Child Neurology: Neurodegenerative Encephalomyelopathy Associated With ACOX-1 Gain-of-Function Mutation Partially Responsive to Immunotherapy

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Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
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Mellad Khoshnood: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Jonathan D. Santoro: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Figure Count: 1

Table Count: 1

Search Terms:

Acknowledgment:

Study Funding:
No targeted funding reported.
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 ACOX-1 had been previously described, gain-of-function mutation of ACOX-1 gene has only been recently identified, with a paucity of known cases. Gain of function mutation results in over production of reactive oxygen species, resulting in progressive neurodegeneration with discrete relapses.

We report a 19-year-old-female with a 5-year history of longitudinally extensive posterior predominant myelopathy, bilateral corneal scars, and white matter lesions presented with first time seizure, progressive sensorineural hearing loss, ichthiosyform rash, and cauda equina syndrome. Extensive work-up was unrevealing. The patient had no response to high dose steroids but stabilization and improvement with return to baseline over six months with IVIg and low dose mycophenolate mofetil. WES performed 4 years prior was non-diagnostic, but subsequent reanalysis revealed a heterozygous mutation 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 non-diagnostic genome/exome sequencing data. Further, the patient’s clinical stability for over one year on immunotherapy raises the possibility of disease modification in an otherwise universally fatal condition.
Introduction:

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 (VLCFA) 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 central nervous system (CNS), this enzyme is particularly present within glial cells. Dysfunction of this enzyme was thought to be secondary to loss of function mutations in 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 paper presents a case of Mitchell Syndrome, and provides an important reminder to reanalyze genetic data as more pathologic genes are identified annually.

Case Report:

A 19-year-old female presented with progressive neurological 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 due to maternal pre-eclampsia. She had an unremarkable childhood except for a severe malar rash diagnosed as eczema in infancy, which improved by one year of age.

She initially presented at 14 years of age with gait instability, frequent falls, and loss of sensation in the lower extremities. Neurological examination showed diminished vibration and proprioception in the lower extremities with positive Romberg test. She also had diminished reflexes in the lower extremities. Evaluations including complete metabolic panel, serum vitamin B12, folate, methylmalonic acid were within normal limits. Infectious workup including rapid plasma reagin (RPR) and human immunodeficiency virus (HIV) was negative. Cerebrospinal fluid (CSF) studies revealed no pleocytosis, normal protein and glucose, negative culture, no oligoclonal bands (OCB), and normal IgG 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 1). She was initially treated with intravenous methylprednisolone, which did not result in any improvement of symptoms. Another MRI two weeks later was unchanged.

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

The patient had an extensive paraneoplastic evaluation. Whole-body imaging did not reveal any neoplasm. The serum paraneoplastic panel was weakly positive for neuronal voltage gated potassium channel (VGPC) and glutamic acid decarboxylase (GAD65), which was felt to be clinically insignificant due to recent IVIg administration. She had negative myelin oligodendrocyte glycoprotein (MOG) and aquaporin-4 (AQP-4) antibodies. Repeat neuroimaging one 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 three years. During this time, the patient was wheelchair bound and dependent on family for most activities of daily living although she remained cognitively intact. Other investigations included a neuropathy genetic panel which detected a variant of unknown significance (VUS) in SBF2 gene (NM_030962.4: c.3283A>G, p.Ser1095Gly), followed by whole-exome sequencing (WES), which detected a VUS in COL6A3 gene (NM_004369.3: c.8359G>A, p.Ala2787Thr).

She presented again at 18-years-of-age 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 erythrocyte sedimentation rate, C-reactive protein, ferritin, and cytokine panel. Autoantibodies were negative except for a positive antinuclear antibody (ANA) (1:640). Serum complements were normal. Congenital disorders of glycosylation and lysosomal enzyme screening were negative. VLCFA level was normal. She had 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 2g/kg. A repeat NCS showed reduced amplitude and decreased velocity in lower extremities, consistent with a predominantly axonal neuropathy.

Due to 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/m²). These treatments were continued following discharge.
A re-analysis of her WES in 2021, four years after the initial study, showed a heterozygous mutation in the ACOX1 gene (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 FDA authorization for N-acetylcysteine amide (NACA).

**Discussion:**

This case adds to previous description of gain-of-function mutation 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 re-analysis of WES in 2021, we identified the gain of function mutation of the ACOX1 gene, which was newly described in 2020. Our patient’s presentation and course was consistent with the previously reported patients with a similar mutation (Table 1).

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

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. This has been studied in the setting of renal transplant, where MMF was used to protect against ROS build up in the setting of tacrolimus. In addition, IVIg has shown to exert antioxidant and neuroprotective effects in vitro and in vivo.

The patient also started several therapies geared towards antioxidant effects such as carnitine and vitamin supplementation (ubiquinol, thiamine, riboflavin, biotin, cyanocobalamin, and cholecalciferol). We hypothesized that 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 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 twelve months after initiation of treatment, she is fully alert, engaging in spontaneous and robust conversation, no longer needing an NG-tube, able to ambulate short distances with improvements in strength, vision and hearing. Outside of her period of neurologic quiescence, this is the longest time she has gone without worsening of symptoms and the most recovery she has made since her initial presentation. The patient’s
clinical stability for over one year on immunotherapy raises the possibility of utilization in an otherwise universally fatal condition. We acknowledge it is difficult to know if this lack of symptom progression is truly a result of treatment or another period of disease quiescence. As her prior period of quiescence lasted for a few years, time will be needed to assess if she truly will benefit from this treatment plan.

At present, given the paucity of clinical cases regarding this syndrome, mutations in \textit{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 \textit{ACOX1} disease.
Learning Points

1. In patients with progressive neurologic disease of unknown etiology, Acyl-CoA oxidase 1 mutations should be considered in the setting of sensorineural hearing loss, skin rash and ocular symptoms.
2. Re-analysis 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.

References


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**Figure 1.** 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 MRI images showing punctate T2/FLAIR hyperintensities within supratentorial white matter (arrows) (E: Axial T2/FLAIR, F: Coronal T2).
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<th>Table 1. Clinical, diagnostic characteristics and treatments for patients with gain-of-function and loss-of function of ACOX-1</th>
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* As of 2020.
ACOX-1: Acyl-CoA Oxidase 1
IVIG: intravenous immunoglobulin
IVMP: intravenous methylprednisolone
NAC: N-Acetylcysteine
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Neurology published online June 17, 2022
DOI 10.1212/WNL.0000000000200935

This information is current as of June 17, 2022

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