Review Article

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Thanatophoric Dysplasia: A Systemic Review of Case Reports

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Abstract

Thanatophoric dysplasia (TD) is a type of lethal skeletal dysplasia having very rare description about its clinical profile in medical literature. Here we discuss the anatomical features, abnormalities and clinical profile of Thanatophoric dysplasia in the present study. A search of PubMed, Web of Science, EMBASE and google search was made to identify previous citations in the English literature reporting sonographic findings in fetuses with Thanatophoric dysplasia. We used key words related to Thanatophoric dysplasia and prenatal ultrasound, including 'thanatophoric dysplasia', 'ultrasound', 'prenatal', 'sonography', 'skeletal dysplasia', 'limb shortening', 'macrocephaly', 'telephone receiver femur' and 'cloverleaf skull' etc. Studies where the diagnosis of thanatophoric dysplasia was confirmed by radiological findings or molecular diagnosis were included in our study. We have found 34 cases of thanatophoric dysplasia from 1971 to 2016. Out of these 34 cases 17 were type 1 and two cases were type 2. Out of 34 cases 5 cases are diagnosed before 20 weeks, 5 cases were diagnosed between 20-26 weeks and 22 cases were diagnosed after 26 weeks. The most common anomalies found are narrow thorax (100%), Platyspondily (41.1%), Hypoplastic pelvic bones (50%), Telephone receiver femur (55.8%), Short ribs (38.2%), Clover leaf skull (26.4%), Frontal bossing (35.2%), brachydactily (26.4%) and Depressed Nasal Bridge (26.4%). Out of nine cases where the the difference between gestational age measured by biparietaldimeter (BPD) and femur length (FL) were reported only one case had been reported to be diagnosed before 20weeks where the difference is 5 weeks. Three cases were diagnosed between 20 and 26 weeks where the difference is 7-8 week, 7+2 week and 8+6 week respectively. In the rest five cases the difference of gestational age ranges from 10-16 weeks to 24 weeks. Any discordance between femur length measurement and abdominal circumference or head circumference in first or early second trimester ultrasound should be suspected for this dysplasia. Counseling of the affected parents about the low recurrence rate is also an important part of management.

Keywords: Thanatophoric Dysplasia; Telephone Receiver Femur; Clover Leaf Skull; Limb Shortening.

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Introduction

Thanatophoric dysplasia (TD) is a type of lethal skeletal dysplasia characterized by marked underdeveloped skeleton and short-limb dwarfism [1]. The word 'thanatophoric dysplasia' meaning as "death-bearing is a greek word. The defect lies in the fibroblast growth factor receptor 3 gene (FGFR 3), which is located on the short arm of chromosome 4 causing some type of mutation in it. This's an activating mutation of FGFR 3 tyrosine kinase independent of its ligands. Hypochondroplasia, achondroplasia and thanatophoric dysplasia appear to be different spectrums of the same mutation

hypochondroplasia being the mildest and Thanatophoric dysplasia, being the most severe form. Since the clinical profile of this anomaly was rarely reported, we discuss the anatomical features, abnormalities and clinical profile of Thanatophoric dysplasia in the present study.

Materials Method

A search of PubMed, Web of Science,EMBASEand google search was made to identify previous citations in the English literaturereporting sonographic findings in fetuses with TD. We usedkey words relatedto Thanatophoric dysplasia and prenatal ultrasound, including 'thanatophoric dysplasia', 'ultrasound', 'prenatal', 'sonography', 'skeletal dysplasia', 'limb shortening', 'macrocephaly', 'telephone receiver femur' and 'clover leaf skull' etc. Studies where the diagnosis of thanatophoric dysplasia was confirmed by radiological findings or molecular diagnosis were included in our study.

Results

We have found 34 cases of thanatophoric dysplasia from 1971 to 2015. Out of these 34 cases 17 were type 1 and two cases were type 2. As shown in Table 1 out of 34 cases 5 cases are diagnosed before 20 weeks, 5 cases were diagnosed between 20-26 weeks and 22 cases were diagnosed after 26 weeks. In two cases the gestational age was not reported. This is because most patients of rural background have attended their first antenatal visit at a later age of gestation.

Table 2 shows the most common anomalies found. These are narrow thorax(100%), Platyspondily (41.1%), Hypoplastic pelvic bones (50%),Telephone receiver femur (55.8%), Short ribs (38.2%), Clover leaf skull(26.4%), Frontal bossing (35.2%) brachydactily (26.4%) and Depressed Nasal Bridge (26.4%).

Nine authors had reported about the the difference between gestational age measured by biparietal dimeter (BPD) and femurlength (FL). This is shown in Table 3. Of these nine only one case had been reported to be dignosed before 20 weeks where the

Table 1: Gestational Age at diagnosis in current practice

Gestational age at diagnosis	<20 wk	Between 20 - 26 wks	>26 week
no. of cases	5(n=32)	5(n=32)	22(n=32)
Percentage(%)	15.62	15.62	68.76

Table 2: Deformities most commonly found in thanatophoric dysplasia

Deformities	No. of cases (n=34)	Percentage (%)
Platyspondily	14	41.1
Telephone receiver femur	19	55.8
Hypoplastic pelvic bones	17	50
Short ribs	13	38.2
Clover leaf skull	9	26.4
Narrow thorax	34	100
Frontal bossing	12	35.2
Depressed Nasal Bridge	9	26.4
Brachydactily	9	26.4

Table 3: Difference Between Gestational Age According To BPD Or HC And FL Found By Different Authors

Sl. No.	Author	Year	Gestational Age at Diagnosis	Gestational Age According to BPD or HC	Gestational Age According to FL	Difference Between Gestational Age Measured by BPD OR HC and FL
1.	L1nnie M. Muller[2]	1985	34 week	36 week	20 week	16 week
2.	L1nnie M. Muller[2]	1985	32 week	-	-	10-16 week
3.	L1nnie M. Muller[2]	1985	32 week	-	-	10- 16 week
4.	M.L. Kulkarni[3]	1994	25 week	22 week	14- 15 week	7-8 week
5.	ACF Lam[4]	2006	36 +4 week	38 week	18 week	20 week
6.	SqnLdr S Sahu[5]	2009	20week	20 week	15 week	5week
7.	RecaiSoner ÖNER[6]	2001	22 week	22+ 5 week	15 +3 week	7+2 week
8.	RecaiSoner ÖNER[6]	2001	23 week	23 + 3 week	14 + 4 week	8+6 week
9.	RecaiSoner ÖNER[6]	2001	32 week	41 week	17 week	24 week

difference is 5 weeks. Three cases were dignosed between 20 and 26 weeks where the difference is 7-8 week, 7+2 week and 8+6 week respectively. In the rest five cases the difference of gestational age ranges from 10-16 weeks to 24 weeks. In one caseof RecaiSoner ÖNER et al [8] the difference was 24 weeks as there was a hydrocephalic fetus. So difference between gestational age due to BPD or HC and FL seems to be a better and early predictor in the diagnosis of Thanatophoric dysplasia although the difference increases as the gestational age advances.

Discussion

Thanatophoric dysplasia (TD) is the most common lethal dominant skeletal dysplasia with an incidence of 2–3 per 100 000 births [7].

It still remains as a lesser studied topic in medical literature. There are a lot of challenges in its management. The prominent challenge being the timing of diagnosis. The prime element in the diagnosis of thanatophoricdyplasia relies on measurement of femur length, chest circumference, abdominal circumference and head circumaference or their ratios. Although it's not difficult to diagnose TD with these parameters after 20 weeks of gestation, the challenge remains in diagnosing it accurately before 20 weeks, so that we can offer medical termination of pregnancy at the perfect time.

Although the antenatal prediction of lethality can be accurate, still there remains the difficulty in making th accurate antenatal diagnosis of skeletal dysplasia. This has been described by Barbara et al [8]. According to them the sonographic criteria suggesting diagnosis of thanatophoric dysplasia are severe rhizomelicmicromelia with bowing, length of limbs being less than third percentile for gestational age. A hypoplastic thorax can be indicated by cardiac circumference greater than 60% of the thoracic circumference. The normal abdomen may appear protuberant in comparison with hypoplastic thorax. The skin appears thick sonographically due to extreme redundancy and may prevent normal movement and positioning of limbs causing them to be oriented at rightangles to the body. The skull can appear trilobed especially in coronal view. This is often seen in Type II variety. The presence of bulging in the temporal location and bilateral involvement are clues to pick up this diagnosis on sonography.

Other published reports suggest that it is possible to accurately predict that cases presenting with sonographic evidence of a skeletal dysplasia are likely to be lethal by evaluation of chest size and configuration [9,10]. Others have used a femur length/AC ratio <0.16 as a sensitive threshold for predicting lethal skeletal dysplasia [11].

Lyn S et al provided charts of fetal size for fetuses with TD for improved sonographic distinction from other skeletal dysplasias. They also conclude that definitive diagnosis of Thanatophoric dysplasia is possible by analysis of cffDNA in maternal plasma [12].

Thanatophoric dysplasia is mainly diagnosed by routine prena-tal ultrasound examination and sometimes by chorionic villous biopsy at 10–12 weeks of gestation or fetal DNA analysis at 15–18 weeks of gestation [13]. The 3D anatomy scan and molecular confirmation may be helpful in early diagnosis and genetic counseling of TD [14]. The timely diagnosis provides the advantage that medical termination of pregnancy can be offered at appropiate time. At the same time the counseling part of management is very important in this disease, especially to the parents of the affected children because most of them are very apprehensive to have further pregnancies [4]. Since the majority of cases of TD occur sporadically, it is important to counsel that the recurrence risk is low for only one previously affected fetus and that the extended family members of the proband are not at increased risk [4].

Conflict of Interest

There is no conflict of interest among authors.

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Conclusion

Thanatophoric dysplasia is an aggressive and lethal form of skeletal dysplasia which needs to be diagnosed early for its proper management. Any discordance between femur length measurement and abdominal circumference or head circumference in first or early second trimester ultrasound should be suspected for this dysplasia. Finally molecular diagnosis can help in confirmation of this diagnosis even before 20 weeks of gestation. So lets be thanatophoric minded and change the tradition of diagnosing TD radiologically (after birth of baby) to diagnose it before 20 weeks of gestation, so that proper management (MTP) can be offered at appropriate time. Counseling of the affected parents about the low recurrence rate is also an important part of management.

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