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Antenatally diagnosed thanatophoric dysplasia

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A case of antenatally diagnosed thanatophoric dysplasia is described. Other syndromes accompanied by chondrodysplastic tetramicromelia were excluded and diagnosis was based on the narrow thorax, secondary pulmonary hypoplasia and macrocephaly detected by ultrasound and on radiological findings of disturbed bone formation. At the mother's request labour was induced and radiological, anatomic and histological examination of the newborn confirmed the prenatal diagnosis. On basis of the literature, the possible aetiology of the disease is discussed and autosomal recessive heredity is suggested. Attention is focussed on the significant hydramnios which led to the suspicion of fetal malformation. The importance in pregnancy of routine ultrasound screening is emphasized, since such malformations can be detected as early as in midtrimester pregnancy.

Thanatophoric dwarfism or dysplasia is one of the twenty-one basic types of osteochondrodysplasia detectable in the newborn period. It has been suggested that instead of the term dwarfism which seemed somewhat offending to the patients or their families, dysplasia should be used [16]. Thanatophoric dysplasia was distinguished from other types of congenital short-limb conditions, especially from classical achondroplasia [10]. The name is derived from the Greek thanatophoros meaning death-bearing because the affected infants die a few hours or days after birth.

The characteristics of the disease are a short stature with markedly shortened extremities (tetramicromelia) and relatively normal trunk length, a narrow thorax with hypoplastic lungs. Respiratory distress which may be caused by the chest deformity, is a prominent feature and so are the comparatively large head (macrocephaly) with depressed nasal bridge, and death in early infancy. Reviewing the literature we found that despite the classical X-ray signs only one case was correctly identified prenatally. This was a thanatophoric dwarf born after another pregnancy that directed attention to the possibility of recurrence, also combined with hydramnios [5]. "Prenatal diagnosis" in the title of publications accessible to us proved to refer to X-rays evaluated retrospectively in the postnatal period [1, 4, 9, 13, 18, 20]. The malformation may not be suspected prenatally due to its rarity, and may be difficult to differentiate from other types of chondrodysplasia.

Radiologically only achondroplasia has been diagnosed in utero, and prenatal diagnosis of this condition

compatible with life has not influenced obstetric management. Therefore we feel justified in reporting a case of thanatophoric dysplasia, a lethal condition, diagnosed prenatally by ultrasound and amniofetography.

Report of a Case

A 23 year old woman, with one healthy child, was admitted at 30 weeks gestation with hydramnios and poor fetal movements. The husband was 25 years old.

There was no family history of dwarfism, no consanguinity nor any history of exposure to teratogenic agents. On examination the uterus was large for dates, and marked hydramnios was present. Ultrasound examination showed a single fetus with 7.5 cm biparietal diameter (mean for 30 weeks gestation = 7.0 cm, range 6.4–7.8 cm), no dilation of the cerabral ventricles, a protuberant fetal abdomen containing a full bladder, and extreme hydramnios.

Transabdominal amniocentesis yielded 400 ml clear fluid containing 2.5 μg/ml (normal) alphafetoprotein. The morphological characteristics and percentile distribution of non-cultured amniotic fluid cells were normal, thus excluding a neural tube defect. The lecithin/sphingomyelin ratio was very low (0.8).

Repeated ultrasound examinations showed remarkably short limbs larger than normal in diameter, extending away from the trunk in central position (Fig. 1). The thorax was depressed, its contours enlarging in cone shape towards the protuberant abdomen (Fig. 2). The abdominal diameters were markedly larger than the thoracic ones. At each examination the fetus was in the supine position.

Amniofetography: following an abdominal X-ray, transabdominal amniocentesis was performed and 10 ml of Lipiodol (lipid-soluble) and 10 ml of 60 % Uromiro (water-soluble) radiopaque dye was injected and 8 and 24 h later X-rays were taken repeatedly. They showed shortened, slightly bowed and broad long tubular bones. The metaphyses were irregular and cupped. The skin of the extremities was folded like an accordion and the many folds could well be discerned by the lipo-soluble contrast medium adhering to the vernix caseosa. No discontinuity of the skin was detected. The skull, though somewhat larger than normal, had a regular bone structure with a protruding forehead and a depressed nasal bridge. The thorax was narrow and the ribs were short. The vertebral bodies were small in vertical diameter and their posterior part was well ossified. The iliac diagonal diameter was larger than usual, the pubic bone and the ischium were broad and short. 24-hour X-rays revealed no obstruction of the gastrointestinal tract, so there was no sign of atresia (Fig. 3).

On the basis of the above findings, the intrauterine fetus was diagnosed as a thanatophoric dwarf. Chondrodysplasia, tetramicromelia, brachydactyly, macrocephaly without hydro-

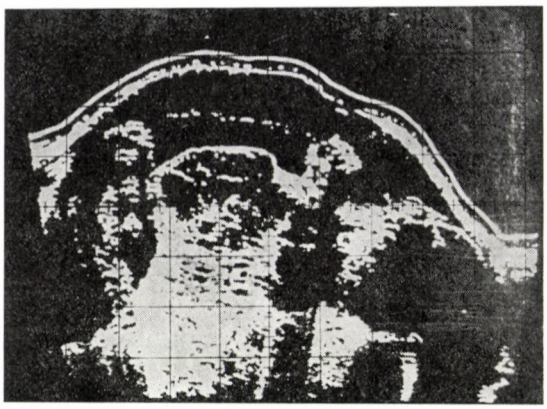

FIG. 1. Ultrasound scan showing the thick limbs and the large head

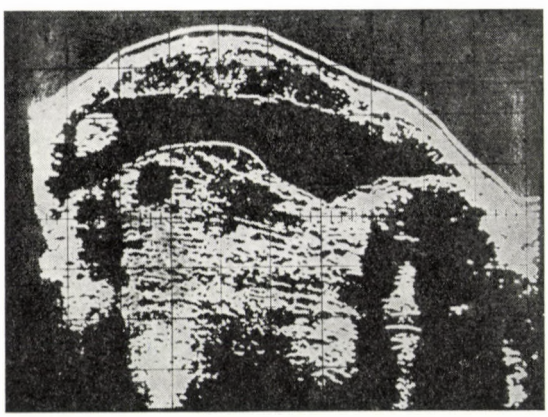

FIG. 2. The narrow thorax assumes a cone shape toward the protuberant abdomen

cephalus and the narrow thorax were the positive diagnostic features. Although prenatal examinations showed a lethal condition, the pregnancy could not be terminated at that time. Two weeks later, however, despite repeated removal of excess amniotic fluid, labour was induced on the basis of the mother's cardiovascular and psychological condition. A female infant weighing 2050 g was delivered; she died of respiratory and cardiovascular failure 12 h after birth (Fig. 4). At post mortem the placenta weighed 500 g and showed no gross change. The head was disproportionally large, with a protruding forehead, a depressed nasal bridge and a large tongue. The thorax was narrow and dilated in cone shape towards the protruding abdomen. The lungs were hypoplastic with patchy areas of atelectasis. The left lung had 3 lobes. The right heart ventricle was dilated. The umbilical cord contained 3 vessels. The tubular bones were all short

FIG. 3. X-rays taken 24 h after injection of contrast medium into the amniotic cavity

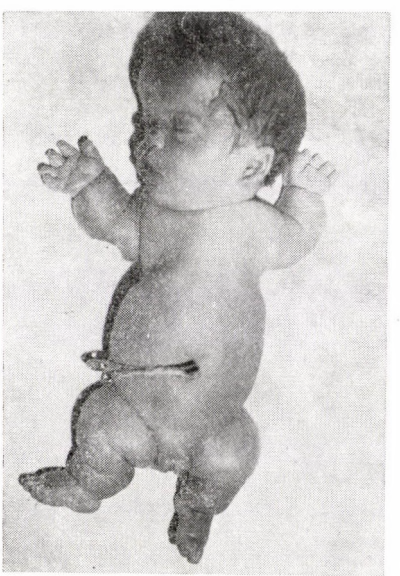

FIG. 4. The newborn infant with short hydropic limbs, protuberant abdomen and depressed thorax

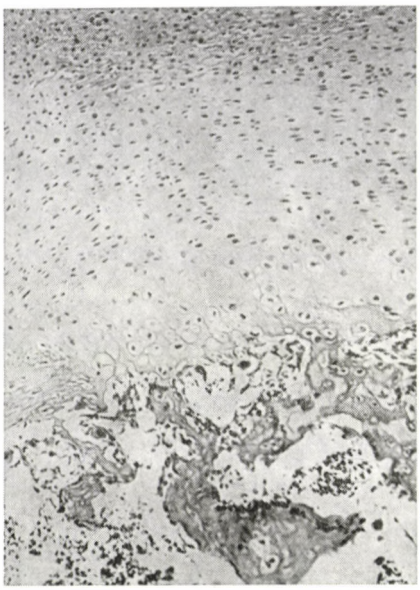

FIG. 5. Irregular columnarization of chondrocytes in the epiphyseal growth zone of the humerus

and slightly bowed, the skin of the limbs displayed many deep folds. Histological examination showed that the basic defect was a disturbance of endochondral ossification. In the epiphyseal growth zone the columnarization of chondrocytes was irregular (Fig. 5). The cartilage matrix was irregularly calcified, the number of bone trabeculae was small and they did not run parallel with the longitudinal axis of the bone as in a normal epiphysis. Periosteal bone formation was well developed. On the proximal epiphyseal side of the humerus the periosteal connective tissues extended over the epiphyseal plate to the cartilage. Electron microscopically, most of the resting chondrocytes resembled the principal cells of normal hyaline cartilage [7].

The majority of vertebral bodies consisted of hyaline cartilage but the ossification centre could be seen and ossification developed well. The skull showed a normal periosteal bone formation and the cartilage of the ribs, larynx, trachea and bronchi displayed a regular hyaline cartilage structure. In the lungs partial atelectasis and passive hyperaemia were noted. The heart, kidneys, spleen and thymus were normal for gestational age. In the liver extramedullary haematopoiesis was seen. Microscopic findings excluded the two types of chondrodysplasia since in achondroplasia the epiphyseal cartilage is well developed and regular [17], while in achondrogenesis the principal cells of the hyaline cartilage are absent thus preventing the formation of a

growth plate [8]. Death was due to acute dilatation of the right ventricle in the postnatal period resulting from an extreme pulmonary hypoplasia.

Discussion

The aetiology of thanatophoric dwarfism has not been clarified. The majority of the reported cases were males [6]. In the present case the neonate was a female. The shift in sex ratio could be explained by assuming that most female fetuses die in the early prenatal period rather than by supposing a sex-linked inheritance. Some authors argue that, as in classical achondroplasia, an autosomal dominant mutation would be responsible for the condition [15] and in support of this theory is the usually advanced paternal age [22]. Still, several authors oppose this view [6].

Discordant twins have been described and these are against the aetiologic role of external factors [11]. Pena and Goodman [15] reviewed the cases reported in the literature and concluded that polygenic inheritance was the most likely mechanism and suggested an empiric recurrence risk in sibs of 2%. As expected, no chromosomal aberration could be detected.

The most probable mechanism, at least in the great majority of cases, seems to be an autosomal recessive inheritance, and this has been suggested by the familial occurrence [2, 5, 6, 14, 15, 19]. If this is accepted, the risk of recurrence of the disease is 25%. This risk was considered lower by some authors [11] but they estimated the predisposition to spontaneous abortion to be higher. This was based on the high proportion of abortions occurring in the gestational history [2, 15].

The use of prenatal diagnostic methods is justified (i) in the case of pregnancy following the birth of an affected child; (ii) when hydramnios suggests a fetal malformation; and (iii) when a reduction of normal fetal movements suggests an abnormality of the limbs.

Hydramnios was observed in 70% of the reported cases [5, 12, 22], although the association has not been fully explained. Defective swallowing by the malformed fetus has also been reported [22]. In our case, the quantity of contrast medium swallowed and its progress through the gastrointestinal tract were monitored, and no important difference could be seen compared with our previous experience with amniofetography. An alternative explanation would be the pulmonary hypoplasia, since the fetal bronchopulmonary circulation has an important role in the circulation of amniotic fluid, affecting both its formation and resorption.

The maternal appreciation of reduced fetal movements might have been due to the hydramnios or to the abnormal extremities. In the absence of real-time ultrasound, fetal movement could not be analysed reliably, but it was remarkable at each examination to find the fetus in exactly

the same position with the extremities leaning against the uterine wall, and the thick bones fixed in an abducted position.

In differential diagnosis, several diseases had to be excluded, since most types of chondrodysplasia with tetramicromelia are compatible with life up to two decades. Heterozygous achondroplasia shows similar osseous changes but they are less severe than those found in thanatophoric dysplasia, only the vertebral bodies are not so flat and the tubular bones not so short, curved and cupped. Homozygous achondroplasia is nearly as severe as thanatophoric dysplasia, but can be excluded on the basis of the parents' bone structure. In both types of achondroplasia the trunk is very short, the ribs are short and horizontal, and there is impairment or complete absence of ossification in the vertebral bodies and tubular bones, thus making the differentiation comparatively easy. In severe hypophosphatasia ossification of the skull may not take place, so a proper calcification of the skull excludes this possibility. Asphyxiating thoracic dysplasia (Jeune syndrome) was excluded by the macrocephaly and the severe dysplasia of the vertebrae and the tubular bones. Chondroectodermal dysplasia (Ellis—van Creveld syndrome), Majewski and Saldino–Noonan type chondroplasias can be excluded by the absence of postaxial polydactyly. Metatrophic dwarfism could be excluded by the normal length of the thorax and limbs. Pathologic head size excludes chondrodysplasia punctata and diastrophic dwarfism.

Differentiation between the different types of dwarfism depends on the exact knowledge of the differences existing between them. Subtle radiological details are of extreme importance in diagnosis. At present, therefore, ultrasound and X-rays play the main roles in the diagnosis of dwarfism. The ultrasonic findings which led to further investigation were a large head, small thorax, protruding abdomen and short extremities. Abnormalities of ossification revealed by X-rays confirmed the exact type of chondrodysplasia. The prenatal diagnosis was further supported by postnatal X-rays and the ossification disturbances characteristic of thanatophoric dysplasia revealed by necropsy and proved by the histological examination of the epiphyseal cartilage. This is important since in contrast with previous suppositions [21] the differences in bone formation in achondrogenesis, thanatophoric dysplasia and achondroplasia are not exclusively qualitative but also quantitative [3].

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