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Case Report

Radiological picture of premature baby with manifestation of brachytelephalangic type chondrodysplasia punctata, myelomalacia

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Chondrodysplasia punctata (CDP) is a heterogeneous disease with multiple syndromic types and characterization of the CDP subtype is important for prognostic purposes. The aim of this study is to provide information about brachytelephalangic CDP, discuss its radiographic findings and emphasize the importance of cervical spine findings. Physicians must be aware of the potentially serious complications of CDP especially its cervical spine findings. In order to prevent morbidity and mortality, early imaging with CT and MRI is recommended.

Key words: brachytelephalangic, chondrodysplasia punctata, myelomalacia, MRI.

Chondrodysplasia punctata (CDP) is a congenital skeletal dysplasia characterized by aberrant epiphyseal bone mineralization.[1] It manifests with punctate calcifications in the non-ossified epiphyseal cartilage. CDP is a heterogeneous group of disorders with genetic variation, and the diagnosis is often missed due to low prevalence rate.[1] According to Nosology and Classification of Genetic Skeletal Disorders: 2015 Revision, chondrodyplasia punctata (CDP) group is classified under the Group 21- CDP group.[2] This group includes CDP X-linked dominant Conradi-Hunermann type, CDP X-linked recessive brachytelephalangic type, CHILD, Keutel syndrome, Greenberg dysplasia, Rhizomelic CDP type1, Rhizomelic CDP type 2, Rhizomelic CDP type 3, CDP tibial-metacarpal type and Astley-Kendall dysplasia.[2] It is critical to characterize the CDP subtype both clinically and genetically due to the fact that the genetic etiology, the accompanying features and the genetic counselling provided to the patient and the family may change prognosis.

The aim of this study is to provide information about brachytelephalangic chondrodysplasia punctata (BTCDP), discuss its radiographic findings and emphasize the importance of cervical spine findings.

Case Report

A 33-week gestation male newborn with facial dysmorphism had a flat nose, hypertelorism, and full cheeks. Skeletal imaging revealed punctate calcifications in the vertebrae, in the epiphysis of the long bones, in the short bones of the hand and foot and hypoplasia of the distal phalanges (Fig. 1-2). Based on the radiologic findings brachytelephalangic chondrodysplasia punctate was suspected. Due to possible association of cervical spine abnormalities in CDP, the patient was initially assessed with magnetic resonance imaging (MRI) followed by computed tomography (CT) scans. On MRI, the brain appeared normal; however, there was stenosis of the craniocervical junction due to abnormal, irregular ossification around the anterior arch of C1 and dens and posterior arch hypoplasia of C3 (Fig. 2). In addition, myelomalacia was noted in the upper cervical spinal cord (Fig. 3). A CT scan of the cervical

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spine was performed without contrast to evaluate the bony abnormalities better. CT demonstrated the irregular ossification at the anterior arch of the C1 (Fig. 2). Mid-facial hypoplasia was noted on the CT. The patient was diagnosed with brachytelephalangic CDP based on the clinical and radiological findings and the diagnosis was confirmed by genetic testing. His karyotype revealed miscellaneous 46 XY. The patient was approved as a de novo case genetically. The patient was monitored in the neonatal intensive care unit for 6 months due to upper airway obstruction and feeding was provided via gastric tube. On clinical follow-up, the patient was noted to have patent foramen ovale with small left to right shunt, mild bilateral pulmonary artery stenosis, trace tricuspic regurgitation, sleep apnea hypotonicity, developmental delay, marked difficulty in ambulation, and bilateral hearing loss. He had no madelung deformity. Follow-up imaging studies revealed moderate progressive obstructive hydrocephalus and macrocephaly due to worsening stenosis at the level of foramen magnum and upper cervical spine (Fig. 4). The patient underwent surgical decompression surgery of the upper cervical spine and foramen magnum and craniocervical fusion was performed by implanting a costal graft (Fig. 4). Genetic counselling was provided to the family.

Informed consent was obtained from the patient's parents for publication

Discussion

CDP is a heterogenous disease with multiple syndromic types and characterization of the CDP subtype is important for prognostic purposes. It has many subtypes such as the lethal autosomal recessive rhizomelic type (described by Conradi in 1914), and X-linked

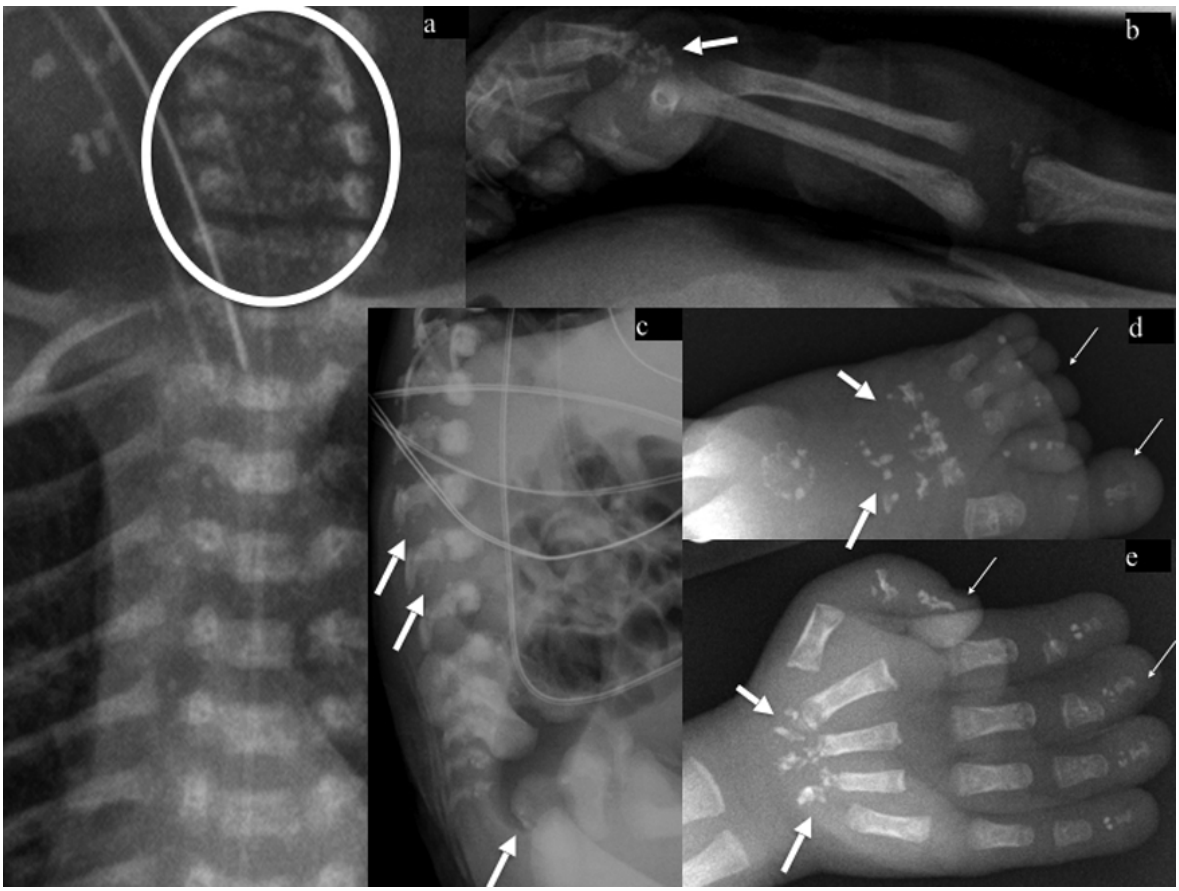

Fig. 1.A-E. A skeletal survey showed punctate calcifications in the cervical, thoracic, and lumbar vertebrae, and epiphyses of long bones, carpal, tarsal, metacarpal and metatarsal bones (thick arrows). **D-E.** There are epiphyseal punctate calcifications with hypoplasia in the distal phalanges (thin arrows).

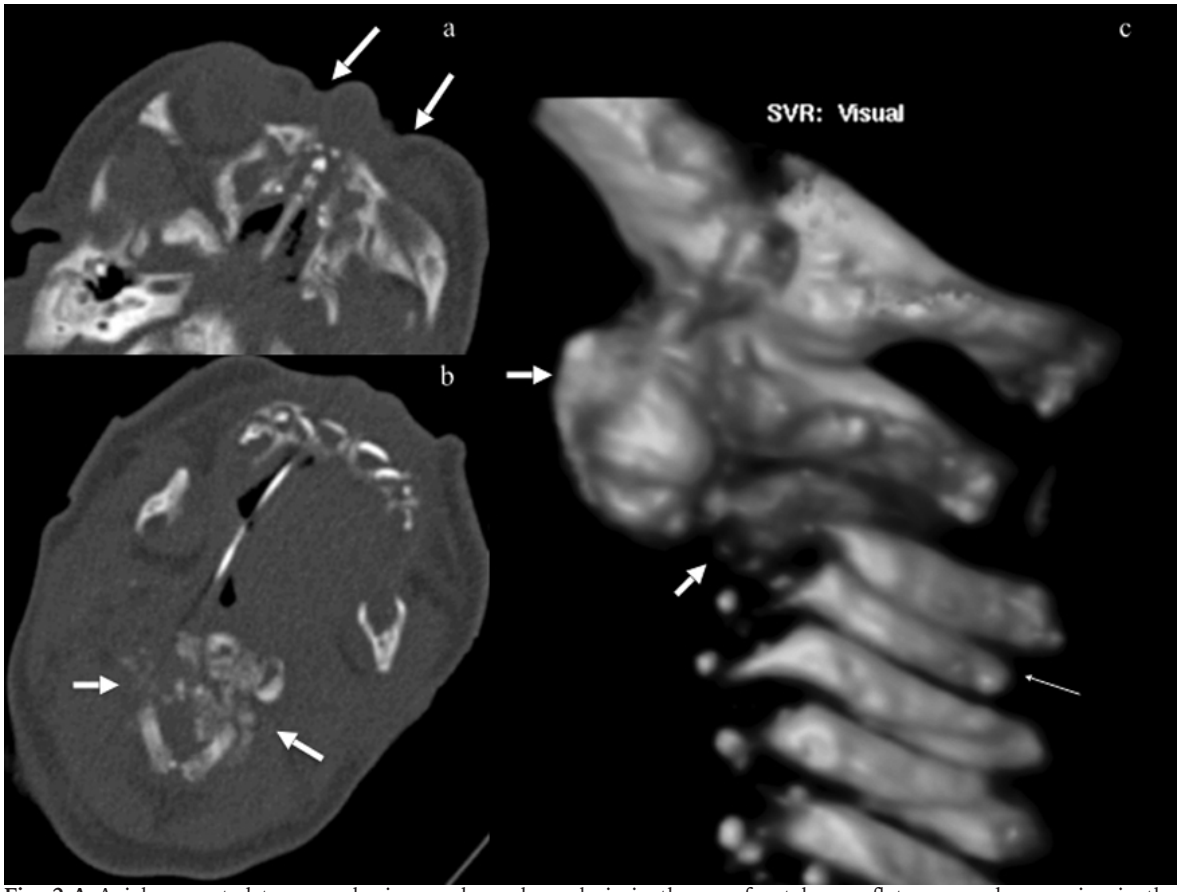

Fig. 2.A Axial computed tomography image shows hypoplasia in the nasofrontal area, flat nose and narrowing in the nasal passages (thick arrows). **B.** Axial CT images show stenotic and dysmorphic craniocervical junction and abnormal calcifications and ossifications (thick arrows). **C.** Three-dimensional volume rendering images show stenotic and dysmorphic craniocervical junction, atlantoaxial subluxation (thick arrows) and narrowing of the spinal canal caused by congenital short pedicles of the third cervical vertebra (thin arrow).

dominant Conradi-Hunerman types.[2,3] Apart from these, there are also rarer atypical forms such as brachytelephalangic type.[3]

Brachytelephalangic type of CDP was first described by Maroteaux in 1989 and has a prevalence of 1 in 500,000.[4,5] In most of the affected children it offers good prognosis without significant physical disability, however if present, cervical spinal instability and airway stenosis may cause severe morbidity and early death.[5,6]

Brachytelephalangic CDP is an X-linked recessive skeletal dysplasia.[5,7] The defect in calcium deposition is considered to be caused by a mutation in vitamin K-dependent arylsulfatase E enzyme gene or a deletion in the X chromosome harboring the gene.[8] The actual function of arylsulfatase E enzyme is unknown, but it has been implicated in normal skeletal development and chemical pathway involving vitamin K.[6,8] The evidences suggest that vitamin K plays an important role in bone development and maintaining bone density.[6,8] The pathophysiological mechanism underlying the radiological findings have not been clearly established.[8] In our case, maternal systemic lupus erythematosus, maternal vitamin K deficiency and vitamin K dependent coagulation defects were ruled out.

Facial dysmorphism characterized by flat nose and chondrodysplasia involving tracheobronchial cartilage, vertebrae and tarsal bones are typically observed in the brachytelephalangic type.[7] Specific radiologic findings include punctate calcifications in the craniocervical area, tarsal and carpal bones and vertebra, hypoplasia of phalanges, metacarpal and metatarsal bones, and triangle-shaped distal phalangeal

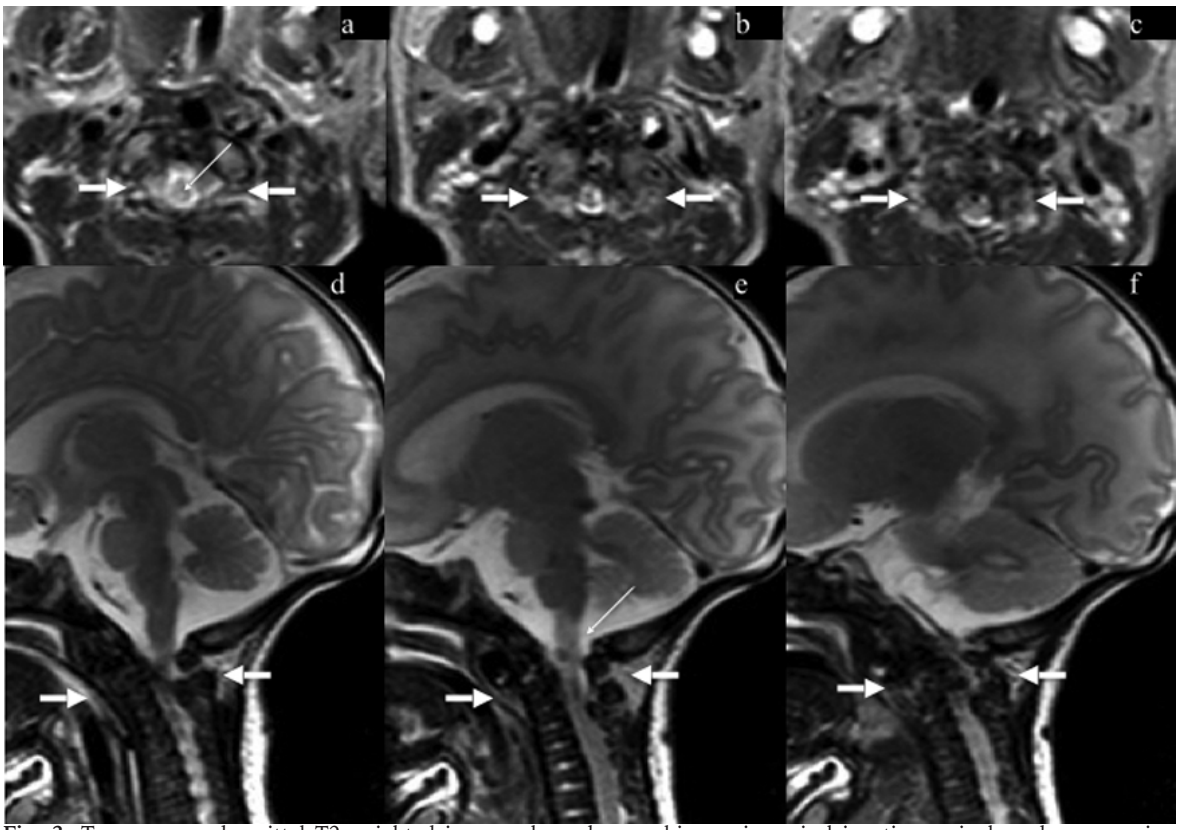

Fig. 3. Transverse and sagittal T2-weighted images show dysmorphic craniocervical junction, spinal cord compression (thick arrows) and increased cord signal intensity in keeping with myelomalacia (thin arrows).

hypoplasia.[3,7,10,11] Among these findings, distal phalangeal hypoplasia is the most characteristic finding.[11] Punctate calcifications observed in the neonatal period usually disappear during infancy and childhood.[7] In our case, the dysmorphic calcifications and ossifications seen in the craniocervical area in the neonatal period were not observed on CT scans at 6 months of age. In addition, respiratory difficulties, conductional or neural hearing loss, developmental delay, cardiac abnormalities, nutritional disorders, cataract, and visual problems such as optic disc atrophy can be seen.[6]

There are case reports of cord compression and myelomalacia in rhizomelic, brachytelephalangic, and Conradi-Hunerman types of CDP with cervical spinal stenosis.[11,12,13,14] A skeletal survey with radiographs of the cervical spine provide relevant information; however, CT and MRI scans give valuable information for diagnosis and treatment planning[12]. CT scans allow more detailed visualization of the accompanying cervical vertebral dysplasia and dysmorphic calcifications in tracheobronchial tree in cases with suspected CDP. Atlantoaxial instability and narrowing of the spinal canal can be assessed with three dimensional volume rendering images and this assessment guides surgical planning. Prenatal ultrasonography and fetal MRI can also capture this group of disorders.[5,9,10] The cervical spinal cord compression and myelomalacia are better demonstrated with MRI.

In this disorder, cervical spinal instability and foramen magnum stenosis can lead to severe spinal cord damage and thereby to neurological morbidities such as tetraplegia and hypotonia and fatal conditions such as respiratory arrest[6]. It must be kept in mind that these findings can be accompanied by hydrocephalus as in the present case. It is therefore recommended to perform cranial and cervical MRI in early neonatal period in suspected cases of CDP. In the present case, radiographic images acquired immediately after birth showed cervical stenosis and myelomalacia but no hydrocephalus. On follow up imaging the patient developed hydrocephalus, and had respiratory failure and

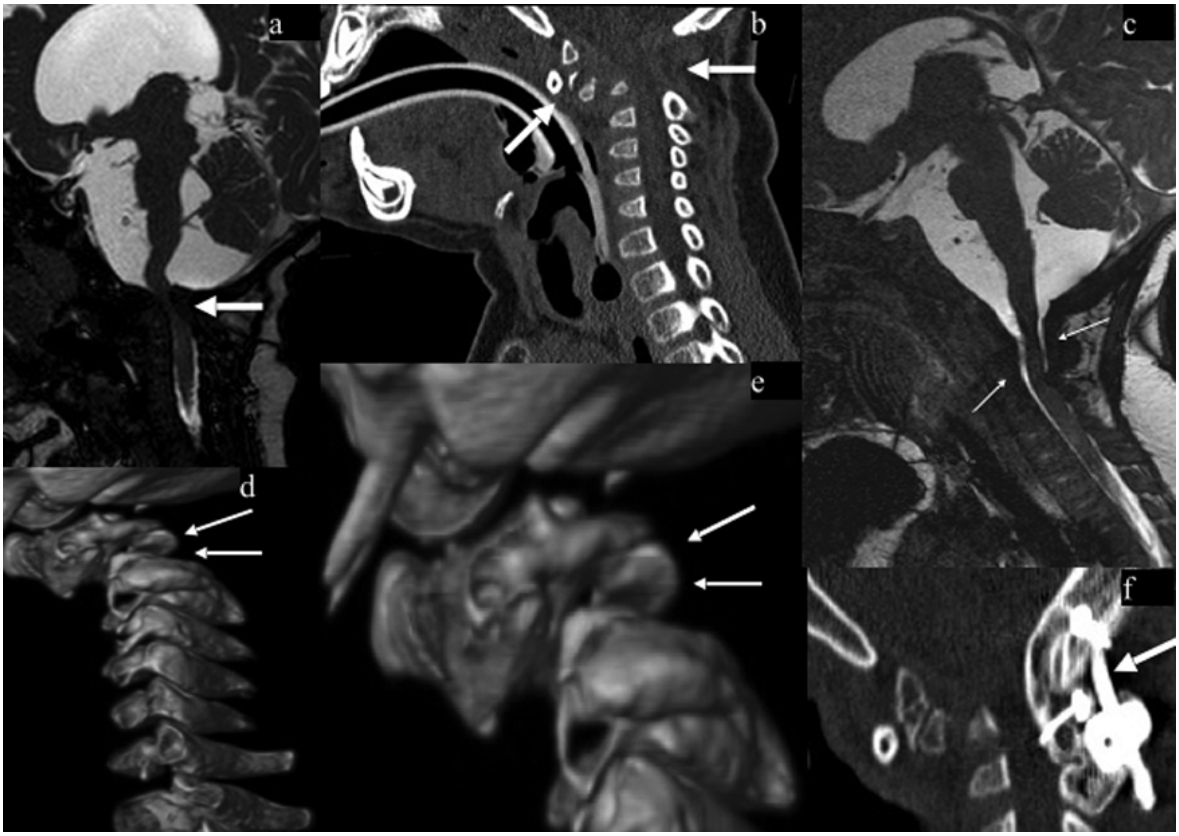

Fig. 4.A In MRI assessment after 5 months, balanced fast field echo images showed increased stenosis and instability of craniocervical junction and development of obstructive hydrocephalus (thick arrow). **B.** Initially, the patient underwent foramen magnum decompression and laminectomy of the first and second cervical vertebrae in order to relieve cervical stenosis (thick arrows). **C.** Postoperative sagittal T2-weighted image shows expansion of cervical canal (thin arrows). **D.** In follow-up radiographic assessment, three-dimensional volume rendering images show abnormality at the level of the atlantoaxial joint, cervical instability and cervical stenosis. The abnormal calcifications disappeared and no longer seen (thick arrows). **E.** Sagittal CT image shows most recently performed suboccipital costal graft and craniocervical fusion with metallic stabilizators (thick arrow).

hypotonicity.

In differential diagnosis of CDP one should consider other conditions that can cause stippled epiphysis including peroxisomal disorders (Zellweger syndrome, adrenoleukodystrophy, infantile Refsum, warfarin, alcohol or phenytoin exposure, maternal disorders (i.e. lupus), and Smith-Lemni-Opitz syndrome.[15]

In surgical management, decompressive laminectomy and vertebrectomy can be performed depending on the severity of stenosis and presence of complications.[1] Cervical spine stability is usually attempted with bone grafts or surgical fixation hardware.[1] Sequential imaging provides important information in terms of preoperative state and postoperative follow-up.

In conclusion, physicians must be aware of the potential serious complications of CDP especially its cervical spine findings. In order to prevent morbidity and mortality, early imaging with CT and MRI is recommended.

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