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 [5]. 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 Fig. 2. This also shows a T2 weighted image on the left displaying demyelination in

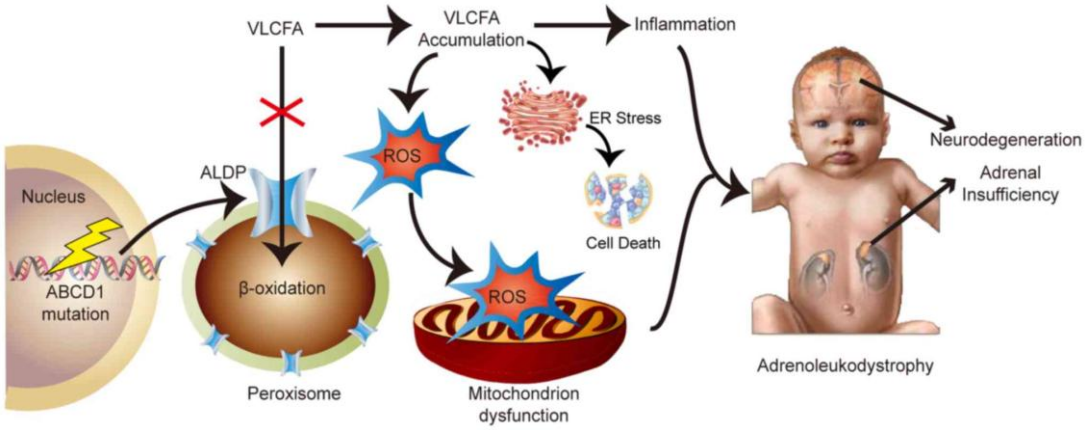

Fig. 1. Schematic representation of the pathogenesis of cALD
Source: https://www.spandidos-publications.com/article_images/etm/18/3/etm-18-03-1945-g00.jpg

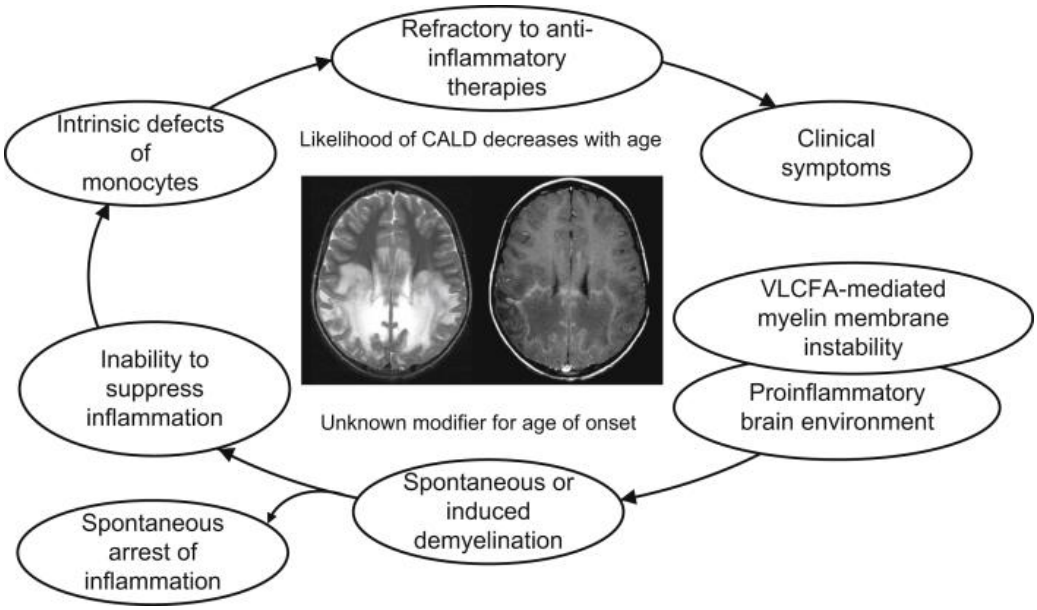

Fig. 2. Sequence of factors that may lead to cALD
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3988840/

the parieto-occipital area. On the right, a T1 image showing hyperintensity of gadolinium and disruption of the blood-brain barrier [12].

2.3 Adrenomyeloneuropathy (AMN)

In AMN, there is an increase of VLCFA in the spinal cord. This has been associated with distal axonopathy and 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 [5].

2.4 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. A study postulated that the expression of 5 alfa reductase isoform2 in some cases may account for some phenotypic findings [11,14]. 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 [15]. 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].

2.5 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 [16]. However, the variation between symptomatic and asymptomatic patients was linked to X-inactivation [15]. This subtype has late onset (30 years or later) and primarily presents with myelopathy. There is no known treatment.

2.6 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 [16]. 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 [5].

3. 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 [17,18].

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 [19].

Adulthood Cerebral type (ACALD): AMN symptoms in men are: slurring speech, behavioral changes, memory, cognitive issues, and inability to take care of themselves [20].

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 [21].

4. DIAGNOSTIC FINDINGS

Early diagnosis is crucial to reverse it when 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 VLCFAs (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 [22,23].

Genetic test: Performed to identify the ABCD1 mutations. Likewise, it helps in accurately identifying other members of the family who might be carriers (females) and do not exhibit symptoms (males) [24].

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 [25] (Fig. 3).

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

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

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

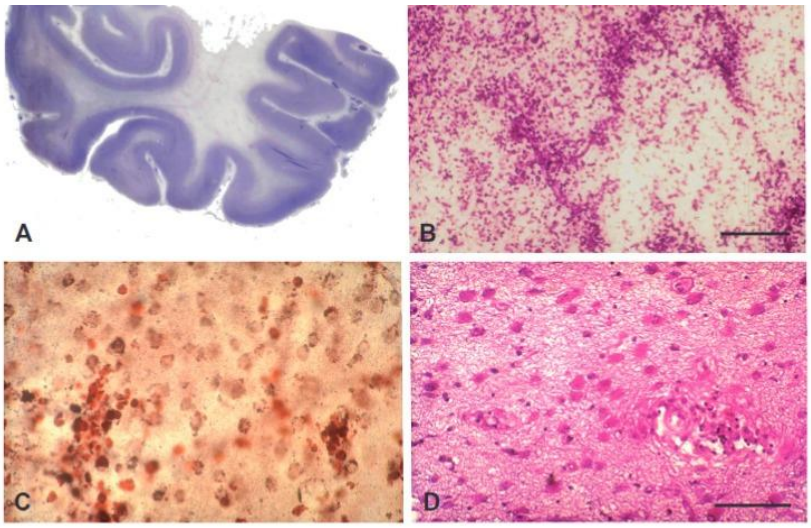

Fig. 3. Shows a biopsy of the disease under different staining techniques. Image A shows the loss of myelin and axons in the white matter of the temporal lobe. While inflammatory infiltrates in the white matter at the border of the demyelinating lesion are shown in B. The image for C shows an infiltrating reactive CD68+ cell in the middle zone between the border of demyelination and the demyelinated area. D shows hypertrophic astrocytes in the demyelinated area [26]

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

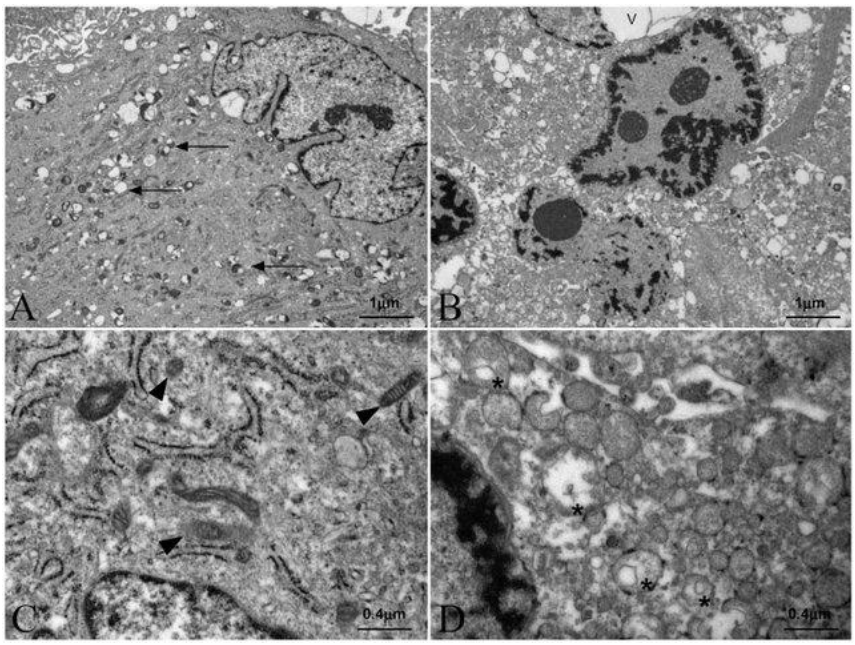

Fig. 4. Electron microscopy showing X-linked adrenoleukodystrophy fibroblasts with necrotic features during galactose-induced cell death. X-linked adrenoleukodystrophy fibroblasts were cultured in glucose (A) (shown at larger magnification in C); or in glucose-free medium containing galactose (B) (shown 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, as seen in MRI of patients below. [Figs. 5 and 6]. According to Loes et al. [27], 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 [Fig. 6]. 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 [28].

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 [7]. 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 [28,29].

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 [22,30].

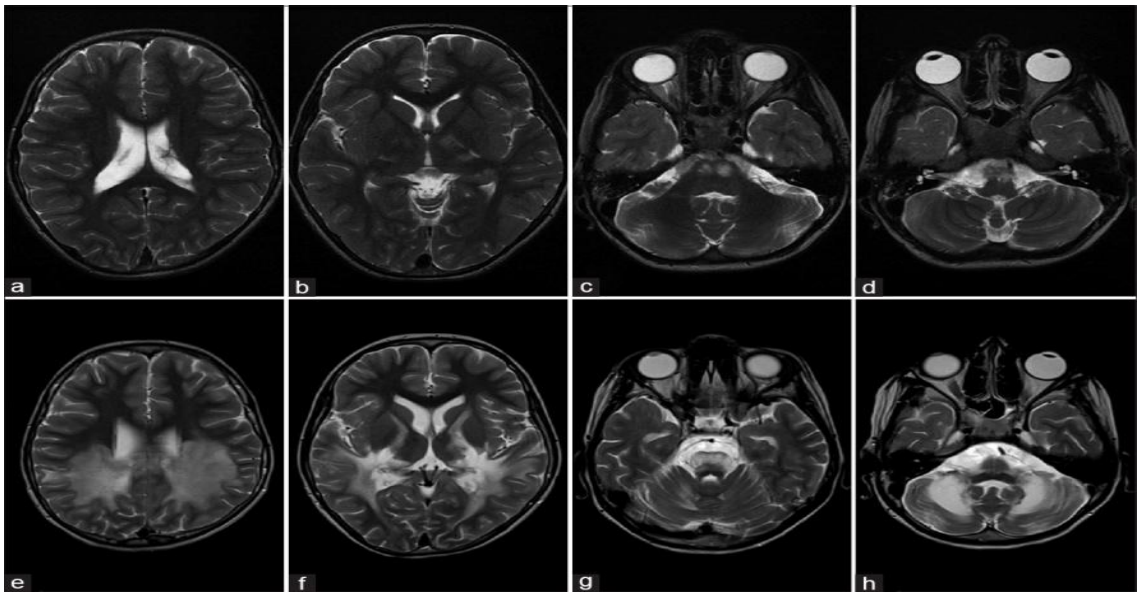

Fig. 5. Shows the diagnosis of ALD using T 2 weighted imaging. Images a-d are the images done on the initial visit. They show hyperintensity on the internal capsule and corticospinal tract. While images e-h are follow-up imaging, showing more extensive hyperintensity that has spread more bilaterally in the brain [29]

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

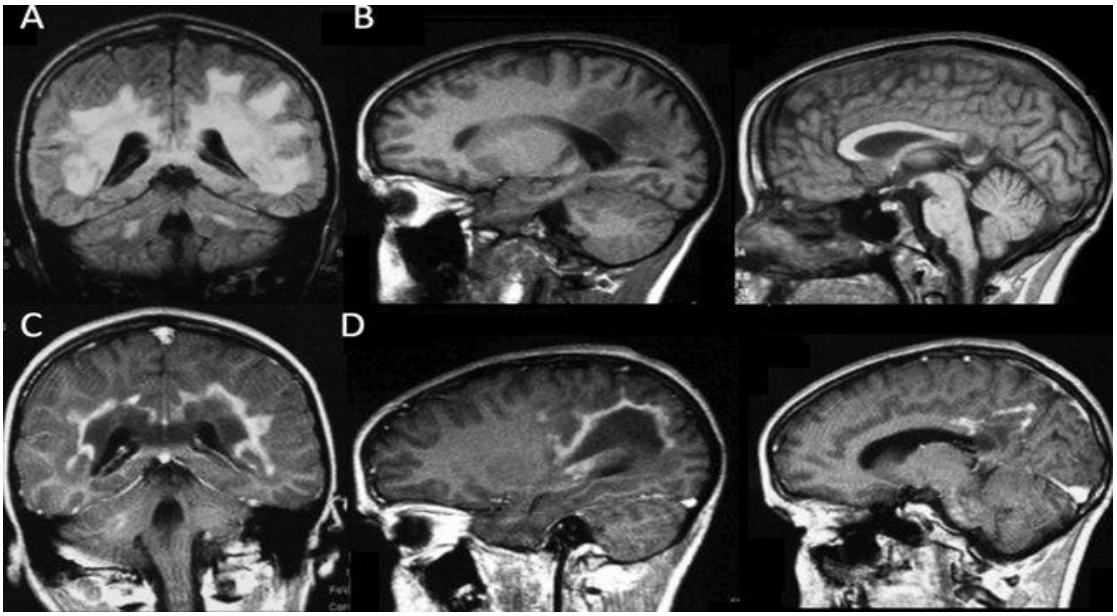

Fig. 6. X-linked adrenoleukodystrophy, typical form: A 12 years old boy. MRI shows bilateral involvement of periventricular WM predominantly in the parietal areas, the splenium of the corpus callosum, and cerebellar WM with a peripheral enhancement

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

5. MANAGEMENT

Since the disease is caused by gene mutations, 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 [30].

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) [5,12,13,30].

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

6. CONCLUSION

Adrenoleukodystrophy (ALD) is a form of a rare group of disorders called leukodystrophy. It is an X-linked genetic disorder associated with ABCD1 gene mutations with a bad prognosis in both males and females, causing an accumulation of VLCFAs in the brain, spinal cord, adrenal gland, and the testis. The mutation in the ABCD 2 and TCN 2 genes, loss of function mutations in the ACSBG1, ABCD 4, and CYP4F2 protein/gene are recently postulated to be associated with a different form of Adrenoleukodystrophy (ALD) [16].

ALD is primarily a 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 [22,25,30]. 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 [22].

More research has to be done to identify the contributory factors to ALD phenotypic differences and roles of 5alfa-reductase isoform 2 gene expression in X-ALD pathogenesis [14].

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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