X-linked adrenoleucodystrophy: diagnosis and progression quantification

Adrenoleucodistrofia ligada ao X: diagnóstico e quantificação da progressão

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Adrenoleukodystrophy (ALD) is a white matter disease whose bone marrow transplant (BMT) as a therapeutic option is allowed for early diagnosis. Because of the high sensitivity of magnetic resonance imaging (MRI) for the diagnosis of WM lesions, the radiologist is frequently asked to give his/her opinion on the differentiation between a case of hypoxia-related sequelae and evolutive lesions such as leukodystrophy. In general, the clinician can distinguish both groups using anamnesis and neurologic evaluation. However, not always the disease presentation is so clear, white or black, most frequently presenting with different shades of gray, with a very confusing history of loss of abilities, behavior disorders, questionable psychomotor involution and different degrees of disorders potentially attributable to psychiatric diseases acting as confounding factors. In such a situation, the opinion of the radiologist about a brain MRI study is critical for the clinical management. The typical presentation of X-linked ALD in association with adrenal insufficiency symptoms is relatively easy to be diagnosed by a radiologist with experience in central nervous system (CNS) diseases, which increases the responsibility of the professional. Recently, the relevance of the role played by diagnostic imaging was enhanced by good outcomes achieved with the treatment by BMT in early diagnosed cases. Thus, the reading of the excellent article published in the present issue of **Radiologia Brasileira**, approaching the utilization of diffusion tensor imaging and developed by researchers at Hospital das Clínicas of Universidade Federal do Paraná, becomes even more interesting.

ALD is a genetic disease classified in the group of peroxisomal disorders whose most frequent presentation is that of a recessive X-linked disease. Thus, women, although being carriers of the gene which fundamentally affects men, are uncommonly affected, in such cases presenting with a variant of the disease. Despite the existence of neonatal and adult-onset forms of the disease, classic childhood adrenoleukodystrophy is more frequent and severe. Such a disease presentation was made widely known by the movie "Lorenzo's Oil" (USA, 1992), directed by George Miller, where it was brightly described with emphasis not only on the patient's suffering but also on the repercussion of the progressive deterioration of the child on the family. Additionally, one should consider the current availability of access to information through the media, which allows to the family to anticipate the possibility of an inexorable deterioration in the absence of an effective treatment.

X-linked ALD is caused by failure in the metabolism of very long-chain fatty acids which accumulate principally in the CNS and adrenal glands. With such accumulation of fatty acids in the brain, there is a breakdown of the myelin sheath and axons, with a perivascular inflammatory component which expresses itself as a blood-brain barrier breakdown on the margin of the area of demyelination. The symptoms onset occurs at the age between five and six years, with diminished visual acuity, auditory impairment, signs of adrenal failure, memory loss, speech and gait difficulties, increasing irritability and relationship difficulties.

MRI features are variable but the typical presentation shows the demyelinating lesion located in the splenium of the corpus callosum and progressing to involve the adjacent parieto-occipital white matter in three layers. At the center, there is an area of necrosis with hyposignal on T1-weighted sequences and hypersignal on T2-weighted sequences, surrounded by an intermediate demyelinating area with perivascular inflammation that is responsible for the barrier breakdown and generally bilateral and protuberant marginal gadolinium enhancement, with foci of discontinuity adjacent to the cortex. Finally, there is another non-inflammatory demyelinating area associated with edema surrounding the contrast-enhanced area. Progressively, the demyelination involves different myelin tracts, including optic e motor-sensory tracts, and anteriorly extending towards the parietal and occipital lobes, cerebral trunk and cerebellum. At MRI, the lesion is progressive and, in general the findings precede the clinical symptoms related to the affected tract. Despite the existence of variants, including a predominantly frontal presentation, the above described classic childhood ALD is the most common presentation of the disease. The symptoms progression demonstrates a very clear correlation with the progressive involvement of the different myelin tracts, so a careful analysis of the MR images is extremely useful to determine the degree of disease severity as well as the stage of CNS involvement. The current scoring system was proposed by Loes in 1994[2] and is known as "Loes score", as described in the study developed by Ono et al.[1]. With the introduction of the proposal for indication of BMT to treat children affected by ALD[3,4], the fundamental dilemma is to establish a limit for the indication of the procedure because, at a certain point in the course of the disease, its effectiveness ceases to exist. In general, the procedure is contraindicated in cases

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where the Loes score is ≥ 9. From the social point of view, it is always difficult to contraindicate BMT, since this is the most effective treatment method, with an estimated survival rate corresponding to twice the survival rate in cases where this therapy is not utilized, regardless the use of other palliative forms of treatment, such as the so called "Lorenzo's oil".

Despite the fact that the ALD diagnosis and scoring are essentially qualitative and based on the identification of inflammatory demyelination at structural images, the utilization of quantitative tools frequently called advanced techniques, includes proton spectroscopy and diffusion-tensor imaging (DTI) and has increasingly gained significance in the investigation of different demyelinating diseases, as already widely known in cases of more common conditions such as neuromyelitis optica[5] and multiple sclerosis[6]. The article by Ono et al.[1] is also very useful as it discusses the ideal parameters for the utilization of DTI, such as the number of directions, for example. So, the reading of this interesting article is highly recommended.

REFERENCES

1. Ono SE, Carvalho Neto A, Gasparetto EL, et al. X-linked adrenoleukodystrophy: correlation between Loes score and diffusion tensor imaging parameters. Radiol Bras. 2014;47:342–9.
2. Loes DJ, Hite S, Moser H, et al. Adrenoleukodystrophy: a scoring method for brain MR observations. AJNR Am J Neuroradiol. 1994;15:1761–6.
3. Loes DJ, Fatemi A, Melhem ER, et al. Analysis of MRI patterns aids prediction of progression in X-linked adrenoleukodystrophy. Neurology. 2003;61:369–74.
4. Peters C, Charnas LR, Tan Y, et al. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999. Blood. 2004;104:881–8.
5. Gasparetto EL, Rueda Lopes FC. Advances in neuromyellitis optica. Radiol Bras. 2012;45(6):ix.
6. Inglese M. Multiple sclerosis: new insights and trends. AJNR Am J Neuroradiol. 2006;27:954–7.