

## CASO CLÍNICO/CASE REPORT

## X-Linked Adrenoleukodystrophy: A Heterogeneous Peroxisomal Disorder you Should Not Miss

## Adrenoleucodistrofia Ligada ao X: Uma Doença Peroxissomal Heterogénea de Diagnóstico Obrigatório

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## Abstract

X-linked adrenoleukodystrophy (X-ALD) is a rare peroxisomal disease caused by a mutation in gene *ABCD1*, impairing peroxisomal  $\beta$ -oxidation of very long-chain fatty acids. It has a heterogeneous clinical presentation that may difficult the diagnosis, with three main phenotypes: an Addison syndrome-like phenotype with adrenal insufficiency; a myeloneuropathic form, which progresses as a spastic paraparesis; a cerebral form with potentially extensive brain demyelination. Females can present with a phenotype resembling the myeloneuropathic form, but with a slow progression. Prompt recognition and diagnosis are essential, as allogenic hematopoietic stem cell transplantation can be offered for the cerebral form of the disease, the phenotype with the worst prognosis.

We present four clinical cases of patients followed in our neurometabolic reference centre with X-ALD, highlighting different clinical presentations, diagnostic workup, management and possible clues for the diagnosis.

## Resumo

A adrenoleucodistrofia ligada ao X (X-ALD) é uma doença peroxissomal rara causada por uma mutação no gene *ABCD1*, e que compromete a  $\beta$ -oxidação peroxissomal dos ácidos gordos de cadeia muito longa. Tem uma apresentação clínica heterogénea que pode tornar o diagnóstico difícil, com três fenótipos principais: um fenótipo síndrome de Addison-like com insuficiência suprarrenal; a forma mieloneuropática, que progride com uma paraparesia espástica; e uma forma cerebral com desmielinização cerebral potencialmente extensa. As mulheres podem apresentar-se com um fenótipo que se assemelha à forma mieloneuropática, mas com progressão lenta. O reconhecimento e diagnóstico atempados são essenciais, uma vez que o transplante alogénico de células estaminais hematopoiéticas pode estar indicado para a forma cerebral da doença, o fenótico com pior prognóstico.

Apresentamos quatro casos clínicos de pacientes com X-ALD seguidos no nosso centro de referência de doenças neurometabólicas, enfatizando as diferentes apresentações clínicas, abordagem diagnóstica, seguimento e possíveis pistas para o diagnóstico.

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## Introduction

X-linked adrenoleukodystrophy (X-ALD) is an inherited metabolic disorder of peroxisomes.<sup>1</sup> It is caused by a mutation in the *ABCD1* gene located at chromosome Xq28, which codes an ATP-binding cassette responsible for the transport of very long-chain fatty acids (VLCFA) into peroxisomes for degradation through  $\beta$ -oxidation.<sup>2</sup> Adrenocortical cells and myelin producing cells (oligodendrocytes and Schwann cells) seem to be particularly vulnerable to the toxic accumulation of VLCFA, which induces mitochondrial dysfunction and oxidative stress.<sup>2</sup> This scenario may result in: (1) adrenal insufficiency, which ultimately will affect 80% of patients<sup>3</sup>; (2) a neuronal dying-back axonopathy, with myelopathy and peripheral neuropathy, caused by axonal disruption in the context of myelin disturbance; and (3) a cerebral demyelination process, which may occur on top of the previous, and that is probably caused by VLCFA-mediated myelin membrane instability inducing a proinflammatory brain environment.<sup>2,4</sup> This inflammatory activity may lead to the disruption of the blood-brain barrier, and clinically progress from behavioural changes to focal neurological deficits, severe disability and ultimately death.

This complex pathophysiology results in four main clinical phenotypes: (1) an Addison-only (AO) phenotype; (2) an adrenomyeloneuropathy (AMN) phenotype, which presents with a progressive spastic paraparesis, sensory ataxia, sphincter dysfunction, and a sensory-motor mostly axonal peripheral neuropathy; (3) a cerebral adrenoleukodystrophy (CALD) phenotype, which may begin at any age (childhood is most common, adolescence and adulthood are rarer), and be the initial presentation of the disease. It starts insidiously with cognitive and behavioural symptoms and may evolve rapidly with extensive cerebral inflammatory demyelinating lesions; finally (4) around 50% of female carriers may develop an AMN-like phenotype by the 4<sup>th</sup> to 5<sup>th</sup> decade of life.<sup>5,6</sup> The heterogeneous clinical presentation and the fact that the phenotype may evolve as disease progresses make diagnosis particularly challenging.

The diagnosis of X-ALD can be suggested by an elevated plasma VLCFA and confirmed by genetic testing.<sup>5</sup> The prompt recognition of this entity is crucially important, as allogeneic hematopoietic stem cell transplantation (AHSCT) may prevent progression of CALD,<sup>7</sup> and recognition of the other phenotypes may guarantee adequate follow-up.<sup>5</sup>

The objective of this article is to present the clinical cases of patients with X-ALD followed in our neurometabolic reference centre, highlighting relevant findings and possible clinical clues in the different phenotypes. After obtaining consent from each patient (or their caregiver), we reviewed their clinical processes, wrote a clinical vignette, and commented on each of them based on recent literature. To ensure anonymity, name initials were changed. The two last cases were found to be recently reviewed elsewhere.<sup>8</sup>

## Case Reports

### Case I – A boy with a changing skin color, abdominal pain and vomiting

A 9-year-old boy when he was admitted to the pediatric hospital. In the last 2 months, his grandmother noticed he was always tired, anorexic, losing weight, with pollakiuria and drinking around 1.5 L of water every day. He had a recent admission in the emergency department due to abdominal pain and persistent vomiting but was discharged after fluid therapy and resolution of hyponatremia and hyperkalemia. His grandmother noticed that his skin color was darker in the last months. His past medical history (including birth history and development milestones) and his family history (besides some cases of diabetes mellitus type 2) presented no relevant changes. His medical examination revealed skin hyperpigmentation without other relevant findings, with a normal neurological examination. The analytical study showed an elevated ACTH. Considering the negativity of the autoimmune study, VLCFA were measured and found elevated. The genetic study showed a hemizygous pathogenic point mutation in the *ABCD1* gene, and his brain magnetic resonance imaging (MRI) was considered normal. He was medicated with corticosteroids. He is followed in our adult metabolic consultation, remains neurologically stable, and his follow-up brain MRIs remain unremarkable.

This boy presented with symptoms that suggest an acute adrenal crisis: abdominal pain, vomiting, dehydration, hyponatremia and hyperkalemia. Hyperpigmentation can support clinical suspicion. The diagnosis of primary adrenal insufficiency (PAI) is established based on elevated ACTH and low serum cortisol. A boy with PAI and a negative autoimmune study (i.e. negative 21-hydroxylase autoantibodies) should prompt the search for a genetic cause, namely X-ALD.<sup>9</sup>

The diagnosis of X-ALD in patients presenting with AO phenotype has major implications for the neurological follow-up of these patients for two important reasons: (1) virtually all male patients with X-ALD mutation will develop AMN by their third and fourth decade of life (i.e. the prevalence of AO phenotype decreases with age)<sup>5</sup>; (2) the risk of developing cerebral demyelination for patients below 18 years of age is around 40%,<sup>4</sup> and periodic brain MRI is necessary to identify early cerebral involvement (from 3 to 12 years of age, biannual MRI is recommended).<sup>10,11</sup> At this early stage of the disease, appropriate treatment has a higher probability of being effective.<sup>12</sup>

### Case 2 – A frightened boy with strange eyes

Was a healthy boy with normal psychomotor development. In a retrospective novel written by his mother and included in his clinical process we read: “my beautiful boy grew without a problem. He was healthy and strong... With one peculiarity... He was really and truly joyful. I never met a child like that... He had an unexplainable happiness.”

In the summer of his eight-year of life, his mother noticed a change in his son's behaviour and abnormal eye movements: “Suddenly, changed. He started with a breathtaking fear of being alone. He just wanted to be close to me. His look also changed... There were times his eyes would run away. (...) My boy was unfocused...” He was examined by a pediatric neurologist that recognized an incomplete right third cranial nerve palsy. A correction with prismatic lenses was attempted without success.

His clinical symptoms progressed in the next 2 weeks: “He was stumbling, falling, banging his head in the walls, he could not see where he was going and was losing peripheral vision”. He was reexamined by pediatric neurology and ophthalmology, revealing difficulty understanding orders, poor visual acuity (OD <1/10, OS 3/10) with optic atrophy, postural instability with retropulsion, ataxic gait impossible in tandem, and global hyporeflexia. Brain MRI showed bilateral periventricular occipito-parietal demyelinating lesions, and blood VLCFA were elevated. A *de novo* pathogenic point mutation in the *ABCD1* gene (c.1553 G>A) was found through genetic study, not present in his mother. Considering the advanced stage of the disease, no therapeutic options were available, and his neurological status evolved unfavorably.

During his follow-up in endocrinology consultation, and due to borderline serum cortisol (4.7 ug/mL), he was started on hydrocortisone 10 + 5 mg.

Is 29 years old now. He has a global aphasia, a spastic tetraparesis and is bedridden. His mother is his caregiver: “I give him a kiss in his forehead. He seems to react. I am afraid that it is not a reaction to my kiss, but an involuntary and unconscious act...”. He is followed in our reference center with supportive therapies.

This clinical case presents a CALD phenotype with devastating neurological progression. In this young onset form of the disease the presentation with behavioural changes is typical (sometimes poor school performance is an initial complaint, suggesting an attention deficit disorder).<sup>5</sup> The presentation with diplopia and exotropia is also described in the literature.<sup>13</sup> Although preferential involvement of frontal white matter is possible in around 15%-17% of patients,<sup>14</sup> most CALD demyelinating lesions affect parieto-occipital regions explaining the low visual acuity.

AHSCT is the standard therapy for childhood CALD.<sup>6</sup> However, the benefit of such an aggressive therapy will depend on the neurologic status and extension of brain lesions before treatment.<sup>15</sup>

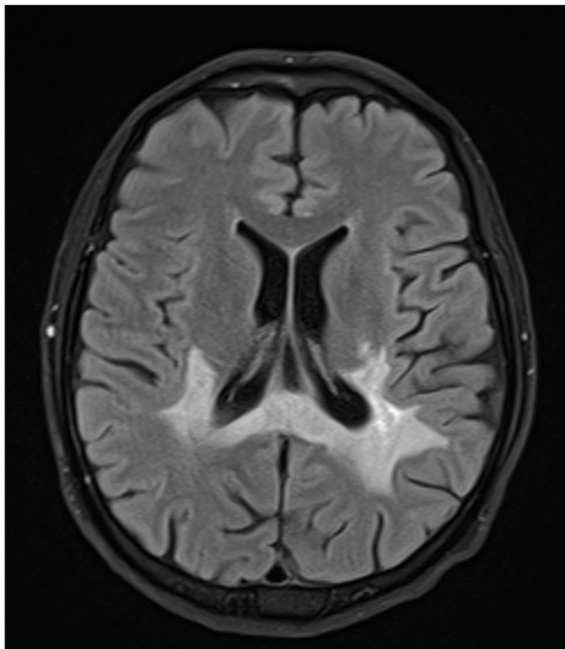
In this case, cerebral involvement occurred with no prior endocrinological or neurological symptoms, and the mutation was *de novo*. In other words, neither personal or family history, nor clinical symptoms alerted us to the possibility of a disease. This raises the importance of considering including X-ALD in the national newborn screening program, which is already available in other countries,<sup>16</sup> and seems to have a favorable economic impact.<sup>17</sup>

### Case 3 – A man with trouble walking and difficulties speaking

Was six years old when he was diagnosed with adrenal insufficiency and medicated with steroids since then. He lost follow-up in the next years.

Around the age of 44, he started complaining about an unsteady gait associated with sexual and urinary dysfunction. His neurological examination presented a spastic paraparesis MRC 4+ with hyperreflexia and bilateral Babinski sign. His brain MRI showed bilateral and symmetrical pyramidal tract demyelination. VLCFA were elevated in plasma and the genetic testing showed an hemizygotic pathogenic point mutation in the gene *ABCD1*.

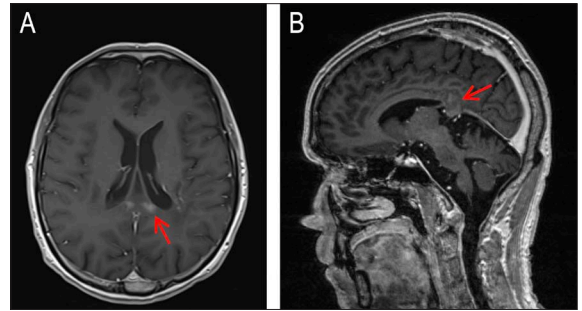
At the age of 47, was admitted to our neurological ward. He complained that in the last months his gait worsened significantly, and in the previous weeks, his speech was less fluent. His neurological examination showed a non-fluent aphasia with intact comprehension, an inappropriate laughter, and a progression of his motor deficit, with a tetraparesis with functional impact on gait (MRC 3 in the lower limbs and MRC 4 in the upper limbs). His brain MRI showed active cerebral parieto-occipital demyelination lesions (**Fig. 1**) with contrast enhancement in the splenium of the *corpus callosum* (**Fig. 2**). He was treated with 3 days of methylprednisolone 1 g with poor clinical response.



**Figure 1.** Patient 3 axial brain MRI T2/FLAIR sequence showing an extensive occipito-parietal hyperintensity, corresponding to a CALD form of X-ALD with demyelinating lesions.

In the next year he was admitted again in our hospital, this time due to an Addisonian crisis and seizures in the context of respiratory tract infection. He was discharged after resolution of infection and adjustment of corticoid therapy but died soon of further medical complications.

This patient presents the entire spectrum of this disease: (1) at an early age, he developed an AO phenotype; (2) around 38 years later he progressed to an AMN with a spastic paraparesis and sexual and urinary dysfunction; (3) three years later, an adult-onset CALD phenotype developed.



**Figure 2.** Patient 3 axial (A) and sagittal (B) brain MRI post-gadolinium T1 sequences showing corpus callosum contrast enhancement (red arrow), compatible with active demyelinating lesions with brain-barrier disruption.

As stated previously, AMN phenotype will develop in virtually all X-ALD male patients. The brain MRI showing pyramidal tract demyelination may represent a non-inflammatory dying-back axonopathy of spinal cord pyramidal neurons (Wallerian degeneration). This is associated with a better prognosis than CALD and does not imply brain involvement.<sup>18</sup> These imaging findings may be wrongly interpreted as amyotrophic lateral sclerosis.<sup>4</sup>

Around 20% of patients with clinical symptoms suggestive of an AMN phenotype will progress to cerebral disease in the next 10 years.<sup>5</sup> Therefore, a regular follow-up of AMN patients with careful neurologic evaluation and annual MRI is recommended.<sup>5</sup> New blood biomarkers of neurodegeneration, like neurofilament light chain, are currently being investigated and may help in monitoring disease progression.<sup>19</sup>

Short recent series of adult X-ALD patients treated with AHSCT seem to support this therapeutic option in highly selected adult patients.<sup>20</sup> In our patient, high doses of steroids were tried in a desperate attempt to stop inflammation, but no evidence currently exists for its use.

The reason why some patients evolve to CALD in childhood and others in adult life is largely unknown. No genotype-phenotype correlation exists, and a multifactorial model with genetic, epigenetic and environmental contributions may offer a better explanation for this heterogeneity.<sup>21</sup>

#### Case 4 – A woman who was run over by a car and had “stuck legs”

Is a 54 years-old woman with gait difficulties. She associates the beginning of her symptoms to an accident she had 5 years before (she was run over by a car, without bone fractures). Since then, she notices her gait is progressively getting worse, because her legs “get

stuck” mainly in the morning. Additionally, she has urinary incontinence.

From her family history, we highlight a nephew who was diagnosed with X-ALD.

Her neurological examination showed a tetraparesis more evident in the lower limbs (upper limbs MRC 4+, lower limbs MRC 4), generalized myotatic hyperreflexia with ankle clonus, bilateral Babinski sign and spastic gait.

Considering her history and to rule out spinal cord compression, she was investigated with an MRI of cervical and dorsal spine that showed bone degenerative disease, with no signal changes of spinal cord. Her MRI of the brain showed T2 biparietal periventricular white matter signal changes, described as being of ischemic etiology.

Her genetic testing was positive for a heterozygous mutation in the *ABCD1* gene (c.1212\_1214delGTC).

This case describes the typical female X-ALD presentation and reminds us that female carriers might be symptomatic and present with AMN phenotype in around 80% of cases. Although the beginning of the symptoms was linked to an accident, the progression of symptoms would be less suggestive of a traumatic/compressive etiology. Female carriers will develop symptoms later in life than men (50% of female carriers by 40 years of age, and 65% by 65 years)<sup>6</sup> and will progress slowly.<sup>22</sup> Women were estimated to increase their EDSS by 0.08 points/year,<sup>22</sup> and above 60 years of age it will reach on average 3.5.<sup>23</sup> Around 44% and 28% will develop urinary (like our patient) and fecal incontinence, respectively.<sup>23</sup>

Only 1% will develop adrenal insufficiency and cerebral involvement is described rarely.<sup>6</sup>

Most importantly, VLCFA measurement might be in the normal range in around 15%-20% of female carriers.<sup>22</sup> Brain MRI shows degeneration of cortico-spinal tract in a lower percentage of cases than men.<sup>5</sup>

In this case, the diagnosis was facilitated by the positive family history, which sometimes is not present as *de novo* mutations are possible (case 2). Genetic testing is very important to confirm etiology and to offer proper genetic guidance in case women want to get pregnant.

## Discussion

With this small case series, we wanted to highlight the following learning points:

1. X-ALD is a rare disease with a heterogeneous clinical

presentation, that spans all ages;

2. X-ALD should be put high in your differential diagnosis list in the following clinical scenarios: (i) males with adrenal insufficiency and negative autoimmune workup; (ii) males and females with spastic paraparesis after acquired and more common genetic causes have been excluded; (iii) subacute behavioural changes in children, possibly associated with cortical signs; (iv) cerebral leukodystrophy with parieto-occipital involvement (or frontal involvement in less than 1/4 of patients), that can present gadolinium enhancement; (v) family history of any clinical X-ALD phenotype, as heterogeneous clinical presentations may occur across the same family<sup>21</sup>;
3. Although the disease is X-linked, remember that female carriers present with an AMN phenotype;
4. Measurement of VLCFA is easily accessible and a sensitive metabolic screening test (only in males), and must be confirmed by genetic testing as it is not totally specific<sup>5</sup>;
5. CALD can be treated with AHSCT, but only if neurologic status and extent of brain lesions are favourable.<sup>15</sup> Once thought to modify AMN progression, Lorenzo's oil shows an analytical “cosmetic effect”, and was proven not to be effective.<sup>4</sup> Corticosteroids might be needed in case of adrenal insufficiency;
6. All X-ALD should be followed in a neurological consultation for life. Clinical symptoms (including behavioural changes or declining school performance) should be carefully questioned, and neurological examination thoroughly performed. Imaging follow-up every 6-12 months or when new symptoms emerge is mandatory.<sup>5,11</sup>

As new therapeutic strategies are successfully developed (like hematopoietic stem cell transplant with autologous cells corrected by lentiviral vector carrying wild-type *ABCD1* gene), and newborn screening strategies start being implemented across the globe,<sup>7</sup> neurologists may enter a new era in the treatment and diagnosis of this devastating disease, offering a new hope to X-ALD patients. ■



**Contributorship Statement / Declaração de Contribuição**

PLN: Study design, manuscript elaboration and final approval.

JD: Study design, manuscript elaboration, manuscript review and final approval.

IM and LD: Manuscript review and final approval.

MCM: Study design, manuscript review and final approval.

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