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Clinical Letter

# Unusual Clinical Course and Imaging of D-Bifunctional Protein Deficiency, a Rare Leukodystrophy

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## Introduction

D-bifunctional protein deficiency is a rare disease caused by failure of peroxisomal fatty acid beta-oxidation. We present a case of D-bifunctional protein deficiency with two significant features of interest: an atypical clinical course of juvenile onset with rapid progression, which is more characteristic of infantile onset, and an imaging appearance mimicking X-linked adrenoleukodystrophy.

## Patient Description

This six-year-old girl, previously healthy and developmentally appropriate, presented to the emergency department with developmental regression. She was evaluated for a one-month history of progressively worsening confusion, urinary incontinence, slurred speech, and unsteady gait. She had difficulty performing simple tasks and following directions. Computed tomography of the head demonstrated symmetric cerebral white matter and thalamic hypodensity. Magnetic resonance imaging (MRI) of the brain (Fig.) demonstrated restricted diffusion in the parietal white matter (A) and bilateral extensive T2/fluid-attenuated inversion recovery (FLAIR) hyperintense signal predominantly in the parieto-occipital lobes and corpus callosum (B). Extensive laboratory evaluation including oligosaccharides and mucopolysaccharides screen, cortisol level, very long chain fatty acid profile, lysosomal enzymes screen, and congenital disorder of glycosylation studies. All returned within normal limits. Electromyogram and nerve conduction studies were normal. Ophthalmologic examination was normal. Targeted exome sequencing focused on genes associated with leukodystrophy showed three variants of uncertain significance in the *AUH, DARS*, and *POLG* genes, not thought to be causative of our patient's symptoms. Our patient was ultimately diagnosed via whole exome sequencing with D-bifunctional protein deficiency, with one likely pathogenic variant, c.936_937delTA (p.T313X), and one variants of uncertain significance, c.1148A > G (p.Q383R), in the *HSD17B4* gene. Subsequent MRI obtained five months after initial presentation demonstrated new areas of restricted diffusion in the deep gray matter (C) and marked progression of the abnormal white matter signal continuing to advance more

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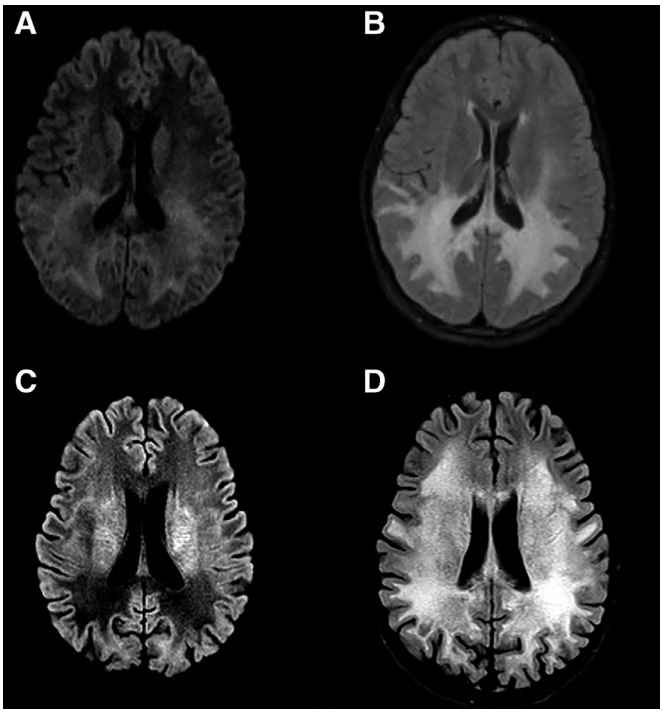


**FIGURE.** Diffusion-weighted imaging (DWI) of the initial MRI of the brain (A) demonstrates restricted diffusion of the parietal white matter including the subcortical U fibers. Initial FLAIR image (B) demonstrates extensive hyperintense signal in the biparietal white matter. DWI at five-month follow-up (C) demonstrates resolution of initial areas of restricted diffusion, but new involvement of the deep gray matter. FLAIR image at five-month follow-up (D) demonstrates extensive progression of the signal abnormality, now with involvement of the frontal white matter.

anteriorly and peripherally (D). Clinically, the patient continued to rapidly decline, with visual impairment, seizure disorder, wheelchair dependence, and feeding intolerance requiring gastrostomy tube placement within nine months of the disease onset.

## Discussion

D-bifunctional protein deficiency, also known as peroxisomal bifunctional enzyme deficiency, is an autosomal recessive disease caused by biallelic mutations of the *HSD14B4* gene. The disease typically presents with neonatal onset and rapid progression. Presenting symptoms include failure to thrive, seizures, and hypotonia.[1] Juvenile onset with slow progression is atypical but has also been reported. The later presentation and slower decline is theorized to be due to residual enzyme activity in these patients.[2] This patient is the first to demonstrate rapid deterioration following presentation beyond the neonatal period.

This girl's imaging features are also of interest. One male neonate also demonstrated the pattern of demyelination classically associated with X-linked adrenoleukodystrophy (X-linked ALD) but was ultimately diagnosed with D-bifunctional protein deficiency.[3] X-linked ALD, like D-bifunctional protein deficiency, features deficient beta-oxidation in peroxisomes. X-linked ALD occurs in approximately 1:20,000 births and is caused by a mutation of the *ABCD1* gene on the X chromosome.[4] The typical cerebral ALD pattern seen in males is exceedingly rare in females. We propose that D-bifunctional protein deficiency must be considered in the symptomatic female pediatric patient presenting with imaging features of X-linked ALD.

## References

1. Nascimento J, Mota C, Lacerda L, et al. D-bifunctional protein deficiency: a cause of neonatal onset seizures and hypotonia. *Pediatr Neurol*. 2015;52:539–543.
2. Lines MA, Jobling R, Brady L, et al. Peroxisomal D-bifunctional protein deficiency: three adults diagnosed by whole-exome sequencing. *Neurology*. 2014;82:963–968.
3. Khan A, Wei XC, Snyder FF, et al. Neurodegeneration in D-bifunctional protein deficiency: diagnostic clues and natural history using serial magnetic resonance imaging. *Neuroradiology*. 2010;52:1163–1166.
4. Engelen M, Kemp S, de Visser M, et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. *Orphanet J Rare Dis*. 2012;7:51.