Diagnostic Approach to Skeletal Dysplasia

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Abstract
The Nosology and Classification of Genetic Skeletal Disorders (2015) is still based on an artificial grouping of more than 370 conditions and is built based on a combination of morphological, pathogenic/ molecular and/ or pure descriptive criteria. The classification has helped to minimize the spectrum of differential and molecular analysis provided accurate diagnosis(1). However before reaching molecular investigation, it is crucial to recognize the phenotype clinically and from there we go through the steps of diagnosis. Ostensibly, as an at-one-go diagnosis is almost impossible even for the skilled physician, a sequence of diagnostic steps is usually followed.
Keywords: Diagnostic Approach, Skeletal Dysplasia

-History and physical examination

A focused history can give invaluable clues towards the diagnosis and differential diagnosis. Aim of the first visit is to recognize the key clinical features. The commonest presenting feature for a patient with SD is disproportionate short statute. Disproportionate short stature is sub-divided into short-trunk or short-limb variety. Sitting and standing heights, upper/lower segment (U/L) ratio, arm span and head circumference should be recorded sequentially on growth charts Upper/ lower segment and arm span/sitting height ratios determine proportions (spine or limb shortening) (2). Patterns emerge when anthropometric measurements are plotted on growth charts. The history should ascertain when the short stature was first recognized: prenatally or later during childhood(3). For genetics syndromes, ancillary signs can be helpful in securing the diagnosis :polydactyly, syndactyly, congenital heart defects, limbs swelling, neck webbing, short stature, edema of hands and feet, nuchal folds, low hairlines, low set ears, small mandible, cubitus valgus, nail hypoplasia, hyperconvex nails and so on. The family history should include parental height, other family members affected and parental consanguinity.

-Biochemical studies

Individuals with proportionate short stature are more likely to have a systemic cause for growth failure (renal, cardiac, endocrine or nutritional) or present as part of a syndrome caused by other genetic aberrations complete blood count, coagulation profile, a basic metabolic panel to evaluated sodium, potassium, calcium, blood urea nitrogen (BUN), creatinine, glucose, Vitamin D, osteocalcin level, cholesterol level as well as triglyceride levels are useful. A baseline hormones level is important for diagnosis of endocrine imbalance and for monitoring improvements. Follicle stimulating hormones (FSH), luteinizing hormone (LH), inhibin B, estradiol, progesterone, Anti Mullerian Hormone (AMH) and testosterone levels are obtained for assessment of ovarian function and estrogen related functions. Parathyroid hormone (PTH) levels, thyroid stimulating hormone (TSH), total or free T4 and thyrotropin levels are measured

-Radiological findings

The radiologist plays a major role in making an accurate diagnosis. The radiologic evaluation of **axial** and **appendicular skeleton** begins with a complete skeletal survey. The bones should be assessed for presence, curvature, degree of mineralization, and fractures. The femur length–abdominal circumference ratio (The clavicles should be measured, since absence or hypoplasia of the clavicles is seen in cleidocranial dysplasia)(4). The presence of the scapula should also be noted, since its absence is a useful defining feature of camptomelic dysplasia(5). Foot length should be measured and any missing bones evaluated. Any postural deformities Foot length should be measured and any missing bones evaluated. Any

postural deformities should also be evaluated. Clubbing of the hand is suggestive of the spectrum of "radial ray" anomalies, Head circumference and biparietal diameter should be measured to exclude skull anomalies(6). The shape, mineralization, and degree of ossification of bone should be evaluated. The spine should be carefully imaged to assess the relative total length and the presence of curvature to exclude scoliosis. Mineralization of vertebral bodies and neural arches should be evaluated.

-Ultrasound (US) imaging

Fetal echocardiography and biometry during the second semester is important and emphasized on specific areas including biparietal diameter (BPD), head circumference (HC) and abdominal circumference (AC) , amniotic fluid (AF)(7), chest circumference and all limbs' bones(8,9) A throughout evaluation from head to toe and any deviation from normative values should raise suspicion of skeletal dysplasia unless proven otherwise(10-12).   Practical guidelines for the ultrasound evaluation are available usually between 17 and 21 weeks(13). 3D ultrasound could identify most anatomical landmarks more than 90% with an accuracy of 95% and assessment of the fetus with 3D US has been shown to improve diagnostic accuracy, since additional phenotypic features not detectable at 2D-dimensional US may be identified (14-17).

-CT scan

Helical CT as a complement to ultrasound examination is key in the diagnosis of fetal skeletal dysplasia from 26 weeks of gestation because of the low level of fetal ossification before then.   The sensitivity of helical CT to detect skeletal dysplasia was excellent (83%) and was therefore diagnostically useful in 82% of cases, confirming, discounting, or consolidating a diagnosis, which had a direct impact on clinical practice.

-Postnatal Evaluation

A substantial percentage of fetuses with a skeletal dysplasia die in utero, are stillborn, die as neonates, or are delivered after elective termination of pregnancy. Establishment of the correct diagnosis of the skeletal dysplasia will likely require pathologic diagnostic work-up.   Minimal postmortem (autopsy) work-up should include (a) external examination with photographs; (b) postmortem whole-body radiographs; and (c) skin or other tissue biopsy specimens for chromosome analysis and preservation of fibroblasts for possible later biochemical, enzymatic, or genetic studies, to be sent to specialty laboratories as indicated. The autopsy findings were predefined as being potentially useful for diagnosis of SD: long bone shape, platyspondyly, vertebral body shape, thorax, metaphyses, extremities, skull and face, pelvic girdle, pectoral girdle, mineralization and ossification of the ischiopubic rami.

-Molecular Diagnosis

Certain types of skeletal dysplasia are lethal conditions. Therefore, diagnostic accuracy is important to appropriately counsel parents and plan obstetric management(18) . Biochemical and molecular genetic methods of prenatal diagnosis, for example, by identification of gene mutation, are often necessary to refine a diagnosis (19,20). The most reliable method for making a definitive diagnosis of skeletal dysplasia depends on biochemical and molecular techniques since, in some skeletal dysplasia, gene mutations can be identified (21-23).   Several techniques are employed based on previously described protocols for the concerned suspected SD. In this way, the actual causative gene mutation is known which facilitates the treatment plan to be undertaken.

1. Discussion

Many new bone dysplasias were identified based on clinical manifestations, radiographic findings, inheritance patterns, and morphology of the growth plate. The focus is shifted toward elucidating the responsible mutations and characterizing the pathogenetic mechanisms by which the mutations disrupt bone growth. Despite latest updates, the basic defect remains unrecognized in many disorders. With increasing molecular discoveries, classification and nomenclature must be constantly updated(24). The available data from the Human Genome Project about the reference Human Genome Sequence and the advent of new, more

powerful techniques for genome analysis led to an explosion of often unpredictable findings.

Although the occurrence of each individual skeletal dysplasia may be rare, as a group they account for a significant number of newborns with congenital anomalies. Many of the prenatal onset skeletal dysplasia is associated with lethality because of pulmonary insufficiency or concomitant visceral abnormalities. Many of these disorders result from new dominant mutations and for the autosomal recessive disorders, many occur in families with no history of skeletal dysplasia. The fetal skeleton develops relatively early in the fetal period and, thus, prenatal diagnosis of these disorders is possible. The appendicular and the axial skeleton undergo a programmed pattern of endochondral ossification, whereas the calvarium and portions of the clavicle and pubis ossify via membraneous ossification. Ossification occurs at relatively early human gestational ages: clavicle and mandible at 8 weeks; the appendicular skeleton, ileum, and scapula by 12 weeks; and the metacarpals and metatarsals are ossified by 12–16 weeks. Secondary (epiphyseal) ossification centers are seen by radiographs at approximately 20 weeks gestation and at a similar time period by ultrasound. Second trimester ultrasound evaluation of the fetus for detection of congenital anomalies has become standard of care in many communities. The fetal skeleton is readily visualized by two-dimensional ultrasound by 14 weeks, and measurements of the fetal femora and humerus are considered part of any basic midtrimester ultrasound evaluation. The fetal ultrasound parameters must be visualized and plotted against normative values when a fetus manifesting a skeletal dysplasia is suspected. 3D imaging may be performed

US, X-rays and 3D-CT contributed to a precise prenatal diagnosis where an SD had been suspected, but no formal diagnosis could be reached. US performs better in the assessment of bone density(25). However, it is not uncommon that whilst an SD is suspected, a precise diagnosis cannot be made. Most SD prenatal series report a diagnostic accuracy < 50% (26).. CT images give a precise view of the bone structure (cortical/medullary bone ratio), metaphyseal deformities and possible fractures, and allow the clinician to appreciate global proportions and morphological deformities (e.g. curved bones, short ribs, spinal shortening, luxations). 3D-CT demonstrates skeletal findings that can be overlooked by US such as deformities of the vertebral column, pelvic bones and ossification centers. The standard of imaging improves as bone mineralization increases and 3D reconstruction is easier as the fetus is less mobile – and for this combination of reasons we chose to perform 3DCT during the third trimester(25). Magnetic resonance provides an alternative method of multiplanar imaging with excellent soft tissue contrast and requires no radiation – but appears to be inferior to US in the evaluation of fetal bones. Helical CT has been used in the diagnosis of fetal skeletal dysplasia(27,28) and also. 3D ultrasound used in addition to two-dimensional (2D) ultrasound(29).

2. Conclusion

In conclusion, the diagnosis of skeletal dysplasia is not difficult but remains complicated. It demands a familiarity with numerous rare conditions and good pattern recognition skills. The sequence of steps in this article provides a framework for establishing a differential diagnosis but consultation with an expert in the field of skeletal dysplasia remains a valuable tool. While ultrasound examination in the second trimester can identify some severe lethal skeletal dysplasia, it can also reveal a large number of bone abnormalities without, however, being able to diagnose with certainty most skeletal dysplasia (30). Advances in molecular diagnostics are at the heart of the area of health care that provide an understanding of the underlying molecular mechanisms of disease and address the corresponding specific treatments. The causative genes and pathognomonic findings are known and these data and be used in prenatal diagnosis for skeletal dysplasia.

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