

RHIZOMELIC CHONDRODYSPLASIA PUNCTATA: A CASE REPORT AND BRIEF LITERATURE REVIEW*

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Abstract The authors present a case of a 2-month-old infant affected by the recessive form of chondrodysplasia punctata, a rare condition radiologically characterized by severe proximal shortening and anomalous ossification (epiphyseal stippling) of the limbs. Clinical and radiological findings as well as main differential diagnoses are emphasized on the basis of data originating from a brief literature review.

Keywords: Chondrodysplasia punctata; Bone dysplasia; Peroxisomal disorders.

Resumo *Condrodisplasia punctata rizomélica: relato de caso e breve revisão da literatura.*

Apresentamos um caso de uma lactente de dois meses de idade acometida pela forma recessiva da condrodisplasia punctata, doença caracterizada, radiologicamente, por acentuado encurtamento proximal e distúrbio de ossificação (epífises puntiformes) dos membros. São enfatizados os achados clínico-radiológicos, bem como seus principais diagnósticos diferenciais, baseados em dados de breve revisão da literatura.

Unitermos: Condrodisplasia punctata; Displasia óssea; Desordens peroxissomais.

INTRODUCTION

Epiphyseal stippling is a radiological sign present in several bone dysplasias, and is associated with different metabolic, teratogenic and chromosomal disorders. These punctate calcifications may result in delayed endochondral ossification process, growth deficiency and deformity of the bones involved⁽¹⁾. Amongst the causes of epiphyseal stippling, special importance is given to chondrodysplasia punctata (CDP), a condition correlated with phenotypic variations and determined by the type of genetic transmission.

CDP corresponds to a heterogeneous group of dysplasias characterized by punctate calcifications in cartilage (mainly the epiphyseal ones), frequently associated with limbs shortening, cataracts, ichthyosis, alopecia, nervous system alterations, mental and growth deficiencies⁽²⁻⁵⁾.

High rate of stillbirth or mortality during the first year of life is reported, as a

result of associated anomalies or intercurrent diseases⁽³⁾. Today, the CDP diagnosis is made by means of clinical analysis concomitant with biochemical and radiological findings. Although quite evident clinical and radiological characteristics might determine an accurate diagnosis, other diseases should be taken into consideration because of findings similarity.

The CPD family includes the autosomal dominant form (Conradi-Hünnermann syndrome), the autosomal recessive (rhizomelic), the X-linked recessive (CDPX1) and dominant (CDPX2 or Conradi-Hünnermann-Happle syndrome)⁽⁵⁾.

The autosomal forms result from a peroxisomal metabolic disorder^(4,6), the X-linked dominant (CDPX2) is caused by defects in cholesterol biosynthesis pathway, and the X-linked recessive (CDPX1) results from defects in arylsulfatase E⁽⁴⁾. Peroxisomes are organelles present in the cytoplasm of several tissular cells (especially in the liver, kidneys and fibroblasts), containing a complex enzymatic system with an array of functions such as: several chemicals oxidation and production of H₂O₂; biliary acid, cholesterol and cell plasmalogen biosynthesis; α -oxidation of fatty acids with long carbon chains; lysine metabolism and glycosylate synthesis/metabolism⁽⁶⁾.

A case of CDP is presented, with a description of the two main variations (auto-

somal recessive and dominant) based on a brief review of the existent literature about this disease etiopathogenesis, clinical-radiological and laboratory manifestations.

CASE REPORT

Female, two-month-old infant, has been referred to the Pediatrics Service of Hospital de Base Ary Pinheiro, Porto Velho, RO, Brazil, because of tachypnea and history of frequent chokings after breastfeeding, as well as evident anatomical alterations in face and limbs. She was kept in a thermoregulated incubator with circulating O₂, during 11 days.

Preterm-born from consanguineous parents (primiparous mother), the patient has presented a series of clinical and radiological findings suggesting a CDP diagnosis. Her mother denied a history of drugs or alcohol abuse or exposure to warfarin (known as teratogenic causes of punctate epiphyses).

Clinically, the patient presented with ichthyotic skin changes, irregular foci of alopecia, shortening of permanently flexed and spastic limbs, micrognathia; flattened nose, small chest with restricted expansion, cephalhematoma, besides the already mentioned tachypnea and groaning. Cardio-pulmonary auscultation showed mild bibasal crepitation and absence of abdominal alterations. Results from somatometry

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were the following: weight 1.755 g, height 37 cm, both cephalic and thoracic perimeters 25 cm (below the fifth percentile). Routine laboratory tests as well as those performed for investigating congenital infections were normal.

On radiographic studies, we have observed: a) micrognathia; b) flattened nasal spine (Figure 1); c) symmetrical, bilateral, proximal shortening of upper and lower limbs (rhizomelic pattern); d) multiple punctate calcifications in the epiphyseal cartilage of long bones, ankle and carp; e) flexed knee and elbow joints; f) slightly enlarged metaphyseal regions (Figures 2 and 3); g) punctate calcifications in costochondral junctions and vertebral bodies pedicles (including the sacrum); h) coronal

clefts of L2 and L5 vertebral bodies; i) sagittal clefts of T9 and L2 vertebral bodies (Figure 4).

The patient was released from the hospital with clinical-radiological diagnosis of CDP. Parents were given information and guidance on the case.

DISCUSSION

Bone dysplasias are characterized by changes in growth, cartilaginous and bone development, as well as in bone remodeling⁽⁷⁾, mainly the autosomal dominant (Conradi-Hünnermann syndrome) and recessive (rhizomelic) forms of the disease.

The CDP dominant form is most frequent and is related to a defect in peroxisomal enzyme biosynthesis. The clinical picture may range from mild disease to an extremely severe condition, with cataracts, asymmetrical shortening of long bones, scoliosis, ichthyotic-type skin lesions, and flattened facies with broad nasal bridge⁽⁶⁾. There is some life expectancy, although early fetal death also occurs. Infants who survive beyond the first year usually present normal life expectancy and mental development. In general, punctate epiphyses present delayed calcification with a dysmorphic aspect, but some of them may progress to a practically normal aspect⁽³⁾.

The rhizomelic CDP is of autosomal recessive origin, characterized by a peroxisomes functional defect resulting in an enzymatic deficiency where there is a decrease in the plasmalogen synthesis, de-

crease in phytanic acid oxidation and presence of a unprocessed (inactive), the 3-oxacyl-Coa-thiolase⁽⁵⁾.

Currently this form of CDP is diagnosed through clinical features compatible with the syndrome associated with biochemical findings including phytanic acid serum levels, screening of plasmalogen synthesis on cultured fibroblasts⁽⁵⁾, as well as in erythrocytes, and plasmatic level of fatty acids with long carbon chain⁽²⁾. The plasmatic level of phytanic acid is high, and the plasmalogen synthesis in fibroblast and erythrocytes is reduced^(2,4,8,9). Usually, the serum level of fatty acids with long carbon chain is normal⁽²⁾. The chromosomal study demonstrates PEX7 mutation, 50% of them in the L292ter allele⁽⁵⁾. None of these biochemical or genetic tests has been performed in the present case. This CDP variant is rare, with an estimate 1:100,000 incidence⁽⁶⁾, and with only 72 cases reported in the literature up to 1995⁽¹⁰⁾.

The main characteristics described in the literature are symmetric and severe rhizomelic micromelia (proximal shortening of limbs); punctate calcifications and long bones metaphyseal and epiphyseal ossification changes; punctate calcifications and coronal clefts in vertebral bodies of the thoracic and lumbar spine; microcephaly and growth retardation, psychomotor delay, spasticity and precocious



Figure 1. Lateral view of skull x-ray showing microcephaly, flattened nasal spine and mild micrognathia.



Figure 2. A: Upper limb x-ray image showing epiphyseal stippling, humeral shortening and flexed limb. **B:** Lower limbs x-ray image showing rhizomelic micromelia with epiphyseal stippling, also in the ankle.



Figure 3. Anteroposterior view of left hand x-ray showing typical punctate calcifications in the carpal region, and distal ulnar and radial epiphyses.

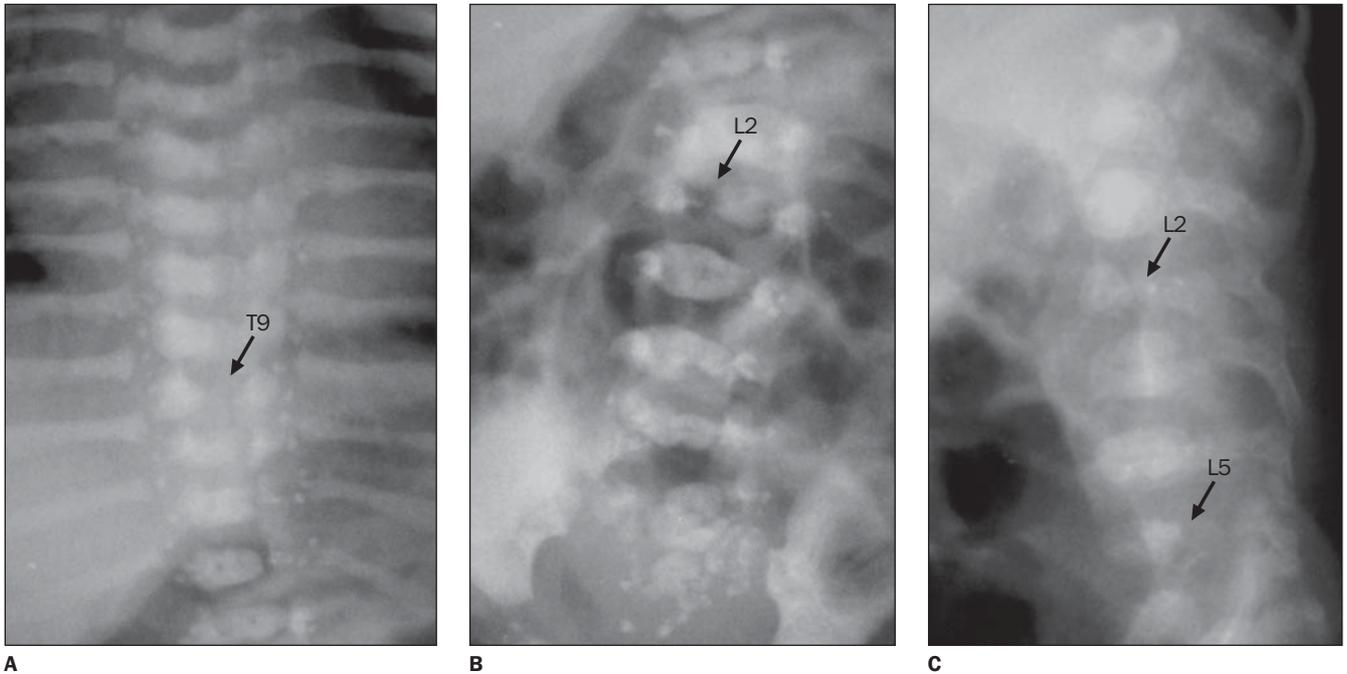


Figure 4. X-ray: dorsal spine anteroposterior view (A), lumbo-sacral spine anteroposterior view (B) and lateral (C) show punctate calcifications in the sacrum, costovertebral junctions and pedicles, as well as coronal cleft in L2 and L5, and sagittal cleft in T9 and L2.

death^(5,6,11). The presence of vertebral clefts, radiotransparent, longitudinal zone observed in the lateral view, previously described as invariable in cases of rhizomelic CDP, has not been present in three of five cases analyzed by Wardinsky et al.⁽²⁾ and in other cases reported in the literature, and is not obligatorily necessary for the diagnosis⁽²⁾.

Other characteristics have been described with a variable frequency, among them ichthyosis, cataracts, restricted joint mobility, sucking and deglutition difficulty, alopecia, auditive and visual deficiencies, seizures, optic nerves hypoplasia, kyphoscoliosis and cleft spine^(2,5,12,13). Patients usually present facies with micrognathia, malar hypoplasia, flattened nasal bridge and bulbous nose, with flattened face appearance. In contrast to the other forms of CDP, the rhizomelic CDP presents a poor prognosis, with repetition infections and death in the first two years of life^(2,4-6).

The differential diagnosis includes other causes for CDP, Keutel syndrome, Zellweger syndrome, Smith-Lemn-Opitz syndrome, classical and neonatal Refsum disease, neonatal adrenoleucodystrophy, neonatal lupus, trisomy 21 or 18, fetal alcoholic syndrome, congenital infections, and

maternal use of coumarin-like compounds or phenitoin during gestation^(4-6,10).

The patient presented ichthyosis, irregular foci of alopecia, feeble skin, shortened neck, flattened facies with saddle nose, permanently flexed knee and elbow joints, besides limbs shortening, microcephaly and micrognathia and history of deglutition difficulty, clinical characteristics corroborating the diagnosis of rhizomelic CDP. An usual characteristic of the rhizomelic CDP is the presence of coronal clefts in vertebral bodies. In the present case, coronal clefts in L2 and L5 vertebral bodies were identified, besides proximal, symmetrical bilateral shortening of upper and lower limbs bones with punctate calcifications on the long bones epiphyses, carp and ankle. These clefts are a result of poor fusion of anterior and posterior halves of vertebral bodies, occurring around the fourth month of gestation^(2,5,14); on the other hand, frequently observed punctate calcifications are caused by a progressive cartilage degeneration represented by chondrocytes with a pycnotic nucleus and eosinophil cytoplasm followed by ossification⁽¹⁴⁾.

Auditive and/or visual deficiencies have been observed, although being found with

variable frequency in the referred literature. However, another typical finding in this type of chondrodysplasia is microcephaly, which has shown to be quite accentuated, considering the values very below than normal.

Based on the data presented by this study, we have inferred the diagnosis as recessive CDP considering the exuberance of the clinical-radiological picture; however, we could not confirm the diagnosis by means of biochemical and genetic tests.

It is important to note that patients with diagnosis of rhizomelic CDP should undergo ambulatorial follow-up, as, in spite of the current inexistence of specific treatment, many clinical manifestations, like alopecia, ichthyosis and cataracts, might not be present at the moment of the diagnosis, showing up with the progress of the disease. Other manifestations, like punctate calcifications, tend to disappear with aging, without resulting in bone deformities⁽⁵⁾. Presently, the patient is being kept in ambulatorial follow-up in our institution.

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