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CASE REPORT

Thanatophoric Dysplasia

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ABSTRACT

A rare case of 'Thanatophoric dysplasia' is described here and its etiology, clinical presentation and management discussed.

Key words: Thanatophoric, dysplasia, chondrodysplasia

INTRODUCTION

Thanatophoric dysplasia was originally described by Morteaux[1] who coined the term "thanatophoric" meaning "death bearing" in Greek. At the time of this designation, death typically due to respiratory failure, occurred invariably within the first few hours or days of birth. This condition is characterized by marked rhizomelic shortness of the limbs with skin redundancy, a narrow thorax with short ribs, markedly flattened vertebral bodies, a short pelvis, a relatively large head with frontal bossing, prominent eyes, hypertelorism and depressed nasal bridge. In some cases, premature closure of cranial sutures results in *kleeblattschädel* or cloverleaf skull.

Thanatophoric dysplasia is one of the most common lethal skeletal dysplasia with a birth incidence of 1:35,000[2–4] to 1:50,000[5]. Most affected newborn infants succumb in the first few days of life. Prolonged survival in this condition is unusual and is associated with poor growth and development and chronic respiratory insufficiency due to reduced chest circumference and/or lower brain stem compression resulting from a diminutive foramen magnum. Additional central nervous system abnormalities have included hydrocephalus, polymicrogyria, neuronal heterotopia, megalencephaly, cerebral gyral disorganization, hippocampal malformation, nuclear dysplasia, abnormal axonal bundles and cerebellar hypoplasia in a small posterior fossa[6,7]. In the past this disorder was often misdiagnosed as a chondroplasia, which is the nonlethal variety of chondrodysplasia[8]. We report here, a rare case of thanatophoric dysplasia.

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CASE REPORT

Mrs. R, a 23 years old with gravida 2 was admitted to the University Hospital, Varanasi with the history of 9 months amenorrhoea and diminished fetal movements for 3 months. Her previous child was normal, 2 years old and delivered by caesarean section due to cephalopelvic disproportion.

For reduced fetal movements she consulted a local doctor who advised her an ultrasonogram, which showed polyhdroamnios, very short fetal upper and lower limbs and diminished fetal activity. She was then referred to our hospital for further management.

On general examination the patient was short statured but in good health. Her pulse rate was 80 minute and B.P. 110/70mmHg. There was no pallor. Her cardiovascular and respiratory systems' examination revealed no abnormality. On abdominal examination the scar of her previous caesarean section was healthy. The uterus was overdistended with excess liquor amnii. Fetal parts were felt with difficulty. There was cephalic presentation, the head was free floating and felt bigger than normal. Fetal heart sound was also heard with difficulty, with a rate of 140/minute.

A repeat ultrasonogram of her abdomen revealed gross polyhydroamnios, single live term sized with diminshed fetal activity. There was cephalic presentation and the

biparietal diameter measured 110mm. All the four limbs were reported to be grossly reduced in size (Figs.1,2 & 3).

In view of the cephalopelvic disproportion and previous caesarean section, her pregnancy was terminated by caesarean section (Destructive operation was considered unsafe in this case).

A male baby was born with birth weight 2660 gms. The baby had birth anoxia and cried feebly after 5 minutes. There was generalized hypotonia, heart rate 140/minute and respiratory rate 70/minute. The baby was shifted to neonatal intensive care unit and was given oxygen inhalation and I.V. fluid therapy. His oxygen saturation was only 88% despite oxygen therapy. The baby was groaning; brooting, sucking and Moro's reflexes were absent.

The crown-heel length of the baby was only 38.8 cm. the head was bigger with circumference 38cm, anterior fontanel was 4 cm × 4 cm and the posterior fontanel open. The nasal bridge was depressed. There were frontal bossing, periorbital oedema, puffy face and low set ears. The neck was short. The chest was long, narrow with small rib cage (circumference 26 cm).

The abdomen was protuberent with hepatospleenomegaly. The ratio of upper and lower segment of the body was 2.5:1. the upper and lower limbs were very short with loose skin folds and oedema. All the fingers were small and of equal size. The palm was broad with single palmer crease. The toes were also small and equal in length (Fig.4).

The ultrasonogram of the head of the baby revealed no hydrocephaly but the cranium was bigger than normal. The ultrasonogram of the abdomen revealed hepatospleenomegaly. X-ray of the whole body of the baby revealed enlarged cranium, long and narrow thoracic cage with thin ribs and their flared up ends. The vertebrae were flat (platyspondyly). The pelvis was square and small. All the long bones of the limbs were small. The femurs were curved and short (telephone receiver shaped) (Fig.5).

The baby was in respiratory distress, breathless and cyanosed. His blood sugar and temperature were, however, maintained. The baby died 48 hours after birth due to respiratory failure despite all possible resuscitative measures. Permission for autopsy could not be obtained from the parents.

On the 7th postoperative day the mother was discharged from the hospital with the advice to come for early and regular antenatal checkup in next pregnancy.

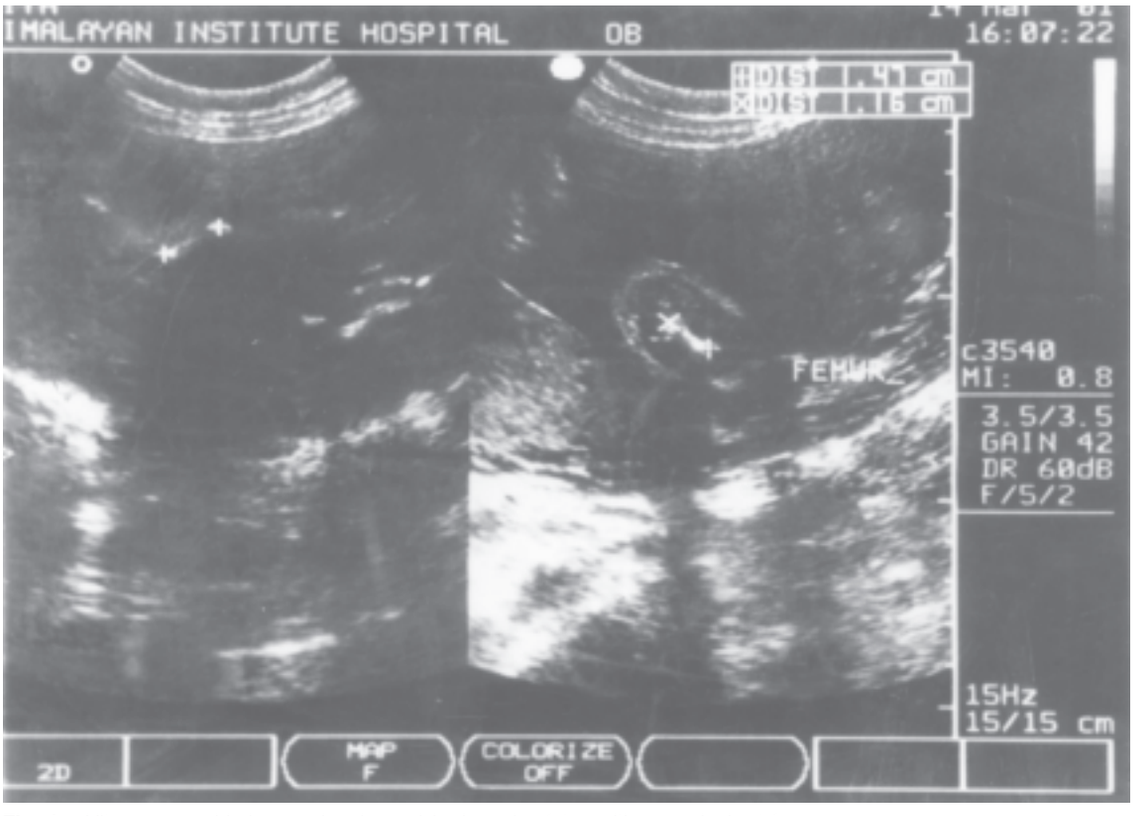

Fig. 1. Ultrasonographic image showing polyhydramnios fetus with curved, short femur

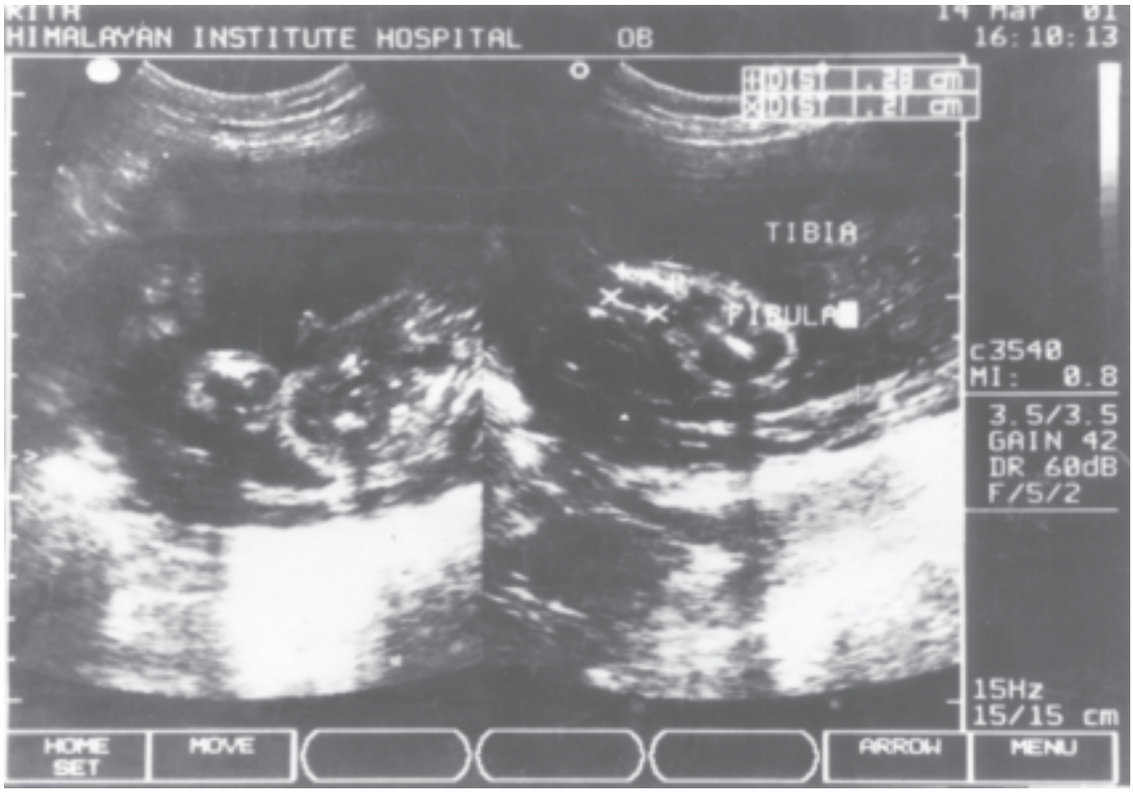

Fig. 2. Ultrasonographic image showing diminished fibula.

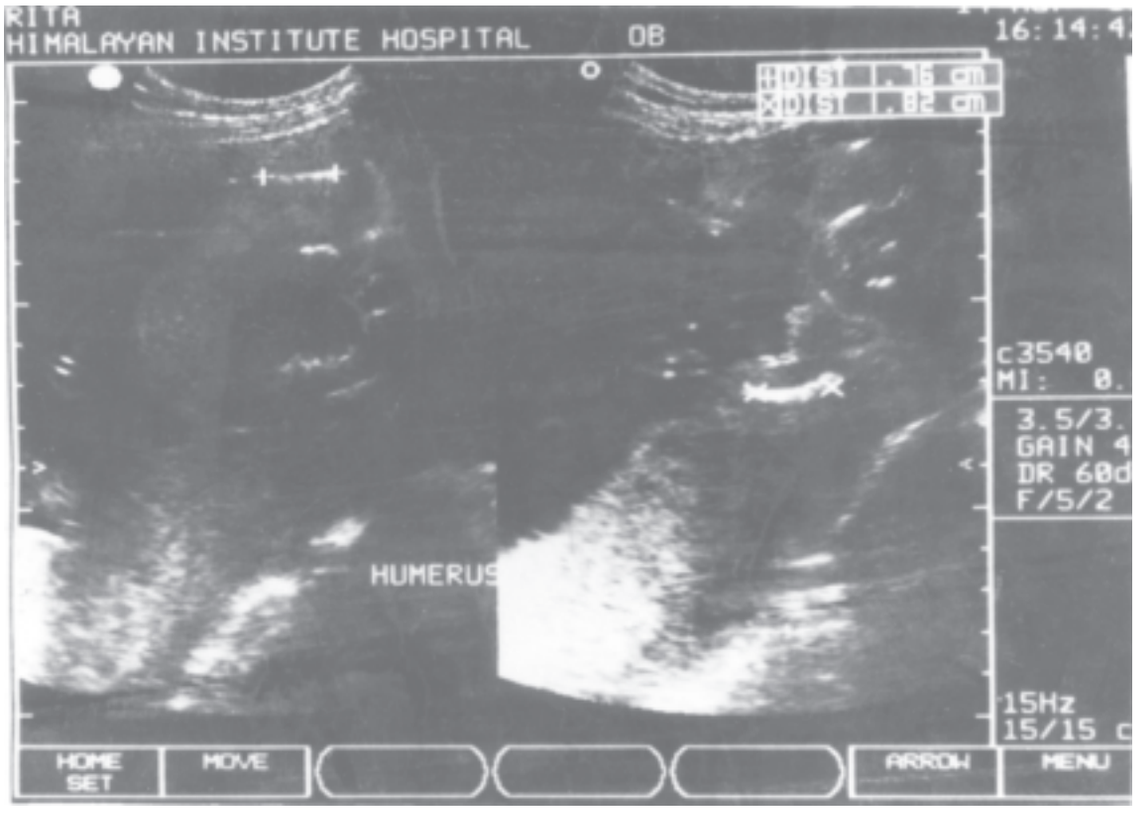

Fig. 3. Ultrasonographic image indicating marked shortening of humerus.

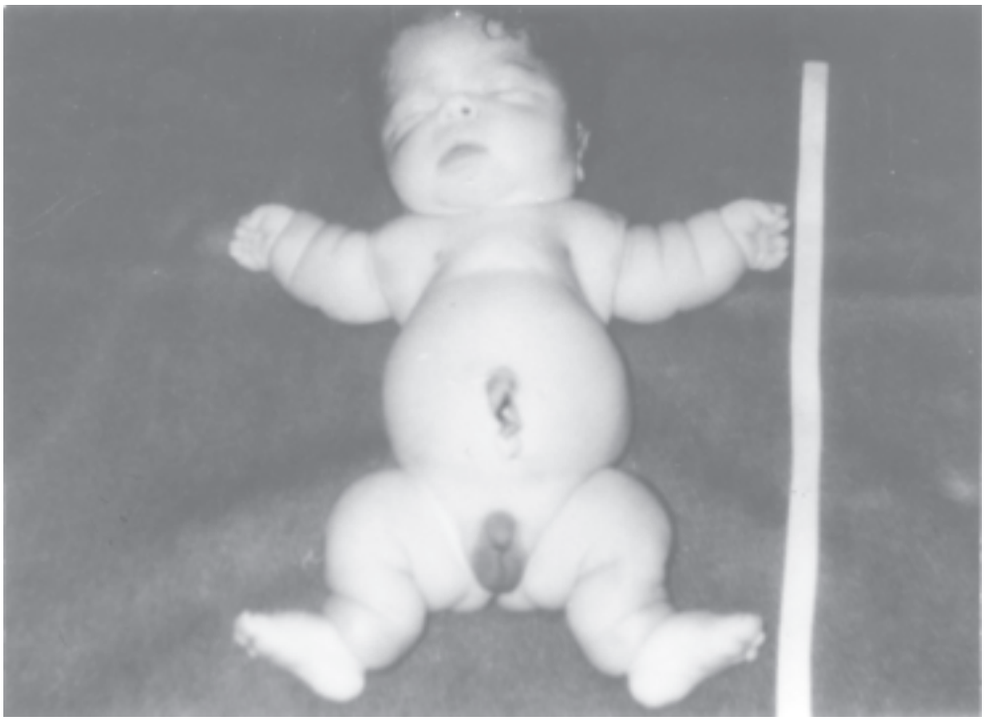

Fig. 4. Full body photograph showing marked limb shortness and thoracic narrowing with the ratio of upper and lower segment of the body being 2.5:1.

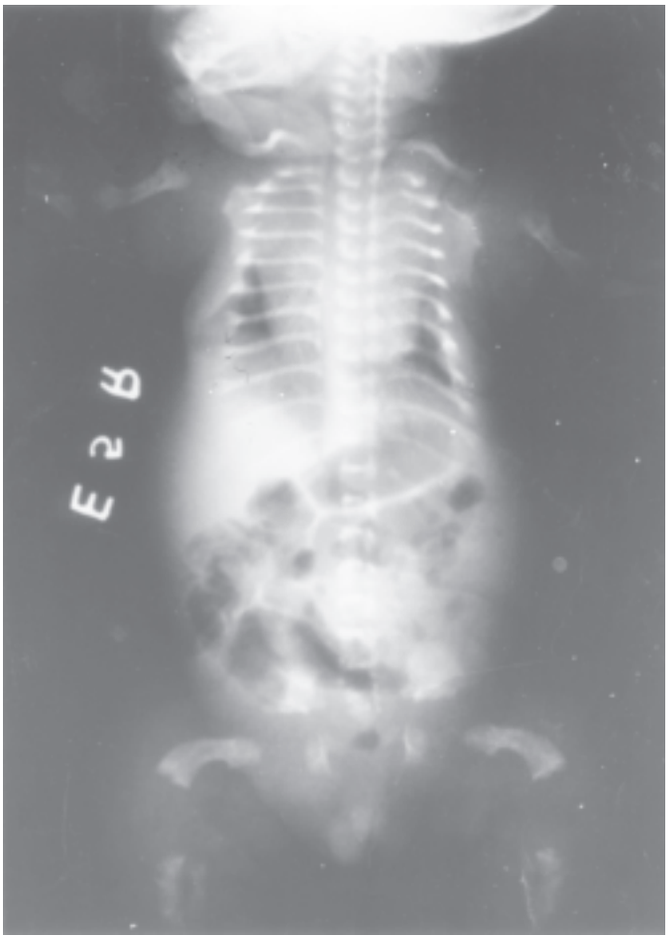

Fig. 5. Radiograph showing narrow thoracic cage with thin ribs and their flared-up ends. Pelvis appear square and small and all long bones of limbs are small. Femur is curved and short ("bowing").

DISCUSSION

Disorders involving transmembrane receptors result from heterozygous mutations of genes encoding these receptors – FGFR3 and PTHrPR. The mutations cause the receptors to become activated in the absence of physiologic ligands, which accentuates normal receptor function of negatively regulating bone growth. The mutations act by gain of negative function. In the FGFR3 mutation group, in which the clinical phenotypes range from severe to mild, the severity appears to correlate with the extent to which the receptor is activated. Both PTHrPR and especially FGFR3 mutations tend to recur in unrelated individuals[1].

Chondrodysplasias belong to this category of disorders and have three subtypes viz. – Thanatophoric dysplasia (lethal), achondroplasia (non-lethal) and hypochondroplasia[1].

All these three subtypes have mutations in a small number of locations in the FGFR3 gene. There is a strong correlation between the mutation site and the clinical phenotype.

Thanatophoric dysplasia presents before or at birth. In the former situation feeble fetal activity and/or polyhydroamnios is frequent. Ultrasonographic examination in midgestation or later reveals a large head and very short limbs. Premature delivery may take place otherwise early induction of delivery is recommended in order to aviod serious delivery problems at a later date (related to large head and/or breech presentation).

At birth the baby presents with hypotonia. There is severe growth deficiency, with an average height of 40cm. The cranio-facial abnormality includes large cranium and fontanel (average 37 cm), small foramen magnum and short base of skull, with full forehead, low nasal bridge, and small facies. The neck is short, the limbs are short with sausage like fingers, bowed long bones with cupped spur like irregular flaring of metaphyses and lack of ossification in secondary centres at knee. Disorganized chondrocytes and bony trabeculae, especially in central epiphyseal-metaphyseal region[2] were noted.

The thorax is long and narrow with short ribs. The vertebral column is short with flattened vertebrae with wider intervertebral disc spaces. There is lack of caudal widening of spinal canal. Ths scapulae are small and squarish. The pelvis is also short and squarish with small schiatic notch and medial spurs[2].

The newborns have severe respiratory distress because of their small thoracic cage. Although this distress can be treated by intense respiratory care, the long term prognosis is poor. Usually these patients die shortly after birth. No medical intervention is recommended toward survival for patients with this disorder.

Occasional abnormalities include hydrocephalous, patent ductus arteriosus, auricular septal defect, horse-shoe kidney, hydronephrosis, imperforate anus, radioulner synostosis, craniostenosis even to the degree of clover leaf skull (known as *kleeblattschädel*)[2].

Abnormalities of uncertain incidence include brain anomalities like microgyria, absent corpus callosum, and faulty organization, especially in temporal lobe and cerebellum. Extramedullary hematopoiesis[2].

Two slightly different varieties of thanatophoric dysplasia viz. TD I and TD II are recognized. The TD I is more common and presents with the classical picture which is described above. In TD II the only difference is that the femurs are longer and straighter unlike in TD I where they are curved and shaped like a telephone receiver. Our case presented with the classical picture of TD I.

The TD II clinical phenotype is associated with mutations that map to codon 650 of FGFR3, causing the substitution of a glutamic acid for the lysine moiety. This activates the tyrosine kinase activity of a receptor that transmits signals to intracellular pathways. Mutations of the TD I phenotype map mainly to two regions in the extracellular domain of the receptor, where they substitute cysteine residues for other amino acids. Free cysteine residues are believed to form disulfide bonds promoting dimerization of receptor molecules, leading to activation and signal transmission.

The exact etiology of this disorder is not known. Most of the documented cases are sporadic. Both TD I and TD II represent new mutations to normal parents. The recurrence risk is negligible. Because the mutated codons in TD are mutable for unknown reasons and because of the theoretical risk for germ cell mosaicism, parents are offered prenatal diagnosis for subsequent pregnancies as was done in our case.

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