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CASE REPORT

Severe phenotype of X-linked dominant chondrodysplasia punctata

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Key Clinical Message

A prenatally ascertained case representing the more severe end of the X-linked dominant chondrodysplasia punctata (CDPX2).

Keywords

Chondrodysplasia, prenatal, punctata, severe, X-linked.

X-linked dominant chondrodysplasia punctata (CDPX2) is caused by mutations in a gene that encodes emopamil binding protein, EBP (OMIM 300205) or 3 beta-hydroxysteroid-delta 8, delta 7-isomerase (sterol- D 8-isomerase) [1-3], an enzyme involved in cholesterol biosynthesis. Radiological features include epiphyseal stippling involving the long bones and vertebrae, asymmetric limb shortening, ectopic cartilaginous calcifications, and vertebral segmentation anomalies. Pertinent findings on clinical examination include midface hypoplasia, a hypoplastic nasal septum, skin abnormalities, and cataracts [4, 5]. CDPX2 is lethal in males, however, affected females manifest a wide range of clinical manifestations due to skewed X-chromosome inactivation [6]. High-resolution fetal ultrasound may detect many of the associated features but a definitive diagnosis is often not possible until after birth or autopsy examination [7]. The demonstration of 8(9)-cholestenol and 8-dehydrocholesterol accumulation in plasma and tissue is diagnostic [1–3].

To date, only fifteen prenatal cases of CDPX2 in females have been reported in the literature [8]. The epiphyseal stippling associated with CDPX2 in these cases ranged from severe to barely identifiable. In this report, we describe a prenatally ascertained case representing the more severe end of the CDPX2 skeletal phenotype spectrum. The report also represents the first CDPX2 case confirmed using a combination of exome sequencing and biochemical analysis on cultured amniocytes.

The mother was a 41-year-old G4P3L3 woman referred to our service after an 18-week detailed fetal ultrasound revealed short upper limbs and femurs with possible club feet. The couple was previously healthy, nonconsanguineous, and of Jamaican descent. The extended family history was unremarkable. The pregnancy was complicated from approximately 11 weeks' gestation by heavy vaginal bleeding, which later resolved. A subsequent fetal ultrasound at our institution revealed a hypoplastic thorax (thoracic-abdominal circumference ratio = 0.6), a thickened nuchal fold

(6.1 mm) and marked micromelia (all limbs <5% for gestational age). The long bones were appropriately mineralized with no evidence of bowing or fractures. In view of the findings, the couple was counseled about a lethal skeletal dysplasia and after discussion, decided to terminate the pregnancy. Postmortem fetal radiographs (22 weeks' and 5 days' gestation) identified widespread symmetrical cartilaginous stippling, profound platyspondyly with irregular calcification of vertebral bodies, hypomineralization of bones, severe symmetric shortening of long bones, a bell-shaped thorax, and hypoplastic gracile ribs (Fig. 1A).

The postmortem examination showed dysmorphic facial features including a flat profile with a flattened nasal bridge, anteverted nares, poorly defined alae, low set ears, a small mouth with thick lips, and a poorly defined philtrum. There was asymmetrical shortening of all long bones, camptodactyly and bilateral talipes equinovarus. Bilateral renal and pulmonary hypoplasia was noted. There was laryngeal atresia at the level of the thyroid cartilage (Fig. 1B and C), accompanied by an irregular anterior ala of the thyroid cartilage, but no evidence of tracheoesophageal fistula. A Meckel diverticulum was identified 14 cm from the ileocecal valve. The differential diagnosis included skeletal dysplasias secondary to a disorder of cholesterol metabolism and Greenberg dysplasia.

The fetal karyotype was 46, XX and a prenatal whole genome oligonucleotide SNP array did not identify any abnormalities. Whole exome sequence using fetal fibroblast DNA revealed a *de novo* novel stop mutation in *EBP* (NM006579: exon2: c. G262T: p. E88X). In addition, sterol analysis was performed in cultured amniocytes as previously described [9] and revealed an increased 8(9)-cholestenol/cholesterol ratio (11.41%, normal value, mean: 0.16%), consistent with sterol-Δ8-isomerase deficiency, confirming a diagnosis of CDPX2. The X-chromosome inactivation status was measured by the analysis of the (CAG)n repeats in the AR gene at Xq11-q12 before and after with methylation sensitive enzymes. Interestingly, the test showed no skewed X-inactivation with a ratio of 16(35%):17(65%).

Chondrodysplasia punctata (CDP) is etiologically a heterogeneous group of conditions characterized by variable degrees of epiphyseal stippling. The differential diagnosis includes other types of CDP such as rhizomelic CDP (type1, type 2, and type 3), X-linked types (CDPX1, brachytelenphalangic), and CDPX2 (Conradi-Hünermann-Happle syndrome), chromosomal abnormalities, maternal diseases such as systemic lupus erythematosus and maternal exposure to viruses such as cytomegalovirus (CMV) or to medications such as coumarin derivatives and hydantoin [10].

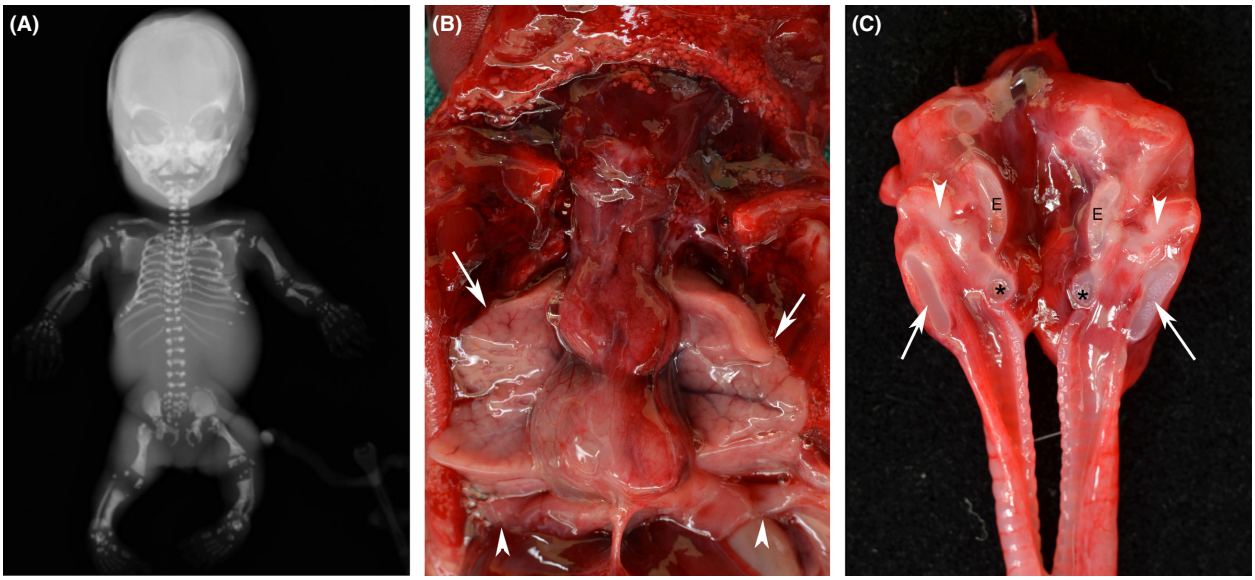

Figure 1. (A) Female fetus at 22 weeks and 5 days of gestation. Radiograph (AP view) demonstrates widespread symmetrical cartilaginous stippling, profound platyspondyly with irregular calcification of vertebral bodies, ectopic paravertebral cartilaginous calcifications, hypomineralization of bones, severe symmetric shortening of long bones, profound platyspondyly, bell-shaped thorax, and hypoplastic gracile ribs. (B) Autopsy pathology. The thoracic contents after removal of the chest plate. The lungs (arrows) are hypoplastic, weighing less than half of their expected weight for gestational age, but were distended, filling the entire thoracic cavity and flattening the diaphragm inferiorly (arrowheads). The larynx could not be probed, and was bivalved sagittally. (C) The thyroid cartilage (arrowhead) was irregular and hypoplastic, with a small epiglottis (marked E) proximal to the obstructed airway, below which the anterior and posterior cricoid cartilages (marked with an arrow and asterix, respectively) are of normal morphology.

As our exonic variant had not previously been reported in any of the known mutation databases, we confirmed the diagnosis of CDPX2 through biochemical sterol analysis in cultured amniocytes. Our patient represents the first reported case of prenatally diagnosed CDPX2 with biochemical confirmation by sterol analysis in cultured amniocytes.

Fifteen females with a severe prenatal presentation of CDPX2 have been previously reported in the literature [8]. In this cohort, the mean gestational age at ultrasound diagnosis was 22 weeks. The diagnosis was suspected because of eccentric stippled epiphyseal and paravertebral cartilaginous calcifications. The authors of this review point out that a key distinguishing sonographic feature in CDPX2 is asymmetric shortening of the long bone. however, this was NOT seen in our case despite a similar severe fetal presentation. Interestingly, the study showed that skewed X-inactivation was found in a mildly symptomatic mother and random X-inactivation in a severe fetal case. In addition, the most severe cases were de novo. Genetic results of our case support these findings.

Several congenital malformations were detected in our case including bilateral talipes equinovarus, bilateral renal hypoplasia with bilateral pelviectasis, Meckel diverticulum, and laryngeal atresia. A variety of congenital malformations have previously been reported including postaxial polydactyly, bilateral or unilateral clubfoot, cleft palate and malformations of the brain renal, and cardiac systems [4]. Only one fetus was reported to have an abnormality of the larynx; laryngeal cartilage calcification; and no cases were reported to have intestinal malformations. Our case represents the first associated with laryngeal atresia and an intestinal malformation, Meckel diverticulum.

Authorship

ND: acquired the data, analyzed and interpreted the data, drafted the manuscript, critically revised the manuscript. KC: analyzed and interpreted the data, acquired the data, critically revised the manuscript. CM: analyzed and interpreted the data, critically revised the manuscript. LK: analyzed and interpreted the data, critically revised the manuscript. RT: acquired the data, critically revised. PS: analyzed and interpreted the data, critically revised. PK: studied the conception and design, analyzed and interpreted the data, critically revised.

Conflict of Interest

The authors have declared that no conflict of interest exists.

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