REVIEW ARTICLE

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SKELETAL DYSPLASIAS

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ABSTRACT

The aim of this study is through a literature review to describe the concept, diagnosis and management of skeletal dysplasias. Skeletal dysplasias are a heterogeneous group of disorders that affect bone and cartilage and are characterized by abnormal skeletal shape, growth, and integrity. These disorders can be inherited in a multitude of genetic patterns – autosomal dominant, autosomal recessive, somatic mosaic, metabolism imprinting errors, X-linked, and teratogenic exposure. Most are monogenic diseases.

Prenatal diagnosis is challenging as the first findings are seen during routine ultrasound. Most skeletal dysplasias have an identifiable pattern of skeletal changes comprised of unique and even pathognomonic findings. The use of multigene panels, using state-of-the-art sequence technology, has improved our ability to quickly identify the genetic etiology, which can impact management during pregnancy and/or neonatal period.

KEYWORDS: SKELETAL DYSPLASIA, BONE DYSPLASIA, DIAGNOSIS, MANAGEMENT

INTRODUCTION

Fetal skeletal dysplasia is a group of systemic bone and cartilaginous disorders that develop in the prenatal period and can be detected by fetal ultrasound[1]. Osteochondrodysplasias, or skeletal dysplasias, constitute a genetically heterogeneous group of many different disorders[1,2].

The global incidence is about 2.4 cases per 10,000 births, and the incidence of lethal dysplasias varies between 0.95 and 1.5 per 10,000 births. Regarding mortality, 44% died in the perinatal period. There is no preponderance as to race or sex (except in X-linked recessive diseases, where males are the most affected)[3].

Bone dysplasia is a large group comprising 436 rare diseases. Many of them are characterized by short stature or decreased growth velocity during puberty. However, the genetic basis remains unknown in many additional skeletal diseases, especially local skeletal injuries, suggesting that new genes or non-genetic factors may cause these diseases[4].

The aim of this study is through a literature review to describe the concept, diagnosis and management of skeletal dysplasias.

METHODS

The bibliographic search was carried out between January 10 and February 20, 2021 in Pubmed, Scielo and Medline databases. The keywords were used as search strategies: skeletal dysplasia or bone dysplasia and their respective terms in Portuguese.

FETAL SKELETAL DYSPLASIA

CONCEPT

Skeletal dysplasias are a heterogeneous group of congenital bone and cartilaginous disorders of genetic etiology characterized by abnormalities in the shape, length, number and mineral density of bone. Skeletal dysplasia is often associated with the manifestation of other organs such as the lung, brain and sensory systems. Skeletal dysplasias or dysostosis are classified under several different names.

Endochondral bone formation is a coordinated event of chondrocyte proliferation, differentiation, and exchange of terminally matured chondrocytes with bone. Impaired endochondral bone formation will lead to skeletal dysplasia, especially associated with short long bones. Adequate bone volume and mineral density are achieved by balancing bone formation and bone resorption and mineralization. The gene encoding fibroblast growth factor receptor [3] is responsible for achondroplasia, a representative skeletal dysplasia with short stature. Osteogenesis imperfecta is characterized by low bone mineral density and fragile bone [5,6].

The disorders affect the extremities or parts of them (dysmelia), the entire skeleton (skeletal dysplasia), the skull (craniosynostosis), and the spine (dysostosis, caudal regression). About half of these diseases are complex. In most cases, complex disorders are caused by mutations in a single gene or numerical or structural chromosomal aberrations. The main diagnostic challenge of limb malformations and craniosynostosis is to discover whether they are isolated symptoms or specific syndromes. In skeletal

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dysplasia, it is clinically important to differentiate lethal from non-lethal entities[7].

The type of dysplasia and associated abnormalities affect the lethality, survival, and long-term prognosis of skeletal dysplasias. It is crucial to distinguish skeletal dysplasias and correctly diagnose the disease to establish the prognosis and obtain better management[6].

DIAGNOSIS

Ultrasonographic evaluation of the fetus in the second trimester for the detection of congenital anomalies has become the standard of care in many communities. The fetal skeleton is readily visualized by two-dimensional ultrasound at 14 weeks, and fetal femur and humerus measurements are considered part of any basic ultrasound assessment.

Any fetus with femoral or humeral length measurements of less than the 5th percentile or -2 SD of the mean in the second trimester (<24 weeks) should be evaluated at a center that is experienced in assessing the entire fetal skeleton and has the ability to provide genetic data in counseling this couple.

The following fetal ultrasound parameters should be visualized and plotted against normative values when a fetus manifesting skeletal dysplasia is suspected; fetal skull (biparietal diameter, occipital-frontal diameter and head circumference), abdominal circumference, mandible, clavicle, scapula, chest circumference and all fetal long bones. Comparison of the relative length of all long bones and normative values will determine whether there is primarily rhizomelia, mesomelia, or that both segments are involved.

A useful ratio is the femur-to-foot length ratio, which approaches 1.0 during pregnancy. Many skeletal dysplasias are disproportionate based on these parameters. For example, disorders that manifest mainly with rhizomelia in the prenatal period show a change in the proportion between the femur and the foot (<1)[2].

In addition to the evaluation of long bones, there are other sonographic parameters that must be evaluated and may be useful in these differentiating disorders. These include fetal facial profile (glabellar bulge, flattened nasal bridge, micrognathia), presence and shape of vertebral bodies, and relative appearance of hands and feet (extra, absent, or malformed fingers). There are many prenatal-onset skeletal dysplasias that are associated with relative and equinovarus brachydactyly.

Fetuses with below-average long-bone measurements should be strongly suspected of having skeletal dysplasia, especially if the head circumference is greater than the 75th percentile. Most prenatal-onset skeletal dysplasias have a relative disproportion in skeletal measurements compared with those of the skull. In addition, close attention should be paid to the shape and pattern of mineralization of the fetal calvaria and fetal skeleton (deficient or ectopic mineralization). The determination of abnormal skeletal elements, together with findings of mineralization and bone shape, can help in the diagnosis[2].

The following fetal sonographic measurements should be visualized in relation to normative values: fetal skull (biparietal diameter and head circumference), facial profile, jaw, clavicle, scapula, thoracic circumference, vertebral bodies, all fetal long bones, hands and feet. Fetuses with long bone parameters >3 SD below average should be strongly suspected of having skeletal dysplasia, especially if the head circumference is greater than the 75^{TH2} percentile.

Prenatal ultrasound can be used to look for predictors of lethality, such as bell-shaped chest, short ribs, severe femoral shortening, and decreased lung volume. Individual lethal or life-limiting dysplasias may have more or less specific characteristics on prenatal ultrasound[6].

Lethality should be determined by the ratio of chest circumference/abdominal circumference and/or femur length/abdominal circumference. A chest-to-abdominal circumference ratio of <0.6 or femur length to abdominal circumference of 0.16 strongly suggests a perinatal lethal disorder, although there are exceptions. Findings should be communicated to the physicians caring for the patient and to the patient[2].

A study to assess the diagnostic accuracy of the diagnosis of skeletal dysplasia in a prenatal population from a single tertiary center, including 178 fetuses, of which 176 had a prenatal diagnosis of skeletal dysplasia by ultrasound. In 160 cases the prenatal diagnosis of a skeletal dysplasia was confirmed; two cases with postnatally identified skeletal dysplasias were not diagnosed prenatally, giving 162 fetuses with skeletal dysplasias in total. There were 23 different classifiable types of skeletal dysplasia. Specific diagnoses based only on prenatal ultrasound examination were correct in 110/162 (67.9%) cases and partially correct in 50/162 (30.9%) cases (160/162 in total, 98.8%). In 16 cases, skeletal dysplasia was diagnosed prenatally but not confirmed postnatally (n = 12 false positives) or the case was lost to follow-up (n = 4). The following skeletal dysplasias were recorded: thanatophoric dysplasia (35 correctly diagnosed prenatally out of 40 in total), osteogenesis imperfecta (lethal and non-lethal, 31/35), short rib dysplasia (5/10), Ellis- van Creveld (4/9), achondroplasia (7/9), achondrogenesis (7/8), campomelic dysplasia (6/8), asphyxiating thoracic dysplasia of Jeune (3/7), hypochondrogenesis (1/6), diastrophic dysplasia (2/5), chondrodysplasia punctata (2/2), hypophosphatasia (0/2), as well as 7/21 more cases with rare or unclassifiable skeletal dysplasias. The prenatal diagnosis of skeletal dysplasias can pose a considerable diagnostic challenge. However, a meticulous ultrasound examination yields high overall detection. In the two most common disorders, thanatophoric dysplasia and osteogenesis imperfecta (25% and 22% of all cases, respectively), typical sonomorphology accounts for the high rates of completely correct prenatal diagnosis (88% and 89%, respectively) in the first diagnosis exam[7]. Figure 1 illustrates a case of thanatophoric dysplasia.

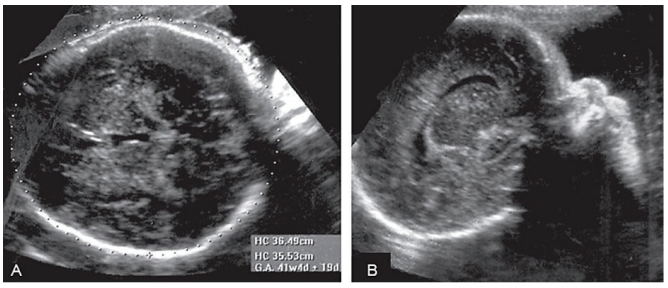

Figure 1 - Thanatophoric dysplasia [10]

The diagnosis of short stature due to skeletal dysplasia is based on:

(i) physical characteristics such as disproportionate trunk/limbs, short limbs or extremities, and/or stocky build,

(ii) adiographic features to analyze bone mineralization, maturation and morphology, and

(iii) whenever possible, genetic characterization [8, 9].

Figure 2 illustrates cases of skeletal dysplasias comparing neonatal photos with postnatal radiological exams.

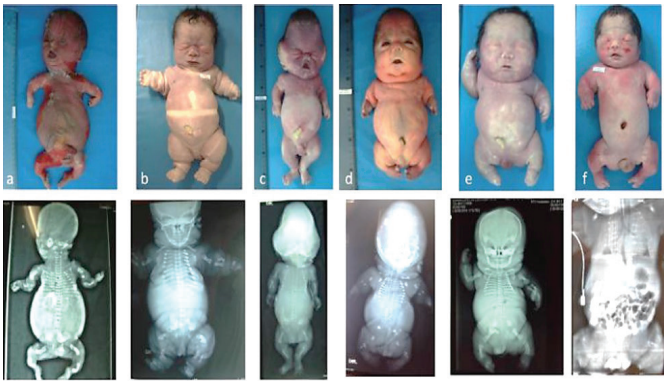

Figure 2. Illustrates photos of fetuses with skeletal dysplasia comparing neonatal images with postnatal x-rays [11]

If a diagnosis of lethal dysplasia or life-limiting dysplasia is suspected prenatally, pediatric evaluation or multidisciplinary clinical evaluation after birth is critical to verify the diagnosis. In all prenatally confirmed cases, genetic counseling for parents is necessary. In the case of lethal dysplasias, all possibilities for further treatment must be presented, both continuation of pregnancy and termination of pregnancy (if this solution is permitted by law). When the pregnancy continues, palliative care after birth is proposed[10].

MANAGEMENT

Differentiating these disorders prenatally can be challenging because they are rare and many of the sonographic findings are not necessarily pathognomonic for a specific disorder. However, differentiating lethal from non-lethal known disorders, providing differential diagnoses before delivery, determining postpartum management plans, and ultimately determining accurate recurrence risks for at-risk couples improves patient care[2].

Bone dysplasia mainly affects many organs and therefore requires multidisciplinary follow-up and care. The role of the pediatric endocrinologist is to assess the growth potential of these patients in coordination with other caregivers, offering the best growth management to limit the psychosocial consequences of extreme short stature and bone deformities[9].

It should be emphasized that genetic counseling of the parents of an affected child or fetus is necessary before the next pregnancy to discuss the risk of recurrence and the possibility of preimplantation or antenatal diagnosis. It should also be emphasized that lethal conditions associated with de novo mutations may have less than a 1% risk of recurrence (not counting the possibility of germline mosaicism), while skeletal dysplasias associated with autosomal recessive inheritance are associated with a risk of recurrence of 25%[10].

All fetuses with suspected skeletal dysplasia should have the diagnosis confirmed by postpartum clinical and radiological evaluation. Postpartum and/or postmortem evaluation includes anteroposterior radiographs of the appendicular skeleton, including hands and feet, and anteroposterior and lateral x-rays of the skull and spine (spinal column). In all appropriate cases, photographs should be taken and autopsies should be offered and encouraged as they provide the most useful information for an accurate diagnosis. Pathologists should collect cartilage and bone, ideally femurs and humerus, for histomorphometric analysis. Tissues (fibroblasts, cartilage and bone) and/or DNA should be saved for molecular analysis whenever possible, because many skeletal disorders are associated with a significant risk of recurrence[2].

FINAL CONSIDERATIONS

Skeletal dysplasias are a heterogeneous group of disorders that affect bone and cartilage and are characterized by abnormal skeletal shape, growth, and integrity. These disorders can be inherited in a multitude of genetic patterns – autosomal dominant, autosomal recessive, somatic mosaic, metabolism imprinting errors, X-linked, and teratogenic exposure. Most are monogenic diseases. Prenatal diagnosis is challenging; findings are first seen during routine ultrasound. Most skeletal dysplasias have an identifiable pattern of skeletal changes consisting of unique and even pathognomonic findings. The use of multigene panels, using state-of-the-art sequence technology, has improved our ability to quickly identify the genetic etiology, which can impact management.

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