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

Saba Jafarpour, MD,* Mellad Khoshnood, MD,* and Jonathan D. Santoro, MD

Neurology® 2022;99:341-346. doi:10.1212/WNL.0000000000200935

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.
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 (lg) 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 IV Ig 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 IV Ig 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 IV Ig 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 IV Ig, along with mycophenolate mofetil (MMF) at a low dose (300 mg/m²). 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.
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>
<thead>
<tr>
<th>Index patient</th>
<th>Patient 1 (Chung et al.)</th>
<th>Patient 2 (Chung et al.)</th>
<th>Patient 3 (Chung et al.)</th>
<th>Patient 4 (Swartwood et al.)</th>
<th>Study of 22 ACOX-deficient patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>14 y</td>
<td>12 y</td>
<td>9 y</td>
<td>3 y</td>
<td>9 y</td>
</tr>
<tr>
<td><strong>Presenting symptom</strong></td>
<td>Sensory ataxia</td>
<td>Clumsiness and mild hearing loss</td>
<td>Hearing loss and lower-limb weakness</td>
<td>Diffuse desquamatory rash</td>
<td>Sensorineural hearing loss</td>
</tr>
<tr>
<td><strong>Seizure</strong></td>
<td>Present</td>
<td>Not reported</td>
<td>Present</td>
<td>Present</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Ataxia</strong></td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Hearing loss</strong></td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Ocular symptoms</strong></td>
<td>Keratitis and corneal scarring</td>
<td>Xerophthalmia and corneal abrasions</td>
<td>Not reported</td>
<td>Corneal haze</td>
<td>Permanent loss of vision</td>
</tr>
<tr>
<td><strong>Skin rash</strong></td>
<td>Ichthyosiform rash</td>
<td>Keratosis pilaris</td>
<td>Atopic dermatitis</td>
<td>Desquamatory rash</td>
<td>Ichthyosiform rash</td>
</tr>
<tr>
<td><strong>Cognition</strong></td>
<td>Intact</td>
<td>Intact until last weeks of life</td>
<td>Normal -&gt; impaired</td>
<td>Impaired</td>
<td>Normal -&gt; encephalopathic</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td>20 (still alive)</td>
<td>Death by 19 y</td>
<td>15 y (coma)*</td>
<td>9 y (still alive)*</td>
<td>Death by 11 y</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>Waxing and waning</td>
<td>Waxing and waning then progressive</td>
<td>Waxing and waning then progressive</td>
<td>Waxing and waning then progressive</td>
<td>Waxing and waning</td>
</tr>
<tr>
<td><strong>VLCFA</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>CSF</strong></td>
<td>Normal</td>
<td>Slightly elevated protein (53)</td>
<td>Elevated protein (118)</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Brain MRI</strong></td>
<td>Few scattered T2 hyperintensities in frontal lobes</td>
<td>Unremarkable, late development of central lesions</td>
<td>T2 hyperintensity in bilateral occipital lobes with meningeal and parenchymal enhancement</td>
<td>Initially enhancement of multiple cranial nerves, later confluent periventricular, deep and subcortical white matter signal abnormalities with cystic leukomalacia</td>
<td>Bilateral periventricular and deep white matter hyperintensities, optic nerves/ chiasm/optic tract enhancement</td>
</tr>
<tr>
<td><strong>Spinal cord MRI</strong></td>
<td>Dorsal column T2-FLAIR hyperintensity, later new enhancement of cauda equina roots</td>
<td>Cervical to thoracic dorsal column T2 hyperintensity with patchy enhancement</td>
<td>Cervical to lumbar T2 hyperintensity with focal enhancement with nerve root enhancement</td>
<td>Enhancement of thoracic and cauda equina roots</td>
<td>Longitudinally extensive transverse myelitis</td>
</tr>
<tr>
<td><strong>NCS</strong></td>
<td>Axonal polyneuropathy</td>
<td>Sensorimotor axonal polyneuropathy</td>
<td>Sensorimotor polyneuropathy</td>
<td>Sensorimotor polyneuropathy</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

*Continued*
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 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 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.

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.
Study Funding
No targeted funding reported.

Disclosure
The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History
Received by Neurology January 10, 2022. Accepted in final form May 19, 2022. Submitted and externally peer reviewed. The handling editor was Whitley Aamodt, MD, MPH.

References

Appendix Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saba Jafarpour, MD</td>
<td>Division of Neurology, Department of Pediatrics, Children's Hospital Los Angeles, CA; Department of Neurology, Keck School of Medicine at the University of Southern California, Los Angeles</td>
<td>Drafting/revision of the manuscript for content; including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data</td>
</tr>
<tr>
<td>Mellad Khoshnood, MD</td>
<td>Division of Neurology, Department of Pediatrics, Children's Hospital Los Angeles, CA; Department of Neurology, Keck School of Medicine at the University of Southern California, Los Angeles</td>
<td>Drafting/revision of the manuscript for content; including medical writing for content; study concept or design; and analysis or interpretation of data</td>
</tr>
</tbody>
</table>

Appendix (continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jonathan D. Santoro, MD</td>
<td>Division of Neurology, Department of Pediatrics, Children's Hospital Los Angeles, CA; Department of Neurology, Keck School of Medicine at the University of Southern California, Los Angeles</td>
<td>Drafting/revision of the manuscript for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data</td>
</tr>
</tbody>
</table>

Get Quick, Convenient Updates with NeuroBytes

NeuroBytes are 5-minute videos that address timely and relevant topics in neurology, along with additional resources for further self-guided exploration—and are free to AAN members! Browse the full catalog of videos and subscribe today. Visit AAN.com/NeuroBytes.

Neurology® Online CME Program

Earn CME while reading Neurology. This program is available to AAN members and to online Neurology subscribers. Read the articles marked CME, go to Neurology.org, and click on the CME link. The American Academy of Neurology (AAN) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. Neurology is planned and produced in accordance with the ACCME Essentials. For more information, contact AAN Member Services at 800-879-1960.
Gain-of-Function Variation Partially Responsive to Immunotherapy

Saba Jafarpour, Mellad Khoshnood and Jonathan D. Santoro

Neurology 2022;99;341-346 Published Online before print June 17, 2022
DOI 10.1212/WNL.0000000000200935

This information is current as of June 17, 2022

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>including high resolution figures, can be found at:</td>
</tr>
<tr>
<td><a href="http://n.neurology.org/content/99/8/341.full">http://n.neurology.org/content/99/8/341.full</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>This article cites 6 articles, 0 of which you can access for free at:</td>
</tr>
<tr>
<td><a href="http://n.neurology.org/content/99/8/341.full#ref-list-1">http://n.neurology.org/content/99/8/341.full#ref-list-1</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subspecialty Collections</th>
</tr>
</thead>
<tbody>
<tr>
<td>This article, along with others on similar topics, appears in the following collection(s):</td>
</tr>
<tr>
<td>All Demyelinating disease (CNS)</td>
</tr>
<tr>
<td><a href="http://n.neurology.org/cgi/collection/all_demyelinating_disease_cns">http://n.neurology.org/cgi/collection/all_demyelinating_disease_cns</a></td>
</tr>
<tr>
<td>Autoimmune diseases</td>
</tr>
<tr>
<td><a href="http://n.neurology.org/cgi/collection/autoimmune_diseases">http://n.neurology.org/cgi/collection/autoimmune_diseases</a></td>
</tr>
<tr>
<td>Metabolic disease (inherited)</td>
</tr>
<tr>
<td><a href="http://n.neurology.org/cgi/collection/metabolic_disease_inherited">http://n.neurology.org/cgi/collection/metabolic_disease_inherited</a></td>
</tr>
<tr>
<td>MRI</td>
</tr>
<tr>
<td><a href="http://n.neurology.org/cgi/collection/mri">http://n.neurology.org/cgi/collection/mri</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Permissions &amp; Licensing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:</td>
</tr>
<tr>
<td><a href="http://www.neurology.org/about/about_the_journal#permissions">http://www.neurology.org/about/about_the_journal#permissions</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reprints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information about ordering reprints can be found online:</td>
</tr>
<tr>
<td><a href="http://n.neurology.org/subscribers/advertise">http://n.neurology.org/subscribers/advertise</a></td>
</tr>
</tbody>
</table>