

## Pseudo-neonatal Adrenoleukodystrophy: A Rare Peroxisomal Disorder

Dear Sir,

Peroxisomes are essential subcellular structures that play an essential role in the alpha- and beta-oxidation of fatty acids, glyoxylate detoxification, and biosynthesis of plasmalogens, bile acids, and docosahexaenoic acid.<sup>[1,2]</sup> Peroxisomal disorders are broadly classified into disorders of peroxisomal biogenesis (PBDs) and single peroxisomal enzyme deficiencies (PEDs).<sup>[1,2]</sup> Pseudo-neonatal adrenoleukodystrophy (peroxisomal acyl-CoA oxidase deficiency) is a rare autosomal recessively inherited peroxisomal disorder belonging to PEDs.<sup>[1,2]</sup> It occurs due to defective beta-oxidation of very-long-chain fatty acids (VLCFA) in the peroxisomes secondary to acyl-CoA

oxidase-1(ACOX1) deficiency, with only around 30 cases reported in the literature.<sup>[3-8]</sup> Herein, we report a novel pathogenic nonsense variant c. 1573C > T (p.Arg525Ter) on exon 11 of *ACOX1* gene in a 2-year 6-months boy with some unique features.

A 2-year 6-month-old boy from India, born to a third-degree consanguineous couple, premorbid developmentally delayed presented to us with regression of acquired milestones for the past 4 months. He was firstborn of twin gestation at 36 weeks and 4 days by lower segment cesarean section (indication oligohydramnios). There was a spontaneous abortion of the second twin at 3.5 months gestation. Parents noticed

the child was floppy and was developmentally delayed since birth. He had a developmental age of 6–9 months before the onset of regression. The best developmental milestones attained were standing with support, immature pincer grasp, recognition of parents, and ability to speak monosyllables. From 2-years 2-months of age, he had a gradual loss of all attained milestones associated with exaggerated startle for loud sounds. There was no history of seizures or extrapyramidal symptoms. Family history was noncontributory. On examination, head circumference

was 47 cm (-1 to -2 Z score, WHO), weight 8 kg (< -3Z score, WHO), and had significant facial dysmorphism with hirsute forehead, broad eyebrows, deep-set eyes, up slanting palpebral fissures, depressed nasal bridge, epicanthic folds, short nose and philtrum, inverted V-shaped wide-open mouth, and retrognathia [Figure 1a]. He had a single transverse palmar crease, convergent strabismus, kyphoscoliosis, joint hyperextensibility, and hepatomegaly [Figure 1b]. He had poor visual fixation and tracking, absent response to sound stimuli, facial weakness, axial and appendicular hypotonia with exaggerated muscle stretch reflexes, and ankle clonus. A clinical possibility of autosomal recessively inherited late infantile-onset neuroregression with multisystemic involvement mainly mitochondrial or lysosomal storage disorder was considered.

Investigations showed normal hemogram, serum vitamin B12, homocysteine, fasting ammonia, lactate, and blood tandem mass spectrometry. Brainstem auditory evoked response showed bilateral absent waveforms. A nerve conduction study revealed sensory-motor axonal polyneuropathy. Skeletal muscle biopsy from the left quadriceps was inconclusive. Nonetheless, mitochondrial assay revealed respiratory chain complex IV deficiency with < 20% residual activity. Electroencephalogram, skin biopsy, and 2D echocardiogram were normal. A skeletal survey showed bilateral acetabular hypoplasia with no bony stippling on the patella [Figure 2a].



**Figure 1:** (a) Illustrating facial dysmorphism with hirsute forehead, broad eyebrows, depressed nasal bridge, short nose and philtrum, inverted V-shaped wide-open mouth, and minimal retrognathia (b) hyperextensibility of the wrist joint. (Consent taken)



**Figure 2:** (a) AP radiograph of the pelvis reveals bilateral acetabular dysplasia (b) Axial T1W Magnetization Prepared - Rapid Gradient Echo (MPRAGE) image of the patient at 31 months shows bilateral perisylvian polymicrogyria (arrows). Axial T2WI (c) and (d) demonstrate hyperintensity (arrows) in bilateral centrum semiovale and corticospinal tracts in the midbrain, respectively. Similar signal changes are appreciated along pyramidal tracts (arrows) involving basipons on coronal T2W (e) and medullary pyramids (f) on axial T2W images. There is also the involvement of peridentate cerebellar white matter (arrowhead) and dentate hilus with sparing of dentate nuclei (f). (Consent taken)

Brain magnetic resonance imaging (MRI) at 2 years 6 months of age showed bilateral posterior perisylvian, parietal polymicrogyria with T2/fluid attenuated inversion recovery (FLAIR) signal changes in the parieto-occipital white matter with extension along the posterior limb of the internal capsule and pyramidal tracts. T2/FLAIR signal changes were also noted in the peridentate cerebellar white matter and dentate hilus with sparing of dentate nuclei suggestive of a peroxisomal disorder [Figure 2b-f]. Blood C26:0 and C24:0 lysophosphatidylcholines (LPC) levels were 0.42  $\mu\text{mol/L}$  (cut off 0.1  $\mu\text{mol/L}$ ) and 0.86  $\mu\text{mol/L}$  (cut off 0.25  $\mu\text{mol/L}$ ), respectively. Genetic analysis revealed a novel homozygous nonsense variant c. 1573C > T (p.Arg525Ter) in exon 11 of the *ACOX1* gene (chr17:g. 73945587G > A; Depth: 90x) that results in a stop codon and premature truncation of the protein at codon 525 (p.Arg525Ter; ENST00000293217.5). The p.Arg525Ter variant has not been reported in the 1000 genomes, Exome Aggregation Consortium (ExAC), and our in-house databases. Genetic analysis of parents (asymptomatic) could not be done due to financial constraints. A final diagnosis of peroxisomal acyl-CoA oxidase deficiency due to a novel mutation in the *ACOX1* gene was made.

Human peroxisomal acyl-CoA oxidase (ACOX) encoded by the *ACOX* gene on chromosome 17q25 has three different enzymes (ACOX1, ACOX2, and ACOX3) with distinct substrate specificity.<sup>[1,2]</sup> ACOX1, also known as straight-chain fatty acyl-CoA oxidase, is expressed in the liver and kidneys which catalyzes the first and rate-limiting step in the beta-oxidation of straight-chain fatty acids in the peroxisomes. The first report of ACOX1 deficiency was described by Poll-The *et al.* in 1988 as pseudo-neonatal adrenoleukodystrophy (NALD) as the clinical and biochemical features mimicked NALD.<sup>[3]</sup> The clinical manifestation of ACOX1 deficiency is marked hypotonia, seizures, deafness, retinopathy, facial dysmorphism, psychomotor retardation followed by neuroregression and death in early childhood. It occurs in the neonatal or infantile period.<sup>[1,2]</sup> Less described features are recurrent miscarriages in the mother, renal caliectasis, bilateral nipple inversion, and osteopenia.<sup>[4-7]</sup> In adults, gait disturbances and cognitive impairment have been described.<sup>[8]</sup> Ferdinandusse *et al.*, (2007)<sup>[6]</sup> reported a large cohort of 22 patients of peroxisomal ACOX1 deficiency with no clear genotype-phenotype correlation. ACOX1 needs to be differentiated from D-bifunctional protein deficiency (DBP) and Zellweger syndrome. Patients with ACOX1 deficiency have less severe seizures, longer lifespan, and normal levels of branched-chain fatty acids in comparison to DBP.<sup>[1,2]</sup> In contrast to Zellweger syndrome, renal cysts, severe liver disease, and epiphyseal stippling are usually not observed in ACOX1 deficiency.<sup>[1,2]</sup>

Biochemically, ACOX1 deficiency results in defective peroxisomal beta-oxidation of straight-chain fatty acids leading to elevated very-long-chain fatty acids (C26:0, C24:0) levels and C26:0/C22:0, C24:0/C22:0 ratios in cells, tissues, and plasma with normal levels of branched-chain fatty acids, bile acid

intermediates, and erythrocyte plasmalogens.<sup>[1,2]</sup> Peroxisomal disorders are sometimes associated with mitochondrial structural and functional abnormalities.<sup>[3,9,10]</sup> Interleukin-1-mediated inflammatory process in ACOX1 deficiency probably explains the complex IV deficiency in our case.<sup>[11]</sup> Neuroimaging findings in peroxisomal ACOX1 deficiency can be normal in the initial few weeks followed by symmetrical de/dysmyelination in the parietooccipital region, cerebellar white matter, brainstem, and posterior limb of the internal capsule.<sup>[12]</sup> Neuronal migration defects have been rarely described. Hemopoietic stem cell transplantation attempted in two siblings by Wang *et al.*,<sup>[13]</sup> failed to show any beneficial response in the disease course though there was a reduction in dysmyelination in the brain parenchyma. Unique findings in our case were the presence of joint hyperextensibility, acetabular hypoplasia, absent left kidney, significantly reduced activity of mitochondrial respiratory chain complex IV activity, and migrational abnormality on imaging with a novel *ACOX1* variant.

## CONCLUSION

Though peroxisomal ACOX1 deficiency is a rare inherited peroxisomal disorder, it needs to be suspected in children presenting with neonatal hypotonia, psychomotor retardation or regression, seizures, dysmorphism, optic atrophy/retinitis pigmentosa, sensorineural hearing loss, and dysmyelination with migrational anomalies on neuroimaging. This case also highlights the importance of evaluation of VLCFA upfront in patients suspected with peroxisomal disorders and expands the phenotypic spectrum of peroxisomal ACOX1 deficiency.

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## Conflicts of interest

There are no conflicts of interest.

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