A CASE OF THANATOPHORIC DYSPLASIA TYPE I: THE FIRST CLINICOPATHOLOGIC REPORT FROM ETHIOPIA

Bethel Dereje,M.D[1], Yirgu Gebrehiwot, M.D,M.Sc.[2], Jakob Schenider,M.D[3]
[1]Department of Obstetrics and Gynecology, St. Paul's Hospital Millennium Medical College
[2]Department of Obstetrics and Gynecology, AAU, School of Medicine
[3]Department of Pathology, AAU, School of Medicine

ABSTRACT

Thanatophoric dysplasia (TD) is a short-limb neonatal dwarfism syndrome that is usually lethal in the perinatal period1. It is characterized by markedly underdeveloped skeleton and short-limb dwarfism. TD is caused by a mutation of the fibroblast growth factor receptor 3 gene (FGFR3), which is located on the short arm of chromosome 42,3.This study reports a neonate born at Tikur Anbessa Teaching Hospital with features of thanatophoric dysplasia which was proven radiologically and pathomorphologically. The mother presented to the hospital at 39 +1 weeks of gestational age with ultrasound diagnosis of achondroplasia. She developed cephalopelvic disproportion and underwent caesarian section. Outcome was an alive anomalous female neonate with a weight of 2900 gms of 4, 2, 2 & 0 in the 1st, 5th, 10th & 20th minute APGAR scores, respectively. The neonate expired due to severe respiratory distress despite resuscitation. The parturient died following pulmonary thromboembolism diagnosed on her second postoperative day.

CONCLUSION:

Thanatophoric dysplasia is a lethal skeletal anomaly which should be diagnosed and managed in the second trimester of pregnancy. Missing this case in the mid-trimester costed note only the physical, psychological and the economic burden but also the life of the mother.

KEY WORDS:

Thanatophoric dysplasia, fibroblast growth factor receptor 3 gene (FGFR3)

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INTRODUCTION

Thanatophoric dysplasia (TD) is the most common form of skeletal dysplasia known to be lethal in neonatal period.[3] The prevalence rate, per live births for thanatophoric dysplasia in Northern Ireland has been calculated to be 0.8/10,0004. It is characterized by markedly underdeveloped skeleton and short-limb dwarfism. The name TD is derived from the Greek word which means "death-bearing." TD presents with macrocephaly, narrow bell-shaped thorax with shortened ribs, normal trunk length, and severe shortening of the limbs[4].

TD is divided into two clinically defined subtypes: TD type I(TD-1) and TD type II (TD-2). The clinical subtypes are defined mainly by the appearance of the long bones; whether they are curved or straight. TD-1 is the most common subtype, is characterized by a normal shaped skull and curved long bones (shaped like old-fashion telephone receivers). TD-II is associated with a cloverleaf-shaped skull and straight femurs[4].The incidence of type 1 TD (TD1) is variously quoted as 1 in 20 000 - 40 000 stillborn and live born infants 1 in 33 000 - 47 000 live births3. TD is caused by a mutation of the fibroblast growth factor receptor 3-gene (FGFR3), which is located on the short arm of chromosome[4]. The penetrance of this mutation is 100%. It was reported that hypochondroplasia, achondroplasia and thanatophoric dysplasia are the different types of mutations in FGFR3 with hypochondroplasia being the mildest and TD, the most severe form [2,3]. The diagnosis is usually made by ultrasonography in the second trimester2. The radiological features of TD1 are characteristic when the infant is delivered at termmacrocephaly, symmetrical micromelic shortening of long bones, metaphyseal cupping of the proximal femora, telephone-receiver shaped femora, hypoplastic or small scapulae, platyspondyly with H-shaped vertebrae in the anterior-posterior view, a narrow thorax with short ribs, and characteristic triradiate acetabulum with short sacrosciatic notches. Interpediculate narrowing of the spinal canal evident on lateral views results in damage to the spinal cord in rare survivors. In TD2, the skull has a marked anterior depression forming the trilobal cloverleaf skull[3].

The possible differential diagnosis are Achondrogenesis, Achondroplasia (homozygous type), Asphyxiating Thorasic dystrophy, Hypophosphatasia, Osteogenesis imperfect type II.

The teartment of TD mainly depends on early prenatal diagnosis and termination of pregnancy via vaginal route. In case of postpartum diagnosis, intubation is performed to treat respiratory distress: the neonate need to be admitted to neonatal intensive care unit (NICU)[4].

Since this anomaly is a lethal congenital anomaly, it should be diagnosed and managed early in the second trimester. We will discuss the anatomical features, pathologic findings and possible option of management of TD in the present report, which would help in the further earlier intervention before significant physical, economical and psychological burden both for the family and the health service as a whole.

CASE REPORT

A 33 years old gravida III, para I mother with one previous history of spontaneous abortion from Addis Ababa presented with rupture of the membranes and pushing down pain of 8 hours at a gestational age of 39 weeks and 1 day. She had two antenatal care visits at a health center. She presented to Tikur Anbessa Teaching Hospital (Addis Ababa, Ethiopia) on December 7, 2011 with an ultrasound report of achondroplasia, and with estimated fetal weight of 4200 gms. She was admitted to the labor ward with the diagnosis of Term pregnancy, latent first stage of labor, pregnancy induced hypertaion, fetal Achondroplasia and Obesity. Sonographic study was not repeated and cesarean delivery was decided for cephalopelvic disproportion (CPD) after the progress of labor was followed in the labor ward. Outcome was an alive anomalous

female neonate with a weight of 2900gms with APGAR score of 4, 2, 2 & 0 in the 1st, 5th, 10th& 20th minute respectively.

The neonate had macrocephally with head circumference (HC) of 41 cm, and frontal bossing, depressed nasal bridge, bell shaped thorax, both upper extremities measured 11 cms, right lower extremities equaled 11cms, left lower extremity was 13cms, abdominal circumference of 34 cms, and crown-heel length of 38 cms. The umbilical cord was 20 centimeters long and fragile with focally adherent placenta. The neonate expired on arrival to NICU after resuscitation was tried in the operation theater. The body was subjected for autopsy and radiographic study after taking consent from the parents (Fig 1). There was no maternal history of drug, alcohol, or tobacco use. The baby's parents were healthy, and there was no family history of congenital abnormalities. Paternal age was 34 years.

The mother had a smooth immediate postoperative period until the second day which she developed sudden onset of respiratory distress with drop in saturation. She was transferred to intensive care unit with possible cause of massive pulmonary thromboembolism for respiratory support, but she couldn't be salvaged.

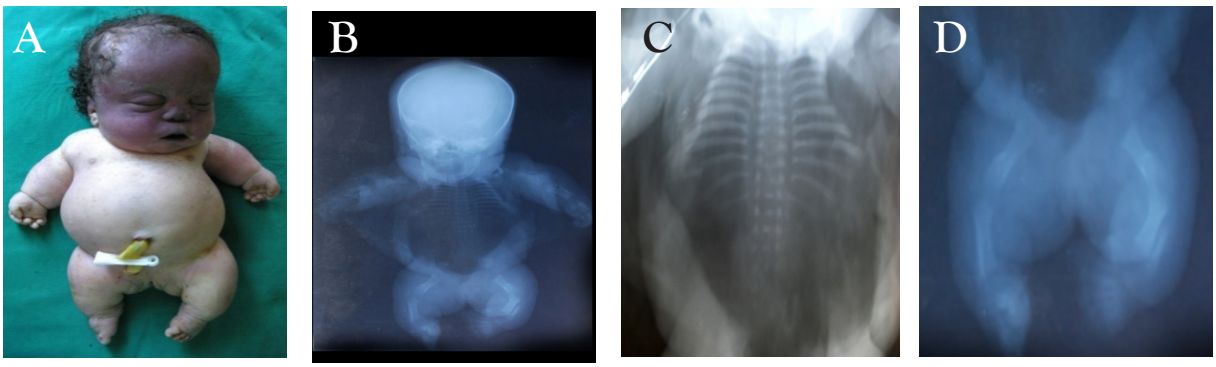

Fig.1 A. Photograph of the neonate taken the day of delivery showing large head, markedly short limbs, and narrow thorax

Fig 1B, 1C &1D. Radiography of the neonate demonstrating thanatophoric dysplasia type I (TD1) findings, including platyspondyly, a severely hypoplastic pelvis, shortness of long bone, hypoplasia of the lungs and thorax, and femoral bowing ("telephone receiver" femur).

RADIOLOGIC FINDINGS:

Radiography of the neonate demonstrating thanatophoric dysplasia type I (TD1) findings including: macrocephaly, platyspondyly, a severely hypoplastic pelvis, shortness of long bone, hypoplasia of the lungs and thorax, and femoral bowing ("telephone receiver" femur).

AUTOPSY FINDINGS:

Autopsy results also confirmed Thanatophoric dysplasia type I. Hypoplastic lungs with malformed veins and persistent fetal circulation. The pertinent autopsy features reported were:

BONES:

VERTEBRAL COLUMN- flat vertebral bodies with small center of mineralized cartilage and minimal bone formation. Cartilaginous part was vascularized.

LONG BONES: both femurs were curved which is the so called "telephone receiver" and showed marked resting bone zone with indistinct or absent proliferation zone (Fig. 2).

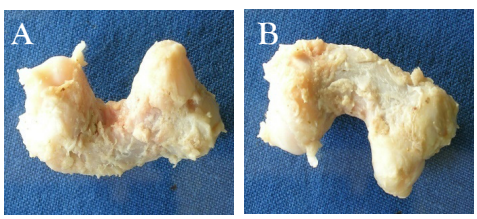

Fig.2: Right and left femur: Short and deformed ("telephone-receiver") but normal thickness (normal periosteal growth).

Zone of hypertrophy was focal and very small. This chaotic zone of cartilage which is seen at the epiphyseal plate (Fig 3a). Mineralization of cartilage, deposition of osteoid, and periosteal bone formation was normal (Fig 3b).

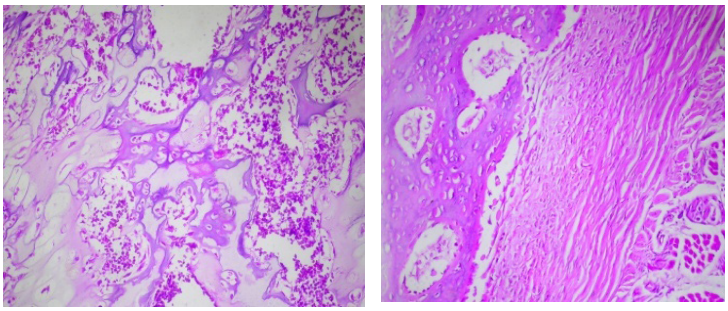

Fig. 3a: The chaotic growth plate of the humerus resulting in disturbed longitudinal growth.
Fig. 3b: Normal periosteal growth resulting in normal thickness of the tubular bones.

RIB: The bony part is side-by-side with the cartilage part. Bony part showed marked periosteal bone formation and cartilage part showed chaotic zones with indistinct columns and central vascular core.

CENTRAL NERVOUS SYSTEM: Choroid plexus showed angiomatoid change with focal hydropic swelling and ectopia. Subependymal ruminants of germinal cells.

RESPIRATORY: Hypoplastic lungs and the left lobe larger than the right. It was poorly inflated. Have features of capillary dysplasia with misalignment of vein (Fig. 4) Persistent fetal circulation.
Autopsy Conclusions: Thanatophoric dysplasia type I: Hypoplastic lungs with malformed veins and persistent fetal circulation, features of right ventricular failure.

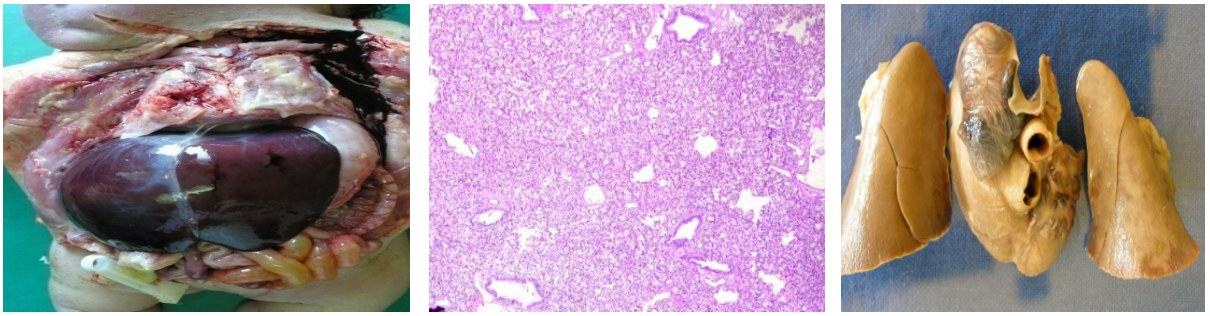

Fig.4a: Situs: Narrow bell-shaped thorax and hepatomegaly.
Fig.4b: Heart and lung: The proportion between heart and lung reveals the severe hypoplasia of the lung.
Fig.4c: Histology of the lung: The arrangement of the veins is abnormal. Instead of being within the interlobular septae some accompany the arteries (misalignment of pulmonary veins)

DISCUSSION

The term thanatophoric dysplasia (TD) originates from a Greek word 'Thanatophores' which means constantly bearing death. It was first described by Maroteaux et al in 1967[6]. It is characterized by a large head with a prominent forehead; macrocephaly occasionally with a cloverleaf–shaped skull known as kleeblattschädel, depressed nasal bridge, shortening of the limbs. A hypoplastic thorax is common, which is disproportionately small in relation to the abdomen. Classically, a bell-shaped thorax has the shape of a champagne bottle cork and results in pulmonary hypoplasia. Characteristic radiologic findings include excessive shortening of the long bones, telephone receiver shape of femur, disproportionate thorax with short hypoplastic ribs and malformed pelvis, with flat speculated acetabulum. Vertebrae are flattened with diminution of the intervertebral space[1,7]. Hydramnios is a common finding. It is commonly mistaken clinically for

achondroplasia, particularly the heterozygous type in which both parents are of normal stature. This confusion is unlikely when one or both parents are achondroplastic dwarfs, since a TD offspring from this combination has not been reported[6]. This scenario occurred in our case the patient came with sonographic report of a diagnosis of Achondroplasia.This dysplasia has two types, differentiated by the skull shape and the femur morphology.

Type I (80%) is characterized particularly by the femur shape which is in a telephone receiver like configuration, severe platyspondylia and no cloverleaf shaped skullType II (20%) differs from type I especially by the cloverleaf-shaped skull, the femur that is straighter and the vertebral bodies that are a little taller than in type I. in our case the diagnosis is confirmed to be TD-1 from both radiologic and pathologic report.

Affected neonates generally die within minutes or days after birth, usually from respiratory failure[1,8]. In our patient the lung was not only hypoplastic, but also showed reduced capillarization of the alveolar septae with some of the veins in abnormal position, features suggestive of capillary dysplasia with misalignment of veins.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. This receptor is particularly abundant in the cartilage growth plates. 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[1,2].

Histologically, resting cartilage has normal cellular density with abundant homogeneous matrix. Enchondral ossification is severely disturbed. Hypertrophic chondrocytes are recognizable but in disordered arrangement.The most characteristic abnormality is hypertrophy of the periphysis with penetration of the growth plate so that fibrous disorganization with formation of plump, haphazardly arranged, bony trabeculae is apparent. This fibrous disorganization of the growth plate is not uniform[9]. In our case the chaotic zones of cartilage that are seen at the epiphyseal plate disturbs the longitudinal growth of the long bones for which reason this anomaly present with shorted long bones. Mineralization of cartilage, deposition of osteoid, and periosteal bone formation was not affected, which resulted a normal bone thickness. Abnormalities in the central nervous system have been described and mainly affect the temporal lobe[9]. In the present case we found angiomatoid changes of the choroid plexus and an ectopic rudimentary ventricle in the subarachnoid space.A definite diagnosis should be established by molecular genetic analysis to find out the abnormal mutations in the FGFR3 gene[1]. But in developing countries like Ethiopia were genetic analysis is not widely available clinical, radiological and pathological knowledge should applied to reach up in a diagnosis.Prenatal diagnosis in the second trimester can allow for elective abortion to be carried out, thereby avoiding possible complications such as later caesarean section, difficult vaginal delivery due to hydrocephalus, and malpresentation later in the pregnancy[10]. In our case late diagnosis brought not only physical, psychological and economic burden but also a grave complication which caused maternal death.

The overall prognosis is poor. Most patients die of respiratory insufficiency due to reduced chest circumference and hypoplastic lung within 48 hours, although four to nine-year survivals have been reported.[1]**Summary**Thanatophoric dysplasia is a lethal skeletal disease. This can be diagnosed with mid-trimester ultrasonographic scan; at which time it can be managed without significant complication.

In the presented case it was diagnosed late in the postpartum period. If it was diagnosed early all the complications could have been prevented. Even if ultrasound is not accessible in all Antenatal care service delivery centers, mid-trimester scan should be route in those centers with ultrasonography.

CORRESPONDING AUTHOR:
Bethel Dereje, M.D
Department of Obstetrics and Gynecology, St. Paul's Hospital Millennium Medical College
Email: drbettyd@gmail.com

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