






Case Report

Neonatal Type 1 Rhizomelic Chondrodysplasia Punctata with a homozygous PEX7 mutation and inguinal hernia

Homozigot PEX7 Mutasyonunda Neonatal Tip 1 Rizomelik Kondrodisplazi Punctata ve İnguinal Herni Birlikteliği

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ABSTRACT

Peroxisomal diseases are a group of genetic diseases caused by defects in peroxisome biogenesis or enzyme deficiencies. Rhizomelic chondrodysplasia punctata type 1 (RCDP) constitutes the group caused by autosomal recessive mutations in the PEX7 gene encoding the PTS2 receptor. This report aims to describe a genetic disease that physicians rarely encounter, explain its basic features, and the importance of diagnostic approach and genetic counseling. A male infant was born at thirty eighth gestational week was born with the history of third degree consanguinity. Shortening of bilateral and symmetrical humerus was demonstrated at birth. Plasma phytanic acid levels were high and genetical analysis showed a homozygote p.Ala218Val (c.653C>T) mutation in PEX7 gene. Patient was operated due to bilateral cataracts in third month. Rhizomelic chondrodysplasia punctata type 1, with a prevalence of 1/100,000, is a group of diseases that many physicians rarely encounter. Different mutations in the PEX7 gene may cause different phenotypes. Although there is no curative treatment, supportive treatment is administered according to the severity of the symptoms. The prognosis of the disease is poor, with the majority of patients dying within ten years. Genetic counseling is critical as there is a 25% risk of the disease recurrence.

Keywords: rhizomelia, punctate calcification, pex7 gene

ÖZET

Peroksizomal hastalıklar, peroksizom biyojenezindeki bozukluklar veya enzim eksikliklerinin yol açtığı bir grup genetik hastalıktır. Rizomelik kondrodisplazi punktat tip 1 (RCDP), PTS2 reseptörünü kodlayan PEX7 geninde görülen otozomal resesif mutasyonların sebep olduğu grubu oluşturmaktadır. Burada amaç, doktorların ender rastladığı genetik bir hastalığı tarif etmek, hastalığın temel özelliklerini, teşhis yaklaşımının ve genetik danışmanlığın önemini ortaya koymaktır. Otuz sekizinci gestasyonel haftada doğan ve üçüncü derece akrabalık öyküsü olan erkek bebeğin doğumunda her iki humerusta bilateral ve simetrik kısalık saptandı. Plazma fitanik asit seviyeleri yüksek bulundu ve yapılan genetik analizde PEX7 geninde homozigot p.Ala218Val (c.653C>T) mutasyonu tespit edildi. Üçüncü ayda bilateral katarakt nedeniyle hasta cerrahi operasyona alındı. Prevalansı 1/100.000 olan rizomelik kondrodisplazi punktat tip 1, birçok doktorun nadir karşılaşılabileceği bir hastalık grubudur. PEX7 genindeki farklı mutasyonlar ile farklı fenotipler ortaya çıkmaktadır. Hastalığın iyileştirici bir

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tedavisi bulunmamakla birlikte semptomların şiddetine göre destekleyici tedavi uygulanmaktadır. Bu hastalığın prognozu zayıf olup, hastaların çoğu ilk on yıl içinde hayatını kaybetmektedir. Genetik danışmanlık, hastalığın tekrarlama riski %25 olduğu için son derece önemlidir.

Keywords: *rizomeli, punktat kalsifikasyon, pex7 geni*

INTRODUCTION

Rhizomelic chondrodysplasia punctata (RCDP) is a class of rare disorders among peroxisomal diseases with neurological, ophthalmological, respiratory, skeletal, and dermatological findings. It was first described clinically in 1914 by Conradi; it was defined clinically, pathologically and radiologically by Hunermann in 1931 with an incidence of 1:100,000 (1). It is a type of epiphyseal dysplasia characterized by punctate calcifications in the epiphysis and metaphysis of long bones, seizures, short stature, cataracts, contractures in the joints and recurrent upper respiratory tract infections (2). Three genetic subtypes of RCDP are acquired by and autosomal inheritance. Rhizomelic chondrodysplasia punctata type 1 which is autosomal recessive type, constitutes the majority of cases and this rate is 90% (3).

Biochemical markers showing peroxisomal functions, such as erythrocyte plasmalogen levels, plasma phytanic acid levels and plasma long chain fatty acid levels, are important in diagnosing RCDP type 1. Although there are five different subtypes of the disease, the definitive diagnosis of this distinction is made by detecting homozygous or heterozygous mutations in the *PEX7*, *GNPAT*, *AGPS*, *FAR1*, and *PEX5* genes, respectively (4–6). The most common genetic mutation is in the *PEX7* gene, which encodes the peroxin proteins involved in transport in peroxisomes. These mutations can be detected with prenatal diagnosis, and the disease can be prevented with appropriate genetic counseling.

Long-term life expectancy in children with RCDP is quite low. Despite optimal supportive care, many patients have died in infancy or early childhood. Severe physical disability and profound cognitive impairment are seen in most of the cases that can reach infancy (7). The long-term prognosis of RCDP is poor, and there is no curative treatment. Better living standards can be achieved in the future in patients followed up with symptomatic treatment and physical therapy as multidisciplinary.

CASE REPORT

A male infant was born by normal spontaneous vaginal delivery at the thirty-eighth gestational week with a birth weight of 3000 grams as the third living child of the third pregnancy of a 31-year-old mother who did not attend regular antenatal follow-up visits. In postnatal physical examination, he was found to have partial cleft palate, bilateral shortening of humerus, flexion contractures of the knee and ankle joints in the lower extremities and indirect inguinal hernia in right scrotum (Figure 1). He had hypotonia, primitive reflexes were found normal and no remarkable finding was detected in the other systemic examination of infant. Third-degree consanguinity was present between mother and father. Both parents and the other children of the family were free of any known structural or genetic disease. The mother had no history of drug use in the prenatal period.

Since multiple congenital anomalies and deformities were defined, detailed examinations were planned. X-ray imaging of all four extremities revealed punctate calcifications in the epiphyses of the long bones (Figure 2). An abdominal ultrasonographic examination found grade 1 pelviectasis in the left kidney (Anterior-Posterior diameter 1,3 mm). In the follow-ups, it was observed that pelviectasis regressed spontaneously. It was evaluated as an indirect inguinal hernia after intestinal loops were observed in the right scrotum on inguinal ultrasound. After evaluation of the pediatric surgery department for inguinal hernia, elective surgery was planned. Echocardiogram revealed a patent ductus arteriosus 1,1 mm in size and secundum atrial septal defect. No accompanying intracranial anomaly was detected in cranial magnetic resonance imaging. Although ophthalmic examination in neonatal period was normal, bilateral cataract appeared at the age of three months and the patient was operated in follow-up visits.



Figure 1. Shortness of both humerus, flexion contractures and right inguinal hernia observed in the first physical examination.

His biochemical and hematological parameters showed no meaningful abnormality. Blood lipids were normal. Plasma phytanic acid levels were determined to be high when metabolic screening was performed. In his genetic studies, a chromosome analysis from peripheral blood revealed a karyotype of 46, XY. A homozygous p.Ala218Val (c.653C>T) mutation was found in the PEX7 gene which is second common mutation in this gene (8,9). Written informed consent was obtained from the patient's parents to publish this case report and any accompanying images.

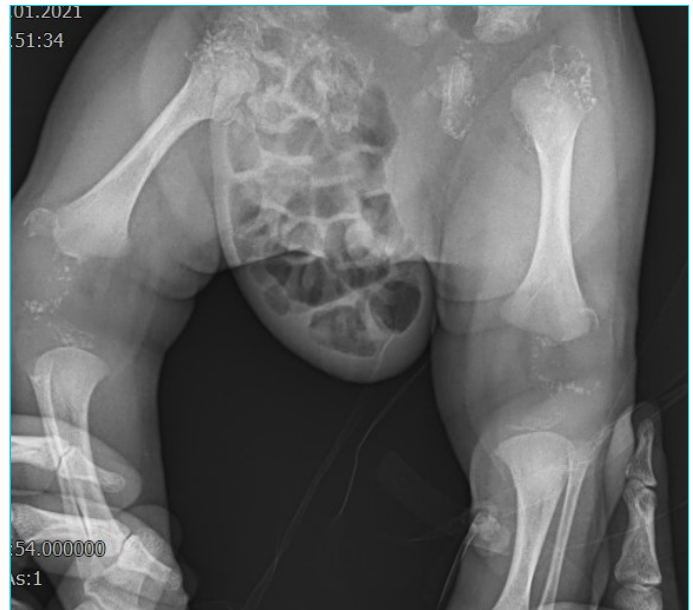


Figure 2. X-ray imaging of punctate calcifications in both femoral epiphysis and intestinal loops in the right scrotum

DISCUSSION

The punctate chondrodysplasia group includes many entities that are very diverse, but combined with the radiological finding of epiphyseal punctuation. Since the genetic etiologies of the diseases in this group are different, the diagnosis of the subgroup should be confirmed by laboratory tests. Rhizomelic chondrodysplasia punctata is a rare disease among peroxisomal diseases with neurological, ophthalmological, respiratory, skeletal, and dermatological findings. There are many different diseases that may cause punctate calcifications in the epiphyses. However, since these diseases are related to defects in different metabolic pathways, it is necessary to make a good differential diagnosis and to provide the most appropriate approach. The punctate appearance in Smith-Lemli Opitz syndrome and CHILD syndrome is associated with defects in cholesterol biosynthesis (2,4). Cholesterol level was normal in our patient. In addition, trisomy 18 and 21 and mucopolysaccharidosis type II can cause punctate calcification in bones. However, differential diagnosis can be made in these diseases because calcifications are often in the calcaneus and rhizomelia is not seen. Coronal fissures and ichthyosis-like skin lesions in the thoracic and lumbar vertebrae have been reported in cases with rhizomelic chondrodysplasia punctata. Coronal fissures, which were more prominent in the lower thoracic vertebrae, were also observed in our case. However, ichthyosis-like skin lesions were not found. Hypotonia is a finding observed in the early period in

patients with RCDP, in our case Prechtel evaluation revealed that he had difficulty in movements against gravity, especially in the upper extremities, and his repertoire of movements was weak. Therefore, our patient was administered appropriate physiotherapy. Cataract appeared bilaterally at the age of three months in our patient's follow-up and he was operated for this reason. Although cataract can be seen together with RCDP, no metabolic disorder was found in the metabolic disease screening (e.g., Galactosemia) performed after bilateral cataract was detected in our case, and it was concluded that the cause of the congenital cataract was the disease itself. The family was referred to the pediatric genetics department for genetic counseling. No new findings other than cataracts were found in the follow-ups performed by us for approximately 1 year after discharge.

CONCLUSION

Our aim in presenting this case is the accurate recognition of diseases, such as RCDP type 1, although very rare, by a health professional from the moment of birth. In such diseases, which in many cases are fatal in early childhood, informing the family with genetic counseling is the first and most critical step of treatment and prevention new cases. Therewithal, disease management relies on supporting patients depending on the severity of phenotype changes, including dietary restrictions, surgeries, physical therapy, vaccinations, gastrostomy, and management of respiratory crises.

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.

Financial Disclosure / Finansal Destek

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