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Case Report

Thanatophoric dysplasia Type 1: A rare case of recurrence

Pawan Ghanghoriya[1], Vineeta Ghanghoriya[2], Kavita N Singh[2], Richa Pahariya[2]

[1]Department of Pediatrics, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India, [2]Department of Obstetrics and Gynecology, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India

ABSTRACT

Thanatophoric dysplasia (TD) is the most common form of lethal dysplasias. The prevalence is low 1/20000-1/40000. Newborns with TD died within the neonatal period. Early diagnosis is of prime importance to terminate the pregnancy in time. Recurrence of TD is not reported, but the possibility is always there.

Keywords: Early antenatal diagnosis, recurrence, thanatophoric dysplasia

INTRODUCTION

Thanatophoric dwarfism literally means death seeking dwarf. This is the most common form of lethal bone dysplasia but rare. It is characterized by macrocephaly, narrow bell-shaped thorax, shortened ribs, and severe shortening of long bones.[1] Thanatophoric dysplasia (TD) occurs in approximately 1/20,000-1/40,000 births.[2] Here, we are reporting a case in which a couple has two babies with TD.

CASE REPORT

A 29-year-old third gravida reported to the Department of Obstetrics and Gynecology Netaji Subhash Chandra Bose Medical College at 22 weeks of gestation. Mother was of average built. There was no history of consanguineous marriage. Husband's age was 33 years. According to the history given by the mother first issue was a full term female delivered vaginaly. Baby had short limbs and long narrow thorax and died of the respiratory problem immediately. No record of a first pregnancy was available with the patient. 2nd baby was preterm female baby delivered with large head size and normal extremities who also died immediately.

She conceived again after ovulation induction. During third pregnancy, ultrasonography (USG) report had shown single live fetus of 20 weeks 3 days of gestational age with extremely short extremities with typical bowing of the femur and a narrow thorax. The head and abdomen appear relatively large. As the patient was not eligible for MTP, pregnancy was continued, and she delivered full term male baby. At birth, baby was limp and respiratory efforts were poor. Baby was resuscitated and died on the 2nd postnatal day. On musculoskeletal examination, baby had large head, wide fontanels, long trunk with narrow chest, short extremities, and short fingers (Figures 1 and 2). Genetic studies were not available at the center, and parents refused to get it done due to unaffordability.

DISCUSSION

TD is caused by a mutation in FGFR3 gene, which is located on 4p16.3.[2,3] This gene makes a protein that is involved in the development and maintenance of bone and brain tissue.

TD is characterized by extremely short limbs, long narrow trunk, large head with bulging forehead, prominent eyes, flat nose bridge, wide fontanels, and occasionally cloverleaf skull deformity.[1] Central nervous system abnormalities are temporal lobe dysplasia, hydrocephalus, megalencephaly, brainstem hypoplasia. Temporal lobe malformation includes temporal lobe enlargement, deep transverse sulci across the inferomedial temporal surface, and hippocampal dysplasia.[4-6] Radiological features are a short femur, flared at metaphases, with a medial spike. Other long bones are also short. The calvarium is large with a short base and small foramen magnum. Vertebrae are

Corresponding Author:
Dr. Pawan Ghanghoriya, Department of Pediatrics, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India.
E-mail: docpawanvineeta06@gmail.com

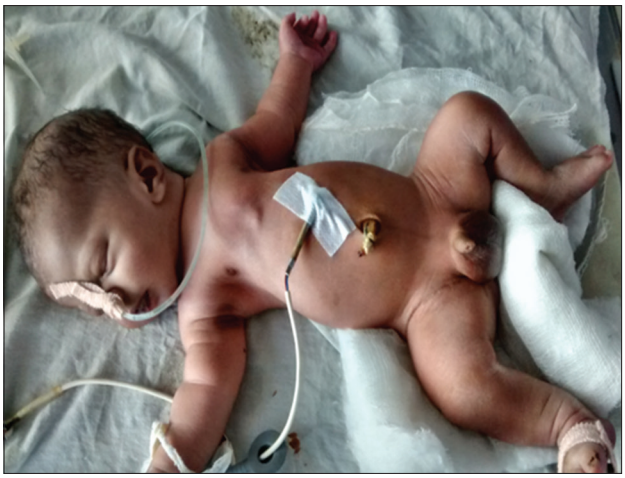

Figure 1: Small extremities, long and narrow thorax, large head, and bulging forehead

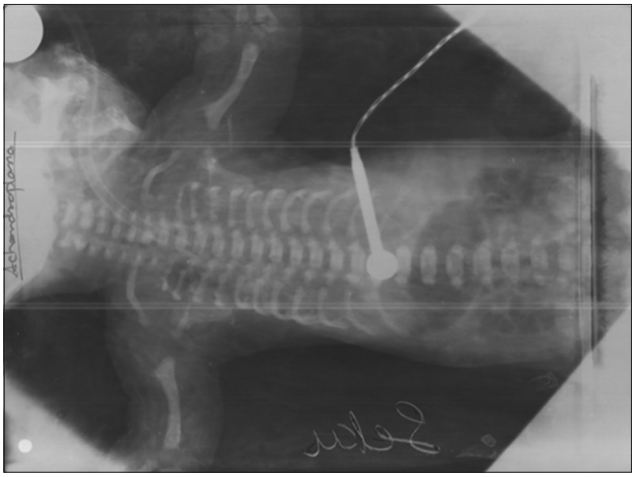

Figure 2: Curved and short humerus, short and curved ribs

flat with notching of superior and inferior aspect on lateral views. Lumbar vertebrae have an inverted U appearance on anteroposterior views. Ribs are short, cupped, and splayed.[5,7]

Two subtypes of TD are recognized. Type 1 is characterized by the curved short femur and very flat vertebral bodies (35% or less of adjacent disk space in lumber region) and Type 2 by the straight femur and cloverleaf skull.[8] TD Type I may present with cloverleaf skull, but it never reaches the strikingly trilobed configuration, histologically, TD Type 2 shows the presence of ossified cartilage canals in the physes of appendicular bones.[9]

Other skeletal dysplasia having similar abnormal features on ultrasound is campomelic dysplasia, achondrogenesis Type 1A, perinatal hypophosphatasia, and severe form of osteogenesis imperfect.[7,10,11]

Osteogenesis imperfect type II is characterized by short, broad, and "telescoped" or "crumped" femur. There is minimal calvarial mineralization. The ribs are short, thin, and wavy with beading due to callus formation. Campomelic dysplasia is characterized by short, bowed, and angulated femur. Calvarium is better ossified. Ribs are thin, wavy, and only 11 pairs are there. Perinatal hypophosphatasia is characterized by short deform bones and under mineralization of the entire skeleton. Achondrogenesis is characterized by extremely short long bones with square, globular or triangular shapes and medial spikes in the metaphyses of the femur. Ribs are short with multiple fractures and callus.[7,10,11]

After a neonatal period, the closest differential diagnosis is achondroplasia. Achondroplasia is characterized by longer limbs, trident fingers, long bones are straight, and metaphyseal abnormalities are less marked. Neonatal deaths are uncommon.[7,10,11]

TD is virtually always lethal in the neonatal period, but survival beyond 9 years of age has been reported.[12] Surviving neonate is almost always ventilator-dependent and mentally deficient.[12] Cause of death is respiratory insufficiency that occurs shortly after birth. Respiratory insufficiency may be secondary to a small chest cavity and lung hypoplasia, compression of brain stem by narrow foramen magnum, or a combination.[9,11,13]

TD is inherited as dominant mutation, but some authors also suggested polygenic inheritance and recessive inheritance.[1,14,15] Risk of recurrence for parents who have had one affected child is not significantly increased over that of the general population. A general empiric recurrence risk for this entity was estimated at only 2%.[3]

Proper genetic counseling is important for families having had a fetus or baby with TD regarding further pregnancy. To relieve parental anxiety in a couple, prenatal diagnosis may be offered in subsequent pregnancies.[13] The second trimester diagnosis by ultrasound to identify features suggestive of TD, such as macrocephaly, vertebral ossification defect, bowed femori, micromelia, and small thorax with protuberant abdomen is crucial, because it gave an alternative option of pregnancy termination when the affected fetus was discovered.[16] 3-D sonography is better than conventional USG.[17] Confirmation can be done by analysis of DNA (FGFR3 sequences) extracted from fetal cells obtained by amniocentesis (15-18 weeks gestation) or chorionic villi sampling (10-12 weeks gestation). Next generation sequencing is useful and noninvasive to the fetus. In this cell-free fetal, DNA in maternal blood is analyzed for prenatal diagnosis of monogenic disorders.[18]

CONCLUSION

A Baby with thanatophoric dysplasia is a painful occurrence to mother and family and recurrence is a curse. Risk of recurrence must be keep in mind if there is history of TD baby and all effort should be done for early diagnosis and termination. Antenatal diagnosis can be made easily by ultrasonography although the features are same in all the lethal dysplasia. Target scan done in second trimester is good opportunity to diagnose TD.

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PEER REVIEW

Nil

CONFLICT OF INTEREST

Nil

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