International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor (2018): 7.426

Thanatophoric Dysplasia – A Case Report Diagnosis and Management

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Abstract: ***Thanatophoric dysplasia (TD) is the most common of the lethal skeletal dysplasias presented in the second trimester. Two subtypes exist: TDI has short curved femurs with or without a clover leaf skull; TDII has straight, longer femurs and generally a more severe clover leaf skull. Sporadic inheritance with extremely small recurrence risk associated with advanced paternal age (>35years). Mutations in fibroblast growth factor receptor 3 (FGFR3) are the underlying basis for the disorder. There is a strong genotype–phenotype correlation. DNA diagnosis is highly accurate. FGFR3 is also expressed in the brain. Rare survivors are uniformly severely developmentally delayed. The incidence of TD ranges from 0.27 in 10,000 to 0.4 in 10,000 live births. In a large series of 126,000 deliveries occurring at one institution, TD was the most common osteochondrodysplasia observed.*** We ***present a case of thanatophoric dysplasia due to its rarity. A 33 y.o. female, G2P1A0 came with polyhydramnion and ultrasonography shown congenital abnormality of the fetus at 29-30 weeks gestational age (GA). Amniocentesis and amnioreduction done at 30 weeks 5 days GA. With the G-binding technique in 40 cells, the chromosome number in each cell obtained is mos 92,XXXX[15]/46,XX [25]. A male baby with 1850 g weight was born at 31 weeks 5 days GA by spontaneous delivery, Apgar scores 3-5, congenital abnormalities (short femur, short humerus, bowel sign, absen nasal bone) which matched with thanatophoric dysplasia type I. In conclusion, Thanatophoric Dysplasia is a congenital, sporadic and the most lethal skeletal dysplasia at birth. Ultrasonography highly indicates the diagnosis of TD. Features like macrocephaly, wide fontanels, micromelia, and telephone receiver like femur, short stubby fingers, deep skin creases, narrow thorax and protuberant abdomen are highly suggestive of thanatophoric dysplasia type I.***

Keywords: Thanatophoric dysplasia, Fibroblast growth factor receptor 3 (FGFR3) mutation, Short femur, Short humerus, Bowel sign, Absen nasal bone

1. Introduction

Thanatophoric dysplasia (TD) is the most common of the lethal skeletal dysplasias presented in the second trimester. Two subtypes exist: TDI has short curved femurs with or without a clover leaf skull; TDII has straight, longer femurs and generally a more severe clover leaf skull. Sporadic inheritance with extremely small recurrence risk associated with advanced paternal age (>35years). Mutations in fibroblast growth factor receptor 3 (FGFR3) are the underlying basis for the disorder. There is a strong genotype–phenotype correlation. DNA diagnosis is highly accurate. FGFR3 is also expressed in the brain. Rare survivors are uniformly severely developmentally delayed.[1]

The incidence of TD ranges from 0.27 in 10,000 to 0.4 in 10,000 live births. In a large series of 126,000 deliveries occurring at one institution, TD was the most common osteochondrodysplasia observed. Prenatal sonographic detection occurs traditionally in the second trimester, at the time of the routine anomaly scan when the fetus is found to have short long bones, a small chest, macrocephaly, frontal bossing, short fingers, cloverleaf skull or telephone receiver-shaped femoral, but with increasing use of first trimester ultrasound, these features are increasingly detected earlier in pregnancy.[2] The accuracy of prenatal diagnosis of TD based on ultrasound findings has been reported to vary from 40% to 88%.[3,4] Here, we present a case of thanatophoric dysplasia due to its rarity.

2. Case Report

33-year-old female patient, second gravida with one C-Section deliveried was admitted in the Obstetrics & Gynecology clinic Sanglah Hospital with an introduction from the Mangusada Hospital with G2P1001 29 weeks 6 days single / life, LMR (SC 1x scars), polyhydramnios, and ultrasonography shown congenital abnormality (short femur, short humerus, bowel sign, nasal absent bone). Abdominal pain (-), child movement (+), vaginal discharge (-). There was no history of fever, rashes, spotting per vaginum, the drug intake and radiation exposure during this pregnancy. She was a non-smoker and a non-alcoholic and not addicted to any drug. There is no past or family history of congenital abnormalities, diabetes mellitus, hypertension, thyroid dysfunction or tuberculosis. The time of admission of her vitals was within normal limits. There was no pallor, edema, thyroid swelling or any significant lymphadenopathy. No abnormal was detected on respiratory, cardiovascular or CNS examination. Abdominal examination - fundal height is 2 finger below proc. Xyphoideus, fetus in longitudinal lie, cephalic presentation. Fetal heart rate was 151 / min and uterus was relaxed.

Ultrasound examination showed a single live intra uterine fetus with cephalic presentation. Placental in Corpus Posterior. No evidence of clover leaf skull deformity. Fetal limbs showed diffuse shortening of long bones and femur was shaped like telephone receiver and abnormal bowel sign[Fig-1]. Effective fetal weight was 1172 g ±172. Fetal biometry showed, BPD-87.4mm = 35 weeks 2 day, HC-302.8mm = 33 weeks 4 days, AC-277.6 mm = 30 weeks±1 day, FL-28.8mm = 18 weeks 6 day. Humerus-37.5mm, Tibia-38.2mm, Ulna-38.4 [Fig-1]. Amniocentesis and amnioreduction done at 30 weeks 5 days GA. With the G-binding technique in 40 cells, the chromosome number in each cell obtained is mos 92, XXXX [15] / 46, XX [25] which means there are 2 cell populations (mosaic), namely; 92,XXXX means the number of chromosomes 92 with the sex chromosome XXXX (tetraploidy), found in 15 cells

studied (37.5%) and 46,XX, means the number of 46 chromosomes with the XX fetal sex chromosome, found in 25 cells learned (62.5%). This mosaic chromosomal abnormality may be caused by a non-disjunction that occurs in the mitotic division phase (cell division phase after fertilization or post-zygotic).

A male baby with 1850 g weight was born at 31 weeks 5 days GA by spontaneous delivery, Apgar scores 3-5, and was a fresh still born and looked dysmorphic. Baby had macrocephaly with HC-302.8 mm. Anterior and posterior fontanelles were wide open and sutures were separated. Face was coarse and oedematous with frontal bossing, mid facial hypoplasia, depressed nasal bridge, low set ears and short neck. Upper and lower limbs were shortened with short stubby fingers and deep skin creases. Thorax was narrow but abdomen was protuberant. Spine was normal. With facial features and skeletal abnormalities the diagnosis of thanatophoric dysplasia type I was made [Fig-2].

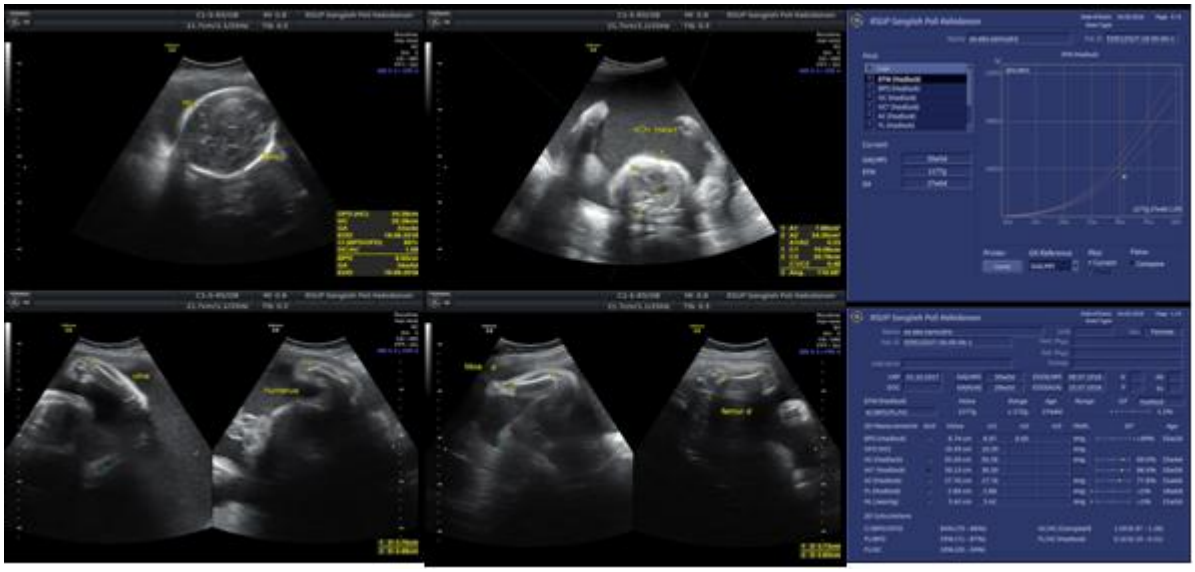

Figure 1: Standart Ultrasonography finding showed abnormal shortening of fetal limbs length

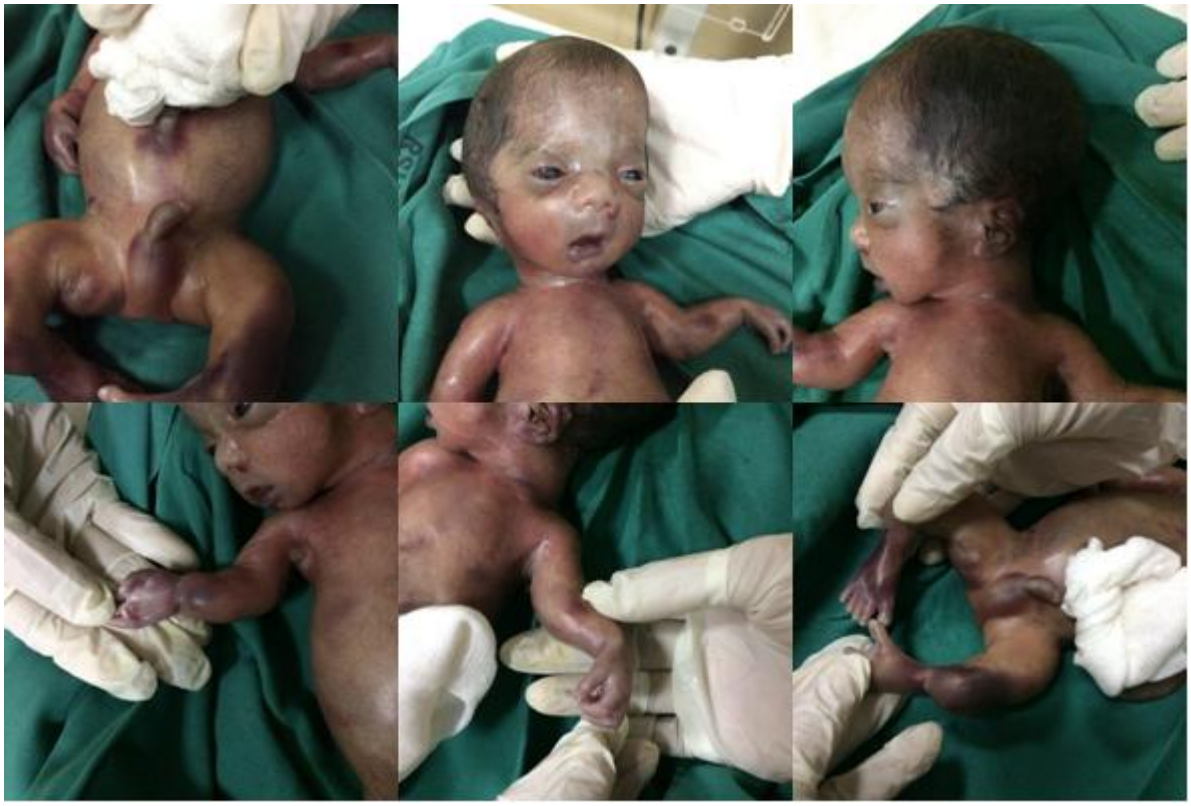

Figure 2: The Appearance of the Baby with Signs Matched for Thanatophoric Dysplasia

Methods

Fetal scanning was done and found evidence of fetal abnormalities from USG screening, confirmed by amniocentesis and analysis of the FGFR3 gene if possible followed by multidisciplinary team meeting.

3. Discussion

Thanatophoric dysplasia (TD) is the most common of the lethal skeletal dysplasias presented in the second trimester. The incidence of TD ranges from 0.27 in 10,000 to 0.4 in 10,000 live births. In a large series of 126,000 deliveries occurring at one institution, TD was the most common osteochondrodysplasia observed.[1]

Mutations in fibroblast growth factor receptor 3 (FGFR3) are the underlying basis for the disorder which has been mapped to chromosome band 4p16.3. Fibroblast growth factors which are associated with cell growth, bind to the FGFR3 receptor and activates a signal transduction pathway that regulates endochondral ossification by inhibition of cell division and stimulation of cell maturation and differentiation. Mutations in the FGFR3 gene give rise to activation of the receptor in the absence of growth factors, thus causing abnormal long bone development.[5] It has been recently proposed that mutated FGFR3 induces premature exit of proliferative cells from the cell cycle and their differentiation into pre hypertrophic chondrocytes thus ascribing to the defective differentiation of chondrocytes the main cause of long bone growth defects in TD I.[6]

There are two subtypes with relative incidence: Type I - 80% and Type II - 20%. Two subtypes exist: TD I has short curved femurs which is in a telephone receiver like configuration and no cloverleaf shaped skull. Also the abdomen appears protuberant in comparison with the chest which is narrow and small with or without a clover leaf skull; TD II has straight, longer femurs and generally a more severe clover leaf skull. Other features common to both TD include small narrow thorax with horizontally placed short ribs, macrocephaly, large anterior fontanel, a small foramen magnum, distinctive facial features (frontal bossing, low nasal bridge, flat faces), severe platyspondyly, marked shortening and bowing of long bones, brachydactly (short broad tubular bones in hands and feet), redundant skin folds along the limbs etc.[7] Dysmorphic facial features and skeletal abnormalities like macrocephaly, wide open anterior and posterior fontanels with suture separation but absence of clover leaf skull deformity, short upper and lower limbs, shape of femur like telephone receiver, short stubby fingers, deep skin creases, narrow thorax and protuberant abdomen with ascites suggested a diagnosis of TD type I in the baby that delivered in our hospital.

Although identification of a lethal skeletal dysplasia in the second trimester is often straight forward but establishing its specific diagnosis can be difficult. A three dimension ultrasound examination aids in visualizing facial features and other soft tissue findings such as cloverleaf skull, very short extremities and small thorax which are suggestive of TD.[8] Since our patient did not have ante natal check up in second trimester, early diagnosis of TD could not be made. Diagnosis was made by ultrasonography when she came with a referral from a colleague in early third trimester. We got dysmorphic facial features and skeletal abnormalities, and than we confirmed by amniocentesis showed mosaic chromosomal abnormality. In these circumstances, the rate of congenital abnormalities in patients / fetuses varies greatly. Final diagnosis of TD type I in our case was made by detecting the clinical features at birth - Dysmorphic facial features and skeletal abnormalities.

Prenatal diagnosis can be confirmed by molecular analysis of the mutation in FGFR3 gene extracted from fetal cells obtained by amniocentesis usually performed at 15-18 weeks gestation or chorionic villous sampling at about 10-12 weeks gestation.[9] Chromosomal analysis and DNA molecular testing for FGFR3 can be done in suspected cases of TD but it was not cost effective in our case because almost all cases of TD are caused by new mutation in the FGFR3 gene and occur in people with no history of the disorder in their family. Affected individuals never survive so disorder never passes to next generation.[10] Recurrence risk is also not increased over that of the general population as it is a de novo mutation.[11]

Most of the fetuses with TD die in utero. The cause of death is due to respiratory insufficiency which may be secondary to the narrow chest cavity and hypoplastic lungs, brain stem compression by the narrow foramen magnum or a combination of both. Surviving neonate is almost always ventilator dependent and mentally deficient.[10,12] In our case baby was a fresh stillborn, though fetal heart was present during labour.

The differential diagnosis includes other skeletal dysplasias that manifest as severe micromelia, such as campomelic dysplasia, Ellis van–Creveld syndrome, and short-rib polydactyly syndrome. Polydactyly is absent in TD. In achondrogenesis, the bones are usually less mineralized than in TD. The cloverleaf skull is occasionally mistaken for an encephalocele. Any soft tissue bulge in the head or neck must be evaluated for its exact position. Encephalocele and cystic hygroma occur in the midline and most often are posterior. The cloverleaf skull is bilateral, with enlargement of the temporal lobes. The standard teaching that the skull is not intact in encephalocele is not helpful to distinguish between encephalocele and cloverleaf skull. This is because the bony calvarium may be expanded, thinned, or partially absent in the cloverleaf skull deformity, and conversely, in cases of encephalocele, the osseous defect in the skull may be very small. A cloverleaf skull may also be noted in Apert, Carpenter, Crouzon, and Pfeiffer syndromes as well as in homozygous achondroplasia.[1]

4. Management

Recently, studies have begun to appear in the literature that document the needs of more aggressive approach to the treatment of infants and children with thanatophoric dysplasia.

5. Conclusion

Thanatophoric Dysplasia is a congenital, sporadic and the most lethal skeletal dysplasia at birth. Ultrasonography highly indicates the diagnosis of TD but confirmation is done by molecular analysis in the prenatal period, clinical features at birth or by autopsy. The anomalous pregnancy can continue up to late 3rd trimester without miscarriage. Most of the fetuses with TD die in utero and those which

survive are dependent on ventilator and mentally deficient. Features like macrocephaly, wide fontanels, micromelia, and telephone receiver like femur, short stubby fingers, deep skin creases, narrow thorax and protuberant abdomen are highly suggestive of thanatophoric dysplasia type I.

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