Skeletal Dysplasias: An Approach to Diagnosis

Rodney K. Beals, MD, and William Horton, MD

Abstract

Skeletal dysplasias are the result of aberration in the growth and development of the skeleton. While they are individually rare, they are important in that they provide an insight into the mechanism of skeletal development. This article offers an approach to the diagnosis of skeletal dysplasias, rather than an exhaustive account of all the possible diagnoses. Dysplastic conditions are suspected on the basis of abnormal stature, disproportion, dysmorphism, or deformity. Diagnosis requires simple measurement of height and calculation of proportionality, combined with a complete physical examination, appropriate radiographs, an investigation of the family pedigree, and occasionally laboratory studies. An accurate diagnosis can usually be made on the basis of these data and a review of descriptive sources. A definitive diagnosis allows the treating physician to project the patient's ultimate height and to prognosticate about likely deformities and the risk of the recurrence of the condition in the family.

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The term "chondrodysplasia" refers to conditions that cause abnormal growth or development of the skeleton, such as achondroplasia. "Osteodysplasia" refers to conditions that involve bone, such as osteogenesis imperfecta. "Osteochondrodysplasia" is a combining term that refers to both bone and cartilage dysplasias. In this article we will use the abbreviated term "skeletal dysplasia" as synonymous with osteochondrodysplasia.

There are many skeletal dysplasias. These conditions are due to mutations in genes involved in skeletal growth and development. Patients with skeletal dysplasia often appear to be similar clinically until a careful analysis is performed. Distinct subgroups can be distinguished on the basis of specific clinical, radiographic, genetic, biomechanical, and microscopic features.

Skeletal dysplasias are not common, but in the aggregate they affect a sizable number of patients. The International Nomenclature of Constitutional Diseases of Bone lists over 150 chondrodysplasias and osteodysplasias. The most common type of chondrodysplasia is achondroplasia, which occurs in approximately 1 of every 26,000 births. Skeletal dysplasias are of special importance because they provide insight into the mechanisms controlling normal skeletal growth and development.

In recent years there have been many advances in the clinical delineation of inherited skeletal dysplasias. The ability to give an accurate diagnosis allows one to project the ultimate height and to prognosticate about deformities and medical problems, not only in the patient but also in future members of the family. The purpose of this review is to describe the process of diagnosis of a skeletal dysplasia and to illustrate that process by review of a few representative conditions.

Diagnosis of Skeletal Dysplasias

The possibility of a skeletal dysplasia is usually suggested by abnormality in height or proportion; by dysmorphic features of the face, hands, or feet; or by deformity (Fig. 1). Additional data are obtained from radiographic evaluation and the family history and occasionally from laboratory evaluation and pathologic studies.

Height

The birth length should be ascertained if possible, but normal birth length does not preclude the presence of a skeletal dysplasia. The percentile of height for the patient's

Dr. Beals is Professor and Head, Division of Orthopaedics and Rehabilitation, Oregon Health Sciences University, Portland. Dr. Horton is Professor of Medical Genetics, Oregon Health Sciences University; and Director of Research, Shriners Hospital, Portland.

Reprint requests: Dr. Beals, Division of Orthopaedics and Rehabilitation, Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, OP13B, Portland, OR 97201-3098.

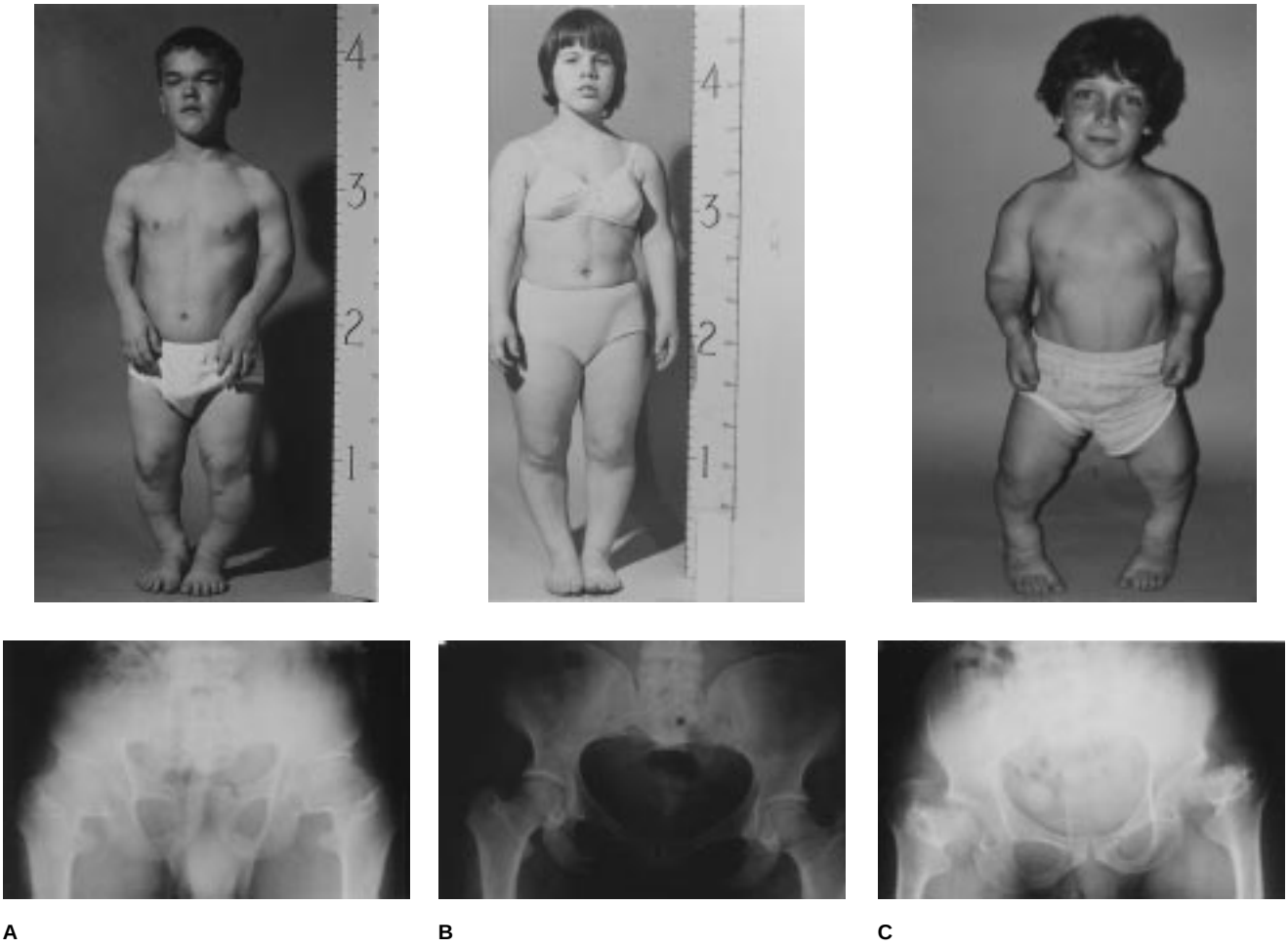

Fig. 1 Clinical appearance and pelvic radiographs of patients with three related forms of skeletal dysplasia. **Left,** Achondroplasia is characterized by rhizomelic short-limbed short stature, abnormal facies, short iliac wings, horizontal acetabula without early hip arthritis, and an adult height of 4 feet. **Center,** Hypochondroplasia is characterized by an adult height of about 4.5 feet, normal facies, and minimal radiologic changes in the pelvis. **Right,** Pseudoachondroplasia is characterized by short-limbed short stature with limb deformities, normal facies, and severe early dysplasia of the hips.

age and the pattern of growth should be determined. In general, if adult height is under 60 inches, consideration of skeletal dysplasia is appropriate.

Most patients with bone dysplasias are short, but some are of normal or greater than normal height. Adult height is an important diagnostic feature because adults affected by specific dysplastic conditions demonstrate little variation in height. For example, a disproportioned adult with a height of 42 inches is more likely to have diastrophic dwarfism; an adult height of 48 inches suggests achondroplasia; and an adult height of 52 inches suggests hypochondroplasia.

Body Proportions

When the patient is short but the body proportions are normal, the diagnosis is usually related to constitutional short stature, endocrine disorders, malnutrition, chronic disease, prenatal dwarfism, or one of the many dysmorphic syndromes. In contrast, disproportionately short stature is the finding in most skeletal dysplasias. Dwarfism combines both short stature and abnormal body proportions.

Trunk-Extremity Ratios

The most useful body proportions to measure are the ratio of arm span to height and the ratio of the lengths of the upper and lower segments of the body. (The length of the lower segment is the distance from

the top of the symphysis to the bottom of the foot. The length of the upper segment is the height minus the length of the lower segment.) These values allow determination of whether the trunk and extremities are normally proportioned. Patients with skeletal dysplasias may have a normal trunk and short limbs (e.g., achondroplasia), short trunk and limbs of normal length (e.g., spondyloepiphyseal dysplasia tarda), or long trunk and long limbs (e.g., Marfan's syndrome). Because body proportions vary with age and sex, review of graphs of normal values (Figs. 2 and 3) is necessary to determine whether the body proportions are normal.

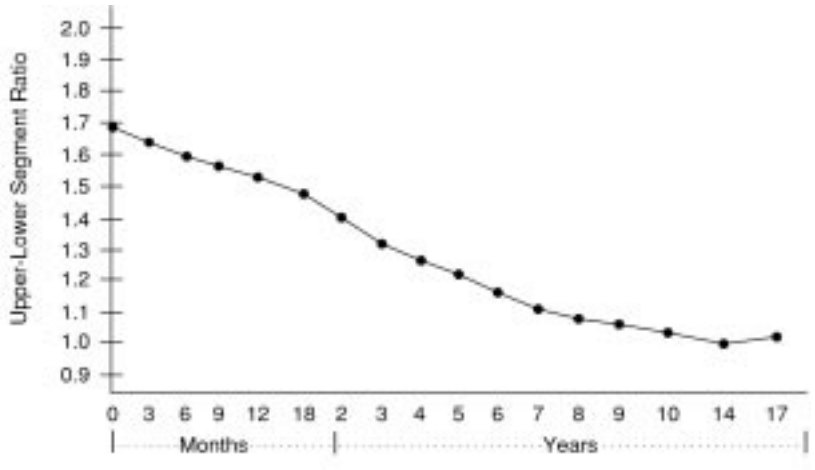

Fig. 2 The ratio of the lengths of the upper and lower segments of the body changes with age. This measurement indicates whether the trunk and lower extremities are of normal proportion. (Adapted with permission from Greene MG [ed]: *The Harriet Lane Handbook: A Manual for Pediatric House Officers*, 12th ed. St Louis: Mosby-Year Book, 1990, p 73.)

Limb-Segment Ratio

There is constancy in the ratio of the lengths of the parts of the limbs in normal children regardless of age or sex. The normal radius-humerus ratio is 75%, and the normal tibia-femur ratio is 82%. These ratios are best calculated from radiographic measurements, because clinical measurements are imprecise. Limbs are often intrinsically disproportionate in skeletal dysplasias. Rhizomelia is characterized by short proximal segments (short humeri or femora, as in achondroplasia); mesomelia, by short middle segments (short forearms or tibiae, as in dyschondrosteosis); acromelia, by short hands or feet.

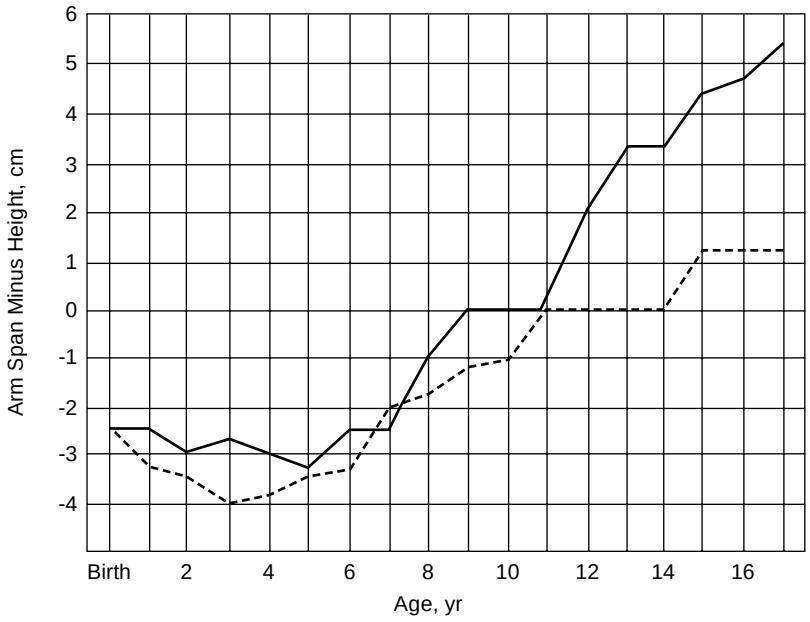

Fig. 3 The value for the arm span minus the height varies with age and sex and is useful to determine whether the trunk and upper limbs are proportionate. Average values (expressed in centimeters) are shown for boys (solid line) and girls (broken line). (Adapted with permission from Wilkins L: *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*, 3rd ed. Springfield, Ill: Charles C. Thomas, 1965, p 33.)

Dysmorphism and Deformity

Patients with bone dysplasias often have minor morphologic variations of the bones and soft tissues, referred to as dysmorphism. Examples of dysmorphic facial features are a depressed nasal bridge, as seen in patients with achondroplasia, and a long philtrum, as seen in those affected with trichorhinophalangeal dysplasia. Examples of dysmorphism in the extremities are bony prominences, which are commonly observed in multiple exostosis; short, broad thumbs, as are seen in multiple epiphyseal dysplasia; and finger deformities, such as cone-shaped epiphyses of the phalanges. Dys-

morphic features associated with short stature suggest an underlying bone dysplasia.

Deformities associated with skeletal dysplasia include lordosis, kyphosis, or scoliosis; varus or valgus deformity of the extremities; and limited joint motion. When a deformity is associated with short stature, a skeletal dysplasia should be a primary diagnostic consideration.

Radiographic Evaluation

If a skeletal dysplasia is suspected, radiographs should be obtained. A limited skeletal survey is the most cost-effective method of screening. A skeletal dysplasia can almost always be diagnosed on the basis of five radiographs: lateral skull, anteroposterior (AP) pelvis, lateral lumbar spine, AP hand and wrist, and AP knee.

These radiographs allow identification of the part of the bone that is affected. The long bones may be abnormal in the epiphysis, metaphysis, and/or diaphysis. In some dysplasias, the spine is affected. On the basis of these observations, dysplasias may be described as epiphyseal, metaphyseal, or diaphyseal or, when the spine is involved, as spondyloepiphyseal, spondylometaphyseal, or spondylodiaphyseal.

Family Evaluation

Skeletal dysplasias are often transmitted by Mendelian inheritance. Thus, family evaluation is an essential part of the evaluation. A pedigree that includes first-degree relatives is usually sufficient for screening, but occasionally a more extensive family history is needed. Many children with skeletal dysplasias are born to normal parents who have no family history of dysplasia. When this *de novo* event occurs, it may represent a new mutation of the relevant gene, gonadal mutation, or a recessive trait, or it may suggest nonpaternity.

Laboratory Evaluation

If the diagnosis of a skeletal dysplasia can be determined from the clinical and radiographic features, no further laboratory tests are necessary. In fact, the findings from a laboratory evaluation are usually normal in skeletal dysplasias. However, if the diagnosis remains uncertain, a blood chemistry profile and a urinalysis should be obtained to exclude treatable metabolic disorders, such as vitamin D–resistant rickets, and endocrine disorders, such as hypothyroidism.

Pathologic Studies

Biopsy of the bone or physis of the iliac crest is rarely indicated to evaluate an unknown bone dysplasia, but it is sometimes useful to confirm a diagnosis of dysplasia. Bone dysplasias known to have distinct microscopic abnormalities include diastrophic dysplasia, Kniest dysplasia, and pseudoachondroplasia. If biopsy specimens are obtained, proper technique, storage, transport, and evaluation are essential. Centers prepared to perform sophisticated diagnostic evaluation can be identified by contacting local pathology departments.

Research

Methods have been expanded and refined in recent years to evaluate cartilage specimens. For example, the substances that constitute the growth plate, such as cartilage collagens, can be studied biochemically. Chondrocytes can be investigated in culture to identify mutations and to explore how they interfere with skeletal development and growth.

Considerable progress has been made in genetically mapping bone dysplasias to specific chromosome locations. For example, diastrophic dysplasia has been mapped to the short arm of chromosome 5; pseudoachondrodysplasia and multiple epiphyseal dysplasia, to chromosome 19; cartilage-hair hypoplasia, to chromosome 9; and achondroplasia, to chromosome 4. Such knowledge frequently leads to identification of specific genes, delineation of mutations, and an understanding of the molecular pathogenesis of the condition, which will be needed to design the therapies of the future. With the growth in technology to assess the human genome, a far more detailed knowledge is likely in the next decade.

Osteogenesis imperfecta and spondyloepiphyseal dysplasia are examples of bone dysplasias delineated at the molecular level. They are due to mutations in the genes for type I and type II collagen, respectively, and result from disturbances in the synthesis and assembly of bone and cartilage matrices, within which these molecules function. Recent research has demonstrated that the gene for diastrophic dysplasia is involved in the biosynthesis of sulfated proteoglycans and that the gene for achondroplasia is a single nucleotide substitution on the short arm of chromosome 4.[1,2]

Examples of Chondrodysplasia

Several of the more common dysplasias will be described in order to illustrate the process of diagnosis.

Achondroplasia

Achondroplasia is the most common cause of dwarfism and is diagnosable at any age. The clinical features suggesting a dysplasia include short stature; a long trunk; short, rhizomelic extremities; and dysmorphic facies, including a large

head, frontal bossing, and a depressed nasal bridge. The upper extremities exhibit mild limitation of elbow extension, lax joints, and trident fingers. Bowlegs are common in childhood. Adult height is about 4 feet. Radiographic abnormalities include short and narrow pedicles in the lumbar spine, short iliac bones, horizontal acetabula, anterior hypoplasia of the upper lumbar vertebrae, and relative elongation of the proximal and distal fibulae. Compression of the brainstem and the upper portion of the spinal cord may cause hypotonia, delay in motor development, and apnea in infancy. Orthopaedic treatment of achondroplasia is most often needed for bowlegs in childhood and kyphosis, spinal stenosis, and vertebral disk abnormalities in adults. Achondroplasia is transmitted by autosomal-dominant inheritance, but most patients have new mutations. The differential diagnosis of achondrodysplasia includes hypochondroplasia and pseudoachondroplasia (Fig. 1).

Hypochondroplasia is typically not diagnosed until the middle or late period of childhood and superficially resembles achondroplasia. It is characterized by mild short stature (an adult height of about 4.5 feet), disproportionate short limbs, and mild bowing of the legs. The radiographic findings include mild broadening and shortening of the long bones. The condition is distinguished from achondroplasia by mild radiographic findings, normal facies, and an adult height taller than that seen in achondroplasia. It is transmitted by autosomal-dominant inheritance.

Pseudoachondroplasia is characterized by short stature (adult height ranging from 3.5 to 4.5 feet) and resembles achondroplasia. The extremities are disproportionately short, with limitation of elbow extension and hip abduction. The radiographic appearance is nearly normal at birth but becomes severely abnormal with growth. Generalized ligamentous laxity contributes to deformity and dysfunction of the growing skeleton. The condition is transmitted by autosomal-dominant inheritance. It is clinically most easily distinguished from achondroplasia on the basis of the multiple joint deformities and normal facies.

Dyschondrosteosis

Dyschondrosteosis (Fig. 4) is the most common mesomelic dysplasia. The clinical features suggesting this dysplasia are mild short stature and mesomelic limb shortening, greater in the upper extremities. Radiographs demonstrate short forearm bones, exaggerated radial bowing, volar angulation of the distal radial epiphyses, and instability of the distal radioulnar articulation (Madelung's deformity). Adult height is about 5 feet. The condition is transmitted by autosomal-dominant inheritance.

Multiple Epiphyseal Dysplasia

Multiple epiphyseal dysplasia (Fig. 5) is relatively common. The clinical features that suggest this condition are mild short stature; short, broad hands and thumbs; and normal facies. Varus or valgus knee deformity is common. The radiographic appearance is normal at birth. The proximal femoral and other epiphyses are delayed in appearance and are small. Epiphyseal abnormalities are general and symmetrical and include the spine in adolescence. The condition is transmitted by autosomal-dominant inheritance. Young adults often develop severe osteoarthritis of weight-bearing joints.

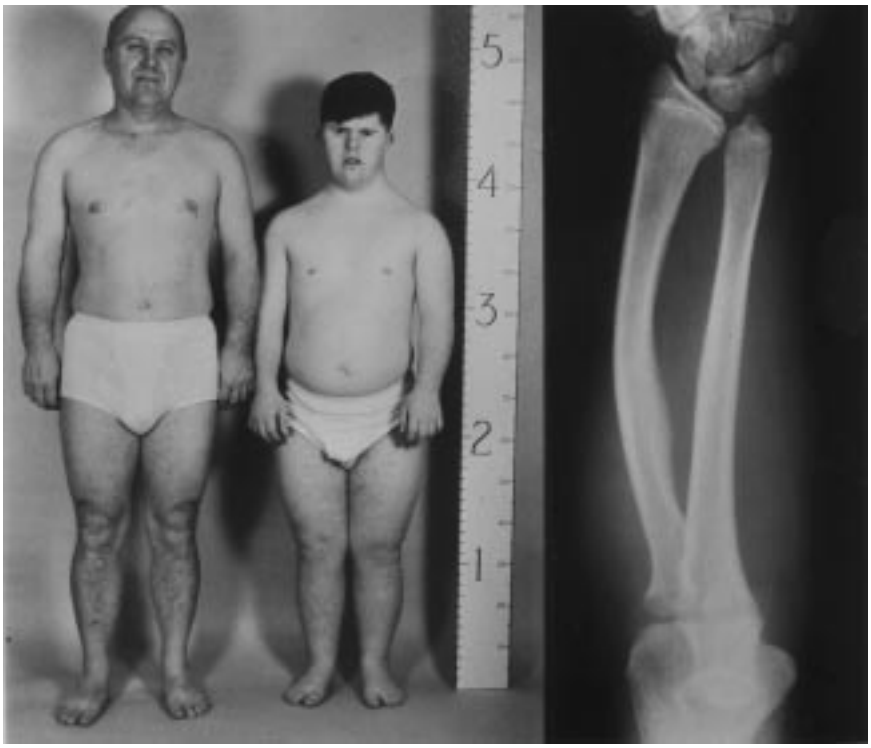

Fig. 4 Dyschondrosteosis is characterized by short forearms, mild short stature, short ulnae, and pronounced radial bowing.

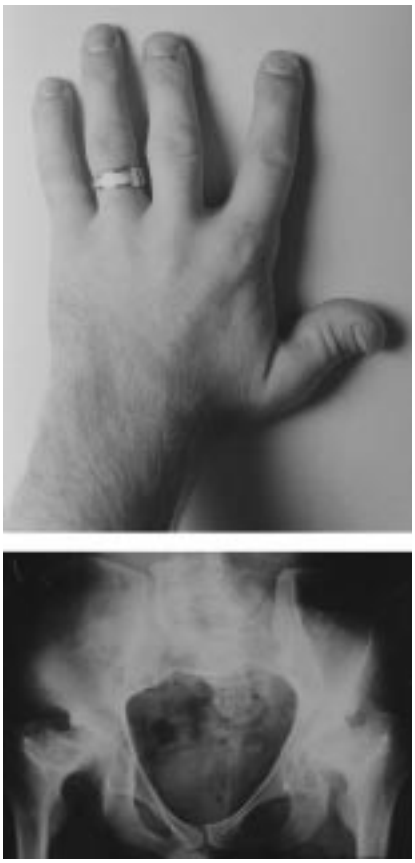

Fig. 5 Multiple epiphyseal dysplasia is characterized by short, broad fingers and thumbs and epiphyseal abnormalities, which are greater in weight-bearing joints.

Trichorhinophalangeal Dysplasia

Trichorhinophalangeal dysplasia (Fig. 6) is the most common dysplasia associated with cone-shaped epiphyses. This dysplasia is suspected on the basis of dysmorphic facies, including a long philtrum, a bulbous nose, and fine, sparse hair. There is often deformity of the proximal interphalangeal joints in the hands. Radiographs demonstrate cone-shaped epiphyses of the phalanges. This condition is transmitted by autosomal-dominant inheritance.

Multiple Exostosis

Multiple exostosis (Fig. 7) is a disorder of disorganized skeletal development. It is the most common skeletal dysplasia, with a frequency of about 1:18,000. There are no clinical features present at birth to cause suspicion of a skeletal dysplasia. Exostoses develop in early childhood. The adult height of those affected is about 2 inches shorter than that of their unaffected siblings. Exostoses are most common adjacent to the fastest-growing physes, which are at the distal femur and proximal tibia. Unequal growth of paired bones in the legs and forearms and growth failure of long bones are common and often cause deformity. Radiographs demonstrate that exostoses occur maximally at the proximal humerus and distal radius and about the knee. The best screening tool is a radiograph of the knee. Exostoses are present in affected patients by age 4. This condition illustrates an evolving skeletal aberration, which cannot be diagnosed at birth but which becomes obvious with skeletal development.

Cartilage-Hair Hypoplasia

Cartilage-hair hypoplasia (Fig. 8) is a rare autosomal-recessive metaphyseal dysplasia. The clinical features that suggest dysplasia include mild short stature; short, broad hands and feet; and fine hair. Radiographs demonstrate widening and irregularity of the physes. The pedigree often reveals consanguinity.

General Approach to Diagnosis

When a skeletal dysplasia is suspected, the evaluation should

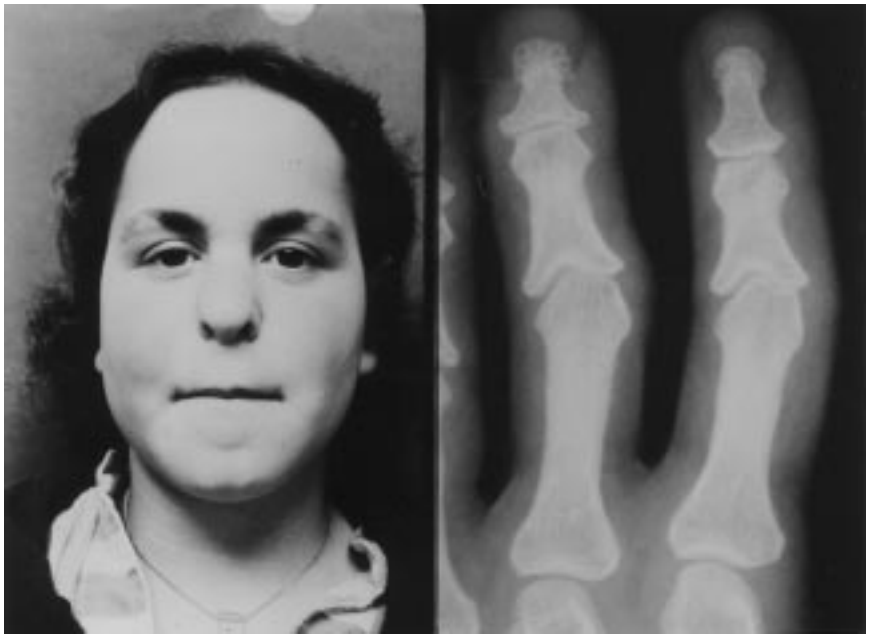

Fig. 6 Trichorhinophalangeal dysplasia is characterized by fine, sparse hair; a bulbous tip of the nose; a long philtrum; and cone-shaped epiphyses of the fingers.

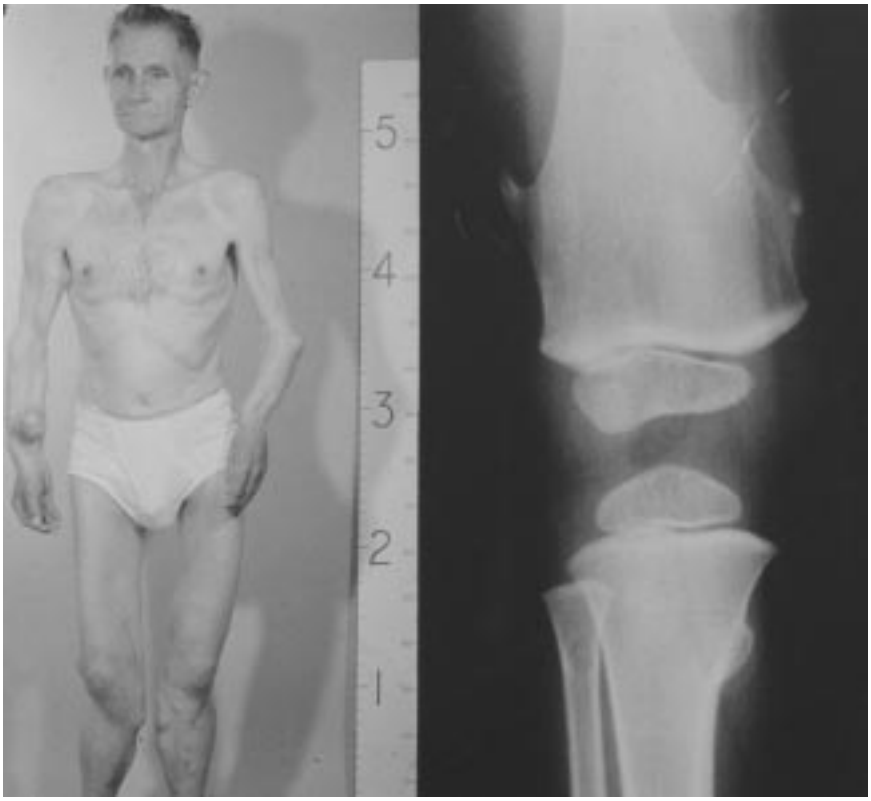

Fig. 7 Multiple exostosis is characterized by mild short stature, exostoses at sites of greatest growth (proximal humerus, distal radius, distal femur, proximal tibia), and disproportionate growth of paired bones, which may create deformity and radial-head dislocation.

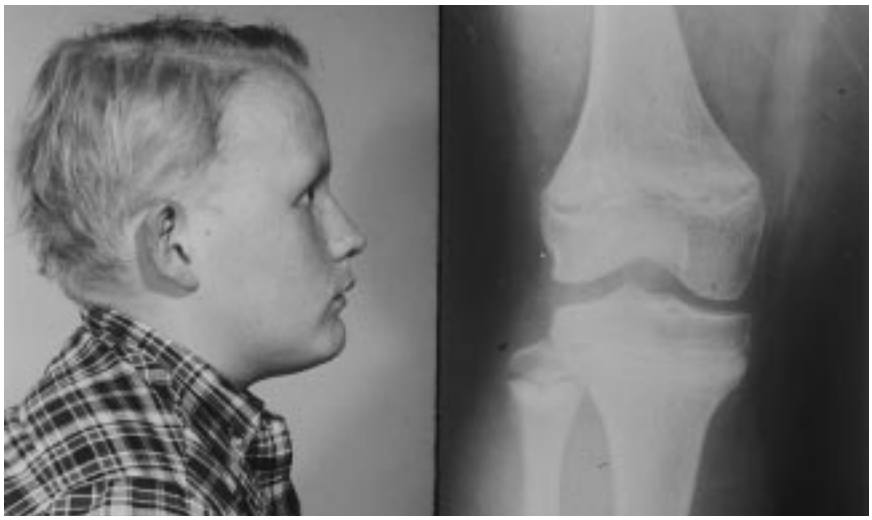

Fig. 8 Cartilage-hair hypoplasia is characterized by fine, sparse hair and moderate widening of the physes.

include ascertainment of birth length, present height percentile, and, when applicable, adult height. Body proportions should be measured, dysmorphism searched for, and deformity evaluated. Screening radiographs and a family pedigree should be obtained. Laboratory screening is occasionally indicated. With these data, it may be possible to diagnose a skeletal dysplasia.

There is no well-developed algorithm for the diagnosis of bone dysplasias. Synthesis of the collected data is most usefully based on key features, such as the adult height, the occurrence of the condition in other family members, the presence of characteristic dysmorphic features, abnormal body proportions, and the part of the bone (epiphysis, metaphysis, or diaphysis) that is radiographically abnormal. Many excellent texts are available to assist in diagnosis.[3-12]

If initial evaluation does not lead to a diagnosis, the patient should be reexamined periodically, with the expectation that there may be evolution of the dysplasia or that new knowledge will allow a diagnosis to be made. Patients with known bone dysplasias are usually followed up at yearly intervals to anticipate problems and provide counsel.

Summary

A skeletal dysplasia is suspected when there is abnormal stature, disproportion, dysmorphism, or deformity. Data useful in diagnosis include birth length, height, proportions, radiographic findings, family pedigree, and, in some instances, laboratory values. Consultation may be valuable when the diagnosis is not apparent.

References

1. Hästbacka J, de la Chapelle A, Mahtani MM, et al: The diastrophic dysplasia gene encodes a novel sulfate transporter: Positional cloning by fine-structure linkage disequilibrium mapping. *Cell* 1994;78:1073-1087.
2. Shiang R, Thompson LM, Zhu YZ, et al: Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. *Cell* 1994;78:335-342.
3. Jones KL: *Smith's Recognizable Patterns of Human Malformation*, 4th ed. Philadelphia: WB Saunders, 1988.
4. McKusick VA: *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*, 10th ed. Baltimore: Johns Hopkins University Press, 1992, vol 1.
5. Maroteaux P: *Bone Diseases of Children*. Philadelphia: JB Lippincott, 1979.
6. Wynne-Davies R, Fairbank TJ: *Fairbank's Atlas of General Affections of the Skeleton*, 2nd ed. Edinburgh: Churchill Livingstone, 1976.
7. Horan F, Beighton P: *Orthopaedic Problems in Inherited Skeletal Disorders*. Berlin: Springer-Verlag, 1982.
8. Spranger JW, Langer LO Jr, Wiedemann HR: *Bone Dysplasias: An Atlas of Constitutional Disorders of Skeletal Development*. Philadelphia: WB Saunders, 1974.
9. Rimoin DL, Lachman RS: Genetic disorders of the osseous skeleton, in Beighton P (ed): *McKusick's Heritable Disorders of Connective Tissue*, 5th ed. St Louis: Mosby-Year Book, 1993, pp 557-689.
10. Goldberg MJ: *The Dysmorphic Child: An Orthopedic Perspective*. New York: Raven Press, 1987.
11. Horton WA, Hecht JT: The chondrodysplasias, in Royce PM, Steinmann B (eds): *Connective Tissue and Its Heritable Disorders: Molecular, Genetic, and Medical Aspects*. New York: Wiley-Liss, 1993, pp 641-675.
12. Wynne-Davies R, Hall CM, Apley AG: *Atlas of Skeletal Dysplasias*. Edinburgh: Churchill Livingstone, 1985.