When multiple sclerosis and X-linked adrenoleukodystrophy are tangled

A challenging case

Anderson Rodrigues Brandão de Paiva, MD, Carlos Rory Pucci Filho, Alan Monteiro Porto, Fabrício Stewan Feltrin, MD, PhD, Fernando Kok, MD, PhD, and Carlos Henrique Ferreira Camargo, MD, PhD

Neurology: Clinical Practice April 2018 vol. 8 no. 2 156-158 doi:10.1212/CPJ.0000000000000431

Correspondence

Dr. Camargo
chcamargo@uol.com.br

Diagnosis of multiple sclerosis (MS) is often difficult because of the wide range of clinical presentations and the absence of biomarkers or specific test to confirm the disease. The condition can therefore be confounded with other inflammatory or genetic conditions that affect the CNS, like inherited leukoencephalopathies. Among inherited leukoencephalopathies, X-linked adrenoleukodystrophy (X-ALD) figures out as one of the most common.^{1,2}

X-ALD is associated with mutations in *ABCD1* on X chromosome, leading to accumulation of very long-chain fatty acids (VLCFAs) and consequent functional changes in adrenal cortex, CNS, bladder, and bowel tissue.^{2,3}

Women who are heterozygous for these mutations may present with neurologic symptoms but are generally asymptomatic. They may present with brisk deep tendon reflexes or mild late-onset spastic paraparesis. Brain or adrenal involvement are exceptionally rare.⁴⁻⁶

PRACTICAL IMPLICATIONS

Differential diagnosis of X-linked adrenoleukodystrophy vs multiple sclerosis may be aided by examining family pedigree for very long-chain fatty acids.

Case report

A 46-year-old woman presented with changed right homonymous hemianopia and dizzy spells that improved spontaneously. After 2 years, she presented with binocular persistent vertical diplopia, ocular skew deviation, upbeat nystagmus, dizzy spells, hyperreflexia, and Babinski sign on the left side. Her family history was remarkable for 2 sons who received a diagnosis of X-ALD—a 21-year-old with genetically confirmed diagnosis of cerebral form X-ALD and a 27-year-old with X-linked adrenomyeloneuropathy. Her MRI showed elongated areas of T2 hyperintensities, some oriented perpendicularly to the cortical or pial surfaces of the cerebral hemispheres. Lesions in the juxtacortical, periventricular, and infratentorial compartments were observed, one of which showed an annular pattern of gadolinium uptake. Lesions were also visible in the callosal-septal interface (figure). There were infratentorial lesions in the pons, one of which followed the intrapontine trigeminal nerve tract. Taken together, these findings are suggestive of demyelinating disease, such as MS.

CSF analysis revealed oligoclonal immunoglobulin G bands (OlgGBs). The patient's symptoms improved after she received methylprednisolone. She was diagnosed with MS and given interferon- β -1b. Her Expanded Disability Status Scale remained at 1.5, and she has been kept on immunomodulatory therapy. Based on her family history, we ordered serum VLCFA dosage, which was elevated.

Faculdade de Medicina (ARBdP, FK), Hospital das Clínicas, University of São Paulo; and Neurology Service (CRPF, AMP, CHFC) and Radiology Unit (FSF), Hospital Universitário, State University of Ponta Grossa, Brazil.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

(A, B) Sagittal T2–fluid-attenuated inversion recovery (FLAIR) images show elongated hyperintense lesions in the white matter oriented perpendicularly to the ependymal surface of the lateral ventricles that are very similar to those found in the classic presentation of multiple sclerosis (MS). (C, D) Axial T1- and T2-FLAIR images show lesions in the brainstem. As in the sagittal T2-FLAIR images, these lesions have an elongated morphology very similar to that observed in the classic presentation of MS. There is no contrast uptake (C). (E) Axial postcontrast T1 image shows annular contrast uptake in a lesion close to the atrium of the lateral ventricle very similar to the uptake pattern observed in MS. (F) Coronal T2 image with lesions in the white matter, brainstem, and cerebellum.

Discussion

The clinical and laboratory findings for our patient were fairly typical of relapsing-remitting MS, but she also had VLCFA accumulation, confirming an X-ALD carrier status. The patient met the diagnostic criteria and responded to pulse methylprednisolone therapy. Unlike other cases of X-ALD in women described previously, this patient did not present spastic paraparesis, and her cerebral symptoms were exceedingly rare for a woman with X-ALD.^{4,6} Her symptoms manifested in 2 clearly defined relapses. Brain MRI also showed multifocal supratentorial and infratentorial white matter changes at various stages, including a gadolinium-enhanced lesion.

In X-ALD, as in MS, MRI findings vary. In more typical cases, these include signs of demyelination starting at the splenium of the corpus callosum with intermediate areas of demyelination and perivascular inflammation, particularly in the frontal, parietal, and occipital lobes. Changes in the corticospinal tract and gadolinium enhancement may also occur. However, only a small proportion of women present with this number of signs of the disease in the brain.^{1,4} While in MS there is usually multifocal demyelination, X-ALD is characterized by extensive confluent demyelination. MRI in MS usually shows multifocal lesions disseminated in the periventricular, juxtacortical, and

infratentorial compartments and can also reveal spinal cord involvement. The lesions, which are very common in the callosal–septal interface, are usually small, elongated, and oriented perpendicularly to the pial surface of the ventricular system or the cortical surface of the brain. MRI findings can also include acute gadolinium-enhanced lesions. These may disappear over time, with little damage to the underlying parenchyma, or may evolve to pronounced tissue damage, usually with axonal damage, and black holes may be seen. To confirm a diagnosis of MS, imaging findings should show dissemination of the lesions in space and time.⁷ In adult-onset X-ALD, a wide range of MRI abnormalities can be seen. These may be restricted to the pyramidal tracts or be diffuse, involving the cerebral hemispheres, posterior limbs of the internal capsules, brainstem, and cerebellum. In this subgroup in particular, it is not uncommon for X-ALD to be misdiagnosed as MS.¹

Another confounding factor in the diagnosis was the finding of OIGGBs, which are common in patients with MS, but this is not specific and can also be present in patients with X-ALD.³ Adrenocortical insufficiency is rare in women (1%), and our patient tested negative.

Obeying Occam's razor, strictly adhering to available diagnostic criteria, is often the best principle to disentangle misleading findings.

Author contributions

A.R. Brandão de Paiva: analysis and interpretation of the data, drafting and revising the manuscript for intellectual content. C.R. Pucci Filho: analysis and interpretation of the data, drafting the manuscript for intellectual content. A. Monteiro Porto: analysis and interpretation of the data. F.S. Feltrin: analysis and interpretation of the data, drafting the manuscript for intellectual content. F. Kok: revising the manuscript for intellectual content. C.H. Ferreira Camargo: design and conceptualization of the study, analysis and interpretation of the data, revising the manuscript for intellectual content.

Study funding

No targeted funding reported.

Disclosure

A.R. Brandão Paiva, C.R. Pucci Filho, A. Monteiro Porto, and F.S. Feltrin report no disclosures. F. Kok serves on the editorial advisory board of *Arquivos de Neuropsiquiatria*; is author on a patent re: Methylmalonic acid determination by tandem mass spectrometry using stable isotope; is Medical Director of

Mendelics Genomic Analysis, a NGS laboratory, since 2013; has received speaker honoraria from Actelion Pharmaceuticals; and is a shareholder in Mendelics Genomic Analysis. C. H. Ferreira Camargo reports no disclosures. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Received September 6, 2017. Accepted in final form November 6, 2017.

References

1. Kumar AJ, Kohler W, Kruse B, et al. MR findings in adult-onset adrenoleukodystrophy. *AJNR Am J Neuroradiol* 1995;16:1227–1237.
2. Minguetti G. Magnetic resonance imaging in multiple sclerosis: analysis of 270 cases. *Arq Neuropsiquiatr* 2001;59:563–569.
3. Jenkins T, Sarasamma P, Gillett G, Coley S, Sharrack B. Multiple sclerosis in an adrenoleukodystrophy carrier. *Clin Pract* 2011;1:e125.
4. Di Filippo M, Luchetti E, Prontera P, et al. Heterozygous X-linked adrenoleukodystrophy associates myelopathy mimicking primary progressive multiple sclerosis. *J Neurol* 2011;258:323–324.
5. Engelen M, Barbier M, Dijkstra IME, et al. X-linked adrenoleukodystrophy in women: a cross-sectional cohort study. *Brain* 2014;137:693–706.
6. Jack GH, Malm-Willadsen K, Frederiksen A, Glintborg D, Andersen M. Clinical manifest X-linked recessive adrenoleukodystrophy in a female. 2013. *Case Rep Neurol Med* 2013;2013:491790.
7. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Ann Neurol* 2016;69:292–302.

Practical Implications

Neurology® Clinical Practice is committed to providing clinical insights helpful to neurologists in everyday practice. Each Full Case includes a “Practical Implications” statement, a pearl of wisdom for the practicing clinician.