

## Rhizomelic Chondrodysplasia Punctata (RCDP) in a Newborn

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### Summary:

*A female newborn baby presented with the features of Rhizomelic chondrodysplasia Punctata (RCDP) characterized by rhizomelic shortening with contracture of lower extremities, ichthyosis, microcephaly, dysmorphic facial features including a depressed nasal bridge, hypoplastic midface, full cheeks & low set ear, breathing difficulties and anthropometric measures below the expected indexes for her age. The patient also presented congenital heart disease, a less common manifestation of the syndrome. Radiological features include epiphyseal stippling &*

*multiple calcification in the epiphyseal cartilage, metaphyseal flaring and clefts in vertebral bodies. It is a rare autosomal recessively inherited skeletal dysplasia. The prognosis is bad and death usually occurs within the first year of age. We report a case of neonatal RCDP which was diagnosed based on the typical clinical and radiological features.*

**Keywords:** *Ichthyosis, Punctate calcification, Rhizomelic shortening*

*(J Bangladesh Coll Phys Surg 2014; 32: 174-177)*

### Introduction:

Rhizomelic chondrodysplasia punctata is a rare autosomal recessive peroxisome disorder characterized by shortened long bones in the arms and legs, abnormalities of the spine, stippled or dotted appearance to the cartilage, seizures, recurrent respiratory tract infections, ichthyosis, cataract, and profound mental retardation<sup>1,2</sup>. It affects fewer than 1 in 100,000 people worldwide.<sup>2</sup>

The diagnosis of RCDP1 is based on clinical findings and confirmed by biochemical or molecular genetic

testing. Biochemical tests of peroxisome function include: red blood cell concentration of plasmalogens (deficient), plasma concentration of phytanic acid (elevated), and plasma concentration of very long chain fatty acids (normal) in cultured fibroblasts which has consistently predicted the PEX7 receptor defect in RCDP1<sup>2</sup>. RCDP Types 2 and 3 and their specific enzyme defect are diagnosed based on deficient enzyme activity in fibroblasts. Radiological features include Punctate epiphyseal calcification, metaphyseal flaring and coronal clefts in the vertebral bodies<sup>2</sup>.

Management is supportive and limited by the multiple handicaps present at birth and poor outcome. The characteristic stippling or dotted cartilage will disappear as the child ages<sup>2</sup>. Cataract extraction may restore some vision. Physical therapy is recommended to improve contractures and orthopedic procedures may improve function in some cases. Genetic counseling may be necessary for individuals who have been determined to be carriers. Monitoring of growth and development, regular assessments for seizure control, vision, hearing, contractures, and orthopedic complications are required in these children on follow up.

The RCDP has a very poor prognosis. The majority of children do not survive beyond the first decade of life and a proportion die in the neonatal period. In a review of 69 children with RCDP diagnosed by the Peroxisomal Diseases Laboratory at the Kennedy Krieger Institute, 60% of children survived the first year and 39% the second; a few survived beyond age ten years<sup>2</sup>. Most deaths were secondary to respiratory complications. Clinical experience suggests that neonatal deaths have

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**Received:** 16 September, 2013

**Accepted:** 25 June, 2014

been associated with congenital heart disease or pulmonary hypoplasia<sup>3</sup>.

#### Case Report:

A one hour old female baby, inborn, 1st issue of a consanguinous parents, delivered by LUCS at 40 weeks of gestation on 01/08/2013 was admitted in the neonatal Intensive Care Unit of Ad-din Medical College Hospital, Dhaka with respiratory distress, rhizomelic shortening and joint contracture. Mother was 26 years old and was on regular antenatal check up. There was no history of any maternal disease or teratogen exposure during the antenatal period. She was neither hypertensive nor diabetic. There was no family history of such deformity of limbs.

Clinically the baby was tachypnic and had dysmorphic facial features including a depressed nasal bridge, hypoplastic midface, full cheeks & low set ear. Her OFC was 32 cm (<3<sup>rd</sup> centile) and length was 40 cm (<5<sup>th</sup> centile). Her upper segment to lower segment ratio was 1.8:1. So, she was disproportionately short infant and microcephalic. Her birth weight was 2900 gm. She had symmetrical rhizomelic shortening of all 4 limbs, with contracture of knee and ankle joints (Figure-1). Her respiratory rate was 68/min and regular, breath sound was equal on both side, heart rate was 150 beats/min, 1<sup>st</sup> and 2<sup>nd</sup> heart sounds were normal, pansystolic murmur was heard over the precordium mostly marked on the left lower sternal border. She had a short neck and a barrel-shaped chest. Her abdomen was soft with no organomegaly. She had a ichthyotic rash in the neck area. Erythema and maculo-papular skin rashes were also noted in the face,



**Fig.-1:** Phenotypic features of RCPD

trunk and lower limb on day 2. Provisionally we diagnosed a case of Achondroplasia with congenital heart disease.

Routine laboratory tests like full blood count, serum electrolyte, serum calcium were done which showed normal findings. On Skeletal survey there was a) epiphyseal stippling, b) multiple calcification in the epiphyseal cartilage, c) Clefts in vertebral bodies (Figure-2) d) metaphyseal flaring (Figure-3). Cranial



**Fig.-2:** A) Epiphyseal stippling B) multiple calcification in the epiphyseal cartilage C) Cleft in second lumbar vertebrae



**Fig.-3:** Upper limb radiograph showing metaphyseal flaring

ultrasonography, and abdominal ultrasonography were normal. Chest X-ray showed cardiomegaly and Doppler echocardiography revealed small ventricular septal defect with persistent patent foramen ovale. Based on clinical and radiological findings, a diagnosis of rhizomelic chondrodysplasia punctata was made. Biochemical tests and genetic assay to identify the mutations in the PEX7 gene was not undertaken owing to financial constraints. Genetic counseling was given to the parents. Child is receiving regular physiotherapy and currently under follow up.

### Discussion:

Chondrodysplasia punctata (CDP) is characterized by shortened bones, punctated or dot-like calcification deposits in the cartilage, and abnormal peroxisomes<sup>1</sup>. There are various types of chondrodysplasia punctata; autosomal recessive forms (RCDP types 1, 2 and 3), X-linked dominant form (Conradi-Hünermann-Happle syndrome), an X-linked recessive brachy-telephalangic type and Sheffield type<sup>4</sup>. Several milder forms of CDP, tibia-metacarpal type and humero-metacarpal type, have also been described<sup>5,6</sup>. Within these variations, there are different syndromes characterized by distinct anomalies, severity, modes of transmission and radiological features. There are patients with CDP, in which known etiologies have been exhaustively investigated, and none has been found<sup>7</sup>.

RCDP is characterized by rhizomelic shortening of the extremities, congenital contractures, dysmorphic facial features (including a depressed nasal bridge, hypertelorism, hypoplastic midface, anteverted nostrils, full cheeks), bilateral congenital cataract, short stature or dwarfism, microcephaly, abnormal hair loss, seizure, recurrent respiratory tract infections, ichthyosis and severe growth and mental deficiency<sup>1,2,4</sup>. Radiological features include punctate epiphyseal calcification, metaphyseal flaring and clefts in vertebral bodies<sup>2</sup>. All these classical radiological findings were present in the present case. Other malformations observed in individuals with RCDP1 include cleft palate, congenital heart disease and ureteropelvic junction (UPJ) obstruction<sup>2</sup>. In the present case, congenital heart disease was found.

RCDP1 is the most frequent form of RCDP<sup>8</sup>. RCDP1 involves mutations in the PEX7 gene, which encodes enzymes responsible for peroxisome function<sup>9,10</sup>. RCDP

Types 2 and 3 are phenotypically similar to RCDP Type 1, but result from deficiencies of the specific peroxisomal enzymes dihydroxyacetone phosphate acyltransferase and alkyl dihydroxyacetone phosphate synthase respectively<sup>2</sup>. Genetic assay to identify the mutations in the PEX7 gene and biochemical tests was not undertaken owing to financial constraints. Other causes of calcific epiphyseal stippling include maternal exposure to warfarin in early gestation, and infants of mothers with presumed vitamin K deficiency and with autoimmune disease<sup>11</sup>, several peroxisomal disorders including Zellweger syndrome spectrum, Smith Lemli Opitz syndrome<sup>12</sup>, Trisomy 18 and 21<sup>13</sup>.

White AL et al.<sup>14</sup> delineate the natural history of RCP through systematic analysis of 35 previously unreported individuals (as well as review of 62 literature cases with respect to survival and cause of death). Rhizomelia and punctate calcifications have been noted on ultrasound examination as early as 18 to 19 weeks<sup>15,16</sup>, analysis of DNA extracted from fetal cells obtained by amniocentesis or chorionic villus sampling, assay of plasmalogen biosynthesis in cultured chorionic villi obtained by CVS or in cultured amniocytes obtained by amniocentesis, preimplantation genetic diagnosis (PGD)<sup>2</sup>. In the present case, ultrasound was done at 22 weeks of gestation which showed rhizomelia and congenital heart disease. An association with fetal ascites and polyhydramnios has been reported<sup>17</sup>. In the present case, polyhydramnios was found.

Routine brain imaging was normal or has shown cerebral and cerebellar atrophy with enlargement of the ventricles and CSF spaces<sup>18</sup>. MR imaging and MR spectroscopy have shown delayed myelinization, signal abnormalities in supratentorial white matter, decreased choline-to-creatine ratios, and increased levels of mobile lipids, thought to reflect the deficiency of plasmalogens, which are substantial components of myelin<sup>19,20</sup>. Computerized tomography (CT) scan was done in the present case at the age of 22 days which showed enlargement of the ventricles with cerebral atrophy. Radiologic and MRI evidence of multilevel cervical stenosis with or without compression of the spinal cord has been observed<sup>21</sup>.

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