Prenatal diagnosis of pfeiffer syndrome type II using ultralow dose CT

Clinical History:
The patient was a G2P0 Japanese woman who conceived by a blastocyst transfer in a cryo-cycle. Amniocentesis at 20 weeks of gestation revealed a normal male karyotype of 46, XY. Fetal ultrasonography (USG) at 30 weeks showed a cloverleaf skull without significant shortening of long bones, and fetal craniosynostosis was suspected. Imaging Findings:

Fetal magnetic resonance imaging (MRI) at 31 weeks revealed a cloverleaf skull, hypoplasia of midface, proptosis, ankylosis of the elbows, and mild ventriculomegaly (Figure 1, 2). Fetal skeletal three-dimensional computed tomography (3D-CT) at 32 weeks of gestation revealed a cloverleaf skull, bilateral radio-ulnar-humeral synostoses, large distal phalanges of the bilateral great toes, and triangular hypoplastic proximal phalanges (Figure 3-5). The fetus was prenatally diagnosed with the Pfeiffer syndrome type II (PSII). The neonate delivered at 38 weeks of gestation exhibited a cloverleaf skull with closure of the anterior fontanel, proptosis, bilateral radio-ulnar-humeral synostoses, broad great toes, and triangular hypoplastic first proximal phalanges, and was clinically diagnosed with PSII (Figure 6-8).

Discussion:

A. Background
PSII is an autosomal dominant craniosynostosis syndrome caused by mutations in the FGFR2 gene, and causes characteristic craniofacial and skeletal anomalies such as a cloverleaf skull, extreme proptosis, synostoses of the elbows, broad thumbs and great toes, and triangular hypoplastic first proximal phalanges [1]. Prenatal diagnosis of PSII is essential for predicting the prognosis, performing neonatal care, and counselling the parents.

B. Clinical Perspective
The usefulness of USG and MRI was previously reported for the diagnosis of fetal PSII [2, 3]; however, it was not easy to distinguish PSII from other types of craniosynostosis because USG and MRI could not clearly image the fetal skeletal structure. Therefore, we conducted fetal 3D-CT, which could construct clear images of the fetal skeletal structure.

C. Imaging Perspective
The bilateral radio-ulnar-humeral synostoses, large distal phalanges of the bilateral great toes, and triangular
hypoplastic proximal phalanges (Fig. 2) were the key findings for the fetus to be diagnosed as PSII with 3D-CT. This fetal 3D-CT was conducted using the ultralow dose CT (ULDCT) protocol (64 MDCT; Discovery 750HD) and model-based iterative reconstruction (MBIR, VEO®, GE Healthcare). The detailed parameter settings were as follows: tube voltage, 100 kV; maximum tube current, 35 mA; volume computed tomography dose index CTDIvol, 0.51 mGy; dose length product (DLP), 18.25 mGycm; noise index, 54.0; An organ dose of the uterus was calculated to be 0.7 mSv using a software (CT–Expo). The CTDIvol in the present study was only 5% of the diagnostic reference level (DRL) obtained by a Japanese nationwide survey [4]. According to ICRP 84, this organ dose of the uterus was slightly less than the estimated fetal dose obtained using plain pelvic radiography (1.1 mSv) in a UK survey [5].

D. Outcome
The patient underwent counselling regarding the expected postnatal prognosis of the fetus and then underwent selective caesarean section owing to the cephalopelvic disproportion at 38 weeks of gestation, and gave birth to a 3,395 g male, who was clinically diagnosed with PSII. Genetic examination of the neonate revealed a W290C mutation in the FGFR2 gene, which was previously reported for the Pfeiffer syndrome [6].

E. Take Home Message, Teaching Points
The fetal 3D-CT conducted using ULDCT with MBIR was useful for evaluating the fetal skeletal structure to perform a precise diagnosis of the fetal PSII and counselling the parents. Although CT can be performed using a low radiation dose, the application criteria for CT should be considered carefully to avoid unnecessary radiation exposure.

**Differential Diagnosis List:** Pfeiffer syndrome type II, Pfeiffer syndrome type I, Pfeiffer syndrome type III, Muenke syndrome, Crouzon syndrome, Apert syndrome, Antley-Bixler syndrome

**Final Diagnosis:** Pfeiffer syndrome type II

**References:**
Description: Magnetic resonance imaging (half-Fourier acquisition single-shot turbo spin-echo) of the fetal head at 31 3/7 weeks of gestation. Coronal image shows a cloverleaf skull with temporal protrusion (arrows) and mild ventriculomegaly (asterisk). Origin: Miyazaki O, Department of Radiology, National Center for Child Health and Development, Tokyo, Japan.
Description: Sagittal image shows proptosis (arrowhead) and mild ventriculomegaly (asterisk). Origin: Miyazaki O, Department of Radiology, National Center for Child Health and Development, Tokyo, Japan.
Description: Three-dimensional computed tomography of the fetus at 32 3/7 weeks of gestation. Volume rendering of full skeletal image shows craniosynostosis, the large distal phalanx (arrowhead) of the left great toe, and bilateral radio-ulnar-humeral synostoses (arrows). Origin: Miyazaki O, Department of Radiology, National Center for Child Health and Development, Tokyo, Japan.
**Description:** Maximum intensity projection of the left upper extremity shows radio-ulnar-humeral synostosis (arrow). **Origin:** Miyazaki O, Department of Radiology, National Center for Child Health and Development, Tokyo, Japan.
Figure 5

Description: Maximum intensity projection image of the right foot also shows large distal phalanges (arrowhead) of the great toe and triangular hypoplastic first proximal phalanx (arrow), as well as volume rendering. Origin: Miyazaki O, Department of Radiology, National Center for Child Health and Development, Tokyo, Japan.
Figure 6

*Description:* Anterior?posterior view of the head shows a cloverleaf skull. *Origin:* Miyazaki O, Department of Radiology, National Center for Child Health and Development, Tokyo, Japan.
Description: Plain radiographs of the right upper extremity shows radio-ulnar-humeral synostosis (arrow). Origin: Miyazaki O, Department of Radiology, National Center for Child Health and Development, Tokyo, Japan.
Description: Plain radiograph of the feet shows broad great toes (arrowheads) and triangular hypoplastic first proximal phalanges (arrows) as well as fetal computed tomography images. Origin: Miyazaki O, Department of Radiology, National Center for Child Health and Development, Tokyo, Japan.