

Visual loss as first clinical manifestation of X-linked adrenoleukodystrophy

Perda visual como primeira manifestação clínica de adrenoleucodistrofia ligada ao X

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ABSTRACT

X-linked adrenoleukodystrophy (X-ALD) represents a group of diseases characterized by the accumulation of very long chain fatty acids (VLCFAs) in the tissues. Its clinical manifestations are usually manifold. Visual changes may be present, but they often appear later in the disease. We describe here the case of a 9-year-old boy with X-ALD, whose first symptom was visual loss, which began at 8 years of age. His ophthalmologic evaluation revealed no alterations. Shortly thereafter, he suffered a head injury. The magnetic resonance imaging of brain revealed findings that led to the suspicion of X-ALD. The plasma VLCFA dosage confirmed this diagnosis. This report aims to show that in cases of visual loss with a normal ophthalmic examination, a high index of suspicion should be given for conditions such as X-ALD, since it affects the cortical routes related to vision. Fundoscopy findings appear late in X-ALD.

Keywords: Adrenoleukodystrophy; Peroxisomal disorders; Vision disorders; Blindness, cortical; Magnetic resonance imaging

RESUMO

A adrenoleucodistrofia ligada ao X (X-ALD) representa um grupo de doenças caracterizadas pelo acúmulo de ácidos graxos de cadeia muito longa (VLCFAs) nos tecidos. Suas manifestações clínicas costumam ser múltiplas. Alterações visuais podem estar presentes, contudo costumam surgir mais tardiamente na doença. Descrevemos aqui o caso de um menino de 9 anos com X-ALD, cujo primeiro sintoma foi perda visual, iniciada aos 8 anos de idade. A sua avaliação oftalmológica não revelou alterações. Pouco tempo depois, ele sofreu um traumatismo craniano. A imagem de ressonância magnética de encéfalo revelou achados que levaram a suspeita de X-ALD. A dosagem dos VLCFAs no plasma confirmou este diagnóstico. Este relato tem como objetivo mostrar que em casos de perda visual com um exame oftalmológico normal, deve-se ter um alto índice de suspeita para condições como a X-ALD, pois a mesma afeta as vias corticais relacionadas à visão. Nessa doença, os achados da fundoscopia aparecem mais tardiamente.

Descritores: Adrenoleucodistrofia; Transtornos peroxissômicos; Transtornos da visão; Cegueira cortical; Imagem por ressonância magnética.

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INTRODUCTION

X-linked adrenoleukodystrophy (X-ALD) represents a group of metabolic diseases characterized by the accumulation of very long chain fatty acids (VLCFAs) in all tissues. This occurs as a result of deficiency of the peroxisomal β -oxidation enzyme, due to a range of function mutations in the ABCD1 gene on chromosome Xq28. X-ALD manifests with multifocal demyelination of the central and peripheral nervous system and atrophy of the adrenal gland cortex. There are several X-ALD phenotypes. The most frequent phenotypes are adult-onset adrenomyeloneuropathy (AMN) and cerebral childhood adrenoleukodystrophy (CCALD).⁽¹⁾ The phenotype with the most severe signs and symptoms is CCALD, which corresponds to 40% of cases of ALD.⁽²⁾ Although there is no detailed and large-scale study of the natural history of the disease, previously published data suggest that X-ALD patients born pre-symptomatic.⁽³⁾ However, its clinical manifestations are usually manifold and appear between 6 and 12 years of age.⁽²⁾ Visual changes may also be present, but they usually appear later.⁽⁴⁾

We describe here the case of a 9-year-old boy with X-ALD, whose first symptom was visual loss.

CASE REPORT

The patient was a 9-year-old boy. He was the third child of a 42-year-old mother and a 64-year-old father. The parents were not blood relatives and there were no similar cases in the family. His gestation evolved without intercurrents, and he presented an adequate neuropsychomotor development, without learning difficulties. There was no evidence of behavioral changes as well.

At 8 years of age, he started with a visual loss complaint. He could not see the blackboard in school properly, and he reported frequent headaches. Over time, he also began to complain of difficulty in listening. He had no previous history of seizures or other neurological signs. The decrease in his performance at school led him to an ophthalmological evaluation. It did not reveal any changes. Visual acuity was 20/20 in both eyes. Biomicroscopy showed photoreactive pupils, transparent corneas, and no crystalline opacities in both eyes. Ocular motility and intraocular pressure also did not indicate marked changes. The funduscopy was normal.

Due to the persistence and progression of the symptoms, the boy was referred to the psychiatric consultation. Shortly thereafter, he suffered a head injury. In consultation with the neurologist, this showed generalized hyperreflexia and bilateral Babinski's sign. Brain magnetic resonance imaging (MRI) revealed areas of T2-weighted hypersignal in brainstem and white matter of posterior, parietal, occipital and temporal frontal regions. Due to this situation, CCALD was suspected. The measurement of very long chain fatty acids (VLCFA) in plasma (C22: 0; C24: 0; C26: 0), with evidence of their increase, confirmed this diagnosis. The measurement of very long chain fatty acids (VLCFA) in plasma (C22: 0; C24: 0; C26: 0) highlighted their increase and confirmed the diagnosis.

DISCUSSION

CCALD is a degenerative disease, that can progress to severe dysfunctions and death within approximately 2 years after onset of symptoms.⁽³⁾ Initially, these patients tend to be diagnosed

with attention deficit hyperactivity disorder, due to learning difficulties and behavioral changes.⁽⁵⁾ However, the disease usually evolves with other symptoms, which include hearing impairment and coordination weaknesses.⁽⁶⁾ The visual system is also frequently affected in X-ALD,⁽¹⁾ and its dysfunction can progress rapidly. The most common visual disturbances are loss of visual acuity, visual field defects, visual agnosia, homonymous hemianopia, strabismus, and cortical blindness.⁽⁴⁾ What is striking in our case is that visual loss usually occurs only years after the onset of systemic disease, when many of the other clinical findings are already present.⁽⁴⁾ In our patient, however, the visual loss appeared as a first and only symptom.

Loss of vision may not be explained by changes in the fundus during the early stages of the disease.⁽⁷⁾ Perhaps for this reason, the ophthalmological evaluation of our patient was normal, since the disease was in its initial phase. The finding of leukodystrophy in MRI suggests that the visual symptoms presented by our patient may have a cerebral origin, such as cortical blindness. One study used optical coherence tomography to determine whether children with CCALD could have subclinical retinal axonal or neuronal loss before the development of neurological symptoms. The conclusion of this study indicated that retinal structural abnormalities are not detectable prior to the development of neurological manifestations in CCALD.⁽⁷⁾ In addition, the visual brainstem evoked responses become abnormal only at more advanced stages of the disease.⁽⁸⁾ Visual deterioration occurs about 6 months after the onset of neurological symptoms, and is believed to be due to the progressive thinning of the ganglion cell layer and inner plexiform layer of the retina, as a consequence of the transneuronal retrograde degeneration of the retinal ganglion cell secondary to optic radiation demyelination.⁽²⁾ Furthermore, some authors suggest that there is a loss of⁽⁹⁾ photoreceptors and dysfunction in the inner retina or synaptic transmission.

CONCLUSION

Thus, this report aims to show that a high index of suspicion is required for conditions such as X-ALD, which affect the cortical routes related to vision, even in the absence of visual symptoms and a normal ophthalmologic examination. The follow-up of patients with X-ALD by an ophthalmologist is relevant, since the findings of funduscopy usually appear with the development of the disease, and they indicate a visual impairment that tends to evolve very quickly.

REFERENCES

1. Grainger BT, Papchenko TL, Danesh-Meyer HV. Optic nerve atrophy in adrenoleukodystrophy detectable by optic coherence tomography. *J Clin Neurosci*. 2010;17(1):122-4.
2. Ohkuma Y, Hayashi T, Yoshimine S, Tsuneoka H, Terao Y, Akiyama M, et al. Retinal Ganglion Cell Loss in X-linked Adrenoleukodystrophy with an ABCD1 Mutation (Gly266Arg). *Neuroophthalmology*. 2014;38(6):331-5.
3. Kemp S, Huffnagel IC, Linthorst GE, Wanders RJ, Engelen M. Adrenoleukodystrophy - neuroendocrine pathogenesis and redefinition of natural history. *Nat Rev Endocrinol*. 2016;12(10):606-15.
4. Gess A, Christiansen SP, Pond D, Peters C. Predictive factors for vision loss after hematopoietic cell transplant for X-linked adrenoleukodystrophy. *J AAPOS*. 2008;12(3):273-6.

5. Shimozawa N, Honda A, Kajiwara N, Kozawa S, Nagase T, Takemoto Y, et al. X-linked adrenoleukodystrophy: diagnostic and follow-up system in Japan. *J Hum Genet.* 2011;56(2):106–9.
6. Suzuki Y, Imamura A, Shimozawa N, Kondo N. The clinical course of childhood and adolescent adrenoleukodystrophy before and after Lorenzo's oil. *Brain Dev.* 2001;23(1):30–3.
7. Aquino JJ, Sotirchos ES, Saidha S, Raymond GV, Calabresi PA. Optical coherence tomography in x-linked adrenoleukodystrophy. *Pediatr Neurol.* 2013 Sep;49(3):182–4.
8. Kemp S, Berger J, Aubourg P. X-linked adrenoleukodystrophy: clinical, metabolic, genetic and pathophysiological aspects. *Biochim Biophys Acta.* 2012;1822(9):1465–74.
9. Courtney RJ, Pennesi ME. Interval spectral-domain optical coherence tomography and electrophysiology findings in neonatal adrenoleukodystrophy. *JAMA Ophthalmol.* 2013;131(6):807–10.

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