Rhizomelic Chondrodysplasia Punctata in a Neonate: A Diagnostic Challenge in Resource-Limited Settings

Sushma[1], Nandipatti[2], Mary Chandrika[3], Aljin V [4*]

Abstract

Background: Rhizomelic chondrodysplasia punctata (RCDP) is a rare autosomal recessive peroxisomal disorder characterized by dwarfism due to symmetrical shortening of the proximal long bones (rhizomelia), cataracts, multiple joint contractures, and specific radiological abnormalities, such as punctate epiphyseal calcification. The condition is often caused by mutations in the PEX7 gene and presents significant diagnostic challenges due to its complex clinical manifestations and overlaps with other peroxisomal disorders. Method: This case report describes a male neonate born at term with features suggestive of RCDP. Clinical evaluation, ophthalmological examination, and skeletal surveys were performed to assess the presence of characteristic findings associated with the disorder. Due to financial constraints, advanced biochemical profiling and genetic assays were not conducted. Results: The neonate presented with proximal limb shortening, dysmorphic facial features, bilateral megalocornea, near-mature cataracts, and multiple joint contractures. Radiological investigations showed bilateral symmetrical shortening of the humerus and femur, stippled calcification, diaphyseal thickening, metaphyseal splaying and fraying, and paravertebral calcific foci. These findings were consistent with the diagnosis of RCDP. Conclusion: This case underscores the importance of recognizing the clinical and radiological hallmarks of RCDP for early diagnosis and management, especially in resource-limited settings where advanced genetic testing may not be available. Genetic counselling is crucial for affected families, considering the autosomal recessive inheritance pattern and recurrence risk in future pregnancies.

Keywords: Rhizomelic Chondrodysplasia Punctata, Peroxisomal Disorders, Skeletal Dysplasia, PEX7 Gene Mutation, Neonatal Diagnosis.

Significance | This case determines the importance of recognizing clinical and radiological features of RCDP for early diagnosis in limited-resource settings.

*Correspondence. Aljin V, Department of Community Medicine, Sree Balaji Dental College and Hospital, Bharath Institute of Higher Education and Research (BIHER), Chennai, Tamil Nadu, India
E-mail: Aljin.v@bharathuniv.ac.in

Editor Johnson Stanslas, Ph.D. And accepted by the Editorial Board January 07, 2022 (received for review November 29, 2021)

Introduction

Rhizomelic chondrodysplasia punctata (RCDP) is a rare, autosomal recessive peroxisomal disorder characterized by distinct clinical and radiological features. The hallmark clinical phenotype of RCDP includes dwarfism due to the symmetrical shortening of the proximal long bones, also known as rhizomelia, cataracts, periarticular calcifications, multiple joint contractures, specific radiological abnormalities, and psychomotor retardation (Braverman, Steinberg, & Moser, 2001). This condition, although rare, presents a significant diagnostic challenge due to its complex clinical manifestations and overlaps with other peroxisomal disorders. Radiological findings such as stippled foci of calcification within hyaline cartilage, shortening of the proximal limb bones, metaphyseal cupping, and coronal clefts in vertebral bodies filled

Author Affiliation.
[1] Department of Anaesthesia, Sree Balaji Dental College and Hospital, Bharath Institute of Higher Education and Research (BIHER), Chennai, Tamil Nadu, India
[2]Department of Anatomy, Sree Balaji Dental College and Hospital, Bharath Institute of Higher Education and Research (BIHER), Chennai, Tamil Nadu, India
[3]Department of Biochemistry, Sree Balaji Dental College and Hospital, Bharath Institute of Higher Education and Research (BIHER), Chennai, Tamil Nadu, India
[4]Department of Community Medicine, Sree Balaji Dental College and Hospital, Bharath Institute of Higher Education and Research (BIHER), Chennai, Tamil Nadu, India

Please Cite This:
Sushma, Nandipatti, et al. (2022). Rhizomelic Chondrodysplasia Punctata in a Neonate: A Diagnostic Challenge in Resource-Limited Settings, Journal of Angiotherapy, 6(1), 1-4, 2182.

with cartilage are essential for a diagnosis of RCDP.

Peroxisomal disorders, including RCDP, are genetically determined and involve the dysfunction of peroxisomes—cellular organelles responsible for various metabolic processes, including the breakdown of very-long-chain fatty acids and the biosynthesis of plasmalogens. RCDP is one of the peroxisome biogenesis disorders where there is a failure to form or maintain functional peroxisomes. The disorder can result from mutations in several genes that affect the normal import and function of peroxisomal proteins. Among these, the PEX7 gene mutation is specifically implicated in RCDP type 1, the most common form, while types 2 and 3 are linked to deficiencies in dihydroxyacetone phosphate acyltransferase and alkyldihydroxyacetone phosphate synthase, respectively (Itzkovitz et al., 2012).

Clinically, RCDP manifests early in life, with affected neonates presenting with characteristic features such as rhizomelia, cataracts, facial dysmorphism, joint contractures, and profound growth retardation. These features, combined with specific radiological findings like punctate epiphyseal calcification and metaphyseal abnormalities, provide critical diagnostic clues. However, a definitive diagnosis often relies on biochemical assays and genetic analysis. Plasma phytanic acid levels, which are increased, and reduced plasmalogen levels in red blood cells are key biochemical markers. Unlike other peroxisomal disorders like Zellweger syndrome and infantile Refsum disease, plasma very-long-chain fatty acid levels remain normal in RCDP, which helps in differential diagnosis (Hoefler et al., 1988).

This case report presents a neonate diagnosed with RCDP based on clinical, radiological, and phenotypic features. The patient, a Hindu male baby born at term, exhibited proximal shortening of the upper and lower limbs, bilateral megalocornea, near-mature cataract, and multiple joint contractures. Additional dysmorphic features such as a depressed nasal bridge, broad nose, coarse facial features, long philtrum, and macrostomia were also noted. The skeletal survey revealed bilateral symmetrical shortening of the humerus and femur with punctate epiphysis due to stippled calcification, along with diaphyseal thickening, metaphyseal splaying and fraying, and paravertebral calcific foci. Despite financial constraints that limited comprehensive biochemical and genetic testing, the characteristic clinical and radiological findings were sufficient to diagnose RCDP. This case underscores the importance of recognizing the clinical and radiological hallmarks of RCDP for early diagnosis and management, especially in resource-limited settings where advanced genetic testing may not be readily available. The case also highlights the need for genetic counseling for affected families, as RCDP is an autosomal recessive disorder with a recurrence risk in future pregnancies. The study contributes to the existing literature by adding valuable clinical and diagnostic insights into this rare disorder, emphasizing the role of radiology and phenotypic assessment in its diagnosis and management.

Case Report

Patient Information

A male neonate was born at term (39 weeks + 6 days) via normal vaginal delivery to a 24-year-old mother and a 28-year-old father. There was no history of consanguinity, prior abortions, or exposure to teratogens during pregnancy. The mother's antenatal history was unremarkable.

Clinical Presentation

At birth, the baby had a weak cry and exhibited signs of respiratory distress, such as fast breathing, which necessitated admission to the Neonatal Intensive Care Unit (NICU). His birth weight was 2100 grams (<3rd centile for gestational age), length was 41 cm (<3rd centile), and head circumference was 33.6 cm (50th centile). The upper segment to lower segment ratio was 1.8:1, indicating disproportionate limb shortening.

Physical Examination

On clinical examination, the neonate presented with proximal shortening of both the upper and lower limbs (rhizomelia). Additional dysmorphic features were noted, including a depressed nasal bridge, broad nose, coarse facial features, a long philtrum, and macrostomia. Joint contractures were observed at the thighs and elbows. The overall appearance was suggestive of a skeletal dysplasia.

Ophthalmological Examination

An ophthalmological evaluation revealed bilateral megalocornea and near-mature cataracts, which are commonly associated with rhizomelic chondrodysplasia punctata (RCDP).

Radiological Findings

A skeletal survey was conducted to further investigate the skeletal abnormalities. The survey revealed bilateral symmetrical shortening of the humerus and femur with punctate epiphyses due to stippled calcification, which is characteristic of RCDP. Other significant radiological findings included diaphyseal thickening with metaphyseal splaying and fraying. Bilateral acetabular erosion was also present. In the cervico-thoracic vertebral region, multiple paravertebral calcific foci were observed, further supporting the diagnosis of a peroxisomal disorder.

Other Investigations

Abdominal and cranial ultrasonography were performed, both of which were normal. A two-dimensional echocardiogram showed no cardiac anomalies.

Diagnosis

Based on the clinical presentation, physical examination, and radiological findings, a diagnosis of Rhizomelic Chondrodysplasia Punctata (RCDP) was made. RCDP is a rare autosomal recessive peroxisomal disorder characterized by rhizomelia, cataracts, dysmorphic facial features, and specific radiological abnormalities such as punctate epiphyseal calcification.

Management and Follow-up

Due to financial constraints, biochemical profiling and genetic assays, which could have provided confirmatory evidence of the PEX7 gene mutation or related enzyme deficiencies, were not performed. Despite the inability to perform these tests, the characteristic clinical and radiological features strongly suggested the diagnosis of RCDP. The parents were counseled regarding the nature of the disorder, its genetic basis, and the implications for future pregnancies. They were informed about the 25% recurrence risk of RCDP in subsequent pregnancies due to its autosomal recessive inheritance pattern.

This case highlights the importance of recognizing the clinical and radiological hallmarks of RCDP, particularly in settings where advanced genetic and biochemical testing may not be available. Early diagnosis is crucial for appropriate management and genetic counseling. The distinctive features of RCDP, such as symmetrical rhizomelia, cataracts, and stippled epiphyses, should prompt clinicians to consider this diagnosis in neonates presenting with similar features. This case report adds to the limited literature on RCDP and emphasizes the importance of comprehensive clinical evaluation and family counseling in managing rare genetic disorders.

Discussion

Rhizomelic chondrodysplasia punctata (RCDP) is a subtype of chondrodysplasia punctata (CDP), a group of disorders affecting peroxisome biogenesis or function. Peroxisomes are essential cellular organelles involved in various metabolic processes, including the breakdown of very-long-chain fatty acids and the synthesis of plasmalogens, which are critical for normal cell function. RCDP, an autosomal recessive disorder, is typically classified into three types based on the specific genetic mutations involved: RCDP type 1 (PEX7 gene mutation), type 2 (dihydroxyacetone phosphate acyltransferase deficiency), and type 3 (alkyldihydroxyacetone phosphate synthase deficiency; Braverman et al., 2001).

The phenotypic presentation of RCDP is characterized by rhizomelia, cataracts, dysmorphic facial features, joint contractures, and psychomotor retardation. Radiologically, the disorder is diagnosed by the presence of stippled epiphyses (punctate calcifications), shortening of the proximal long bones, and other skeletal abnormalities such as metaphyseal splaying and fraying, which are well-documented in this case. The typical radiological findings, combined with the clinical presentation of proximal limb shortening, facial dysmorphism, and cataracts, form the cornerstone of diagnosing RCDP, especially in settings where advanced biochemical or genetic testing is not available (Irving et al., 2008).

The differential diagnosis for RCDP includes other peroxisomal biogenesis disorders such as Zellweger syndrome and infantile Refsum disease, which also present with overlapping features. However, these conditions can often be distinguished based on specific biochemical markers and genetic mutations. For instance, RCDP is unique in having normal levels of very-long-chain fatty acids, a key differential point from other peroxisomal disorders (Wanders & Waterham, 2006). The definitive diagnosis of RCDP requires a combination of clinical, radiological, and biochemical findings, with genetic analysis confirming the specific mutation involved, such as the PEX7 gene defect in RCDP type 1 (Braverman et al., 2002).

In this case, while financial constraints precluded the use of genetic testing, the diagnosis was strongly supported by the distinctive clinical and radiological features. The patient's presentation with bilateral symmetrical shortening of the humerus and femur, stippled calcifications, and characteristic facial dysmorphism aligns with the typical phenotype of RCDP. Moreover, the absence of increased very-long-chain fatty acid levels and the clinical exclusion of maternal autoimmune diseases like systemic lupus erythematosus (SLE) or phenylketonuria, which have been occasionally associated with CDP (Costa et al., 1993), further corroborates the diagnosis.

Management of RCDP primarily involves supportive care and symptomatic treatment, as there is no definitive cure for the disorder. Genetic counseling for the family is crucial, considering the autosomal recessive inheritance pattern and a 25% recurrence risk in future pregnancies (Fallatah et al., 2021). Early diagnosis and intervention can help manage complications such as joint contractures and cataracts, improving the quality of life for affected individuals. The case presented here underscores the importance of recognizing the clinical and radiological hallmarks of RCDP, particularly in resource-limited settings where genetic testing may not be feasible. The integration of clinical acumen with radiological expertise remains vital in diagnosing rare genetic disorders like RCDP (Bams-Mengerink et al., 2013).

This case adds to the limited literature on RCDP and highlights the need for comprehensive clinical evaluation, early diagnosis, and genetic counseling for effective management. Future research may focus on advancing diagnostic techniques and developing targeted therapies for peroxisomal disorders, potentially offering more hope for affected patients and their families (Braverman & Moser, 2012; Waterham & Ebberink, 2012).

Conclusion

Rhizomelic chondrodysplasia punctata (RCDP) is a rare and complex autosomal recessive peroxisomal disorder characterized by distinctive clinical and radiological features, including rhizomelia, cataracts, and stippled calcifications. This case report highlights the significance of recognizing the clinical and radiological hallmarks of RCDP, particularly in settings with limited access to advanced genetic and biochemical testing. The

presented neonate demonstrated key diagnostic features such as proximal limb shortening, facial dysmorphism, and characteristic radiological abnormalities, which were crucial for the diagnosis despite the lack of confirmatory genetic tests.

Early diagnosis of RCDP is essential for effective management and genetic counseling, given the disorder's autosomal recessive inheritance pattern and the associated recurrence risk in future pregnancies. This case underscores the need for heightened clinical awareness and the integration of radiological findings in the diagnostic process. Comprehensive clinical evaluation and family counseling remain pivotal in managing rare genetic disorders like RCDP, especially in resource-constrained environments where genetic testing may not be readily available. Continued research into diagnostic advancements and targeted therapies for peroxisomal disorders holds promise for improving outcomes for affected individuals and their families.

Author contributions

S.N, N.N, M.C, and A.V oversaw the study's supervision. All authors were involved in the discussion of the results and contributed to the writing and revision of the manuscript.

Acknowledgment

The authors were grateful to their department.

Competing financial interests

The authors have no conflict of interest.

References

Bams-Mengerink, A. M., Koelman, J. H., Waterham, H., Barth, P. G., & Poll-The, B. T. (2013). The neurology of rhizomelic chondrodysplasia punctata. Orphanet Journal of Rare Diseases, 8(174). https://doi.org/10.1186/1750-1172-8-174

Barøy, T., Koster, J., Strømme, P., et al. (2015). A novel type of rhizomelic chondrodysplasia punctata, RCDP5, is caused by loss of the PEX5 long isoform. Human Molecular Genetics, 24(5845-5854). https://doi.org/10.1093/hmg/ddv305

Braverman NE, Moser AB, Steinberg SJ. 2001. Rhizomelic Chondrodysplasia Punctata Type 1. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. GeneReviews [Internet] Seattle: University of Washington; 2001. Nov, p. 16.

Braverman, N. E., & Moser, A. B. (2012). Functions of plasmalogen lipids in health and disease. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1822(1442-1452). https://doi.org/10.1016/j.bbadis.2012.05.008

Braverman, N. E., Steinberg, S. J., Fallatah, W., et al. (2001). Rhizomelic chondrodysplasia punctata type 1. In GeneReviews. University of Washington.

Braverman, N., Chen, L., Lin, P., et al. (2002). Mutation analysis of PEX7 in 60 probands with rhizomelic chondrodysplasia punctata and functional correlations of genotype with phenotype. Human Mutation, 20(284-297). https://doi.org/10.1002/humu.10124

Buchert, R., Tawamie, H., Smith, C., et al. (2014). A peroxisomal disorder of severe intellectual disability, epilepsy, and cataracts due to fatty acyl-CoA reductase 1 deficiency. American Journal of Human Genetics, 95(602-610). https://doi.org/10.1016/j.ajhg.2014.10.003

Costa T, Tiller G, Chitayat D, Silverman E. 1993. Maternal Systemic Lupus Erythematosus and Chondrodysplasia Punctata in Two Infants: Coincidence or Association? Abstract Book; First Meeting of the Bone Dysplasia Society; June 17-19, 1993.

Fallatah, W., Schouten, M., Yergeau, C., et al. (2021). Clinical, biochemical, and molecular characterization of mild (nonclassic) rhizomelic chondrodysplasia punctata. Journal of Inherited Metabolic Disease, 44(1021-1038). https://doi.org/10.1002/jimd.12349

Hoefler G, Hoefler S, Watkins PA, Chen WW, Moser A, Baldwin V, et al. 1988. Biochemical abnormalities in rhizomelic chondrodysplasia punctata. J Pediatr 1988;112:726-33. https://doi.org/10.1016/S0022-3476(88)80689-9

Irving MD, Chitty LS, Mansour S, Hall CM. 2008. Chondrodysplasia punctata: A clinical diagnostic and radiological review. Clin Dysmorphol 2008;17:229-41. https://doi.org/10.1097/MCD.0b013e3282fdcc70

Irving, M. D., Chitty, L. S., Mansour, S., & Hall, C. M. (2008). Chondrodysplasia punctata: A clinical diagnostic and radiological review. Clinical Dysmo

Itzkovitz, B., Jiralerspong, S., Nimmo, G., et al. (2012). Functional characterization of novel mutations in GNPAT and AGPS, causing rhizomelic chondrodysplasia punctata (RCDP) types 2 and 3. Human Mutation, 33(189-197). https://doi.org/10.1002/humu.21623

Kliegman R, Stanton B, St Geme J, Schor N, Behrman R, Kleigman R, et al., editors. 2012. Disorders of Very Long Chain Fatty Acids. Nelson Textbook of Pediatrics. 19th ed. Philadelphia: Elsevier Publishers and Distributors; 2012. p. 462-7.

Luisman, T., Smith, T., Ritchie, S., & Malone, K. E. (2021). Genetic epidemiology approach to estimating birth incidence and current disease prevalence for rhizomelic chondrodysplasia punctata. Orphanet Journal of Rare Diseases, 16(300). https://doi.org/10.1186/s13023-021-01889-z

Phadke SR, Gupta N, Girisha KM, Kabra M, Maeda M, Vidal E, et al. 2010. Rhizomelic chondrodysplasia punctata type 1: Report of mutations in 3 children from India. J Appl Genet 2010;51:107-10. https://doi.org/10.1007/BF03195717

Steinberg SJ, Dodt G, Raymond GV, Braverman NE, Moser AB, Moser HW. 2006. Peroxisome biogenesis disorders. Biochim Biophys Acta 2006;1763:1733-48. https://doi.org/10.1016/j.bbamcr.2006.09.010

Wanders, R. J., & Waterham, H. R. (2006). Biochemistry of mammalian peroxisomes revisited. Annual Review of Biochemistry, 75(295-332). https://doi.org/10.1146/annurev.biochem.74.082803.133329

Wardinsky, T. D., Pagon, R. A., Powell, B. R., McGillivray, B., Stephan, M., Zonana, J., & Moser, A. (1990). Rhizomelic chondrodysplasia punctata and survival beyond one year: A review of the literature and five case reports. Clinical Genetics, 38(84-93). https://doi.org/10.1111/j.1399-0004.1990.tb03554.x

Waterham, H. R., & Ebberink, M. S. (2012). Genetics and molecular basis of human peroxisome biogenesis disorders. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1822(1430-1441). https://doi.org/10.1016/j.bbadis.2012.04.006

White, A. L., Modaff, P., Holland-Morris, F., & Pauli, R. M. (2003). Natural history of rhizomelic chondrodysplasia punctata. American Journal of Medical Genetics Part A, 118A(332-342). https://doi.org/10.1002/ajmg.a.20009