Peroxisomal acyl CoA oxidase deficiency: a rare inherited disorder of nervous system

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ABSTRACT

Background: Peroxisomal acyl CoA oxidase deficiency is a very rare neurodegenerative disorder characterised by postnatal hypotonia, seizures, and neurological regression in early infancy.

Case Presentation: Here, we present a case of two children in a family affected with peroxisomal acyl CoA oxidase deficiency. Early onset of hypotonia, seizures, and psychomotor delay was observed in both the sibs. Plasma levels of very long chain fatty acids showed normal levels of phytanic acid, pristanic acid, C22, C24, C26, C26/C22, and C24/C22 ratios. Here, we describe a case where women in her second trimester and with two affected siblings with peroxisomal acyl CoA oxidase deficiency was referred to institute for genetic counselling.

Conclusion: Clinical exome analysis of the couple, two affected sibs and the fetus adds new insight into the clinical, neuroradiological, and molecular aspects of this disorder that represents one of the rarer inherited defects of peroxisomal function.

Keywords: Peroxisomal acyl CoA oxidase deficiency; neurological regression; fatty acids.

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Background

Peroxisomes are the small organelles present in the cytoplasm of all eukaryotic cells and are responsible for reducing cell toxicity through metabolism of hydrogen peroxide to water and oxygen. The substrates metabolized by oxidative reactions in the peroxisomes include uric acid, amino acids, fatty acid, etc. Peroxisomes play a critical role in cellular metabolism, providing compartments where metabolic pathways are controlled by post-translationally importing all the matrix and membrane proteins required for its function [1]. Malfunctioning of peroxisomes is vital in the developmental brain disorders.

In addition to these, peroxisomes are also involved in biosynthesis of certain lipids known as plasmalogens [1]. Defective peroxisomal fatty acid β-oxidation pathway plays a crucial role in several peroxisomal disorders. The defect may arise due to the specific enzyme deficiency or transporter involved in peroxisomal β-oxidation or the absence of the complete organelle resulting from defective genes involved in peroxisome biogenesis and maintenance [1,2]. Furthermore, Danda et al. [3], demonstrated role of ubiquitinization in different aspects of peroxisome formation, maintenance, and degradation.

Several enzymes are involved in the metabolism of fatty acids and other biomolecules and any variation in the genes encoding these enzymes will result in accumulation of medium chain and very long chain fatty acids which in turn lead to impaired conversion to energy rich compounds resulting in signs and symptoms characteristic of peroxisomal disorders.

ACOX-1 gene codes for the enzyme acyl-CoA oxidase involved in the oxidation and break down of very long-chain fatty acids (VLCFAs) whereby it shortens to form acetyl-CoA, which is recycled to the cell for further energy driven functions. Up until now, more than 20 *ACOX1* gene mutations have been identified to be associated with peroxisomal acyl-CoA oxidase deficiency that prevents the breakdown of VLCFAs efficiently and lead to the accumulation of these fatty acids in the body, triggers inflammation and breakdown of myelin, leading to loss of myelin-containing tissue (white matter) of the brain and spinal cord that ultimately results in peroxisomal

acyl CoA oxidase deficiency. A variety of inherited diseases, such as ichthyosis, macular degeneration, myopathy, mental retardation, and demyelination, are caused by mutations in the genes encoding VLCFA metabolizing enzymes [4]. Dysfunction of peroxisome biogenesis leads to the occurrence of peroxisomal disorders and even death in early infancy [1,5-7].

Clinical heterogeneity with respect to this disorder is often noticed among infants and children with the characteristic features being neonatal hypotonia, seizures and neuroregression in early infancy. Facial dysmorphism includes hypertelorism, epicanthus, low nasal bridge, and low-set ears. Some children report polydactyly and hepatomegaly. Furthermore, psychomotor development is delayed, but children usually walk and talk in monosyllabels. Hypotonia is replaced by hypertonia with hyperreflexia in late infancy. Even severe epilepsy with sensory neural hearing loss may result due to this deficiency. Strabismus, nystagmus, and optic atrophy can also be seen on clinical screening, enlightening on the variable expressivity of this gene.

In the present context, we report the clinical, biochemical, and molecular characterization of a couple with acyl co A oxidase deficiency in two of her children with emphasis on the prenatal diagnosis of the condition with appropriate genetic counselling strategy.

Case Presentation

We describe a family wherein a 26-year-old female with a history of consanguinity and miscarriage in her second trimester along with her two sons, one with acyl CoA oxidase deficiency and other delayed milestones was referred for genetic Institute of Genetics for evaluation and prospective counselling for present pregnancy (Figure 1).

Methodology

The clinical and demographic details of the family members were obtained with the help of a proforma after examination by a clinician at institute. Both the sibs were evaluated for plasma levels of very long chain fatty acids by gas chromatography and mass spectrometry. Previous exome sequencing report of sib 1 revealed a homozygous variant in exon 10 of the *ACOX1* gene which was further validated by Sanger's sequencing. Based on the findings of sib one, exome sequencing analysis was commercially done by Medgenome Private Limited, Bangalore for the couple, sib 2 and prenatal diagnosis of the developing fetus by amniocentesis. Informed written consent was obtained from the proband.

Results

Clinical analysis

The 6-year-old child (sib one) was delivered by caesarean section at 36th week of gestation and presented with global developmental delay, facial dysmorphism, squint eye, low birth weight, seizures, hypertonia, delayed speech, walking inability and history of hypoglycemia. The MRI brain was not carried out for sib 1. The younger boy (sib 2) aged 4 years was also delivered by caesarean section at 36th week gestation, presented with global developmental delay, squint in left eye, delayed speech, delayed milestones, hypotonia and neonatal seizures. MRI of brain showed mild cerebral atrophy.

Biochemical studies

Both the sibs showed normal plasma levels of very long chain fatty acid like phytanic acid, pristanic acid, and C22, C24, C26, C26/C22, and C24/C22 ratios. The biochemical analysis was not carried out for the couple.

Molecular studies

Based on the clinical indications, biochemical analysis of sibs and exome analysis of sib 1 revealing a homozygous missense variant in exon 10 of the *ACOX1* gene (chr 17; 73945940; T>C: c.1337A>G) that resulted in the amino acid substitution of arginine for lysine at codon 446 (R446K) a pre-test counselling was given to the couple, *in silico* predictions were reported to be damaging by Likelihood Ratio Test (LRT) and Mutation Taster2.

For further extension of the findings, exome sequencing analysis was also evaluated for the couple and sib 2 followed by prenatal diagnosis of the developing fetus by amniocentesis. The couple along with sib 2 and foetus were found to be heterozygous/ carrier for C.1337A>G variant at exon 10 of *ACOX-1* gene.

Based on the above findings, the couple was offered genetic counseling by providing them with various options and advised to proceed with assisted reproductive technology to have an unaffected child since the disorder

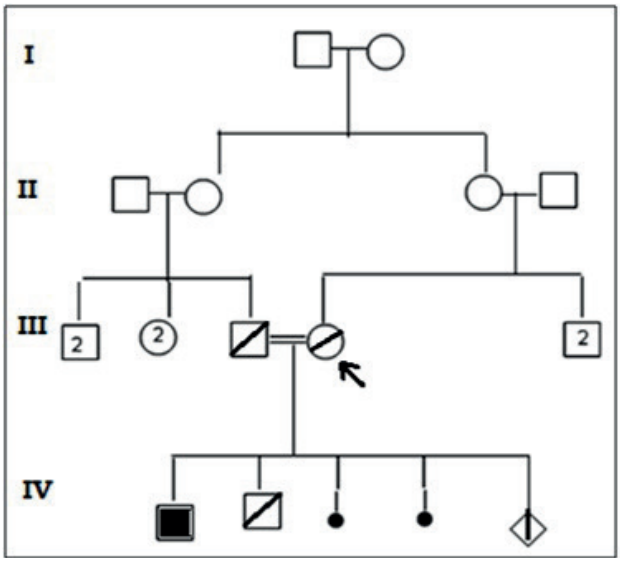

Figure 1. *Three generation pedigree of the couple referred for genetic counselling.*

is inherited in an autosomal recessive manner with the recurrence risk being 25%.

Discussion

Peroxisomal acyl CoA oxidase deficiency is a neurodegenerative disorder that leads to deterioration of nervous system at early infancy or childhood and seems to be inherited in an autosomal recessive fashion. It is caused due to mutations in the *ACOX1* gene, responsible for the oxidation of straight-chain fatty acids with different chain lengths.

The two sibs of the proband, referred to institute, presented with clinical manifestations like neonatal hypotonia, seizures, and psychomotor delay as reported by Carrozzo et al [8]. Biochemical analysis revealed normal plasma levels of very long chain fatty acids which was misleading as reported by Suzuki et al. [9,10] who reported involvement of increased levels of very long chain fatty acids in the diagnosis of peroxisomal disorders. However, molecular analysis helped in confirmation of *ACOX1* deficiency in both the sibs. A 1337 A>G variant (R446K) was identified in exon 10 which on *in silico* analysis found to be damaging. There is no confirmation that the substitution is causing debilitating effect. Sib one being homozygous for the particular variant with severe phenotypic expression compared to the sib 2, heterozygous for the same mutation indicating variable expressivity and proven genotype phenotype correlation.

In peroxisomal disorder, lipid derivatives with an abnormally high proportion of VLCFA residues have been proposed to trigger the initial cascade of the inflammatory process [11]. The severity of the metabolic disruption associated with peroxisomal *ACOX1* deficiency underlines the crucial role of peroxisomes in synthesizing or degrading highly specific metabolites, accumulation or deficit of which may impact peroxisome biogenesis itself and/or collaborative working with other cellular organelles such as mitochondria and endoplasmic reticulum.

Animal studies on mice by Fan et al. [12] demonstrated that mice lacking *ACOX1* manifest inflammatory and oxidative stress responses that may trigger TNFα production by Kupffer cells. Eichler et al. [13] revealed oxidative, inflammatory, and apoptotic processes in the brain lesions of patients with deficit peroxisomal β-oxidation. An increased expression of macrophages producing cytokines like IL-6, IL-8, and TNFα have also been reported to be associated with *ACOX1* deficiency [14]. Furthermore, overexpression of *ACOX1* causes activation of caspase-9 and caspase-3 and decrease of mitochondrial membrane potential while downregulation of *ACOX1* lead to increased p73 expression that ultimately form the basis for apoptosis [15].

The speculation of appropriate genetic counselling was a herculean task because of manifestation of mild form of disease in heterozygous condition. Thus, the couple were counselled about the pros and cons of the disease due to the heretozygous condition for the *ACOX-1* gene and advised for termination of pregnancy which was the only alternative.

Conclusion

In conclusion, the present study reports a rare familial case of peroxisomal acyl CoA deficiency for prenatal molecular diagnosis followed by genetic counselling adds new insight into the clinical, neuroradiological and molecular aspects of this disorder that represents one of the rarer inherited defects of peroxisomal function. Accurate diagnosis of this disorder, prenatal diagnosis at proper time followed by genetic counselling is necessary for preventing the birth of affected child with such rare disorders and suggest for assisted reproductive technologies for future pregnancies.

What is new?

The present study reports a rare familial case of peroxisomal acyl Co A deficiency, which adds new insight into the clinical, neuroradiological and molecular aspects of this disorder that represents one of the rarer inherited defects of peroxisomal function. Accurate diagnosis of this disorder, prenatal diagnosis at proper time followed by genetic counselling is necessary for preventing the birth of affected child and suggest for assisted reproductive technologies for future pregnancies.

List of Abbreviations

ACOX	acyl-CoA oxidase
IL6	Interleukin 6
IL8	Interleukin 8
LRT	Likelihood Ratio Test
TNFα	Tumor Necrosis Alpha
VLCFAs	Very long-chain fatty acids

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this case report.

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Consent for publication

Written informed consent was taken from the patient.

Ethical approval

Institutional ethical approval was obtained to publish this case report.

Author details

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References

1. Wanders RJ, Waterham HR. Biochemistry of mammalian peroxisomes revisited. Annu Rev Biochem. 2006;75:295–332. https://doi.org/10.1146/annurev.biochem.74.082803.133329
2. Oaxaca-Castillo D, Andreoletti P, Vluggens A, Yu S, van Veldhoven PP, Reddy JK, et al. Biochemical characterization of two functional human liver acyl-CoA oxidase isoforms 1a and 1b encoded by a single gene. Biochem Biophys Res Commun. 2007;360(2):314–9. https://doi.org/10.1016/j.bbrc.2007.06.059
3. Danda N, Williams C. Detection of ubiquitinated peroxisomal proteins in yeast. Methods Mol Biol. 2017;1595:233–41. https://doi.org/10.1007/978-1-4939-6937-1_22
4. Sassa T, Kihara A. Metabolism of very long-chain fatty acids: genes and pathophysiology. Biomol Ther (Seoul). 2014;22(2):83–92. https://doi.org/10.4062/biomolther.2014.017
5. Nagotu S, Kalel VC, Erdmann R, Platta HW. Molecular basis of peroxisomal biogenesis disorders caused by defects in peroxisomal matrix protein import. Biochim Biophys Acta. 2012;1822(9):1326–36. https://doi.org/10.1016/j.bbadis.2012.05.010
6. Poll-The BT, Gärtner J. Clinical diagnosis, biochemical findings and MRI spectrum of peroxisomal disorders. Biochim Biophys Acta. 2012;1822(9):1421–9. https://doi.org/10.1016/j.bbadis.2012.03.011
7. Waterham HR, Ebberink MS. Genetics and molecular basis of human peroxisome biogenesis disorders. Biochim Biophys Acta. 2012;1822(9):1430–41. https://doi.org/10.1016/j.bbadis.2012.04.006
8. Carrozzo R, Bellini C, Lucioli S, Deodato F, Cassandrini D, Cassanello M, et al. Peroxisomal acyl-CoA-oxidase deficiency: two new cases. Am J Med Genet A. 2008;146A(13):1676–81. https://doi.org/10.1002/ajmg.a.32298
9. Suzuki Y, Shimozawa N, Yajima S, Tomatsu S, Kondo N, Nakada Y, et al. Novel subtype of peroxisomal acyl-CoA oxidase deficiency and bifunctional enzyme deficiency with detectable enzyme protein: identification by means of complementation analysis. Am J Hum Genet. 1994;54(1):36–43.
10. Suzuki Y, Iai M, Kamei A, Tanabe Y, Chida S, Yamaguchi S,et al. Peroxisomal acyl CoA oxidase deficiency. J Pediatr. 2002;140(1):128–30. https://doi.org/10.1067/mpd.2002.120511
11. Paintlia AS, Gilg AG, Khan M, Singh AK, Barbosa E, Singh I. Correlation of very long chain fatty acid accumulation and inflammatory disease progression in childhood X-ALD: implications for potential therapies. Neurobiol Dis. 2003;14(3):425–39. https://doi.org/10.1016/j.nbd.2003.08.013
12. Fan CY, Pan J, Usuda N, Yeldandi AV, Rao MS, Reddy JK. Steatohepatitis, spontaneous peroxisome proliferation and liver tumors in mice lacking peroxisomal fatty acyl-CoA oxidase. Implications for peroxisome proliferator-activated receptor alpha natural ligand metabolism. J Biol Chem. 1998;273(25):15639–45. https://doi.org/10.1074/jbc.273.25.15639
13. Eichler FS, Ren JQ, Cossoy M, Rietsch AM, Nagpal S, Moser AB, et al. Is microglial apoptosis an early pathogenic change in cerebral X-linked adrenoleukodystrophy? Ann Neurol. 2008;63(6):729–42. https://doi.org/10.1002/ana.21391
14. El Hajj HI, Vluggens A, Andreoletti P, Ragot K, Mandard S, Kersten S, et al. The inflammatory response in acyl-CoA oxidase 1 deficiency (pseudoneonatal adrenoleukodystrophy). Endocrinology. 2012;153(6):2568–75. https://doi.org/10.1210/en.2012-1137
15. Zheng FM, Chen WB, Qin T, Lv LN, Feng B, Lu YL, et al. ACOX1 destabilizes p73 to suppress intrinsic apoptosis pathway and regulates sensitivity to doxorubicin in lymphoma cells. BMB Rep. 2019;52(9):566–71. https://doi.org/10.5483/BMBRep.2019.52.9.094

Summary of the case

1	**Patient (gender, age)**	Female, 26 years
2	**Final diagnosis**	Acyl CoA oxidase deficiency
3	**Symptoms**	Symptomless
4	**Medications**	-
5	**Clinical procedure**	Amniocentesis followed by exome sequencing
6	**Specialty**	Genetic counselling