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THANATOPHORIC DWARFISM - A LETHAL SKELETAL DYSPLASIA

Paediatrics

Bhanu Prakash Inukonda Junior Resident
Harischandra YV Professor

ABSTRACT

Thanatophoric dwarfism is a lethal, congenital skeletal dysplasia caused by mutations in the FGFR3 gene. It is characterized by extreme shortening of the limbs, narrow thorax, macrocephaly, and distinctive facial and skeletal abnormalities. Its rarity and high perinatal lethality make early diagnosis and genetic counseling critical.We report the case of a preterm female infant delivered vaginally at 33 weeks of gestation with no prior family history of congenital anomalies. Antenatal ultrasonography showed micromelic limb shortening, severe thoracic hypoplasia, macrocephaly, and polyhydramnios. On examination, the neonate presented with dysmorphic features, notably relative macrocephaly, depressed nasal bridge, narrow thorax, and short limbs with redundant skin folds. Radiographs confirmed features consistent with thanatophoric dysplasia type 2, including straight femora and a cloverleaf-shaped skull. Despite supportive measures, the infant was not revived.Prenatal diagnosis of thanatophoric dwarfism allows for prompt counseling, anticipatory guidance, and informed decision-making. This case highlights the importance of detailed antenatal imaging and genetic evaluation for rare skeletal dysplasias.

KEYWORDS

Thanatophoric dysplasia, skeleteal dysplasia, FGFR3 gene, Antenatal scan, Genetic counselling

INTRODUCTION

Thanatophoric dysplasia (TD) is a type of neonatal lethal skeletal dysplasias. It is characterized by marked underdeveloped skeleton and short-limb dwarfism.[1]In 1967, Maroteaux et al.,[2] described a specific chondrodystrophy calling thanatophoric dwarfism. In 1977, this term was changed to thanatophoric dysplasia at the Second International Conference of the Nomenclature of Skeletal dysplasias [3]

TD is caused due to mutation of the fibroblast growth factor receptor 3 gene (FGFR3), which is located on the short arm of chromosome 4. The mutation results in the activation of FGFR3 tyrosine kinase independently of ligands such as fibroblast growth factor 8. This activation of FGFR3 results in decreased apoptosis and increased proliferation.

TD has an estimated incidence of 1:20,000–1:50,000 live births.[4]Mutations in the fibroblast growth factor receptor 3 (FGFR3) gene are responsible. TD is classified into two subtypes:

- **Thanatophoric Dysplasia Type 1 (TD1):** Characterized by micromelia with bowed femurs and, uncommonly, the presence of craniosynostosis of varying severity.
- **Thanatophoric Dysplasia Type 2 (TD2):** Characterized by micromelia with straight femurs and uniform presence of moderate-to-severe craniosynostosis with a cloverleaf skull deformity.

Due to its grave prognosis, early prenatal diagnosis is crucial for proper parental counseling and management planning.

Case Study

A 24-year-old G3P2 with previous preterm vaginal deliveries presented at 33 weeks' gestation with preterm premature rupture of membranes. Notably, there was no history of congenital anomalies in previous pregnancies or family history. There was no history of Fever, rashes, spotting per vaginum, drug intake and radiation exposure during the pregnancy.

Antenatal Findings

Ultrasound At 32 Weeks Identified:

- Limb shortening and micromelia
- Narrow thoracic cavity with a low chest/abdominal circumference ratio
- Macrocephaly
- Cardiac abnormalities, including complete atrioventricular septal defect
- Polyhydramnios and moderate ascites

O/E, Uterus overdistended with clinically excess liquor, Ultrasound showed SLIUG of 32weeks 5 days corresponds to 25 weeks 2 days with above features.

Delivery & Clinical Features

The patient delivered a female infant weighing 1.78 kg, having severe respiratory distress, who could not be revived despite resuscitation, and exhibited overt dysmorphic features:

At Birth, Baby's face was congested and swollen.(Fig.1) Head was relative macrocephalic, prominent forehead, depressed nasal bridge, wide and open fontanelles and sutures. Thorax being Small, narrow, bell-shaped chest suggestive of Pulmonary Hypoplasia. Limbs were severely shortened upper and lower limbs (micromelia) with redundant skin folds with Protuberant abdomen, normal external genitalia, spine normal.

Radiological Findings

Radiographs demonstrated: large skull with narrow base, horizontally placed ribs, flattened vertebral bodies (Platyspondyly), bicycle handle appearance of both clavicle**,** Rhizomelic shortening of the long bones; Irregular metaphyses of the long bones; Straight femurs suggestive of TD 2; Cloverleaf skull, Narrow chest cavity with short ribs

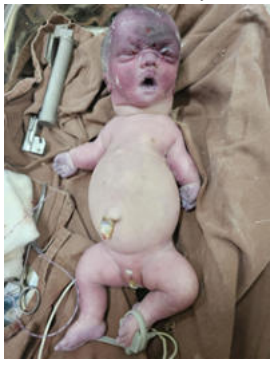

Fig.1 Gross findings of the newborn, congested face, a depressed nasal bridge with cranium-facial disproportion. Note the short thorax, protruding abdomen and short limbs.

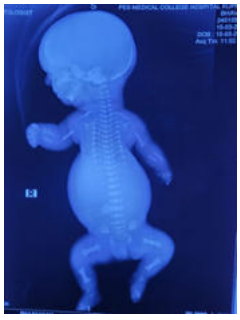

Fig. 2: Horizontally placed ribs, flattened vertebral bodies (Platyspondyly), bicycle handle appearance of both clavicle, Rhizomelic shortening of the long bones; Straight femurs suggestive of TD 2

DISCUSSION

Thanatophoric dwarfism (TD) stands as one of the most severe and universally fatal skeletal dysplasias encountered in clinical practice. Its lethality springs largely from profound thoracic hypoplasia, which results in critical pulmonary insufficiency.[5]

The genetic basis of TD lies in gain-of-function mutations in the FGFR3 gene, triggering aberrant chondrocyte proliferation and disorganized enchondral bone formation.[6] The consequences of these molecular derangements are evident throughout the skeletal system, with pronounced micromelia, severe shortening of the limbs, and characteristic craniofacial features such as macrocephaly and the cloverleaf-shaped skull in type II TD. The accuracy of fetal ultrasonography hinges on observing combinations of micromelia, decreased thoracic circumference, unusual cranial shapes, and associated findings like polyhydramnios[7] —features that can suggest the diagnosis before birth and prompt further genetic evaluation if resources permit.

Despite advances in molecular genetics, most diagnoses in resource-constrained settings still rely heavily on integrating clinical phenotypes with classical radiological findings. Distinguishing TD from other lethal skeletal dysplasias, such as achondrogenesis, osteogenesis imperfecta type II, and camptomelic dysplasia, necessitates careful analysis. Nonetheless, diagnostic uncertainties persist, especially in the absence of access to confirmatory FGFR3 gene testing. The diagnosis is usually suspected by antenatal ultrasound examination and confirmed by molecular analysis on amniocytes[8]

Early detection enables healthcare providers to offer evidence-based counseling to families, preparing them psychologically for the probable outcome and assisting in critical decision-making regarding perinatal management and supportive care. In many situations, antenatal detection may prompt consideration of pregnancy termination or the initiation of palliative-only postnatal care. Furthermore, timely diagnosis averts unwarranted and invasive neonatal interventions that offer no survival benefit and may only prolong suffering.[9]

Prenatal radiography for documenting characteristic skeletal anomalies. DNA mutation analysis of FGFR3 in fetal cells from amniocentesis or CVS[10]. Noninvasive prenatal diagnosis: nextgeneration sequencing (NGS) for the analysis of cell-free fetal DNA in maternal blood.[11] Prenatal and preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified

Genetic counseling following a diagnosis of TD is also a cornerstone of long-term family support. Given the almost universal de novo nature of FGFR3 mutations in TD, parents are generally advised of the exceedingly low recurrence risk in future pregnancies.[12]

CONCLUSIONS

The literature reinforces the vital contribution of published case reports to ongoing clinical education and enhanced diagnostic acumen. Each additional report brings greater recognition of the phenotypic variability of TD and underlines the evolving capabilities of prenatal diagnostics in resource-limited and developed settings alike. It also helps define the standard of care for such rare disorders, ensuring that affected families receive compassionate, holistic care void of unnecessary procedures, and informed by the latest genetic and radiological understandings.

This also reinforces the value of meticulous prenatal ultrasound and radiologic assessment in diagnosing rare, lethal skeletal dysplasias. Early recognition facilitates appropriate counseling, prevents unnecessary interventions, and aids in family planning.

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