Six lethal skeletal dysplasias which a pediatrician should never miss

Sheela Nampoothiri

Department of Pediatric Genetics, Amrita Institute of Medical Sciences & Research Centre, Cochin, Kerala, India

Email: sheelanampoothiri@aims.amrita.edu

Lethal in Greek denotes 'death bearing'. Lethal dysplasias present with short limbs or narrow thorax and lead to pulmonary hypoplasia. They are included in the classification of genetic bone disorders (Warman et al., 2011). Availability of a lot of photographs of radiographs in atlas of skeletal dysplasias help in radiological diagnosis (Schumacher et al., 2013; Spranger et al., 2002). The incidence is around 1:5000 live births and these fetuses die in utero or shortly after birth or can present as non-immune hydrops. Antenatal detection of almost all lethal dysplasias is possible by 20 weeks of gestation but osteogenesis imperfecta (OI) type II can be identified even by 14 weeks of gestation. During an anomaly scan if all long bones are less than 4SD below the mean, then careful evaluation of other parameters should be done to rule out lethal dysplasias (Krakow et al., 2009; Krakow, 2015).

Ultrasound markers of lethal dysplasias include,

1. Thoracic circumference (TC) less than 5th percentile of mean for gestational age
2. Thoracic circumference (TC)/ Abdominal circumference (AC) <0.89 (narrow thorax)
3. Femur length/AC <0.16
4. Femur length/foot <0.8

The other parameters to be seen are:

1. Increased nuchal translucency (NT) in first trimester
2. Poor mineralization of bones
3. Fracture or bent bones
4. Poor mineralization of skull and compressible skull
5. Vertebral anomalies
6. Associated anomalies-cleft lip/cleft palate, polydactyly, etc.

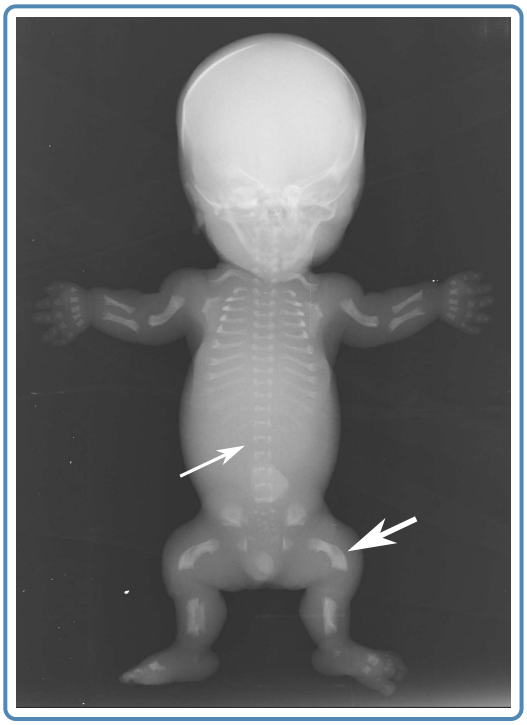

Figure 1 Thanatophoric dysplasia type I - Infantogram showing marked bowing of femur and humeri, narrow thorax with short ribs, wafer thin vertebral bodies / platyspondyly (thin arrow), telephone receiver shaped femur (thick arrow) and trident acetabulum.

For confirmation of specific types of skeletal dysplasias an infantogram and lateral radiograph of spine are essential following termination of pregnancy. Detailed clinical evaluation of fetus should be done for associated anomalies (cleft lip, cleft palate, polydactyly, facial dysmorphism, dimples in the skin and, deformity of skull e.g. clover leaf skull in thanatophoric dysplasia type II).

A clinical photograph and fetal autopsy and storage of DNA for molecular confirmation are extremely helpful for delineating the type which is extremely important for counseling as the risk of recurrence is up to 25% in autosomal recessive disorders (e.g. Short rib polydactyly (SRP) syndrome) (Taylor et al., 2015). Six cases of lethal skeletal dysplasia are illustrated here.

Thanatophoric dysplasia

Thanatophoric dysplasia type I presents with severe platyspondyly (wafer thin vertebrae), small thorax, telephone receiver shaped femur and trident acetabulum (Fig. 1). In Type II, clover leaf shaped skull is the differentiating point from type I and the long bones are not as curved as in type I. This is an autosomal dominant disorder and both types are due to mutation in the *FGFR3* gene. Many cases of thanatophoric dysplasias are labeled as achondroplasia during antenatal scans but a very important clue is that radiological features for achondroplasia will manifest only after 24 weeks of gestation.

SRP syndrome (Short rib polydactyly syndrome)

There are 4 different types:

I Saldino Noonan
II Majewski
III Verma Naumoff
IV Beemer Langer (polydactyly is unlikely)

All are autosomal recessive.

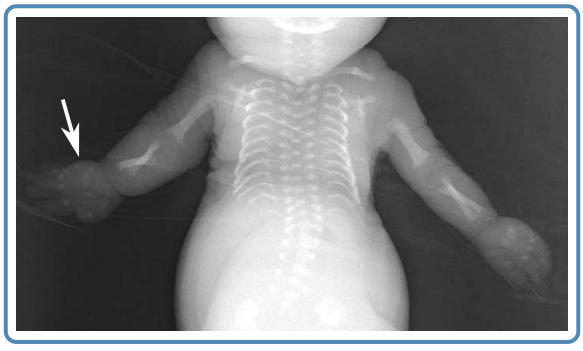

Figure 2 Short-rib polydactyly syndrome type 1 and 3: note the narrow thorax with short ribs and postaxial polydactyly (arrow).

Type I and III (these two types cannot be distinguished clinically) (Fig. 2): They present with long thorax, very short ribs, trident acetabulum, platyspondyly and postaxial polydactyly. These are due to mutations in *DYNC2H1* gene which is the same gene responsible for asphyxiating thoracic dystrophy.

Type II: Fusion of metacarpals and short oval tibia are two differentiating features from I and III.

Type IV: Tibia is normal. Polydactyly is unlikely.

Prenatally SRP, Ellis van Creveld and Jeune Asphyxiating Thoracic dystrophy are indistinguishable.

Hypophosphatasia

This condition can be suspected prenatally by 14 weeks of gestation. All bony structures are sonolucent. The classical features include absent skull ossification, large metaphyseal defects in long bones extending to diaphysis, lack of ossification of most of the vertebrae, absent ulna or fibula and very slender few ribs (Fig. 3). Spurs arising from forearm and legs which are covered by skin are good clues and are well seen with 3 dimensional ultrasound scan. Serum alkaline phosphatase level is undetectable in fetal blood sample. The defect is in *ALPL* gene.

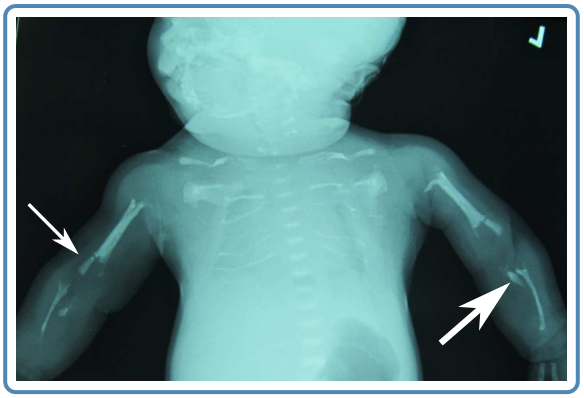

Figure 3 Hypophosphatasia - Severe hypomineralisation, osteochondral spurs from forearm (thin arrow) and legs, shortening of all long bones, very slender ribs with fractures, absent ulna (thick arrow) and fibula and unossified vertebrae and skull

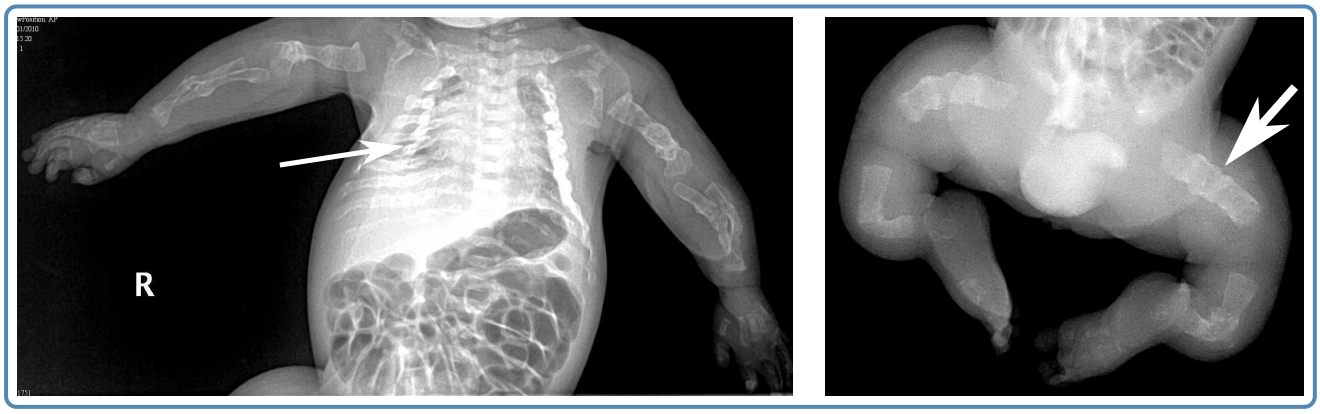

Figure 4 Osteogenesis imperfecta type II - severe beading of the ribs (thin arrow), thick short crumpled shafts of long bones in older fetuses due to continuous fracture & reunion (thick arrow).

Osteogenesis Imperfecta Type II

Typical features include absent ossification of skull, beaded ribs (due to repeated fractures and re-union) and hypomineralistaion of long bones with severe angulation (Fig. 4). In type II, they have severe angulation of tibia which is not a feature in type III (non lethal). In older fetuses the ribs are broad due to repeated fracture and reunion. The perinatally lethal types are caused by *COL1A1 / COL1A2* which are transmitted as an autosomal dominant manner due to a *de novo* mutation in all cases. There are many newly described genes which are transmitted in autosomal recessive manner leading to perinatally lethal OI (*CRTAP, LEPRE1, SEERPINH1, P3H1*)

Campomelic dysplasia

Angulation of femur and tibia are the most prominent features. Angulation of femur is at junction of upper1/3 and lower 2/3 and for tibia it is between the upper 2/3 and lower 1/3. Angulation of tibia can be seen as a spike under the skin. Skin dimples give a clue regarding the underlying bowing of long bones in the lower limb. They have only 11 pairs of ribs. Another feature is absent ossification of pedicle of thoracic vertebrae. Wing of the scapula is missing and they have very short bowed fibula (Fig. 5). Abnormal male genitalia with sex reversal is seen in fetuses with 46,XY karyotype. This disorder is caused by heterozygous dominant mutation in the *SOX 9* gene.

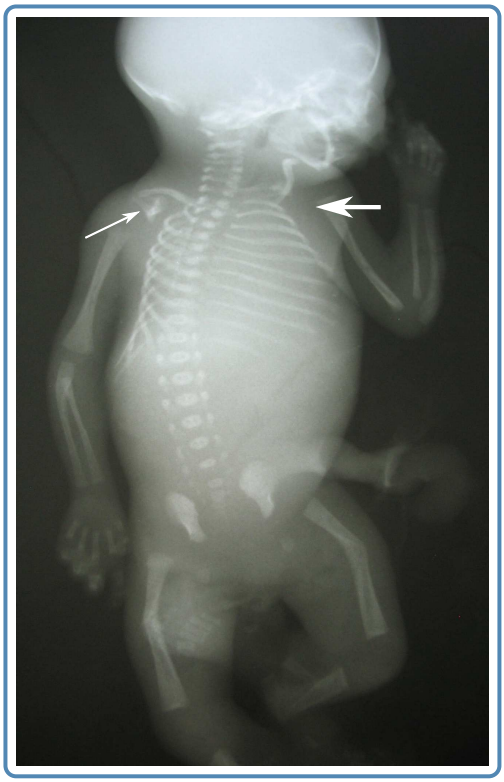

Figure 5 Campomelic dysplasia - Angulation of femur is at the junction of upper 1/3 and lower 2/3 and for tibia at the junction of the upper 2/3 and lower 1/3. The right wing of the scapula is missing (thin arrow) and left scapula is absent (thick arrow), fetus has only 11 pairs of ribs.

Achondrogenesis

Type IA: Beaded ribs due to healing fractures, absent ossification of vertebral bodies, severe micromelia, absent ossification of skull, and crescentic iliac wings characterize this condition. This is an autosomal recessive disorder due to mutations in *TRIP1*.

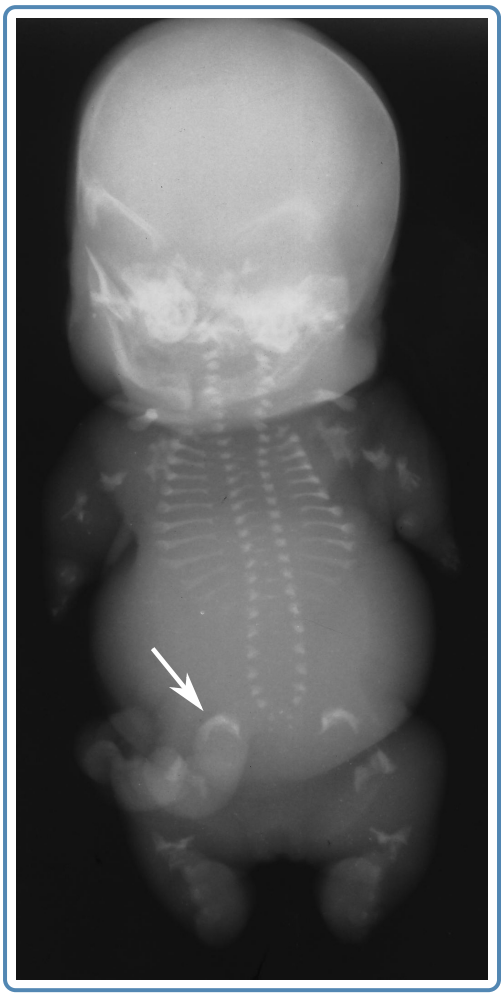

Figure 6 Achondrogenesis IB - The thorax is small with short ribs with expanded and cupped ends. The crescentic iliac wings (arrow) and cobra head appearance of vertebral column are good clues for diagnosis.

Type IB: They do not present with beaded ribs. Other features include well ossified vertebral pedicles with unossified vertebral bodies, better ossification of skull, short long bones and crescentic iliac wings. There is significant widening of the interpedicular distance in both cervical and lumbar region giving the "Cobra head appearance". This is an autosomal recessive disorder caused by mutations in *DTDST* gene.

Type II: has well ossified skull, absent ossification of vertebral body, ossified vertebral pedicles, handle bar clavicles and cupping and spiking of femur. This autosomal dominant disorder is caused by mutations in *COL2A1*.

Accurate identification of lethal dysplasias help in genetic counseling and would help the clinician to choose the right molecular test for future prenatal diagnosis

Acknowledgments

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