

Halil ASLAN
Volkan ÜLKER
Necla ÜLKER
Neslihan YEREBASMAZ
Cemal ARK

Prenatal Diagnosis of Thanatophoric Dysplasia in Second Trimester*

Department of Perinatology, SSK Bakırköy
Maternity and Children Hospital, İstanbul,
Turkey

Received: October 22, 2001

Key Words: Prenatal diagnosis, thanatophoric
dysplasia

Thanatophoric dysplasia (TD) is the most common type of lethal skeletal dysplasia in fetuses and neonates. It is characterized by extreme rhizomelia, a normal trunk length with a narrow chest and a large head with a prominent forehead. It occurs in 0.24-0.69/10 000 births. Mutations in the fibroblast growth factor receptor 3 (FBGFR3) gene, on the short arm of chromosome 4, have been described in cases of TD (1). TD can be detected by ultrasonography but other skeletal system anomalies such as osteogenesis imperfecta, achondrogenesis and achondroplasia should be taken into consideration for the differential diagnosis (2).

TD has two subtypes. Type I is characterized by short curved femurs and wider bones and is rarely combined with cloverleaf skull. Type II has straight femurs, wider bones and is nearly always associated with cloverleaf skull deformity (3). Prenatal sonographic findings depend upon the specific variety.

Case Report

The patient was a 18-year-old G2P1 woman who was referred at 19 weeks' gestation because of polyhydramnios. In her first pregnancy she had delivered a baby with Chiari type II malformation complicated with occipital encephalocele. Ultrasonographic examination of the patient showed a narrow chest with short ribs, a protuberent abdomen (Fig. 1), short and curved femora and platyspondyly. Biparietal diameter was 44.7 mm. No other anomalies were detected.

According to these findings, the diagnosis of TD was made. The family were informed about the grave

prognosis and the pregnancy was terminated. The patient delivered a male fetus weighing 750 g with severe micromelia, a protuberent abdomen and a narrow chest. X-ray examination revealed macrocephaly, platyspondyly and short and curved ribs. All tubular bones were short and curved (Fig. 2). Autopsy showed midface hypoplasia, prominent nose, low-set ears and a large mouth. Limbs were short and bowed.

TD is a common, lethal condition due to mutations in the fibroblast growth factor receptor 3 (FBGFR3) gene. Mutations in the FBGFR3 gene that cause two subtypes of this disorder, type I and type II, have recently been identified. This discovery has now made it possible to make a definite diagnosis of TD by molecular methods. To date, prenatal diagnosis of TD has been accomplished by ultrasonography in the second trimester. The majority of cases of TD are sporadic although some familial cases of type II have been reported.

Sonographic findings depend on the specific type of the disease. Polyhydramnios beginning in the second trimester is usual (4). Screening of extremities for skeletal system anomalies should be done carefully. In our case the typical bowed "telephone receiver" femurs were present and the length of the femurs was under the 3rd percentile. However, it is not always possible to distinguish TD fetuses *in utero* from the other osteochondrodysplasias by ultrasonography or radiography. Chondroectodermal dysplasia, asphyxiating thoracic dysplasia, short rib-polydactyly syndrome and homozygous achondroplasia should be considered in the differential diagnosis. If type II is suspected, conditions that have an association with craniosynostosis and

*This case was presented at the 4th Turkish-German Gynecology Society Congress in May 2001, Antalya-Turkey



Figure 1. Sonography of the fetal thorax. Note the narrow chest compared to the protuberent abdomen.



Figure 2. Radiogram. Note the platyspondyly, and short ribs, short and curved femurs.

cloverleaf skull should be excluded. Horseshoe kidney, hydronephrosis, atrial septal defect, defective tricuspid valve, imperforate anus and radioulnar synostosis may be associated with TD (5). In our case no associated anomalies were detected.

TD is a uniformly lethal disorder, although survival of several months has been reported in some isolated cases (6). An eight-year-old male patient having a mutation in the FGFR3 gene has been reported. All of the assays of his serum and urinary bone formation- or resorption-related substances were within normal limits for his age (7). Early diagnosis of TD is important since it gives an alternative option of termination of pregnancy when an affected fetus is detected. However, genetic counseling

and evaluation of the prognosis on the basis of molecular results should be considered an important issue, because mutations that are generally associated with extremely different diseases have been recorded in the same phenotype (8).

Correspondence author:

Halil ASLAN

Defne 02 Daire 17

Bahçeşehir

İstanbul-Turkey

E mail: aa5712310@isbank.net.tr

References

1. Mesoraca A, Pilu G, Perolo A et al. Ultrasound and molecular midtrimester diagnosis of a de novo achondroplasia. *Prenat Diagn* 16:764-768, 1996.
2. Fink IJ, Filly RA, Callen PW, Golbus MS. Sonographic diagnosis of thanatophoric dwarfism in utero. *J Ultrasound Med* 1:337-339, 1982.
3. Nerlich AG, Freisinger P, Bonaventure J. Radiological and histological variants of thanatophoric dysplasia are associated with common mutations in FGFR-3. *Am J Med Genet* 63:155-159, 1996.
4. Elejalde BR, Elejalde MM. Thanatophoric dysplasia: fetal manifestations and prenatal diagnosis. *Am J Med Genet* 22: 669-683, 1985.
5. De Biasio P, Prefumo F, Baffico M, Baldi M et al. Sonographic and molecular diagnosis of thanatophoric dysplasia type I at 18 weeks of gestation. *Prenat Diagn* 20: 835-7, 2000.
6. Baker KM, Olson DS, Harding CO, Pauli RM. Long-term survival in typical thanatophoric dysplasia type I. *Am J Med Genet* 70: 427-429, 1997.
7. Kuna T, Fujita I, Miyazaki S, Katsumata N. Markers for bone metabolism in a long-lived case of thanatophoric dysplasia. *Endocr J* 47: 41-4, 2000.
8. Camera G, Baldi M, Strisciuglio G, Concolino D et al. Occurrence of thanatophoric dysplasia type I (R248C) and hypochondroplasia (N540K) mutations in two patients with achondroplasia phenotype. *Am J Med Genet* 104: 277-281, 2001.