Thanatophoric dysplasia

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Abstract

Thanatophoric Dysplasia (TD) is a severe skeletal disorder that is lethal in the neonatal period. Two clinically defined TD subtypes have been classified: type I (TDI), characterized by micromelia with bowed femurs and, occasionally, by the presence of cloverleaf skull deformity of varying severity and type II (TDII), characterized by micromelia with straight femurs and a moderate to severe cloverleaf skull deformity. TD is caused by specific autosomal dominant mutations in the gene that codifies for the Fibroblast Growth Factor Receptor 3 (FGFR3). The mutations constitutively activate the tyrosine kinase activity of the receptor. As normally FGFR3 is a negative regulator of bone growth, the gain-of-function mutations associated to TD allow the activated receptor to send negative signals within the cells of the cartilage (chondrocytes), thus leading to the generalized disorganization of endochondral ossification at the bone growth plate.

The estimated birth incidence is approximately 1/20,000 to 1/50,000 TDI being more frequent than TDII. Most individuals with TD die within the first few hours or days of life by respiratory insufficiency secondary to reduced thoracic capacity or compression of the brainstem. Currently, specific therapeutic regimens other than sustenance of symptoms do not exist. Prenatal diagnosis is available, both by ultrasonography and by molecular studies.

Keywords
Thanatophoric dysplasia, dwarfism, Fibroblast Growth Factor Receptor 3 (FGFR3), Tyrosine Kinase, endochondral ossification
a cloverleaf skull and the neonates have straight femurs. Other common features to both TD include prominent platyspondyly of the vertebral spine, a small foramen magnum with a severe risk for brain stem compression and redundant skin folds along the limbs.

**Diagnosis criteria**

Diagnosis can be performed according to the following criteria:

- **Prenatal ultrasound examination**
  - growth deficiency recognizable by 20 weeks gestation
  - well-ossified spine and skull
  - platyspondyly
  - ventriculomegaly
  - narrow chest cavity with short ribs
  - polyhydramnios
  - bowed femurs (TDI)
  - cloverleaf skull (kleeblattschaedel) for TDII; sometimes in TDI.

For references see: Loong, 1987; Sawai et al. 1999; De Biasio et al. 2000; Chen et al. 2001. The identification of a severe skeletal dysplasia in the second trimester is usually straightforward, but establishing a specific diagnosis like TD can be rather difficult (Sawai et al. 1999, Parilla et al. 2003).

- **Postnatal physical examination**
  - macrocephaly
  - large anterior fontanel
  - frontal bossing, flat facies with low nasal bridge, proptosis
  - marked shortening of the limbs (micromelia)
  - trident hand with brachydactyly
  - redundant skin folds
  - narrow, bell-shaped thorax with short ribs and protuberant abdomen
  - relatively normal trunk length
  - generalized hypotonia.


- **Radiographs**
  - rhizomelic shortening of the long bones
  - irregular metaphyses of the long bones
  - platyspondyly
  - small foramen magnum with brain stem compression
  - central nervous system (CNS) abnormalities including temporal lobe malformations, hydrocephaly, brainstem hypoplasia, neuronal migration abnormalities
  - bowed femurs (TDI).

For references see: Wilcox et al. 1998; Lemyre et al. 1999; Gorlin et al. 2001.

**Histopathology**

- disorganized chondrocytes columns
- poor cellular proliferation
- lateral overgrowth of the metaphyses
- mesenchymal cells extending inward forming a fibrous band at the periphery of the metaphyses
- increased vascularity of the resting cartilage

For references see: Tavormina et al. 1995; Lemyre et al. 1999; Wilcox et al. 1998.

**Molecular genetic testing**

FGFR3 mutants are the cause of both TDI and TDII.

For TDI a series of missense mutations have been identified: R248C*, Y373C*, S249C, G370C, S371C (Rousseau et al. 1996; Passos-Bueno et al. 1999). The most common mutants (*) account for 60-80% of TDI (of note all mutations create new, unpaired cysteine residues in the FGFR3). Furthermore, stop codon mutations (X807L, X807G, X807R, X807C, X807W) have been identified (Rousseau et al. 1995; Rousseau et al. 1996).

For TDII a single point mutation in the FGFR3 gene (K650E) has been identified in all TDII analyzed (Rousseau et al. 1996; Gorlin 1997; Bellus et al. 2000).

**Differential diagnosis**


- Asphyxiating thoracic dysplasia (Jeune syndrome), a rare autosomal recessive chondrodysplasia that often leads to death in infancy because of a severely constricted thoracic cage and respiratory insufficiency.
- Homozygous achondroplasia has a similar clinical presentation and should be a part of the differential diagnosis when both parents have achondroplasia.
- Achondrogenesis, type IA, type IB and type II, Schneckenbecken dysplasia.
- SADDAN (Severe Achondroplasia with Developmental Delay and Acanthosis Nigricans).
- Short-rib polydactyly syndromes (especially the Saldino-Noonan type). Metatropic dysplasia.
Osteogenesis Imperfecta (OI) type II that is the perinatal lethal form. OI type II has mutations in either COL1A1 or COL1A2 genes and is inherited in an autosomal dominant manner.

Campomelic syndrome. This is an entity characterized by congenital bowing and angulations of long bones, together with other skeletal and extra skeletal defects. It is caused by mutation in the SOX9 gene.

Rhizomelic chondrodysplasia punctata also shows micromelia but this is almost exclusively rhizomelic. Radiologically the stipping is characteristic; it is caused by mutations in the PEX7 gene, which encodes the peroxisomal type 2 targeting signal (PTS2) receptor (Marzioch 1994).

Hypophosphatasia.
The group of platyspondylic lethal skeletal dysplasia, such as Torrance-Luton type (Gorlin et al. 2001). The latter was originally grouped with TD however, it is not caused by mutations in the FGFR3 (Neumann et al. 2003). Dyssegmental dysplasia, Silverman-Handmaker type (DDSH). DDSH is not caused by mutations in the COL1A1 or COL1A2 genes.

Frequency
TD has an incidence of approximately 1/20,000 to 1/50,000 live births (Orioli et al. 1986; Wilcox et al. 1998; Sawai et al. 1999, Bartner et al 2000; Chen et al. 2001).

Etiology
The long bones elongation is governed by a process known as endochondral ossification, a tightly regulated developmental process that occurs in the epiphyseal growth plate (Caplan and Pechak 1987). Chondrocytes of the growth plate are arranged in columns that sequentially and synchronously progress through proliferative, pre-hypertrophic and hypertrophic stages. FGFR3 has been identified as a negative regulator of endochondral growth since the targeted disruption of the mouse fgfr3 gene causes a skeletal overgrowth (Colvin et al. 1996; Deng et al. 1996). FGFR3 belongs to the receptor tyrosine kinase family (RTKs).

FGFR3 is a glycosylated transmembrane protein (Keegan et al. 1991, Lievens and Liboi 2003) that upon binding with FGF ligands and heparin dimerizes and undergoes interchain autophosphorylation of key tyrosine residues, thus transmitting signals into the cells (Basilico and Moscatelli 1992; Plotnikov et al. 1999). The TD mutations in FGFR3 are gain-of-function mutations that produce a constitutively active receptor capable of initiating intracellular signal pathways in the absence of ligand binding.

TDI - All reported mutations cause constitutive FGFR3 activation through the creation of new, unpaired cysteine residues that induce ligand-independent dimerization (Rousseau et al. 1996; Cohen 2002) or the creation of an elongated protein through destruction of the native stop codon (Rousseau et al. 1995; Rousseau et al. 1996). It has been recently proposed that mutated FGFR3 induces premature exit of proliferative cells from the cell cycle and their differentiation into pre-hypertrophic chondrocytes thus ascribing to the defective differentiation of chondrocytes the main cause of long bone growth defects in TDI (Legal-Mallet et al. 2004).

TDII - A single FGFR3 mutation (K650E) has been identified in all cases of TDII (Rousseau et al. 1996; Bellus et al. 2000). The K650E mutation is located within a critical region of the tyrosine kinase domain activation loop. Indeed, amino acid substitution at this codon results in strong autophosphorylation of multiple tyrosine residues within the intracellular domain (Webster et al. 1997). In in vitro studies and in mice carrying the TDII mutation it was shown that the signal transduction and activator of transcription STAT1 is activated and translocated into the nucleus (Iwata et al. 2000). This, together with activation of the cell cycle inhibitor p21\(^{waf1}\) was proposed as the molecular mechanism responsible for the TDII pathology (Su et al. 1997). Furthermore, ligand-independent activation of the STAT signalling pathway was demonstrated in cultured TD cells and confirmed by immunodetection of activated STAT1 associated to apoptosis of chondrocytes in TD fetus (Li et al. 1999; Legal-Mallet et al. 1998). More recently, in vitro studies with chondrocytic cells (RCS) and human epithelial cells (HEK293) show that the TDII mutation hampers the complete maturation of FGFR3 leading the immature phosphorylated FGFR3 forms to signal from the Endoplasmic Reticulum, which fails to be degraded (Lievens and Liboi 2003). Consequently, it was proposed that the defect in down regulation of the highly activated receptor results in the increased signalling capacity.
from intracellular compartments that may determine the severity of the disease. This has been associated to the high level of FGFR3 tyrosine kinase activity caused by the K650E substitution (Lievens et al. 2004).

**Clinical description**
Prenatal diagnosis allows determining both TDI and TDII. Most affected individuals die of respiratory insufficiency within the first hours of life. Some die after a few days of life. Respiratory insufficiency may be secondary to a small chest cavity and lung hypoplasia, compression of the brain stem by the small foramen magnum or a combination of these (Baker et al. 1997). Rare long-term survival (a 4.7 year male and a 3.7 year female) has been reported (MacDonald et al. 1989). Both had birth length and weight below the third percentile. In both, growth plateaued after 10 months of age. Clinical profile includes micromelia, redundant skin folds, hydrocephalus and a small foramen magnum. Furthermore, a 9 year-old male with TDI (R248 mutation) with extensive acanthosis nigricans and a severe developmental delay with no language has been reported (Baker et al. 1997).

A 47-year-old female with TDI (R248C mutation) presents asymmetrical limb length, bilateral congenital hip dislocation, focal areas of bone bowing and an S-shaped humerus, extensive acanthosis nigricans, redundant skin folds along the length of the limbs and a flexion deformities of the knees and elbows (Hyland et al. 2003).

No strong genotype-phenotype correlation for FGFR3 mutations causing TD exists.

**Genetic counseling**
Thanatophoric dysplasia type I and thanatophoric dysplasia type II are caused by de novo autosomal dominant mutations in FGFR3. Recurrence risk is not significantly increased over that of the general population. Germline mosaicism in healthy parents, although not previously reported, remains a theoretical possibility. Prenatal diagnosis is clinically available, and is reliable both through sonography and through molecular studies.

**Diagnostic methods**
Prenatal diagnosis is performed by analysis of DNA (FGFR3 sequences) extracted from fetal cells obtained by amniocentesis usually performed at 15-18 weeks gestation or chorionic villus sampling at about 10-12 weeks gestation. Routine prenatal ultrasound examination may identify skeletal alterations associated to TD such as cloverleaf skull, very short extremities, and a small thorax.

**Management**
Most individuals with TD die within the first few hours or days of life by respiratory insufficiency secondary to reduced thoracic capacity or compression of the brainstem. Management concerns are limited to extreme life support measures for the newborn. In the rare cases of long-term survival, the management consists in treatment of manifestations:
- respiratory support (tracheostomy, ventilation)
- medication to control seizures
- shunt placement when hydrocephaly is identified
- suboccipital decompression for relief of craniocervical junction constriction
- hearing aids when hearing loss is identified
- orthopedic evaluation upon the development of joint contractures or joint hypermobility.

**References**
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