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Case Report

A Case Report of Zellweger Syndrome with a de Novo Mutation from Azerbaijan

De Novo Mutasyonlu Zellweger Sendromu: Azerbaycan'dan Olgu Sunumu

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ABSTRACT

Zellweger syndrome (ZS) is a rare autosomal recessive disorder characterized by the absence or malfunction of peroxisomes in cells, leading to a variety of metabolic problems. We present a female neonate who was admitted to the neonatal intensive care unit on the second day of life due to poor feeding and lethargy and was found to have hypotonia, a poor sucking reflex, and facial dysmorphism. Based on the clinical symptoms, biochemical tests, and genetic analysis, a diagnosis of neonatal ZS was reached. Biochemical testing showed high levels of very long-chain fatty acids, characteristic of peroxisomal diseases. Genetic testing revealed abnormalities in the PEX genes, confirming the ZS diagnosis. Unfortunately, our patient died within the second month of life.

Keywords: *Zellweger syndrome, neonate, peroxisome*

ÖZET

Zellweger sendromu (ZS), hücrelerdeki peroksizomların eksikliği veya arızası ile karakterize edilen ve çok çeşitli metabolik problemlere yol açan nadir otozomal resesif bir hastalıktır. Burada, beslenme yetersizliği ve uyuşukluk nedeniyle yaşamının ikinci gününde YYBÜ'ye başvuran, hipotoni, kötü emme refleksi ve yüz dismorfizmi saptanan kız yenidoğanı sunuyoruz. Klinik semptomlara, biyokimyasal testlere ve genetik analize dayanarak yenidoğanlarda ZS tanısı ortaya çıktı. Biyokimyasal incelemede peroksizomal hastalıkların özelliği olan yüksek miktarda çok uzun zincirli yağ asitleri ortaya çıktı. Genetik testler PEX genlerindeki anormallikleri ortaya çıkardı ve ZS teşhisini doğruladı. Maalesef hastamız yaşamının ikinci ayında vefat etti.

Keywords: *Zellweger sendromu, yenidoğan, peroksizom*

INTRODUCTION

The absence or dysfunction of peroxisomes in cells characterizes Zellweger syndrome (ZS), also known as cerebrohepatorenal syndrome, a rare autosomal recessive disorder. Peroxisomes are critical organelles involved in various metabolic processes, including the degradation of fatty acids, amino acids and reactive oxygen species. In the absence of functional peroxisomes, harmful chemicals accumulate and metabolic abnormalities may occur, leading to the clinical symptoms of ZS. It is estimated that ZS affects one in 50,000 live births, making it a rare disorder with a high morbidity and mortality rate (1).

Patients with ZS exhibit considerable clinical heterogeneity. The symptoms can affect many organs due to reduced or absent peroxisome activity. Low muscle tone, facial dysmorphism, reduced growth, sensory and

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neurological dysfunction, renal and endocrine insufficiency, skeletal abnormalities and developmental delay are some of the clinical symptoms.

Physiological fluids and tissues can measure abnormalities in various peroxisome biochemical processes to diagnose ZS. Peroxisomes carry out the β-oxidation of very long-chain fatty acids (VLCFAs) and pristanic acid and the α-oxidation of phytanic acid, as well as other metabolic processes, such as pipecolic acid metabolism, bile acid production and plasma lipid synthesis. Because of this, decreased or absent peroxin protein activity affects the function of peroxisomes in many metabolic pathways, which can be checked for the biochemical diagnosis of ZS. We strongly recommend genetic testing for individuals suspected of having ZS. Pathogenic variants in the PEX1 gene are responsible for nearly 2/3 of all ZS cases, and more than one-third of cases are caused by pathogenic variants in one of the following genes: PEX6, PEX12, PEX26, PEX10, PEX2, PEX5, PEX13, PEX16, PEX3, PEX19, PEX14, and PEX11β (2, 3). In this case report, we present a newborn with ZS.

CASE REPORT

We report a female neonate born at 39 weeks gestation weighing 3400 g (head circumference 34 cm and height 49 cm) from the second pregnancy (the first was a miscarriage) of a 26-year-old healthy mother and father who were related by blood. The mother's sister had global growth retardation. The prenatal examination was completely normal, and in the second trimester of pregnancy, *Ureaplasma urealyticum* was detected and treated. On the second day of life, the infant was admitted to the neonatal intensive care unit due to poor feeding and lethargy. Cyanosis and hypoxia were detected on examination, and an oxygen supply was initiated using a hood. We noted hypotonia, hyporeflexia, poor sucking reflex, and facial dysmorphism characterized by a high forehead, large fontanels, and epicanthal folds (Figure 1). An abdominal examination revealed no evidence of hepatomegaly. These clinical signs raised the suspicion of a metabolic disorder and prompted further testing.

Investigations: Hypoalbuminemia and prolonged prothrombin time were detected, and supportive treatment was initiated. After the lumbar puncture, we initiated antibacterial and antiviral therapy. No hypoglycemia or acidosis was detected during the follow-up. The antibiotic regimen was revised after thrombocytopenia was detected in the blood count and Klebsiella pneumonia in the blood culture. The cerebrospinal fluid was free of viral and bacterial pathogens, and the biochemical parameters were normal. Baseline metabolic testing revealed no organic aciduria, no defects in the urea cycle, and no quantitative changes in the concentrations of specific amino acids in CSF, urine, or blood plasma. Biochemical analysis showed high levels of VLCFAs (C26:0 - 4.25 µmol/L (0.00-0.92), C24:0/C22:0 - 1.29 (0.51-1.19), and C26:0/C22:0 - 0.169 (0.006-0.014), indicating a peroxisomal abnormality. Abdominal ultrasonography showed cysts in the renal cortex, while magnetic resonance imaging showed brain atrophy, all suggesting ZS. No epileptiform discharges occurred during 2-hour electroencephalography. An echocardiographic examination revealed a patent foramen ovale and a small patent ductus arteriosus. Genetic testing revealed a homozygous de novo autosomal recessive *c.888-889del p.Leu297ThrfsTer12* mutation in exon 3 of the PEX12 gene, confirming the diagnosis of ZS (Figure 2).

Treatment and outcome: The infant received approved ventilatory support (using a bonnet), antiseizure treatment (levetiracetam 20 mg/kg/day), and supportive treatment, including nutritional support and physiotherapy to improve muscle tone and strength. In our case, despite aggressive treatment, the infant's condition continued to deteriorate, and he died at two months of age. The consent of the patient parents was obtained for this case study.

Figure 1.

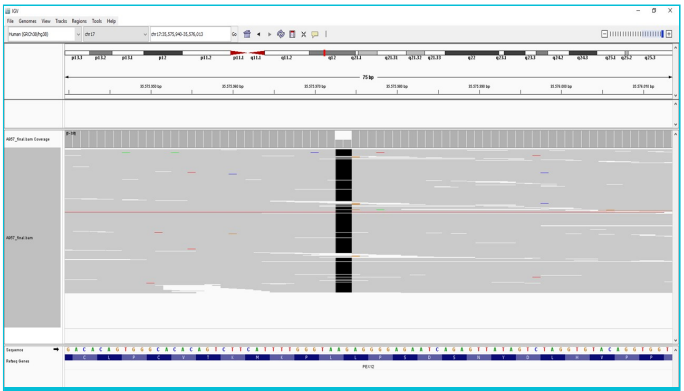

Figure 2.

DISCUSSION

In this case report, we describe a patient from Azerbaijan with a homozygous PEX12 mutation *(p.Leu297ThrfsTer12 c.888-889del)*, and parental consanguinity suggests an autosomal recessive pattern of inheritance. The clinical and laboratory findings of our patient correspond to the classic picture of ZS, a disorder of peroxisomal biogenesis. Consistent with the cases described in the literature, our patient showed hypotonia, hyporeflexia, facial dysmorphism and increased VLCFAs. For example, Baumgartner et al. described a cohort of patients with ZS in whom hypotonia and prominent craniofacial features were consistently present, which is consistent with our findings (4).

Patients with early onset showed motor and cognitive delay and failure to thrive. Similar studies have found hypotonia, developmental delays, failure to thrive and feeding difficulties within the first year of life (5, 6). In addition, we investigated the presence of causative mutations in all family members and successfully carried out a prenatal diagnosis.

ZS (cerebrohepatorenal syndrome) is a rare genetic disorder characterized by the absence or malfunction of peroxisomes in cells, leading to severe developmental disorders. Defective peroxin can prevent the formation of peroxisomes or lead to low concentrations of key enzymes. Incomplete peroxisomes cannot perform essential metabolic functions, such as β-oxidation of long-chain fatty acids, α-oxidation of phytanic acid, pipecolic acid oxidation and early plasmalogen synthesis. This leads to the accumulation of VLCFAs, which damage organs, such as the liver, bones, kidneys and especially the brain (2, 7). A notable problem is the migration defect of the cortical neurons, which affects the development and structure of the brain and causes abnormalities, such as lissencephaly, pachygyria, polymicrogyria, leukoencephalopathy and brain atrophy (8).

There are 16 known human PEX genes, with mutations identified in 13. PEX1 and PEX6 mutations account for two-thirds of Zellweger spectrum disorders, while PEX5 mutations are frequent in the Middle East. Serum biochemical abnormalities cannot predict a patient's specific PEX mutation and only tissue culture analysis can reveal the biochemical effects of these genetic mutations (8). The genetic results show our patient has a homozygous *c.888-889del p.Leu297ThrfsTer12* mutation in the PEX12 gene. This mutation is similar to others that have been linked to ZS. For example, a study by Ebberink et al. identified several mutations in the PEX12 gene, including frameshift mutations similar to the one observed in our patient. This confirms the genetic heterogeneity of ZS (9).

Patients with PEX12 gene mutations and early-onset disease showed motor and cognitive impairments as well as failure to thrive. Other studies reported hypotonia, developmental delays, failure to thrive and feeding problems in the first year of life (5, 6, 10). The outcome of our patient, who died at the age of two months, corresponds to the severe prognosis typically associated with ZS. According to Klouwer et al., most infants with ZS do not survive beyond the first year of life despite intensive care (1).

However, our case also has unique aspects when compared to the literature. Patients typically present

with brain atrophy leading to neurological impairments, such as developmental delay and seizures, as well as renal cortical cysts that affect renal function. Abdominal ultrasonography rarely reveals renal cortical cysts and patent ductus arteriosus (PDA). In a review by Steinberg et al.(7), renal abnormalities have been found in a subset of ZS cases, but cardiovascular involvement, such as PDA, which is similar to our case, has been documented less frequently. Hypertrophic cardiomyopathy can occur in ZS (11, 12), but it was not present in this case. This could indicate a broader spectrum of organ involvement in ZS than previously thought. Liver dysfunction is also common, as are marked craniofacial features and skeletal abnormalities in our patient. The disease has a poor prognosis, as most affected individuals do not survive early childhood, and treatment is primarily supportive (1).

CONCLUSION

ZS is a rare peroxisomal disorder associated with severe morbidity and mortality. In summary, although our patient's clinical presentation and laboratory findings are largely consistent with other cases of ZS reported in the literature, identifying specific genetic mutations and additional organ involvement emphasizes the variability within the disorder. Ongoing documentation and analysis of such cases are critical to understanding the full clinical spectrum and determining treatment strategies. Despite developments in genetic testing, the prognosis for patients with ZS remains poor. This emphasizes the need for further research to develop specific therapeutics for this life-threatening disease.

Patient Consent Form / Hasta Onam Formu

The parents' of this patient consent was obtained for this study.

Conflict of Interest / Çıkar Çatışması

The authors declared no conflicts of interest with respect to authorship and/or publication of the article.

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