Consultant360 Multidisciplinary Medical Information Network

PHOTOCLINIC

PEER REVIEWED

A Case of X-Linked Adrenoleukodystrophy

Tiffany Hnatow, MD; Nunilo Rubio, MD; Monaliza Evangelista, MD; David Rodriguez-Buritica, MD; and Michael Yafi, MD

Department of Pediatrics, University of Texas Medical School at Houston

A 5-year-old boy with no past medical history presented to the emergency department with a 6-month history of nausea and vomiting and a 3-week history of lower extremity weakness, foot dragging with gait disturbance, slurred speech, vision difficulties, and drooling.

He had been born at full term via cesarean delivery and had no developmental delays. His family history was remarkable for a maternal uncle with multiple sclerosis who had died at age 12.

Physical examination. The patient was alert, smiling, and interactive. His pupils were equally round and reactive to light, with extraocular movements intact. Cardiac, pulmonary, and abdominal examinations were normal. His speech was dysarthric, and his gait was ataxic with decreased strength in his lower extremities.

A magnetic resonance imaging (MRI) scan of the brain demonstrated bilateral posterior white matter changes with extension into the corticospinal tracts suspicious for leukodystrophy (**Figure**).

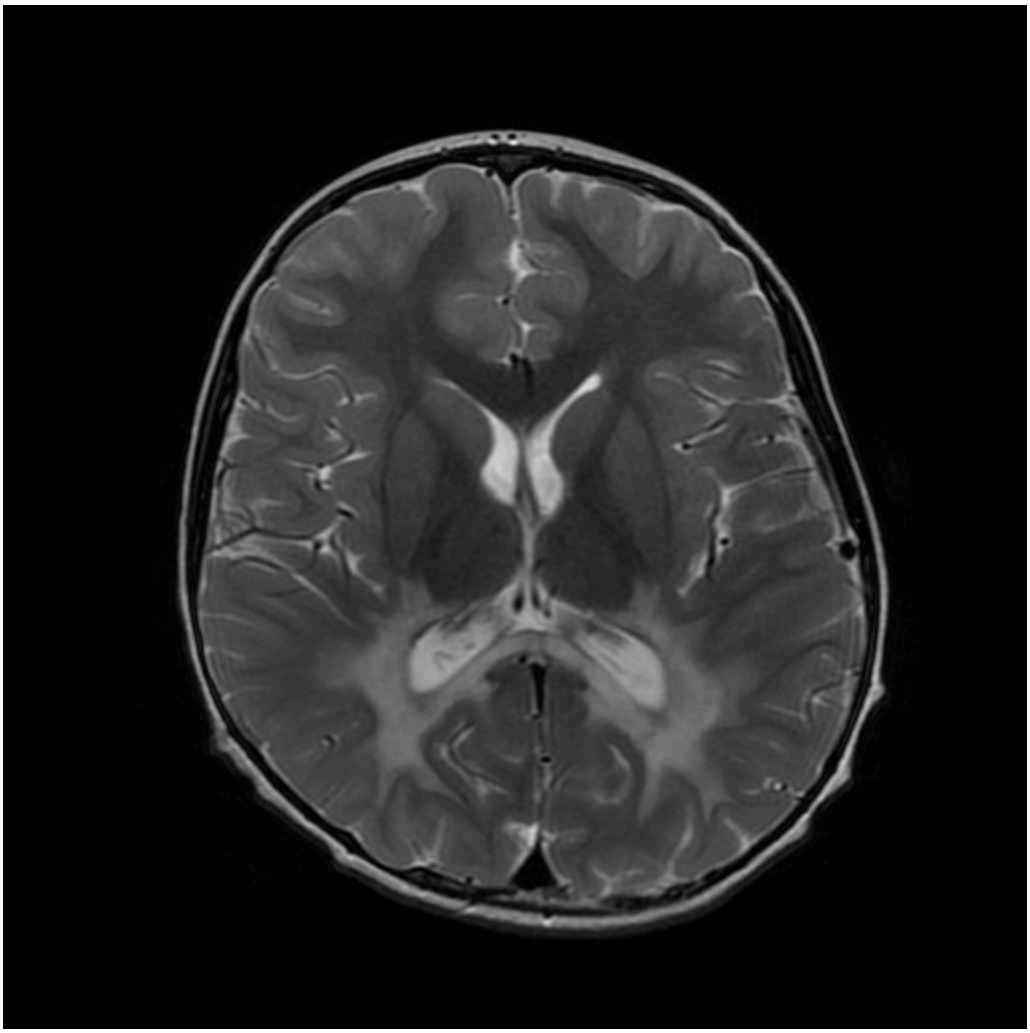

Figure. *Contrast-enhancing regions suggestive of active demyelination involving bilateral deep parietal as well as periventricular white matter and involving the posterior body and splenium of corpus callosum, bilateral posterior thalamocapsular regions with extension along the white matter tracts in the brainstem.*

Pediatric neurology, endocrinology, physical medicine and rehabilitation, and genetics specialists were consulted due to the high suspicion for X-linked adrenoleukodystrophy (X-ALD). Adrenocorticotropic hormone (ACTH) level was markedly elevated, with a low-normal cortisol level and mildly elevated plasma very-long-chain fatty acids (VLCFA), suggestive of X-ALD. The patient was started on prednisolone for adrenal insufficiency. He was transferred to another facility for further testing and stem cell transplantation. Despite engraftment, he continued to have significant neurologic decline and now has a life expectancy of less than 6 months—about 1 year from the onset of symptoms.

Discussion

X-ALD is a peroxisomal disorder affecting β-oxidation of VLCFA, resulting in its accumulation in plasma and tissues, particularly in cerebral white matter, the spinal cord, and the adrenal cortex.[1,2] All affected persons possess a mutation in the ATP-binding cassette subfamily D

member 1 gene (*ABCD1*) that encodes the adrenoleukodystrophy protein (ALDP), which transports VLCFA-coenzyme A into the peroxisome, where it can undergo β-oxidation. A deficiency of ALDP allows for an accumulation of VLCFA.[1] The mechanism by which elevated VLCFA levels results in the various phenotypes is not known, but it is speculated that it is due to the induction of oxidation stress and apoptosis in combination with disruption of the cell membranes.[3]

The 2 main forms of X-ALD are cerebral ALD and adrenomyeloneuropathy (AMN).[2] Cerebral ALD is a rapidly progressive inflammatory demyelination that results in devastating neurologic deterioration within 2 to 5 years of onset of symptoms. This phenotype typically presents in children aged 5 to 12 years with initial symptoms of hyperactive behavior or decline in school performance that is misdiagnosed as attention deficit disorder.[1] Patients then develop ataxia, dysarthria, dysphagia, visual field defects, and epileptic seizures.

AMN is the most common phenotype of X-ALD and usually presents between ages 20 and 30 years. It is characterized by a slow, progressive development of spastic paraparesis, incontinence, and erectile dysfunction.[2] Although this is an X-linked recessive disorder, greater than 80% of female carriers develop myelopathy by age 60 years.[1] X-ALD is also associated with the development of adrenal insufficiency, affecting 86% of hemizygous males and less than 1% of heterozygous female carriers. These patients present with fatigue, anorexia, nausea, vomiting, loss of appetite, poor weight gain or weight loss, abdominal symptoms, and skin hyperpigmentation. Patients with adrenal crisis may present with hypotension, hypoglycemia, or altered mental status. X-ALD has an incidence of 1 in 17,000 and has been reported in patients of all ethnicities.

X-ALD is diagnosed based on key clinical features, radiologic findings, and elevated plasma VLFCA levels. Typical MRI findings of cerebral ALD involve gadolinium-enhancing demyelinating lesions. Early detection of ALD is important because it increases the chance of early treatment to decrease disease progression.[1,3] Given the presence of symptomatic males on the maternal side, the patient's mother is likely a carrier of an *ABCD1* pathogenic variant, with a 50% chance of passing it on to her offspring. Genetic counseling and molecular genetic testing are important to determine the status of at-risk relatives and potentially discover presymptomatic cases of X-ALD.[4]

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only treatment for cerebral ALD.[5] However, the outcome is poor unless treatment is initiated at an early stage of the disease, and successful HSCT does not prevent the development of AMN in adulthood.[1] Lorenzo's oil is a dietary therapy that lowers plasma VLCFA levels, but it has not been shown to prevent or reverse the progression of X-ALD. Lorenzo's oil and HSCT do not reverse or prevent

adrenal insufficiency. Glucocorticoid supplementation is necessary for the treatment of adrenal insufficiency.

Conclusion

In young, particularly male patients with neurologic decline, adrenal insufficiency, and a family history of early death due to a neurologic disorder, clinicians should have high suspicion for X-ALD. Early diagnosis and intervention are paramount for optimal prognosis.

References:

1. Kemp S, Huffnagel IC, Linthorst GE, Wanders RJ, Engelen M. Adrenoleukodystrophy—neuroendocrine pathogenesis and redefinition of natural history. *Nat Rev Endocrinol.* 2016;12(10):606-615.

2. Kemp S, Berger J, Aubourg P. X-linked adrenoleukodystrophy: clinical, metabolic, genetic and pathophysiological aspects. *Biochim Biophys Acta*. 2012;1822(9):1465-1474.

3. Burtman E, Regelmann MO. Endocrine dysfunction in X-linked adrenoleukodystrophy. *Endocrinol Metab Clin North Am.* 2016;45(2):295-309.

4. Steinberg SJ, Moser AB, Raymond GV. X-linked adrenoleukodystrophy. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. *GeneReviews*. Seattle, WA: University of Washington, Seattle. https://www.ncbi.nlm.nih.gov/books/NBK1315. Published March 26, 1999. Updated April 9, 2015. Accessed August 17, 2017.

5. Engelen M, Kemp S, Poll-The B-T. X-linked adrenoleukodystrophy: pathogenesis and treatment. *Curr Neurol Neurosci Rep*. 2014;14(10):486.