Dubai Medical Journal
Volume 8, Issue no. 2, DOI 10.18502/dmj.v8i2.18997
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Case Report

Neonatal Presentation of Rhizomelic Chondrodysplasia Punctata: Spot Diagnosis and Myriads of Unmet Needs

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Abstract

Background: Rhizomelic chondrodysplasia punctata (RCDP) is an uncommon inborn error of metabolism related to peroxisome. The inheritance pattern of this problem is autosomal recessive in nature. Five genetic subtypes have been reported which are clinically indistinguishable. Majority of cases have arthrogryposis, cataract, and significant growth and neurodevelopmental impairments. Diagnosis is made by observing skeletal changes, cataract, and biochemical changes of peroxisomal dysfunction, including raised phytanic acid and reduced red cell plasmalogen level, and is confirmed by genetic analysis. The mainstay of treatment is supportive measures.

Case Report: We present a term male neonate born with cataract and bilateral contracture at hip, knee, elbow, and wrist. Skeletal radiographs suggested shortening of proximal long bones of the limbs (both humerus and femur) as compared to distal long bones (suggesting rhizomelia) and asymmetric multiple punctate calcifications in epiphyseal regions of femur and humerus.

Conclusion: A multidisciplinary approach including neonatology/pediatrics, pediatric neurology, ophthalmology, physical and occupational therapy, cardiology, and pediatric orthopedic services would bring about optimal results for the infant and the family. The use of genetic epidemiological approaches to compute the struggles of individuals affected with this disorder will help in understanding their unmet medical needs, improving diagnostic support, and furthering therapeutic development efforts.

Keywords: chondrodysplasia punctata, rhizomelic, contracture, cataract, infant, newborn

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Received: October 30, 2024
Accepted: December 7, 2024
Published: June 30, 2025

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OPEN ACCESS

How to cite this article: Prasad A, Kumar C, Shedabale DS, Alam MS, Chand S, Romana A. Neonatal Presentation of Rhizomelic Chondrodysplasia Punctata: Spot Diagnosis and Myriads of Unmet Needs. *Dubai Medical Journal*. 2025;8(2):133–139. DOI 10.18502/dmj.v8i2.18997

1. Introduction

Peroxisome is an important organelle for the synthesis of phospholipids and the metabolism of fats. Peroxisomal metabolic diseases are of two types: The first one is due to deficiency of single enzyme and the second one is peroxisomal biogenesis disorder (PBD) [1]. *PEX5* and *PEX7* encode the cytoplasm receptor complex which acts as a channel for the entry of matrix proteins into the peroxisome for further metabolic steps. This is a crucial step in peroxisomal biogenesis. These receptors respond to the proteins carrying peroxisomal targeting signals 1 or 2 (PTS1 or PTS2). *PEX7* mutation induces a single enzyme deficiency leading to RCDP type 1 while *PEX5* mutation induces a PBD called Zellweger spectrum disorders (ZSDs) [2].

Rhizomelic chondrodysplasia punctata (RCDP) is an uncommon inborn error of metabolism related to peroxisome. The inheritance pattern of this disorder is autosomal recessive in nature. It involves multiple systems of the body. Five genetic subtypes have been reported which are clinically indistinguishable. Type 1 (*PEX7* mutation) is the commonest subtype and has been reported to be associated with almost 90% of the affected individuals. RCDP types 1 and 5 are PBDs while types 2, 3, and 4 are single peroxisomal enzyme deficiency responsible for plasmalogen biosynthesis. The genes responsible for type 1, 2, 3, 4, and 5 are mutations in *PEX7*, *GNPAT*, *AGPS*, *FAR1,* and *PEX5* respectively [3, 4].

RCDP is categorized into two types based on its clinical severity: Classic and non-classic (mild). Majority of cases have arthrogryposis, cataract, and significant growth and neurodevelopmental impairments [5]. Other clinical manifestations include spasticity, epilepsy, thermoregulatory problems, swallowing difficulties, and repeated respiratory and ear infections [6]. Due to its rare occurrence, the prevalence of RCDP is difficult to estimate which might be helpful in formulating the policy for its treatment. Moreover, neonatal presentation of RCDP is scarcely reported in literature. Hence, there is a vast scope to explore its unmet needs. This case report aims to describe the neonatal presentation of RCDP and the need for genetic epidemiological approach to estimate its burden and unmet needs. Ethical approval from the institute and parental consent were obtained.

2. Case Presentation

We present a term male neonate born by cesarian delivery to a third-degree consanguineous couple. There was no requirement of resuscitation at birth. On head-to-toe examination, he had contractures at bilateral hip, knee, elbow and wrist, short proximal bones, bilateral lamellar opacities in eyes, facial dysmorphism including high arched palate, micrognathia, long philtrum, and depressed nasal bridge. Skeletal radiographs (Figure **1**) showed shortened humerus and femur as compared to distal long bones (suggesting rhizomelia), asymmetric multiple punctate calcifications in the epiphyseal regions of humerus and femur (left more than right), underdeveloped pubic bones, and flexion at proximal interphalangeal

joints of both hands. Ultrasonography of hips showed bilateral acetabular dysplasia. He also had right retractile testis and congenital hydrocele. Cardiac evaluation was normal. Neonatal screening for common metabolic disorders was negative. The clinical and radiographic features suggested a diagnosis of RCDP. The genetic testing showed *PEX7* mutation (homozygous variant), confirming the diagnosis.

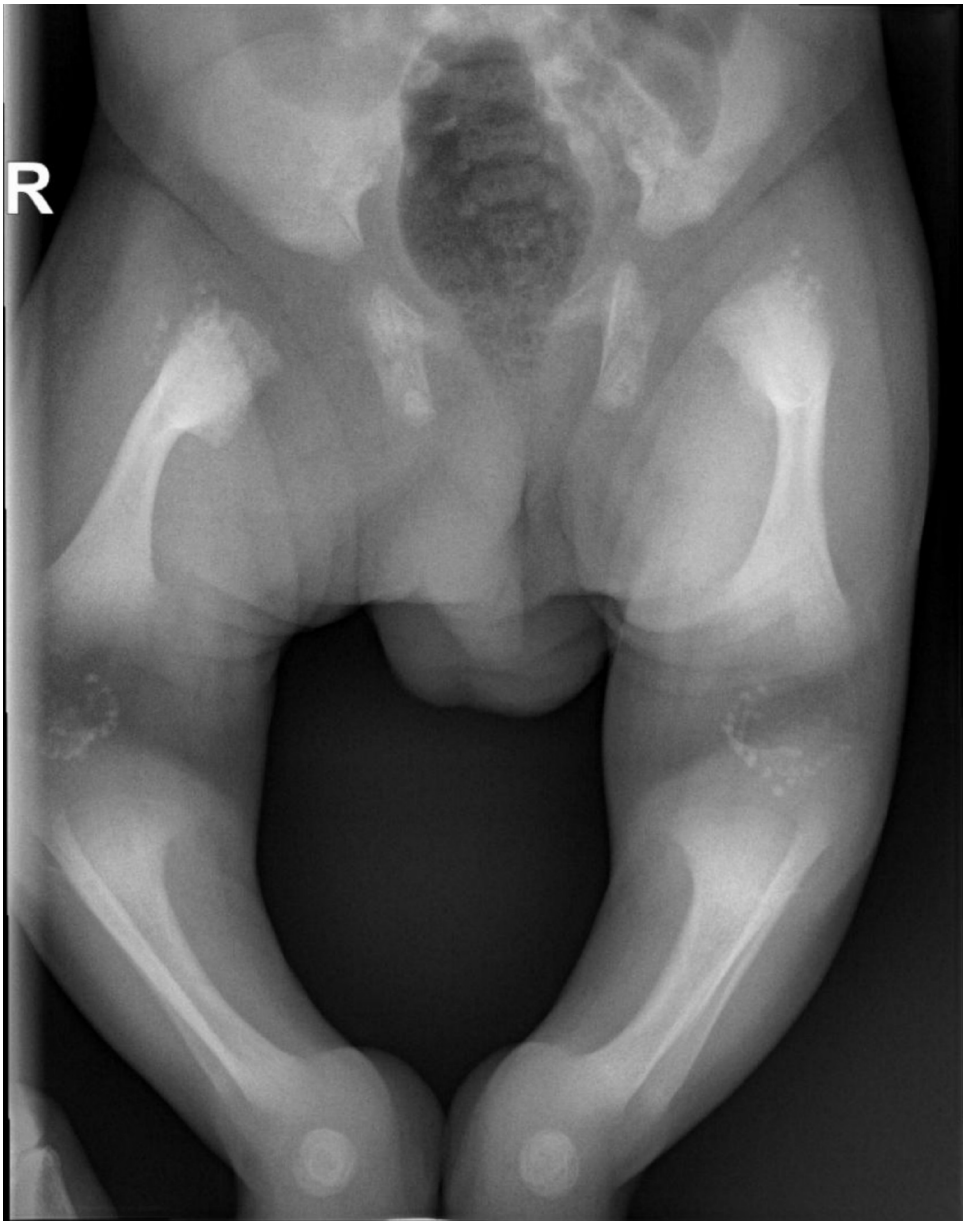

Figure 1: Skeletal radiograph shows bilateral short femurs, widened epiphyses, punctate calcification, and acetabular dysplasia.

The neonate was initiated on physiotherapy and double diapers for developmental dysplasia of hip (DDH). A multidisciplinary approach was instituted which included expert consultation by pediatrician/neonatologist, pediatric orthopedician and surgeon, pediatric ophthalmologist, developmental pediatrician, geneticist, physiotherapist, and occupational therapist. Magnetic resonance imaging (MRI) of the brain was planned in follow-up. Bilateral lens removal was planned at 3-6 months of age. Hearing

screening was normal. Genetic counseling was provided to the parents. The infant had growth and developmental delays at 6 weeks follow up.

3. Discussion

Peroxisome is an important organelle responsible for plasmalogen biosynthesis. Plasmalogens are a class of phospholipids that have an important physiological role in the metabolic and developmental process of various tissues like brain, bone, lung, lens, kidney, and heart. The disease severity correlates with erythrocyte plasmalogen level [3].

RCDP is a group of skeletal dysplasia with an estimated incidence of one in 100,000 births [7]. The inheritance pattern of this disorder is autosomal recessive in nature [3]. The diagnosis is made by observing skeletal changes, cataract, and biochemical changes of peroxisomal dysfunction including raised phytanic acid and reduced red cell plasmalogen level. Skeletal changes include shortening of proximal long bones (rhizomelic shortening), asymmetric multiple punctate calcifications in the epiphyseal regions of long bones, and underdeveloped pubic bones [8-10]. Congenital heart disease is common in up to one-third of cases, with atrial septal defect being the most common [8, 9]. The index case did not have any congenital heart defect. The index case also had right retractile testis and congenital hydrocele. One case report described presence of inguinal hernia in a neonate [11]. Short femur bone in the fetus is the most common antenatal ultrasonographic finding which leads to the consideration of RCDP as the possible diagnosis especially with family history of skeletal dysplasia [12, 13]. Growth and developmental deficit are almost universal and it was present in the index case as well [14]. Contractures in neonatal period and radiographic changes should direct the neonatologist for genetic counseling of the family. Earlier reports suggested a very high mortality rate. However, recent observational studies have reported the survival outcome of 90% and 50% at 1 year and 5 years respectively [14]. The major cause of death is respiratory complications.

Neurological manifestations include global developmental delay, spasticity, and epilepsy. MRI of the brain may be normal in nonclassic type. However, in the classic type, this may include signal abnormalities in the white matter, delay in the myelination, and diffuse atrophy of cerebrum and cerebellum. Erythrocyte plasmalogen levels correlate with the severity of cerebellar atrophy suggesting critical plasmalogen levels necessary for its protection [5, 15].

An accurate assessment of the incidence and prevalence of RCDP is highly challenging due to the rare nature of this disease. However, the use of genetic epidemiological approaches is recommended to compute the burden of individuals affected with RCDP [4]. This will help in appreciating the unmet medical needs and improving diagnostic support and further therapeutic development efforts.

Other differential diagnoses include X-linked chondrodysplasia punctata, fetal alcohol syndrome, maternal ingestion of warfarin, and trisomy 18 [3].

The mainstay of treatment is supportive measures. The management strategies are based upon clinical manifestations. This includes cataract surgery, gastrostomy for feeding difficulties, orthosis for bone deformities, physiotherapy and general developmental follow-up for developmental delays, seizure control, special formula for phytanic acid restriction, and genetic counseling for the family. A multidisciplinary approach including neonatology/pediatrics, pediatric neurology, ophthalmology, physical and occupational therapy, cardiology, and pediatric orthopedic services would bring about optimal results for the infant and the family [8].

4. Conclusions

Neonatal presentation of contracture at multiple joints, dysmorphic facies, and cataract with parental consanguinity should direct the clinician to consider RCDP, which helps in early diagnosis and genetic counseling of the family. The use of genetic epidemiological approaches to compute the burden of individuals affected with this disorder will help in appreciating the unmet medical needs and improvement in diagnostic support and further therapeutic development efforts.

Acknowledgments

The authors thank radiologist for assisting in the diagnosis.

Statement of Ethics

The case is prepared and compiled with the guidelines of the Helsinki Declaration. Written informed consent was obtained from the parent for publishing the case and accompanied images. Ethical approval is not required as per the hospital ethics committee policies.

Conflict of Interest

Authors declare that there is no conflicts of interest.

Artificial Intelligence (AI) Disclosure Statement

AI-unassisted work.

Funding

No funding received.

Author Contributions

Chanchal Kumar, Amarendra Prasad, and Dhiraj Sidagonda Shedabale conceptualized the study, gathered clinical data, provided patient care, and helped with manuscript drafting, writing, and editing. Mohammad Shahbaz Alam, Suvas Chand, and Ayesha Romana wrote the manuscript and reviewed relevant literature. Chanchal Kumar, Amarendra Prasad, and Dhiraj Sidagonda Shedabale supervised experimental work and helped with manuscript writing and editing. All authors approved the final version to be published and are accountable for all aspects of the work.

Data Availability

All data generated during this case are included in the article. Further inquiries to be addressed to the corresponding author.

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