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CASE REPORT

Prenatal Diagnosis of Thanatophoric Dysplasia in Songklanagarind Hospital

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ABSTRACT

Skeletal dysplasias (osteochondrodysplasias) from a heterogeneous group of disorders are characterized by generalized abnormalities of skeletal growth and development. About half of skeletal dysplasias are lethal, usually because of a narrow thorax and hypoplastic lungs. Thanatophoric dysplasias are the most common lethal disorders. Most cases are detected on the basis of abnormal measurements of long bones. Prenatal detection of these disorders may influence obstetric and perinatal management of affected fetuses. We report a series of four cases of thanatophoric dysplasia detected within 5 years.

Key words : thanatophoric dysplasia, skeletal dysplasia, prenatal diagnosis

Thanatophoric dysplasia manifests as severe micromelia.[1] but it has normal trunk length. This dysplasia is divided into 2 types. Type I has an appearance of typical bowed "telephone receiver" femurs without cloverleaf skull. Whereas, Type II consisted of cloverleaf skull and short, straight long bones.[2] A precise diagnosis is not always easy to achieve in utero because it should be differentiated from other lethal skeletal dysplasias such as achondrogenesis, homozygous achondroplasia or osteogenesis imperfecta.[3,4] Obstetric ultrasonography allows antenatal detection of affected fetuses. The long bones are short, bowed and normal mineralization. Fetal head reveals brachycephaly, macrocephaly, frontal bossing or cloverleaf deformity of skull.[1,2,5] Biparietal diameter is usually above the 95th percentile for gestational age.[6] Frontal bossing is prominent forehead in lateral view of fetal head which can be detected as early as 18 weeks of gestation. The cloverleaf skull (kleeblattschadel) results from cranio-synostosis causing bulging of temporal, occipital and frontal bones.[7] However, this finding can be seen with thanatophoric dysplasia as well as with other dysplasias.[8]

The osteochondrodysplasias can be further divided into those disorders that are lethal before or shortly after birth (such as achondrogenesis type I and II, thanatophoric dysplasia) and those that are

nonlethal (such as achondroplasia, certain forms of osteogenesis imperfecta). Many of dysplasias detected during the second trimester are lethal, and most fetuses die at birth from associated lung hypoplasia with respiratory failures, for example, thanatophoric dysplasia, achondrogenesis, homozygous achondroplasia, osteogenesis imperfecta type II and short rib-polydactyly syndrome.[1,2,8] Lung hypoplasia can be predicted readily in utero by measuring the chest diameter or circumference.[4] The relatively small chest and normal abdominal circumference shows champagne cork appearance in a longitudinal anteroposterior view.[1] Other ultrasound findings of thanatophoric dysplasia are platyspondyly (flattened vertebrae), short ribs, polyhydramnios in late second trimester or early third trimester or hydrops fetalis.[1,2,8] Nonlethal skeletal dysplasias are not usually diagnosed until after 24 weeks of gestation.[9] Predicting fetal outcome is important to prenatal diagnosis and counseling because it may bear on the mother's decision to continue with the pregnancy or with obstetric management issues in later pregnancy. Four cases of thanatophoric dysplasias were diagnosed in Songklanagarind hospital within 5 years periods. All cases were determined in utero by ultrasonography, but only two cases were confirmed by postmortem examinations.

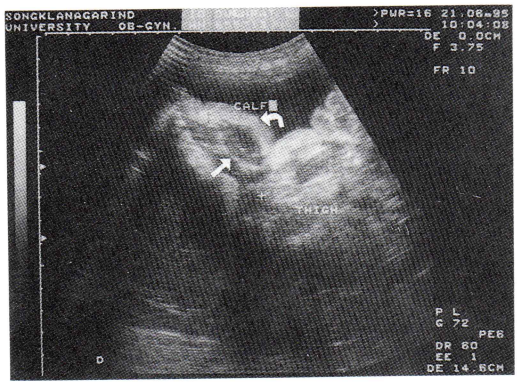

Fig. 1. Case 1. fetal leg shows shortening of tibia (straight arrow) and prominent calf (curved arrow).

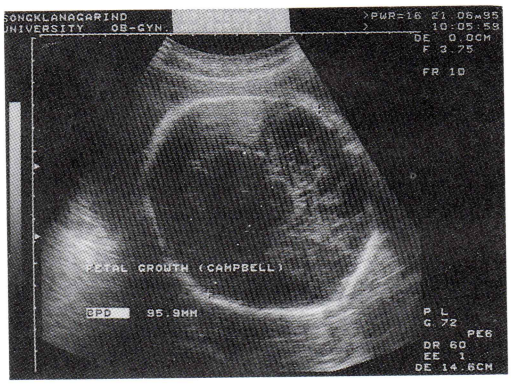

Fig. 2. Case 1. fetal head on a transverse scan showing large biparietal diameter for gestational age (megalocephaly), normal mineralization and no evidence of ventriculomegaly.

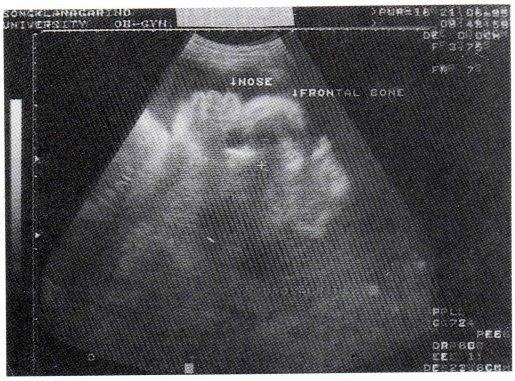

Fig. 3. Case 1. The lateral view of fetal head showing prominent forehead (frontal bossing) and saddle nose.

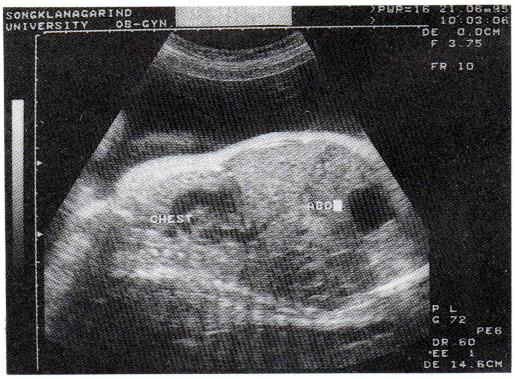

Fig. 4. Case 1. The longitudinal enteroposterior view of fetus shows the relatively small chest and normal abdominal circumference (Champage cork appearance).

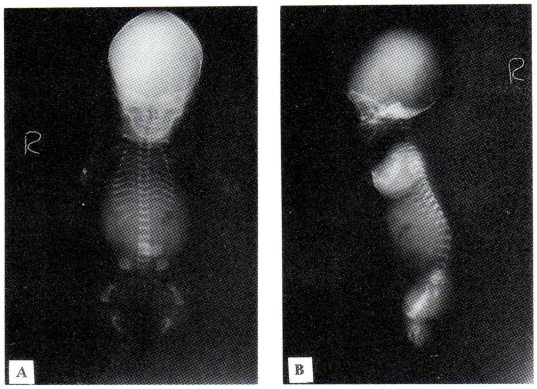

Fig. 5 A, B. Case 1. Postmortem radiography confirms frontal bossing, micromelia, Telephone receiver" femurs, small thorax, platyspondyly and normal vertebral ossification.

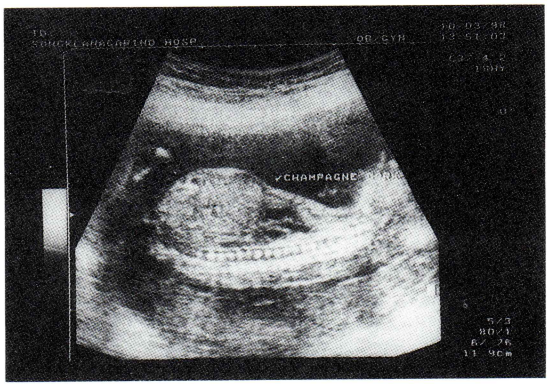

Fig. 6. Case 4. The champagne cork appearance is show. The thoracic/abdominal circumference ratio is 0.6.

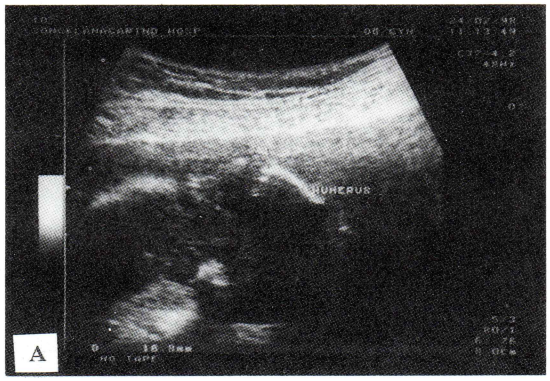

Fig. 7 A. Case 4. Fetal humerus (16.8 mm. in length) isbelow the fifth percentile for gestational age.

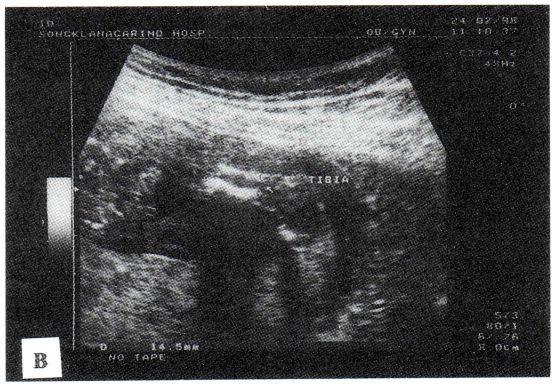

Fig. 7 B. Case 4. Fetal tivia (straight arrow) and fivula (between crosses) are short.

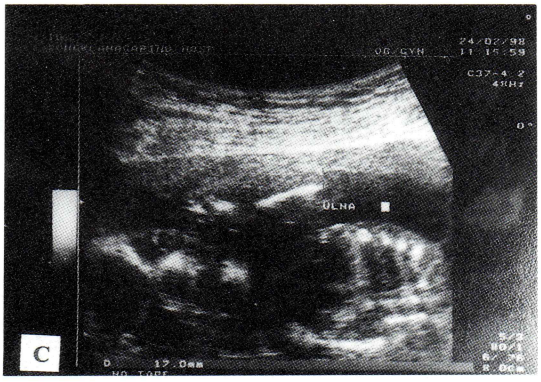

Fig. 7 C. Case 4. The ulna shows straight shape and 17.0 mm. in length (below the fifth percentile for gestational age.)

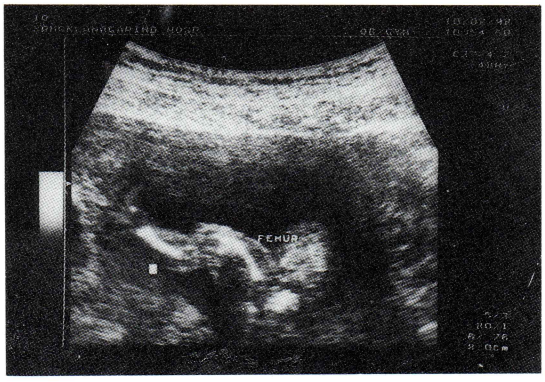

Fig. 8. Case 4. Shortened bowed femur is shown. Bowed femur shows typical telephone receiver configuration.

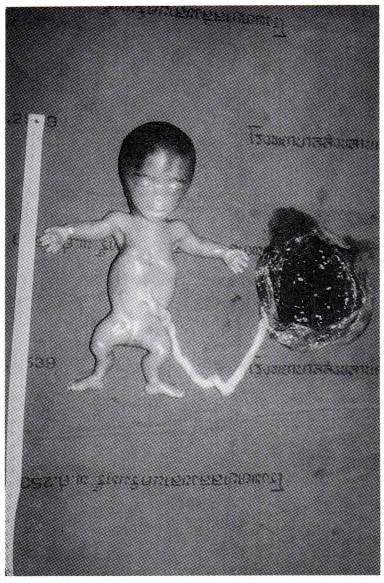

Fig. 9 C. Case 4. Postmortem of twenty-one week fetus with normal trunk length, megalocephaly, micromelia and small chest.

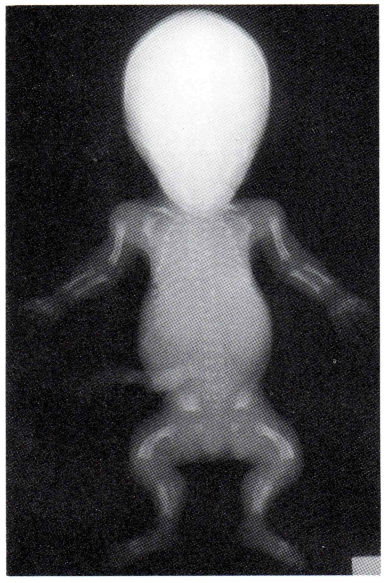

Fig. 10. Case 4. Radiograph confirms short all long bones, "Telephone erceiver" femurs, normal mineralization of long bones and spine. The platyspondyl and short ribs are shown.

CASE 1

A 30 year old woman, third pregnancy, was referred from Pattani province. She attended antenatal care at 12 weeks of gestation until 28 weeks of gestation. Ultrasonography was performed because she wanted to know fetal sex. The finding revealed small chest. Her doctor advised her to confirm this finding to established the final diagnosis. Detailed ultrasonographic study showed short and bowed all humerus, femurs, tibias and fibulas (Fig. 1). All limbs were measured below the fifth percentile for gestational age. Megalocephaly with normal mineralization (Fig. 2) and frontal bossing (Fig.3) were found. Small chest diameter resulted in champagne cork appearance was presented (Fig. 4). A prenatal diagnosis of thanatophoric dysplasia was made. Counseling was done and she requested pregnancy termination. The postmortem examination confirmed macrocephaly with separated suture, depressed nasal bridge, small chest and short extremities. The chromosomal study revealed 46, XX. Postmortem radiography also showed shortening, bowing of all long bones and platyspondyly (Fig. 5A, B). The autopsy's diagnosis was premature female infant with thanatophoric dysplasia.

CASE 2

This was the fourth pregnancy for a 34 year old woman at 31 weeks of gestation. She was referred from Trang hospital because polyhydramnios and fetal abnormalities were suspected. The ultrasono graphy showed megalocephaly, severe micromelia, small chest circumference and polyhydramnios. Normal mineralization of fetal spine was presented. Elective abortion was performed after counseling and postmortem examination showed female infant with normal trunk length, large head, prominent forehead, flattened occiput, saddle nose, ear anomalies, short sternum and short all extremities. The chromosome of fetus was 46, XX. Neither postmortem radiography nor autopsy was done. The photographys of ultrasound findings were not recorded.

CASE 3

A 25 year old woman, primigravida, 29 weeks of gestation visited antenatal care at Hat Yai hospital. Ultrasonography was performed for fetal sex. It showed shortening of long bones. She was referred for confirming diagnosis. The further ultrasound findings revealed cloverleaf skull, frontal bossing, champagne

cork appearance and short limbs. The diagnosis of thanatophoric dysplasia was made. She wanted termination of pregnancy at Hat Yai Hospital. The recorded photographs were lost.

CASE 4

A 38 year old, primigravida,visited Songklanagarind hospital at 17 weeks' gestation for genetic counseling. The ultrasonography was performed. It showed brachycephaly and shortening of all long bones. Bone lengths were at the fifth percentile for gestational age. The diagnosis of thanatophoric dysplasia was suspected. An amniocentesis was done and the result revealed 46,XX. A follow - up sonographic study showed brachycephaly, frontal bossing, small thorax (Fig. 6), shortening and bowing of all long bones (Fig 7A-C). All long bone measurements were below the fifth percentile for gestational age. The "Telephone receiver" femurs were presented (Fig. 8). The femur/foot ratio was less than normal range (0.7, normal = 0.99 ± 0.06). The chest /abdominal circumference ratio was 0.6 and femur/ abdominal circumference ratio was 0.12. These findings determined lung hypoplasia and lethal disorder. After extensive counseling, a therapeutic abortion was performed. Postmortem examination showed female fetus, flattened facial profile, flattened occiput and short limbs (Fig. 9). Postmortem radiographs revealed telephone receiver appearance of femurs, shortening and bowing of all long bones (Fig.10). The autopsy confirmed the diagnosis of thanatophoric dysplasia.

Discussion

The prenatal diagnosis of thanatophoric dysplasia or other forms of skeletal dysplasias is important to predict fetal outcome and proper management.[1,2,4,9] Ideal sequence of diagnostic steps in diagnosis of skeletal dysplasias are the presence of short long bones, recognition of disproportion and greatest shortness, identification of deformities or malformations, roentgenographic examination of entire skeleton, final categorization and genetic counseling.[3]

All cases in this report presented with shortening and bowing of long bones, megalocephaly or brachycephaly, frontal bossing and small chest. The long bones should be evaluated in term of length, shape and degree of mineralization.[10] The number of millimeters below the 2-SD line is an accurate, easy criterion for evaluating femoral shortening.[4] If the femur is markedly short (consistently 5 mm. or more below the 2-SD line), especially in the presence of other abnormalities, one can be sure that a significant skeletal dysplasia is present.[11] A way of differentia ting between bone dysplasia and IUGR is to use the femur/foot length ratio with a value of 0.99 ± 0.06 in normal or growth retarded fetuses but which is markedly decreased in skeletal dysplasia.[4] The availability of nomograms for limb growth permits the identification of abnormal short bones.[6] Measurements for thanatophoric dysplasia and osteogenesis imperfecta tend to overlap, falling in the range of 40 to 70% of the mean for gestational age. Long bone measurements in achondrogenesis clustered around and below the line representing 1/4 of the mean for gestational age. In thanatophoric dysplasia and osteogenesis imperfecta type II, long bone measurements were distributed between 1/4 and 3/4 of the mean for gestational age.[6]

The finding of limb shortening prior to 20 weeks' gestation is most associated with a lethal fetal skeletal dysplasia.[7] Limbs shortening with small thorax are found in thanatophoric dysplasia, achondrogenesis, osteogenesis imperfecta type II, homozygous achondroplasia, congenital hypophosphatasia, asphyxiating thoracic dysplasia, short rib - polydactyly syndrome and campomelic dysplasia.[1,2,8] Small thorax strongly suggests that the fetus is affected with a lethal anomaly.[8] The thoracic circumference was measured in a cross-sectional view of the fetal thorax at a level in which a four-chamber view of the heart was visualized.[2,12] The thoracic/abdominal circum ference ratio ranged from 0.77 to 1.01.[8] All four cases showed significantly small thorax that indicated lung hypoplasia. With these results, elective termination was

performed in all cases. In case 4, due to the champagne cork appearance and the fact that thoracic/abdominal circumference ratio was 0.6, small thorax was comfirmed. The femur length/abdominal circumference ratio can be used as one of the criteria to predict lethality. The ratio was less than 0.16 or less than 70 percent of the control value for gestational age that resulted in a lethal outcome.[9]

In thanatophoric dysplasia, the risk for fathers age 35 years and older was 3-fold that of younger ones, but only double when mothers were younger than age 30 years.[13] Evaluation of the scapula can be useful in the diagnosis of skeletal dysplasias and helpful for the classification and delineation of new entities.[14] Recent advances in molecular and cellular biology have contributed significantly to the elucidation of the pathogenesis of many kinds of skeletal dysplasia. Thanatophoric dysplasia is also caused by mutations of the FGFR 3 gene. This gene is expressed dominantly in the central nervous system and growth plate.[15] The importance of second trimester diagnosis is that, not only the family can be counseled of the recurrence risk and prognosis, but also an opportunity to consider therapeutic abortion in case of lethal anomaly.[16] Thanatophoric dysplasia was the most accurately diagnosed prenatally, probably because it is the most common and most familiar neonatal lethal skeletal dysplasia.[17] This dysplasia differs from other dysplasias by normal mineralization, no evidence of bone fracture, telephone receiver femur, platyspondyly and no associated anomalies. Advances in ultrasonography technology and scanning expertise have had a major impact on prenatal diagnosis. To provide the family with accurate genetic counseling, a postmortem evaluation of the fetus including radiologic, morphologic, biochemical and molecular studies should be performed.

Acknowledgments

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