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Prenatal findings and postnatal confirmed of perlman syndrome: a case report

Perlman sendromu: Prenatal ve postnatal bulgular

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ABSTRACT

Perlman syndrome is an extremely rare syndrome characterized by polyhydramnios, fetal overgrowth, facial dysmorphism and visceromegaly, and inherited in an autosomal recessive fashion. We here report a male infant born to consanguineous parents with prenatal history of polyhydramnios, fetal ascites, nephromegaly, corpus callosum agenesis and choroid plexus cysts, and presented with nephromegaly, hepatomegaly, cholestasis, cardiomegaly, cryptorchidism, respiratory distress, hypoglycemia, generalized muscle hypotonia after birth, and died due to progressive respiratory decompensation at the age of 6 months. He was diagnosed with Perlman syndrome (#267000) confirmed with a homozygous variant mutation in the DIS3L2 gene.

Keywords: Perlman syndrome, nephromegaly, polyhydramnios, fetal ascites, DIS3L2 gene

ÖZ

Perlman sendromu, polihidramnios, fetal aşırı büyüme, yüz dismorfizmi ve visseromegali ile karakterize edilen ve otozomal resesif olarak kalıtılan son derece nadir bir sendromdur. Bu vakamızda, akraba evliliği yapmış ebeveynlerden doğan bir erkek bebeği bildirmekteyiz. Doğum öncesi dönemde polihidramnios, fetal asit, nefromegali, korpus kallozum agenezisi ve koroid pleksus kistleri öyküsü bulunan bebek, doğum sonrası nefromegali, hepatomegali, kolestaz, kardiyomegali, inmemiş testis, solunum sıkıntısı, hipoglisemi, genel kas hipotonisi ortaya çıktı ve 6 aylıkken ilerleyici solunum yetmezliği nedeniyle hayatını kaybetti. DIS3L2 geninde homozigot varyant mutasyonu ile Perlman sendromu (#267000) teşhisi doğrulandı.

Anahtar Kelimeler: Perlman sendromu, nefromegali, polihidramnios, fetal asit, DIS3L2 geni

INTRODUCTION

Perlman syndrome is a rare autosomal recessively inherited syndrome characterized by overgrowth of the body or body parts and is seen with a frequency of 1/1,000,000. It shows autosomal recessive inheritance. Homozygote or compound heterozygous mutations in the DIS3 like 3'-5' exoribonuclease 2 genes (DIS3L2, 614184) have been identified in patients with Perlman syndrome by Astuti et al. (1). So far, 39 cases have been described in the literature (2-5).

The characteristic features of renal morphology were described by Liban and Kozenitsky, but the first clinical cases in the literature who were siblings and born by consanguineous parents were described by Perlman (6-10). Neri et al. designated the syndrome and proposed the name, Perlman (10). Additional patients have been described since that time until today.

Alessandri et al. summarized the clinical features of all 28 patients reported in the literature in the whole world (11). Prenatal ultrasonography (USG) showed macrosomia, polyhydramnios, and nephromegaly. The postnatal clinic was marked by large for gestational (LGA; Birth weight more than 90th percentile) macrocephaly, dysmorphic facial features like a depressed broad nasal bridge with a short nose, long anteverted and inverted V-shaped upper lip, micro-retrognathia, deep-set eyes with epicanthic fold, low-set ears, round facial fullness and upsweep of anterior scalp hair, abdominal distention and visceromegaly mainly nephromegaly and hepatomegaly, cardiovascular anomalies, central nervous system (CNS) anomalies, hypotonia, developmental delay, and intellectual disability.

Histological examination shows nephroblastomatosis (75%) and pancreatic cell hyperplasia (71%) in patients (11, 12). Predisposition to renal hamartoma, nephroblastoma known as Wilms' tumor (WT)

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has been reported. The average developing age for WT in Perlman syndrome is <2 years old and is lower than sporadic WT cases which develop at 4 years old children and renal cell carcinoma is seen in long-term follow-up.

Prognosis is severe with high mortality where half of them die in the neonatal period (<28 days) and only some patients (19%) have been reported to survive. This high neonatal mortality occurs due to respiratory problems like pulmonary hypoplasia and hypoxemia or other systemic problems like hypoglycemia and renal failure. (3) A long life span has been reported in some cases. A 9-years-old patient who had a normal neurodevelopmental outcome was reported by Piccione, and a 34-years-old patient who survived with mild psychomotor delay (12, 13).

The differential diagnosis of other overgrowth syndromes, especially Beckwith–Wiedemann syndrome (BWS) and Simpson–Golabi–Behmel syndrome (SGBS), Weaver and Sotos are difficult to distinguish from Perlman syndrome. Macroglossia and exomphalos presented in BWS and polydactyly presented in SGBS are absent in Perlman. Genetic testing should be considered.

We here presented a case that prenatally described to have nephromegaly, bilateral choroid plexus cyst (CPC), partial agenesis of the corpus callosum, and ascites and postnatally diagnosed as Perlman syndrome with clinical features and genetic testing.

CASE PRESENTATION

The male infant was the fourth, but the second alive child of consanguineous parents. The previous pregnancies had resulted in infants of which one antenatally diagnosed bilateral hydronephrosis and died at the third day of life with an, and the other died at 3-months old due to aspiration syndrome. One sibling who is 18-months old is healthy. The 27-year-old mother reported no medical problems, exposure to teratogens or alcohol. She was referred to our perinatal center at 18 weeks of gestation. At 22 weeks of gestation, a detailed ultrasound examination showed enlarged kidneys (29,26*40,92 mm) (Abonyi 2019), pericardial effusion choroid plexus cyst, and partial agenesis of corpus callosum (PACC). (Figure 1 and Figure 2) Amniocentesis revealed a normal karyotype (46, XY).

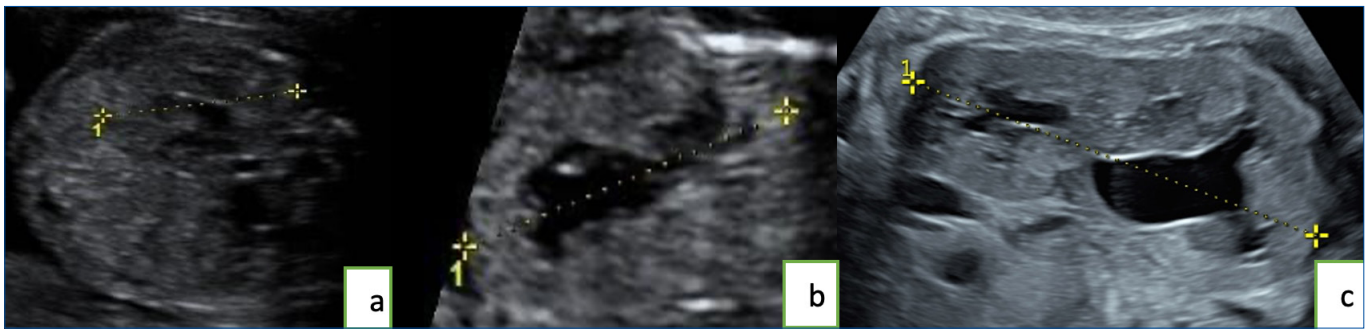

Figure 1. Prenatal renal meassurment. **a:** 29 mm (length) and **b:**40 mm (width) (22 w 6 day). **c:**78 mm (length) (34 w 2 day)

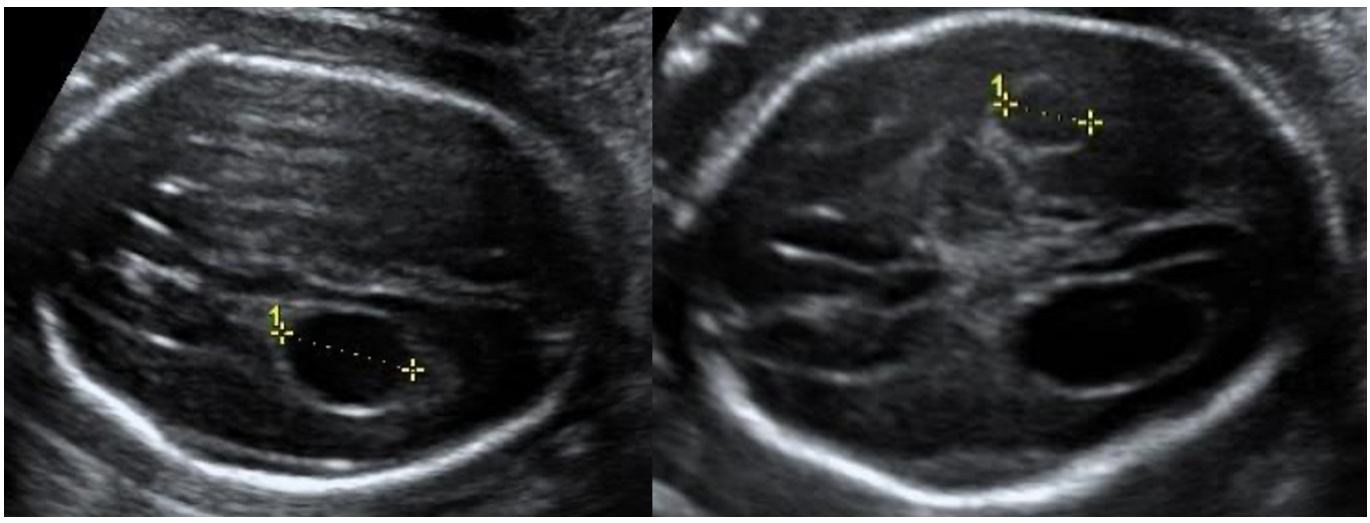

Figure 2. 17,06 mm and 9,93 mm CPC. (22 w6 d)

CPC: Choroid plexus cyst

Figure 3. Postnatal view of the neonatal baby.

The baby was born at 38 weeks of gestation by cesarean section with a birth weight of 3850 g, a length of 47 cm, and a head circumference of cm. Apgar scores were 5 and 6 at the 1th and 5th minutes, respectively. He received nasal continuous positive airway pressure (nCPAP) after birth, then intubated at following hours. He had marked abdominal distention and enlarged kidneys were palpated. Facial anomalies included depressed nasal bridge, prominent forehead, deep-set eyes, low-set ears, high arched palate (Figure 3). Renal ultrasonography showed enlarged and hyperechogenic kidneys (left: 105x55x50 mm, right: 102x50x48 mm) with small cystic lesions, a pattern indistinguishable from polycystic kidney disease. The graphics of the skeleton were normal. Echocardiography showed a secundum atrial defect. MR imaging was performed at which the lateral ventricle appears dilated and the CC was thin.

He received phototherapy due to jaundice on the 2nd day of his life. There was neither rhesus nor blood group incompatibility. On the 5th day of his life, an exchange transfusion was performed due to indirect hyperbilirubinemia (29.7 mg/dL). The direct bilirubin level was 2.5 mg/dL and increased gradually. The evaluations for cholestasis were all normal (viral serology, thyroid function test, metabolic test, liver ultrasound). UDCA treatment was started at a dose of 10 mg/kg/d. Cholestasis resolved in 6 weeks.

We identified a homozygous deletion of exon 9 in the DIS3L2 gene in our patient. Both mother and father were heterozygous for this mutation (HGMD ID: CG1312724/CG121615).

The infant was transferred back to a lower-level care nursery close to the family's home at the age of 3-months. We learned that he died at the age of 6 months due to progressive respiratory decompensation and sepsis.

DISCUSSION

Perlman syndrome is a rare syndrome characterized by visceromegaly, renal lesion, and high neonatal mortality. The first cases were described by Liban and Kozenitzky in 1970 in two siblings (6). Later, three siblings in the same family were identified by Perlman (8, 9). Multiple metanephric hamartomas and nephroblastomatosis were reported in male neonates, and, and diffuse-type WT was described in their sister. Patients reported having features as typical facial appearance, protruding forehead, flattened nose, V-shaped flat-wide upper lip. Until 2012, the genetic basis of Perlman syndrome was unknown. In 2012, Astuti et al. identified the Perlman syndrome and the cancers that may be caused by Perlman syndrome (1). They defined 2q37.1 as chromosome and region and DIS3L2 as gene mutation. They claimed that the genetic cause of Perlman syndrome would also lead to other cancer-causing causes. To our knowledge, this is the first case report from our country that has prenatally described features and diagnosed as Perlman syndrome with postnatal features which was confirmed as genetically in both infant and his parents.

Perlman syndrome has a poor prognosis. In a review, 11 of 28 patients lived until 1-year-old. The vast majority of patients died

from respiratory distress syndrome, sepsis, and kidney failure. WT developed in 7 of 11 patients who survived (11). The case presented by Piccone had a normal neurodevelopmental outcome (12). Although the genetic cause of Perlman syndrome has been elucidated, the clinical variability between cases is unknown.

Unlike other findings, the presented case had CPC that we detected during early pregnancy. Other nephromegaly and visceromegaly syndrome were considered in the differential diagnosis. But the absence of macroglossia, abnormal tongue structure or hemi hyperplasia distanced us from the diagnosis of BWS. The absence of polydactyly, lip, and palate problems led us to exclude the diagnosis of Simpson-Golabi-Behmel syndrome.

There are many reported antenatal USG findings of Perlman syndrome. Deroche et al. reported a fetus with lymphedema, dextrocardia, placentomegaly detected at 18. gestation weeks with elevated α-fetoprotein and human chorionic gonadotropin (14). They found intracranial hemorrhage, sinus venous thrombosis, and peripheral calcification in sella turcica in the neonatal period. Activated C protein resistance was detected in thrombophilia tests. The difference between this case from our case and other literature cases is still unknown.

Unlike other cases reported in the literature, our patient did not have macrosomia as described by Demirel et al. (15). Hyperbilirubinemia and jaundice were also detected in our patient. The cause of hyperbilirubinemia in these cases is still unclear.

CONCLUSION

The management of Perlman syndrome includes a multidisciplinary team of specialists according to features observed in patients. Genetic counseling and prenatal genetic diagnosis should be offered in the next pregnancy. A quick diagnosis and accurate follow-up are needed for these patients to give support to high rates of morbidities and mortality. Infants should be followed up for possible malignancies. Gene therapy can be the future focus in Perlman syndrome.

Conflict of interest

The authors report no conflicts of interest.

No financial support has been received.

This article has not been previously published and has not been posted elsewhere at the same time.

Written informed consent was obtained from the patient.

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