Skeletal dysplasias: an overview

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Abstract

Skeletal dysplasias are a large group of rare diseases, with over 400 distinct entities recognised. Diagnosis is challenging, largely reflecting the rareness of individual conditions; yet collectively these disorders affect as many as 1:3000 individuals. The phenotypic diagnosis of skeletal dysplasia is based on careful clinical evaluation and, critically, on assessment of radiological appearances of the skeleton, which in most cases requires specialist expertise. Powerful modern genetic testing is transforming the approach to diagnosis of rare genetic disease, but does not obviate the need for accurate clinical and radiological evaluation. Management of children with skeletal dysplasias must pay attention to detection and prevention of potentially severe complications, particularly those involving compromise of the central nervous system, such as foramen magnum narrowing or atlanto-axial subluxation. Surgical management aims to treat these complications, but can also enhance function and in some cases address short stature. Targeted molecular treatments are emerging with potential to reverse these disorders, and are already transforming the lives of some children with debilitating diseases. We discuss 5 skeletal dysplasia conditions in more detail: Achondroplasia, Pseudoachondroplasia, Spondyloepiphyseal Dysplasia Congenita, Cartilage Hair Hypoplasia and Hypophosphatasia.

Keywords achondroplasia; hypophosphatasia; next generation sequencing; osteochondrodysplasia; pseudoachondroplasia; radiology; skeletal dysplasia; spondyloepiphyseal dysplasia congenita

Introduction

The skeletal dysplasias are a large, heterogeneous group of genetic disorders of the skeleton, with a reputation for being diagnostically challenging. The most recent classification of these diseases includes 436 entities, divided into 42 groups, and involving 364 known genes. Even the commonest disorders (achondroplasia and osteogenesis imperfecta), affect only 1:20,000−30,000 individuals; yet, collectively, skeletal dysplasias affect between 1:3000−5000 people. Skeletal dysplasias are *individually very rare* (hence the reputation for diagnostic difficulty), whilst *collectively relatively common*.

Skeletal dysplasias result from mutations in genes involved in every part of the skeletal development process (Table 1). Classifying such a diverse range of entities is in itself challenging, requiring a flexible approach; some disorders can be grouped according to known genes, some according to shared biological pathways, and some according to phenotype. This 'hierarchical' approach to classification is the basis for the most widely utilized classification, the Nosology and Classification of Genetic Skeletal Disorders, most recently issued in 2015.

We review the clinical, radiological and genetic approach to establishing a correct diagnosis for suspected skeletal dysplasia; in addition we provide an overview of the clinical management of affected children, and explore a few conditions in more detail.

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Diagnosis

Pre-natal diagnosis

Many severe skeletal dysplasias can be detected prenatally by ultrasound examination at 20 weeks gestation. Although a specific diagnosis is often not achievable, sonographic measurements can reliably predict those disorders, such as thanatophoric dysplasia, with a likely fatal outcome, and may guide decisions around termination of pregnancy or perinatal management. In some cases, invasive prenatal diagnostic techniques can verify a diagnosis genetically, and more recently, analysis of free fetal DNA in maternal blood has been shown to reliably detect some disorders; in general, however, the final precise diagnosis of a skeletal dysplasia is not made until after delivery.

Post-natal diagnosis of skeletal dysplasias

An attempt at diagnosing a case of suspected skeletal dysplasia should not be undertaken lightly. Provisional or speculative diagnoses are often incorrect, yet may be hard to dispel, as both clinicians and families may latch on to the first diagnostic offering. For clinicians working in general paediatric practice, the critical tasks are:

1) Identifying that a child might have a skeletal dysplasia
2) Arranging first line investigations, *including storage of samples for DNA analysis*
3) Referring on to an appropriately skilled team for definitive diagnosis

Clinical assessment

Modes of presentation in skeletal dysplasia are variable, and may occur from the first trimester through to adulthood. Short stature is the commonest symptom, but patients may also present because of facial dysmorphism, joint and gait problems, or with extraskeletal features. Some children present acutely, for example in the neonatal period with respiratory insufficiency in severe skeletal dysplasias, or with recurrent or multiple fractures in osteogenesis imperfecta. Regardless of presentation, a detailed family history, expressed as a pedigree chart, is essential.

A common clinical sign of skeletal dysplasias is disproportionate short stature, and the physical proportions should be documented, particularly the arm span and both sitting and standing height. Facial dysmorphism is also common in skeletal dysplasia, whilst its absence in the presence of skeletal abnormalities is also a helpful finding. Recording of facial photographs (with consent) aids multi-disciplinary diagnostic discussions. Ear and eye problems are common in many skeletal dysplasias, and should be clinically evaluated, if necessary supported by formal opthalmological or audiological assessment. Assessment of the

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Molecular and genetic processes involved in the aetiology of skeletal dysplasia

Process	Example	Gene (s)
Skeletal patterning in fetus	Holt-Oram Syndrome	*TBX5*
Skeletal growth factors and their receptors	Achondroplasia	*FGFR3*
Collagen proteins	Sponyloepiphyseal dysplasia congenita	*COL2A1*
	Osteogenesis Imperfecta	*COL1A1, COL1A2*
Non-collagenous matrix proteins	Pseudoachondroplasia	*COMP*
Post translation modification of structural proteins	Diastrophic dysplasia	*DTDST*
Degradation of skeletal matrix proteins	Metaphyseal Anadysplasia	*MMP9, MMP13*
Chondrocyte maturation	Metaphyseal dysplasia, Jansen type	*PTHR1*
Ribosomal assembly	Cartilage Hair Hypoplasia	*RMRP*
Osteoclast function	Infantile osteopetrosis (OPTB1)	*TCIRG1*
Lysosomal function	Hurler disease	*IDA*
Non-motile ciliary function	Ellis Van Creveld Syndrome	*EVC1, EVC2*
Ion channels	Metatropic dysplasia	*TRPV4*
Organisation of actin cytoskeleton	Melnick-Needles Syndrome	*FLNA*
Sterol biosynthesis pathways	Chondrodysplasia Punctata Conradi-Hunermann type	*EBP*
Golgi apparatus formation	Dyggve-Melchior-Clausen syndrome	*DYM*
Krebs cycle enzymes	Ollier Disease	*IDH1, IDH2*
Degradation of organic phosphate	Hypophosphatasia	*TNSALP*

Table 1

joints for laxity or stiffness, and of the hair and skin are also valuable.

Radiological assessment

Clinical assessment alone may occasionally lead to the correct diagnosis in some disorders; however, full evaluation of the skeletal phenotype requires direct assessment of skeletal morphology by radiological examination. Despite significant advances in imaging technology, the radiographic skeletal survey remains the key investigation in most cases of suspected dysplasia. A recommended protocol is given in Table 2. Radiation dose, if performed correctly on modern imaging equipment, is low, significantly lower than for a CT scan.

Skeletal surveys for dysplasia should be interpreted by a suitably trained radiologist; whilst most paediatric radiologists are comfortable in diagnosing some commoner disorders, such as achondroplasia, rarer or more complex phenotypes require interpretation by a radiologist or geneticist with special interest in skeletal dysplasia.

Protocol for standard skeletal survey for suspected skeletal dysplasia[a]

Site	Projections	Comments
Skull	AP and lateral	A Towne's view can be added for Wormian bone assessment
Thoracic, lumbar and sacral spine	Lateral	Add dedicated cervical spine view if relevant condition is suspected
Chest	AP or PA	Should include shoulders, also acts as AP view of thoracic spine
Pelvis	AP	Should include entire lumbar spine
One upper limb	AP	Either left or right
One lower limb	AP	Either left or right
Left hand	DP	Include distal radius and ulna. Allows bone age assessment

[a] Can be modified according to clinical presentation.

Table 2

A comprehensive guide to the interpretation of skeletal surveys is beyond the scope of this article. Experienced radiologists in the field make many diagnoses through a process of pattern recognition; for those less experienced, or when the diagnosis is less clear, a systematic approach to the description of the skeletal phenotype is suggested. One such approach is outlined in Table 3.

Putting it all to together: establishing a differential diagnosis

The combination of clinical, radiological and other findings may in some cases establish a clear clinical phenotype. In other cases, the pattern present may suggest a broad diagnostic category; for example, a delay in pubic ossification combined with an immature pattern of spinal ossification points to a disorder of type 2 collagen, whilst broadening of long bones with constrictions of the posterior ribs, proximal metacarpals and inferior iliac bones ('dysostosis multiplex') indicate a lysosomal storage disorder.

When the diagnosis is not immediately apparent even to the specialist, further help is needed. Discussion at a regular MDT is helpful, and wider forums may also be available, such as "Dysmorphology Clubs" and meetings of the UK Skeletal Dysplasia Group. International expertise for difficult cases is available via the European Skeletal Dysplasia Network.

Consultation with databases of rare diseases may be helpful. An ordered approach is beneficial. One such approach is the 'Reductionist' method described by Professor Jurgen Spranger. The clinical and radiological features present are listed, and distilled down to the most 'pivotal' findings. Pivotal findings have one or more of the following characteristics:

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