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Prenatal diagnosis of short-rib polydactyly syndrome type 3 (Verma-Naumoff type) by three-dimensional helical computed tomography

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Short title for running head:
Prenatal diagnosis of SRP type 3 by 3D-CT

Keywords: short-rib polydactyly syndrome (SRP), Jeune syndrome (asphyxiating thoracic dystrophy: ATD), 3D-CT, prenatal diagnosis

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Abstract

We present a case of short-rib polydactyly syndrome (SRP) type 3 in which accurate prenatal diagnosis was feasible using both ultrasonography and 3D-CT. SRPs encompass a heterogeneous group of lethal skeletal dysplasias. However, the phenotypes overlap with those of nonlethal skeletal dysplasias, *i.e.*, Ellis-van Creveld syndrome and Jeune syndrome. As accurate prenatal diagnosis of SRPs is helpful for parents, we used 3D-CT in the early third trimester to examine a fetus suggested to have phenotypes of "short-rib dysplasia group" on ultrasonography. 3D-CT showed mild modification of the vertebral bodies, small ilia with horizontal acetabula and triangular partial ossification defects, and subtle metaphyseal irregularities of the femora. These CT findings and an extensive literature search regarding the phenotypes of various diseases categorized as "short-rib dysplasia group" led to a correct prenatal diagnosis of SRP type 3. This case exemplified the usefulness of 3D-CT for the precise prenatal diagnosis of skeletal dysplasias.

Introduction

Short-rib polydactyly syndromes (SRPs) encompass a heterogeneous group of lethal skeletal dysplasias that are inherited in an autosomal recessive manner. SRPs are classified into four types: type 1 (Saldino-Noonan; OMIM 263530), type 2 (Majewski; OMIM 263520), type 3 (Verma-Naumoff; OMIM 263510), and type 4 (Beemer-Langer; OMIM 269860). "Nosology and Classification of Genetic Skeletal Disorders: 2006 revision" lists these disorders as "short-rib dysplasia (with or without polydactyly) group."[1] The constellation of a severely narrow thorax, short limbs, and polydactyly allows prenatal diagnosis of SRPs with fetal ultrasonography. However, the phenotypes of SRPs overlap with those of nonlethal, but occasionally semilethal, skeletal dysplasias that belong to the "short-rib dysplasia group," *i.e.*, Ellis-van Creveld syndrome (EvC; OMIM 225500) and asphyxiating thoracic dystrophy (ATD: Jeune syndrome; OMIM 208500). Recent reports have suggested the usefulness of three-dimensional helical computed tomography (3D-CT) in the differential diagnosis of skeletal disorders.[2] Here, we report a fetus with SRP type 3 diagnosed

prenatally based on fetal ultrasonography and additional 3D-CT. The present case represents another example indicating the powerful capability of 3D-CT in the prenatal diagnosis of fetal skeletal dysplasias.

Case report

A 23-year-old primigravida was referred for further investigation of fetal short limbs at 28 weeks of gestation. She was in a non-consanguineous marriage and had neither relevant medical history nor significant family history. Ultrasonography of the fetus revealed a narrow and small thorax covering only the dorsal part of the viscera, short femora of 30 mm (–7.26 SD), short humeri of 29 mm (–6.27 SD), mild ulnar deviation of the hands, short digits, bilateral postaxial polydactyly in the hands and feet, and long biparietal diameter (BPD) of 79.0 mm (+2.7 SD) suggestive of macrocephaly. Bilateral renal dysplasia and penile hypoplasia were also suspected. The volume of amniotic fluid was normal. These findings suggested a lethal or semilethal skeletal dysplasia classified as belonging to the short-rib dysplasia group shown in Table 1. After obtaining informed consent,

computed tomography (CT) was performed at 33 weeks of gestation with a 64-detector row CT scanner (Aquilion64; Toshiba Medical Systems, Tokyo, Japan) with the following parameters: collimation, 0.5 mm; peak tube potential, 100 kVP; gantry rotation time, 0.75 s; beam pitch, 53; and tube current between 260 and 335 mA using an automatic tube current modulation technique. The volume CT dose index (CTDIvol.) was 21.5 mGy. The data from the CT scanner were stored and transferred onto a workstation (ZIOSTATION; Ziosoft, Tokyo, Japan). Multiplanar reconstruction (MPR) and three-dimensional reconstruction by shaded surface display (SSD) images of fetal bones were created and reviewed interactively on the workstation. They provided additional information, including high-rising clavicles, mild modification of the vertebral bodies, subtle metaphyseal irregularities of the femora, and hypoplasia of iliac bones (Figures 1A, B, C). The acetabular roofs were horizontal and arched with triangular ossification defects at the inferior aspect of the lateral iliac margin (Figure 1C). After 3D-CT, a diagnosis of SRP type 3 was made prenatally based on Table 1. The parents chose cesarean section even after

receiving full information regarding SRP type 3, and a male infant weighing 2328 g was delivered (Figure 2A). The infant died of respiratory failure 3 h after birth. The skeletal manifestations on postmortem radiographs corresponded to those seen on 3D-CT (Figures 1D, E; Table 1).

Macroscopic pathological examination at autopsy showed lung hypoplasia (left lung, 7.6 g; right lung, 10.0 g; lung/body weight ratio, 0.75%), hypoplasia of the bilateral kidneys, bilateral dilated ureter, hydropic scrotum, and absent penis (Figure 2A). Chromosomal analysis using cultured lymphoblasts from cord blood showed a normal 46,XY karyotype.

Histological examination of growth plate cartilage at the costochondral junction revealed reduced numbers of resting and hypertrophic chondrocytes, a disorganized hypertrophic zone with loss of columnization, residual cartilaginous nests in the metaphyseal trabeculae, and PAS-positive intracytoplasmic inclusion bodies. Dispersed hypertrophic chondrocytes were separated by the normal cartilaginous matrix, but not by the fibrous tissue. Notably, calcified cartilage islands were observed in the metaphyseal trabeculae, and some were continuous with the physis *via* a

narrow bridge (Figures 2B, C). All of these histological findings were consistent with those of SRP type 3.[3–5]

Discussion

Measurement of fetal size, including femoral length, is currently a routine practice in obstetrics, facilitating identification of skeletal dysplasias with short limbs. Once limb shortening is identified, the subsequent diagnostic task involves assessment of the thorax to ascertain the presence or absence of thoracic hypoplasia, which allow determination of the clinical outcome of the fetus. Disorders that belong to the “short-rib dysplasia group” constitute a considerable portion of cases of skeletal dysplasia with thoracic hypoplasia. Prenatal diagnosis of “short-rib dysplasia group” using ultrasonography is feasible.[6–9] In the present case, the ultrasonography findings, including visceral anomalies, favored a diagnosis of SRP. However, detection of subtle skeletal abnormalities is generally difficult with ultrasonography. Additional information on subsequent 3D-CT and MPR, including mild spondylar dysplasia, subtle metaphyseal changes, and

irregular ossification defects in the outer iliac margin, eventually led to a diagnosis of SRP type 3 in this case.

Differential diagnosis between SRPs, ATD, and EvC is known to be difficult.[10,11] Antenatal diagnosis of SRP subtypes also appears difficult as there have been reports of common abnormalities, such as macrocephaly and polydactyly, as shown in Table 1. However, meticulous formulation of imaging findings on ultrasonography and 3D-CT helped in the prenatal diagnosis of SRP type 3 in the present case (Table 1). 3D-CT is particularly useful to delineate the axial skeleton. Although 3D image reconstruction tends to conceal fine bone details, such as mild metaphyseal dysplasia, this drawback was compensated by MPR (Figure 1B). We evaluated the general skeletal structures first by 3D image reconstruction, and then examined the fine bone details by MPR, in which we were able to view any 2D images of bones as MPR and 3D images without rescanning independent of the fetal presentation.

The histological observations in the present case supported the suggestion that ATD type 1 and SRP type 3 may belong to the spectrum of

the same pathogenetic entity.[3–5] In fact, mutations of *DYNC2H1* have recently been reported as a common cause of ATD and SRP3.[12] However, mutations of *IFT80* have also been reported as a cause of ATD, indicating genetic heterogeneity.[13]

In summary, the present case further exemplified the diagnostic capability of precise prenatal diagnosis of skeletal dysplasia. As shown in Table 1, meticulous interpretation of ultrasonography and CT imaging findings enabled us to subclassify SRPs. To our knowledge, this is the first report of prenatal diagnosis in this group using 3D-CT.

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intraflagellar transport protein, is mutated in Jeune asphyxiating thoracic dystrophy. *Nat Genet*. 2007; 39:727–729.

Figure legends

Figure 1

Fetal CT showed a narrow thorax (1), high-rising clavicles (2), mild modification of the vertebral bodies (3), small ilia with horizontal acetabula and triangular ossification defects at the inferior aspect of the lateral iliac margin (4), subtle metaphyseal irregularities of the femora (5), and brachydactyly with postaxial polydactyly (6) (A, B, C). The radiological findings on postnatal radiographs were identical to those of fetal CT (D, E).

Figure 2

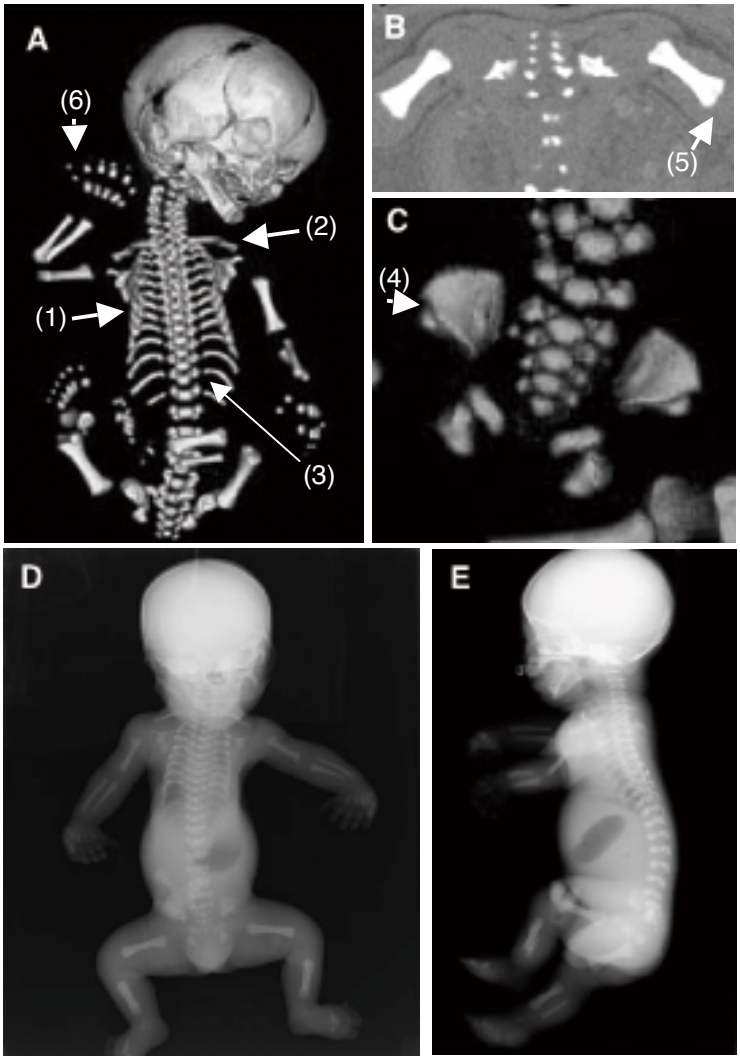
A: Macroscopic view of the infant. The infant had macrocephaly, shortened frenula, clubhands, polydactyly in the bilateral hands and feet, a bell-shaped narrow thorax, a protruding abdomen, hypoplasia of the bilateral kidneys, bilateral dilated ureter, hydropic scrotum, and absent penis. B – C: Histological findings of growth plate cartilage at costochondral junction. B: There was loss of columnization with irregularly dispersed hypertrophic cells. The numbers of resting and hypertrophic chondrocytes were markedly reduced in some areas. Arrow: calcified cartilage islands. C: Irregularly

dispersed hypertrophic cells hypertrophic chondrocytes with PAS-stained cytoplasmic inclusion bodies in chondrocytes. B: H.E. stain. C: PAS stain. Original magnification: B: ×50, C: ×200.

Table 1–Differential diagnosis and comparison between results of ultrasound, 3D-CT, and postnatal examination in this case

	This case								
	Prenatal		Postnatal						
	Ultrasonography	3D-CT	Radiograph	Phenotype	SRP1	SRP3	SRP2/4	ATD	EvCD
-Head and face									
Macrocephaly	++	++	++	++	+	+	+	–	–
CNS abnormalities	–	N/A	N/A	–	+	+	+	–	+
Cleft lip	–	N/A	N/A	–	–	–	++	–	+
Shortened frenula	unclear	N/A	N/A	++	++	++	++	–	+
High clavicles	unclear	++	++	++	++	++	++	++	++
-Bones									
Short limb	++	++	++	++	++	++	+	+	+
Polydactyly	++	++	++	++	++	++	++	+	++
Narrow thorax with short-rib	++	++	++	++	++	++	++	+	+
Hypoplasia of tibia	–	–	–	–	–	–	++	–	–
Flaring of the metaphyses	+	++	++	++	–	++	–	–	–
Irregularity of the metaphyses	unclear	+	+	+	+	+	–	+	–
Pointed metaphyses	unclear	–	–	–	++	–	–	–	–
Spondylar dysplasia	unclear	+	+	+	+	+	–	+	–
Hypoplasia of iliac bones	unclear	++	++	++	++	++	–	++	++
-Other organs									
Congenital heart defect	–	N/A	N/A	–	+	+	–	–	++
Renal abnormalities	–	N/A	N/A	+	+	+	+	+	–
Genital abnormalities	++	N/A	N/A	++	++	++	+	–	–

++ : prominent, + :present, – : absent, N/A: not applicable, This table is made based on findings of previous reports [3,4,10,11]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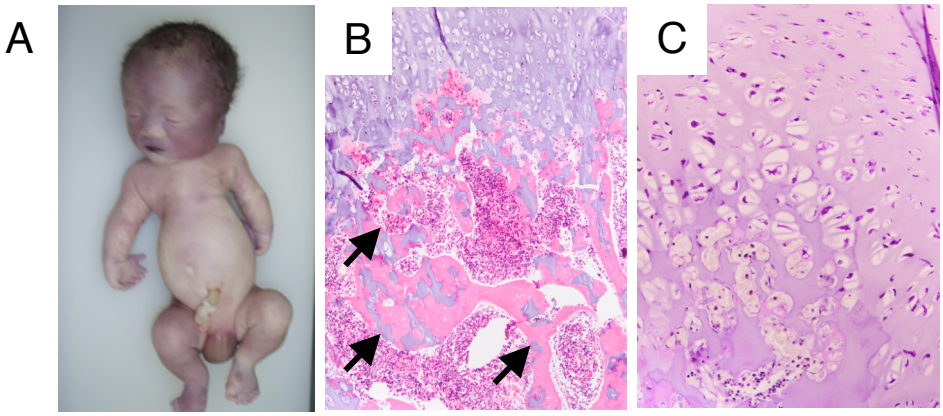
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