Case Report

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Alpha-methyl acetyl-coA racemase deficiency. Magnetic resonance imaging findings of three patients with encephalopathy, epilepsy, and stroke-like episodes

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Abstract

Alpha-methyl acyl-CoA racemase deficiency (AMACRD) is a rare peroxisomal disorder that results in the accumulation of pristanic acid and 16 cases have been reported in the literature. Here, we present three additional patients, two confirmed by genomic study and one suspected. Three siblings who were born to healthy unrelated parents developed recurrent episodes of encephalopathy, seizures, and behavioral disturbances. In all 3, brain MRI showed lesions in the thalami, cerebral peduncles, and mesencephalic tegmentum, as well as brain volume loss. In addition, one patient had a chronic hemispheric infarct and an acute contralateral infarct, and another had a subacute infarct involving multiple vascular territories without abnormalities on MR angiography.

Keywords

Alpha-methyl acetyl-coA racemase, encephalopathy, epilepsy, dysfunction, single peroxisomal

Introduction

Alpha-methyl acyl-CoA racemase deficiency (AMACRD) is a rare autosomal recessive peroxisomal disorder resulting in the accumulation of pristanic acid (a branched-chain fatty acid). It can also lead to the deposition of C27 bile acid intermediates and, to a lesser extent, phytanic acid.[1]

Most branched-chain fatty acids, due to a methyl group on their carbon chain, cannot be immediately metabolized in mitochondria and are metabolized in peroxisomes. The oxidative degradation pathways of lipids include α- and β--oxidation. In all metabolic pathways, alpha-methyl acyl-CoA racemase is a fundamental regulator of lipid and drug metabolism. Deficiency of this enzyme occurs when there is a mutation in the gene encoding it leading to the accumulation of toxic branched-chain fatty acids such as pristanic acid.[2,3,4]

To the best of our knowledge, AMACRD has been described in 16 patients, mainly adults. Initially, this disorder was reported as a late-onset sensorimotor neuropathy.[5] However, subsequent reports suggested that the disorder may be characterized by cholestatic liver disease in the neonatal period and variable neurodegenerative symptoms affecting the central and peripheral nervous systems at later ages. Clinical features include rhabdomyolysis, seizures, visual impairment, spasticity, migraine, ataxia, dysarthria, neuropathy, depression, and stroke-like cerebral dysfunction with encephalopathy.[6,7]

In this report, we describe two new cases of confirmed AMACRD and one probable case comprised of three adult siblings of healthy non-consanguineous parents who presented with seizures and recurrent encephalopathy similar to other reported late-onset AMACRD.

Case series

Case 1

A 46-year-old male presented with progressive encephalopathy and aphasia. Medical history included an episode of altered consciousness at age 17, a hemianopsia episode with complete recovery at age 27, and another episode of altered consciousness at age 31. Cerebrospinal fluid and other laboratory analyses were unremarkable.

Brain MRI (Figure 1) showed volume loss (especially in the occipital regions) and gyriform contrast enhancement in the left temporal and occipital lobes without restricted diffusion. T2-weighted hyperintense lesions were observed in the thalami, cerebral peduncles, mesencephalic tegmentum, red nuclei, and quadrigeminal colliculi (Figure 1). Based on the MRI findings and the family history of similar episodes in two siblings a mitochondrial disease was considered but mitochondrial DNA testing did not reveal any mutations. Subsequently, a complete genomic analysis was performed and a homozygous variant in the alpha-methyl acyl-CoA racemase gene (c826 G>C p.Ala276Pro) was found. During hospitalization, the patient developed status epilepticus and eventually died despite treatment.

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Case 2

A 51-year-old man presented with a 22-year history of recurrent behavioral changes and epilepsy. He also had biliary obstruction and chronic cholestasis.

Brain MRI (Figure 2) showed volume loss and T2-weighted hyperintense juxtacortical lesions in cerebral hemispheres, thalami, cerebral peduncles, midbrain tegmentum, red nuclei, quadrigeminal colliculi, and to a lesser extent in the pontine tegmentum (Figure 2). Given the family history of his brother (Case #1), a genomic study was requested which revealed the same homozygous mutation in the alpha-methyl acyl-CoA racemase gene (c826 G>C p.Ala276Pro). Currently, the patient is clinically stable with sporadic episodes of encephalopathy and adequate control of epilepsy.

Case 3

A 35-year-old woman presented with acute behavioral changes, disorientation, aphasia, hallucinations, and cognitive decline. She underwent video telemetry which suggested an extensive structural lesion affecting her right cerebral hemisphere. No epileptiform discharges were observed, and no clinical events were recorded. Cerebrospinal fluid was normal. Her medical history included a right cerebral infarction 13 years previously with normal catheter angiography at that time resulting in left hemiplegia and epilepsy.

Brain MRI (Figure 3) showed volume loss in the right hemisphere with T2-weighted hyperintense lesions in the deep white matter and juxta- and sub-cortical regions with an extensive area of encephalomalacia and gliosis. There were lesions in the thalami, left striatum, insular cortex, and T2-weighted hyperintensity in the cerebral peduncles (Figure 3). Despite hospital management, she continued to have focal seizures progressing to status epilepticus and deterioration of consciousness requiring mechanical ventilation. Subsequently, the patient had spastic quadriparesis with complete dependence on basic activities of daily living and she eventually died without a precise diagnosis but given her family history and the alpha-methyl acyl-CoA racemase gene

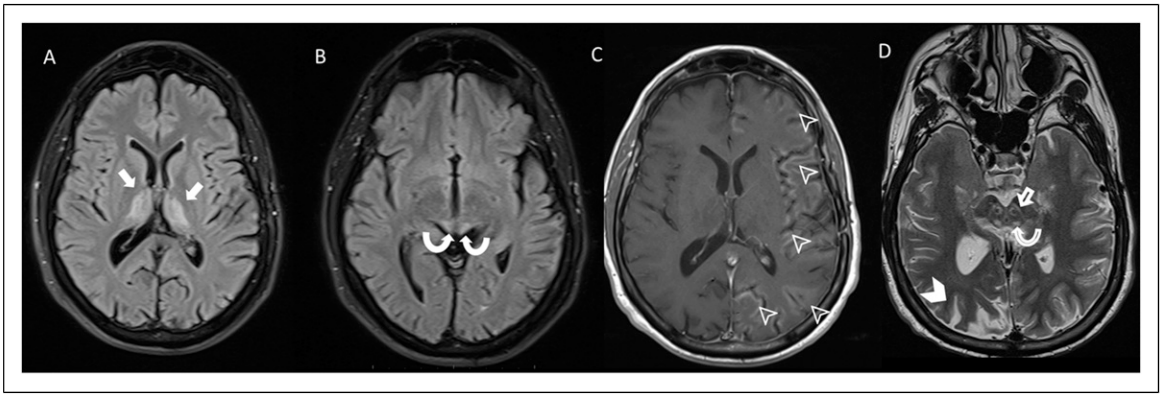

Figure 1. 46-year-old male presented with progressive encephalopathy and aphasia. A and B. Axial T2-FLAIR-weighted sequences show hyperintensity of the thalami (arrows) and superior colliculi (curved arrows). C. Post-contrast axial T1-weighted shows gyriform enhancement (arrowheads) in the left hemisphere cortex with a "stroke-like" appearance. D. Axial T2-weighted image shows hyperintensity around the red nuclei (open arrow) and inferior colliculi (curved arrow). Right occipital lobe volume loss is also present (arrowhead).

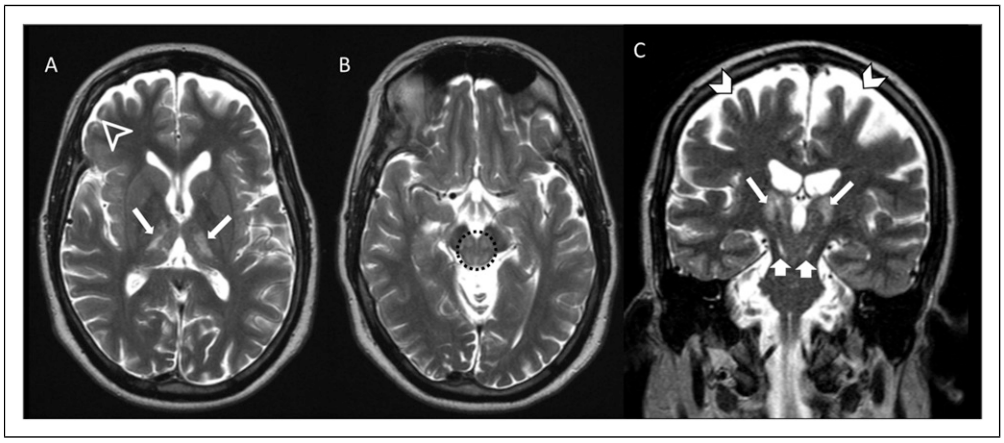

Figure 2. 51-year-old man presented with a 22-year history of recurrent behavioral changes and epilepsy. A. Axial T2-weighted image shows thalamus lesions (arrows) and right frontal juxtacortical hyperintensity (arrowhead). B. Axial T2-weighted image shows hyperintensity in the mesencephalic tegmentum compromising red nuclei and inferior colliculi (circle). C. Coronal T2-weighted image shows hyperintensity in the thalami (long arrows) the dentatothalamic tract (short arrows) and volume loss in the frontal lobes (arrowheads).

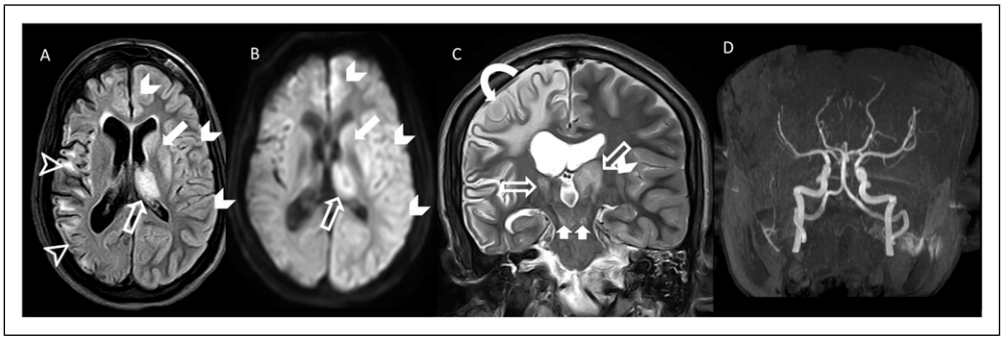

Figure 3. 35-year-old woman presented with acute behavioral changes, disorientation, aphasia, hallucinations, and cognitive decline. A. Axial T2-FLAIR-weighted image shows hyperintensity in the left thalamus (open arrow) and basal ganglia (solid arrow). Right hemisphere volume loss with juxtacortical areas of gliosis due to a previous stroke-like event is present (open arrowheads). The left hemisphere cortex (solid arrowheads) is slightly bright and thick in T2-FLAIR-weighted and in DWI images (B) without restriction. C. Coronal T2-weighted image shows hyperintensity in thalami (open arrows), thalamic tracts (short arrows), and right hemispheric volume loss and gliosis (curved arrow). D. Unremarkable time of flight sequence.

mutation in both brothers, we consider it highly probable that she also had this disease.

Discussion

Peroxisomes are non-autonomous cell organelles with essential catabolic and metabolic functions including lipid and some drug metabolism.[8] The oxidative degradation pathways of lipids include α- and β-oxidation. α-oxidation breaks down dietary phytanic acid which is derived primarily from dairy products, meat, and certain fish. This metabolic step produces pristanic acid which is degraded by β-oxidation. In addition, this oxidation allows for the synthesis of docosahexaenoic acid, an omega-3 fatty acid enriched in neuronal tissue and the outer segments of photoreceptors, and in bile acids.[8,9,10] Alpha-methyl acyl-CoA racemase is essential for lipid oxidation processes. It catalyzes the conversion of certain compounds with a 2R methyl branch, such as pristanic acid and bile acid intermediates to their S stereoisomers which is the form that can be degraded by peroxisomal beta-oxidation. Therefore, patients with AMACRD have markedly elevated levels of pristanic acid and C27 bile acid intermediates. Phytanic acid may also be slightly elevated.[10] Pristanic acid and phytanic acid are cytotoxic in excess and induce nitric oxide-dependent apoptosis in vascular smooth muscle cells. It has also been reported that cell death may occur, particularly in oligodendrocytes, due to calcium influx, mitochondrial membrane rupture, and generation of reactive oxygen species.[11]

Similar features have been identified among the adult cases of AMACR deficiency and those seen in Refsum disease.[1] Refsum disease results from a genetic deficiency in the α-oxidation pathway upstream of AMACR and presents with three phenotypic cardinal features: retinitis pigmentosa, demyelinating neuropathy, and progressive ataxia. Although AMACR deficiency presents with a Refsum-like phenotype, the clinical picture also includes epilepsy, encephalopathy, pyramidal tract signs, and migraines.[6]

To date, 16 cases of AMACRD have been reported in the literature, 12 adults and four children. Our report adds two confirmed cases and one probable. In previous reports, the most common homozygous pathogenic variant was (c.154 T>C, p.(Ser52Pro)) of the alpha-methyl acyl-CoA racemase gene in 9 cases.[1,5,6,12–17] Two of our patients underwent genome sequencing, which identified a homozygous variant of uncertain significance in the alpha-methyl acyl-CoA racemase gene, c826 G>C p.Ala276Pro. Since both presented the same variant with similar clinical and imaging characteristics, it should be considered among the pathogenic variants.

The onset of symptoms in this disease is usually between the 2nd-7th decades of life with an average presentation around the 3rd decade. Most patients (10 cases) developed an encephalopathy resembling mitochondrial stroke-like episodes with hemispheric symptoms, seizures, coma, and fever, and in 3 cases the attacks were recurrent[1,6,18] a finding seen in our three patients who had episodes of encephalopathy at their admission and seizures. Two of them developed status epilepticus which led to fatal outcomes.

In previously reported cases, decreased oral intake and vomiting preceded the episodes of encephalopathy. Other triggers include pregnancy and weight loss.[1,17,19] In our patients, we could not identify a clear trigger. Encephalopathic events in AMACRD are thought to be due to metabolic neurotoxicity from elevated pristanic acid levels;[17] however, this remains to be confirmed.

Seizures are common in patients with AMACRD and half are recurrent, our three patients had recurrent seizures.[1,6,12,14,15,17,19,20] Other symptoms include axonal and demyelinating neuropathies.[18] Ophthalmologic findings include cataracts, retinitis pigmentosa, retinal pigment atrophy, and optic atrophy.[17] In one of our patients, a visual disturbance was self-limited and resolved. Other neurological findings include tremors and isolated reports of ataxia, cognitive impairment, and spastic paraparesis.[17]

Regarding imaging findings, volume loss, and hyperintensities on T2-weighted sequences involving the thalami, pons, midbrain, and white matter, both juxtacortical and subcortical have been reported.[1,5–7,12–14,16–19,21] Progressive changes in T2-weighted signal intensity of the afferent and efferent pathways of the cerebellum are presumably specific for AMACRD and were present in most previous reports.[17] These findings were found in our three patients, including hyperintensity in the dentatothalamic tract and thalamic tracts. However, we did not see an important cerebellum compromise. Diffusion restriction may also occur during episodes of encephalopathy. Table 1 provides a summary of known cases with AMACR deficiency and its findings in images when were available.

Table 1. Summary of known cases with AMACR deficiency.

Author	Age at diagnosis/ gender	Clinical features	Gene variant	Brain MRI
Ferdinandusse et al[5]	48 years/F	Spastic paraparesis, demyelinating neuropathy	c.154 T>C	N/A Normal MRI of cervical spine
McLean et al[12]	44 years/M	Retinitis pigmentosa, optic atrophy, cataracts, axonal neuropathy, recurrent seizures, lerning disabilities hypogonadism and micrognathia	c.154 T>C	Minor cerebral atrophy
Clarke et al[13]	53 years/F	Upper limb, head, and voice tremor. Severe depression. Cataracts, retinitis pigmentosa, and optic atrophy	c.154 T>C	High signal in the pons, basal ganglia, thalami, and cerebral peduncles
Thompson et al[1]	57 years/F	Decline in cognition, apathy, and unsteadiness of gait. Epilepsy. Depression. Encephalopathy	c.154 T>C	Diffuse involutional changes and high signal involving the cortex and subcortical white matter, pons, and thalami
Smith et al[6]	45 years/M	Seizures since early adulthood. Encephalitis resulting in global encephalopathy and left hemiparesis. Retinitis pigmentosa	c.154 T>C	T2 hyperintensity in the right temporal, occipital, and parietal cerebral cortex
Kapina et al[18]	23 years/M	Schizophrenia with recurrent bouts of neuroleptic malignant syndrome with rhabdomyolysis. Right sensorimotor deficit, aphasia, right hemianopsia, and seizures	c.559 G>A	T2-weighted increased signal in thalami, the pons, and cerebral peduncles. Edema involving the hemicortex of the left cerebral hemisphere. Spectroscopy showed a nonspecific lactate peak and decreased NAA/choline ratio in the left parietal cortex
Dick et al[14]	58 years/M	Gait unsteadiness, slurred speech, a few tonic/clonic seizures, and a decline in short-term memory	c.154 T>C	High signal on T2-weighted images in the white matter of both hemispheres, thalami, midbrain, and pons with associated brainstem atrophy
Stewart et al[22]	45 years/M	Seizures, encephalopathy, hemiparesis, and retinal pigmentary atrophy	–	Flair/T2 abnormalities in the thalamus, left hemisphere, pons, and midbrain
Haugarvoll et al[19]	30 years/M	Demyelinating peripheral neuropathy. Encephalopathic episode. Retinitis pigmentosa. Seizures. Diabetes	c.367 G>A	Degeneration of the cerebellothalamic tract; including prolongation of the T2 signal in the dentate nucleus, atrophy and hyperintense T2-signal of the superior cerebellar peduncle (SCP). Chronic degeneration of both the dentatorubral and the dentatothalamic tracts
Haugarvoll et al[19]	33 years/F	Epilepsy. Several episodes of dysphasia, right sided central facial palsy and upper right limb numbness. Diabetes. Tremor	c.367 G>A	Degeneration of the cerebellothalamic tract; including prolongation of the T2 signal in the dentate nucleus, atrophy and hyperintense T2-signal of the superior cerebellar peduncle (SCP). Chronic degeneration of both the dentatorubral and the dentatothalamic tracts
Krett et al[15]	51 years/M	Subclinical seizures, depression, bipolar and recurrent rhabdomyolysis	c.154 T>C	–
Van Veldhoven et al[23]	Newborn/F	Vitamin K deficiency and giant cell neonatal hepatitis	–	–
Setchell et al[16]	Newborn/F	Vitamin K deficiency and deranged liver function tests	c.154 T>C	Mild undermyelination of the pre and postcentral gyri bilaterally but was otherwise normal for age
Verhagen et al[24]	9 months/M	Incidental AMACR deficiency while investigating oculocutaneous albinism	Deletion 5p13.3	–
Gündüz et al[7]	10 months/M	Elevated liver enzymes	c.596 G>A	Normal

(continued)

Table 1. (continued)

Author	Age at diagnosis/ gender	Clinical features	Gene variant	Brain MRI
Tanti et al[17]	Seven decade/F	Atypical stroke-like episodes of expressive dysphasia, dysarthria, headache, and right-hand sensory disturbance. Tremor. Cataracts, hypothyroidism, glaucoma, central apnea	c.154 T>C	White matter, thalamic and pontine hyperintensity Acute swelling and hemispheric signal change
Index case 1	46 years/M	Progressive encephalopathy and aphasia. Hemianopsia episode with complete recovery	c826 G>C p.Ala276Pro	Volume loss (especially in the occipital regions) and gyriform contrast enhancement in the left temporal and occipital lobes without restricted diffusion. T2-weighted hyperintense lesions in the thalami, cerebral peduncles, mesencephalic tegmentum, red nuclei, and quadrigeminal colliculi
Index case 2	51 years/M	Recurrent behavioral changes and epilepsy. Biliary obstruction and chronic cholestasis	c826 G>C p.Ala276Pro	Volume loss and T2-weighted hyperintense juxtacortical lesions in cerebral hemispheres, thalami, cerebral peduncles, midbrain tegmentum, red nuclei, quadrigeminal colliculi, and to a lesser extent in the pontine tegmentum
Index case 3	35 years/F	Acute behavioral changes, disorientation, aphasia, hallucinations, and cognitive decline	–	Volume loss in the right hemisphere with T2-weighted hyperintense lesions in the deep white matter and juxta- and subcortical regions with an extensive area of encephalomalacia and gliosis. Lesions in the thalami, left striatum, insular cortex, and T2-weighted hyperintensity in the cerebral peduncles

Some mitochondrial syndromes have similar findings on MRI and should be considered in the differential diagnosis. Leigh syndrome shows bilateral lesions in the basal ganglia, medial aspects of the thalami, and brainstem. However, Leigh syndrome mainly involves gray matter structures such as the substantia nigra, subthalamic nucleus, and red nuclei, rather than white matter tracts as does AMACRD.[20] Other differential diagnoses are mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), and polymerase gamma encephalopathy (POLG), in which there are bilateral thalamic lesions and stroke-like lesions with clinical features like those of our patients but generally do not have the brainstem lesions seen in AMACRD.[22]

Medical management of AMACRD consists of dietary restriction of pristanic and phytanic acids but the benefit of this therapy has not been proven. In previous reports, three patients had satisfactory results with dietary modifications, and two recovered from encephalopathy.[6,22] However, the long-term benefit of such treatment remains to be determined.

Conclusion

In summary, we used genome sequencing in two patients to diagnose α-methyl acyl-coA racemase deficiency. A homozygous variant of uncertain significance was found in the alpha-methyl acyl-CoA racemase gene, c826 G>C p.Ala276Pro. Based on symptoms and MRI findings in our patients, we believe that this presentation should be considered a pathogenic variant as both brothers presented with a complex neurological syndrome beginning in adulthood, epilepsy, recurrent encephalopathy, stroke-like episodes, and bilateral thalamic lesions on MRI. We also presented the sister in who we could not identify the mutation but who presented with similar clinical behavior and imaging findings. Finally, it is important to emphasize that in all three patients, we initially suspected a mitochondrial disease based on imaging findings and clinical course; however, genomic studies diagnosed AMACRD in two instances. Thus, there may be a significant overlap in imaging findings between mitochondrial diseases and AMACRD should be considered in the differential diagnosis of patients with recurrent encephalopathy, "stroke-like" episodes, and seizures, in addition to MRI abnormalities including T2 hyperintensities in the thalami, white matter, cerebral peduncles, mesencephalic tegmentum, and pons.

Author contributions

Conception and design, analysis and interpretation of data: Palacio-Montoya, Vargas drafting the article or revising it critically for important intellectual content: Herrera, Castillo final approval of the version to be published: All authors.

Declaration of conflicting interests

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Appendix

Abbreviations

AMACRD	Alpha-methyl acyl-CoA racemase deficiency
MELAS	Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes
POLG	Polymerase gamma