

# A Case of Rhizomelic Chondrodysplasia Punctata Complicated with Fetal Arrhythmia

## Fetal Aritmi Gelişen Rizomelik Kondrodizplazi Punktatalı Bir Olgu

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#### Abstract

Rhizomelic chondrodysplasia punctata (RCDP) is a rare autosomal recessive syndrome characterized by punctuate calcifications of the cartilage associated with proximal limb shortening, joint contractures, cataracts, failure to thrive, and severe mental-motor retardation. Here we described RCDP in a male newborn based on typical clinical, biochemical, and radiological findings. He was reported as he was complicated with fetal arrhythmia because of congenital heart defect which is rarely seen in RCDP.

**Key words: Arrhythmias, Cardiac; Chondrodysplasia Punctata, Rhizomelic.**

#### Özet

Rizomelik kondrodizplazi punktata (RCDP) ekstremelerde proksimal kısalık, eklem kontraktürleri ve epifizlerde punktata kalsifikasyonlar ile katarakt, gelişme geriliği ve ağır mental retardasyonla karakterize otozomal resesif kalıtılan nadir görülen bir sendromdur. Bu yazıda sunulan yenidoğan olguya klinik, biyokimyasal ve radyolojik bulgular ile RCDP tanısı konuldu. Olgu, RCDP' de nadir görülen konjenital kalp hastalığının neden olduğu fetal aritmi komplikasyonu gelişmiş olması nedeniyle sunuldu.

**Anahtar Kelimeler: Kondrodizplazi Punktata, Rizomelik; Kardiyak Aritmiler.**

## Introduction

The skeletal dysplasias are a clinically and genetically heterogeneous group of conditions affecting the development of the osseous skeleton and fall into the category of rare genetic diseases in which the diagnosis can be difficult for the nonexpert (1). Rhizomelic chondrodysplasia punctata (RCDP) is a rare skeletal dysplasia classified under peroxisomal disorders (2). RCDP constitutes a group of heterogeneous bone dysplasia characterized by symmetric proximal shortening of the limbs, cataract, hearing loss, ichthyosis and other abnormalities. The skeletal manifestations of RCDP include severe shortening of the proximal long bones, flaring of the metaphyses, stippling of the epiphyses, and coronal clefts within the vertebral bodies. The prognosis is generally poor and death occurs in the majority of patients within the first year of life. RCDP is rarely associated with congenital heart defects. Here we present a case of RCDP presenting with fetal arrhythmia.

## Case Report

A male baby was born at 38 weeks of gestation as the first child of 23-yr-old primigravida woman and 28-year-old related father (first cousin). The mother was under routine prenatal follow-up by a gynecologist during pregnancy. There was no history of exposure to any known embryopathic agents and in particular, no warfarin therapy had been given. Prenatal ultrasonographic assessments reported proximal limb shortening and valvular pulmonary stenosis. The baby was born two weeks earlier than the due date by caesarean section because of fetal arrhythmia detected on fetal echocardiography. His birth weight was 2550 g (10-25th percentile), birth length 43 cm (<10th percentile) and head circumference 32 cm (10-25th percentile). The newborn was admitted to neonatal intensive care unit immediately after delivery because of neonatal respiratory distress and cardiac arrhythmia.

At birth, typical facial dysmorphism including prominent forehead, upslanting palpebral fissures, broad nasal bridge, long philtrum, thin upper lip, and short neck was noted. He had shortened proximal limbs of all four extremities with joint contractures. Erythema and maculo-papular skin rashes were noted. Genital examination showed scrotal hyperpigmentation, bilateral inguinal hernia, and micropenis (penis length=1.9 cm, N=3.5±0.4 cm). Both testes were inguinal, and the scrotum was hypoplastic. There were no family members with findings similar to those of the patient (Picture 1).

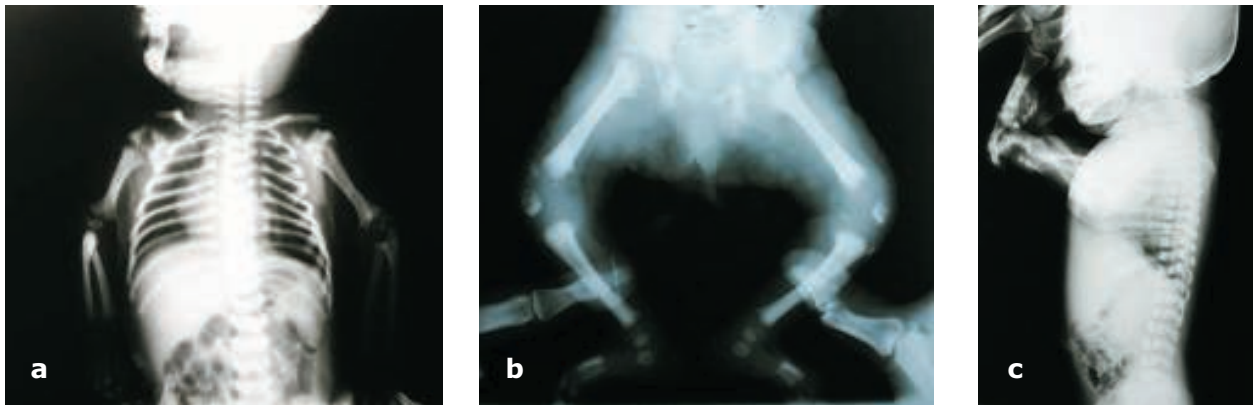


**Picture 1.** Lateral aspect of the patient with rhizomelia of the arms and legs and a dysmorphic facial appearance, including a prominent forehead, upslanting palpebral fissures, broad nasal bridge, long philtrum, thin upper lip and short neck. Note maculo-papular skin rashes. (A written permission to use the photograph was taken from the parents)

The patient's chromosomal analysis was normal and a screen for TORCH (toxoplasmosis, other infections, rubella, cytomegalovirus infection, and herpes simplex) was negative. Serum electrolytes, glucose, creatinine, aminoacides, lactate, ammonia, urinary aminoacides and mucopolisaccarides were all normal. At hormonal analyses, thyroid function tests were within normal ranges, but serum free and total testosterone levels were low according to age (free testosterone: 1.0 pg/ml, N= 3.3-18 pg/ml and total testosterone: 27 ng/dl, N= 60-400ng/dl). Further biochemical studies showed decreased plasmalogen biosynthesis and phytanic acid oxidation in fibroblasts with normal very long chain fatty acid oxidation.

Electrocardiography showed multifocal premature atrio-ventricular extrasystoles. At echocardiography, aberrant intracardiac band, mild pulmonary stenosis (gradient 22 mmHg), patent foramen ovale and ductus arteriosus were noted.

Conventional radiographs of the skeleton revealed shortening of humeri and femora, multiple punctate calcific stippling of joints localized in the shoulders, elbows, ribs, hips, knees, posterior segments of vertebra with coronal fissures of cervical and thoracic vertebral bodies. There were calcifications around the joints (Picture 2).



**Picture 2. a:** X-ray showing short humeri with multiple stippled calcification on shoulder, elbow and ribs; **b:** X-ray showing short femora with severe stippled calcification on knees and hips and **c:** X-ray showing multiple punctate calcifications at posterior segments of vertebra with coronal fissures of cervical and thoracic vertebral bodies (A written permission to use the all photographs was taken from the parents)



**Picture 3.** Sagittal T2-weighted MRI of the cervical and thoracic spine. Note multilevel cervical and thoracic stenosis (A written permission to use the photograph was taken from the parents)

When he was aged 21 days, a complete MRI evaluation was performed with 1.5 T. The MRI protocol included T1-weighted imaging and T2-weighted imaging. MR images of the brain were normal, without any atrophic or edematous feature, in supratentorial areas and in the posterior fossa. The spine MRI showed diffuse cervical and thoracic stenosis without cord compression. The spinal canal has a sagittal diameter of 4mm between C1–T12 levels (Picture 3).

Thus, bone abnormalities were highly suggestive of a peroxisomal disorder and RCDP was diagnosed based on clinical, biochemical, and radiological criteria. He was discharged with a clinical diagnosis of RCDP, prescribed digoxin and instructions were given.

The patient was subsequently seen in routine follow-up at 2 months of age. The mother complained from inadequate weight gain and recurrent respiratory infections. His weight was 3000 g, length 48 cm, and head circumference 35 cm; all below the 5th percentile. Flexion contractures were noted at the elbows, hips and knees. His neck and trunk muscles were hypotonic. He had bilateral cortical cataract and hearing loss.

The patient was followed-up by many different specialists including pediatrician, pediatric neurologist, ophthalmologist, ear-nose-throat surgeon, pediatric cardiologist, orthopedist, and neurosurgeon. He died at 10 months of age because of severe pneumonia. The parents were young and the patient was the first child. Therefore, they were informed about the risk for hereditary diseases, and genetic counseling was offered.

## Discussion

Chondrodysplasia punctata describes a group of heterogeneous bone dysplasia characterized by punctate calcifications of the cartilage consisting of shortened limbs, cataracts, ichthyosis, mental and growth deficiencies (3). There are several forms of chondrodysplasia punctata, including a dominant autosomal form (Conradi-Hunerman), X-linked dominant (happle), X-linked recessive (Curry), Sheffield, humero-metacarpal, tibial-metacarpal family and a recessive autosomal form (rhizomelic) (4).

RCDP has a defect in the peroxisomal import of proteins and a defect at 2-hydroxy phytanic acid decarboxylation. Peroxisomes are present in every cell in the organism, which explains the great variation between clinical manifestations presented by the syndrome. The peroxisomal diseases are genetically determined disorders caused by either the failure to form or maintain the peroxisome or a defect in the function of a single enzyme that is normally located in this organelle. These disorders cause serious disability in childhood and occur more frequently and present a wider range of phenotype than has been recognized in the past. Absence or reduction in the number of peroxisomes is pathognomonic for disorders of peroxisome biogenesis. Pathologic changes are observed in many organs and include profound and characteristic defects in neuronal migration; micronodular cirrhosis of the liver; renal cysts; chondrodysplasia punctata; cataract, congenital glaucoma, congenital heart disease; and dysmorphic features (5).

In RCDP, genital abnormalities are rarely seen and the etiopathogenesis is unclear, although it had been suggested that any pathology in cholesterol biosynthesis leading to hormonal disorder might cause genital abnormalities (6). Our patient had scrotal hyperpigmentation, bilateral inguinal hernia, and hypoplastic genitalia.

(RCDP) is characterized by the presence of stippled foci of calcification within the hyaline cartilage and is associated with dwarfing, cataracts, and multiple malformations due to contractures. Vertebral bodies have a coronal cleft filled by cartilage that is a result of an embryonic arrest (7). Disproportionate short stature affects the proximal parts of the extremities. Radiological abnormalities consist of shortening of the proximal limb bones, metaphyseal cupping, and disturbed ossification. Height, weight, and head circumference are less than the 5th percentile, and these children are severely retarded mentally. Skin changes such as those observed in

ichthyosiform erythroderma are present in about 25% of patients. Clinically, patients with RCDP demonstrate a high association with spasticity, psychomotor retardation, growth failure, seizures, thermoregulatory instability, feeding difficulties, recurrent otitis media and pneumonia [8]. Kozłowski *et al* [9] described two new cases of a rare form of lethal chondrodysplasia punctata (so-called X-linked dominant, non-rhizomelic form), a condition characterized by widespread multicentric stippled calcifications of the cartilaginous parts of the long bones, spine, ribs and flat bones.

Radiological and clinical findings detected in our patient including proximal limb shortening, multiple punctate calcific stippling of joints, skin rashes, cataract, hearing loss, spasticity, mental-motor retardation, growth failure, feeding difficulties and respiratory infections were consistent with RCDP.

Prenatal diagnosis of RCDP is possible from the first trimester onwards by demonstration of peroxisomal dysfunction in cultured chorionic villous or amniotic fluid cells. In all cases reported hitherto, the prenatal diagnosis had been established after the birth of a previous affected child. In contrast to those studies in pregnant multiparous women at risk for RCDP, *et al*. [10] reported on the first case of prenatal ultrasound diagnosis of RCDP at 19 weeks' gestation in a primigravida. They described a complex cardiac malformation associated with hypoplasia of the thymus (Di George anomaly). In our patient, prenatal ultrasonographic assessments reported proximal limb shortening and cardiac anomaly. RCDP is sometimes accompanied by heart lesions, but the literature is not specific or consistent regarding the incidence or types of cardiac anomalies. Fetal echocardiography is very useful in the diagnosis and management of fetal arrhythmia and can be constructed by combined use of two dimensional imaging and simultaneous M mode recording and matching the atrial and ventricular contractions (11, 12). Sheng-Mou Hsiao *et al*. investigated the outcome for fetuses with prenately detected congenital heart disease and cardiac arrhythmias in Taiwan and they found that outcome for fetuses with prenately detected congenital heart disease remained poor, with the prognosis negatively influenced by the presence of complex heart defects as well as extracardiac and chromosomal anomalies (13). Our patient had multiple congenital anomalies and presented with fetal arrhythmia due to cardiac malformation, a less common manifestation of the syndrome.

According to our literature review, there was a few reported case of RCDP leading to spinal stenosis. The development of abnormal ossification of the cervical spinal instability with resultant cervical myelopathy has been reported in warfarin-related chondrodysplasia (14, 15). Our patient had minimal cervical and thoracic stenosis. There was no history of maternal exposure to warfarin. In our patient, spinal stenosis was not severe and there was no cord compression. The decision was made to follow-up the patient rather than surgical decompression of the spinal canal.

Patients with RCDP must be distinguished from patients with other causes of chondrodysplasia punctata. In addition to warfarin embryopathy and Zellweger syndrome, these disorders include the milder autosomal dominant form of chondrodysplasia punctata (Conradi-Hunermann syndrome), which is characterized by longer survival, absence of severe limb shortening, and usually intact intellect; an X-linked dominant form; and an X-linked recessive form associated with a deletion of the terminal portion of the short arm of the X chromosome. The most decisive laboratory test is the demonstration of abnormally low plasmalogen levels in red blood cells and an impaired capacity to synthesize plasmalogens in cultured skin fibroblasts. These biochemical defects are not present in other types of chondrodysplasia punctata [16]. Here, RCDP was suspected clinically because of the symmetric shortening of the proximal limbs, cataract and other findings. Further biochemical studies showed decreased plasmalogen biosynthesis and phytanic acid oxidation in fibroblasts with normal very long chain fatty acid oxidation and he was diagnosed based clinical, biochemical, and radiological criteria.

As conclusion, RCDP may be associated with congenital heart defects. Close follow up would be better because heart defects could cause fetal arrhythmia.

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