INTERNATIONAL SEVEN JOURNAL
OF HEALTH RESEARCH
ISSN: 2764-9415

X-linked adrenoleukodystrophy: Clinical review and case report

DOI: 10.56238/eSvjH3N3-005
Receipt of originals: 04/30/2024
Acceptance for publication: 05/20/2024

Carolina Meller Jost
Universidade de Passo Fundo (UPF), Passo Fundo, Rio Grande do Sul, Brazil
ORCID: https://orcid.org/0000-0002-1314-6530
E-mail: carolinajost6@gmail.com

Claudiane Machado Visintin
Universidade de Passo Fundo (UPF), Passo Fundo, Rio Grande do Sul, Brazil
ORCID: https://orcid.org/0000-0001-8832-1885

Eduarda Vogel Wollmeister
Universidade de Passo Fundo (UPF), Passo Fundo, Rio Grande do Sul, Brazil
ORCID: https://orcid.org/0000-0002-6075-802X

Giovanni Cândido Volino
Universidade de Passo Fundo (UPF), Passo Fundo, Rio Grande do Sul, Brazil
ORCID: https://orcid.org/0000-0001-7766-7821

Barbara Polli
Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Rio Grande do Sul, Brazil
ORCID: https://orcid.org/0009-0008-2022-9562

Thaís Caroline Fin
Universidade de Passo Fundo (UPF), Passo Fundo, Rio Grande do Sul, Brazil,
ORCID: https://orcid.org/0000-0002-2384-0905

ABSTRACT

Introduction: Adrenoleukodystrophy is a rare, recessive, hereditary X-linked genetic disease with degenerative and incurable characteristics, which preferentially affects males. It directly affects the non-development of the adrenal/adrenal glands and the white matter of the brain by the accumulation of long-chain fatty acids at these sites, causing a destabilization of the myelin sheath and affecting the transmission of nerve impulses. Objective: The objective that triggered the realization of this study is based on the scarcity of literature on this rare pathology, which affects about 1:15,000 to 25,000 individuals, seeking to portray the clinical trajectory of this disease. Case presentation: A 34-year-old male patient diagnosed with X-linked Adrenoleukodystrophy after investigation due to the death of a 13-year-old brother with the disease, has been undergoing multidisciplinary follow-up since diagnosis, with genetics, endocrinology, neurology and psychology teams, undergoing annual consultations and control laboratory tests, as well as magnetic resonance imaging of the brain. At the age of 19, he communicated that he did not want to have a bone marrow transplant. He has been following clinical follow-up since then. Discussions: The diagnosis can be made in prenatal tests, the gold standard score for grading the pathology is the LOES Score, totaling 34 points, according to the patient's score, it is possible to observe if the patient will benefit from the treatment through hematopoietic cell transplantation, since patients with a score lower than 9 respond better to transplantation, preferably less than 4

points. Thus, there is a need for early diagnosis of the pathology, in order to provide early treatment.

Keywords: Adrenoleukodystrophy, Hereditary diseases, Adrenal insufficiency.

1 INTRODUCTION

Adrenoleukodystrophy (ALD) is a rare genetic pathology with a recessive pattern, with degenerative character of the central nervous system (CNS) (4). It affects more males and can develop in different age groups (1). The initial symptomatology tends to be nonspecific and is commonly confused, directly hindering the purpose of making an early diagnosis and ensuring longer survival and better quality of life (2). Generally, the diagnosis of X-linked adrenoleukodystrophy (X-ALD) is related to the presence of concomitant endocrinopathy, but in addition to laboratory tests, the patient's clinical history as well as family history are crucial (3). Early diagnosis of ALD is necessary for the patient to have a greater chance of survival. Although there are still no treatments that guarantee a total cure of the disease, there are possibilities for a normal life according to its limitations (1). Adrenal insufficiency is often the first manifestation of X-ALD (5), it can occur decades before neurological symptoms (6).

Although there are no treatments that guarantee the cure of the pathology, it is necessary to emphasize that there is the possibility of a normal life, according to the limitations. "Lorenzo's oil" when associated with a diet low in very long chain fatty acids, reduces plasma levels in up to four weeks, but does not associate clinical or radiological improvement, if used before symptoms it can delay the development of lesions or onset of neurological symptoms. Bone marrow transplantation (BMT) is currently the only available and effective alternative to stop the progression of ADL, but it is only effective when the investigation is carried out early, however most patients do not detect it in a timely manner for transplantation, reducing their chances of regression of the lesions caused by the disease, thus emphasizing the importance of early diagnosis. Genetic counseling is an important tool to significantly reduce the occurrence of new cases, and to carry out appropriate and early treatment in family members who may be affected by ADL (1).

The theoretical framework that triggered the realization of the present work is based on the scarcity of literature about this rare pathology, seeking to portray, in a simplified way, the clinical trajectory of this disease, the present work seeks to portray its pathophysiology, clinical characteristics, the systems that are frequently affected, the implications of this disease in the patient's life, in addition to the multidisciplinary treatment, and sequential follow-up, which is

necessary throughout the patient's trajectory. This work is carried out through the perspective of a case report.

2 CASE REPORT

The proband is a 34-year-old man, diagnosed with X-linked Adrenoleukodystrophy, diagnosed in 2005, at the age of 16, through genetic investigation indicated after the death of a 13-year-old brother with the disease. He started his clinical follow-up asymptomatic. She has a positive family history, a cousin previously diagnosed with the disease and a daughter, who is a mandatory carrier due to the pathology occurring through mutations in the ABCD1 coding gene, located on the long arm of the X chromosome.

At the age of 18, after being diagnosed with X-ALD, he began follow-up with the genetics team of the Hospital de Clínicas de Porto Alegre (HCPA), without complaints, asymptomatic, and presenting only mucosal hyperpigmentation in the first evaluation. In this evaluation, the attending physician requested laboratory tests to detect very long-chain fatty acids (VLCFA) with subsequent altered results, in addition to adrenocorticotropic hormone (ACTH), which presented results above normal limits (Table 1) and magnetic resonance imaging (MRI) of the brain (Table 2), which showed initial brain involvement (LOES 7). On this occasion, due to his laboratory and imaging results, the patient was prescribed "Lorenzo's Oil" at a dosage of 2 ml/kg/day and was referred for follow-up with the endocrinology and psychology team, in addition to hematology evaluation for BMT planning.

Patient returns reporting to the team that he had started using Prednisone 5mg/day by prescription of an endocrinologist in his hometown. On physical examination at the present consultation, the patient presented mild dysmetria, dysdiadochokinesia in the left hand, hyporeflexia, finger flexors, and radial style on the left.

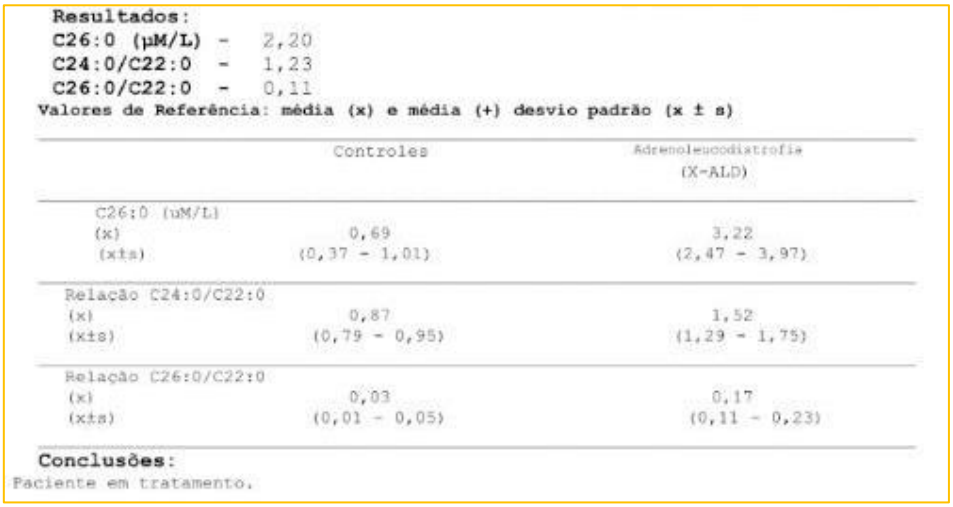
Since the diagnosis, the patient has been in multidisciplinary follow-up with genetics, endocrinology, neurology and psychology teams, undergoing annual consultations and laboratory control tests, as well as magnetic resonance imaging of the brain. At the age of 19, the patient communicated his desire not to undergo an evaluation by pediatric oncology, as he did not wish to undergo BMT. In addition, he was temporarily using half the recommended dose of "Lorenzo's Oil", due to the lack of access to the drug.

At 21 years of age, in 2010, the dose of prednisone was increased to 10mg/day by laboratory examination with elevated ACTH (Table 1). At the age of 22, in a routine consultation, the physical examination presented positive Romberg and hyperreflexia on the right. At the age

of 23, she presented prediabetes and received dietary guidance. At the age of 24 (2012): he started adrenomieloneuropathy.

At the age of 25, in 2013, after laboratory results (figure 1), she stopped using Lorenzo's Oil, with a stable condition, she was only advised a diet rich in B12. On physical examination, the patient presented mild tandem imbalance, mild hypertonia of the lower limbs, and increased reflexogenous area of the patellar artery.

Figure 1 - Laboratory results of tests collected in 2013, when the patient was recommended to discontinue the medication.



Resultados:

C26:0 (µM/L) - 2,20
C24:0/C22:0 - 1,23
C26:0/C22:0 - 0,11

Valores de Referência: média (x) e média (+) desvio padrão (x ± s)

	Controles	Adrenoleucodistrofia (X-ALD)
C26:0 (uM/L)		
(x)	0,69	3,22
(±s)	(0,37 - 1,01)	(2,47 - 3,97)
Relação C24:0/C22:0		
(x)	0,87	1,52
(±s)	(0,79 - 0,95)	(1,29 - 1,75)
Relação C26:0/C22:0		
(x)	0,03	0,17
(±s)	(0,01 - 0,05)	(0,11 - 0,23)

Conclusões:

Paciente em tratamento.

From 28 to 33 years of age, the patient was followed up in multidisciplinary follow-up, following no changes in the physical examination and denying any other changes. There were no complaints or complications during the period. At 34 years of age, he starts with reduced vibratory sensitivity (9-10s) in the right lower limb (MID).

Table 1 - Sequential results of ACTH for laboratory control of the pathology.

	2006	2010	2013	2022
ACTH	1206 pg/ml	234 pg/ml	182 pg/ml	634 pg/ml

Table 2 - Reports of magnetic resonance imaging of the brain, grading the extent of the pathology with cerebral involvement.

MRI of the brain	Result:
2006/2007/2008	Envolvimento parieto-occipital (LOES 7).
2013/2014/2015	Parieto-occipital involvement, splenium corpus callosum, stable examination with no changes in time, no contrast uptake
2022	Presence of areas with signal hyperintensity on T2-weighted and FLAIR sequences, located in the peritrigonal white matter bilaterally, in the splenium of the corpus callosum, in the knee and posterior arm of the internal capsule bilaterally, in the cerebral peduncles, determining a slight reduction in brain volume, being unchanged in relation to the study carried out on 01/22/2021. Presence of cystic formation in the pineal gland.

Since the diagnosis, the patient has been regularly monitored by the HCPA genetics team, as well as an endocrinologist, neurologist and psychologist in his hometown. In addition, he undergoes laboratory tests and control MRI annually via the Basic Health Unit, since the aforementioned patient refused to follow up for subsequent BMT. In addition, at the beginning of the condition, after the diagnosis, he reports having been advised about the risks of biological paternity, since all his future daughters would be carriers of the mutated gene and, consequently, would develop the disease.

3 DISCUSSION

Adrenoleukodystrophy (ALD) is a rare genetic pathology with a recessive pattern that has a degenerative character of the central nervous system (CNS). The disease presents in its classic form as an inflammatory demyelinating due to mutations in the ABCD1 encoding gene, located on the long arm of the X chromosome. Because they cannot penetrate the peroxisomes for their metabolization, they remain in the blood plasma, causing an accumulation in various tissues, resulting in adrenal insufficiency and axonal demyelination (1), with ALD being the most common peroxisomal disorder (4). Because it is linked to the X chromosome, it primarily affects the male population, approximately 1:20,000 men (1). Regarding its pathophysiology, there is nothing that can explain the disease in its entirety, however, one of its possible causes is the accumulation of very long-chain fatty acids (VLCFA), mainly hexachosanoic acid (C26:0) and tetrachosanoic acid (C24:0), in places such as the cerebral white matter; spinal cord; in the testes and adrenal glands

(7). The accumulation occurs mainly because of the abnormal mutation of the ABCD1 gene, which is responsible for the formation of the peroxisomal transmembrane protein ALDP, the function of this protein is to transport the VLCFA into the peroxisome and thus be metabolized (8). The accumulation of VLCFA destabilizes the myelin sheath and results in a demyelination of the sheaths, thus causing important neurological damage such as inflammation of the brain tissue, affecting both the sensory and motor parts. At sites outside the central nervous system (CNS), VLCFA accumulation is toxic to the tissues present, in the adrenal cortex results in cellular apoptosis, and the increase in ACTH is a primary manifestation of the damage caused. In the adrenal gland, abnormal VLCFAs alter their function, which causes ACTH to have its effect inhibited directly on adrenocortical cells, or indirectly, thus causing an autoimmune response (9).

Clinically, there is a range of neurological and endocrine manifestations. Among the manifestations, progressive leukodystrophy is common in males and, even more frequent, slowly progressive polyneuropathy, a spinal cord disease progressing with peripheral neuropathy, and also adrenal insufficiency (9). For females, adrenal insufficiency and leukodystrophy are no longer common, unlike myeloneuropathy. Leukodystrophy progresses with learning difficulties, behavioral problems, followed by neurological deterioration, causing blindness and quadriparesis, in about 20% of male patients the first manifestation is seizures (9). Myeloneuropathy, on the other hand, presents with progressive rigidity, weakness of the lower limbs, sensory ataxia, abnormal control of the sphincter, sexual dysfunction, numbness, and pain due to polyneuropathy. In adrenal insufficiency, the patient may present fatigue, gastrointestinal symptoms, vomiting, headache, skin hyperpigmentation, and fasting hypoglycemia (9).

The diagnosis of the disease can be made in prenatal tests in cases of women with affected children or a positive family history, analyzing peroxisomal biogenesis disorders and women with a defective ABCD1 gene (9). And, in some countries, such as the United States and the Netherlands, it is already possible to perform neonatal screening, a fact that benefits early diagnosis and treatment (9). When not performed in prenatal tests, plasma analysis is used to check VLCFA levels as a diagnostic test (8), however, the diagnosis must be confirmed by genetic tests that analyze the mutation of the ABCD1 gene (9). It is possible to detect the presence of the disease earlier through magnetic resonance imaging (MRI), since it is common at the beginning of the condition for the patient to be oligosymptomatic, or even asymptomatic, but already present findings that can be verified on an MRI image, in addition, it is possible to verify the affected region early and be able to grade the level of CNS involvement and the stage of the disease that is related with the patient's age, the affected location, and the initial LOES score (7-8).

The gold standard score for the grading of the disease is the LOES Score, which is a 34-point scale, involving the affected location and the extent of the involvement, the presence of local or global atrophy. The commonly affected sites described by the score are temporoanterior white matter, frontal and parieto-occipital white matter, corpus callosum, visual and auditory tracts, projection fibers, cerebellum, and basal ganglia. It is considered a very early stage if the score is <4, between 4 and 8 in the score represents an initial stage, a result obtained in the first MRI of the aforementioned patient, between 9 and 13 a late stage, and > 13 is an advanced stage of the condition. Due to this, it is possible to observe whether the patient will benefit from the treatment through hematopoietic cell transplantation (HCT), since it is better to perform the transplant with a score lower than 9, preferably lower than 4 points. (1-7).

Among the therapeutic approaches are the dietary restriction of VLCFA, associated with Lorenzo's oil, with the aim of reducing the internal VLCFA, and when there is a neuroinflammatory process, it is recommended to perform HCT. This procedure has been shown to be very effective in improving motor function and performance (6). However, ALD requires multidisciplinary care with psychologists, endocrinologists, genetic and neurological teams, as well as performed by the reported patient.

Thus, it would be appropriate to implement a national neonatal screening program, given the importance of early diagnosis to provide a possible treatment and, consequently, significantly improve quality of life.

REFERENCES

Antunes LRC, Nunes AN, Silva HO, Costa HFS, Alencar MAMO, Vargas AB, et al. Adrenoleukodystrophy Disease: a diagnostic approach, clinical evolution and review [internet]. Brazilian Journal of Health Review, Curitiba. 2023;6(5):21922-21931. DOI:10.34119/bjhrv6n5-225. [cited 2024 feb 01]. Available from: https://ojs.brazilianjournals.com.br/ojs/index.php/BJHR/article/download/63182/45448/153982.

Oliva NO, Silva GB da, Sousa EJS de, Soares SF, Maia LS, Leão T do SB, et al. ADRENOLEUCODISTROFIA LIGADA AO X EM UMA CRIANÇA: RELATO DE CASO E REVISÃO DE LITERATURA. RECIMA21 [Internet]. 29 de abril de 2023 [citado 2024 fev 3]; 4(5):e453098. Disponível em: https://recima21.com.br/index.php/recima21/article/view/3098.

Papierska L, Rabijewski M. Delay in Diagnosis of Adrenal Insufficiency Is a Frequent Cause of Adrenal Crisis [Internet]. International Journal of Endocrinology. 2013;2013:Article ID 482370, 5 pages. DOI: 10.1155/2013/482370. [cited 2024 feb 3]. Available from: https://www.hindawi.com/journals/ije/2013/482370/.

Morigaki MT. Prevalência de adrenoleucodistrofia em crianças de 5 a 12 anos: uma revisão integrativa da literatura [Trabalho de Conclusão de Curso]. Curso da residência de pediatria: Universidade Federal da Grande Dourados; 2022. 20 p. [citado 2024 fev 5]. disponível em: https://repositorio.ufgd.edu.br/jspui/handle/prefix/5450

Polgreen LE, Chahla S, Miller W, Rothman S, Tolar J, Kivisto T, et al. Early diagnosis of cerebral X-linked adrenoleukodystrophy in boys with Addison's disease improves survival and neurological outcomes [internet]. Eur J Pediatr. 2011;170:1049-54. [cited 2024 feb 5]. Available from: https://link.springer.com/article/10.1007/s00431-011-1401-1

Furlan FLS, Lemes MA, Suguimatsu LC, Pires CTF, Santos MLSF. Adrenoleucodistrofia Ligada ao x no Brasil: uma série de casos. Paul Pediatr. (Ed. Port., Online). 2019. [citado 2024 fev 5]. Disponível em: https://www.scielo.br/j/rpp/a/NNRFHCLpSvmDLVjG9FhRxGt/?lang=en

Ono SE, de Carvalho Neto A, Gasparetto EL, de Mattos Coelho LO, Escuissato DL, Bonfim CMS et al. X-linked adrenoleukodystrophy: correlation between Loes score and diffusion tensor imaging parameters [internet]. Radiol Bras. 2014 Nov/Dez;47(6). doi: 10.1590/0100-3984.2013.1886. [cited 2024 feb 6]. Available from: https://www.scielo.br/j/rb/a/gqczwPqmTJmWKtLJrztm54K/?lang=pt

Marchetti DP. Processos oxidativos, inflamatórios e alterações comportamentais induzidas por ácido hexacosanóico na adrenoleucodistrofia ligada ao cromossomo X e o efeito de antioxidantes [dissertação]. Porto Alegre: Universidade Federal do Rio Grande do Sul, Instituto de Ciências Básicas da Saúde, Programa de Pós-Graduação em Ciências Biológicas: Bioquímica; 2019. [citado 2024 fev 6]. Disponível em: https://lume.ufrgs.br/bitstream/handle/10183/196667/001092813.pdf

Wanders RJA, Engelen M. Clinical features, evaluation, and diagnosis of X-linked adrenoleukodystrophy. UpToDate. 2023 Aug 30. [cited 2024 feb 6]. Disponível em: https://sso.uptodate.com/contents/clinical-features-evaluation-and-diagnosis-of-x-linked-adrenoleukodystrophy?search=adrenoleukodystrophy&source=search_result&selectedTitle=1~55&usage_type=default&display_rank=1#H.