

# Prenatal Diagnosis of Zellweger Syndrome: Case Report

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Zellweger syndrome (ZS) (Cerebro-Hepato-Renal syndrome) is a rare autosomal recessive disorder characterized by an absence or marked decrease in peroxisomes, resulting in profound muscular hypotonia and death in the neonatal period. The clinical presentation of ZS is dominated by craniofacial dysmorphic features, neurological abnormalities, hepatomegaly, and chondrodysplasia punctata. Prenatal diagnosis is possible by analysis of dihydroxyacetone-phosphate acyltransferase (DHAPAT) activity, which catalyzes the first step in the biosynthesis of ether-phospholipids, in chorionic villi or amniotic fluid cells. We report the prenatal diagnosis of three pregnancies of a mother who had lost two children previously due to ZS.

**Key Words:** Zellweger syndrome, DHAPAT, Prenatal diagnosis, Peroxisomal disorders, PEX gene

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## Introduction

Zellweger syndrome (ZS; OMIM #214100) is an autosomal recessive disorder of peroxisome biogenesis and is characterized by the absence of or marked decrease in the number of peroxisomes. Children with ZS show muscular hypotonia, facial dysmorphism, renal cysts, hepatomegaly, severe psychomotor retardation, and failure to thrive.<sup>1</sup> Death usually occurs within the first year of life.

Due to the severe nature and inability to treat this disorder, many couples with an affected child seek prenatal counselling for future pregnancies.<sup>2</sup> Prenatal diagnosis of ZS can be offered to parents with a previously affected child. Specific prenatal biochemical diagnosis of the disorder is possible, both in chorionic villi and in amniotic fluid.<sup>1</sup> The peroxisomal enzyme dihydroxyacetone-phosphate acyltransferase (DHAPAT), which catalyzes the first step in the biosynthesis of ether-phos-

pholipids, is deficient in tissues and cultured skin fibroblasts of patients with ZS.<sup>3</sup> Prenatal diagnosis is possible by analyzing DHAPAT activity in chorionic villi or amniotic fluid cells. We report the prenatal diagnosis of three pregnancies of a woman at risk for ZS.

## Case Report

A healthy 32-year-old, gravida 3, para 2, liveborn 2 and her healthy 37-year-old husband were referred for prenatal diagnosis because two of their children had died due to ZS. There was consanguinity (first cousins) between the parents, but the family history was otherwise unremarkable. She was HBsAg positive. They had lost two one-month-old children. They were followed in different medical centers. We were informed about the two children by epicrisis. No biochemical data were available for the first child, but the clinical information strongly suggested that two previous children born to the couple had ZS. Their first child was female and born at term with a birth weight of 2100 g, after an uneventful pregnancy. We learned that she had hypotonia, poor sucking and convulsion. She required nasogastric tube because of poor feeding. Her skin was dry and icteric. Her anterior fontanelle showed mild collapse. Cranial ultrasonography and computerized tomography (CT) were normal. Her newborn reflexes were absent. Right paracardiac infiltration was seen on the chest X-ray. She was suspected as having mitochondriopathy. She died in the seventh week of life.

Their second child was male and born at term with meconium aspiration and a birth weight of 3400 g. He had similar clinical and physical findings as observed in the previous

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child. He had an atypical face with hypertelorism, and hypotonia and bilateral pes equinovarus were noted. Dilated lateral ventricles were seen on cranial ultrasonography. Cranial agnetic resonance (MR) imaging was normal. Echocardiography showed patent ductus arteriosus. He had left undescended testis. He was given phototherapy because of indirect hyperbilirubinemia. He was profoundly hypotonic with poor sucking and required nasogastric feeding. He had generalized seizures and was treated with phenobarbital. He was suspected as having mitochondrial cytopathy or congenital myopathies. His muscle biopsy showed normal results. Chromosome analysis showed a normal male karyotype (46,XY). Right paracardiac infiltration and punctate calcifications were seen coincidentally on radiography. Abdominal ultrasonography showed bilateral renal cortical cysts. The optic disc was pale (probably due to atrophic changes) on the ophthalmologic examination. Based on these results, he was considered as ZS. Fatty acid analysis revealed increased levels of very-long-chain fatty acids (VLCFAs) in plasma. It was noted that C26:0 was 6.45 micromol/L (Control: 0.6-1.2) and C26:0/C22:0 was 0.32 (Control: 0.011-0.022). He died in the fifth week of life.

Prenatal diagnosis was performed in three further pregnancies of the mother and indicated two normal and one abnormal fetuses. We sent the chorionic villous biopsy materials to Prof. Dr. Ronald J.A. Wanders, Laboratory of Genetic Metabolic Diseases, Amsterdam, the Netherlands. In that center, DHAPAT activity was measured and, in addition, immunoblot analysis of peroxisomal acyl-CoA oxidase and peroxisomal 3-oxoacyl-CoA thiolase were performed.

In the couple's third pregnancy, chorionic villous sampling (CVS) was done at 12 weeks and 2 days. Activity measurement of the peroxisomal enzyme DHAPAT and immunoblot analysis were normal. The pregnancy progressed uneventfully and a healthy girl with a birth weight of 3800 g was born at term.

In their subsequent fourth pregnancy, the results of the DHAPAT measurement in villi were deficient, and ZS was concluded. The pregnancy was terminated at 16 weeks.

In their fifth pregnancy, results of the analysis for CVS were normal. The pregnancy progressed uneventfully and a healthy male infant with a birth weight of 3100 g was born at term and has subsequently been confirmed to be unaffected.

## Discussion

Zellweger syndrome was first described by Bowen et al.<sup>4</sup> as a familial syndrome of multiple congenital defects in two pairs of siblings. The clinical presentation of ZS is dominated by the typical craniofacial features and neurological aberrations. Facial features include a large anterior fontanel with widely spaced sutures, a broad, full forehead, micrognathia,

external ear deformity, low and broad nasal bridge, shallow orbital ridges, and redundant skin folds in the neck. The neurological picture is dominated by profound hypotonia resulting in poor sucking, depressed neonatal and deep tendon reflexes, and a flat occiput. Other neurological abnormalities include an abnormal Moro response, hypo/areflexia and seizures. Ocular abnormalities including corneal clouding, congenital cataracts, and glaucoma are frequently encountered, as are Brushfield spots and abnormal retinal degeneration.<sup>5</sup>

Zellweger syndrome is genetically heterogeneous and to date, at least 13 different PEX genes have been found associated with this condition (PEX 1-3, 5-7, 10, 12-14, 16, 19 and 26).<sup>6</sup>

Prenatal diagnosis is available by assessment of peroxisomal beta-oxidation activity.<sup>7</sup> Prenatal molecular diagnosis can be offered in cases where the molecular defect has been identified in the index patient. Prenatal diagnosis was performed in three pregnancies of the mother. Our prenatal samples were sent to a laboratory in the Netherlands, and DHAPAT activity was measured and immunoblot analysis was performed. Two of the fetuses were unaffected and one was affected.

The second child of the couple was diagnosed as ZS according to clinical and biochemical findings. The consanguinity of the couples suggested autosomal recessive inheritance. The couple received genetic counselling during the next pregnancy. They were informed that ZS is an autosomal recessive disorder with 25% recurrence risk.

It is important to know the diagnosis of the index patient in order to make a prenatal diagnosis. We also emphasize that peroxisomal disorders should be included in the differential diagnosis in patients with infantile hypotonia and craniofacial dysmorphic features.

## Zellweger Sendromunun Prenatal Tanısı:

### Olgu Sunumu

Zellweger sendromu (ZS) (Serebro-Hepato-Renal sendrom), peroksizomların belirgin azlığı veya yokluğu ile karakterize, yenidoğan döneminde kas hipotonisi ve ölüme yol açan otozomal resesif geçiş gösteren nadir bir hastalıktır. ZS'nun klinik bulguları arasında kraniyofasiyal dismorfik özellikler, nörolojik bozukluklar, hepatomegali ve kondrodizplazi punktata ön plandadır. Prenatal tanısı, koryonik villüs veya amniyotik sıvı hücrelerinde, eter-fosfolipidlerin biyosentezinde ilk basamağı katalizleyen dihidroksiaseton-fosfat açıltransferaz (DHAPAT) aktivitesinin analizi ile mümkündür. Burada ZS nedeniyle daha önce iki çocuğunu kaybeden bir annenin üç gebeliğinin prenatal tanısı sunuldu.

**Anahtar Kelimeler:** Zellweger sendromu, DHAPAT, Prenatal tanı, Peroksizomal hastalıklar, PEX geni

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