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CASE REPORT

Childhood Cerebral Adrenoleukodystrophy: Case Report and Literature Review Advocating for Newborn Screening

Hamrish Kumar Rajakumar*, Varsha Coimbatore Sathyabal*, Revathi Nachiappan, Sivakumar Krishnaswamy Vijayaramanujam

Department of Pediatrics, Government Medical College, Omandurar, Government Estate, Chennai, Tamilnadu, India

*These authors contributed equally to this work

Correspondence: Hamrish Kumar Rajakumar, Tel +91-9150510826, Email hamrishkumar2003@gmail.com

Background: X-linked adrenoleukodystrophy (ALD) is a rare genetic disorder caused by a pathogenic variant of the ABCD1 gene, leading to impaired peroxisomal function and the accumulation of very long-chain fatty acids (VLCFAs). ALD presents a wide range of neurological and adrenal symptoms, ranging from childhood cerebral adrenoleukodystrophy to adrenomyeloneuropathy and adrenal insufficiency. Newborn screening (NBS) for ALD is available in some regions but remains lacking in others, such as India.

Case Presentation: We present a case of a 10-year-old boy with ALD who presented with seizures, progressive weakness, visual impairment, and adrenal insufficiency. Despite symptomatic management and dietary adjustments, the disease progressed rapidly, leading to respiratory failure and eventual demise. The diagnosis was confirmed through molecular analysis and elevated VLCFA levels. Neuroimaging revealed characteristic white matter changes consistent with ALD.

Conclusion: ALD is a devastating disease with no cure, emphasizing the importance of early detection through newborn screening and genetic testing. Management strategies include adrenal hormone therapy, gene therapy, and allogenic stem cell transplantation, as well as investigational treatments such as VLCFA normalization. Our case advocates the need for worldwide NBS and pediatric neurologic follow-up to enable early intervention and improve patient outcomes. Additionally, the association between ALD, recurrent febrile seizures, and unexplained developmental delay warrants further investigation to better understand disease progression and potential therapeutic targets.

Keywords: optic atrophy, developmental delay, adrenoleukodystrophy, adrenal insufficiency, case report, newborn screening

Background

X-linked adrenoleukodystrophy (ALD) is a rare X-linked recessive disorder resulting from a pathogenic variant of the ABCD1 gene on the X chromosome, which is responsible for encoding the adrenoleukodystrophy protein (ALDP). ALDP is an ATP-binding cassette transporter, that plays a pivotal role in loading very long-chain fatty acids (VLCFAs) into peroxisomes for degradation. When mutated, ALDP fails to carry out this function, leading to an accumulation of fatty acids with a carbon length of 24 or more in the bloodstream.[1]

Patients commonly present with myelopathy and adrenocortical insufficiency symptoms. This disease is clinically evident in most males. Among females with ALD, 88% exhibit neurological disease symptoms after the age of 60.[2] The clinical spectrum of ALD ranges from childhood cerebral adrenoleukodystrophy, which is a rapidly progressive form of this disease with a poor prognosis, to adrenomyeloneuropathy (AMN), a milder form of the disease compatible with life, to Addison ALD, which only manifests with adrenocortical insufficiency.[3] The phenotypic range is significant and correlates with the patient's age: cerebral forms typically appear during childhood, Addison ALD manifests in the 1st decade of life and may progress to AMN or cerebral forms later, and AMN typically presents in the 2nd to 3rd decade of life. The various phenotypic presentations are tabulated in Table 1.[2,4,5]

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Table 1 Phenotypic Range of X-Linked Adrenoleukodystrophy in Males

Incidence	Age	Phenotypic Range	Clinical Presentation	Prognosis
35% to 40%	4 to 8 years	Childhood cerebral ALD	The progressive neurological deficit with delayed developmental milestones, behavioral and focal neurologic deficits. Adrenocortical insufficiency symptoms as mentioned above. Bowel and bladder dysfunction are seen in rare cases	Poor
5%	11 to 21 years	Adolescent cerebral ALD		Poor
3%	>21 years	Adult cerebral ALD		Moderate to poor
20%	Males: 20 to 30 years	Adrenomyeloneuropathy	Muscle weakness and spasticity, abnormalities in gait along with bowel and bladder dysfunction	Moderate to poor
8%	Childhood (2 years) to adulthood (40 years)	Addisonian ALD	Primary adrenocortical insufficiency presents with weakness, weight loss, hypotension, hyperpigmentation, alopecia, electrolyte imbalance	Compatible with life if proper treatment measures undertaken

The clinical presentation of ALD is highly variable, with common features including hypotonia, developmental regression, cognitive disabilities, and hypotension. The nervous system and adrenal glands can be independently affected, resulting in different ALD phenotypes.[3] The ophthalmic manifestations of ALD include optic atrophy, strabismus, and disturbances of ocular motility. Additional findings are retinal pigmentary changes, cataracts, loss of corneal sensation, optic nerve hypoplasia, and visual field abnormalities. These symptoms are found to progress over time.[6]

Newborn screening (NBS) for ALD is available in the US, Netherlands, and Taiwan.[7–9] In New York, a three-tier algorithm is used: tandem mass spectrometry of C26:0, followed by measurement of C26:0 high-performance liquid chromatography, and then sequencing all 10 exons of the ABCD1 gene.[8] In India, the absence of ALD NBS means that cases are only identified during diagnostic evaluations for symptoms at an advanced stage.[10]

In this case, we aimed to shed light on the possible link between leukodystrophies, febrile seizures, and unexplained developmental delays. Our focus was on stressing the importance of pediatric neurologic follow-up in similar cases. Furthermore, we stress the importance of NBS to detect ALD prior to the emergence of cerebral symptoms, especially in regions like India where such screening is presently unavailable.

Case Presentation

We present a case of a 10-year-old boy who reported to the Emergency Department (ED) after experiencing a seizure. He also had complaints of weakness in his right upper and lower limbs, along with bilateral vision impairment for the past two weeks. The weakness was insidious in onset and displayed a progressive nature. The weakness particularly affected the flexor muscle group and manifested as a spastic, proximal to distal muscle weakness. It was also associated with involuntary, purposeless movements (choreoathetosis) predominantly affecting his right limbs. The visual impairment was progressive and not associated with pain.

The primary survey began with the initial assessment using the Glasgow Coma Scale (GCS), where the boy scored 9 out of 15. Subsequently, his vital signs were measured, which revealed that he presented with hypotension (blood pressure of 90/58 mmHg), a rapid pulse (134 beats per minute), a respiratory rate of 24 breaths per minute, and an oxygen saturation of 99% at room air. To stabilize him, we administered 20 mL/kg of normal saline as an IV bolus using pull-push technique along with an adrenaline infusion at 0.1 µg/kg/min.

During his assessment, he suffered another seizure episode that was terminated with successive doses of lorazepam (0.1mg/kg) two doses and IV phenytoin (20 mg/kg in normal saline at 1 mg/kg/min).

Routine blood investigations, such as Complete Blood Count (CBC), Renal Function Test (RFT), Liver Function (LFT), Serum Electrolytes, and Random Blood Glucose (RBG) were conducted in the ED. All results were found to be within normal limits except for the electrolyte panel. The patient's serum sodium level was low at 115 mmol/L, indicating hyponatremia, while the serum potassium level was elevated at 7.0 mmol/L, indicating hyperkalemia.

Suspecting a cerebrovascular accident as the cause of his presentation. A (Computed tomography) CT-Brain scan without contrast was immediately performed. The scan revealed hypodense areas in the frontal, parietal, and occipital regions without calcifications. Subsequent post-contrast CT indicated abnormal enhancement in the white matter of these regions. There was no evidence of ischemic changes, ruling out a stroke.

He was transferred to the Pediatric Intensive Care Unit (PICU) for further treatment and management. Following his stabilization, the adrenaline infusion was tapered off. A secondary survey was initiated, which began with documentation of the boy's detailed medical history and other reported complaints from his mother. She reported that he had been experiencing speech difficulties for the past year. His appetite had diminished, and he also struggled with urinary and fecal incontinence for the last 20 days. The child experienced recurrent febrile seizures starting at 18 months of age, which were frequent, prolonged (lasting more than 15 minutes), and often recurred within 24 hours. As a result, the child required multiple hospitalizations during childhood to manage and terminate these seizure episodes. His mother also reported that he had a delay in achieving developmental milestones. Unfortunately, these delays had not been evaluated or addressed by his parents. By the time he reached 10 years of age chronologically, his developmental age was at a significantly younger range approximately 7 to 8 years. The developmental quotient assessed for all domains are listed in Supplementary Table 1 indicating global developmental delay. The family history reveals that the child currently has no siblings. The mother had a history of abortion, and the child's maternal uncle passed away on the third day of life.

Upon admission to the PICU, Ryle tube feeding was initiated along with urinary catheterization to facilitate micturition. Clonazepam and trihexyphenidyl were administered to address involuntary movements. The child was kept on maintenance fluids. Antiseizure medications phenytoin was given at maintenance dose to prevent seizure recurrence.

The child underwent a thorough physical examination, which revealed an irritable, moderately nourished bedridden child. The child was on verbal state according to the AVPU scale and not responding appropriately to oral commands. Pallor along with hyperpigmented patches on the lips and trunk was also identified. The oral cavity also had white creamy patches, suggestive of oral candidiasis, which was subsequently treated. Anthropometric measurements are charted in Supplementary Table 2.

Additional investigations, such as Cerebrospinal fluid (CSF) analysis and early morning adrenocorticotropic hormone (ACTH) levels, were carried out. Biochemical CSF analysis yielded normal results, but early morning serum ACTH levels were elevated at 86 pg/mL (reference range of 10–50 pg/mL). The combination of elevated ACTH and abnormal serum electrolytes suggested the presence of adrenal insufficiency. The patient had previously received dexamethasone, which explains the lack of further elevation in ACTH levels. Plasma renin activity and cortisol values were not measured in this case. To address the adrenal insufficiency, hormone replacement therapy was initiated with hydrocortisone and fludrocortisone.

For further assessment, a complete central nervous system examination was performed. During this evaluation, the patient was found to be conscious but notably irritable He displayed a lack of orientation to time, place, and person, rendering cognitive assessments impossible. On examining the motor system, the child exhibited decreased muscle bulk on both sides, and the tone of his muscles was increased bilaterally. Strength assessments indicated a discrepancy between his right and left extremities, with a strength rating of 3/5 for all movements on the right side and 4/5 on the left side. Additionally, the Babinski sign was elicited on the right lower limb whereas other reflexes were found to be normal.

It should be noted that the examination of cerebellar functions and sensory functions could not be executed due to the child's bedridden state. The patient's condition was further evaluated by examining his cranial nerves. His pupils were bilaterally dilated, fixed, and unresponsive to light, suggestive of bilateral optic nerve dysfunction. Drooling of saliva and the absence of a nasolabial fold on the right side pointed to an upper motor neuron type of facial nerve palsy on the left side. Dysphagia and speech difficulties signified dysfunction of the glossopharyngeal and vagus nerves. Other cranial nerves were found to be normal during examination.

Due to complaints of vision impairment, an ophthalmic examination was carried out. His pupils remained bilaterally fixed, failing to react to light and measuring 5 mm in diameter. Visual acuity could not be assessed due to his uncooperative and bedridden state. Nevertheless, fundoscopic examination revealed a pale optic disc, which suggested optic disc atrophy. The corresponding fundoscopic image is available in the Supplementary Figure 1.

Following the initial CT findings, magnetic resonance imaging (MRI) of the brain was conducted to offer a more detailed view. T2 and FLAIR hyperintense regions, characterized by multiple cystic spaces, were identified within the posterior periventricular white matter, primarily in the parietal-occipital region. These findings also extended to involve the splenium of the corpus callosum, suggesting white matter demyelination with encephalomalacia (Figure 1).

Additional areas of mild demyelination were observed in the genu of the corpus callosum and the bilateral dentate nucleus, with relative sparing of subcortical U-fibers. Mild to minimal white matter demyelination changes were also detected in the frontal region (Figure 2).

Subsequent post-contrast MRI with gadolinium enhancement revealed mild focal linear enhancement on both sides (Figure 3). All these findings collectively pointed toward a demyelinating disease. The Loes severity score was 18.

We proceeded by estimating serum VLCFAs using the liquid chromatography method. The results revealed elevated levels of hexacosanoic acid (C26:0 = 3.126 µmol/L, reference range: 0.20–1.39 µmol/L) and tetracosanoic acid (C24:0 = 60.572 µmol/L, reference range: 13.1–55.0 µmol/L), while levels of docosanoic acid remained within the normal range (C22:0 = 34.628 µmol/L, reference range: 32.0–85.5 µmol/L). Phytanic acid and pristanic acid levels were found to be normal. Molecular analysis was carried out by whole exome sequencing test which revealed a hemizygous pathogenic variant on ABCD1 gene transcript NM_000033.4, located on exon 1 with the variant identified as c.796G>A, resulting in the amino acid change p.Gly266Arg (depth 86X).

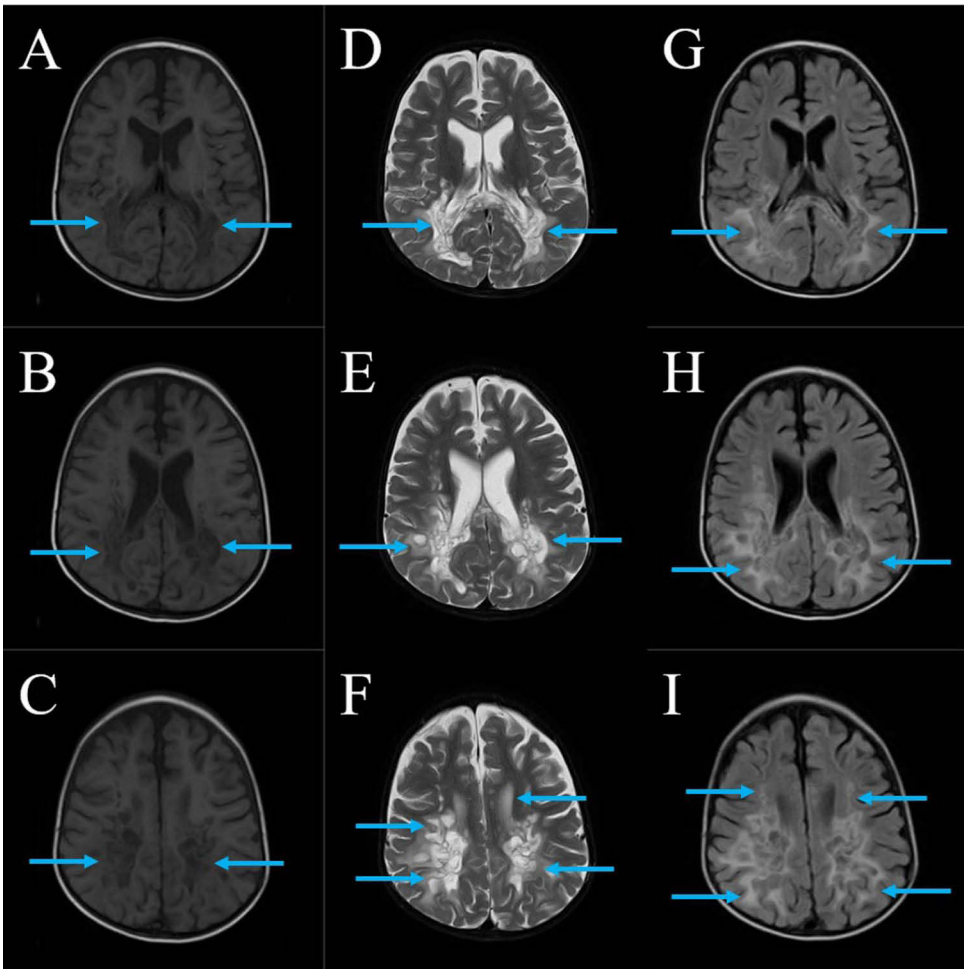

Figure 1 MRI (Plain) of the Brain. (**A**–**C**) are T1-weighted; (**D**–**F**) are T2-weighted; (**G**–**I**) are FLAIR-weighted. (**A**–**C**) show hypointense regions and (**D**–**I**) show hyperintense regions in the periventricular white matter with multiple cystic spaces. The splenium of corpus callosum is also involved. Blue arrows mark the abnormal regions.

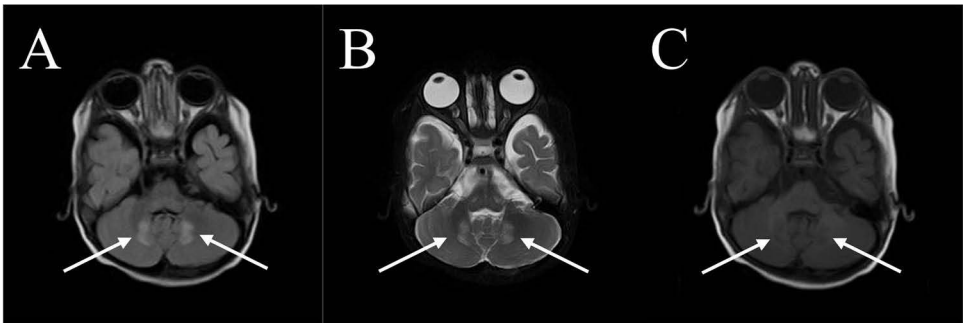

Figure 2 MRI (Plain) of the Brain. (**A**–**C**) are FLAIR-weighted, T2-weighted, and T1-weighted MRI respectively. (**A** and **B**) show hyperintensity in the bilateral dentate nucleus, whereas (**C**) shows hypointensity in the bilateral dentate nucleus (marked by white arrows).

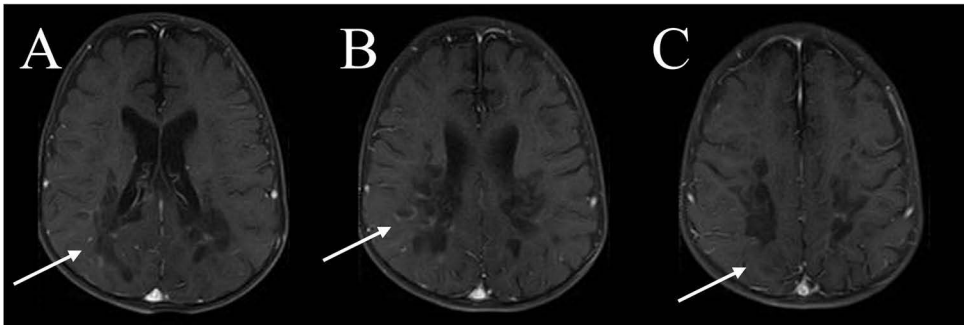

Figure 3 Postcontrast study with gadolinium-enhanced MRI of the brain; (**A**–**C**) show mild focal linear enhancement on both sides with greater enhancement on the right side (marked by white arrows).

The patient was ultimately diagnosed with ALD, complicated by adrenal insufficiency and optic atrophy. To manage and potentially slow the progression of the disease, dietary adjustments were made. VLCFAs were restricted. Additionally, coconut oil, rich in medium chain fatty acids, was added to the feed. Despite the multifaceted treatment approach, the progression of the disease ultimately proved relentless. Six months following discharge, the child succumbed to respiratory failure.

Discussion & Conclusion

Leukodystrophies are rare, primarily inherited, and progressive neurological disorders that Leukodystrophies are rare, primarily inherited, and progressive neurological disorders that predominantly affect myelin-forming cells, such as oligodendrocytes. They result from the abnormal production, processing, and development of myelin and other components of the white matter of the CNS.[11] There are 50 identified forms of leukodystrophies, and one among them is ALD. In the USA, it's estimated that 1 in every 21,000 men is affected by ALD, while 1 in 16,800 women are carriers.[3] Upon the introduction of newborn screening for ALD in New York, it was discovered to have a birth prevalence of 1:15,000.[12]

ALD is a rare disorder characterized by impaired peroxisomal function leading to the accumulation of VLCFAs. The ALDP protein is involved in the transport of VLCFAs from the cytoplasmic site into the peroxisomes for degradation. The defective loading of VLCFAs into the peroxisomes leads to reduced peroxisomal beta-oxidation of VLCFAs, and the concurrent increase in the levels of VLCFAs in tissues and the bloodstream causes deleterious effects on the human body. These excess unsaturated fatty acids transform into saturated fatty acids, generating reactive oxygen species. This oxidative stress causes inflammatory damage to the myelin sheath, leading to demyelination. These abnormal VLCFAs cause cell membrane damage along with the induction of oxidative stress, ultimately leading to the apoptotic trigger of cell death. Along with this cellular destructive process, abnormally increased levels of VLCFAs lead to lipotoxicity-induced neuroinflammatory demyelination. The alteration in lipoxidative metabolism is evident in ALD, where there are increased biochemical levels of 5-lipoxygenase (5-LOX) derived leukotrienes in cerebral demyelinated regions.[13]

The organs most affected, such as the brain and adrenal glands, have the highest content of cholesterol in the body. While some investigations into the involvement of cholesterol metabolism in ALD have been made, it is proposed that cholesterol transport dysfunction may play a pathogenic role in oxidative response and inflammatory-mediated processes. In the brain, the majority of cholesterol is synthesized locally because lipoprotein-bound cholesterol from the circulation cannot cross the blood-brain barrier. About 70% of brain cholesterol is stored in myelin as free cholesterol with a slow turnover, while the rest is in the plasma membranes of neurons and glial cells, which turnover more rapidly. Excess cholesterol in neurons and other cells is stored as esters, with only about 1% of brain cholesterol in the normal adult brain as cytoplasmic cholesterol esters in lipid droplets. Neurotoxic agents and oxidative stress enhance ACAT1 activity in neurons. In the demyelinating white matter of the ALD brain, there is a marked excess of cholesterol esters containing VLCFA and a diminished amount of free cholesterol, indicating that the accumulation of VLCFA-containing cholesterol esters is a secondary phenomenon. This is due to the inability of macrophages and microglia to degrade the excess VLCFA scavenged from myelin debris because of the lack of ALDP and increased ACAT1 activity in response to inflammation and oxidative stress.[14]

Additionally, VLCFAs are esterified to cholesterol in the adrenal cortex. However, the VLCFA-cholesterol complex cannot be cleaved by the cholesterol side-chain cleavage enzyme (activated by ACTH), leading to primary adrenal insufficiency.[2] The increased esterification of cholesterol with VLCFAs may further impair cortisol secretion by creating a relative shortage of substrate necessary for steroidogenesis.[15] The affected adrenal cells show decreased rough endoplasmic reticulum and are often in contact with mitochondria, smooth endoplasmic reticulum, and lipid droplets. The striated material in these cells is a lamellar-lipid containing 3β-hydroxysterol suggesting a defect in cholesterol metabolism. Over time, there is cytoplasmic ballooning and atrophy of the adrenal cortex due to continuous stimulation by ACTH and subsequent cell degeneration.[16] Patients with adrenocortical insufficiency experience a range of symptoms, including hypotension, weakness, weight loss, skin changes, vomiting, and electrolyte imbalance, ultimately leading to coma.

Intrafamilial variability in disease expression, including phenotypic differences among monozygotic twins, suggests the involvement of additional factors in ALD pathophysiology. Environmental influences, modifier genes, and epigenetic mechanisms likely contribute to the observed variability in ALD phenotypes. There is an absence of a direct genotype-phenotype relationship in ALD.[17] In a study by Semmler et al, an association was found between the G-allele of the Tc2 c.776C>G polymorphism and CNS demyelination. This polymorphism affects the affinity of transcobalamin 2 protein for vitamin B12, crucial for S-adenosylmethionine synthesis needed for CNS myelination. The study suggests a role for methionine metabolism in X-ALD progression, with the GG-genotype potentially predisposing patients to CNS demyelination. However, this association was considered weak when corrected for multiple testing or analysed by ethnicity.[18] Hence the practical significance of this polymorphism is not well understood.

The diagnosis of ALD includes complete clinical neurological evaluation and neuroimaging with MRI, where prominent demyelinating lesions can be identified. The most important component of the ALD diagnosis is the evaluation of VLCFAs in blood. The three VLCFA parameters noted are the concentration of C26:0, the ratio of C24:0 and C22:0, and the ratio of C26:0 and C22:0 carbon compounds.[19] Carbon lengths exceeding C26 are associated with severe forms of the disease, and the accumulation of long-chain fatty acids does not contribute to the phenotypic manifestations of the disease. Serum electrolyte levels, ACTH levels, and ACTH stimulation tests are a mainstay for the diagnosis of associated adrenal insufficiency in these patients. Molecular testing to confirm the pathogenic variant is essential in these genetic disorders, and proper neonatal screening and identifying genotypic correlation within families to prevent further deleterious events.[20]

Regrettably, there is currently no cure for ALD. Management of the disease encompasses several strategies. First, adrenal hormone therapy is administered to address adrenal insufficiency, alleviating some of its associated symptoms. Stem cell transplantation and gene therapy are approved treatments for early stages of cerebral ALD (Loes score 0.5 to 10).

Hematopoietic stem cell transplantation involves autologous transplantation of genetically modified CD34+ cells using a lentiviral vector. These CD34+ cells are initially isolated from the patient's peripheral blood, following stimulation with the granulocyte-colony stimulating factor. Subsequently, they are genetically corrected using a lentivirus before being reinfused into the patient. Once engrafted in bone marrow niches, these genetically modified

cells proliferate and produce sufficient quantities of the ALD protein, which is lacking in ALD patients. This breakthrough therapy has demonstrated its efficacy in arresting cerebral demyelination and slowing disease progression, especially when administered during the early stages of the disease or in younger patients with milder neurological symptoms. Nonetheless, it is essential to acknowledge the risk of graft-versus-host disease associated with stem cell transplantation, which could worsen the patient's condition.[21] No reports exist of myelodysplastic syndrome with allogenic stem cell transplants. While gene therapy poses a lower risk for graft-versus-host disease compared to allogenic stem cell transplants, it has been associated with myelodysplastic syndrome.[22]

Another avenue of treatment is normalizing VLCFA levels in the bloodstream. Lorenzo's oil, a mixture of 4:1 glyceryl trioleate and glyceryl triucate derived from oleic and erucic acids respectively, is used to achieve this. This investigational therapy operates by inhibiting the enzyme responsible for VLCFA production, restoring balance to saturated very long-chain fatty acids in the blood and potentially slowing the disease's progression. However, it is still in developmental stages and is currently not available in the US. Treating ALD with restriction of VLCFA is not considered standard practice due to limited evidence supporting its efficacy. Studies investigating interventions such as Lorenzo's oil and dietary restrictions have been hindered by the absence of controls and small sample sizes. Moreover, restricting VLCFA intake has been associated with adverse effects such as thrombocytopenia and neutropenia.[23]

In summary, ALD is a complex genetic disorder affecting the nervous system and adrenal function. Although a definitive cure remains elusive, ongoing research and early stem cell transplantation offer hope for halting or mitigating its progression. In our case, the boy had advanced disease, leaving only symptomatic management possible, as he was unfit for stem cell transplant or gene therapy. Early diagnosis could have prevented disease progression. The absence of a family history delayed suspicion and diagnosis. Therefore, we advocate for worldwide newborn screening especially in regions like India to enable early detection and treatment. In areas lacking gene testing facilities, a simple MRI and pedigree chart can help identify potential cases for further assessment. Developmental regression is the hallmark of ALD, However the boy in our case had recurrent febrile seizures along with unexplained developmental delay. We speculate that there could be an association between the two which requires further investigation. Since this disease has no cure, we propose that pediatric patients with complaints of recurrent febrile seizures along with unexplained developmental delay should be subjected to neurological follow-up.

Abbreviations

ALD, X-Linked Adrenoleukodystrophy; VLCFAs, Very long-chain fatty acids; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; ACTH, Adrenocorticotrophic Hormone; 5-LOX, 5-lipoxygenase; ALDP, Adrenoleukodystrophy Protein; CSF, Cerebrospinal Fluid; AMN, Adrenomyeloneuropathy; PICU, Paediatric Intensive Care Unit; ED, Emergency Department; NBS, Newborn Screening.

Data Sharing Statement

All the necessary data that help the results of the case report are incorporated in the manuscript.

Ethics Approval

As per our institutional protocol, ethical approval is required to publish a case report. This case was approved by the Institutional Ethics Committee of Government Medical College, Omandurar, Government Estate (Registration Number: ECR/1492/Inst/TN/2021) with approval number 52/IEC/GOMC/2023.

Consent for Publication

Written informed consent was obtained from the parents of the child for the publication of this case report.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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