ACOX1 Gain-of-Function Variant in Two German Pediatric Patients, in One Case Mimicking Autoimmune Inflammatory Disease

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Neuropediatrics 2024;55:140–145.

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Abstract

Mitchell syndrome is a very rare genetic disorder due to a specific de novo gain-of-function variant in acyl-CoA oxidase 1 (*ACOX1*). So far, only five patients with this disease have been described worldwide. We present here two additional unrelated German patients found to carry the same heterozygous *ACOX1* N237S variant through exome sequencing (ES). Both patients showed neurodegenerative clinical features starting from ~4 to 5 years of age including progressive hearing loss, ataxia, ichthyosis, as well as progressive visual impairment leading to amaurosis, and died at the ages of 16 and 8 years, respectively. The first patient was clinically suspected to have anti–myelin oligodendrocyte glycoprotein-antibody-associated myelitis, but the disease course overall deteriorated despite extensive immunomodulatory therapy. The second patient was originally suspected to have a mitochondrial disorder due to intermittent elevated blood lactate. Since Mitchell syndrome has only been identified in 2020, the diagnosis in this second patient was only established through re-evaluation of ES data years after the original analysis. Comparison of all seven reported patients suggests that Mitchell syndrome often (but not always) clinically mimics autoimmune-inflammatory disease. Therefore, in patients with autoimmune central nervous system disease who do not respond adequately to standard therapies, re-evaluation of this diagnosis is needed and genetic analyses such as trio ES should be considered.

Keywords
- ACOX1
- Mitchell syndrome
- exome sequencing

Introduction

Biallelic mutations in the gene encoding acyl-CoA oxidase 1 (ACOX1) on chromosome 17q25.1 cause peroxisomal ACOX1 deficiency, a very rare autosomal recessive disorder of metabolism, leading to an accumulation of very long chain fatty acids (VLCFA) with subsequent glial degeneration.[1] Affected children show neonatal muscular hypotonia, seizures, visual and hearing impairment, and a global developmental delay, followed by psychomotor regression.[1] Clinically relevant variants associated with autosomal recessive ACOX1 deficiency comprise deletions, nonsense, missense and splicing mutations, expected to lead to a loss of function.[1] Recently, however, a single de novo missense variant in *ACOX1* (N237S), leading to a

received
June 20, 2023
accepted after revision
September 12, 2023
article published online
October 16, 2023

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Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0043-1776013.
ISSN 0174-304X.

gain of function, has been described as causative for a different neurodegenerative disorder with myelitis, progressive hearing impairment, gait disturbances, and polyneuropathy in three patients.[2] The disease was fatal for the first patient at the age of 19 years, the second was alive, but comatose at 15 years, and the third was 9 years of age and alive at the time of publication. Subsequently, two additional patients were described, one of which was still alive at 20 years,[3] while the other died at 9 years of age.[4] This novel disorder was named Mitchell disease after the first identified patient.[2]

We describe here two additional German patients representing the sixth and seventh cases of Mitchell disease worldwide. Patient 1 received diagnostic trioanalysis (Tübingen) and patient 2 was investigated as part of the MitoNET research project (Munich). For data assessment, the medical records were reviewed retrospectively. Both families gave informed consent for genetic analyses, data assessment, and publication of the results.

Case Reports

Patient 1

The patient is the first son of nonconsanguineous healthy German parents. Pregnancy and delivery (cesarian section at 35 weeks of gestation), neonatal period, and early psychomotor development were uneventful. The patient walked independently at 12 months and started speaking in an age-appropriate matter. At 4 years of age, bilateral sensorineural hearing loss was detected that was treated with hearing aids and later (at 10 years) with cochlear implants (CIs). Due to problems with expressive language development, the patient attended a special school for children with hearing deficits. A cerebral magnetic resonance imaging (MRI) at this stage was normal. Starting at 5 years, he showed ocular problems with sensitivity to light and watering eyes. At 9 years, he developed subacute progressive ataxia over the course of 2 weeks. MRI of the spinal cord then showed longitudinal extensive transverse myelitis (►**Fig. 1A, B**), and anti–myelin oligodendrocyte glycoprotein (MOG) antibodies were positive in serum (1:320). Additional analyses, including oxysterols, phytanic acid, VLFCA, organo acids in urine, amino acids in plasma and cerebrospinal fluid (CSF), tests for M. Refsum and mitochondrial disease, showed normal results. The patient received the diagnosis of anti-MOG-antibody-associated myelitis und was treated with prednisolone and intravenous immunoglobulins, initially leading to a small improvement. However, the symptoms soon worsened again with additional new brain lesions

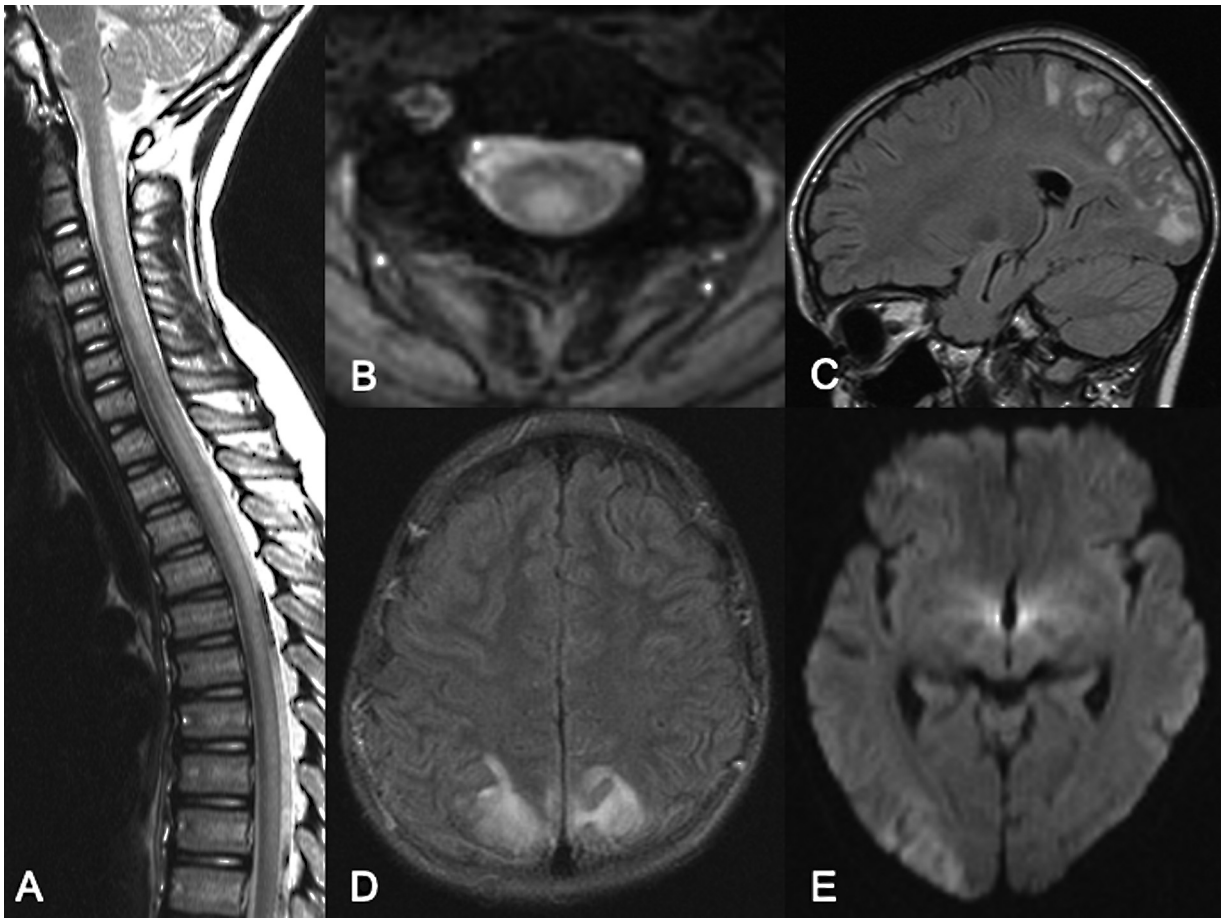

Fig. 1 (**A–E**) Sagittal and axial T2-weighted images of the spinal cord at the age of 9 years revealed a longitudinal extensive intramedullary T2 lesion of the entire myelon, centrally located with swelling of the spinal cord (**A, B**). Short-term follow-up brain MRI scan further presented symmetrical PRES-like T2 lesions in parieto-occipital areas as shown on sagittal and axial T2/FLAIR images (**C, D**) with partial diffusion restriction on the corresponding DWI (**E**). DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; PRES, posterior reversible encephalopathy syndrome.

parieto-occipital (►**Fig. 1C–E**), so that plasmapheresis had to be applied. Anti-MOG-antibodies went down to 1:80, but shortly after, the patient showed the first seizure, and the antibodies were again at 1:160. Despite extensive immunomodulatory therapy, anti-MOG immunoglobulin G remained positive, and the patient developed tetraplegia and diaphragmatic paralysis. He further developed a dry and scaling skin, suggesting ichthyosis, as well as subepithelial clouding and chalk deposition plus corneal degeneration, leading to bilateral amaurosis. The patient further showed peripheral neuropathy with dysregulation of the autonomous nervous system. Ultimately, he was bedridden with a tracheostoma, a percutaneous endoscopic gastrostomy tube and a suprapubic bladder catheter.

Molecular karyotyping and evaluation of the *GJB2* gene (keratitis-ichthyosis-deafness syndrome) gave normal results. Ultimately, trio exome sequencing (ES) revealed the de novo N237S variant in *ACOX1*, leading to the diagnosis of Mitchell syndrome. The patient died at the age of 16 years due to sepsis and multiorgan failure.

Patient 2

This boy was the second child of nonconsanguineous German parents. Family history, pregnancy and delivery, and early psychomotor development were unremarkable (walking freely at 13 months). With 3 years of age, he developed recurrent eye problems with episodes of sudden stinging pain, photophobia and/or conjunctivitis. From the age of 5 years, he developed a progressive bilateral sensorineural hearing deficit, which was treated by hearing aids and later by CIs. In parallel, he became atactic and insecure in gross motor function. Additionally, at the age of 6 years, he developed follicular hyperkeratosis which was undulating in severity in the following years. At 7 years, he showed a rapid decline in visual function with optic atrophy and became blind as well as unable to walk for exacerbating ataxia. Muscle tendon reflexes vanished and he developed a mild peripheral neuropathy. At 8 years, he deteriorated further with a neurogenic bladder. He died in a crisis necessitating mechanical ventilation with left ventricular cardiomyopathy.

Extensive metabolic work-up showed intermittent elevated blood lactate as well as a cystinuria (later also found in his healthy elder brother) and no other abnormalities in particular for VLCFA, phytanic and pristanic acids. A cerebral MRI at 5 years (before CI) was normal. Considering the elevated lactate in blood, a mitochondrial disorder was clinically suspected and a muscle biopsy was performed. Histology showed minor unspecific abnormalities, and mitochondrial enzyme activities were normal in muscle as well as in fibroblasts. CSF diagnostics and screening for autoimmune diseases were normal. He was included in an exome analysis project on a research basis which did not reveal a causative variant at that time but showed the heterozygous N237S variant in *ACOX1*, published many years later as causing Mitchell syndrome. Therefore, through re-evaluation of exome data, the diagnosis Mitchell syndrome was established in this patient.

Discussion

Only five patients with Mitchell syndrome have been described worldwide.[2–4] We add here two additional German patients who were identified through trio ES shortly after publication of the first three cases and re-evaluation of exome data originally analyzed 13 years earlier, respectively. This latter case clearly indicates the importance of re-evaluation of next-generation sequencing data, as the analysis pipelines always depend on current knowledge about disease-associated genes and modes of inheritance. As pathogenic variants in *ACOX1* had only been known as causative for autosomal recessive ACOX1 deficiency before 2020, a single heterozygous variant of so far unknown relevance would most likely not have been reported before that time. Therefore, even though Mitchell disease appears to be ultra-rare, there is still the possibility that additional cases will be described with reanalysis of ES data worldwide.

What makes the correct diagnosis of Mitchell syndrome challenging is that it appears to mimic autoimmune central nervous system (CNS) disease in most cases described so far. In three of the seven patients, a (probably autoimmune) myelitis or an unknown autoimmune myeloneuropathy was clinically suspected, and one patient was initially diagnosed with chronic inflammatory demyelinating polyneuropathy. Further, two patients had positive antinuclear antibodies, and the first patient in this report was positive for anti-MOG antibodies.[5] Whether these are unspecific findings or some autoimmune reaction may actually be part of the syndromic disease is still unclear. Interestingly, our first patient as well as a few other patients from the literature showed at least intermittent and/or short-term responsiveness to immunomodulatory therapy. However, it is still unclear whether these seemingly improvements under therapy are true treatment responses or rather reflect the undulating course of the disease with phases of partial recovery and acute or subacute deterioration that has been observed more or less in all patients so far. On the other hand, our second patient did not show autoimmune phenomena and was originally suspected to have mitochondrial disease because of intermittently elevated serum lactate levels.

Pathophysiologically, the N237S variant increases levels of reactive oxygen species in glia cells,[2] and N-acetylcysteine amide (NACA) was shown to be beneficial in drosophila. However, this substance is not approved for therapy in humans, and NAC, which was used instead in few patients,[2–4] does not cross the blood–brain barrier. Our two patients received the diagnosis either shortly before or even years after death, so that a therapeutic trial with NAC was not possible; however, the few patients given this substance so far did not show substantial benefit.

Conclusion

Taken together, our study suggests that Mitchell syndrome often (but not always) clinically mimics autoimmune-

Table 1 Clinical symptoms of the seven patients with Mitchell syndrome described worldwide, all carrying the *ACOX1* gain-of-function variant N237S (modified from Jafarpour et al, 2022)

Symptom	Patient 1 (Chung et al)	Patient 2 (Chung et al)	Patient 3 (Chung et al)	Patient 4 (Swartwood et al)	Patient 5 (Jafarpour et al)	Patient 6 (Patient 1 of the current study)	Patient 7 (Patient 2 of the current study)
Sex	M	F	M	F	F	M	M
Age at onset	12 y	9 y	3 y	9 y	14 y	4 y	3 y
First symptom	Clumsiness, hearing loss	Hearing loss, weakness of the lower limbs	Diffuse desquamatory rash, difficulty walking	Sensorineural hearing loss	Sensory ataxia	Progressive hearing impairment	Recurrent eye problems
Survival	19 y (death)	15 y (coma[a])	9 y (alive[a])	11 y (death)	20 y (alive[a])	16 y (death)	8 y (death)
Myelitis/other lesions in spinal MRI	Longitudinally extensive T2 hyperintensity, primarily in the dorsal columns of the cervical and thoracic cord	Longitudinally extensive transverse myelitis spanning from the cervical to lumbar spine with T2 hyperintensity	Enhancement of multiple thoracic roots and all cauda equina roots	Longitudinally extensive transverse myelitis	Extensive T2 signal hyperintensity throughout the spinal cord, particularly dorsal column	Extensive myelitis longitudinal extensive intramedullary T2 lesion of the entire myelon, centrally located with swelling of the spinal cord	n.d.
Cerebral lesions in brain MRI	Normal at 12 y; central lesions at 19 y during final deterioration	Normal at beginning; T2 hyperintense lesions in the bilateral occipital lobes and meningeal and parenchymal enhancement after 2 mo	Cranial nerves III, V, VII, and VIII enhancement; later periventricular, deep and subcortical white matter confluent signal abnormalities	n.a.	Few scattered T2 hyperintensities in frontal lobes	Normal at 5 y	Normal at 5 y
Autoantibodies	Antinuclear antibody (1:320)	Not reported	Not reported	Not reported	Antinuclear antibody (1:640)	Anti-MOG antibodies (1:320)	7 y: normal for ANA, ANCA, dsDNA
Polyneuropathy	+	+	+	+	+	+	+
Ataxia	+	+	+	+	+	+ (subacute at 9y)	+
Cognition/ developmental delay	Normal	Normal until development of encephalopathy	Impaired cognition	Normal before encephalopathy	Normal	Speech delay	Normal
Seizures	n.a.	+	+	n.a.	+	+	−
Sensorineural hearing loss	+	+	+	+	+	+	+
Ocular symptoms	Sicca symptoms; xerophthalmia and corneal abrasions	Not reported	Eye pain, ptosis; lagophthalmos and corneal haze	Permanent loss of vision	Keratitis and corneal scarring	Subepithelial clouding; subepithelial chalk deposition; corneal degeneration; amaurosis	Stinging pain, photophobia, conjunctivitis; follicular hyperkeratosis, optic atrophy; amaurosis
Skin abnormalities	Keratosis pilaris of bilateral upper extremities	Atopic dermatitis, worsening skin rash	Diffuse desquamatory rash, follicular hyperkeratosis	Ichthyosiform rash, alopecia	Ichthyosiform rash	Dry and scaling skin; ichthyosis	Follicular hyperkeratosis

(*Continued*)

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Table 1 (*Continued*)

Symptom	Patient 1 (Chung et al)	Patient 2 (Chung et al)	Patient 3 (Chung et al)	Patient 4 (Swartwood et al)	Patient 5 (Jafarpour et al)	Patient 6 (Patient 1 of the current study)	Patient 7 (Patient 2 of the current study)
VLCFA	Normal	Normal	Normal	Not reported	Normal	Normal	Normal
CSF	Slightly elevated protein	Elevated protein	Normal	Normal	Normal	Normal	Slightly elevated lactate (maximum 2.7 mM)
Autoimmune disease clinically suspected	Unknown autoimmune myeloneuropathy	Autoimmune transverse myelitis with peripheral neuropathy	Guillain–Barre's syndrome; chronic inflammatory demyelinating polyneuropathy	Not reported	Not specified	Anti-MOG-antibody-associated myelitis	None
Response to immunomodulatory treatment	Short-term improvement with methyl-prednisolone/ plasmapheresis plus rituximab; period of stability and improvement under monthly plasmapheresis and IVIg plus methotrexate	Temporary stable period under azathioprine and IVIg	Improvement of rash under corticosteroids; no other long-term responses	Brief period of stable disease while on immunomodulating therapies, then rapid neurological decline	Partial improvement and lack of progression under mycophenolate mofetil and IVIg	Short-term improvement under cortisone/IVIg/ plasmapheresis, no long-term improvement	No benefit from short-course glucocorticoid treatment
Other	–	–	Mildly elevated IL-18 level	–	–	–	Left ventricular dilative cardiomyopathy, neurogenic bladder, intermittently elevated lactate in blood (maximum 6.3 mM)

Abbreviations: CSF, cerebrospinal fluid; IL, interleukin; IVIg, intravenous immunoglobulin; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; n.a., not available; n.d., not done; VLCFA, very long chain fatty acids.
[a]At the time of publication.

inflammatory disease. From comparison of seven known cases so far (see ►**Table 1**), the main clinical features of this disease comprise a (mostly) normal development in early childhood, progressive hearing loss in infancy as one of the first symptoms, progressive ataxia often with signs of myelitis in MRI of the spine, an ichthyosiform rash, progressive ocular symptoms, and an undulating disease course that often ends fatal. The combination of a newly developed ataxia and myelitis with progressive hearing loss in a child might give a hint toward this diagnosis. Unfortunately, there are no laboratory markers to suggest Mitchell disease, since VLCFA and all other metabolic tests were normal. Despite short-term improvement with immunomodulatory treatment, the disease course was overall deteriorating for almost all patients. Therefore, in patients with suspected autoimmune CNS disease who do not benefit adequately from standard therapies, re-evaluation of this diagnosis is needed and genetic analyses such as trio ES should be considered.

Conflict of Interest
None declared.

Acknowledgment
We gratefully thank the patients and their families for participating in this work and allowing publication of the results.

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