RESIDENT & FELLOW SECTION

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Child Neurology: Two sisters with dystonia and regression

PLA2G6-associated neurodegeneration

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CLINICAL CASE, PART 1 A 19-month-old girl presented for neurologic consultation for delayed walking. She rolled at 6 months, sat unsupported at 8 months, but never walked independently. She babbled only. Her examination was notable for slightly decreased bulk in her legs, mild truncal hypotonia, and decreased deep tendon reflexes. She had difficulty pulling to stand and could only walk with support. She exhibited a steppage gait with hyperextension of her knees, exaggerated lifting of her feet, and out-turning of her ankles. Birth history was unremarkable and parents were not consanguineous. A head CT performed at 13 months for mild head trauma was normal.

The initial diagnostic workup was directed at causes of gait abnormality and developmental delay. Initial metabolic screening labs, including serum lactate/pyruvate, amino acids, creatine phosphokinase, carnitine, lipid panel, and coenzyme Q10 profile, were normal. MRI of the spine was normal. At age 23 months, brain MRI showed new mild to moderate cerebellar atrophy and minimal brainstem volume loss (figure).

By age 26 months, the patient developed pain and dystonia in her legs. On examination, she had striatal toes (spontaneous extensor plantar response without fanning of the toes) and continued decreased deep tendon reflexes. She could no longer stand, although she still crawled. Repeat brain MRI at 29 months showed progressive cerebellar volume loss.

By age 31 months, she developed a mild spastic quadriparesis and continued to have significant painful dystonic posturing of lower extremities. Developmental regression continued. She was no longer able to sit independently or crawl and only made occasional sounds. She developed bilateral optic atrophy and intermittent left esotropia.

Differential diagnosis. Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.[1] The differential diagnosis for dystonia in children is broad (table e-1 on the *Neurology*® Web site at Neurology.org) but can be narrowed by presence of other neurologic manifestations. Dystonia associated with cerebellar atrophy and developmental delay or regression is concerning for an inherited neurodegenerative process. Etiologies to consider include neurodegeneration with brain iron accumulation (NBIA), neuronal ceroid lipofuscinosis, pontocerebellar hypoplasia, Rett syndrome, Wilson disease, and Leigh syndrome or other mitochondrial diseases.

CLINICAL CASE, PART 2 Genetic testing results included normal karyotype and interstitial duplication of 129 kb of DNA at 17q21.31, likely benign, on chromosomal microarray. The Cerebellar/Pontocerebellar Hypoplasia Sequencing Panel (University of Chicago Genetic Services Laboratory, 2013) detected no pathogenic variants. Copper and ceruloplasmin were normal. Mitochondrial DNA (mtDNA) Deletion/Duplication and mtDNA Common Mutation Panels (Cincinnati Children's Molecular Genetics Laboratory, 2014) showed no abnormalities.

Continued hyporeflexia and pain, and new intermittent episodes of leg flushing, raised concern for peripheral neuropathy. This, in conjunction with regression, dystonia, and MRI findings, prompted sending the NBIA Sequencing Panel (University of Chicago Genetic Services Laboratory, 2014) at age 33 months. The panel showed 2 mutations in the *PLA2G6* gene (*PLA2G6* c.1674del and *PLA2G6* c.2370T>G), both pathogenic variants previously described in *PLA2G6*-related disorders.[2,3] Based on the phenotype (clinical history, neurologic examination, and neuroimaging), the patient was diagnosed with the infantile neuroaxonal dystrophy (INAD) subtype of *PLA2G6*-associated neurodegeneration (PLAN). At the time of diagnosis the patient had 2 younger siblings, one of whom was displaying signs of developmental regression. Given the patient's family history, her classic presentation, and the identification of 2 previously reported pathogenic variants, parental genetic testing was not thought necessary. Genetic counseling was provided.

The patient was prescribed docosahexaenoic acid (DHA) 250 mg per day. During the 18 months following diagnosis, she continued to have dystonia,

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From the Department of Neurology, Cincinnati Children's Hospital Medical Center, OH.
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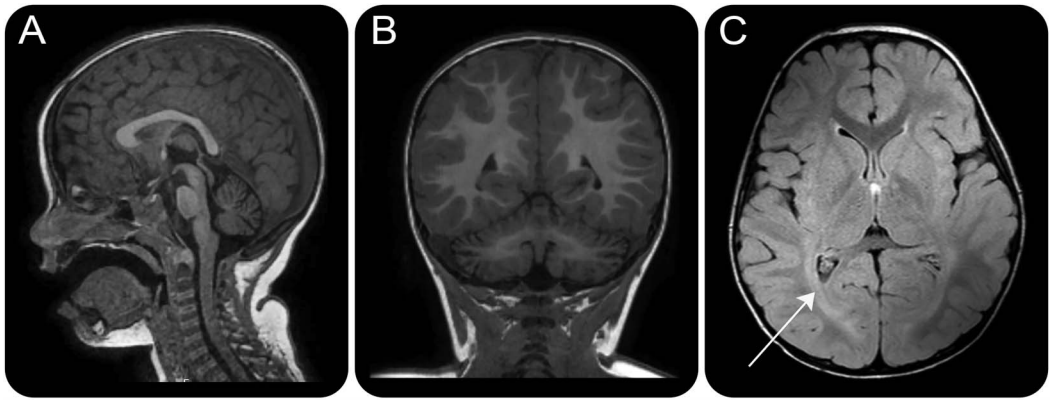
Figure Brain MRIs from patient in case presentation



T1-weighted images at age 23 months in midsagittal (A) and coronal (B) views demonstrate atrophy of vermis and cerebellar hemispheres and minimal brainstem volume loss. Axial fluid-attenuated inversion recovery image at age 33 months (C) shows nonspecific white matter changes (arrow), but no sign of iron deposition or other signal abnormality in basal ganglia.

tight heel cords, and lower extremity pain, which were treated symptomatically with baclofen, trihexyphenidyl, gabapentin, diazepam, and tramadol. After video swallow study showed silent aspiration, a gastrostomy tube was placed. She developed epilepsy with occasional generalized tonic-clonic seizures. Sleep study showed brief central and obstructive sleep apnea, and she was placed on overnight oxygen. Her last brain MRI, performed at age 33 months, showed stable volume loss in the cerebellum and brainstem, subtle nonspecific hyperintense T2/fluid-attenuated inversion recovery signal in the supratentorial white matter, but no radiographic evidence of brain iron accumulation (figure). Palliative services were engaged, and the patient expired at age 4 years from respiratory causes.

The patient's younger sister developed motor delays by age 1 year. By age 2, the younger sister could not walk independently, displayed a steppage gait when supported, and spoke only 2 recognizable words. Over the next few months, she regressed in motor and language skills and developed dystonia in her lower extremities. A brain MRI showed cerebellar volume loss similar to her sister's. Given the similar phenotype, she was given a presumptive diagnosis of PLAN.

DISCUSSION PLAN, also known as NBIA2, is a rare autosomal recessive disorder first reported by Seitelberger[4] in 1952 and later clinically defined by Aicardi and Castelein[5] in 1979. The incidence of PLAN is unknown. It falls in the broader disease category of NBIA. NBIA is a heterogeneous group of rare diseases characterized by progressive extrapyramidal symptoms, intellectual impairment, and excessive iron deposition in the brain, especially the globus pallidus. The 2 most common NBIA diseases are pantothenate kinase–associated neurodegeneration (PKAN, also known as NBIA1), which accounts for approximately 50% of all NBIA cases, and PLAN, which accounts for about 20%.[6] Because of the rarity of NBIA, knowledge of the clinical characteristics, response to treatment, and prognosis are based mostly on case series.

PLAN has 3 distinct clinical phenotypes.[6,7] The first, often referred to as *infantile neuroaxonal dystrophy* or INAD, typically presents between 6 months and 3 years of age with neurodevelopmental arrest and then devastating regression in all domains. Motor symptoms include early truncal hypotonia, limb dystonia, and eventual development of spastic quadriparesis. Many children develop an axonal-type sensorimotor neuropathy with hyporeflexia and paresthesias. Cerebellar ataxia commonly but not invariably develops. Early visual disturbances due to optic atrophy occur in the form of strabismus, nystagmus, and eventual blindness. Seizures occur in up to 17% of patients. Most children with INAD die before age 10 years.

A second phenotype referred to as atypical neuroaxonal dystrophy presents between early childhood and the end of the second decade. It has a slower progression than INAD and presents with heterogeneous clinical features including language difficulties, autism spectrum disorder, eye movement abnormalities, spastic quadriparesis, and progressive dystonia and dysarthria.[6]

A third phenotype called *PLA2G6*-related dystonia-parkinsonism has been described. Patients with this phenotype present between childhood and the third decade of life and experience dystonia, bradykinesia, rigidity, and marked cognitive decline.[6]

In contrast, the more well-known PKAN typically presents in the first decade of life with gait disturbance, dystonia, rigidity, and dysarthria. Slow progression leads to loss of ambulation within 15 years.

PKAN is not typically associated with ataxia or peripheral neuropathy, and visual disturbances occur primarily due to pigmentary retinopathy.[6]

Brain MRI shows cerebellar atrophy in virtually all well-established PLAN cases. Other neuroimaging findings are more variable. Diffuse T2 white matter hyperintensities, thinning of corpus callosum, and thinning of the optic nerves and chiasm are commonly seen. Unlike PKAN, in which the majority of patients will have the classic "eye of the tiger" sign in globus pallidus, the neuroradiologic evidence of iron deposition in PLAN is much more variable. Many patients with advanced PLAN never have clear radiographic evidence of brain iron accumulation. The gold standard for diagnosis of PLAN used to be demonstration of dystrophic axonal spheroids in nerve and conjunctival biopsies. Now most diagnoses are confirmed through the detection of mutations in the *PLA2G6* gene.

The *PLA2G6* gene, located on chromosome 22q13, encodes the protein iPLA2-beta, which is a subunit of the calcium-independent phospholipase A_2 enzyme. Phospholipase A_2 is important in the synthesis of free fatty acids and lysophospholipids. A recent study demonstrated that loss of normal *PLA2G6* activity leads to elevated mitochondrial lipid peroxidation, mitochondrial dysfunction, and subsequent mitochondrial membrane abnormalities.[8] Mouse models of PLAN reveal decreased incorporation of DHA into the brain.[9] DHA is a precursor of anti-inflammatory neuroprotectins, and decreased brain DHA metabolism may increase vulnerability to neuroinflammation. However, it remains unclear how these disturbances lead to brain iron accumulation or the clinical findings seen in PLAN. There is not a clear correlation between specific *PLA2G6* gene mutations and clinical presentation.

The standard of care for PLAN is supportive care and symptomatic treatment of dystonia, spasticity, and epilepsy. There is no disease-specific treatment for PLAN. Some current clinical trials are evaluating treatment of NBIA with iron chelators,[10] but most only enroll patients with PKAN. Some centers have treated individual patients with supplementary DHA, although efficacy is unclear and results have not been published. Multinational consortia will be needed to enroll sufficient numbers of patients for any treatment trials of this rare disease.

CONCLUSION PLAN is a form of NBIA that should be considered in any child with developmental regression, especially when associated with dystonia, truncal hypotonia, peripheral neuropathy, ataxia, visual disturbance, and/or cerebellar atrophy. The lack of radiographic evidence of iron accumulation, especially early in disease course, should not dissuade clinicians from including this rare neurodegenerative disease in their differential.

AUTHOR CONTRIBUTIONS

Robert B. Blake, MD: conceptualized, drafted, and revised the manuscript for intellectual content. Donald L. Gilbert, MD: provided significant revisions of manuscript for intellectual content. Mark B. Schapiro, MD: conceptualized, drafted, and revised the manuscript for intellectual content.

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