

CASE REPORT

RHIZOMELIC CHONDRODYSPLASIA PUNCTATA: A RARE CASE REPORT

P. Yashodhara¹, B. Elizabeth², N. Madhavi³, B. Deeva Kumar⁴, A. Tirupathi Reddy⁵

HOW TO CITE THIS ARTICLE:

P. Yashodhara, B. Elizabeth, N. Madhavi, B. Deeva Kumar, A. Tirupathi Reddy. "Rhizomelic Chondrodysplasia Punctata: A Rare Case Report". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 4, Issue 04, January 12; Page: 711-715, DOI: 10.14260/jemds/2015/102

ABSTRACT: Rhizomelic chondrodysplasia punctate (RCDP) is a rare autosomal recessive peroxisomal disease. The main features of the disease are shortening of the proximal long bones (Rhizomelia), punctate calcifications located in the epiphyses of long bones (Chondrodysplasia) and in the soft tissues around joints and vertebral column, vertebral clefting, dysmorphic face, and severe growth retardation, cervical spinal stenosis may also rarely be present. Imaging of the brain and spinal cord in patients with this disorder may aid prognosis and guide us to take management decisions. We report a rare case of RCDP diagnosed in a newborn. Our aim is to discuss current knowledge on etiopathogenesis as well as radiological and clinical symptoms of diseases associated with CDP.

KEYWORDS: Rhizomelia, chondrodysplasia, autosomal recessive inheritance,

INTRODUCTION: Rhizomelic chondrodysplasia punctata (RCDP) is a rare disorder of peroxisomal metabolism with an estimated incidence of 1: 1, 00, 000. There are 3 genetic subtypes. RCDP type 1 is the most common type and is caused by mutations in the PEX7 gene. RCDP type 2 and 3 are single enzyme deficiencies in the plasmalogen biosynthesis pathway. RCP type 2 arises secondary to mutations in the dihydroxyacetone phosphate acyltransferase (DHAPAT) gene and RCP type 3 arises from mutations in the alkyl-dihydroxyacetone phosphate synthase (ADAPS) gene.^[1,2]

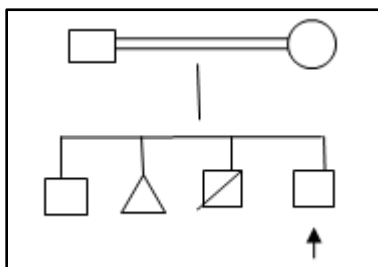
The main features of the disease are shortening of the proximal long bones, punctate calcifications in the metaphysis and epiphysis of long bones and the thoracic and lumbar vertebrae, dysmorphic facies and severe growth retardation. Cervical stenosis is very rarely reported in rhizomelic CDP cases.^[1,3]

CASE REPORT: A 1 day old full term male neonate, appropriate for gestational age, born out of 3rd degree consanguineous parentage was brought to OPD with complaints of limb anomalies and atypical facial appearance noticed immediately after birth. The baby was born at 38wks gestation to 24 yrs old healthy mother with no history of exposure to any known embryopathic agents.

On physical examination his birth weight was 3.25 kg, with length of 46cm, head circumference of 32cm, chest circumference was 36 cm and Canthal index of 40cm. Limb length measurements showed upper arm 3cm, forearm 7cm, thigh 7cm, leg 10cm. Baby had dysmorphic facies (Microcephaly, prominent forehead, widely spaced eyes, upturned nose, depressed nasal bridge, full cheeks and micrognathia), congenital cataracts, rhizomelia, joint contractures and spasticity. Anterior fontanallae and posterior fontanallae were patent. Examination of Locomotor system showed rhizomelia with flexion contractures are present Cardiovascular System showed systolic murmur. Other system were normal

CASE REPORT

PEDIGREE ANALYSIS:



1ST sibling is a 7 year old healthy boy, second one was an abortion, third sibling died on 20th day of life with similar features and 4th one is the index case.

INVESTIGATIONS: Neurosonogram showed bilateral hyperechoic lesions with specks of calcification in the basal ganglia. Infantogram showed multiple small calcifications noted at multiple epiphyseal regions suggestive of CDP and rhizomelia was noted in both upper and lower limbs. 2D ECHO showed moderate sized ASD. Computerized Tomography Brain showed diffuse cerebral atrophy and hypodense white matter suggestive of hypomyelination. Hemogram, Chest X-ray, Ultrasound abdomen were normal. Biochemical investigations like RBC plasmalogen levels and phytanic acid levels could not be done because of financial constraints.

Baby is regularly followed up. He is now 4 months old weighing 4.2 kg with feeding problems and failure to thrive and increasing contractures with spasticity.

DISCUSSION: Chondrodysplasia punctata (CDP) is a rarely occurring skeletal dysplasia characterized by stippled, punctate calcifications around joints and within cartilages. [1] CDP is associated with a number of disorders including inborn errors of metabolism involving peroxisomal and cholesterol pathways, embryopathy and chromosomal abnormalities. [2-7] Several classification systems of the different types of CDP have been suggested earlier. More recently, the biochemical and molecular basis of a number of CDP syndromes has been elucidated and a new etiological classification has emerged.[2]. Rhizomelic chondrodysplasia punctata is a disorder caused by abnormal peroxisomal function which can be mediated both through disorders of biosynthesis, for example, peroxisomal assembly (RCDP1) and by single enzyme defects affecting plasmalogen synthesis (RCDP2, RCDP3).

Clinically, depending on genetic mutations, It is classified into 3 types:

RCDP 1 - PEX 7 gene mutation.

RCDP 2 - GNPA5 gene mutation.

RCDP 3 - AGP gene mutation.

These genes are involved in peroxisomal metabolism. Mutation of these genes causes defect in peroxisomal metabolism. As a result, plasmalogens which are required for normal brain and skeletal formation are abnormal resulting in clinical manifestations. RCDP1, RCDP2, and RCDP3 are characterized by rhizomelic shortening, mainly affecting the humerus, facial dysmorphism, seizures, cataracts, and joint contractures. Growth and development are severely restricted. Life expectancy is considerably reduced.[1,2,8] Pathognomonic finding for RCDP is a reduced level of plasmalogens with normal very long chain fatty acids (VLCFA).[1]

CASE REPORT

The following situations should be considered in the differential diagnosis of CDP: peroxisomal diseases (Zellweger Syndrome, Adrenoleukodystrophy and Infantile Refsum disease), maternal exposure to warfarin, Smith-Lemli-Opitz Syndrome, and foetal alcohol syndrome.^[2,9,10] Spinal stenosis is a frequent sign of bone dysplasia, while it is rarely reported in rhizomelic CDP cases^[11-13] RCDP2 is caused by deficiency of the peroxisomal enzyme dihydroxyacetone phosphate acyltransferase (DHAPAT), encoded by GNPAT. RCDP3 is caused by deficiency of the peroxisomal enzyme alkyl-dihydroxyacetone phosphate synthase, encoded by AGPS. The clinical features resemble that of RCDP1, emphasizing the role of plasmalogen deficiency in determining the RCDP phenotype. RCDP2 and RCDP3 are inherited in an autosomal recessive manner and are rarer than RCDP1. The specific enzyme defect is confirmed by measurement of the enzyme activity in cultured skin fibroblasts and/or identification of two disease causing mutations by sequence analysis of AGPS or GNPAT. Estimated life span of RCDP is around 10 years

MANAGEMENT: Antenatal diagnosis of RCDP is possible from the first trimester onwards by demonstration of peroxisomal dysfunction in cultured chorionic villous or amniotic fluid cells. Parents were counseled about the baby's condition and associated co-morbidities and advised to come for regular follow up for early detection of complications. Genetic counseling was given to them about the risk of giving birth to similar babies in future pregnancies.

REFERENCES:

1. M. Bams-Mengerink, J. H. Koelman, H. Waterham, P. G. Barth, and B. T. Poll-The, "The neurology of rhizomelic chondrodysplasia punctata," *Orphanet Journal of Rare Diseases*, vol. 8, no. 1, article 174, 2013.
2. M. D. Irving, L. S. Chitty, S. Mansour, and C. M. Hall, "Chondrodysplasia punctata: a clinical diagnostic and radiological review," *Clinical Dysmorphology*, vol. 17, no. 4, pp. 229–241, 2008.
3. T. Yalin, I. K. Bayrak, M. Danaci, and L. Incesu, "Case report: rhizomelic chondrodysplasia punctata and foramen magnum stenosis in a newborn," *Turkish Journal of Diagnostic and Interventional Radiology*, vol. 9, no. 1, pp. 100–103, 2003.
4. S. C. Morrison, "Punctate epiphyses associated with Turner syndrome," *Pediatric Radiology*, vol. 29, no. 6, pp. 478–480, 1999.
5. Leicher-Duber, R. Schumacher, and J. Spranger, "Stippled epiphyses in fetal alcohol syndrome," *Pediatric Radiology*, vol. 20, no. 5, pp. 369–370, 1990.
6. J. L. D. Alessandri, D. Ramful, and F. Cuillier, "Binder phenotype and brachytelephalangic chondrodysplasia punctata secondary to maternal vitamin K deficiency, " *Clinical Dysmorphology*, vol. 19, no. 2, pp. 85–87, 2010.
7. K. Poznanski, "Punctate epiphyses: a radiological sign not a disease," *Pediatric Radiology*, vol. 24, no. 6, pp. 418–424, 1994.
8. L. White, P. Modaff, F. Holland-Morris, and R. M. Pauli, "Natural history of rhizomelic chondrodysplasia punctata," *American Journal of Medical Genetics*, vol. 118, no. 4, pp. 332–342, 2003.
9. L. Shanske, L. Bernstein, and R. Herzog, "Chondrodysplasia punctata and maternal autoimmune disease: a new case and review of the literature," *Pediatrics*, vol. 120, no. 2, pp. e436–e441, 2007.

CASE REPORT

10. Singh, G. H. Johnson, and F. R. Brown III, "Peroxisomal disorders. Biochemical and clinical diagnostic considerations," American Journal of Diseases of Children, vol. 142, no. 12, pp. 1297–1301, 1988.
11. P. Violas, B. Fraisse, M. Chapuis, and H. Bracq, "Cervical spine stenosis in chondrodysplasia punctata," Journal of Pediatric Orthopaedics B, vol. 16, no. 6, pp. 443–445, 2007.
12. T. E. Herman, B. C. P. Lee, and W. H. McAlister, "Brachytelephalangic chondrodysplasia punctata with marked cervical stenosis and cord compression: report of two cases," Pediatric Radiology, vol. 32, no. 6, pp. 452–456, 2002.
13. E. Jurkiewicz, B. Marcinska, J. Bothur-Nowacka, and A. Dobrzanska, "Clinical and punctate and review of available literature," Polish Journal of Radiology, vol. 78, no. 2, pp. 57–64, 2.



Figure 1: New born with RCDP

Note the dysmorphic faces (Broad fore head, full cheeks, upturned nose, micrognathia) and rhizomelia.



Fig. 2: INFANTOGRAM

Note the characteristic punctate calcifications and epiphyseal stippling around the joints and soft tissues.

CASE REPORT



Fig. 3: Follow up of the child after 4 months

Note There is failure to thrive and increase in spasticity.

AUTHORS:

1. P. Yashodhara
2. B. Elizabeth
3. N. Madhavi
4. B. Deeva Kumar
5. A. Tirupathi Reddy

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Pediatrics, Guntur Medical College, GGH, Guntur.
2. Assistant Professor, Department of Pediatrics, Guntur Medical College, GGH, Guntur.
3. Associate Professor, Department of Pediatrics, Guntur Medical College, GGH, Guntur.

5. Assistant Professor, Department of Pediatrics, Guntur Medical College, GGH, Guntur.
6. Assistant Professor, Department of Pediatrics, Guntur Medical College, GGH, Guntur.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. P. Yashodhara,
Government General Hospital,
Guntur.
E-mail: dr.yashodhara.hod@gmail.com

Date of Submission: 02/01/2015.
Date of Peer Review: 03/01/2015.
Date of Acceptance: 07/01/2015.
Date of Publishing: 10/01/2015.