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Case Report

A Case of X-linked Chondrodysplasia Punctata with EBP Mutation, c.204G>T

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Abstract Chondrodysplasia punctata is characterised by punctate or popcorn-like calcium deposits in cartilage observed on X-rays. X-linked dominant chondrodysplasia punctata (CDPX2) is characterised by bone, skin, and eye abnormalities. Mutations in emopamil binding protein (*EBP*) gene cause CDPX2. *EBP* gene mutation leads to defect of cholesterol biosynthesis pathway. CDPX2 is an X-linked dominant disorder so there are different clinical phenotypes between male and female. We report a variant in the *EMP* gene in a 2-day-old female with a variable CDPX2 phenotype including typical skeletal anomaly (stippling), skin defect, and cataract. The prenatal ultrasound found the fetal asymmetric femur but chondrodysplasia punctata was not suspicious. After birth, in the next-generation sequencing panel for skeletal dysplasia, a heterozygous mutation in the *EBP* gene (NM_006579.2) was detected (c.204G>T, p.Trp68Cys). The clinical phenotype of CDPX2 is variable, especially in affected females, so early diagnosis can result in early treatment with medicine and surgery for significant ocular (cataract) and skeletal anomaly and a better prognosis can be expected.

Key words *Chondrodysplasia; Punctata; X-linked*

Introduction

Chondrodysplasia punctata is a rare, heterogeneous congenital skeletal dysplasia. This disorder is characterised by punctate or popcorn-like calcium deposits in cartilage observed on X-rays.[1]

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X-linked dominant chondrodysplasia punctata (CDPX2, Online Mendelian Inheritance in Man 302960), also known as Conradi-Hünermann-Happle syndrome, is characterised by bony abnormalities such as short stature, asymmetric rhizomelic shortness, radiographic epiphyseal stippling, midface hypoplasia, transient skin defect. This disorder is caused by a mutation of emopamil binding protein (*EBP*) gene.[1,2] The prevalence of CDPX2 is estimated at less than 1 in 400,000 newborns. But real prevalence may be higher because a female patient with mild symptoms and signs can be underdiagnosed. Most cases of CDPX2 occur in females.

When this disorder is inherited, it is inherited in an X-linked dominant pattern. The *EBP* gene associated with CDPX2 is located on the short arm of the X chromosome (Xp11.22-p11.23). The *EBP* gene provides instructions for making an enzyme called 3β-hydroxysteroid-Δ8, Δ7-isomerase. This enzyme is involved in the distal cholesterol biosynthesis pathway.

Cholesterol is necessary for normal embryonic development and it is also functionally important for

embryos and neonates. It is a structural component of the cell membrane, so it is essential for the barrier function of the skin and the membrane of the lens and plays an important role in the regulation of hedgehog signaling necessary during development.[2]

In females, a mutation in one of the two copies of the *EBP* gene in each cell can cause the disorder. Some cells produce a normal amount of 3β-hydroxysteroid-Δ8, Δ7-isomerase and other cells produce none. Symptoms and signs of CDPX2 vary depending on the degree of the total reduction of this enzyme. However, in males, a mutation of the *EBP* gene results in a total loss of this enzyme. Also, few males have been born with CDPX2 because it is usually lethal without this enzyme at all in the early stages of development.[3]

Although the symptoms and signs of CDPX2 are variable, almost all patients with chondrodysplasia punctata have a body abnormality that appears on X-rays as spots in epiphysis and cartilage. The stippling of CDPX2 typically is found at the long bones of the arms and legs, the ribs, and the vertebrae. So, these typical radiologic findings lead to the suspicion of CDPX2.[4]

In addition, there are transient skin defects including striated palmoplantar hyperkeratosis, patchy ichthyotic skin following the lines of Blaschko., follicular atrophoderma, and pigmentary defects but skin lesion can resolve during early infancy. The hair is coarse and lusterless. Also scarring alopecia is common. Unilateral or segmental cataracts are commonly found on ophthalmic examination.[5] We report a female newborn with many clinical manifestations of X-linked dominant chondrodysplasia punctata and mutation of *EBP*.

Case Report

A 2-day-old female newborn was admitted to our hospital because of a short right femur. She was born at 38+6 weeks by cesarean section. The pregnancy had progressed normally. She was the first baby and the family history was unremarkable. At the prenatal ultrasound, the right fetal femur was shorter than the left but anther abnormal findings including polyhydramnios were not found and prenatal genetic testing was not performed.

Physical examination showed skin lesions, dysmorphic face, and skeletal anomaly. Yellowish hyperkeratotic scaly patches of skins were observed throughout the whole body except for the face, hands, and feet (Figure 1). Asymmetric face, low nasal bridge, and hypoplastic midface were observed. The right leg was shorter than the left. Infantogram showed popcorn-like calcifications at metaphysis of proximal and distal right femur, proximal right tibia, right talus, both tarsal bones, along with both paravertebral spaces, both costosternal junctions of 1st ribs, and right scapula. Also widening of the metaphysis of distal tibia and fibula were observed (Figure 2). Hip ultrasound showed the asymmetric femoral head (right 1.3 cm, left 1.6 cm) and amorphous hyperechoic lesion at the cartilage of the right greater trochanter. Based on these skeletal and skin anomalies, we became suspicious of skeleton dysplasia and conducted further evaluations. Echocardiogram showed atrial septal defect (size 5.5*4.9 mm) and ophthalmic examination found congenital cataract on the right eye. Transcranial and abdominal ultrasound showed no abnormal findings of the brain and abdomen. The metabolic screening test was normal. Genetic skeletal dysplasia was suspicious so genetic study was performed. We performed several tests to find the genetic cause of skeletal dysplasia. The peripheral blood karyotype of the patient was normal female (46, XX). In the next-generation sequencing panel for skeletal dysplasia, a heterozygous mutation in the *EBP* gene (NM_006579.2) was detected (c.204G>T, p.Trp68Cys).[6,7] It was classified as a likely pathogenic variant according to American College of Medical Genetics (ACMG) guideline.

We did not perform maternal testing because she was not clinically unaffected.

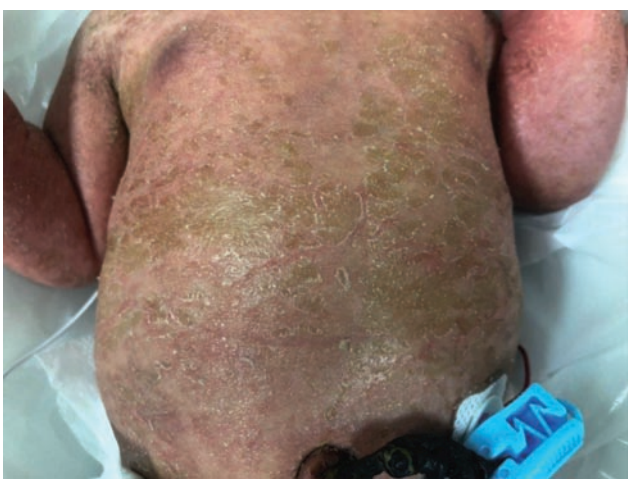

Figure 1 Skin lesions on the chest and abdomen of a patient with CDPX2. Yellowish hyperkeratotic scaly patches of skins were observed throughout the whole body except for the face, hands, and feet.

Discussion

Almost all patients have a stippling in epiphysis and cartilage, but this abnormality disappears in early childhood. Other bony abnormalities in patients with CDPX2 include asymmetric shortening of the long bones (upper arms and thighs) and progressive kyphoscoliosis. These skeletal abnormalities cause patients with CDPX2 to tend to have short stature.

Most patients with CDPX2 have cataracts from birth. Another eye abnormalities include small eyes (microphthalmia) and small corneas (microcornea). The cornea is the clear front surface of the eye. These eye abnormalities can result in impaired vision. Therefore, early treatment is essential for normal visual development.[8]

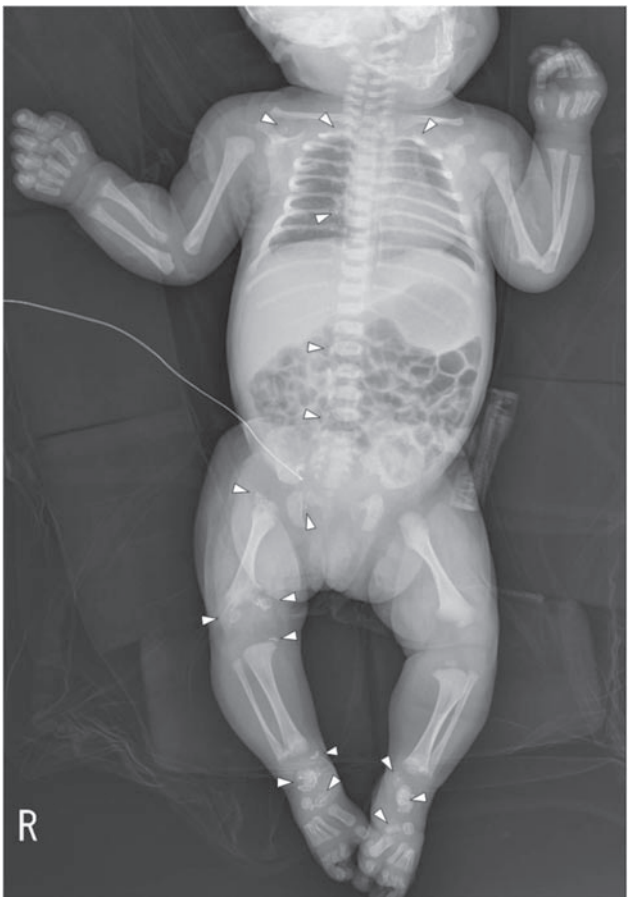

Figure 2 Radiological features of female patients with CDPX2. Popcorn-like calcifications at metaphysis of proximal and distal right femur, proximal right tibia, right talus, both tarsal bones, along with both paravertebral spaces, both costosternal junction of 1st ribs, right scapula, and chondroid lesions. Widening of the metaphysis of distal tibia and fibula were observed.

Females with CDPX2 typically have normal intelligence and can expect a normal lifespan but not in males. Males with CDPX2 have hypotonia, structural brain changes, seizures, moderate to severe developmental delay, typical facial characteristics, and other birth defects, these clinical features are some of the same features in females with CDPX2.[2]

EBP mutation can lead to 2 phenotypes, CDPX2, and male emopamil-binding-protein disorder with neurological defects (MEND) syndrome. MEND syndrome is inherited in an X-linked recessive pattern and has typically neurological defects.[9] The inherited pattern and neurologic defect are the important points that distinguish CDPX2 from MEND syndrome.

We report a variant in the *EBP* gene in a 2-day-old female with a variable CDPX2 phenotype including typical skeletal anomaly (asymmetric rhizomelia and stippling), skin defect, facial asymmetry, and cataract. The prenatal ultrasound found the fetal asymmetric femur but chondrodysplasia punctata was not suspicious. At birth, she has many phenotypes of CDPX2 and typical radiologic findings so the early diagnosis was possible. Even though clinical phenotype of CDPX2 is variable but an early diagnosis can result in early treatment with medicine and surgery including significant ocular (cataract) and skeletal anomaly and a better prognosis can be expected.

Conclusion

We report a variant in the *EBP* gene in a 2-day-old female with a variable CDPX2 phenotype including typical skeletal anomaly (stippling), skin defect, and cataract. Early diagnosis by genetic study and early treatment is very important for a better prognosis.

Declaration of Interest

The authors declare that there is no conflict of interest.

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