

## X-linked adrenoleukodystrophy: A case of acute childhood cerebral presentation

### Adrenoleucodistrofia ligada a X: Un caso de presentación aguda cerebral infantil

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Received: September 23, 2020; Approved: January 7, 2021

#### What do we know about the subject matter of this study?

X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder that causes accumulation of very long-chain fatty acids in the central nervous system leading to progressive cerebral demyelination which can cause spastic paraplegia, adrenal insufficiency, and cognitive impairment.

#### What does this study contribute to what is already known?

Patient with X-ALD with rapidly progressive cerebral presentation, associated with adrenal insufficiency, with progressive demyelination showed in brain MRI in three months, with a de novo mutation in the family, and not a candidate for bone marrow transplant.

#### Abstract

X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disease due to a mutation in the ABCD1 gene that leads to the accumulation of very-long-chain fatty acids in tissues. **Objective:** To describe one patient with severe childhood cerebral X-ALD and to analyze his diagnostic process and therapeutic possibilities. **Clinical Case:** 7-year-old male child, with a six-month history of decreased visual acuity, learning difficulties due to lack of attention, reading and writing impairment, and social isolation. On physical examination, he presented bilateral decrease in visual acuity, hypoprosopia, hyperpigmented lesions on the hands, and gait abnormality. Brain MRI showed bilateral white matter signal alteration in parieto-occipital regions, with 12 points on the Loes' scale. He also presented adrenal insufficiency, meeting clinical criteria for X-ALD. Very-long-chain fatty acid was elevated, confirming the diagnosis. Three months later, the patient progressed to vision loss and inability to walk. MRI was repeated showing 15 points in the Loes' scale due to extensive structural involvement of the central nervous system, with rapidly progressive deterioration. Therefore, he was not considered a candidate for bone marrow transplantation. **Conclusion:** This case of X-ALD was of severe childhood cerebral presentation, with rapid progression. The clinical evaluation and classification of radiological findings according to the Loes' scale should guide the choice of management.

#### Keywords:

X-linked  
Adrenoleukodystrophy;  
Demyelination;  
Adrenal Insufficiency;  
Fatty Acids

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How to cite this article: Andes pediater. 2021;92(4):602-608. DOI: 10.32641/andespediatr.v92i4.3345

## Introduction

X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal neurodegenerative disease caused by mutation of the ABCD1 gene, which is the most common leukodystrophy worldwide, with high variability of clinical expression, even in the same family<sup>1</sup>. The clinical spectrum can vary from a progressive cerebral form, leading to severe disability in the first decade of life, to an adult-onset adrenoleukomyelopathy, or presentation of Addison's disease<sup>2</sup>. The objective of this communication is to present a case of X-ALD of childhood cerebral form, which had a rapid progression of symptoms.

## Clinical Case

Seven-year-old male, first child, well-controlled pregnancy, non-consanguineous parents, previously healthy, with neurodevelopment according to his age and adequate school performance until his first year of school.

He presented with rapidly progressive symptoms, which started with visual acuity alteration associated with left exotropia. Two months later, he presented school difficulties due to inattention, difficulties in following instructions, with loss of some skills acquired in reading and basic calculation. At 4 months, he presented hearing impairment, with need to repeat instructions to perform tasks, pseudobulbar affect, social isolation, and poor interest in social relations observed by teachers. At 6 months of evolution, there was evidence of frequent falls and the need for walking with support in unfamiliar places due to increased visual impairment, which led him to drop out of school.

On neurological examination, he was alert, with difficulty in following instructions, hypoprosopexia, difficulties in calculation and reading, as well as in abstraction and analogy thinking for his age, with a bilateral visual acuity of 20/150, positive Rinne test, without alteration of other cranial nerves, no alterations in strength and sensitivity, normal reflex response, gait with increased base of support, and no ataxia. Given this acute developmental regression, differential diagnoses were considered (See table 1). A striking finding was hyperpigmentation on the knuckles of the hands and gums, which led to the suspicion of X-ALD.

A brain MR spectroscopy showed in T2 weighted-sequence white matter hyperintensity with deep bilateral parieto-occipital and posterior-temporal predominance, involvement of the splenium of the corpus callosum, corticospinal tracts without diffusion restriction, spectroscopy curves with increased choline, N-acetylaspartate, and lactate peak, which led to sus-

pect X-linked adrenoleukodystrophy as a first possibility (figure 1 and 2).

Laboratory tests ruled out electrolyte abnormalities. The patient presented ACTH levels five times above normal values, indicating adrenal insufficiency, which was asymptomatic for the moment. Hydrocortisone supplementation was started. A very-long-chain fatty acid profile showed increased tetracosanoic acid (C24) and hexacosanoic acid (C26), with elevated C24/C22 and C26/C22 ratios, and an alteration in the discriminant function between men and women with peroxisomal disease, according to previous studies<sup>3</sup>, which was compatible with X-linked adrenoleukodystrophy.

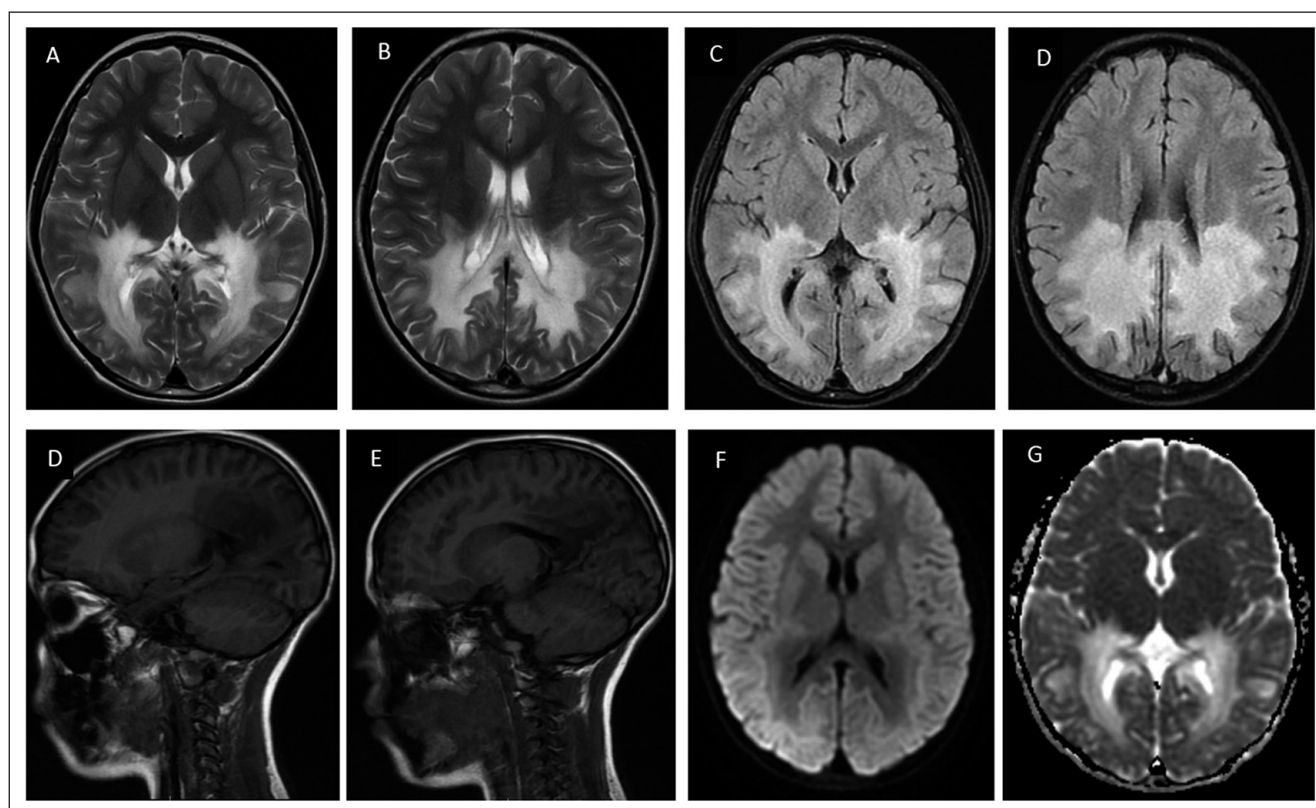
A genetic study was performed with full-length sequencing of the ABCD1 gene, identifying that he is a hemizygous carrier of the pathogenic variant c.900 + 1G > A, which confirmed the diagnosis at the molecular level. His clinical picture was a rapidly progressive presentation in childhood.

With the confirmation of the diagnosis, the MR images were evaluated to quantify the degree of central nervous system involvement, according to the Loes' scale<sup>4</sup>, concluding with a score of 12 points.

After three months, the patient evolved with loss of vision and inability to walk independently. Brain MRI was repeated, showing increased neuroradiological involvement, scoring 15 points in the Loes' index, and tractography showing marked anisotropy alteration of the white matter pathways in posterior regions (see figure 3).

**Table 1. Possible differential diagnoses to consider in cases of developmental regression in schoolchildren**

X-linked adrenoleukodystrophy
Pantothenate kinase-associated neurodegeneration
Mitochondrial encephalopathies
Huntington's disease
Krabbe disease
Wilson's disease
Multiple sclerosis
Gangliosidosis type II
Metachromatic leukodystrophy
Neuronal ceroid lipofuscinosis - juvenile
Subacute sclerosing panencephalitis
Juvenile form sialidosis
Brain tumor



**Figure 1.** Brain MRI. **A** and **B**: T2 FLAIR, **C** and **D**: T2; **E** and **F**: T1 FLAIR, hyperintensities in T2 sequences and hypointensities in T1 in bilateral parieto-occipital and posterior temporal white matter with involvement of the splenium of the corpus callosum. **G**: Diffusion and **H**: ADC, Prolongation of diffusion and increased intensity in ADC, in bilateral parieto-occipital white matter.

Considering that the only therapy that has shown benefit in delaying the disease is bone marrow transplant in patients with mild or no neurological impairment, with Loes' score less than 9 points, and without cognitive deficit, it was concluded that the patient is not a candidate for bone marrow transplant since its benefits are less than its possible complications, therefore, support management, genetic counseling, and interdisciplinary follow-up were initiated.

The patient progressed at one year with neurological deterioration, generalized spasticity, severe swallowing disorder, and apparent vegetative state.

## Discussion

X-ALD is the most common peroxisomal disorder, present in all regions worldwide. It is a rare disease in the pediatric population, with an estimated incidence of 1 in 17000 to 35000 live births<sup>5,6</sup>.

It is characterized by altered peroxisomal beta-oxidation of very-long-chain fatty acids (VLCFA;  $\geq$  C22) accumulating in all tissues, including the white matter of the brain, spinal cord, and adrenal cortex. It is cau-

sed by mutations in the ABCD1 gene located on the X chromosome<sup>7</sup>. Our patient presented elevation of tetracosanoic acid (C24) and hexacosanoic acid (C26), with increased C24/C22 and C26/C22 ratios.

Currently, the molecular basis for the clinical heterogeneity of X-ALD remains unclear<sup>8</sup>. There is no general genotype-phenotype correlation. All patients have a mutation in the gene coding for the peroxisomal ATP-binding cassette transporter (ABCD1), which produces the ALDP protein (adrenoleukodystrophy protein), whose function is to transport activated very long-chain fatty acids by adding coenzyme A from the cytosol to the peroxisome for degradation<sup>9</sup>.

This disease has an X-linked inheritance form, with about 4% of *de novo* mutations. More than 800 types of mutations have been described and are registered in the database available online ([www.x-ald.nl](http://www.x-ald.nl))<sup>6,10</sup>. In our patient, there is no family history of the disease. He was confirmed as a hemizygous carrier of the pathogenic variant c.900 + 1G > A, which is associated with reduced levels of ALDP protein, the causal mechanism of the disease.

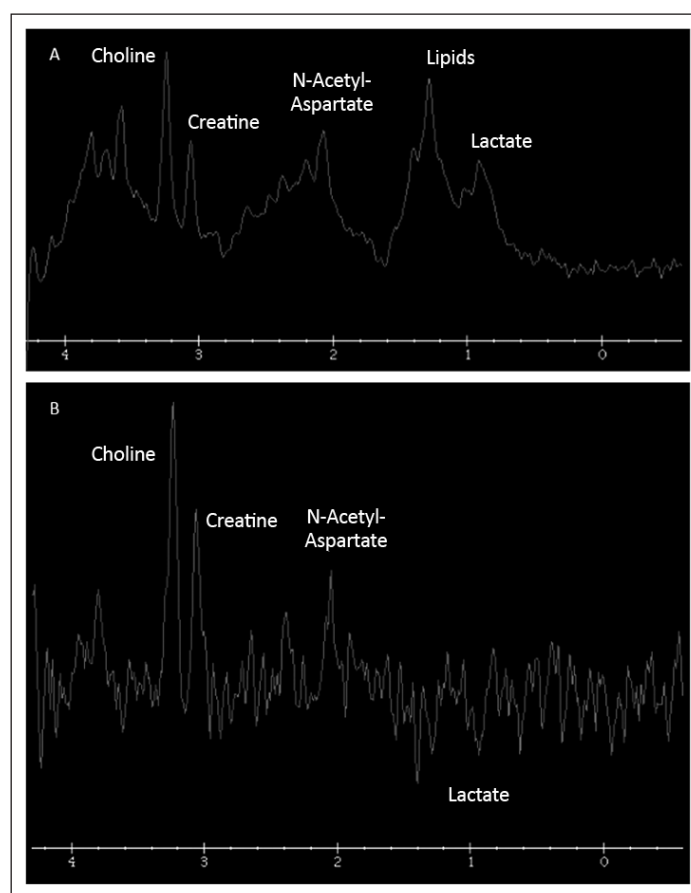
As mentioned above, the clinical presentation of X-ALD is variable. The presented case was the cerebral

presentation, with a rapidly progressive and devastating phenotype<sup>5</sup>. In childhood, the clinical presentation is characterized by an insidious onset, with deficits in cognitive skills, involving visuospatial, visuomotor, attention, and reasoning functions, as well as hyperactive or withdrawn behavior, as exemplified in the case<sup>11</sup>. The initial manifestation may be a decrease in academic performance and may be categorized as a learning disorder or attention deficit hyperactivity disorder, which could delay the diagnosis, as in our case. In any pediatric patient with impaired school performance and/or loss of acquired skills, a neurodegenerative disease should be suspected, especially in the absence of a history of previous neurodevelopmental disorder (see Table 1).

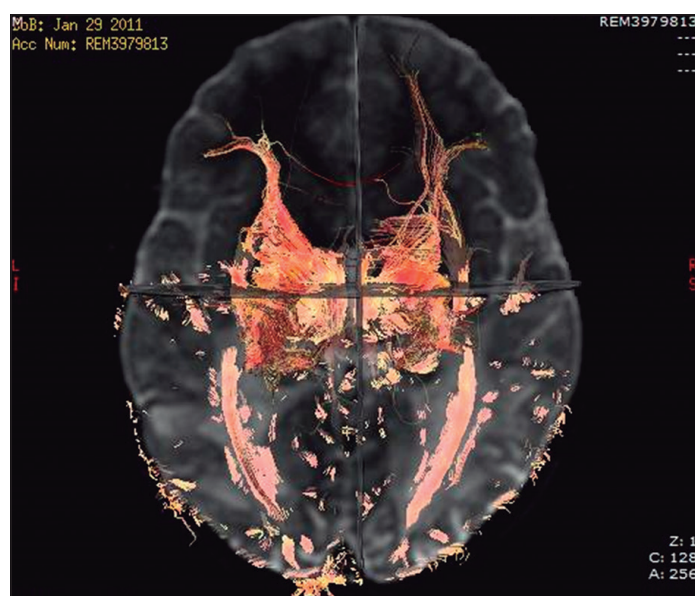
As the disease progresses, new neurological deficits appear, such as apraxia, astereognosis, hearing impairment, decreased visual acuity, hemiparesis, ataxia, or epileptic seizures<sup>11</sup>. In this case, at the time of consultation, visual acuity and hearing impairment were already present, which shows the rapid clinical progression. The evolution of the disease progresses to the inability to understand language, cortical blindness, abnormal gait, inability to communicate, need for feeding by orogastric tube or gastrostomy, and evolution towards a vegetative state. It is described that in these patients, death occurs two to four years after the onset of symptoms<sup>5,6</sup>. In this case, within three months the child had significant visual impairment and loss of gait, and one year after the onset of the disease he was in a vegetative state.

Brain involvement begins in 80% of patients in the splenium of the corpus callosum and progresses to involve the adjacent parieto-occipital white matter<sup>12</sup>. Lesions initially affect the pyramidal tracts in the pons or internal capsule and extend to the white matter of the semioval center<sup>12</sup>. Brain MRI shows abnormal intensities (increased in T2 and FLAIR and decreased in T1) in the corpus callosum, parieto-occipital or frontal white matter, pyramidal tract within the stem, pons, and internal capsule<sup>5</sup>. MRI always shows abnormal brain imaging and added to these findings and the clinical manifestation make up a high suspicion of the disease, as in our case, which had bilateral symmetrical involvement of the parieto-occipital white matter, the splenium of the corpus callosum, and corticospinal tracts.

In 1994, Loes proposed a scoring scale according to brain involvement determined by MRI which allows measuring the degree of involvement and which is accepted to measure the progress of the disease, as well as an evaluation criterion to define the best candidates for access to bone marrow transplant<sup>4</sup>. Previous studies show a correlation between structural involvement by MRI and prognosis, which makes this image essential for the diagnosis and follow-up of these patients<sup>13</sup>.



**Figure 2.** Univoxel brain magnetic resonance spectroscopy. **A.** Short echo time: **A** slight increase in Choline and N-Acetyl-Aspartate is observed, with an increase in Lactate. **B.** Mean echo time: Lactate peak inversion is observed.



**Figure 3.** Reconstruction of the optic pathway by magnetic resonance tractography. Confirms marked alteration subsequent impaired white matter fascicles that form the optical radiation.



Primary adrenal insufficiency is a very important clinical feature in patients with X-ALD. It is characterized by elevated ACTH levels, low cortisol levels, patients may present hyperpigmentation, and has a variable presentation in patients ranging from 50% to 100%<sup>6</sup>. In a prospective study of a cohort of neurologically pre-symptomatic children, it was found that 80% had biochemical evidence of silent adrenal insufficiency<sup>14</sup>, which demonstrates the importance of searching for and treating patients with adrenal insufficiency jointly with Endocrinology, considering that it may be the first finding of the disease. There is even a phenotype of this disease that only manifests with primary adrenal insufficiency<sup>15,16</sup>. In the case described, the patient had biochemical findings of adrenal insufficiency, and only presented discrete hyperpigmentation on the hands, self-limited episodes of altered state of consciousness, and vomiting, thus treatment with corticosteroids was started immediately.

The diagnosis of X-ALD is confirmed by biochemical tests or genetic testing, as occurred in this case. If a man presents with a clear clinical picture and adrenal insufficiency, the finding of elevated plasma very-long-chain fatty acids confirms the diagnosis<sup>6</sup>. In women with adrenoleukodystrophy, between 10 and 15% have normal levels of VLCFA, so it is recommended to perform a genetic study of the ABCD1 mutation<sup>18</sup>.

Currently, in our sphere, the only treatment that has been shown to delay its progression is allogeneic bone marrow transplant, and it is known that patients who benefit from this therapy are those with mild or asymptomatic neurological symptoms, with a Loes' scale score lower than 10 points and without cognitive alteration<sup>18</sup>. In a series of Chinese patients, it was found that transplantation in patients with advanced brain disease could further accelerate its progression<sup>19</sup>. In our patient, the family requested curative treatment, which represents a challenge for the clinical group in this neurodegenerative disease. The possibility of transplantation was evaluated, however, given that he presented a rapidly progressive phenotype, with high neurological compromise, a Loes' score higher than 10, and cognitive dysfunction, and also considering that mortality related to transplantation and its complications is high<sup>18</sup>, this possibility was ruled out.

Management with bone marrow transplant remains under discussion. Regarding patients presenting adequate clinical criteria for transplantation, in a long-term follow-up of 62 patients, 67% presented severe neurocognitive deficit, even showing that the greatest benefit was found in patients with Loes' scores between 0.5 and 4, which corresponds to patients whose diagnosis is made by prenatal screening or family history<sup>20</sup>. Currently, there are questions about whether the only possibility of establishing an effective treatment with

really good results is to perform neonatal screening, which would provide a treatment opportunity to patients such as the one presented<sup>21</sup>.

Other therapeutic options have been studied. Lorenzo's oil, based on the administration of C18 and C22 fatty acids, does not alter the concentration of VLCFA in the central nervous system and does not improve endocrinological or neurological function in patients with adrenoleukodystrophy<sup>22</sup>. Lovastatin also did not show a reduction in VLCFA levels, nor did it have an impact on clinical variables<sup>23</sup>. Finally, there have been advances in the development of gene therapy with lentivirus, which has shown to be safe, but follow-up studies are needed to evaluate its clinical outcome<sup>24</sup>.

## Conclusion

X-ALD is the most common peroxisomal disease, with variable clinical presentation. We present a patient with a rapidly progressive cerebral form, with no family history, with visual acuity alterations and learning difficulties at the onset, with typical imaging of this disease, biochemical level with adrenal insufficiency, and with confirmatory study with elevated very long-chain fatty acids and compatible genetic study, in which bone marrow transplant was ruled out as a management option given the neurological involvement.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

## Financial Disclosure

Authors state that no economic support has been associated with the present study.

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