Skeletal dysplasia

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Abstract

Skeletal dysplasias are genetic conditions causing a structural abnormality in the bone and cartilage leading to growth disturbance. There are many different types of dysplasias most of which are rare. Although the incidence of the each individual types of skeletal dysplasia is low, skeletal dysplasia as a group should be recognized early for appropriate management. The aim of this article is to present a brief overview of skeletal dysplasia and the management of the more common among these presenting to the orthopaedic surgeon.

Keywords Dysplasia; genetics; osteogenesis imperfecta

Introduction

Skeletal dysplasias or osteochondral dysplasias are a genetic condition causing structural abnormality in bone or cartilage that leads to a disturbance in growth in the extremity and/or trunk. The 2015 revision of the comprehensive *Nosology and classification of genetic disorders* lists 436 disorders in 42 phenotypically related groups.[1] The incidence of skeletal dysplasia as a group is reported to be 2.3–7.6 per 10,000 in various epidemiologic studies.[2] Many of these are rare and it would be beyond the scope of this article to describe all of them.

The condition is caused by mutation of genes that are either inherited from parents or due to spontaneous mutation during fetal development. The diagnosis can often be difficult and hence this article aims at describing a simplified approach to diagnose various commonly presenting dysplasias.

There are various classifications for skeletal dysplasia. Rubin's classification is based on the type of abnormality (hypo/hyperplasia) and the site involved in the bone (Table 1). There are lethal and non-lethal skeletal dysplasias most of which can be diagnosed in utero.

Work-up of skeletal dysplasia

The diagnosis of a skeletal dysplasia can be made from history, clinical examination, imaging and genetic studies. Importance and relevance of each of these with regard to the diagnosis is described later with each dysplasia separately.

History: time when the condition manifests is important. A family history over multiple generations is essential. Consanguinity should be noted as it increases the risk of autosomal recessive conditions. Maternal and paternal age should be noted as increased paternal age has an increased risk of point mutations and increased maternal age has increased risk of chromosomal abnormalities. Antenatal and post-natal complications including abortions and still births should be noted. Developmental history and past medical history with problems related to eyes, hearing and respiration should be noted.[3]

Physical examination: standing and sitting height should be measured (short stature is height less than 3rd percentile). Trunk extremity ratios differentiate proportionate vs disproportionate shortening. Children have larger upper segment length compared to adults who have equal upper segment and lower segment lengths. Disproportionate shortening can be in the trunk or limbs. Shortening in limb segments is termed rhizomelic, mesomelic, acromelic and micromelic to describe proximal, middle, distal or entire limb shortening respectively.

Spine examination is performed to analyse sagittal and coronal plane deformity. Lower limb alignment should be noted and also joint movement and laxity. Typical features are seen specific to some of the dysplasias which will be described separately with the respective dysplasias.

Imaging: imaging consists of ultrasound used as part of antenatal screening and radiographs/CT radiography. These together can diagnose many of the skeletal dysplasias. Radiographs include skeletal survey (Table 2) which help establish which bones are affected and in which anatomical location (epiphysis, metaphysis, diaphysis).

Further follow-up tests in the high-risk group comprise of amniocentesis and chorion villus sampling in the antenatal period and genetic tests in the post-natal period.

Genetic studies: genetic testing of the affected individual as well as of the family helps confirm the diagnosis and counsel further regarding the condition.

Blood tests are done in some of the conditions and include bone profile for hypophosphataemia, Jansen-type metaphyseal chondrodysplasia and pseudohypoparathyroidism.

Below is a summary of a few commonly presenting dysplasias.

Achondroplasia

It is the most common form of short stature with an incidence of 1/15,000 live births.

History: it presents at birth or can be diagnosed prenatally using the ultrasound finding of short femora. The inheritance is autosomal dominant with complete penetrance; however, 90% of cases are spontaneous mutations. This has been linked to increased paternal age. The risk of achondroplasia in the offspring of two unaffected individuals is 0.02%.[4]

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Rubin's classification

Location	Nature	Mechanism	Example
Epiphysis	Hypoplasia	Failure of articular cartilage	Spondyloepiphyseal dysplasia congenita and tarda
		Failure of ossification centre	Multiple epiphyseal dysplasia congenita and tarda
	Hyperplasia	Excess articular cartilage	Dysplasia epiphysealis hemimelica
Physis	Hypoplasia	Failure of proliferating cartilage	Achondroplasia congenita and tarda
		Failure of hypertrophic cartilage	Metaphyseal dysostosis congenita and tarda
	Hyperplasia	Excess of proliferating cartilage	Hyperchondroplasia
		Excess of hypertrophic cartilage	Enchondromatosis
Metaphysis	Hypoplasia	Failure to form primary spongiosa	Hypophosphatasia congenita and tarda
		Failure to absorb primary spongiosa	Osteopetrosis congenita and tarda
		Failure to absorb secondary spongiosa	Craniometaphyseal hyperplasia
	Hyperplasia	Excessive spongiosa	Multiple exostosis
Diaphysis	Hypoplasia	Failure of periosteal bone formation	Osteogenesis imperfecta congenita and tarda
		Failure of periosteal bone formation	Idiopathic osteoporosis congenita and tarda
	Hyperplasia	Excessive endosteal bone formation	Hyperphosphatasaemia
		Excessive periosteal bone formation	Progressive diaphyseal dysplasia

(From Rubin P: *Dynamic classification of bone dysplasias*, Chicago, 1964, Year Book Medical Publishers, p 82.)

Table 1

Skeletal survey

Area imaged	View
Skull	AP and lateral
Thoracolumbar spine	AP and lateral
Chest	AP
Pelvis	AP
One upper limb	AP
One lower limb	AP
Left wrist	AP (bone age)

AP, anteroposterior.

Table 2

Physical examination: patients display disproportionate short stature with rhizomelia (Figure 1a). Soft tissues are spared giving rise to bulky appearance around thighs due to excessive muscle compared to length of bone. Ligament laxity is often noted. Typical facial features include frontal bossing, depressed nasal bridge and maxillary hypoplasia. Flexion contracture may be present at the elbow resulting in dislocation of the radial head. Relative shortening of the middle finger gives rise to the appearance of all fingers being the same length (starfish hand). An abnormally increased separation of middle and ring finger gives appearance of 'trident hand'. Bowing of lower limbs is also noted.[5]

Hypotonia, sleep apnoea and sometimes sudden death is due to foramen magnum hypoplasia leading to craniocervical stenosis.

Thoracolumbar kyphosis is commonly seen in infants which resolves with growth and maturity as muscle tone improves. Stenosis of the spinal canal often occurs in the 3rd decade of life due to secondary thickening of pedicles and hypertrophy of facets and enlarged lamina. Not all develop symptoms, however night pains and radiculopathy should be noted.

Radiographs: Extra-axial: metaphyses are widened with physes that are U- or V-shaped. Champagne glass pelvis is seen with a width of inlet more than the depth.[6] There is relative overgrowth of fibula relative to tibia. Genu varum, tibia vara and ankle varum is often seen. Relative overgrowth of greater trochanter gives the appearance of femoral neck in varum (not true coxa vara). Radial heads may demonstrate posterior dislocation. Short metacarpals and bullet-shaped phalanges are seen.

Axial: pedicles are short and broad with decreasing interpedicular distance.

Genetic studies: the mutation is a glycine-arginine substitution in the gene encoding the fibroblast growth factor receptor-3 (FGFR-3) on chromosome 4p.[7] This mutation leads to a failure of enchondral ossification. FGFR-3 regulates linear growth by inhibiting physeal chondrocyte proliferation and differentiation resulting in short stature. Periosteal ossification is unaffected hence long bones are shortened but have normal diameter. Intramembranous ossification is also unaffected hence skull and clavicles are normal.

Management: limb lengthening is controversial in achondroplasia as excessive amount of lengthening is required. Lengthening only lower limb results in a negative body image with the upper limb at a non-functional length. Lower limb angular deformities are rarely associated with degenerative changes as epiphysis is not affected. Surgery and deformity correction is therefore recommended for those symptomatic and to align the mechanical axis (Figure 1b,c). Spinal decompression is required for those with symptomatic stenosis. Growth hormone has been

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