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Answer

A rare case of neonatal dwarfism – Answer

Manuela Gallo[1], Valentina Ibba[1], Lucrezia Giua Marassi[1], Luisa Anedda[1], Maria Antonietta Marcialis[2], Maria Cristina Pintus[2]

[1]School of Pediatrics, University of Cagliari, Cagliari, Italy
[2]Neonatal Intensive Care Unit, AOU Cagliari, Cagliari, Italy

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Corresponding author

Valentina Ibba, School of Pediatrics, University of Cagliari, Cagliari, Italy; email: ibba.valentina91@gmail.com.

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Answers

1. The baby-gram whole body radiography (**Fig. 1**) shows several interesting elements useful for diagnosis. The most significant evidence is represented by the shortening of the long bones, which appear curved and with cup-deformation of the metaphyses, giving the characteristic "telephone receiver" appearance (**Fig. 2**). The hand and feet bones also appear short and with stocky morphology. The pelvis is squat with a very small iliac index and frayed acetabula. Another characteristic feature is the column: the vertebral bodies appear well ossified but flattened in the central part with bulbous lateral margins, platyspondylia (**Fig. 3**). The intervertebral spaces are enlarged. The pasterns and the phalanges are short and broad. The thorax appears narrow and elongated like a shape: the anterior root of the ribs are short with a broad end "like a drumstick" (**Fig. 3**). The lungs are hypoplastic. Trying to ventilate, they stretch towards the posterior pleural breaches giving the impression of a "floating" heart (**Fig. 3**). Macrocranium is present, with prominence of the frontal drafts and craniofacial asymmetry.

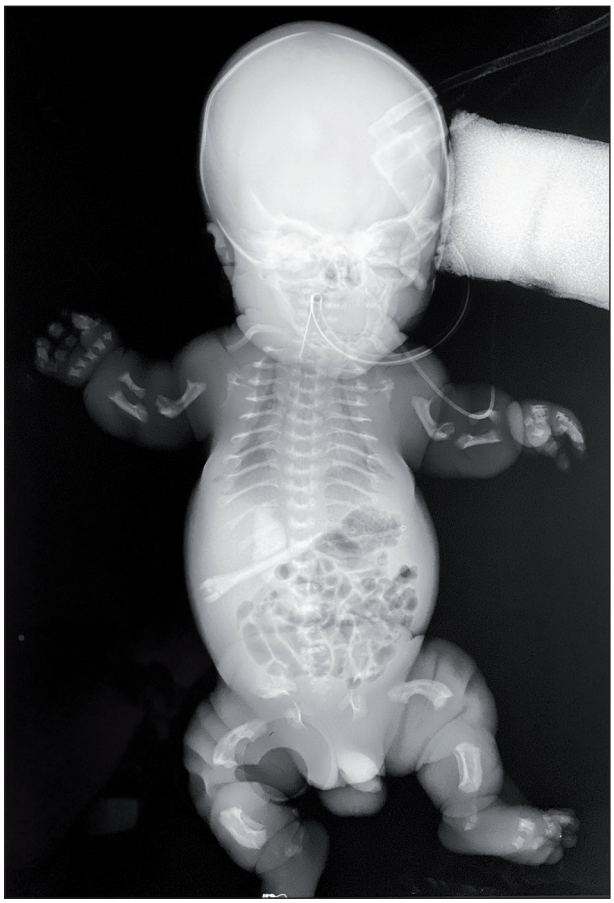

Figure 1. The baby-gram whole body radiography.

2. The diagnosis is dwarfism due to thanatophoric dysplasia (TD). As reported in the scientific literature, the diagnosis of TD is clinical and radiological [1-3]. In our case, the diagnosis was allowed by the identification of pathognomonic aspects at physical examination and by the whole body radiography. In particular, the physical examination shows a micromelic dwarfism, with very short limbs and a length less than -4 SDs, large head with prominent frontal bulges, short neck, narrow bell-shaped chest, brachydactyly

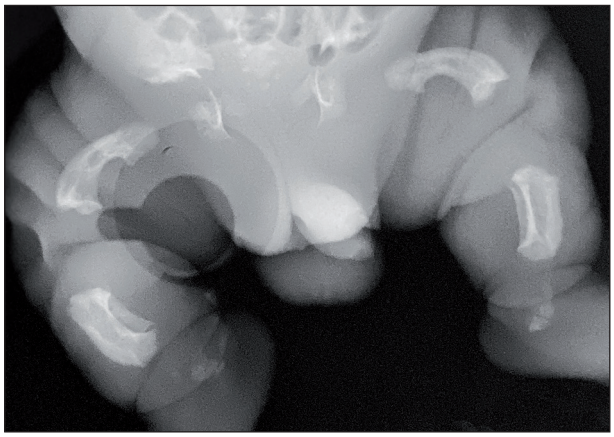

Figure 2. Shortening of the long bones, which appear curved and with cup-deformation of the metaphyses, giving the characteristic "telephone receiver" appearance.

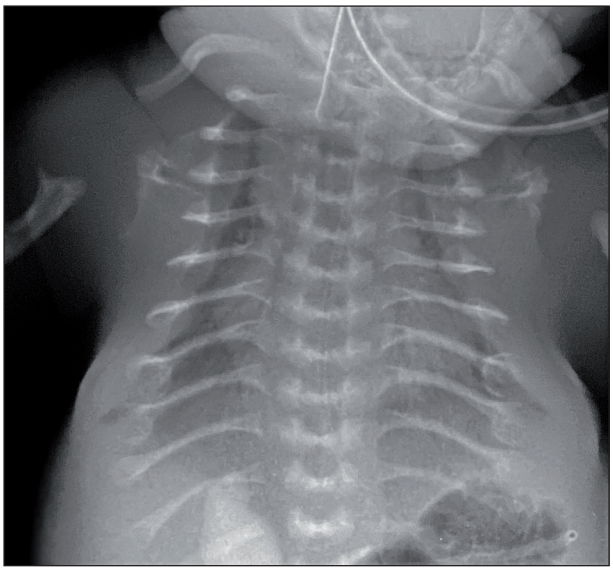

Figure 3. The vertebral bodies appear well ossified but flattened in the central part with bulbous lateral margins, platyspondylia. The intervertebral spaces are enlarged. The pasterns and the phalanges are short and broad. The thorax appears narrow and elongated like a shape: the anterior root of the ribs are short with a broad end "like a drumstick". The lungs are hypoplastic. Trying to ventilate, they stretch towards the posterior pleural breaches giving the impression of a "floating" heart.

of the hands that have a trident aspect, plication, redundant skin on the arms and legs. The radiological pictures show some characteristic features [4]: a marked enlargement of the metaphyses with "telephone receiver" curvature, pathognonomic of this form, the platyspondylia and hypoplasia of the vertebral bodies, which appear ossified, the hypoplastic pelvic bones with roof flat acetabular, the macrocranium with prominent frontal bulges, a very narrow rib cage especially in the upper and elongated portion with very thin ribs, and the pulmonary hypoplasia. In addition, prenatal ultrasound offers other elements of support for the diagnosis: a short and curved femur and the presence of polyhydramnios, detected in at least half of TD's cases [2].

Discussion

Main forms of skeletal dysplasia

The differential diagnosis is between the different forms of skeletal dysplasia. They are an extremely heterogeneous group of conditions affecting bone formation and growth, among which the main forms are achondroplasia, achondrogenesis, hypophosphatasia, osteogenesis imperfecta and asphyxiating thoracic dystrophy [5, 6].

Achondroplasia is a form of short-limbs dwarfism, as the TD (rhizomelic shortening). Long bones are abnormally short with enlarged metaphysis only in the proximal segment (humerus and femur). The iliac wings are hypoplastic and square with a flat acetabular roof as in the TD. The vertebral bodies are less flattened [7].

Achondrogenesis is a micromelic dwarfism with severe shortening of the limbs. A characteristic feature is the absence of ossification of the lower dorsal, lumbar and sacral vertebral bodies [8].

Perinatal lethal hypophosphatasia is a form of micromelic dwarfism in which there is widespread bone demineralization, with very thin bones and non-ossified vertebrae, both at the level of the bodies and at the level of the posterior arches of the vertebrae, and the absence of hand ossification [9].

Perinatal lethal osteogenesis imperfecta is characterized by diffuse bone demineralization with very thin bones and multiple fractures. The long bones may consequently appear shortened and/or angled. Platyspondylia is present and marked [10].

Asphyxiating thoracic dystrophy, suspected on prenatal ultrasound, is characterized by a very narrow and elongated chest similar to that of TD; the long bones are shorter and wider than normal, resulting in a slight dwarfism. There is no curvature of the long bones, nor platyspondylia [11].

Thanatophoric dysplasia

TD is the most lethal, rare, sporadic birth defect due to *de novo* mutation in the fibroblast growth factor receptor-3 (*FGFR3*) gene [12, 13]. TD is considered an autosomal dominant disorder with an incidence of 1 case in 20,000-50,000 births.

FGFR3 gene is located in chromosome 4p16.3, responsible for giving instructions for making a protein that is involved in the development and maintenance of bone and brain tissue.

TD is traditionally divided into two forms on the basis of the radiographic appearances – type 1 (TD1) with curved femora and usually a normal skull, and type 2 (TD2) with straight femora and frequently a trilobal clover-leaf skull [14]. TD1 is more common than TD2.

Features common to both TD include: marked symmetrical shortening of the limbs (micromelia) with redundant skin folds, brachydactyly (short, broad tubular bones of the hands and feet), macrocephaly with distinctive facial features (frontal bossing, low nasal bridge, flat faces), severe platyspondyly, small conical thorax with horizontally placed short ribs and large protuberant abdomen. Both defects are autosomal dominant [15].

TD is the most severe form of the *FGFR3* phenotypes. The prognosis is unfavorable, almost all of the patients die during the neonatal period; there are rare descriptions of patients who survived to infancy with significant medical interventions. Most infants with the disease die from respiratory failure due to reduced rib cage volume and pulmonary hypoplasia [14].

Differential diagnosis

Skeletal dysplasias can be diagnosed by prenatal ultrasound examination. They are suspected when the presence of a short fetal femur for gestational age is detected, above all if the femur is markedly short (consistently 5 mm or more below the -2SD line) [16].

The differential diagnosis of the various skeletal dysplasias is possible by combining the ultrasound evaluation of the length of the bones, the shape (straight or curved), the ossification and the possible presence of fractures.

A complete ultrasound evaluation is possible starting at ≥ 14 weeks of gestation, considering that

much of the skeleton (clavicle, mandible, ileus, scapula and long bones) ossifies within 12 weeks of gestation, while the epiphyseal ossification centers are visible at around 20 weeks of gestation and the carpal bones ossify after birth [17]. The evaluation of ossification allows to distinguish TD and achondroplasia, in which bone mineralization is normal, from the forms of perinatal lethal osteogenesis imperfecta, hypophosphatasia and achondrogenesis, in which there is a more or less severe picture of demineralization. An alteration in the normal compressibility of the cranial vault during neonatal brain ultrasound is indicative of a mineralization defect in the cranial vault.

Platyspondylia can be difficult to identify with prenatal ultrasound [18]. Its finding is severe in TD, even lethal in osteogenesis imperfecta.

Antenatal diagnosis of TD requires expertise, especially in the early first trimester [19]. At 12 weeks, there may be subtle features such as frontal bossing, rarely an increase in nuchal translucency and short limbs.

Polyhydramnios occurs in approximately 50% of skeletal dysplasia cases and may be related to a combination of factors, including esophageal compression (from a small chest), micrognathia, associated gastrointestinal abnormalities, and hypotonia with impaired swallowing [2, 20].

In many fetal skeletal dysplasias, the skin and subcutaneous layers grow faster than long bones, resulting in relatively thickened skin folds, which can be mistaken for fetal hydrops. In some forms, for example in achondrogenesis, fetal hydrops is present.

Clinical course

The little patient, always subjected to invasive ventilation and oxygen therapy, presented a progressive worsening of the respiratory system and died after 96 hours of life. The diagnosis was then confirmed by genetic analysis, which revealed an X807C mutation of the *FGFR3* gene described in patients with TD1.

Declaration of interest

The Authors declare that there is no conflict of interest.

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