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# ZELLWEGER SYNDROME: A PEDIATRIC CASE AND LITERATURE REVIEW

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## ABSTRACT

**Introduction:** Zellweger syndrome is a rare, autosomal recessive disorder of peroxisome biogenesis and represents the most severe end of the peroxisome biogenesis disorder (PBD) spectrum. Classically, it presents from the neonatal period with facial dysmorphism, profound hypotonia, and severe multi-organ involvement, and is generally fatal within the first year of life. **Case presentation:** We report a 7-month-old infant born to consanguineous parents who exhibited major axial hypotonia from birth and neonatal seizures. Clinical examination revealed macrocephaly and characteristic facial dysmorphism (high forehead, wide anterior fontanelle, bulbous nose, high-arched palate, micrognathia, etc.), nystagmus, and absent visual tracking. Brain MRI showed hypoplasia of the corpus callosum. Skeletal radiographs demonstrated irregular epiphyseal ossification centers suggestive of chondrodysplasia punctata. Plasma very-long-chain fatty acids (VLCFA) were elevated, confirming the diagnosis of Zellweger syndrome. **Conclusion:** Also termed the cerebro-hepato-renal syndrome, Zellweger syndrome should be considered in any neonate with severe hypotonia, dysmorphic features, and early neurologic impairment, particularly in the setting of consanguinity. Diagnosis is confirmed by peroxisomal metabolite profiling (VLCFA, phytanic/pristanic acids, etc.), enabling appropriate genetic counseling. No curative therapy is currently available; management is supportive and prognosis is most often fatal before one year of age, underscoring the importance of prenatal diagnosis for future at-risk pregnancies.

**KEYWORDS:** Zellweger syndrome, Peroxisome biogenesis, Very-long-chain fatty acids, Neonatal dysmorphism, Pediatrics.

## INTRODUCTION

Zellweger syndrome is an autosomal recessive disorder of peroxisome biogenesis and represents the most severe phenotype within the PBD spectrum. Peroxisomes are essential for multiple metabolic pathways, including the biosynthesis of certain phospholipids (plasmalogens), bile acid synthesis, β-oxidation of very-long-chain fatty acids, and detoxification of peroxides.[1] PBDs comprise a clinical continuum ranging from classic Zellweger syndrome (the most severe) to milder forms such as neonatal adrenoleukodystrophy (NALD) and infantile Refsum disease (IRD).[2] ZS is also known as the cerebro-hepato-renal syndrome given its concurrent involvement of the central nervous system, liver, and kidneys. It results from mutations in PEX genes, which encode peroxins required for normal assembly and function of peroxisomes. In the absence of functional peroxisomes, toxic metabolites accumulate and essential products are deficient, leading to multisystem injury—most notably a characteristic neuronal migration defect in the brain.[2,3] ZS is a rare and lethal pediatric disease, with an estimated prevalence of approximately 1 in 50,000 births.[4] We report a typical ZS case in an infant and discuss clinical features and recent advances from the literature.

## CASE PRESENTATION

The patient is a 7-month-old female, third child of first-degree consanguineous parents. Pregnancy was well monitored and prolonged beyond term. Vaginal delivery occurred at 42 weeks' gestation; the neonate cried immediately with Apgar scores 10/10/10 and a birth weight of 3,585 g. On day 1 of life, she was admitted to the neonatal ICU for status epilepticus requiring tracheal intubation and assisted ventilation.

Neonatal examination noted severe axial and appendicular hypotonia (Figure 1). Craniofacial features were suggestive: macrocephaly, high/bossed forehead with parietal bulges, enlarged anterior fontanelle, low-set ears, upward and outward slanting palpebral fissures, broad nasal base with bulbous tip, high-arched palate, tongue protrusion, and micrognathia (Figure 2).

**Figure 1: Two photographs of the infant demonstrating axial hypotonia.**

**Figure 2: Two photographs of the infant demonstrating the characteristic facies.**

Additionally, the patient exhibited bilateral nystagmus and absence of visual tracking.

Neurologic examination found generalized areflexia. Brain MRI at 3 months revealed hypoplasia of the corpus callosum. Ophthalmologic evaluation showed manifest latent nystagmus, hyperopia, and astigmatism; optic discs were slightly pale on funduscopy. Abdominal ultrasound was normal. Skeletal radiographs demonstrated bilaterally irregular ossification centers of the distal femora and tibiae (Figure 3).

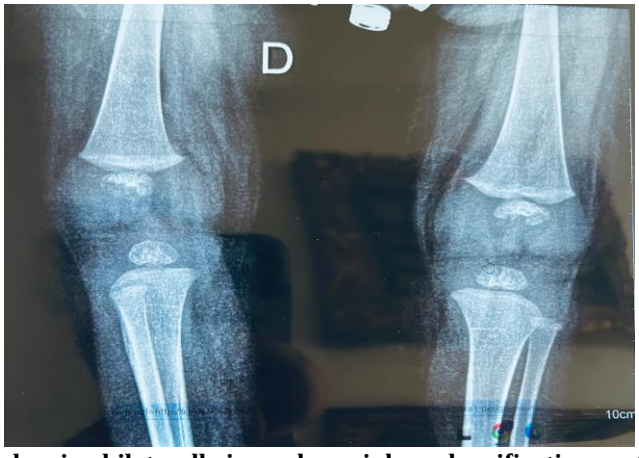


**Figure 3: Knee radiographs showing bilaterally irregular epiphyseal ossification centers of the distal femora and proximal tibiae.**

Metabolic testing confirmed peroxisomal dysfunction. Plasma VLCFA profiling showed a marked increase of the C24:0/C22:0 ratio (1.95; reference 0.57–1.01) and C26:0/C22:0 ratio (0.119; reference 0.004–0.017), with elevated absolute C26:0 (hexacosanoic acid), while phytanic and pristanic acids were within normal limits. Altogether, the clinico-biological findings supported the diagnosis of Zellweger syndrome in this girl.

## RESULTS AND DISCUSSION

### Pathophysiology

Peroxisomes are indispensable organelles for fundamental metabolic functions, including VLCFA β-oxidation; degradation of substrates such as phytanic acid and hydrogen peroxide; and synthesis of plasmalogens (ether phospholipids critical for myelin) and bile acids.[1] Global peroxisomal dysfunction therefore causes substrate accumulation and deficient synthesis of key molecules. PBDs are autosomal recessive and clinically heterogeneous, spanning classic ZS in neonates to later-onset, attenuated forms such as NALD and IRD.[2]

ZS reflects a near-complete absence or severe dysfunction of peroxisomes in all tissues. It is usually due to mutations in PEX genes encoding peroxins that mediate peroxisome formation and protein import. Mutations yield nonfunctional/absent peroxins, preventing import of matrix enzymes into nascent peroxisomes, resulting in "empty" or absent peroxisomes incapable of metabolic functions. Intracellular accumulation of VLCFA (from failed peroxisomal β-oxidation) causes progressive organ damage (liver, kidney, bone), and profoundly disrupts brain development.[3] A hallmark neuronal migration defect leaves cortical neurons stranded and unable to reach upper cortical layers.[3,4] Neuropathology and MRI typically show gyral anomalies (pachygyria, polymicrogyria) predominating in frontal and parietal lobes, with incomplete myelination and progressive leukoencephalopathy.[4,7]

### Typical Clinical Presentation

ZS is often recognizable from birth. Dysmorphic features include a high, broad forehead; cranial suture anomalies (large fontanelles; dolichocephaly with fronto-parietal bossing); upward-slanting palpebral fissures with epicanthus; broad, flattened nasal bridge with anteverted nares; long philtrum; and micro-retrognathia.[5,6] Neurologically, profound axial hypotonia with areflexia, psychomotor delay, and early neonatal seizures are common.[5] Intrauterine or postnatal growth retardation is frequent, as is congenital hepatomegaly. Within weeks, hepatic dysfunction may develop (prolonged cholestatic jaundice potentially progressing to failure), along with nonspecific gastrointestinal issues (feeding difficulties, vomiting, diarrhea) contributing to malnutrition and osteopenia/osteoporosis.[6] Skeletal anomalies include epiphyseal stippling (chondrodysplasia punctata) on radiographs, typically at the knees and patellae.[6]

Sensory and visceral involvement is frequent. Ophthalmologic findings include cataract, congenital glaucoma, retinitis pigmentosa, corneal opacity, and optic atrophy leading to blindness.[6] Sensorineural hearing loss is also common.[6] Renal involvement with multiple cortico-medullary microcysts is characteristic of ZS but rare in NALD, aiding differential diagnosis.[6] Genitourinary anomalies may coexist—cryptorchidism and hypospadias in males; clitoromegaly in females.[6]

Prognosis is poor in the short term; survival rarely exceeds a few months, with most deaths occurring before one year of age.[4,5] In our patient, some complications reported in the literature (e.g., cirrhosis, large renal cysts, cataract) were not observed, likely due to young age and limited follow-up (7 months).

### Diagnostic Work-up and Confirmation

In a suggestive clinical context, diagnosis is confirmed by characteristic peroxisomal biochemical abnormalities. First-line testing is plasma VLCFA analysis, which, as in our patient, typically shows markedly elevated C24:0/C22:0 and C26:0/C22:0 ratios, reflecting VLCFA accumulation from defective peroxisomal β-oxidation.[8,9] Additional ZS abnormalities include elevated plasma pipecolic acid, phytanic and pristanic acids, and bile acid precursors, together with decreased erythrocyte plasmalogens.[3,8,9] These alterations demonstrate global peroxisomal failure and allow reliable PBD screening.

Specialized studies complement diagnosis. Immunocytochemistry of cultured fibroblasts (or hepatocytes) shows near-absence of functional peroxisomes: catalase, normally concentrated within peroxisomes, is diffusely cytosolic, indicating an import defect.[3] Dihydroxyacetone phosphate acyltransferase (DHAP-AT) activity—key to plasmalogen synthesis—is severely reduced in classic ZS.[8] These findings confirm a generalized defect of peroxisome assembly.

### Genetics and Counseling

PBDs are genetically heterogeneous. The ZS spectrum's clinical and biochemical features do not pinpoint the causal gene. At least 13 PEX genes (PEX1–PEX26) have been implicated.[10,11] These peroxins function in peroxisomal membrane formation (e.g., PEX3, PEX16, PEX19) and matrix protein import (PEX1, PEX2, PEX5, PEX6, PEX10, PEX12, PEX13, PEX14, PEX26, etc.).[10,11] Five genes account for most mutations—PEX1, PEX6, PEX10, PEX12, PEX26—with PEX1 alone responsible for roughly 70% of cases.[10]

Genotype–phenotype correlations exist for some variants. PEX26 mutations can cause a wide phenotypic range from classic ZS to NALD/IRD.[12] Functional studies suggest clinical severity relates to which import routes are affected: in ZS due to PEX26, import of catalase and PTS2-targeted proteins is nearly abolished,

with relatively preserved import of PTS1 proteins; these defects are milder in NALD/IRD due to PEX26.[12]

Molecular diagnosis relies on sequencing PEX genes to confirm ZS, define genotype, identify carriers, and enable genetic counseling. Given locus heterogeneity and rarity, some centers use targeted strategies prioritizing the most frequently mutated genes (especially PEX1), identifying at least one mutation in ~80% of cases.[11] Because of the severe prognosis, prenatal diagnosis is warranted in at-risk pregnancies, either by VLCFA assay on fresh chorionic villi in the first trimester or by molecular testing if parental mutations are known.

## CONCLUSION

Zellweger syndrome is a rapidly fatal hereditary metabolic disease. Diagnosis should be considered at birth when characteristic facial dysmorphism, severe neonatal hypotonia, and multi-system dysfunction (neurologic, hepatic, ophthalmologic, etc.) co-occur—especially in families with consanguinity. Our case illustrates these typical clinical features. Etiologic confirmation rests on signature biochemical findings (notably elevated plasma VLCFA), followed by identification of the underlying PEX mutation(s). No curative treatment exists; management is supportive (seizure control, nutritional support, visual and hearing follow-up), yet short-term vital prognosis remains poor. Genetic counseling is essential for families, and prenatal diagnosis should be proposed for future at-risk pregnancies.

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