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Case Report

A rare case of proximal short limb dwarfism-rhizomelic chondrodysplasia punctata type-2

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ABSTRACT

Rhizomelic chondrodysplasia punctata (RCDP) is one of the rare peroxisomal disorder (autosomal recessive inheritance) due to altered phytanic acid alpha oxidation and plasmalogen synthesis. RCDP 1 is the most frequent form of RCDP. It is a peroxisomal biosynthesis disorder. RCDP 2 and RCDP 3 are disorders of individual peroxisome enzyme. Authors described a case of RCDP type 2 in a 13 months old girl with characteristic features of typical chondrodysplastic facies, bilateral cataract, rhizomelic shortening of limbs, growth and global developmental delay; radiological features showed epiphyseal stippling. Genetic analysis showed apparent homozygous deletion of c.1848delC after full sequencing of her GNPAT genes.

Keywords: Chondrodysplasia, Epiphyseal stippling, Plasmalogens, Phytanic acid

INTRODUCTION

RCDP is a lethal inherited disease and is very much rare (incidence 1 in 100000).[1] It is an autosomal recessive metabolic disorder affecting mainly peroxisomal function. There are 3 genetic subtypes. Type 1 consists of individuals with homozygous or compound heterozygous mutations in the PEX7 gene. This is the largest group. Type 2 is secondary to mutations in the GNPAT gene. Type 3 forms by mutations in the AGPS gene.[2,3] RCDP 2 is caused by homozygous or compound heterozygous mutation in the DHAPAT gene (GNPAT), which encodes acyl-CoA: dihydroxyacetone phosphate acyltransferase, on chromosome 1q42. RCDP is characterized by dwarfism due to symmetrical shortening of long bones (rhizomelia), cataracts, periarticular calcifications, a typical facial appearance including a broad nasal bridge, epicanthus, high-arched palate, dysplastic external ears, micrognathia, multiple joint contractures with spasticity, psychomotor retardation and specific radiological abnormalities.[4,5] Specific radiological abnormalities include shortening of the proximal limb bones, presence of stippled foci of calcification within hyaline cartilage, metaphyseal cupping.[4,5]

CASE REPORT

On our routine visit of nutrition and neurostimulation of 1st 1000 days program, a 13 months 22 days old female child with rhizomelic shortening of limbs and facial dysmorphism was seen and called to MNR hospital OPD and further evaluated. She was a 2nd born child to a 25 year old mother and 28 year old father out of 3rd degree consanguinous marriage, conceived after infertility treatment (ovulation induction). Mother was not known to have any autoimmune disorder, chronic diseases and there was no history of exposure to any known teratogenic agents in particular with warfarin therapy or alcohol. No history of fever with rash during pregnancy. One antenatal scan done during 2nd trimester was told to

be normal. Child was born term through spontaneous vaginal delivery with birth weight of 2.7 kgs. There was no history of birth asphyxia or NICU admission.

Developmental history

She had attained partial neck holding, hands predominantly closed, coos, responds by smiling on listening to sounds. She has global developmental delay with DQ <70% in all 4 domains.

Anthropometry

Height-55 cm (<1st centile), weight-4.6 kgs (<1st centile), HC-36 cm (<3rd centile), weight/height (between 50th and 3rd centile) height/age (<3rd centile) according to IAP. US:LS couldn't be measured due to contractures.

Examination

Microcephaly, bitemporal narrowing, upslanted eyes, hypertelorism, B/L congenital cataract, depressed nasal bridge, short tubular nose, low set ears, absent philtrum, thin inverted v shaped upper lip (cupid's bow upper lip), bifid uvula, proximally shortening of both upper and lower limbs with crossed leg position, over lapping of 2nd digit, bilateral simian crease, flexion contratures of bilateral knee, ankle joint and broad hallux (Figure 1).

Figure 1: Typical facies of chondrodysplasia punctata along with rhizomelia of all limbs and contracture of lower limbs.

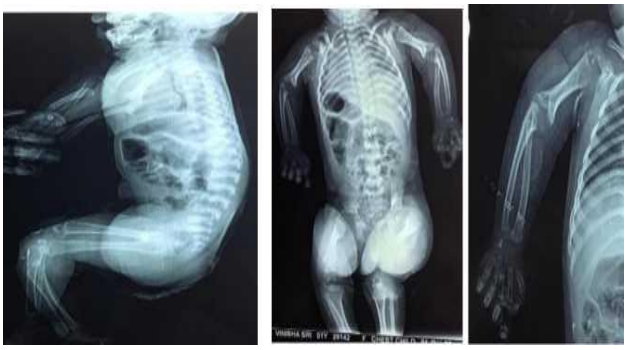

Figure 2: X-rays showing rhziomelic shortening of humerus and femur, epiphyseal stippling.

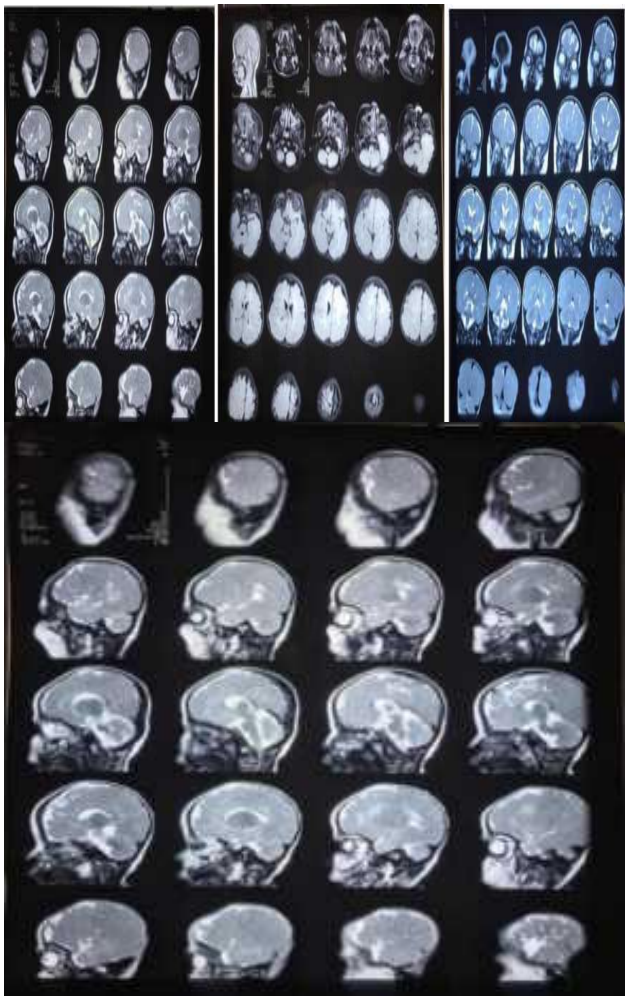

Figure 3: MRI brain showing incomplete periventricular deep white matter myelination; bilateral temporal and frontal atrophy.

Tone increased in all limbs, relatively more in lower limbs. Power-occasional antigravity movements, relatively more in upper limb. Reflexes-biceps (2+), triceps (2+), supinator (2+), knee (-), ankle (-).

No abnormality was detected in other systemic examination.

Investigations

Hemogram revealed mild anemia , normal liver and renal function tests. Serum electrolytes, USG abdomen, 2D echo, BERA was normal.

Specific biochemical work up (RBC plasmalogen, phytanic acid level) could not be done. Diagnosis was supported by typical radiological changes in X-ray of limbs-rhziomelic shortening of humerus and femur, epiphyseal stippling (Figure 2). MRI brain showing atrophied brain with incomplete white matter myelination (Figure 3). Clinical exome sequencing identified c.1848delC deletion in GNPAT genes (Table 1).

Table 1: Genetic analysis-clinical exome sequencing.

Gene and transcript	Variant	Location	Zygosity	Disorder (OMIM)	Inheritance	Classification
GNPAT NMJ14236.3	c.1848delC (p.Ser617Leufs*16)	Exon 14	Homozygous	Rhizomelic Chondrodysplasia Punctata; type 2 (222765)	Autosomal recessive	Likely pathogenic

DISCUSSION

Chondrodysplasia punctata (CDP) is one of the peroxisomal disorders which are genetically determined disorders, they were either due to failure to form or maintain peroxisome or defect in function of a single enzyme that was normally located in peroxisome.[6] CDP was one of the disorders of peroxisome import while others being Zellwegar syndrome, neonatal adrenoleukodystrophy, infantile refsum disease. CDP has four main types autosomal dominant (conradi-Hunermann's type), autosomal recessive (rhizomelic type), X-linked dominant form (Happle) and the X-linked recessive form.[7] There are three types of RCDP. Type 1 involves PEX7 gene mutation. Type 2 and 3 are phenotypically similar to RCDP type 1 but result from deficiencies of dihydroxyacetone phosphate acyltransferase and alkyldihydroxyacetone phosphate synthase, respectively.[8]

Our patient had characteristic facial dismorphism b/l congenital cataract, proximal limb shortening with joint contractures and physical parameters less than the normal centile values for age. Typical radiological findings further strengthened the diagnosis of RCDP. RCDP was a radiological diagnosis with specific finding of stippled calcification and shortening of proximal bones with biochemical parameters confirming it and with clinical exome sequencing showing GNPAT NM gene defect.

Management was basically supportive. This included extraction of cataract, physiotherapy, occupational therapy, vision and hearing assessment, growth and development monitoring and genetic counseling.

CONCLUSION

Meticulous newborn examination is needed for early postnatal diagnosis and genetic counselling. Genetic counselling is very important as these disorders can be diagnosed prenatally and carries 25% recurrence risk in future pregnancies. Prenatal ultrasound diagnosis has been reported during the second trimester of pregnancy between 19 and 21 weeks detecting rhizomelic shortenings of humerus and femur and punctate stippling. Prenatal diagnosis is also possible from the first trimester onwards by demonstration of peroxisomal dysfunction in cultured chorionic villious or amniotic fluid cells.

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