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CASE REPORT

Saudi patient with peroxisome biogenesis disorder with novel variant: a case report

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ABSTRACT

Background: Peroxisomes are cells' organelles that responsible for the metabolism of branched-chain and very-long-chain fatty acids (VLCFA), polyamines, and amino acids. Peroxisomal biogenesis factor 6 (*PEX6*) is one of the factors required for the import of the proteins into peroxisomes. Mutation in any one of *PEX* genes will result in Zellweger syndrome (ZS), one of the peroxisome biogenesis disorder.

Case Presentation: A 11-year-old girl referred was with central hypotonia and global developmental delay and feeding problems. She has an open and flat fontanel. Liver function tests and thyroid-stimulating hormone were elevated. Plasma VLCFA C26, VLCFA C24/C22, and VLCFA C26/C22 were elevated. Cerebrospinal fluid flow artifact and posterior displacement of the basilar artery findings raised the possibility of increased intracranial pressure. X-ray showed mild irregularity in the end plates of the lumbar vertebrae, bilateral coxa valga, irregularity in the articular surfaces of the ossified epiphysis of the upper and lower limbs, and generalized osteopenia. The audiological assessment profound hearing loss in both ears. Inborn error of metabolism, next-generation sequencing gene panel analysis, and whole exome sequencing showed that no pathogenic or likely pathogenic variants explaining the phenotypes. The single nucleotide polymorphisms testing showed a deletion in *PEX6* gene (homozygous variant of uncertain significance).

Conclusion: We report a case of ZS associated with a new *PEX6* mutation that has not been previously reported in the literature.

Keywords: Peroxisome biogenesis disorder, *PEX6* gene, Saudi Arabia, VLCFA, Zellweger syndrome.

Introduction

Peroxisomes are single membrane organelles that exist in almost all eukaryotic cells (1). In human cells, the peroxisomes are important for the metabolism of branched-chain and very-long-chain fatty acids (VLCFA), ether lipids, polyamines, amino acids, and glyoxylate (2). It has been estimated that at least 85 proteins are associated with peroxisome structure and function in humans based on genetic, bioinformatic, and proteomic analyses (3). Peroxisome matrix proteins are synthesized on free ribosomes in the cytosol before import into the peroxisome (4). Peroxins, which are encoded by a group of 16 human *PEX* genes, are involved in peroxisome biogenesis, their major function ranges from membrane synthesis and matrix protein import to organelle division (5). Peroxisomal biogenesis factor 6 (*PEX6*) is one of the factors required for the import of the proteins into peroxisomes. Mutation in any one of the *PEX* genes is found to result in Zellweger syndrome (ZS) (6). In this study, we present a case with ZS caused by a rare deletion mutation in the *PEX6* gene.

Case Presentation

SA was 11 months old girl from Hail region in Saudi Arabia. She was born full-term via spontaneous vaginal delivery with no complications. Her birth weight was 2.9 kg. She was referred with central hypotonia, global developmental delay, and feeding problems which were noticed at 2 months of age. She has no history of seizures or recurrent admissions. No family history with a similar condition. Her parents are first-degree cousins, and she

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has a healthy 2-year-old sister. Her head circumference at birth was 33 cm. The clinical examination at the age of 11 months showed that she looked well and afebrile and could and move her limbs against gravity. Her weight (4.7 kg) and height (72 cm) were below the normal percentile. Her head circumference was 42 cm which is less than the third percentile. She had minor dysmorphic features including epicanthic folds of the eyes and depressed nasal bridge; however, it was not an ideal dysmorphic feature of ZS. She had a wide anterior fontanel, which was open and flat. The cardiovascular examination revealed that S1 and S2 heart sounds were heard and normal. Her abdomen was soft, lax, without organomegaly. She had mild jaundice. Her pupils were equal, round, and reactive to light with no facial asymmetry. She had axial hypotonia more than appendicular hypotonia. Her deep tendon reflexes were normal (2+), and her toes normal plantar reflex. Her back examination was normal. Her investigation showed that she had normal renal function tests. Her liver function tests were abnormal [alanine aminotransferase was 95.1 U\l (normal level 13–45 U/l), and aspartate aminotransferase was 272 U\l (normal level 9–80 U/l)]. The thyroid-stimulating hormone was elevated (4.64 mIU\l). Plasma VLCFA revealed elevated VLCFA C26 (4.237 μmol/l; normal range 0.450–1.320 μmol/l), VLCFA C24/C22 (1.29; normal level ≤1.20), VLCFA C26/C22 (0.110; Normal level ≤0.028), and phyanic acid (17.43 μmol/l; Normal level ≤12.01 μmol/l). The pristanic acid and biotinidase levels were normal. Plasmalogen level was not done.

The abdominal ultrasound showed mild hepatomegaly while the kidneys, pancreas, spleen, and gallbladder were normal. Brain magnetic resonance imaging revealed that there was no gross structural abnormality. The myelination process was up to the patient's age, characterized by T2 hypo-intensity and slightly faint along with the margin's areas of both frontal lobes. Mild diffuse cerebral volume loss, and this is nonspecific in origin. Prominent cerebrospinal fluid (CSF) spaces in peri-optic nerve sheath with flattening of optic nerve/global junction were detected. The sagittal T2 demonstrates compression of the diaphragm Sella, CSF flow artifact slightly, and posterior displacement of the basilar artery; findings raised the possibility of increased intracranial pressure.

X-ray doesn't show stippling. However, mild irregularity in the endplates of the lumbar vertebrae, bilateral coxa valga, irregularity in the articular surfaces of the ossified epiphysis of the upper and lower limbs, and generalized osteopenia was seen in the X-ray.

She was assessed in the Ophthalmology clinic, and there was no papilledema. The normal flash of visual evoked potential indicated that she could see, and some visual input reaches the cortex but not indicated that the visual system intact or visual perception is preserved. Electroretinography was present bilaterally.

The audiological assessment revealed that she had severe to profound hearing loss in both ears. Based on the bone conduction click auditory brainstem response assessment threshold and tympanometry test results, the hearing loss is sensorineural. A significant worsening was noticed in hearing thresholds at tested frequencies in both ears compared to the previous assessment. Histochemistry, skin fibroblast electron microscopy, and complementation study were not done at present.

Inborn error of metabolism , next-generation sequencing gene panel analysis, and Whole exome sequencing were made to figure out the genetic cause for her phenotypes (failure to thrive, microcephaly, fine, intellectual disability, developmental delay, and elevated VLCFA and to rule out peroxisomal disorders. No pathogenic or likely pathogenic variants explaining the phenotype were identified. The single nucleotide polymorphisms testing showed a deletion in the *PEX6* gene (homozygous variant of uncertain significance), SNPs of parents showed that they are heterozygous for this variant. However, the older sibling was normal. Our case is highly likely to have a peroxisome biogenesis disorder as ZS.

Discussion

ZS is an autosomal recessive disease that result from defective peroxisome biogenesis (7). This disorder is caused by any defect in one or more of the 16 *PEX* gene factors responsible for importing the required protein to the peroxisome (6–8). *PEX6* is a protein-coding gene that encodes a member of the ATPases associated with diverse cellular activities proteins (AAA) ATPases. This member is a cytoplasmic protein that helps in the import of proteins in the peroxisome, in addition to its role in the activation of the peroxisomal targeting signal zx1receptors (9). Defects in the complementation group four and complementation group six result from the peroxisome biogenesis disorders caused by mutations in this gene (10). Several transcript variants encoding different isoforms have been found for this gene. Still, in this case, the patient has a transcript variant and isoform, which has not been reported before, according to https://databases.lovd.nl/shared/genes/PEX6. In this study, the *PEX6* variant is caused by a deletion in a portion of the DNA from 227 to 253 (c.227_253del).

In this study, we report a patient with a novel variant in the *PEX6* gene that proved pathogenicity with elevated VLCFA. Our patient was presented with a feeding problem, central hypotonia, global developmental delay, and profound hearing loss. The patient's genetic analysis revealed a mutation in the *PEX6* gene that has not been previously described in the literature, likely to have a peroxisome biogenesis disorder like ZS. The diagnosis of ZS was depended not only on clinical phenotype but also on particular laboratory and genetic abnormalities. Our patient also had elevated VLCFA, which was consistent with the diagnosis of ZS (11). The long fatty chain of VLCFA metabolized in peroxisomes rather than mitochondria. Defects in multiple peroxisome enzyme pathways caused by mutations in the *PEX* family lead to the accumulation of downstream fatty chains (12). Moreover, *PEX6* gene mutations are the second most common cause of ZS disorders (approximately 16%). The *PEX6* mutational spectrum comprises of 104 different mutations. One-third of mutations are found in exon1. Among the 104 mutations, 37 missense, 5 nonsense, 32 deletion, 9 insertion, 1 indel, and 20 splice site mutations has been identified (10). Although many mutations have

been reported, this study presents a novel *PEX6* gene deletion mutation that has not been reported before.

Conclusion

In summary, we report a case of ZS associated with a novel *PEX6* mutation. This case broadens the spectrum of ZS patients' clinical expression because of the presence of severe hypotonia, failure to thrive, and deafness and the absence of some clinical expression of ZS as dysmorphic features and seizures.

Author contribution

AA, RR, ZR conceived, designed the study, and edited of the manuscript. AA collected the data. AAA helped in writing the manuscript. All authors reviewed and approved final draft of the manuscript.

List of abbreviations:

AAA	ATPases associated with diverse cellular activities proteins
ABR	Auditory Brainstem Response
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
CSF	Cerebrospinal Fluid
ERG	electroretinography
IEM	Inborn error of metabolism
NGS	next-generation sequencing
PEX	Peroxisome Biogenesis Factor
SNP	Single Nucleotide Polymorphisms
TSH	thyroid-stimulating hormone
US	Ultrasound
VEP	visual evoked potential
VLCFA	Very long chain fatty acids
WES	Whole exome sequencing
ZS	Zellweger syndrome

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The authors of this report have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Consent for publication

Written informed consent was obtained from the parents.

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