DOI: 10.7860/JCDR/2015/13201.6702

Case Report

Obstetrics and Gynaecology Section

Thanatophoric Dysplasia: A Case Report

MANISHA SHARMA[1], JYOTI[2], REKHA JAIN[3], DEVENDRA[4]

ABSTRACT

Thanatophoric Dysplasia (TD) is a congenital, sporadic and the most lethal skeletal dysplasia caused by new mutation in the FGFR3 gene. At birth, it is characterized by shortening of the limbs (micromelia), small conical thorax, platyspondyly (flat vertebral bodies) and macrocephaly. TD is divided into two clinically defined subtypes: type I and II with some clinical overlap between the two subtypes. They can be differentiated by the skull shape and femur morphology. Ultrasound examination in the second trimester is often straight forward in diagnosing the congenital anomaly. We report a case of pre term fresh stillborn baby with dysmorphic facies, macrocephaly, micromelia with short stubby fingers and deep skin creases, narrow thorax and protuberant abdomen which delivered at our hospital. The ultrasound examination showed shortening of long bones with femur shaped like telephone receiver. Dysmorphic facial features and skeletal abnormalities in the baby lead us to make the diagnosis of TD type I. Because of the rarity of this condition we report this case of thanatophoric dysplasia with a short review of literature.

Keywords: Congenital, Micromelia, Platyspondyly, Skeletal dysplasia

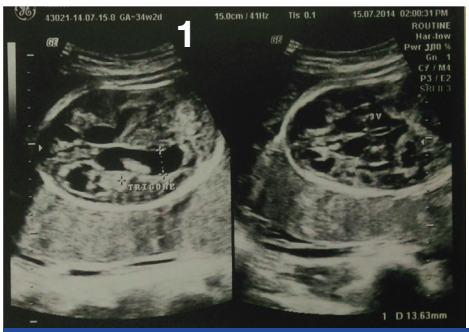
CASE REPORT

A 24-year-old female patient, second gravida with one abortion was admitted in the labour room of Hindu Rao hospital with chief complaints of amenorrhea for 8 months (34 weeks) and leaking per vaginum for one week. She was an unbooked case and had no antenatal examination or investigation in her present pregnancy. There was no history of fever, rashes, spotting per vaginum, drug intake and radiation exposure during this pregnancy. She was married for two years with history of spontaneous abortion of 2 months period of gestation followed by dilatation and curettage and no investigations were done after the abortion. She was a non-smoker and a non-alcoholic and not addicted to any drug. There was no past or family history of congenital abnormalities, diabetes mellitus, hypertension, thyroid dysfunction or tuberculosis. At the time of admission her vitals were within normal limits. There was no pallor, oedema, thyroid swelling or any significant lymphadenopathy. No abnormality was detected on respiratory, cardiovascular or CNS examination. Per abdomen examination - fundal height was 30-32 weeks with fetus in longitudinal lie, breech presentation with reduced liquor. Fetal heart rate was 138/min and uterus was relaxed. On vaginal examination leaking was observed and Bishop's score was very poor.

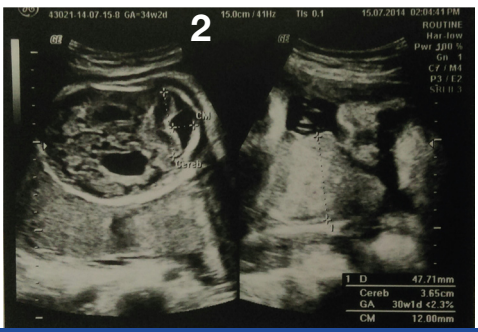
Her investigations – Complete blood with ESR showed raised leucocyte count. Her urine routine, Blood sugar, LFT and KFT were within normal range. HIV, HBsAg and VDRL were non reactive. Her CRP was positive. Ultrasound examination showed a single live intra uterine fetus with breech presentation. Placental thickness was increased - 4.7 cm in AP axis. Fetal skull showed 3rd and 4th ventricles dilated suggesting hydrocephalous [Table/Fig-1]. Cisterna magma was prominent 12 cm in AP axis [Table/Fig-2].

No evidence of clover leaf skull deformity. Fetal thorax was abnormally small with reduced circumference and abdomen showed gross ascites with no gastric bubble [Table/Fig-3]. Fetal limbs showed diffuse shortening of long bones and femur was shaped like telephone receiver [Table/Fig-4]. Liquor was reduced with amniotic fluid index 3. Effective fetal weight was 951 gm ±139. Fetal biometry showed, BPD-70.1mm = 28 weeks±l day, HC-302.4mm = 33 weeks±2 days, AC-260.6 mm = 30 weeks±1 day, FL-28.4mm = 18 weeks 5 day, Humerus-22.1mm = 16weeks 5 days, Tibia-18mm = 17 weeks±1day [Table/Fig-4].

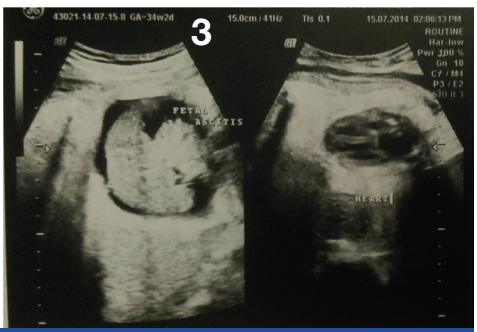
Her labour was induced in view of greatly reduced liquor and risk of chorioamnionitis. Patient delivered a preterm female baby of 1.3 kg vaginally which didn't cry after birth and was a fresh still born and looked dysmorphic. Baby had macrocephaly with HC-302.4 mm. Anterior and posterior fontanelles 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 [Table/Fig-5].



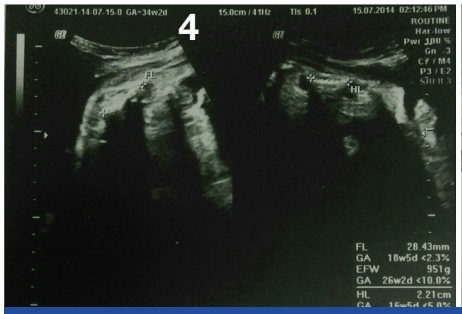
[Table/Fig-1]: USG showing Dilated 3rd Ventricle

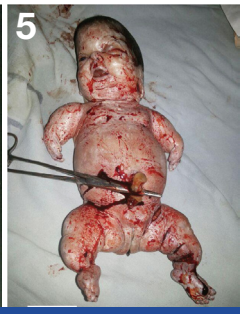


[Table/Fig-2]: USG depicting Cisterna Magnae



[Table/Fig-3]: Fetal abdomen with ascites





[Table/Fig-4]: Femur and Humerus (Telephone receiver like)
[Table/Fig-5]: Thanatophoric Dysplasia

DISCUSSION

Thanatophoric Dysplasia (TD) is a congenital, sporadic and usually lethal skeletal dysplasia at birth characterized by micromelia, small conical thorax, platyspondyly (flat vertebral bodies) and macrocephaly. Its incidence is 1 in 20,000 to 1 in 50,000 of live births [1]. Thanatophoric dysplasia (TD) or dwarfism literally meaning death bearing dwarf was first described by Maroteaux et al., [2]. TD is caused by de novo autosomal [3] dominant mutations in the fibroblast growth factor receptor 3 (FGFR3) gene, 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 [4]. 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 [5].

There are two subtypes with relative incidence: Type I - 80% and Type II - 20%. The two subtypes can be differentiated by the skull shape and femur morphology [6,7]. TD type I, the most common subtype, characterized by curved and short femur 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 [7]. The fetuses with type II TD are reported to have cloverleaf skull which means a trilobed skull. The premature closure of coronal and lambdoid sutures is commonly seen with the cloverleaf skull [8]. 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-dimensional 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 [9]. 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 reported to the hospital for leaking per vaginum in early third trimester. 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 [10]. 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 [8]. Recurrence risk is also not increased over that of the general population as it is a de novo mutation [3].

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 [8,11]. The said baby was a fresh stillborn, though fetal heart was present during labour.

Postnatal autopsy of the affected fetus shows disorganized chondrocytes columns, poor cellular proliferation, lateral overgrowth of metaphyses, and increased vascularity of cartilage [1,11]. Autopsy to confirm the diagnosis by histopathology could not be performed in our case as consent was not given by the parents. A very few cases have been reported till date. [Table/Fig-6] depicts the details of cases of TD reported earlier in literature from India.

Differential diagnosis of TD includes homozygous achondroplasia (both parents suffer from the achondroplasia), achondrogenesis (bones demineralization that are 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 (micromelia is rhizomelic with characteristic stippling radiologically and punctuate calcification in cartilage), severe hypophosphatasia and severe osteogenesis imperfect (generalized hypo mineralization of bones with multiple bone fractures) [11,12]. 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.

Author's name and year	Age of baby/ Weight of baby	Diagnostic modalities	Outcome
SV Phatak et al., 2004 [9]	30 weeks	Radiograph & clinical features	stillborn
NS Naveen et al., 2011[8]	22 weeks	Sonogram & clinical features	Dead fetus
Neelima Tirumalasetti 2013 [6]	26 weeks / 780gm	Sonogram, radiograph & clinical features	stillborn
Hemlatha A Lingappa et al., 2013 [11]	28 weeks / 1.3kg	Clinical features & autopsy	stillborn
Reshma S Devangeri 2013 [13]	20 weeks / 400gm	clinical features, radiograph & autopsy	stillborn
Keerthi Kocherla et al., 2014 [3]	26 weeks	Sonogram, radiograph & clinical features	Dead fetus
Girish Gopal et al., 2014 [14]	34 weeks / 2.1 kg	clinical features, radiograph & autopsy	Live birth died 24 hrs after birth
Our Case (2014)	34 weeks / 1.3 kg	Sonogram & clinical features	stillborn

[Table/Fig-6]: Review of cases of thanatophoric dysplasia reported earlier in literature from India

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.

REFERENCES

[1] Wilcox WR, Tavormina PL, Krakow D, Lachman RS, Wasmuth JJ, Thompson LM, et al. Molecular radiologic and histopathologic correlations in thanatophoric dysplasia. *Am J Med Genet*. 1998;78:274-81.

[2] Maroteaux P, Lamy M, Robert JM. Thanatophoric dwarfism. *Presse Med.* 1967;75:2519-24.

[3] Kocherla K, Kocherla V. Antenatal diagnosis of Thanatophoric Dysplasia: a case report and review of literature. *Int J Res Med Sci*. 2014;2(3):1176-79.

[4] 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):1056-59.

[5] 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.

[6] Tirumalasetti N. Case report of Thanatophoric dysplasia: A lethal skeletal dysplasia. *J NTR Univ Health Sci*. 2013;2:275-77.

[7] Brodie SG, Kitoh H, Lipson M, et al. Thanatophoric dysplasia type I with syndactyly. *Am J Med Genet*. 1998;80:260-62.

[8] Naveen NS, Murlimanju BV, Kumar V, Pulakunta T, Jeeyar H. Thanatophoric Dysplasia: A Rare Entity. *Oman Medical Journal*. 2011;26(3):196-97.

[9] Phatak SV, Pandit MP, Phatak MS, Kashikar R. Antenatal sonography diagnosis of thanatophoric dysplasia: A case report. *Indian Journal of Radiology and Imaging*. 2004;14(2):161-63.

[10] Rousseau F, el Ghouzzi V, Delezoide AL, Legai-Mallet L, Le Merrer M, Munnich A, et al. FGFR3 mutations create cysteine residues in thanatophoric dwarfism type I (TD I). *Hum Mol Genet*. 1996;5:509-12.

[11] Lingappa HA, Karra S, Aditya A, Batra N, Chamarthy NP, Ravi Chander KWD. Autopsy Diagnosis of Thanatophoric Dysplasia. *J Indian Acad Forensic Med*. 2013;35(3):296-98.

[12] Gorlin RJ, Cohen MM, Hennekam RCM. Syndromes of head and neck. Chapter 7. The chondrodysplasias. *Oxford University Press*, 4th edition (2001).

[13] Davanageri RS, Shokeen PD, Bannur HB, Patil KP. Thanatophoric Dysplasia Type I: A Rare Case Report at Fetal Autopsy. *Journal of Labouratory Physicians*. 2014;6(2):121-23.

[14] Gopal G, Belavadi GB. Thanatophoric Dysplasia in newborn. *Journal of Evolution of Medical and Dental Sciences*. 2014;3(14):3665-69.

PARTICULARS OF CONTRIBUTORS:

1. Senior Specialist, Department of Obstetrics and Gynaecology, Hindu Rao Hospital and NDMC Medical College, NDMC, Delhi, India.
2. Student, Department of Obstetrics and Gynaecology, Hindu Rao Hospital and NDMC Medical College, NDMC, Delhi, India.
3. CMO NFSG, Department of Obstetrics and Gynaecology, Hindu Rao Hospital and NDMC Medical College, NDMC, Delhi, India.
4. Medical Officer, Department of Radiology, Hindu Rao Hospital and NDMC Medical College, NDMC, Delhi, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Manisha Sharma,
26, SFS DDA Flats, Mukherji Nagar, Delhi-110009, India.
E-mail : drmanishasharma63@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jan 27, 2015**
Date of Peer Review: **Jun 03, 2015**
Date of Acceptance: **Sep 03, 2015**
Date of Publishing: **Nov 01, 2015**