

Thanatophoric Dysplasia; a Rare Case Report on a Congenital Anomaly

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Abstract

The rare form of skeletal dysplasia is thanatophoric dysplasia. The meaning for thanatophoric dysplasia is death bearing which is derived from Greek word. It occurs 1 in 20,000 to 50,000. It is mainly due to mutations in the fibroblast growth factor receptor 3 gene. Features of thanatophoric dysplasia are frontal bossing, prominent eyes, narrow thorax, protruded abdomen and bowed legs. The knowledge about this condition is useful in the fields of Anatomy, Paediatrics, Obstetrics and Gynaecology, Ultrasonography and Genetics, for future research purpose.

Key Words: Cloverleaf skull, Dysplasia, FGFR3, Thanatophoric.

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1- INTRODUCTION

Skeletal dysplasia's also known as Osteochondrodysplasias or Skeletal dysplasias, are a large heterogeneous group of disorders comprising of abnormalities of bone or cartilage development or texture. They occur due to genetic mutations and their phenotype continues to evolve throughout life. Skeletal dysplasias are malformations of single or multiple bones in combination, that are due to abnormal blastogenesis in-utero and phenotypically remain static throughout life (1). Presently, there are around 450 well-characterized skeletal dysplasias that are classified based on the clinical, radiographic, and molecular criteria (2). The most common form of lethal skeletal dysplasia is osteogenesis imperfecta type II. The second next rare lethal skeletal dysplasia is Thanatophoric dysplasia (TD). The meaning for thanatophoric dysplasia is 'death bearing', which is derived from a Greek word. The first person to describe thanatophoric dysplasia was Maroteaux and Lamy in 1967 (3). It occurs 1 in 20,000 to 50,000 (4), due to mutations in the fibroblast growth factor receptor 3 gene (FGFR3). Features seen in thanatophoric dysplasia are curved femur, protruded abdomen, narrow chest, and micromelia, clover leaf skull and mild skeletal dysplasia (5). The knowledge about this condition will be useful for paediatricians, obstetricians

sonologists and geneticists in their clinical practice.

2- CASE REPORT

A 26-year old healthy, first degree consanguineously married woman with history of one previous lower segment caesarean section (LSCS) with normal, healthy baby was brought to the hospital at 26 weeks of gestation for antenatal evaluation. Ultrasound examination (**Figure.1**) showed a single live male foetus with adequate amniotic fluid. The morphometric sonographic measurements observed (**Table.1**). The limb bones also exhibited features of dwarfism. The other features seen were narrowed thoracic cavity relative to the abdominal circumference and clover leaf skull. These features were consistent with the diagnosis of thanatophoric dysplasia. A medical termination of pregnancy was performed the day following an ultrasonographic examination. On examination, the male foetus (**Figure.2**), was weighing 650 grams and was small in length for gestational age, also showed features of macrocephaly, frontal bossing, clover leaf skull, short extremities corresponding to gestational age of 15 weeks. The femur measured to 21mm. The hands and feet appeared normal and no features of brachydactyly was seen. The foetus showed thoracic cage proportionate to the abdomen. All features were consistent with thanatophoric dysplasia, type-II.



Fig.1: Ultrasound scan picture of foetus showing thanatophoric dysplasia.

Table-1: Ultrasound parameters of the foetus

Fetal Maturity	Measurement (MM)	Corresponding to Weeks/Days
BPD	63	25/5
HC	234	25/3
AC	170	22/0
Femur	19	15/6
Foot	38	-
EFW	334gms ± 33gms	-

BPD: Biparietal diameter; Hc: Head circumference; Ac: Abdominal circumference; Efw: Estimated fetal weight.



Fig.2: Foetus showing shortening of limbs, clover leaf skull and macrocephaly.

4- DISCUSSION

Thanatophoric dysplasia is one form of lethal osteochondrodysplasia which occurs sporadically as a result of new autosomal dominant mutation affecting FGFR3 gene (6, 7). The FGFR3 gene is located on the short (p) arm of chromosome 4 at position 16.3. More precisely, the FGFR3 gene is located from base pair 1,793,299 to base pair 1,808,872 on chromosome 4. At least 10 FGFR3 gene mutations have been found to cause type I thanatophoric dysplasia. Most of these mutations change

a single amino acid in the FGFR3 protein. The most common mutation substitutes the amino acid cysteine for the amino acid arginine at protein position 248. Only one mutation has been shown to cause type II thanatophoric dysplasia. It replaces the amino acid lysine with the amino acid glutamic acid at position 650 of the FGFR3 protein. The genetic changes responsible for both types of thanatophoric dysplasia are due to over activation in FGFR3 gene which leads to the severe

problems with bone growth that occur in this condition. Thanatophoric dysplasia is characterized by severe limb shortening, bowing of limbs, narrow thorax, protuberant abdomen, polyhydramnios, large head, frontal bossing, clover leaf skull (**Figure.3**), prominent eyes, hypertelorism, small pelvis and a depressed nasal bridge (8-10). Abnormalities of the head include megacephaly, occasionally with clover leaf shape skull known as kleeblattschädel (11). The skin appears thick due to extreme redundancy and may prevent normal movement and positioning of limbs causing them to be oriented at right angles to the body. The spine characteristically shows platyspondyly and with H or U shaped configuration of the vertebrae on anteroposterior film due to normal size pedicles of the flattened vertebrae.

Thanatophoric dysplasia is classified into two types, Type I and Type II:

- Type –I, is more common and is characterized by curved long bones

and severe platyspondyly usually with or without a cloverleaf skull.

- In Type-II, the long bones are relatively straight the platyspondyly is less severe and clover leaf skull is usually present.

In both the types, there are thickening of nuchal translucency in the first trimester, ventriculomegaly, agenesis of corpus callosum cardiac defects and hydronephrosis. It is always lethal (12), mainly due to the severe pulmonary and thoracic hypoplasia (13, 14). Both types are due to de novo mutations and the recurrence risk is very low (15). The diagnosis is usually done in second trimester by antenatal ultrasound examination and confirmed by molecular analysis on aminocytes. Three dimensional ultrasound has an important role in the descriptions of the fetal morphology, the structure of the fetal bones and the cranial sutures (16). It was reported that with modern day obstetric care full term thanatophoric dysplasia is less commonly seen.



Fig.3: Ultrasound scan picture of foetus showing clover leaf skull.

5- CONCLUSION

Proper counselling is a part of the management in this condition, especially to parents who have had affected children and should be advised to undergo thorough

foetal screening during subsequent pregnancies.

6- CONFLICT OF INTEREST: None.

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