CASE REPORT

Prenatal Diagnosis of Achondroplasia with Ultrasound, Three-Dimensional Computed Tomography and Molecular Methods

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A 29-year-old female was transferred to our clinic because of short femurs (<2 percentile) on ultrasound scan. She had nonspecific medical and obstetrical history. The ultrasound scan at 32 weeks of gestational age revealed rhizomelic shortening of the extremities, frontal bossing and the over rounded metaphyseal-epiphyseal interface at the femur ends while connecting to diaphysis, also called "collar hoop" sign. A 3D helical computed tomography (3D-HCT) scan reported rhizomelic limbs, narrowing of the interpediculate distance of the lumbosacral spine, rounded iliac wings and bilateral "collar hoop" sign of the proximal femurs. All these findings led to diagnosis of achondroplasia, which was confirmed by DNA testing. A well, active male baby was born. Postnatal x-ray also confirmed antenatal findings of ultrasound and 3D-HCT.

Introduction

Achondroplasia is one of the best known and most common types of nonlethal skeletal chondrodysplasia1. The incidence is about one in 10,000 to 30,000 [1–5]. Before the relationship between fibroblast growth factor receptor III (FGFR3) gene and this disease was identified it was hard to differentiate between variant types of chondrodysplasias, such as metatropic dysplasia, Ellis-van Creveld syndrome, or diastrophic dysplasia [6,7]. Nowadays, because prenatal ultrasound examinations are routinely performed, more fetuses influenced by this disease are identified. The gold standard method of diagnosis is DNA testing for mutations of FGFR3 [1,2]. If family history is not present, early diagnosis is hard because of the late appearance of ultrasound
signs of this disease. We report a case of prenatal diagnosis of achondroplasia with ultrasound, three-dimensional helical computed tomography (3D-HCT) and genetic testing.

Case

A 29-year-old female, gravida 2 para 0, was transferred to our clinic for further examination because of short femurs (<2 percentile) seen on ultrasound examination. This woman had unremarkable medical and obstetrical history. She had regular antenatal examinations at our hospital branch and the fetus had normal growth pattern before 24 weeks of gestational age. The ultrasound scan at 32 weeks of gestational age revealed rhizomelic shortening of the extremities (Fig. 1), frontal bossing and the over rounded metaphyseal-epiphyseal interface at the femur ends with wide angle 143.55° while connecting to diaphysis (Fig. 2). This also called "collar hoop" sign. After 6 days, 3D-HCT scan was done, which also revealed rhizomelic limbs, narrowing of the interpediculate distance of the lumbo-sacral spine, rounded iliac wings and bilateral "collar hoop" sign of the proximal femurs (Fig. 3). All these findings led to the diagnosis of achondroplasia, which was confirmed because heterozygote mutation in Exon 8 of fibroblast growth factor receptor III (FGFR3) was found in genetic molecular testing of amniotic fluid (Fig. 4). After counseling, patient and her husband chose to keep pregnancy. A well, active male baby was born by elective cesarean section. Postnatal radiograph was also compatible with antenatal findings of ultrasound and 3D-HCT (Fig. 5).

Fig. 1 Two-dimensional ultrasound at 32 weeks’ gestation revealed rhizomelic shortening of the extremities. Femur length (FL) = 4.85 cm; about 26 weeks’ gestation.

Fig. 2 Two-dimensional ultrasound at 32 weeks’ gestation reported an over-rounded metaphyseal-epiphyseal interface at the femur ends with wide angle 143.55° while connecting to diaphysis. This also called "collar hoop" sign.

Fig. 3 Three-dimensional helical computed tomography scan at near 33 weeks’ gestation revealed (A) rhizomelic limbs, rounded iliac wings (arrowhead) and (B) bilateral "collar hoop" sign of the proximal femurs (arrowhead).
Discussion

Nowadays, achondroplasia is suspected only after the third trimester due to the late appearance of this disease [2]. These fetuses almost always have a long bone below the third percentile for gestational age but normal size of head and abdominal circumference [2,8–10]. Conventional 2D ultrasound alone is extremely challenging for diagnosing achondroplasia. Several case series reports have speculated that the accurate diagnosis rate ranges from 30% to 70% [11–13]. Boulet et al identified a new prenatal ultrasound finding of “collar hoop” sign at the proximal end of the femur in fetuses with achondroplasia. All five "collar hoop" cases had translucent metaphysis; four cases had wide metaphyseal-diaphyseal angle and the other case was not measured. They concluded that a normal type of metaphysis can rule out achondroplasia. These new specific signs in 2D ultrasound seemed to improve the prenatal diagnosis of achondroplasia [14]. Our case had similar ultrasound findings. However, more cases are still needed to prove the specificity of these signs.

Because there is no radiation concern of exposure, fetal magnetic resonance imaging has gained popularity in prenatal diagnosis. As the bones are of intermediate signal intensity in T2 weighted imaging, they can be hard to evaluate precisely. Moreover, fetal motion and resulting off-axis imaging usually limit the utility of MRI in the diagnosis of skeletal dysplasia [15]. On the other hand, there are several reports on the usefulness of 3D-HCT in the diagnosis of skeletal dysplasia in spite of fetal radiation exposure risk. 3D-HCT can give images based on X-ray attenuation without superposition of the maternal skeleton. Additionally, the dose of fetal exposure to radioactivity is similar to that of conventional fetal radiological examination (3 mGy) [16–18]. Ruano et al reported that 3D-HCT and 3D-ultrasound were more reliable than 2D ultrasound in prenatal diagnosis of skeletal dysplasia [16]. Compared to 3D-ultrasound, 3D-HCT can identify more characteristic findings because it is not dependent on amniotic fluid volume, maternal obesity, or fetal position [19]. According to Cassart et al, 3D-HCT had better diagnostic yield than in 2D ultrasound in vertebral anomalies and pelvic bone malformations [16]. In our case, 3D-HCT showed obvious ultrasound findings of "collar hoop" sign at the proximal end of the femur, short limbs, small round iliac wings and narrowing of interpedicular distance between vertebral bodies. Due to increased pelvic tilt, lumbar lordosis was also found. According to these findings, we can certainly exclude other types of chondrodysplasias. The postnatal radiograph also confirmed these findings.

Achondroplasia belongs to an autosomal-dominant disease and most affected individuals are born from normal parents who do not carry an FGFR3 mutation. It cannot be denied that prenatal molecular diagnosis of achondroplasia is the standard method [1,2]. The current case reports that combined use of conventional ultrasound...
and 3D-HCT can also be effective in prenatal diagnosis of achondroplasia. While the uneven rounded femoral metaphyses are noted on the traditional ultrasound and 3D-HCT can be used to detect other systemic symptoms in the next examination. Then, if molecular methods are available, it can be used as final confirmation. Some experts speculate that 3D-HCT is not necessary in prenatal diagnosis of achondroplasia, because some new signs in 2D ultrasound such as “collar hoop” combined with the genetic test can give a precise diagnosis [14]. However, using conventional 2D ultrasound to detect “collar hoop” sign is experience dependent. With the help of 3D-HCT, all characteristics of achondopasia can be recognized prenatally, as with a postnatal radiograph, so the development of a confirmatory molecular genetic method is not too urgent.

In conclusion, we speculate that 2D ultrasound, 3D–HCT, and final molecular diagnosis can reliably diagnose achondroplasia. Fetal 3D helical CT can provide good image of systemic signs of skeletal dysplasia. We still need more cases to prove the well efficiency of these three combined methods.

References