Retinal Dystrophy and Leukodystrophy Caused by ACBD5 deficiency in Five Omani Patients: A Case Series

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Abstract

Acyl-Coenzyme A-Binding Domain-Containing Protein 5 (ACBD5) is an Acyl-CoA-binding peroxisomal membrane protein. Its deficiency was shown to impair peroxisomal beta-oxidation of very long chain fatty acids (VLCFAs) and leads to an autosomal recessive disorder with main findings of retinal dystrophy and leukodystrophy. We report five patients with ages ranging between 4 and 30 years. First presentation was in infancy with nystagmus and photophobia and progressed to legal blindness by 10 years of age. Electroretinogram (ERG) confirmed severe cone-rod dystrophy. Motor neuroregression with variable ages of onset and signs of progressive cerebellar ataxia were seen in all whereas cognitive decline was observed in some. Brain MRI revealed diffuse T2 signal abnormality in deep white matter with involvement of corticospinal tracts. Plasma VLCFA profile showed mild elevation of C26 and C26/22 ratio. Two homozygous variants in *ACBD5* gene were identified; exons 7 and 8 deletion and exon 4 deletion. This series confirms retinal dystrophy and leukodystrophy as key features of ACBD5 deficiency with main symptoms of early onset visual decline, progressive spasticity, and cerebellar ataxia. Retinal dystrophy is characterized by early cone involvement. This case series is valuable in adding to the understanding of this ultra-rare neurometabolic disease.

Keywords: cone-rod dystrophy, ataxia, spastic paraplegia, *ACBD5*, peroxisomal disorder.

Introduction

Defects in human genes encoding peroxisomal proteins can result in different peroxisomal disorders with variable severity ranging from early lethality to subtle neurosensory abnormalities.[1] Acyl-CoA-Binding Domain-Containing Protein 5 (ACBD5) is a peroxisomal membrane protein with a C-terminal membrane-spanning region and an N-terminal cytosolic acyl-CoA binding domain that is postulated to function as a peroxisomal membrane-bound receptor for very long chain fatty acids (VLCFA) facilitating their transport into the peroxisome and subsequent β-oxidation.[2,3] The absence of ACBD5 in human skin fibroblasts did not affect the biogenesis of peroxisomes, but impaired peroxisomal beta-oxidation of VLCFA leading to elevation of the level of cellular phospholipids containing VLCFA without affecting peroxisomal biogenesis.[3,4]

Biallelic pathogenic variant in the *ACBD5* gene was first described in 2013 to be associated with retinal dystrophy and leukodystrophy in three siblings from a consanguineous Saudi family.[5] In 2017, Ferdinandusse et al described a nine-year-old girl from the United Arab Emirates (UAE) who had retinal dystrophy, leukodystrophy in addition to cleft palate and facial dysmorphism.[3] In 2021, Bartlett et al described a 36-year-old Brazilian female with retinal dystrophy, leukodystrophy, and psychomotor regression[6] followed by a report of two Turkish sisters aged five and nine years with early onset nystagmus, progressive motor decline and ataxia[7] making a total of seven reported cases

up to date. Here we report five Omani patients from four families to further emphasize the consistent clinical, radiological, and biochemical findings and expand the phenotypic spectrum of this relatively newly recognized disorder.

Case Reports

Case one

Case 1 is a ten-year-old boy, the first child to non-consanguineous parents. He was noticed to have nystagmus at the age of three months. Spasticity was noted at the age of 14 months. Ophthalmic examination revealed horizontal and pendular nystagmus, sensitivity to light, severe visual impairment in both eyes, and mild compound myopic astigmatism. Fundus examination showed pale discs with attenuated vessels and pigmentary changes at the macula which progressed to atrophy with mild tessellation of the background retina. Electroretinogram (ERG) showed severe cone-rod dysfunction. Very long chain fatty acids (VLCFA) profiling showed elevated C26:0 (1.36 umol/L, normal 0.23+/-0.09) and C26:0/C22:0 ratio 0.27 (0.01-0.004) along with elevated pristanic and phytanic acids suggestive of a peroxisomal disorder. Other investigations included normal echocardiography and nerve conduction study (NCS). Intelligence Quotient (IQ) test by Stanford Binet 5th edition at the age of six years showed a total IQ of 65 corresponding to mild intellectual disability. Brain magnetic resonance imaging (MRI) showed demyelinated periventricular and deep white matter [Table 1, Figure 1: A, B, C, D, E, F]**.** Whole Exome Sequencing (WES) of his younger affected sibling (Case 2) identified a homozygous deletion in exons 7 and 8 of the *ACBD5* gene. Upon assessment at the age of ten years, the patient had worsening mobility, intention tremor, and scanning speech. He was wheelchair-bound and was able to type with great difficulty. He had full bladder and bowel control. He was microcephalic (head circumference at -3.6SD) with weight and height below the 2nd percentile as well (both at -2.7SD). Neurological examination was remarkable for central hypotonia, severe lower limb spasticity and scissoring, ankle joint contractures, and brisk deep tendon reflexes.

Table 1: Summary of the clinical features of the Omani patients with ACBD5-related Retinal Dystrophy with Leukodystrophy/

	Family 1		**Family 2**	**Family 3**	**Family 4**
	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**
Age at the time of reporting (years)	10	4	7	10	30
Anthropometry: Head circumference Weight Height	 -3.6SD -2.7SD -2.7SD	 10th %ile 8th %ile 2nd %ile	 -3SD -4.8SD -4.5SD	All at the 5th-10th percentile	 2nd %ile 57 kg 171 cm
Genetic variant in *ACBD5* gene	homozygous deletion of exons 7-8	homozygous deletion of exons 7-8	homozygous deletion of exons 7-8	homozygous deletion of exon 4	homozygous deletion of exon 4
Ophthalmological features					
Age at presentation	2 years	2.5 years	18 months	16 months	17 years
Age of onset	3 months	3 months	5-6 months	3 months	< 6 months
Age of last ophthalmic assessment	9 years	4 years	7 years	7 years	21 years
Photophobia	+	+	+	+	+
Nystagmus (Horizontal, Pendular)	+	+	+	+	+
Visual Acuity at presentation	OU: <6/60*	OD: FF; CUSM OS: FF; CUSM	OD: FF; CSM OS: FF; CSM	OU: <6/60*	OU: <6/60*

(Qualitative assessment)					
Vision when last seen	OU<6/60	OU FF; CUSM	OU< 6/60*	OU: < 6/60	OU: <6/60
Refractive error	mild myopic astigmatism	mild mixed astigmatism	moderate myopic astigmatism	mild compound astigmatism	mild myopia
Pupils reaction to light	sluggish	sluggish	sluggish	sluggish	sluggish
Fundus					
Disc pallor	+	+	+++	++	++
Vessel attenuation	++	+	+++	++	+++
Macula	atrophic	dull	atrophic	dull	dull
Pigmentary changes in the retinal background	- not present	not present	mild granularity	not present	mild granularity
ERG	severe cone-rod dysfunction	severe cone-rod dysfunction	severe cone-rod dysfunction	severe cone-moderate rod dysfunction	severe cone-rod dysfunction
Age when ERG done	2 years	2.5 years	2 years	7 years	25 years
Neurological features					
Onset of symptoms	14 months old	3 years 6 months	11 months	13-14 months	15yrs
Central hypotonia	+	+	+	NA	NA
Lower limbs Spasticity	+	-	+	+	+
Intention tremor	+	+	-	+	+
Cognitive disabilities	mild intellectual disability	not assessed	learning difficulty-no formal assessment	learning difficulty-no formal assessment	No
Overall motor function	wheelchair-bound	can walk with support	pull up to stand and cruise around furniture	able to walk with support	wheelchair-bound
NCS (age)	normal (6 years)	normal (3years 7 months)	not done	not done	mild motor neuropathy (25 years)
Brain MRI findings	bilateral signal abnormalities in deep white matter with posterior pattern	bilateral deep white matter signal abnormalities with posterior pattern	bilateral signal abnormalities of deep white matter with posterior pattern	bilateral confluent white matter changes mainly periventricular and splenium	abnormal signal in bilateral CS tracks reaching up to the brain stem, atrophy of brain stem, cerebellum, and thoracic spinal cord

** Vision tested with sugar pearl test (single dark pearl identification is equivalent to Snellen 6/60)*
C S M: Central, Steady, Maintained; FF: Fixing and Following; US: Unsteady; OD: - right eye, OS: left eye, OU: both eyes;
Grading of findings: + mild, ++ moderate, +++ severe, - absent; ERG: Electroretinogram; NCS: nerve conduction studies; CS: corticospinal, NA: not available

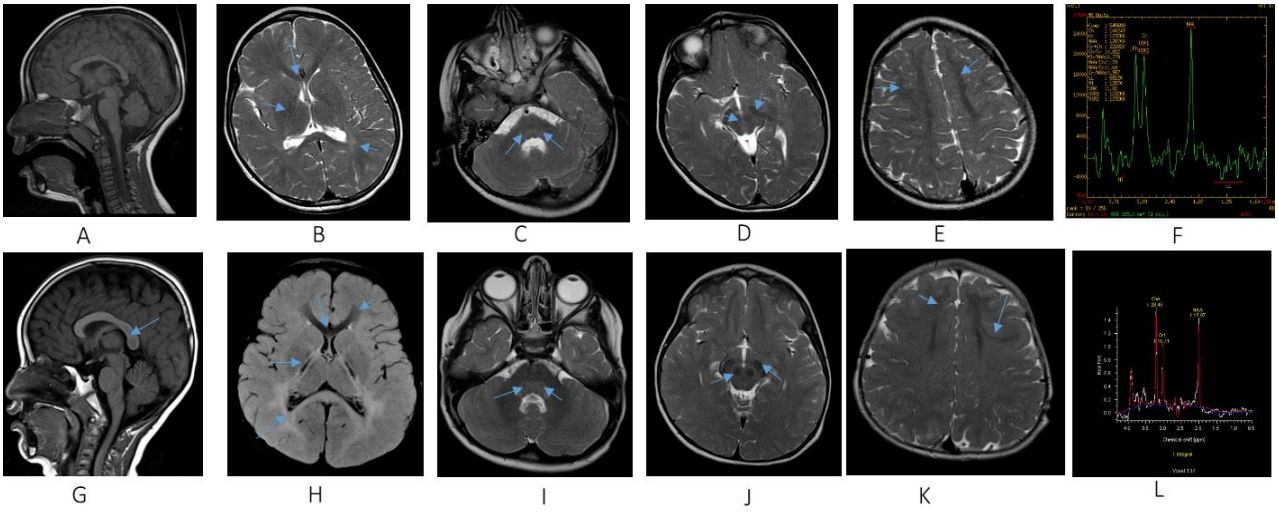


Figure 1. Comparative MR brain of 10 years old boy (Case 1) obtained at age of 4 years (A, B, C, D, E, F) and MR brain of his sibling (Case 2), 4 years old boy obtained at age of 3 years (G, H, I, J, K, L): sagittal T1W (A,G), axial FLAIR (H), axial SE T2W (B, C, D, E, I, J, K) images and MRS (F, L) showing diffusely altered hypomyelinated/demyelinated periventricular and deep white matter with posterior pattern due to dominant involvement of parietal and occipital lobes (B, H), splenium corpus callosum (B, G, H) and posterior pontine tegmentum (C, I); visible residual preserved hypointense myelinated white matter at frontal lobes (E, K), also with sparing subcortical fibers (E, K) and genu of corpus callosum (B, H); consequent striking appearance of posterior limb of internal capsule (B, H), substantia nigra and red nuclei in midbrain (D, J) and medial lemniscus identified as hypointense dots in posterior pontine tegmentum (C, I); MR Spectroscopy correlates with metabolic disorder presenting in Case 1 with moderately decreased N acetylaspartate (NAA) and increased Choline (F) and more significantly lower NAA and elevated Choline in Case 2 (L); all described structures are marked with arrows on mentioned images.

Case two

Case 2 is the four-year-old male sibling of case 1 who started to have nystagmus and photosensitivity at the age of 5 months. He started to walk independently at the age of 15 months. At the age of three years, he presented with rapid deterioration with unsteadiness followed by a complete loss of independent walking. His speech progressed well in the first two years but regressed thereafter. Assessment at the age of four years showed head circumference at the 10th percentile, weight at the 8th percentile and height at the 2nd percentile. Physical examination revealed head titubation with intention tremor, hypotonia with hyperextensible large joints, contractures in Achilles' tendons bilaterally, and brisk deep tendon reflexes. Visual evoked potential (VEP) showed no response in the right eye and the left eye response appeared to be normal. Ophthalmic examination showed nystagmus, photosensitivity, severe visual impairment, mild mixed astigmatism, pale discs, attenuated vessels, as well as a dull foveal reflex in both eyes. ERG showed severe cone-rod dysfunction. Brain MRI/MRS features as detailed in Table 1 [Figure 1: G, H, I, J, K, L]. WES (Centogene, Rostock, Germany) revealed a homozygous deletion by CNV analysis in exons 7 and 8 of the *ACBD5* gene.

Case three

Case 3 is a seven-year-old female child who is the second-born to a first-cousin couple. She started to have nystagmus and photophobia at the age of five months. Lower limb spasticity was noted at the age of 11 months when she started to pull to stand. At the age of seven years, all her growth parameters were below the second percentile with weight at -4.8SD, height at -4.5SD, and head circumference at -3SD. She was cruising around furniture and crawling but was unable to take independent steps. She had clear speech but significant learning disability. Neurological examination revealed upper limb hypertonia, severe lower limb spasticity, hyperreflexia, and extensor plantar response bilaterally. There was no intention tremor or dysarthria. Ophthalmic examination was positive for nystagmus, photosensitivity, moderate myopic astigmatism and severe visual impairment. Fundus examination revealed disc pallor, attenuated vessels, and mild granularity of the background retina with pigmentary changes at the macula which progressed to an atrophic macula. VEP showed significant delayed P2 latency and severely reduced P2 amplitude indicating a severe nerve fibre loss and ERG showed severe cone-rod dysfunction. Brain MRI at the age of three years showed bilateral

signal abnormalities of deep white matter, mainly involving the posterior limb of the internal capsule and splenium. VLCFA profile showed elevated C24:0 at 84.25 umol/L (18.99 - 72.54) and C26:0 at 1.71 umol/L (0.00 - 1.08) with normal C26:0/C22 and C26:0/C24:0 ratios and normal phytanic acid. Retinal dystrophy gene panel (Manchester University, NHS Foundation Trust, Manchester, UK) revealed a homozygous deletion of exons 7 and 8 of the *ACBD5* gene.

Case four

Case 4 is a ten-year-old girl who was the first-born to double-first-cousin parents. She presented with horizontal nystagmus and photophobia at the age of three months. Findings on ophthalmic examination included severe visual impairment, pale optic discs, attenuated retinal arterioles, dull foveal reflexes and pigmentary retinopathy [Figure 2]. ERG confirmed the presence of severe cone-rod dystrophy. The patient attained independent walking at the age of 13 months and by the age of 2 years, she was found to have gait unsteadiness, intention tremors, and lower limb hyperreflexia. By the age of three, her gait worsened with frequent falling and eventually progressed to limited independent walking and severely spastic gait. She is having poor school performance. Physical examination at the age of eight years revealed weight, height, and head circumference were at the 5^{th} to 10^{th} percentile. Neurological examination was remarkable for intention tremors, lower limb spasticity, and generalized hyperreflexia with bilateral ankle clonus.

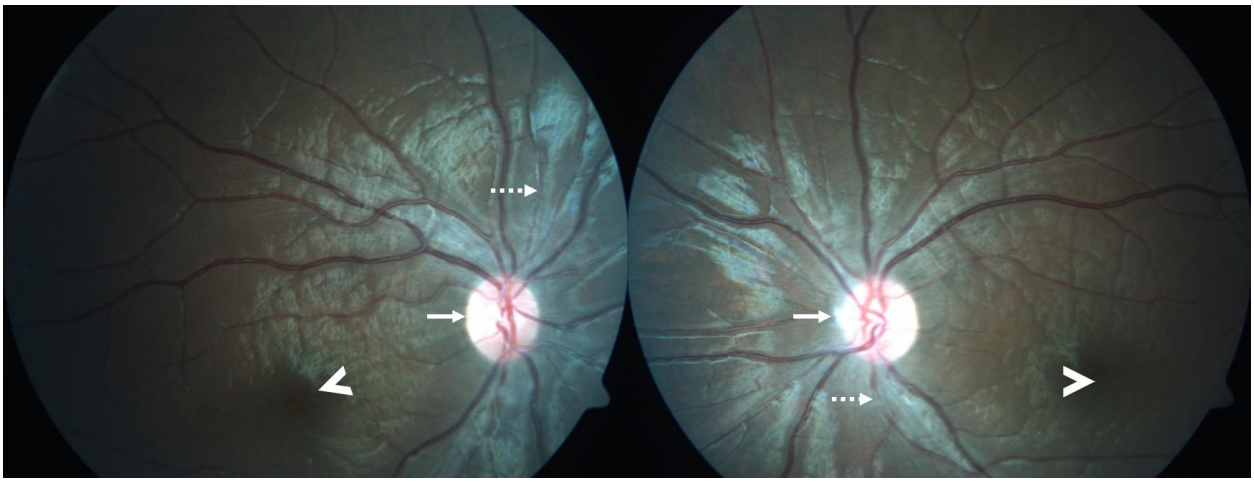


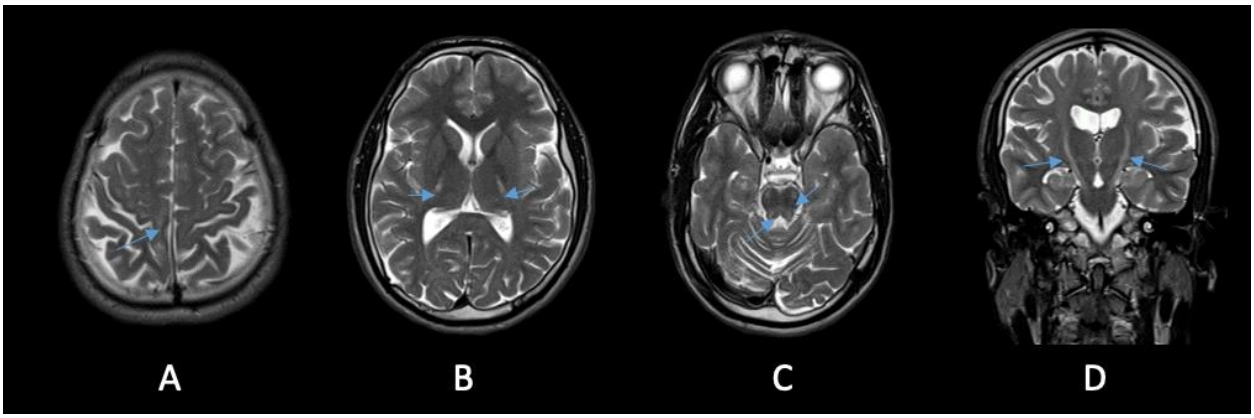
Figure 2: Fundus photographs (Case 4) showing moderate diffuse optic disc pallor (solid arrows), moderate arteriolar attenuation (dashed arrows), dull macular and foveal reflexes (arrow heads), and normal retinal background.

Brain MRI at the age of four years showed bilateral confluent white matter changes- mainly in periventricular and splenium areas. MRS showed moderately decreased NAA and elevated Choline. VLCFA showed mildly elevated C26:0 at 1.24 umol/L (0.00 - 1.08) and elevated C24:0/C22:0 1.288 (0 - 1.158) ratio with a normal pristanic acid level. WES (Breda Genetics, Brescia, Italy) identified a homozygous deletion in exon 4 of the *ACBD5* gene.

Case five

Case 5 is a 30-year-old man who was born to consanguineous parents. Photophobia and nystagmus were noted in the first months of life with progressive visual impairment leading to attending a school for children with visual needs. Gait unsteadiness was noted first at the age of 15 years and by the age of 17 years, he had progressive walking difficulties and ataxia. He joined university and is currently working as a medical recorder in a hospital. During the last assessment, he was fully wheelchair-dependent. He did not report any swallowing difficulties and has no dysarthria. There was no history of urine or bowel incontinence, seizures, memory impairment or behavioral changes. Physical examination showed a thin man with body mass index of 19 and a head circumference on the second percentile. He had normal muscle tone and deep tendon reflexes with normal muscle strength in the upper limbs. Lower limb examination showed bilateral pes cavus and significant distal weakness with no joint contractures. His muscle tone was increased with hyperreflexia and bilateral extensor plantar response. Temperature, pain and touch sensation was intact but lower limbs' sense of joint position was impaired. Coordination was impaired with intention tremor and dysmetria.

Ophthalmology assessment done at 21 years of age showed nystagmus, severe visual impairment, disc pallor, attenuated vessels, and pigmentary changes at the macula. ERG confirmed severe cone-rod dysfunction. NCS at the age of 25 years showed mild motor neuropathies (axonopathy). MRI brain at 17 years and 25 years of age are detailed in Table 1 and Supplementary Figure 1. WES (Centogene, Rostock, Germany) identified a homozygous deletion in exon 4 of the *ACBD5* gene.



Supplementary Figure 1: Brain MRI of Case 5, a 30-year-old male, obtained at the age of 25 years: A, B, and C axial T2-weighted images showing hyperintensity of corticospinal tracts (marked with arrows) bilaterally from perirolandic cortex (A) throughout posterior limb of internal capsule (B) reaching the pontine level (C); visible atrophic changes of cerebellum (C) and parietal lobes on brain convexity (A); also presenting signal alteration at posterior pontine tegmentum and both superior cerebellar peduncles (C). Figure 2D: coronal T2W image showing bilateral involvement of corticospinal tract.

Discussion

The physiological importance of the *ACBD5* gene in peroxisomal β-oxidation of very-long-chain fatty acids (VLCFAs) was highlighted in 2013 through the discovery of three symptomatic siblings with retinal dystrophy and severe white matter disease through exome sequencing for a cohort of syndromic and non-syndromic retinal dystrophy patients.[5] The cardinal features of ACBD5-related retinal dystrophy with leukodystrophy (RDLKD) were consistent with subsequent reports and included infantile-onset nystagmus followed by motor deterioration, spasticity, cerebellar symptoms and cognitive disability.[3,6,7] Ferdinandusse et al proved that ACBD5 defect leads to accumulation of VLCFAs as a result of an impaired peroxisomal β-oxidation of these fatty acids. They demonstrated increased levels of C26:0 lysophosphatidylcholine (C26:0 lysoPC) and/or C26-acylcarnitine in plasma, dried blood spot and fibroblasts from their patient with other peroxisomal parameters in blood being normal (ie, plasma phytanic acid, pristanic acid and pipecolic acid, and plasmalogens in erythrocytes) in a pattern that was similar to patients with X-linked adrenoleukodystrophy. The group also confirmed the absence of ACBD5 protein in the HeLa cells (HeLaΔACBD5) by immunoblotting.[3]

The oldest patient reported to date, a 36-year-old Brazilian lady who, in addition to being wheelchair-bound, had developed significant cognitive decline, upper extremity weakness and difficulty with fine motor movements, sphincter incompetence, and neurogenic bladder during the second decade of life and severe dysphagia with gastrostomy dependence during the fourth decade.[6] However, the patient from UAE had additional malformations exhibited by facial dysmorphism and a cleft palate. This patient, interestingly, was homozygous for the exon 7 and 8 deletion in the *ACBD5* gene that was also identified in three patients in this cohort. None of our five patients, including the three with the same variant of the UAE patient, nor the additional patients reported by Bartlett et al and Gorukmez et al had the extra features described by the Ferdinandusse group supporting the assumption that the malformations observed in the UAE child are likely to be unrelated to ACBD5 deficiency.

In all, the onset of neurological symptoms was evident by the first three years of life except for case 5. This 30-year-old man had no motor limitations until the age of 15 years. He is also the only patient with normal cognitive function and at the age of 30. It is difficult to correlate the difference in his neurological function on his genotype, as he shares the same homozygous deletion of exon 4 with case 4, a patient with earlier age of onset of neurological manifestations.

Growth restriction and microcephaly were also frequent features among the patients in this group, specifically those who have a homozygous deletion in exons 7 and 8 and there was no growth abnormality or microcephaly in cases 4 and 5, both harboring the same homozygous out-of-frame deletion of exon 4.

Retinopathy is a recurrent pathology in patients suffering from disorders in peroxisome biogenesis. Studies on the murine retina[8] showed that peroxisomes can be detected in all retinal layers and there is high expression of ACBD5 in retinal outer segments.[9] The high expression of ACBD5 in retinal outer segments suggests that polyunsaturated fatty acids (PUFA) and VLCFA, besides being recycled to the photoreceptors, can be taken up and degraded by peroxisomes.[9] As well, it was shown that ACBD5 functions to tether peroxisomes to the endoplasmic reticulum.[10] Retinopathy in *ACBD5* mutations is assumed to be related to impairment in these functions and impaired metabolism of VLCFA and PUFA that are crucial components of the retina. Retinal dystrophy occurred in virtually all patients with *ACBD5* null mutations reported to date and the ocular manifestations in all patients were very similar in the age of onset, presenting symptoms and fundus findings and ERG finding of cone-rod dystrophy. It seems that retinal involvement does not correlate with age of onset or severity of the neurological disease leading to the assumption that milder missense variants may manifest as isolated non-syndromic retinal dystrophy.

The VLCFAs level was done in three patients and showed a similar pattern to the four previously reported patients with elevations of C26:0 with or without elevations of C24:0, C26:0/C22:0 and C24:0:C22:0 ratios. Although nonspecific, this biochemical parameter can provide an important clue on the diagnosis of this peroxisomal disorder in patients with consistent clinical findings.

The neuroradiological features of patients in this cohort are fairly consistent and show a recognizable pattern similar to previously reported patients with hypomyelination with diffuse hyperintense T2 and Flair signal abnormality in white matter with relative sparing of the subcortical U fibers that extend along the cerebrospinal tracks involving bilateral cerebral peduncles up to the brain stem. The demonstration of atrophic changes in the bilateral cerebellar hemispheres, brainstem and the thoracic spinal cord in the eldest reported patient was consistent with the more pronounced atrophic changes described by Bartlett et al[6] and supports the observed progressive neurodegenerative nature of this disease. The MRS metabolites were consistent as well in all our five patients and previously reported with decreased NAA and increased Choline.

Conclusion

This report supports the previous observations that ACBD5-related RDLKD is a well-recognized neurodegenerative disease of peroxisomal fatty acids beta-oxidation with early onset cone-rod dystrophy and variable age of onset of neurological decline that is characterized by progressive spastic paraparesis, ataxia and cognitive decline. RDLKD should be included in the differential diagnosis of patients with retinal dystrophy associated with progressive spastic paraparesis and cerebellar symptoms.

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