Case Report

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Zellweger Syndrome with Novel PEX1 Variants and Unusual Periventricular Leukomalacia in a Term Infant: A Case Report

Paediatrics Section

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ABSTRACT

Zellweger syndrome is a rare disorder due to mutations in PEX genes, resulting in defective peroxisome biogenesis and multi-systemic features. This is a case of a male infant born at term via caesarean section due to breech presentation, who experienced perinatal asphyxia and demonstrated the characteristic features of the syndrome such as facial dysmorphism, hypotonia, renal cysts and hepatic dysfunction along with a novel finding of Periventricular Leukomalacia (PVL). Despite intensive supportive care, the infant's condition progressively worsened, with complications such as aspiration pneumonia and sepsis leading to death at five months. Genetic testing revealed two previously unreported heterozygous variants in the PEX1 gene: a splice site variant within intron 13 and a frameshift mutation in exon 5, both predicted to significantly impair protein function. The PVL, which is rarely seen in a term infant with Zellweger syndrome, is caused by oxidative stress, mitochondrial dysfunction, and defective myelination. This case highlights the importance of genetic testing for diagnosis as well as genotype-phenotype correlation, thereby adding to the existing mutation database. There is no cure and life expectancy is short, but early diagnosis and supportive care can improve quality of life.

Keywords: Cyst, Dysmorphism, Mitochondrial, Mutation, Myelin

CASE REPORT

A male neonate, second born to a consanguineously married couple, was referred from a local hospital two days after birth due to perinatal asphyxia and inability to maintain oxygen saturation.

The neonate was delivered at 37 weeks of gestation via Lower Segment Caesarean Section (LSCS) due to breech presentation after an uneventful pregnancy with normal antenatal scans with no significant family history or maternal comorbidities. The newborn had a feeble cry after tactile stimulation. Abnormal facies, hypotonia, a weak sucking reflex and a limp tone were noted. A wide anterior fontanelle, prominent occiput, a low nasal bridge with anteverted nares, micrognathia, redundant neck skin, simian crease, cryptorchidism, moderate pinna deformation, joint hyper-flexibility and Congenital Talipes Equinovarus (CTEV) were present as shown in the [Table/Fig-1].

The baby was admitted in the neonatal intensive care unit due to clinically suspected sepsis with tachypnoea and tachycardia. Gentamicin 10 mg once daily and amoxicillin–clavulanate potassium 100 mg twice daily were administered empirically for 10 days, and oxygen saturation was maintained.

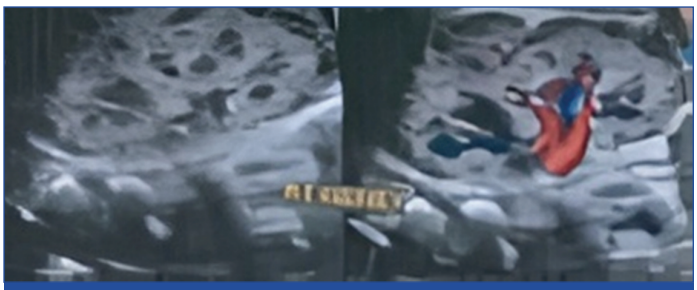
Karyotyping was done, suspecting Down's syndrome but it was negative. Ultrasonography (USG) of the abdomen revealed bilateral polycystic kidneys as shown in [Table/Fig-2]. The Common Bile Duct (CBD) was dilated to 4.6 mm and mild central Intrahepatic Biliary Radicle Dilatation (IHBRD) with a measurement of 3.4 mm was noted. PVL with cystic changes was observed in USG cranium [Table/Fig-3] which explained the neonate's hypotonia and abnormal neurologic examination findings.

Blood culture revealed no bacterial growth. The neonate received supportive care and was closely monitored for feeding intolerance and respiratory compromise. All other anomalies were managed conservatively with multidisciplinary consults and planned outpatient follow-up. He was haemodynamically stable and took feeds well, hence he was discharged on the 10th day.

One and a half months later, the infant presented with jaundice for one day, lethargy and refusal of feeds. He was floppy on examination

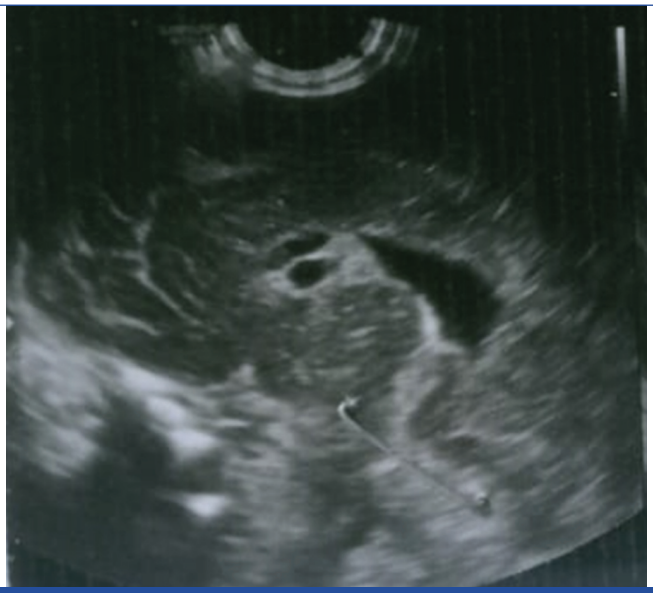
[Table/Fig-1a]: Facial dysmorphism showing low nasal bridge with anteverted nares, micrognathia and muscle wasting.

[Table/Fig-1b]: Shows redundant neck skin, prominent occiput and ear abnormalities.



[Table/Fig-2a]: Shows bilateral polycystic kidneys with increased echogenicity and numerous small cysts.

[Table/Fig-2b]: Shows loss of corticomedullary differentiation.



[Table/Fig-3]: Shows a sagittal section of a neurosonogram demonstrating Periventricular Leukomalacia (PVL), showing a well-defined, anechoic, sub-centimetric cystic lesion in the lateral aspect of the frontal horn of the lateral ventricle.

with stable vital signs. Failure to thrive was indicated by his weight of 2.12 kg at admission which was 15.2% less than his birth weight of 2.5 kg. Ballotable kidneys were appreciated and the liver was palpated 2 cm below the right costal margin.

Liver function tests revealed elevated aminotransferases—Aspartate Aminotransferase (AST) 253 U/L (9-80 U/L) and Alanine Aminotransferase (ALT) 136 U/L (12-45 U/L)—along with hyperbilirubinaemia, with a total bilirubin of 10 mg/dL (<2 mg/dL) and a direct bilirubin of 7.14 mg/dL (<0.2 mg/dL). The coagulation profile revealed a prolonged Prothrombin Time (PT: 16.2 s; control: 15 s) and Activated Partial Thromboplastin Time (APTT: 44 s; control: 30 s). Haemoglobin (Hb) was 8.9 g/dL (reference range: 10.5-14 g/dL). Serum creatinine was within normal limits, while blood urea was elevated at 57.5 mg/dL (2-20 mg/dL). Serum ferritin was markedly raised at 2000 ng/mL (14-647.2 ng/mL). Serum magnesium was also elevated at 2.84 mg/dL (1.5-2.5 mEq/L).

By using whole exome sequencing two likely pathogenic variants in the PEX1 gene were identified. Variant 1: A heterozygous 3' splice site variant in intron 13 of the PEX1 gene (chr7:g.92502081T>C; Depth: 61x) that affects the invariant AG acceptor splice site upstream of exon 14 (c.2227-2A>G; ENST00000248633.9) was detected. Variant 2: A heterozygous one base pair deletion in exon 5 of the PEX1 gene (chr7:g.92517671del; Depth: 108x) that results in a frameshift and premature truncation of the protein two amino acids downstream to codon 282 (p.Pro282LeufsTer2; ENST00000248633.9) was detected. Both variants have not been reported in the 1000 genomes, gnomAD (v3.1), gnomAD (v2.1), topmed and other databases.

The infant was discharged upon parental request after four days. The couple has a healthy four-year-old son. Unfortunately, his condition deteriorated gradually. He developed recurrent episodes of aspiration due to poor cough and swallowing reflexes.

At around five months of age, the infant was brought to the hospital with fever and lethargy. A chest X-ray confirmed aspiration pneumonia. After five days of admission, he died due to sepsis.

Within the Zellweger spectrum, Neonatal Adrenoleucodystrophy (NALD) and Infantile Refsum Disease (IRD) were considered, but these milder phenotypes were excluded based on the severe and early-onset hypotonia, profound dysmorphic features, bilateral renal cysts, and periventricular cystic changes seen on imaging, all indicative of classic Zellweger Syndrome (ZS). Additionally, the compound heterozygous PEX1 variants predicted complete loss of function, correlating with the severe neonatal course and rapid deterioration, whereas NALD and IRD typically present later with milder multisystem involvement and prolonged survival.

DISCUSSION

Zellweger syndrome is the most severe phenotype among the Zellweger Spectrum Disorders (ZSDs). It involves multi-system features like renal cysts, hepatic dysfunction, craniofacial dysmorphism and severe neurological abnormalities [1]. The present case shares all these features; however, PVL-like cystic changes in a term neonate are unusual and has been rarely associated with ZSD.

Periventricular and subependymal cysts, common in preterm neonates, arise from hypoxic-ischaemic lesions in periventricular watershed areas due to impaired perfusion [2]. There have been isolated reports of these cysts in preterm infants with ZS; however, most cases demonstrate widespread white matter involvement rather than localised periventricular injury [3]. The presence of periventricular cysts in our early-term (37 weeks) neonate with ZS is an atypical finding requiring an alternate explanation.

ZS disrupts peroxisome formation and leads to mitochondrial dysfunction. Mislocalised peroxins form abnormal protein complexes on mitochondrial membranes, causing structural damage, metabolic dysfunction, and cellular hypoxia [4]. Oxidative stress further damages mitochondrial components like cardiolipin, impairing mitochondrial respiratory chain enzyme activity. The accumulation of toxic metabolites, such as Very Long-Chain Fatty Acids (VLCFAs), exacerbates these dysfunctions, highlighting the interplay between peroxisomal and mitochondrial pathologies in ZS [5].

Oxidative stress and inflammatory cytokines released along with microglial activation lead to disruption of the axonal development, thalamocortical connections, and myelination, resulting in periventricular cyst formation and long-term neurological deficits [6]. Late preterm (34-36 weeks) and early-term (37-38 weeks) infants are vulnerable to periventricular cysts due to critical and rapid brain growth during this period [7].

This case presents two novel PEX1 gene variants. The first variant is a heterozygous splice site mutation in intron 13, which disrupts the AG acceptor site, likely leading to aberrant splicing and unstable transcripts subject to Nonsense-Mediated Decay (NMD). The

second variant is a heterozygous frameshift mutation that introduces a premature stop codon, resulting in a truncated and non-functional protein. Together, these mutations severely affect protein function, leading to a more severe clinical presentation. The severity of ZS is also determined by the type of mutation. Recent studies have revealed that truncating and frameshift PEX1 variants are associated with more severe phenotypes whereas missense variants retain partial peroxisomal function and present with milder disease.

This case strengthens genotype-phenotype correlations in ZSD by linking these novel mutations to severe neonatal manifestations. This case report adds to the growing database of PEX1 mutations which would assist in the evolution of newer diagnostic methods for Peroxisomal Biogenesis Disorders (PBDs) and aid in predicting the phenotypic presentations associated with specific mutations [8].

There is no curative treatment for ZS. Therapeutic interventions like gene editing, antioxidant therapies and pharmacological stimulation of peroxisome proliferation using phenylbutyrate are still being actively studied [9]. Currently, cholic acid is the only approved adjunctive treatment for patients with ZSDs to control hepatic dysfunction [10].

CONCLUSION(S)

This report describes the pathophysiology behind the development of PVL in ZS, a finding that has not been widely reported in association with the condition. Genetic testing confirmed the diagnosis of ZS with novel mutations which lead to severe neonatal manifestations.

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