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Case Report

Thanatophoric dwarfism

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ABSTRACT

Thanatophoric Dwarfism (TD) literally meaning 'death seeking dwarf' in Greek, is the most common form of sporadic lethal skeletal dysplasia. This condition is both sporadic and autosomal dominantly inherited and is characterized by severe micromelia, short limbs, short ribs, narrow thorax, macrocephaly, coarse facial features, brachydactyly, hypotonia and X-ray features of 'telephone receiver hand' femur. TD has an estimated prevalence of 0.28 to 0.60 per 1000 births. In this study we report the clinical profile, radiological features and detailed genetic work up of the case with relevant review of literature. Currently, specific therapeutic regiments do not exist. Prenatal diagnosis is available by ultrasonography and molecular studies.

Keywords: Thanatophoric, Sporadic, Micromelia, Telephone receiver hand, Genetics

INTRODUCTION

Thanatophoric Dysplasia (TD) is a rare osteochondro dysplasia usually lethal in the perinatal period. It is characterized by marked underdeveloped skeleton and short-limb dwarfism. The name, 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.[1] It was reported that hypochondroplasia, achondroplasia and thanatophoric dysplasia are the different types of mutation in FGFR3 with hypochondroplasia being the mildest and TD, the most severe form.[3] We discuss the clinical profile, radiological investigations and detailed genetic work up of TD in the present report.

CASE REPORT

A female baby born at 30 week of gestation to non-consanguineous couple was admitted to our NICU in view of not cried immediately after birth, anomalies and low birth weight. Mother was 19 year old primigravida with no previous abortions and had not undergone regular antenatal check-ups and antenatal scans were not done .She had developed signs of severe pregnancy induced hypertension and was in second stage of labour at the time of hospitalisation. On examination, baby weighed 750 grams, looked dysmorphic (Figure 3) and general condition was poor. There was central and peripheral cyanosis, tachypnoea and oxygen saturation with head box oxygen was 70-75%. Baby was euglycemic, hypothermic and had poor cry and activity. Baby's length was 36 cm with US:LS ratio of 2.5:1. There was macrocephaly (head circumference of 39 cm), anterior and posterior fontanelle were wide open with sutural separation and soft skull (Figure 2 & 3). Baby had a coarse facies with frontal bossing, mid facial hypoplasia, hypertelorism with prominent eyes with hazy and large cornea (Figure 2), depressed nasal bridge, low set ears and high arched palate. Neck was short, upper and lower limbs were shortened (Rhizomelic dwarf) with short stubby fingers trident hand and deep skin creases (Figure 3 & 4). Thorax was narrow and bell shaped and abdomen was protuberant (Figure 3). Spine was normal. Baby had bilateral decreased air entry and cardiac examination was

normal. With the characteristic facial features and skeletal anomalies we considered the diagnosis of TD.[3-6]

On investigation, infantogram showed large size skull with short base, small face, flat vertebral bodies (platyspondyly), typical "bicycle handle appearance" of clavicles, while both the humerii and femora revealed "telephone receiver handle" appearance. Thorax was narrow with horizontally placed ribs and widened costochondral junctions. Brachydactyly with absence of carpal and tarsal bones were also noted on the infantogram (Figure 3). Baby was managed with mechanical ventilation and other supportive measures as per unit protocol. However, the general condition did not improve and baby died after 6 hours of NICU stay. Following death, for academic interest baby was subjected to CT scan and autopsy, both on CT & autopsy the findings were suggestive of TD[2,7,8] and pulmonary hypoplasia was labeled as the most probable cause of death. Karyotyping was normal (Figure 1) and genetic sequencing was done, DNA from the sample was isolated & primers were created for 6 exonic regions of FGFR3 (Exon 3, 11-15). PCR was performed. Sample was purified & eluted. Then sample was outsourced for sequencing as an end result we got mutation (synonymous) in Exon 14 of FGFR3 & five mutation were found to be in introns of FGFR3, including branch point mutation interrupting splicing.

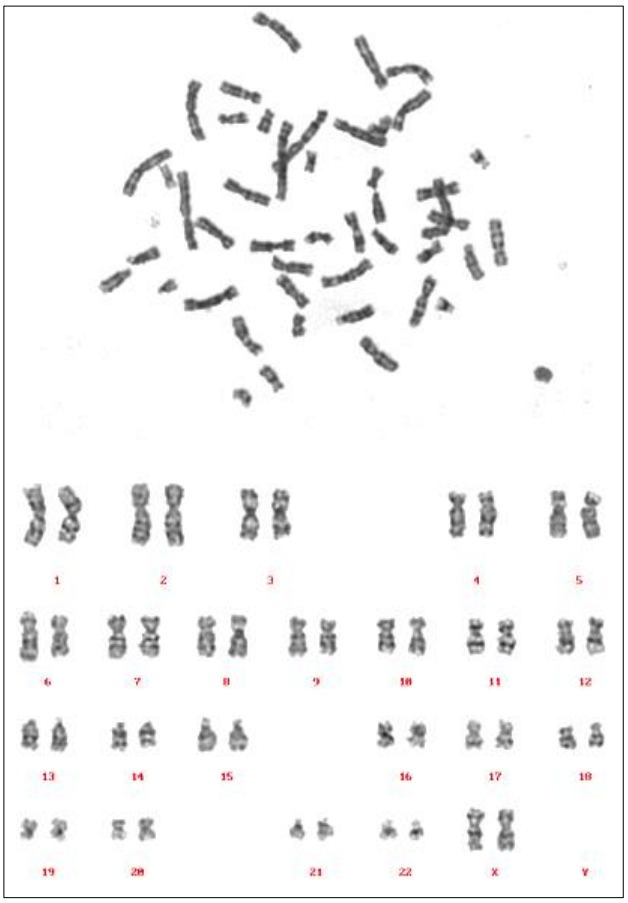

Figure 1: Normal karyotyping.

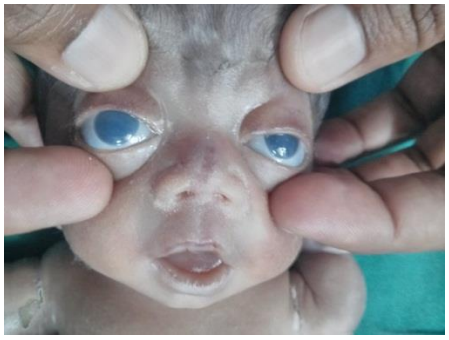

Figure 2: Megalocornea hazy cornea flat nasal bridge epicanthal fold hypertelorism.

Figure 3: Coarse facies with frontal bossing, mid facial hypoplasia, hypertelorism with depressed nasal bridge, low set ears Neck short, upper and lower limbs were shortened (Rhizomelic dwarf) with short stubby fingers trident hand and deep skin creases.

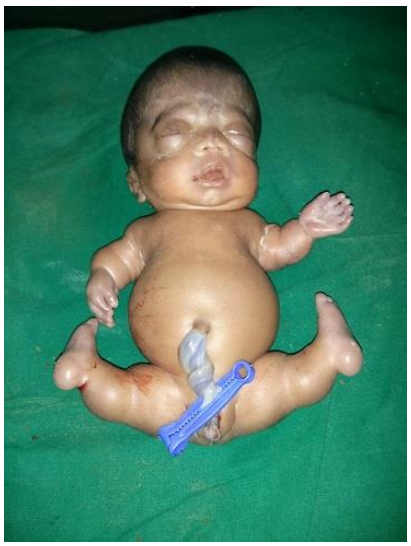

Figure 4: Large head soft skull narrow thorax and bell shaped protruberant abdomen, lax joints and rhizomelia.

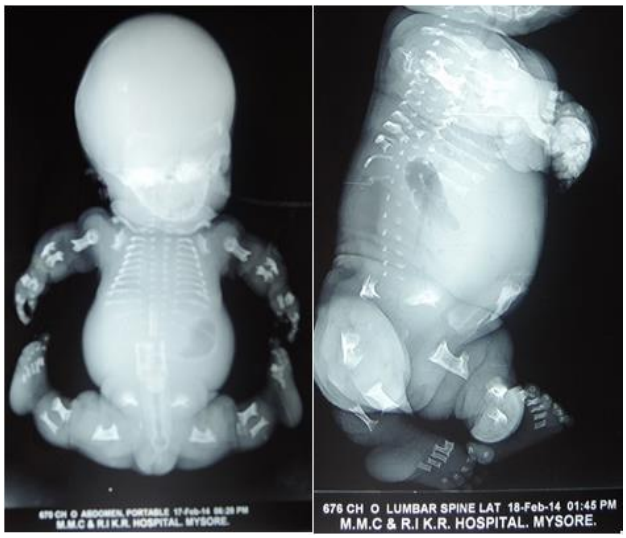

Figure 5 & 6: Radiographs showing (i) large skull with narrow base (ii) horizontally placed ribs (iii) flattened vertebral bodies (iv) bicycle handle appearance of both clavicles (v) characteristic telephone receiver appearance of both humerii and femora.

SEQUENCE TRIMED TDRV04

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FGFR3       CTTCCACTGCTGTGTCTGTAAACGGTGCCGGGTTTGGGGGTGCCTGCCTCATGGTTGCCC
TDRV04      ------------------------------------------------------------

FGFR3       ATCTTCCCCACAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGC
TDRV04      ---CTTCCCACAGAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGC
                 * ************************************************

FGFR3       AGCGGGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACT
TDRV04      AGCGGGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACT
            ************************************************************

FGFR3       GTCTGGGTCAAGGATGGCACAGGGCTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAG
TDRV04      GTCTGGGTCAAGGATGGCACAGGGCTGGTGCCCTCGGAGCGTGTCCTGGTGGGGCCCCAG
            ************************************************************

FGFR3       CGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTACAGCTGCCGGCAGCGG
TDRV04      CGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTACAGCTGCCGGCAGCGG
            ************************************************************

FGFR3       CTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGGTGAGCTCTGGGGCCAC
TDRV04      CTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGGTGAGCTCTGGGGCCAC
            ************************************************************

FGFR3       GCCAGCTACAGAAAGGAGCCGAGTGCCGGGCTCCCTGAGTCCCTGCGTGGGTCAGGAGCG
TDRV04      GCCAGCTACAGAAAGGAGCCGAGTGCCGGGCTCCCTGAGTCCCTGCGTGGGTCAGGAGCG
            ************************************************************

FGFR3       GCTGGGGGTCTCTCTGGTCATTGGTGGAGAGGAGGGCACCCCCAGGAAGTGCTGCCCAAA
TDRV04      GCTGGGGGTCTCTCTGGTA-----------------------------------------
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Figure 7: FGFR3 gene sequencing.

Missense mutation in the branch point of introns ACG is replaced with ACA coding for tryptophan….

DISCUSSION

TD presents as a short limb dwarfism usually lethal in the perinatal period. At present two forms of thanatophoric dysplasia are recognized.[3,9] Type I is more common than type II.

TD type I is characterized by curved femur (telephone receiver hand) and very flat vertebral bodies and type II by straighter femur, wider bones, flatter vertebral bodies (platyspondyly) and clover leaf skull.[3,4] In our case curved long bones were present which is characteristic of type I TD, which is now considered as an autosomal dominant condition with a high new mutation rate[1] but there have been a few reports of familial occurrence suggesting autosomal recessive inheritance also. The two conditions which present a difficulty in diagnosis are achondroplasia and achondrogenesis.[3] In classical achondroplasia limbs are longer, neonatal deaths uncommon, long bones not curved and metaphyseal abnormalities less marked. In rare patients with homozygous achondroplasia, the differentiation becomes still difficult, while a family history of dwarfism makes differentiation possible. In achondrogenesis radiological features of extreme degree of deficient ossification in vertebral bodies is highly suggestive.[3,5]

Sonographic features of TD include narrow thorax, protruberant abdomen, hydramnios, marked shortening of the ventriculomegaly and clover leaf skull, major long bones, bowing of extremities, platyspondylosis has been difficult to diagnose sonographically.[4,10] Although, clover leaf skull is also seen as an isolated entity, its presence with short limbs is highly suggestive of TD type 11.[1,5] Recently, cephalometric analysis by ultrasound is used for prenatal diagnosis of TD.[7] All long bones should be examined to determine distal versus proximal limb shortening. Osteogenesis imperfecta is suggested by fractured limbs or ribs, while achondrogenesis is characterized by fewer than three ossification centers per spinal segment.[5] When lethal forms of dwarf ism are suspected, foetal radiographs are recommended to provide corroborative data regarding the specific type of dwarfism

Early neonatal death in TD may be due to reduced thoracic dimensions causing pulmonary hypoplasia. Malformations, deformations and potentially significant neuroaxial injury, principally at the level of the atlas vertebrae may also contribute to the death.[8,9] Recently, many reports of patients with TD surviving the neonatal period have been documented in literature and one patient had survived 9 years.[13] Respiratory failure is the common cause of death.[15] Brain stem compression resulting from hydrocephalus which may develop beyond the neonatal period also contributes to ventilator insufficiency.[8-10] Surgical interventions by decompressions of brain stem in small foramen magnum has allowed prolonged survival in some of these cases.[8,9]

Both types of TD are caused by mutations in FGFR3 gene. In TD type II a single FGFR3 mutation at exon15 has been identified. Upto 99% disease mutations causing TD type I and >99% of mutations causing TD type II can be detected by sequence analysis of selected exons of FGFR3 (exons 7, 10, 15, and 19 for TD type I; and exon 15 for TD type II). No affected individuals are known to have had children. Hence the majority of probands have a de novo gene mutationthough (TD) is inherited in an

autosomal dominant manner with complete penetrance. Pathologic allelic variants are also found. In TD type I, FGFR3 mutations responsible for the TD type I phenotype can be divided into two categories[16] missense mutations and stop codon mutations. In missense mutations most of these mutations create new, unpaired cysteine residues in the protein. The two common mutations p.Arg248Cys and p.Tyr373Cys probably account for 60%-80% of TD type I.[16] In Stop codon mutations these mutations cause a read-through of the native stop codon, adding a highly hydrophobic alpha helix-containing domain to the C terminus of the protein. Mutations that obliterate the stop codon represent 10% or more of TD type I mutations. In TD type II. A single FGFR3 mutation (p.Lys650Glu) has been identified in all cases of TD type II.

Management

Treatment of manifestations: Management focuses on the parents' wishes for provision of comfort-care for the newborn. Newborns require respiratory support (with tracheostomy and ventilation) to survive. Anesthetic management includes intubation with a flexible fiberoptic scope with the cervical spine in a neutral position; use of evoked potential monitoring during the procedure; and avoidance of volatile anesthetic agents and muscle relaxants that may interfere with evoked potential recordings.[9] Other treatment measures may include: antiepileptic drugs to control seizures, shunt placement for hydrocephaly, suboccipital decompression for relief of craniocervical junction constriction, and hearing aids.

In our case baby survived only 6 hours after birth and died of respiratory failure.

Surveillance: TD is lethal disease usually dies in the neonatal period long-term survivors need neurologic, orthopedic, and audiologic evaluations, CT to monitor for craniocervical constriction, and EEG to monitor for seizure activity.

CONCLUSION

TD is a both sporadic and autosomal dominant skeletal dysplasia which is usually lethal in perinatal period. Short and curved long bones, micromelia, narrow thorax and platyspondyly are the hallmarks of TD. Good quality antenatal sonography will detect foetuses with features of TD in utero. Diagnosis is confirmed with genetic sequencing and mutational analysis of FGFR3 gene. Post-mortem autopsy is helpful in doubtfull cases. Prenatal diagnosis and genetic counselling helps parents make wise decisions with regard to the continuation and outcome of pregnancy.[15]

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