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THANATOPHORIC DYSPLASIA; LETHAL SKELETAL DYSPLASIA - A CASE REPORT

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ABSTRACT
The common types of skeletal dysplasia include thanatophoric dysplasia (TD), achondrogenesis (ACH), and osteogenesis imperfecta (OI) type II. An accurate diagnosis of a specific skeletal dysplasia is challenging due to its rarity, the variety of the causative genes and the spectrum of pathogenesis. However, recognizing the accurate clinical condition by prenatal sonography is crucial for proper genetic counselling and reproductive decision.

KEYWORDS: Thanatophoric dysplasia (TD), achondrogenesis (ACH), osteogenesis imperfecta (OI), ultrasonography.

INTRODUCTION

Skeletal dysplasias are heritable connective tissue disorders affecting bone growth resulting in abnormal shape and size of the skeleton. They represent a heterogeneous group of genetic disorders with more than 200 different entities being delineated to date. Thanatophoric dysplasia is one of the rare, lethal bone dysplasia.[1] The term "thanatophorus" was first described by Maroteux derived from Greek word which means death bringing. Thanatophoric dysplasia (TD) is caused due to mutation of fibroblast growth factor receptor 3-gene (FGFR3)4, which is located on the short arm of chromosome 4. The mutation results in the activation of FGFR3 tyrosine kinase, which results in decreased apoptosis and increased proliferation. It has been reported that hypochondroplasia, achondroplasia and thanatophoric dysplasia represents different types of mutation in FGFR3 with hypochondroplasia being the mildest and TD, the most severe form. Characteristics of TD include severe shortening of the limbs, a narrow thorax with protuberant abdomen, macrocephaly and a normal trunk length.[2] The diagnosis is usually made with ultrasonography in second trimester during anomaly scan. In this study, we report a case of this rare entity diagnosed antenatally on routine prenatal ultrasound screening, with emphasis on its characteristic anatomical abnormalities and relevant review of literature.

CASE REPORT

A G3P2L2, 28 years old healthy, non-consanguineously married women with previous two normal vaginal deliveries reported to the hospital at 19 weeks 2 days period of gestation for routine antenatal care. Her previous two pregnancies were uneventful and resulted in healthy, live babies at term. The pregnancy was reported uneventful. There was no history of excessive vomiting, fever, rashes, spotting or bleeding per vaginum, drug intake or radiation exposure during this pregnancy. At the time of presentation, her general systemic examination was normal. On Per abdomen examination, fundal height was corresponding with period of gestation. Single live intrauterine fetus seen on ultrasonography with biparietal diameter of 3.2 cm corresponds to 16 weeks POG, head circumference of 14.6 cm which is about 17+5 weeks of POG, abdominal circumference of 12 cm corresponding to 18 weeks of POG, humerus length was 2.2cm, femur length 2.5 cm corresponding to16 week. Thoracic diameter anteroposterior at the level of heart was 12cm and transverse 2.6 cm. There was bilateral bowing of humerus and femur which was shortened was showing telephone handle appearance.

Based on these findings, a diagnosis of skeletal dysplasia was made, most probable being thanatophoric dysplasia (TD-1).

The parents were counselled regarding the fetal prognosis and a medical termination of pregnancy was planned and performed at 19+5 weeks period of gestation with their consent. Following termination on examination, the fetus weighed 180 grams. Skull with head circumference about 15 cm, measured at the level of the fetus eyebrows, upper limbs measured 4.5 cm (2.5 cm + 2 cm) and lower limbs measured 6 cm (2.5 cm +3.5 cm) . Chest circumference was 10 cm and abdominal circumference 14 cm.

There was facial hypoplasia with depressed nasal bridge, and low set ears. There was bowing of both the upper and lower limbs. Thorax was narrow and small and abdomen appeared protuberant in comparison with the chest which was narrow.

Post abortion radiograph showed short humerus, femur, forearm bones and tibiae with metaphyseal flaring, the thoracic cage was narrow, ribs were short, spine was normal.

With coarse facial features and skeletal abnormalities both on gross evaluation and on radiograph, the diagnosis of thanatophoric dysplasia type 1 was made.

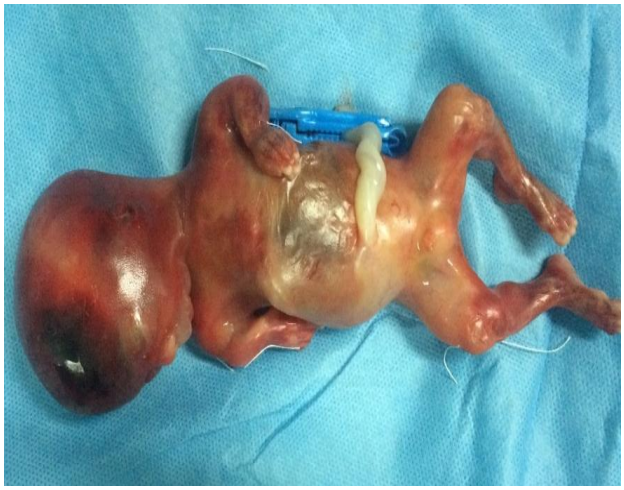

Fig. 1:

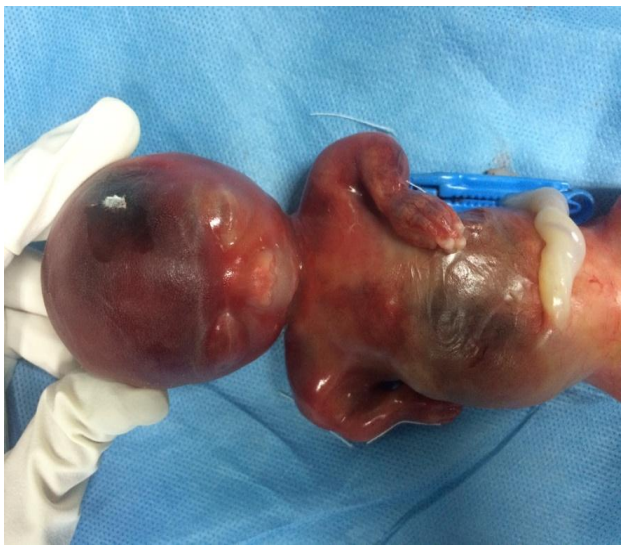

Fig. 2:

Fig. 1 & 2: Thanatophoric dysplasia: long bones with shortening and bowing, narrow thoracic cage, protuberant abdomen, mid face hypoplasia, depressed nasal bridge, and low set ears.

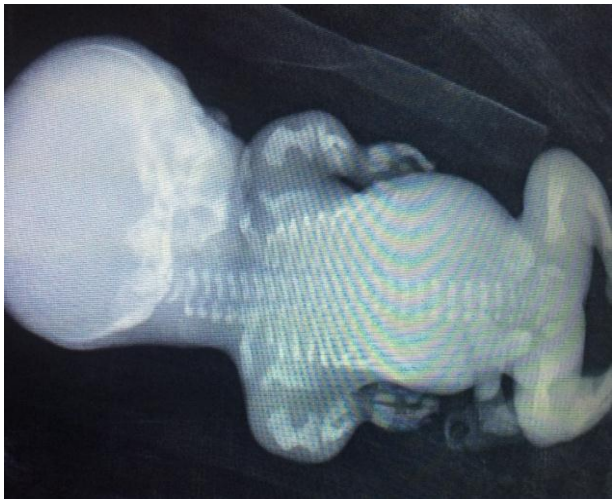

Fig. 3: Radiograph showing short and bowed limbs with metaphyseal flaring, macrocephaly, thoracic cage is narrow with short ribs.

DISCUSSION

Thanatophoric dysplasia is a congenital, sporadic and usually lethal skeletal dysplasia. It is characterized by severe limb shortening, bowing of limbs, narrow thorax and protuberant abdomen.[3] Other features include large head with frontal bossing, clover leaf skull, prominent eyes, hypertelorism and depressed nasal bridge.

TD has a reported incidence of 1 in 20,000 to 50,000 live births.[4] As it has autosomal dominant inheritance so both sexes are equally affected. It does not have any racial or ethnic predisposition. It is considered to be caused by de novo autosomal dominant mutation.[5] in fibroblast growth factors receptor 3 gene (FGFR-3), which has been mapped to chromosome band 4p16.3 and regulates development and maintenance of bone and brain tissue. Mutation in this gene causes the FGFR3 protein to be overly active, which leads to the severe disturbances in bone growth characteristic of thanatophoric dysplasia.[6] It has been recently proposed that mutated FGFR3 induces premature proliferative cells and their differentiation into pre hypertrophic chondrocytes leading to defective long bone growth.[7]

There are two recognized subtypes of thanatophoric dysplasia (TD) which can be differentiated by the skull shape and femur morphology.[8]

- Type 1(80%) – more common, characterized by curved and short femur which is in a telephone receiver like configuration and no cloverleaf shaped skull. The abdomen appears protuberant while the chest is narrow and small
- Type 2 (20%) – the presence of cloverleaf skull is distinctive feature. Limb shortening is milder and bones are not bent.

Other features common to both TD include small narrow thorax with horizontally placed short ribs, macrocephaly, large anterior fontanelle, a small foramen magnum, distinctive facial features (frontal bossing, low nasal

bridge, flat faces), severe platyspondyly (flattened bones of the spine), marked shortening and bowing of long bones, brachydactly (short broad tubular bones in hands and feet), redundant skin folds along the limbs etc.

As the name thanatophoric meaning 'death bearing' suggests, the condition is lethal in utero or shortly after birth, therefore, correct diagnosis is imperative for proper genetic counselling and prognostication. Early diagnosis can be made by second trimester ultrasonography. Prenatal diagnosis can be confirmed by molecular analysis of the targeted mutation in FGFR3 gene from fetal cell obtained by amniocentesis or chorionic villous sampling. Chromosomal analysis is not very cost effective and the condition is always lethal.

Most of the fetuses die in utero, so the condition does not pass into the next generation and thus the occurrence is sporadic. Recurrence risk is not increased over that of the general population as the mutation is de novo. The cause of death is respiratory insufficiency secondary to narrow chest cavity and hypoplastic lungs or brain stem compression due to narrow foramen magnum.

Postnatal autopsy of the affected fetus shows disorganized chondrocytes and poor cellular proliferation. In our case autopsy to confirm the diagnosis by histopathology could not be done as consent was not given by the parents.

The counseling of the affected parents is crucial in this disease, they should be explained that though the affected pregnancy needs termination but further pregnancy not necessarily will get affected with the disease. Since the majority of cases of TD occur sporadically, the recurrence risk is low and is estimated as only 2%. The extended family members of the proband are not at increased risk. Prenatal diagnosis of TD has been well established with ultrasound examination usually in the second trimester and should be offered in subsequent pregnancies. If indicated, amniocentesis may be offered and the diagnosis may be done by molecular analysis.

Early diagnosis of TD is important as it gives an option of termination of pregnancy when an affected fetus is detected. Differential diagnosis of TD includes homozygous achondroplasia (both parents suffer from the achondroplasia), achondrogenesis (extreme hypomineralization of bone, most marked in the calvarium and vertebral bodies, shortened trunk length), campomelic dwarfism (bowing and angulation of long bones with immature ossification), rhizomelic chondrodysplasia punctata (rhizomelic micromelia with characteristic stippling radiologically and punctuate calcification in cartilage), severe hypophosphatasia and severe osteogenesis imperfect (generalized hypo mineralization of bones with multiple bone fractures). The presence of a characteristic cloverleaf skull with telephone receiver appearance of humerus and femur with platyspondyly, small conical thorax and a very high mortality differentiates TD from the other causes of severe short stature with micromelia.

CONCLUSION

Thanatophoric dysplasia is a rare congenital, sporadic and the most lethal skeletal dysplasia. The diagnosis can be made on ultrasonography by the presence of macrocephaly, wide fontanelles, micromelia and telephone receiver like femur with narrow thoracic cavity and protuberant abdomen. Confirmation in utero can be done by molecular and genetic testing and after birth by clinical features and autopsy. Since the affected fetuses die in utero, the disease never passes off to the next generation.

REFERENCES

1. Orioli I, Castilla EE, Barbosa-Neto JG. The birth prevalence rates for the skeletal dysplasias. J Med Genet, 1986; 23: 328-32.
2. Martínez-Frías ML, Ramos-Arroyo MA, Salvador J. Thanatophoric dysplasia: An autosomal dominant condition? Am J Med Genet, 1988; 31: 815-20.
3. Fink IJ, Filly RA, Callen PW, Fiske CC. Sonographic diagnosis of thanatophoric dwarfim in utero. J Ultrasound Med, 1982; 1(8): 337-9.
4. Lam AC, Lam YY, Tong TM, Chan DK, Lau WL, Ng DKK, et al. Thnatophoric dysplasia type 1 (TD1) without "telephone receivers". HK J Paediatr, 2006; 11: 320-3.
5. Kocherla K, Kocherla V. Antenatal diagnosis of Thanatophoric Dysplasia: a case report and review of literature. Int J Res Med Sci., 2014; 2(3): 1176-9.
6. van Ravenswaaij-Arts CM, Losekoot M. From gene to disease; achondroplasia and other skeletal dysplasias due to an activating mutation in the fibroblast growth factor. Ned Tijdschr Geneeskd, 2001; 145(22): 1056-9.
7. Legeai-Mallet L, Benoist-Lasselin C, Munnich A, Bonaventure J. Over expression of FGFR3, Stat1, Stat5 and p21Cip1 correlates with phenotypic severity and defective differentiation in FGFR3-related chondrodysplasias. Bone, 2004; 34: 26-36.
8. Tirumalasetti N. Case report of Thanatophoric dysplasia: A lethal skeletal dysplasia. J NTR Univ Health Sci., 2013; 2: 275-7.