Child Neurology: Neurodegenerative Encephalomyelopathy Associated With *ACOX1* Gain-of-Function Variation Partially Responsive to Immunotherapy

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Abstract

Acyl-CoA oxidase 1 (ACOX1) is a peroxisomal enzyme involved in beta-oxidation of very-long-chain fatty acids. Although loss of function of *ACOX1* had been previously described, gain-of-function variation of *ACOX1* gene has been only recently identified, with a paucity of known cases. Gain-of-function variation results in overproduction of reactive oxygen species, resulting in progressive neurodegeneration with discrete relapses. We report the case of a 19-year-old woman with a 5-year history of longitudinally extensive posterior predominant myelopathy, bilateral corneal scars, and white matter lesions who presented with first-time seizure, progressive sensorineural hearing loss, ichthyosiform rash, and cauda equina syndrome. Extensive workup was unrevealing. The patient showed no response to high-dose steroids but stabilization and improvement with return to baseline over 6 months with IVIg and low-dose mycophenolate mofetil. Whole-exome sequencing performed 4 years before was nondiagnostic, but subsequent reanalysis revealed a heterozygous variation in the *ACOX1* gene (NM_004035.6: c.710A>G, p.Asn237Ser), now considered to be pathogenic. This case reports a rare condition and highlights the importance of reanalysis of previously nondiagnostic genome/exome sequencing data. Furthermore, the patient's clinical stability for over 1 year on immunotherapy raises the possibility of disease modification in an otherwise universally fatal condition.

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Fatty acid beta-oxidation is an important function for physiologic homeostasis. Although most beta-oxidation takes place within the mitochondria, the metabolism of very-long-chain fatty acids (VLCFAs) occurs within peroxisomes. The first step is via acyl-CoA oxidase 1 (ACOX1), yielding hydrogen peroxide and producing reactive oxygen species (ROS) as byproducts. Given high energy demands within the CNS, this enzyme is particularly present within glial cells. Dysfunction of this enzyme was thought to be secondary to loss-of–function variation in the *ACOX1* gene (MIM: 264470). This is an autosomal recessive disease characterized by seizures and hypotonia with rapid clinical deterioration.[1-3] The gain-of-function form has only recently been described, with a paucity of cases.[1,4] The clinical presentation, referred to as Mitchell syndrome (MIM: 619860), is an autosomal dominant, progressive degenerative process with sensorineural hearing loss, polyneuropathy, cognitive decline, and seizures.[1,4] This article presents a case of Mitchell syndrome and provides an important reminder to reanalyze genetic data because more pathologic genes are identified annually.

Case Report

A 19-year-old woman presented with progressive neurologic deficits including extremity weakness, sensory deficits, sensorineural hearing loss, and blurred vision. She had an unremarkable birth history and was born full-term via Cesarean section because of maternal preeclampsia. She had an unremarkable childhood except for a severe malar rash diagnosed as eczema in infancy, which improved by age 1 year.

She initially presented at age 14 years with gait instability, frequent falls, and loss of sensation in the lower extremities. Neurologic examination showed diminished vibration and proprioception in the lower extremities with a positive Romberg test. She also had diminished reflexes in the lower extremities. Evaluations including complete metabolic panel, serum vitamin B12, folate, and methylmalonic acid were within normal limits. Infectious workup including rapid plasma reagin and HIV was negative. CSF studies revealed no pleocytosis, normal protein and glucose, negative culture, no oligoclonal bands, and a normal immunoglobulin (Ig) G index.

Spinal neuroimaging demonstrated longitudinally extensive T2 signal hyperintensity throughout the spinal cord, more prominently affecting the dorsal cord. There was no restricted diffusion or contrast enhancement. Brain MRI showed a few punctate T2 hyperintensities (Figure). She was initially treated with IV methylprednisolone, which did not result in any improvement of symptoms. Another MRI 2 weeks later was unchanged.

A repeat lumbar puncture 1 year later, at age 15 years, revealed similarly nondiagnostic CSF. Extensive workup for metabolic diseases, including serum and CSF lactate/pyruvate, amino acids, acyl carnitine profile, and urine organic acids, was unremarkable. A chromosomal microarray was obtained, which was unremarkable. EMG and nerve conduction studies (NCSs) were performed, which were unremarkable except for absent F wave in the lower extremities, and slowed F wave in the upper extremities, consistent with myelopathy. The patient subsequently received IVIg at 2g/kg, which resulted in some return of vibration in the left lower extremity.

The patient underwent an extensive paraneoplastic evaluation. Whole-body imaging did not reveal any neoplasm. The serum paraneoplastic panel was weakly positive for neuronal voltage-gated potassium channels and glutamic acid decarboxylase, which was considered to be clinically insignificant because of recent IVIg administration. She had negative myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies. Repeat neuroimaging 1 month after presentation was stable. The patient also reported progressively blurred vision. Ophthalmologic examination was concerning for bilateral central keratitis and corneal scarring. She received supportive management.

Almost a year later, the patient entered a period of stability of symptoms, which lasted for 3 years. During this time, the patient was using a wheelchair and was dependent on her family for most activities of daily living although she remained cognitively intact. Other investigations included a neuropathy genetic panel that detected a variant of unknown significance (VUS) in the *SBF2* gene (NM_030962.4: c.3283A>G, p.Ser1095Gly), followed by whole-exome sequencing (WES), which detected a VUS in the *COL6A3* gene (NM_004369.3: c.8359G>A, p.Ala2787Thr).

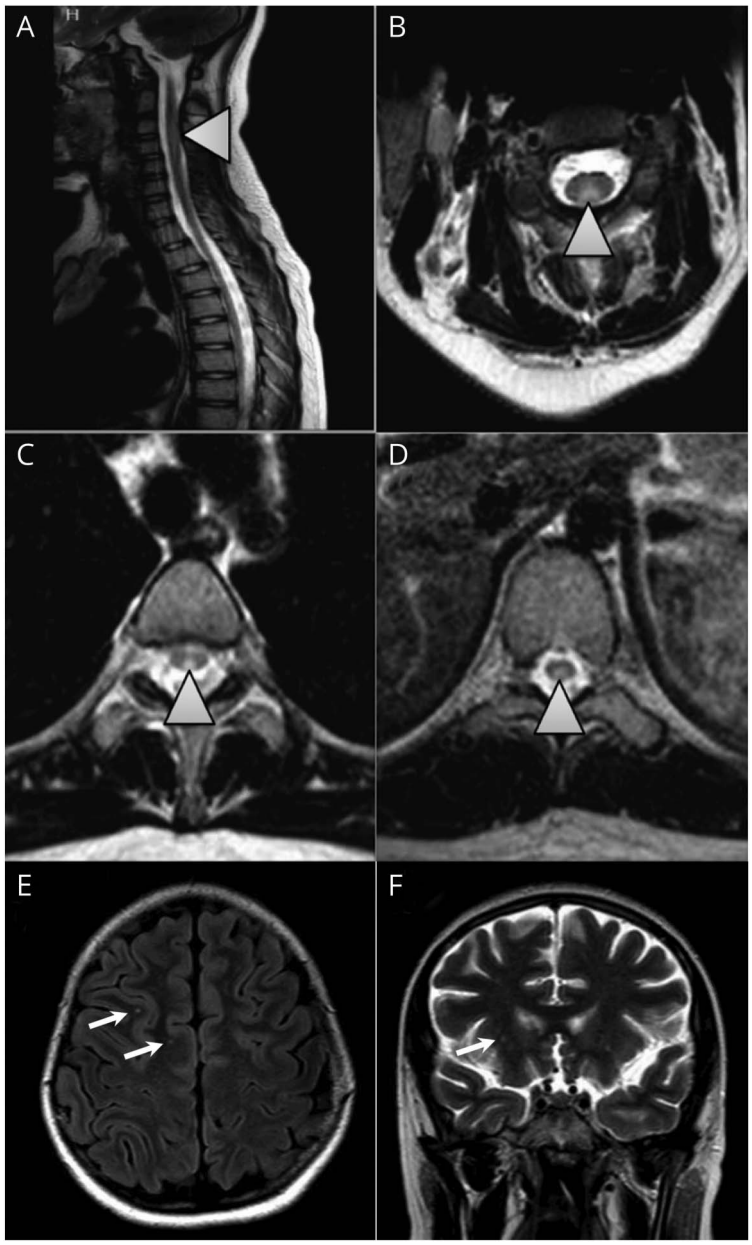
She presented again at age 18 years with an acute generalized erythematous desquamating rash along with conjunctivitis. She was also found to have sensorineural hearing loss. She also had a first-time generalized tonic-clonic seizure. An extensive autoimmune/inflammatory workup was unrevealing, with normal inflammatory markers, including the erythrocyte sedimentation rate, C-reactive protein, ferritin, and cytokine panel. Autoantibodies were negative except for a positive antinuclear antibody (1:640). Serum complements were normal. Congenital disorders of glycosylation and lysosomal enzyme screening were negative. The VLCFA level was normal. She underwent a biopsy of skin lesions, which revealed ichthyosiform dermatitis without evidence of lipid inclusion.

She developed acute onset of urinary retention. Spine MRI showed new enhancement of cauda equina nerve roots. She completed a course of IVIg at 2 g/kg. A repeat NCS showed reduced amplitude and decreased velocity in the lower extremities, consistent with a predominantly axonal neuropathy.

Because of the relapsing-remitting course and the dermatologic manifestations often predating the onset of neurologic symptoms, a trial of immunotherapy regimen was considered, consisting of monthly IVIg, along with mycophenolate mofetil (MMF) at a low dose (300 mg/m^2). These treatments were continued following discharge.

A reanalysis of her WES in 2021, 4 years after the initial study, showed a heterozygous variation in the *ACOX1* gene

Figure Contiguous T2 Signal Hyperintensity Affecting the Dorsal Columns of the Entire Spinal Cord (Arrowheads)



Sagittal view (A). Axial views at the upper cervical (B), upper thoracic (C), and lower thoracic (D) levels. Brain MRIs showing punctate T2/FLAIR hyperintensities within supratentorial white matter (arrows; E: axial T2/FLAIR, F: coronal T2). FLAIR = fluid-attenuated inversion recovery.

(NM_004035.6: c.710A>G, p.Asn237Ser). At follow-up in July 2021, she was noted for improvement of her lower extremity strength, vision, hearing, and upper extremity functionality. She was also able to discontinue nasogastric (NG) tube feeds and fully eat and drink by mouth without dietary modification. In August 2021, she was started on high-dose N-acetylcysteine (NAC), awaiting Food and Drug Administration authorization for N-acetylcysteine amide (NACA).

Discussion

This case adds to the previous description of a gain-of-function variation of *ACOX1* leading to a progressive neurologic disease. In this patient, the diagnosis remained unclear despite extensive workup and WES initially performed in 2017. After reanalysis of WES in 2021, we identified the gain-of-function variation of the *ACOX1* gene, which was newly described in 2020.[1] Our patient's presentation and course were consistent with those of the previously reported patients with a similar variation (Table).[1]

The pathophysiology of this disease is believed to be via excessive ROS.[1] The use of NACA has been demonstrated in drosophila to be beneficial in limiting disease activity through antioxidant effects.[1] Because NACA is not approved for human use, NAC is used instead; however, patients treated in this manner continued to have deterioration believed to be secondary to poor blood-brain barrier penetrance of NAC.[1]

Table Clinical, Diagnostic Characteristics and Treatments for Patients With Gain-of-Function and Loss-of-Function of ACOX1

	ndex patient	Patient 1 (Chung et al.)[1]	Patient 2 (Chung et al.)[1]	Patient 3 (Chung et al.)[1]	Patient 4 (Swartwood et al.)[4]	Study of 22 ACOX-deficient patients[2]
***ACOX1* variant**	GoF (p.N237S)	GoF (p.N237S)	GoF (p.N237S)	GoF (p.N237S)	GoF (p.N237S)	LoF (22 mutations)
Phenotype	Mitchell syndrome (MIM: 618960)	Mitchell syndrome (MIM: 618960)	Mitchell syndrome (MIM: 618960)	Mitchell syndrome (MIM: 618960)	Mitchell syndrome (MIM: 618960)	Peroxisomal ACOX1 deficiency (MIM: 264470)
Onset	14 y	12 y	9 y	3 y	9 y	0–3 y (mean 28 mo)
Presenting symptom	Sensory ataxia	Clumsiness and mild hearing loss	Hearing loss and lower-limb weakness	Diffuse desquamatory rash	Sensorineural hearing loss	Neonatal hypotonia and seizures
Seizure	Present	Not reported	Present	Present	Not reported	91%
Ataxia	Present	Present	Present	Present	Present	Present
Hearing loss	Present	Present	Present	Present	Present	77%
Ocular symptoms	Keratitis and corneal scarring	Xerophthalmia and corneal abrasions	Not reported	Corneal haze	Permanent loss of vision	Impaired vision 38%
Skin rash	Ichthyosiform rash	Keratosis pilaris	Atopic dermatitis	Desquamatory rash	Ichthyosiform rash	Not reported
ICognition	Intact	Intact until last weeks of life	Normal -> impaired	Impaired	Normal -> encephalopathic	Significantly impaired
Survival	20 (still alive)	Death by 19 y	15 y (coma)[a]	9 y (still alive)[a]	Death by 11 y	Mean 5 y (max 10)
Progression	Waxing and waning	Waxing and waning then progressive	Waxing and waning then progressive	Waxing and waning then progressive	Waxing and waning	Severe early on
VLCFA	Normal	Normal	Normal	Normal	Not reported	Accumulation
CSF	Normal	Slightly elevated protein (53)	Elevated protein (118)	Normal	Normal	Not reported
Brain MRI	Few scattered T2 hyperintensities in frontal lobes	Unremarkable, late development of central lesions	T2 hyperintensity in bilateral occipital lobes with meningeal and parenchymal enhancement	Initially enhancement of multiple cranial nerves, later confluent periventricular, deep and subcortical white matter signal abnormalities with cystic leukomalacia	Bilateral periventricular and deep white matter hyperintensities, optic nerves/ chiasm/optic tract enhancement	Abnormal white matter signals
Spinal cord MRI	Dorsal column T2-FLAIR hyperintensity, later new enhancement of cauda equina roots	Cervical to thoracic dorsal column T2 hyperintensity with patchy enhancement	Cervical to lumbar T2 hyperintensity with focal enhancement with nerve root enhancement	Enhancement of thoracic and cauda equina roots	Longitudinally extensive transverse myelitis	Not reported
NCS	Axonal polyneuropathy	Sensorimotor axonal polyneuropathy	Sensorimotor polyneuropathy	Sensorimotor polyneuropathy	Not reported	Not reported

Continued

Table Clinical, Diagnostic Characteristics and Treatments for Patients With Gain-of-Function and Loss-of-Function of ACOX1 *(continued)*

	ndex patient	Patient 1 (Chung et al.)[1]	Patient 2 (Chung et al.)[1]	Patient 3 (Chung et al.)[1]	Patient 4 (Swartwood et al.)[4]	Study of 22 ACOX-deficient patients[2]
Treatments	IVMP, monthly IVIg, mycophenolate mofetil, and oral NAC	IVMP, monthly plasmapheresis and IVIg + weekly methotrexate, rituximab, tocilizumab, oral and IV NAC, and infliximab	IVMP, plasmapheresis, azathioprine, and monthly IVIg	Monthly IVIg, corticosteroid, rituximab and tacrolimus, tofacitinib, anakinra, oral NAC	IVMP, IVIg, azathioprine, rituximab, anakinra, cyclosporine, and NAC	Supportive
Response		Worsening after weaning of steroid/IVIg/plasmapheresis	Mild improvement with azathioprine and monthly IVIg. No additional disease progression over 2 y after discontinuing immune modulation	Resolution of rash and progression of white matter injury	Minimal to no improvement	NA

Abbreviations: ACOX1 = acyl-CoA oxidase 1; FLAIR = fluid-attenuated inversion recovery; IVIg = IV immunoglobulin; IVMP = IV methylprednisolone; NAC = N-acetylcysteine; NCS = nerve conduction study; VLCFA = very-long-chain fatty acid.
[a] As of 2020.

We had initiated MMF at a dose lower than the typical immunosuppressive dose, as suggested by dermatology for treatment of similar skin conditions. However, MMF has been reported to exert antioxidant properties at low doses.[5,6] This has been studied in the setting of renal transplant, where MMF was used to protect against ROS buildup in the setting of tacrolimus.[6] In addition, IVIg has been shown to exert antioxidant and neuroprotective effects in vitro and in vivo.[7] The patient also started several therapies geared toward antioxidant effects such as carnitine and vitamin supplementation (ubiquinol, thiamine, riboflavin, biotin, cyanocobalamin, and cholecalciferol). We hypothesized that the use of therapies that produced an antioxidant effect could be beneficial in slowing progression of disease. As such, she was continued on MMF and IVIg, along with these supplements.

It was notable that while on MMF and IVIg, she had partial improvement of her symptoms and has not had any progression of symptoms. At symptomatic nadir, she had a depressed level of consciousness, oral-motor dysfunction necessitating NG tube feeding, inability to ambulate or with 2/5 strength of lower- and distal-upper extremity strength, blurred vision, and sensorineural hearing loss. At the time of this report, roughly 12 months after initiation of treatment, she is fully alert, engaging in spontaneous and robust conversation, no longer needing an NG tube, and able to ambulate short distances with improvements in strength, vision, and hearing. Outside her period of neurologic quiescence, this is the longest time she has gone without worsening of symptoms and the greatest recovery she has made since her initial presentation. The patient's clinical stability for over 1 year on immunotherapy raises the possibility of utilization in an otherwise universally fatal condition. We acknowledge that it is difficult to know whether this lack of symptom progression is truly a result of treatment or another period of disease quiescence. Because her prior period of quiescence lasted for a few years, time will be needed to assess whether she truly will benefit from this treatment plan.

At present, given the paucity of clinical cases regarding this syndrome, variations in *ACOX1* beyond loss of function are not regularly reported. Time and elucidation of additional cases will be necessary to better understand the clinical course of such patients with gain-of-function *ACOX1* disease.

Learning Points

1. In patients with progressive neurologic disease of unknown etiology, acyl-CoA oxidase 1 variations should be considered in the setting of sensorineural hearing loss, skin rash, and ocular symptoms.
2. Reanalysis of previously performed whole-exome and whole-genome sequencing should be considered if a genetic or neurodegenerative disorder is suspected.
3. Immune-modulating treatments with antioxidant properties, including mycophenolate mofetil and monthly IVIg, could be beneficial in patients with Mitchell syndrome.

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