O MUNDO DA SAÚDE

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X-linked chondrodysplasia punctata type 1 (CDPX1) - case report with atypical phenotype

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Abstract

Chondrodysplasia punctata (CDP) is a group of bone dysplasias characterized by punctate calcifications in the cartilage, mainly epiphyseal. Among the various forms of CDP, the X-linked form is rare and has been described in 50 male patients in the literature. The aim of this study is to describe an atypical case of CDPX1 and compare it with previous literature. Preschooler, male, four years old, born full-term, small for gestational age and with no similar cases in the family. He developed disproportionate short stature, eutrophy, cervical and dorsal scoliosis with *pectus carinatum*, slight asymmetry in the lower limbs, ocular hypertelorism with blue-gray sclera and hair loss. He did not present fractures or bone pain and had neuropsychomotor development appropriate for his age. The exams showed no changes in the osteometabolic profile or in pituitary hormones. The karyotype was 46,XY and the genetic panel for skeletal dysplasias showed a hemizygous pathogenic variant in the ARSL gene (*Arylsulfatase L*) chrX:2.934.859 C>T (p.Trp581* ENST00000381134) diagnosed with X-linked chondrodysplasia punctata type 1. CDPX1 is directly related to the deficiency of ARSL enzyme activity, which can result in changes in neuropsychomotor development, hearing loss and episodes of respiratory failure. However, these characteristics were not presented by the proband. Thus, the proband has a milder form of CDPX1. Early diagnosis of skeletal dysplasias such as CDPX1 is important for adequate outpatient follow-up, family counseling and prevention of the development of long-term comorbidities.

Keywords: Genetics. Chondrodysplasia Punctata. Child.

INTRODUCTION

Chondrodysplasia punctata (CDP) corresponds to a heterogeneous group of skeletal dysplasias, characterized by changes in the growth and development of cartilaginous and bone tissues. Despite being considered a rare disease, early diagnosis is extremely necessary in the therapeutic management of these patients. CDP describes the radiographic appearance of abnormal cartilaginous stippling resulting from abnormal calcium deposition during endochondral bone formation. This radiographic phenomenon is observed in a number of diseases, such as inborn errors of metabolism (IEM), abnormalities in vitamin K metabolism and chromosomal anomalies, as well as in a series of rare syndromes. However,

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the case studied in this report has a peculiarity in its presentation that differentiates it from the majority, the absence of punctate lesions on imaging. CDP includes several forms of clinical manifestation, whose phenotypic variants are related to the type of pathogenic variant and the pattern of genetic inheritance. The autoso mal dominant form (*Conradi-Hünnermann* disease) and the X-linked forms stand out, which may be recessive (CDPX1 - OMIM#302950) or dominant (CDPX2 or *Conradi-Hünermann--Happle* disease - OMIM#302960) and the autosomal recessive (rhizomelic) form. X-linked chondrodysplasia punctata 1 (CDPX1) is characterized by punctate epiphyses, brachyphalangia (shortening of the distal phalanges), and nasomaxillary hypoplasia[1].

According to the article by Figueirêdo, S. da S. *et al.*[2], the X-linked inheritance pattern, the recessive form results from a problem in the *arylsulfatase gene E*, while the dominant form is due to a defect in the cholesterol biosynthesis pathway. Autosomal forms are linked to changes in peroxisomal metabolism, responsible for the oxidation of several compounds, biosynthesis of cholesterol, bile acid and plasmalogen synthesis.

The main characteristic of patients affected by CDP are punctate calcifications of the cartilage, mainly epiphyseal, related to the shortening of the limbs. In addition, they may pre sent cataracts, alopecia, growth and nervous system changes, delayed neuropsychomotor development and ichthyosis[1,2,3].

Regarding the diagnosis of CDP, clinical suspicion is made through the association between typical clinical and radiological findings of the disease, but biochemical changes, such as reduced levels of plasmalogen, can be enlightening in autosomal forms, such as rhizomelic chondrodysplasia punctata. Despite this, diagnostic confirmation is carried out through molecular analysis[1].

In this case report, we aim to describe an atypical case of CDPX1 that presented adequate psychomotor development and absence of bone fractures and respiratory failure, comparing it with previous literature.

CASE REPORT

Preschooler, four years old, male, born full--term, small for gestational age, with non-consanguineous parents and no similar cases in the family, was admitted to the Darcy Vargas Children's Hospital in São Paulo.

Subsequently, he developed disproportionate short stature (height Z score -2.9 standard deviations and sitting height/height ratio < -2.5 standard deviations), eutrophy (body mass index Z score 0.85 standard deviations), cervical and dorsal scoliosis with *pectus carinatum*, slight asymmetry in the lower limbs (left greater than the right), ocular hypertelorism with blue-gray sclera and hair loss - Figure 1. Furthermore, he evolved with age-appropriate neuropsychomotor development, assessed by the Denver Test widely applied in childcare consultations.

Despite the spinal deformities, he did not present fractures, muscle weakness or bone pain, in addition the patient also had an adequate intake of elemental calcium and vitamin D for his age.

Laboratory tests did not show changes in the osteometabolic profile or in the levels of pituitary hormones.

A simple skeletal radiograph revealed lower and dorsal cervical scoliosis on the left, with an increase in the cervical-dorsal angle, multiple spondylo-costal anomalies in the dorsal, upper and middle column, asymmetry between the lower limbs of 0.1 cm and pes valgus with varus distal phalangeal on the fourth and fifth fingers - Figure 2.

46,XY karyotype [50] and the NGS genetic panel for skeletal dysplasias showed a hemizygous pathogenic variant in the ARSL gene (*Arylsulfatase L* - (OMIM *300180)) chrX:2.934.859 C>T (p.Trp581* ENST00000381134) with a diagnosis of X-linked chondrodysplasia punctata type 1.

Currently, the patient is undergoing multidisciplinary follow-up with conservative treatment

in genetics, endocrinology, orthopedics and ophthalmology with good clinical evolution.

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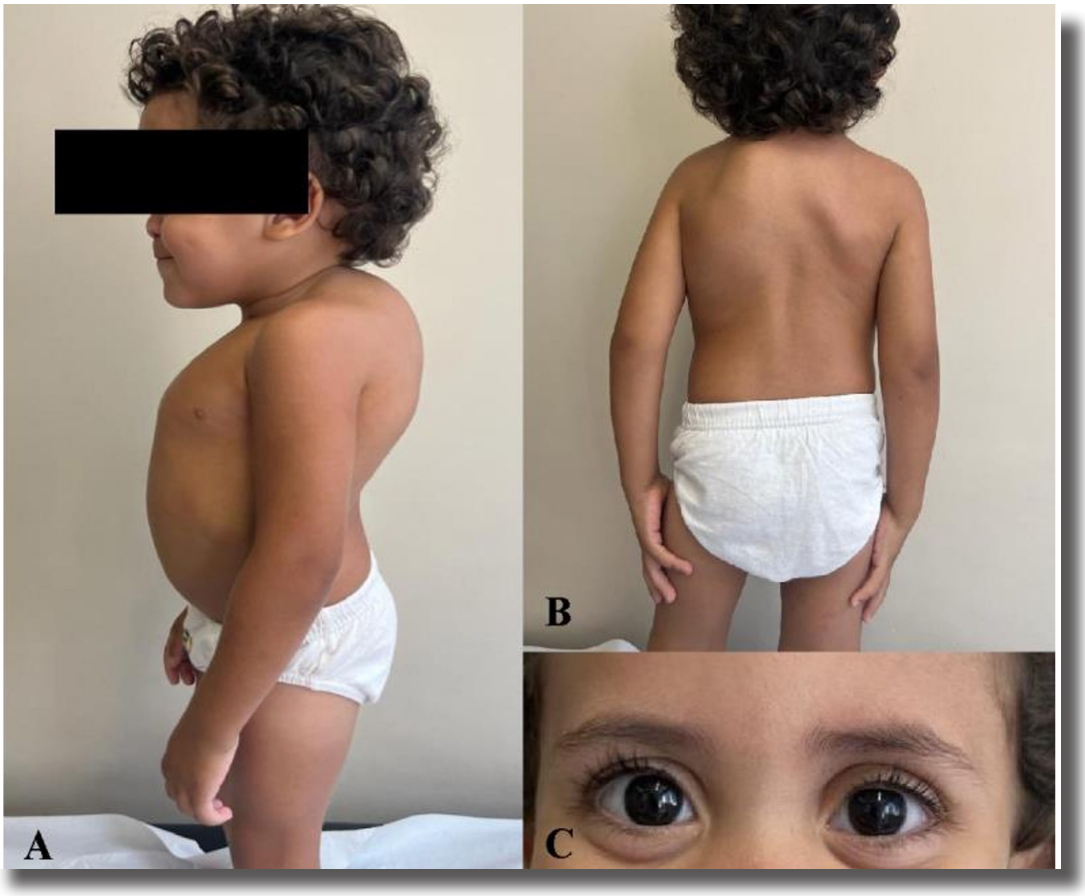

Figure 1 – A and B - Cervical and dorsal scoliosis with *pectus carinatum*; C: ocular hypertelorism with grayish sclera.

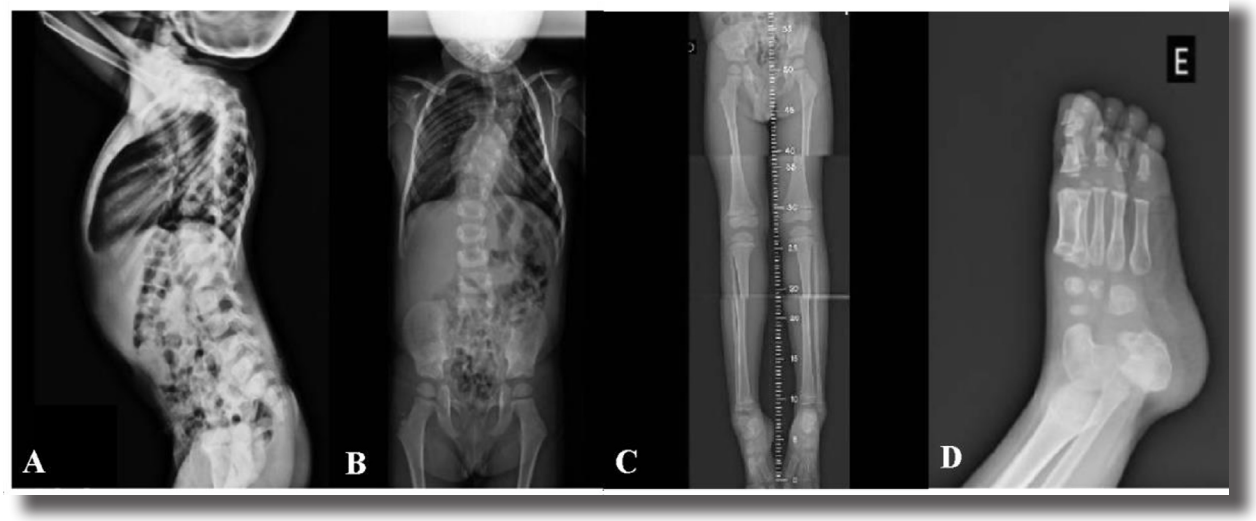

Figure 2 – A and B - X-ray of the thoracolumbar spine showing inferior cervical and dorsal scoliosis on the left and spondylocostal anomalies; C: scanometry with asymmetry between lower limbs; D: valgus foot with distal phalangeal varus in the fourth and fifth toes.

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DISCUSSION

Chondrodysplasias are a group of rare and hereditary disorders of skeletal development and growth, characterized by genetic and clinical heterogeneity. Affected patients have short stature and/or skeletal deformities, commonly manifesting disproportionately short limbs and/or changes in the spine, such as scoliosis, kyphosis and lordosis. These conditions originate from pathogenic variants in genes essential to the endochondral ossification process, which is responsible for skeletal growth. Although typically described as disorders of the cartilaginous components of the developing skeleton, other tissues can also be affected[4,5].

The pathogenic variants that cause chondrodysplasias act through several mechanisms, involving genes that encode different types of proteins, such as transcription factors, growth regulators, cartilaginous matrix proteins, membrane receptors, modifying enzymes and ion transporters.

One of the genes involved in the formation of the musculoskeletal system is the *Arylsulfatase L* gene. It is responsible for encoding the enzyme *arylsulfatase L*, which belongs to the group of sulfatases, enzymes that play an essential role in the processing of molecules containing chemical groups called sulfates. These sulfatases have significant relevance in the development of cartilage and bones. *Arylsulfatase L* is located in the intracellular Golgi apparatus, a structure responsible for modi fying newly produced enzymes and proteins. Despite this, its specific function is not yet completely understood[6,7].

According to the article by Braverman, NE *et al.*[3], CDPX1 is a genetic disease that should be considered suspicious in a male individual with specific clinical and radiographic findings, such as: Lower cervical and dorsal scoliosis with convexity to the left; Increased cervico-dorsal angle; Multiple spondylocostal anomalies in the upper and middle dorsal column; Foot valgus + distal phalangeal varus in the fourth and fifth toes. Characteristic clinical signs include brachytelephalangia, nasomaxillary hypoplasia, hypoplasia of the anterior nasal spine, flattened nasal base, crescent-shaped nostrils and, in some cases, vertical grooves within the wings of the nose. Furthermore, patients with CDPX1 have short stature after birth and may experience delayed neuropsychomotor development and respiratory changes. The patient described presents skeletal changes characteristic of the disease, but does not present associated comorbidities, presenting, at this age, a milder phenotype.

On plain radiographs, dotted epiphyses are evident. The stippling pattern is symmetrical and age-dependent, disappearing after normal epiphyseal ossification at around two to three years of age. Therefore, the patient described would not present this important sign for radiological diagnosis at this time. Additionally, an inverted triangular shape is visualized on the distal phalanges, with lateral stippling at the apex. Vertebral abnormalities are common, with dysplastic and hypoplastic vertebrae and coronal or sagittal fissures, which can result in complications such as cervical kyphosis, cervical stenosis and atlantoaxial instability, which are present in the patient described[3,8].

Also, anomalous calcifications may occur in structures that are not normally ossified, such as the larynx, trachea and main bronchi, causing stenosis, which was not seen in the patient studied[3,8].

These clinical findings, associated with specific radiographic characteristics, can help direct the correct diagnosis and appropriate clinical management of these individuals. Despite this, diagnostic confirmation occurs using molecular analysis methods. Currently, given the clinical suspicion of skeletal dysplasia, NGS gene sequencing panels are available, which include genes involved in the develop ment of cartilaginous and bone tissue, which have helped with diagnostic elucidation, as in

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the patient reported[9].

Despite the absence of specific treatments for this genetic condition, even in milder cases, the approach is expectant with treatment and monitoring of possible comorbidities. Respiratory impairment must be assessed through polysomnography and cardiorespiratory assessment. Changes in the thoracolumbar spine should be monitored with regular x-rays. Cervical spinal stenosis and cervical instability must be evaluated in order to define the need for surgical decompression or corrective spinal surgeries. In addition, audiometry and visual assessment must be evaluated annually. In the reported case, due to early diagnosis, the patient benefited from receiving treat ment involving a multidisciplinary team. This monitoring prevented several complications such as respiratory, cardiac and neurological problems from developing. It is worth highlighting that genetic counseling is essential in the monitoring of rare diseases and must be carried out with the family, guardians and the patient himself[3].

CONCLUSION

According to the case report, we realized that the early diagnosis of skeletal dysplasias such as CDPX1 is important for adequate outpatient follow-up, family counseling and prevention of the development of long-term comorbidities. Despite the milder presentation of the disease, the recognition of these clinical and radiographic findings enabled appropriate clinical management and the establishment of a multidisciplinary care plan for the patient in question.

CREdiT author statement

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REFERENCES

1. Irving MD, Chitty LS, Mansour S, Hall CM. Chondrodysplasia punctata: a clinical diagnostic and radiological review. Clin Dysmorphol. 2008 Oct;17(4):229-41. doi: 10.1097/MCD.0b013e3282f44043. PMID: 18799974.
2. Figueirêdo SS, Araújo JS, Kozan JEM, Santos NCL, Tanganeli V. Condrodisplasia punctata rizomélica: relato de caso e breve revisão da literatura. Radiologia Brasileira. 2007;40(1):69–72. doi: 10.1590/S0100-39842007000100018.
3. Braverman NE, Bober MB, Brunetti-Pierri N, Suchy SF. Chondrodysplasia Punctata 1, X-Linked. 2008 Apr 22 [updated 2020 Oct 15]. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2023. PMID: 20301713.
4. Schwartz NB, Domowicz M. Chondrodysplasias. In: Martini L, editor. Encyclopedia of Endocrine Diseases. Elsevier; 2004. p. 502-509. ISBN: 9780124755703.
5. Brunetti-Pierri N, Andreucci MV, Tuzzi R, Vega GR, Gray G, McKeown C, et al. X-linked recessive chondrodysplasia punctata: spectrum of arylsulfatase E gene mutations and expanded clinical variability. Am J Med Genet A. 2003 Mar 1;117A(2):164-8. doi: 10.1002/ajmg.a.10063. PMID: 12567415.
6. Daniele A, Parenti G, d'Addio M, Andria G, Ballabio A, Meroni G. Biochemical characterization of arylsulfatase E and functional analysis of mutations found in patients with X-linked chondrodysplasia punctata. Am J Hum Genet. 1998 Mar;62(3):562-72. doi: 10.1086/301764. PMID: 9497243; PMCID: PMC1376941.
7. Nino M, Matos-Miranda C, Maeda M, Chen L, Allanson J, Armour C, et al. Clinical and molecular analysis of arylsulfatase E in patients

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with brachytelephalangic chondrodysplasia punctata. Am J Med Genet A. 2008 Apr 15;146A(8):997-1008. doi: 10.1002/ajmg.a.32264. PMID: 18348268.
8. Ochiai D, Takamura K, Nishimura G, Ikeda T, Yakubo K, Fukuiya T. Prenatal diagnosis of cervical spinal cord compression in chondrodysplasia punctata brachytelephalangic type: A case report and literature review. Congenit Anom (Kyoto). 2013 Dec;53(4):160-2. doi: 10.1111/cga.12053. PMID: 24712475.
9. Kim SJ, Lee SM, Choi JM, Jang JH, Kim HG, Kim JT, et al. Genetic analysis using a next generation sequencing-based gene panel in patients with skeletal dysplasia: A single-center experience. Front Genet. 2021;12:670608. doi: 10.3389/fgene.2021.670608.

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