Thanatophoric dysplasia was originally described by Maroteaux et al. in 1967. The term “thanatophoric” was coined to mean “death bearing” in Greek. Thanatophoric dysplasia is probably the most common lethal neonatal dwarfism with an estimated incidence of 0.2–0.5 per 10,000 births.

GENETICS/BASIC DEFECTS

1. Genetic heterogeneity
   a. Sporadic in most cases
   b. A new autosomal dominant mutation
   c. Caused by mutations in the transmembrane domains of the fibroblast growth factor receptor 3 (FGFR3)

2. Having the most extreme micromelia and the most extensive craniofacial involvement, compared to two other short limb skeletal dysplasias (achondroplasia and hypochondroplasia) which are also caused by mutations of FGFR3

3. Pathogenesis for the phenotypic features of thanatophoric dysplasia
   a. Normal function of FGFR3: to regulate endochondral ossification by “putting the brakes on growth”
   b. “Gain-of-function” type of known mutations on FGFR3
      i. Primarily affect the cranial base and nasal capsule (endochondral bones)
      ii. With secondary effect on membrane bones which articulates with endochondral bones

4. Two major forms (TD1, TD2) of thanatophoric dysplasia, postulated based on subtle differences in skeletal radiographs and the underlying genetic mutation
   a. TD1
      i. Curved femora
      ii. Very flat vertebral bodies
      iii. Very few TD1 patients with cloverleaf skull
      iv. Molecular defect consisting of a stop codon mutation or missense mutation in the extracellular domain of the FGFR3 protein, resulting in a newly created cysteine residue (Arg248Cys, most common)
   b. TD2
      i. Straight femora
      ii. Taller vertebral bodies
      iii. Most TD2 patients with cloverleaf skull (severe craniosynostosis)
      iv. Molecular defect consisting of a single nucleotide substitution resulting in replacement of lysine with glutamine at position 650 (Lys650Glu) in the tyrosine kinase 2 domain of the receptor

CLINICAL FEATURES

1. Unique and homogeneous clinical features observed in patients with TD1

2. General features
   a. Virtually lethal neonatally
   b. A few reports with survival up to 4–5 years of age with aggressive neonatal intervention
      i. Markedly limited growth potential
      ii. Markedly delayed cognitive development
      iii. Respiratory insufficiency
      iv. Neurologic abnormalities
      v. Long-term medical care and chronic ventilator dependence

3. Craniofacial features
   a. Head
      i. Disproportionally large (macrocephaly)
      ii. Frontal bossing
      iii. With or without cloverleaf (Kleeblattschdel) anomaly of the skull resulting from premature closure of cranial sutures
   b. Facial features
      i. Bulging eyes
      ii. Hypertelorism
      iii. Severely depressed or indented nasal bridge

4. Short neck

5. Chest
   a. Extremely narrow
   b. Constricted thoracic cage
   c. Reduced size of the thoracic cavity
   d. Short ribs
   e. Hypoplastic lungs

6. Protuberant abdomen

7. Limbs
   a. Extremely short
   b. Thickened skin
   c. Excessive skin folds
   d. Usually outstretched arms
   e. Externally rotated legs with abducted thighs
   f. Syndactyly

8. Early death in most children secondary to:
   a. Chest constriction and consequent respiratory insufficiency
   b. Foramen magnum stenosis resulting in failure of respiratory control

9. A few children with longer survival (up to 9–10 years)
   a. Respiratory insufficiency
      i. Reduced chest circumference
      ii. Upper cervical cord compression resulting from a diminutive foramen magnum
   b. Markedly limited growth potential
   c. Markedly delayed cognitive development
   d. Seizures
   e. Hearing loss
   f. Additional CNS anomalies
      i. Hydrocephalus
      ii. Polymicrogyria

955
iii. Neuronal heterotopia
iv. Megalencephaly
vi. Hippocampal malformation
vii. Temporal lobe malformations
viii. Nuclear dysplasia
ix. Abnormal axonal bundles
x. Cerebellar hypoplasia in the small posterior fossa
xi. Partial agenesis of the corpus callosum
xii. Spinal stenosis
xiii. Hyperreflexia
xiv. Clonus
g. Acanthosis nigricans, an associated rare skin disorder

10. Differential diagnosis
   a. Achondroplasia
      i. Autosomal dominant disorder
      ii. Rhizomelic shortening of the bones, less prominent than thanatophoric dysplasia
      iii. Macrocrania
      iv. Heterozygous achondroplasia
         a) Compatible with normal life span
         b) Normal intelligence
      v. Homozygous achondroplasia with two affected parents
   b. Campomelic dysplasia
      i. Autosomal recessive disorder
      ii. Typical anterior bowing of the lower limbs
      iii. Hypoplastic fibula
      iv. Hypoplastic scapulae
      v. A sex reversal phenomenon (phenotypical female with male karyotype)
   c. Osteogenesis imperfecta type II and type III
      i. Varying degree of bone demineralization
      ii. Shortened long bones with multiple fractures
      iii. Blue sclerae
      iv. Polyhydramnios frequently associated with type II
   d. Hypophosphatasia
      i. Demineralization of bone tissue
      ii. Lack of calcification of the fetal skull
      iii. Mild to moderate shortening of limb bones
      iv. Difficult to differentiate from osteogenesis imperfecta if fractures are present
   e. Achondrogenesis
      i. Severe Micromelia
      ii. Poor ossification of the vertebral bodies, cranium, pelvis and sacrum
      iii. Narrow and shortened thorax
      iv. Frequent complications with fetal hydrops and hydramnios
   f. Short rib-polydactyly and other rare skeletal dysplasia syndromes

DIAGNOSTIC INVESTIGATIONS
1. Radiographic features
   a. Skull
      i. Relatively large calvarium
      ii. A small foramen magnum
      iii. Trilobed skull with a towering calvarium and bitemporal bulging in the cloverleaf skull type (type 2)
   b. Ribs
      i. Very short ribs with cupped anterior ends
      ii. Short ribs (type 2)
   c. Vertebrae
      i. Flat vertebral bodies (platyspondyly)
      ii. Increasing intervertebral disc space
      iii. “Inverted U-shaped or H-shaped” vertebral bodies
      iv. Narrow interpedunculate distance at the lumbar level
      v. Taller vertebral bodies (type 2)
   d. Pelvis
      i. Short
      ii. Small sacrosciatic notches
   e. Tubular bones
      i. Extremely shortened long bones of the limbs
      ii. Rhizomelic shortening of the limbs
      iii. Flared metaphyses
      iv. “Telephone-receiver”-like curved femora in the noncloverleaf type
      v. Relatively straight femora (type 2)

2. Histologic features
   a. Generalized disruption of endochondral ossification
      i. Hallmark of the histologic findings
      ii. Physal growth zone shows minimal proliferation and hypertrophy of chondrocytes with absence of column formation.
      iii. Lateral overgrowth of metaphyseal bone around the physes
      iv. Mesenchymal cells extending inward from the perichondrium as a narrow band at the periphery of the physal zone (the so-called fibrous band)
      v. Increased vascularity of the resting cartilage
   b. Brain
      i. Neuronal migration abnormalities of the temporal lobe
      ii. Hydrocephalus
      iii. Partial agenesis of the corpus callosum
      iv. Upper cord compression
      v. Spinal stenosis

3. DNA mutation analysis of FGFR3
   a. TD1
      i. 742C→T (Arg248Cys): most common
      ii. Tyr373Cys
      iii. Ser249Cys
      iv. Other missense mutations
      v. Stop-codon mutations
   b. TD2: missense mutation of 1948A→G (Lys650Glu) in TD2

GENETIC COUNSELING
1. Recurrence risk
   a. Patient’s sib: about 2%
   b. Patient’s offspring: not surviving to reproduction
2. Prenatal diagnosis
   a. Ultrasonography
      i. Hydramnios in most cases
      ii. Megacephaly with or without cloverleaf-shaped skull
      iii. Progressive hydrocephaly
iv. Hypoplastic thorax disproportionately small in relation to the abdomen
v. Small chest and lung measurement to predict severe pulmonary hypoplasia
vi. Short ribs
vii. Short limbs with curved “telephone handled” or straight femurs
viii. Excessive skin giving fetus a “boxer’s face” appearance
ix. Flattened vertebrae with increased intervertebral spaces, giving the vertebral bodies the form of an “H”
b. Prenatal radiography for documenting characteristic skeletal anomalies
c. DNA mutation analysis of FGFR3 in fetal cells from amniocentesis or CVS

3. Management
a. Limited intervention
i. Appropriate because of the inevitable lethal outcome
ii. Aggressive neonatal management, at times, not even resulting in short-term survival
b. Debatable issues about the level of intensity of medical care for unanticipated long-term survival
i. Long-term medical care
ii. Chronic ventilator support
iii. Requiring extensive health maintenance measures
iv. Anticipate frequent medical exacerbations requiring recurrent hospitalizations
v. Possibility of lethal complication, an ever-present concern
vi. Special education programs for the longer survivors

REFERENCES

Fig. 1. Front views of 3 infants showing frontal bossing, flat facies, short neck, micromelia, and small chest.
Fig. 2. AP radiographic views of three infants with typical findings of TD1 showing profound platyspondyly, decreased thoracic volume, characteristic pelvic configuration, micromelia, and so-called “telephone receiver” femoral bowing.

Fig. 3. Lateral radiographic views of the spines in two infants with typical TD1 showing extreme platyspondyly and short ribs.

Fig. 4. Gross appearance of a femur resembling “telephone-receiver”.

Fig. 2. AP radiographic views of three infants with typical findings of TD1 showing profound platyspondyly, decreased thoracic volume, characteristic pelvic configuration, micromelia, and so-called “telephone receiver” femoral bowing.
Fig. 5. Prenatal radiographs of two fetuses affected with thanatophoric dysplasia showing platyspondyly, short ribs, and micromelia.
Fig. 6. Thanatophoric dysplasia in identical twin fetuses. The pregnancy was terminated following ultrasonographic diagnosis at 22 weeks gestation. The placenta was diamniotic monochorionic, consistent with monozygotic pregnancy.

Fig. 7. Thanatophoric dysplasia with cloverleaf skull in a neonate. The head is large and trilobed. The narrow chest and rhizomelic shortening of limbs are similar to those of classic thanatophoric dysplasia. Radiograph revealed platyspondyly and small ilium that are similar to those of classic thanatophoric dysplasia (not shown). However, the femur is straight and not as curved as seen in the classic type.

Fig. 8. Photomicrograph of the cartilage-bone junction, cloverleaf skull type of thanatophoric dysplasia. The physeal growth zone is markedly retarded and disorganized. Similar changes are seen in the classic type thanatophoric dysplasia. A partially ossified cartilage canal is present at the center of physis. It is more prominent in size and number in cloverleaf type than in classic type.