CHAPTER 7

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The Skeletal Dysplasias

GENERAL PRINCIPLES

Osteochondral dysplasias are rare disorders of growth and development that affect cartilage and bone. Knowledge about these dysplasias is important to orthopaedic surgeons as an aid to understanding skeletal development. In the preface to the classic text, *McKusick's Heritable Disorders of Connective Tissue* (1), the late Victor McKusick stated, "Nature is nowhere more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path…." It may be true that there is a mutation and a disorder representing nearly each step of skeletal development. Although there is substantial overlap between conditions that primarily affect cartilage and those that primarily affect bone because of shared matrix elements, metabolic pathways, hormonal influences, and other processes (2), this chapter focuses on those that affect cartilage (for a summary, see Appendix 1).

A useful tool for diagnosis and additional research is the Online Mendelian Inheritance in Man. This web-based compendium is publicly available and readily accessible on the PubMed Web site of the National Library of Medicine (http://www.ncbi.nlm.nih.gov/omim). It allows a user to search by physical features or diagnosis and provides a compilation of applicable knowledge on each (3).

Terminology. Most skeletal dysplasias result in short stature, defined as height more than 2 standard deviations below the mean for the population at a given age. The term "dwarfing condition" is used to refer to disproportionate short stature. The disproportion is commonly referred to as "short trunk" or "short limb." The short-limb types are further subdivided into categories based on which segment of the limb is short. "Rhizomelic" refers to shortening of the root (proximal) portion of the limb; "mesomelic," to the middle segment; and "acromelic," to the distal segment. Achondroplasia is a classic example of rhizomelic involvement, with the femora and especially the humeri being most affected by shortening. Some of these disorders are named after the appearance of the skeleton (diastrophic means "to grow twisted," camptomelic means "bent limbs," and chondrodysplasia punctata refers to stippled cartilage). Eponyms such as Kneist, Morquio, and McKusick are used to name others.

Pathogenesis. Although their pathogenesis is only slowly being investigated, a number of mechanisms have been discovered to lead to skeletal dysplasia. Some result from an alteration in transcription or in the intracellular or extracellular processing of structural molecules of the skeleton (Fig. 7-1). Others are caused by a defect in a receptor or signal transduction in pathways of skeletal differentiation and proliferation. These abnormalities tend to occur in the pathway of cartilage differentiation, growth, and development.

Abnormalities in the form of a structural macromolecule may occur, as in type-II collagen causing spondyloepiphyseal dysplasia (SED). In some cases, the effect may be magnified—a phenomenon termed a "dominant negative" effect. This phenomenon occurs as the defective gene product binds to normal copies of the product, leading to early destruction of normal and defective copies, as seen in osteogenesis imperfecta type II. Pseudoachondroplasia provides another example, with the abnormal cartilage oligomeric matrix protein (COMP) accumulating in the rough endoplasmic reticulum and causing secondary retention of type-IX collagen and other proteins. By contrast, models in which COMP is completely knocked out and not expressed display no disease.

Another pathway through which mutations may act is the alteration of the transport of structural molecules. One example of this mechanism is the group of conditions that includes diastrophic dysplasia (DD) and achondrogenesis type 1, the result of a defect in sulfate transport. This alteration disturbs proteoglycan assembly, leading to diffuse changes in the articular surface cartilage, growth plate, and other areas. An example of receptors gone awry is the family of disorders that includes achondroplasia, hypochondroplasia, and thanatophoric dysplasia. These disorders occur as a result of varying defects in fibroblast growth factor receptor protein. These mutations result in a constitutively active receptor

(gain of function). Because this receptor down-regulates endochondral growth, mutations result in decreased endochondral growth. Another example is Jansson metaphyseal dysplasia, which is the result of a constitutively active mutation in parathyroid hormone receptor protein. This protein inhibits the expression of the signaling factor Indian hedgehog, which is needed to stimulate terminal differentiation to hypertrophic chondrocytes and produce normal metaphyseal growth. Disorders of transcription may also cause skeletal dysplasia, as seen in cleidocranial dysplasia, a defect in core-binding factor 1. Because this transcription factor stimulates osteoblast differentiation, a defect in this factor leads to a cartilage model that is well formed but not normally ossified.

Classification. The classification of skeletal dysplasias has traditionally been structured according to the pattern of bone involvement, as in the International Classification of Osteochondrodysplasias (4) (Table 7-1). Another approach, however, is to group them according to the specific causative gene defect for cases in which the defect is known (Table 7-2). A schematic representation of the effects of the known mutations on cartilage development is shown in Figure 7-1. It is also useful for the orthopaedic surgeon to classify the dysplasias into those that are free from spinal deformity [for instance, hypochondroplasia and multiple epiphyseal dysplasia (MED) rarely have significant spinal abnormalities] versus those for which spinal deformity is a frequent problem (such as SED, DD, and metatropic dysplasia). Which disorders are free from epiphyseal involvement and therefore from risk of subsequent degenerative joint disease (DJD)? Achondroplasia and hypochondroplasia, cleidocranial dysplasia, and diaphyseal aclasia rarely present these problems in adulthood, but SED, MED, DD, and others commonly do.

TABLE 7-1 International Nosology and Classification of Genetic Skeletal Disorders 2006 (Partial List)

FGFR3 group
Type-II collagen group
Sulfation disorder group
Perlecan group
Filman group
MED/pseudoachondroplasia group
Metaphyseal dysplasias
Spondylometaphyseal dysplasias
Spondyloepimetaphyseal dysplasias
Acromesomelic dysplasias
Mesomelic and rhizomelic dysplasias
Bent bone dysplasias
Slender bone dysplasias
Dysplasias with multiple joint dislocations
Chondrodysplasia punctata group
Increased bone density group
Decreased bone density group
Lysosomal storage diseases
Cleidocranial dysplasia group

TABLE 7-2 Classification of Skeletal Dysplasias Based on Pathogenesis (Partial List)

Defects in extracellular structural proteins
- *COL1* (OI)
- *COL2* (achondrogenesis, hypochondrogenesis, SEDC, SEDC, Stickler, Kneist)
- *COL9* (MED)
- *COL10* (Schmidt)
- *COL11* (Stickler variant)
- COMP (pseudoachondroplasia, MED)
- *MATN3* (MED)

Defects in metabolic pathways
- AP (hypophosphatasia)
- *DTDST* (achondrogenesis B, DD, rMED)

Defects in processing and degradation of macromolecules
- Sedlin (SED-X-linked type)
- Lysosomal enzymes (mucopolysaccharidoses, mucolipidoses)
- *EXT*1, *EXT*2 (*MHE*1,2)

Defects in hormones, growth factors, receptors, and signal transduction
- *FCGR*s 1–3 (craniosynostoses, achondroplasia, thanatophoric)
- *PTH/PTHrP* (Jansen metaphyseal dysplasia)
- *GNAS*1 (McCune Albright, pseudohypoparathyroidism)

Defects in nuclear proteins and transcription factors
- *SOX1* (camptomelic dysplasia)
- *CBFA*1 (cleidocranial dysplasia)
- *SHOX* (Leri-Weill)

Defects in RNA processing and metabolism
- *RMRP* (cartilage-hair hypoplasia)

Defects in cytoskeletal proteins
- Filamins (Larsen syndrome, Melnick-Needles)

Prenatal Diagnosis With the increasing availability of prenatal screening, many individuals with skeletal dysplasia are being diagnosed before birth. When ultrasound shows a fetus with shortening of the skeleton, femur length is the best biometric parameter to distinguish among the five most common possible conditions. In one study, fetuses with femur length <40% of the mean for gestational age most commonly had achondrogenesis, those with femur length between 40% and 60% most commonly had thanatophoric dysplasia or osteogenesis imperfecta type II, and those with femur length >80% most commonly had achondroplasia or osteogenesis imperfecta type III (5). Additional testing may be performed, if indicated, by chorionic villous sampling and mutation analysis.

Evaluation. In evaluating for skeletal dysplasia in a patient with short stature or abnormal bone development, there are several aspects of the medical history that should be investigated as an aid to diagnosis and coordination of care. Birth length

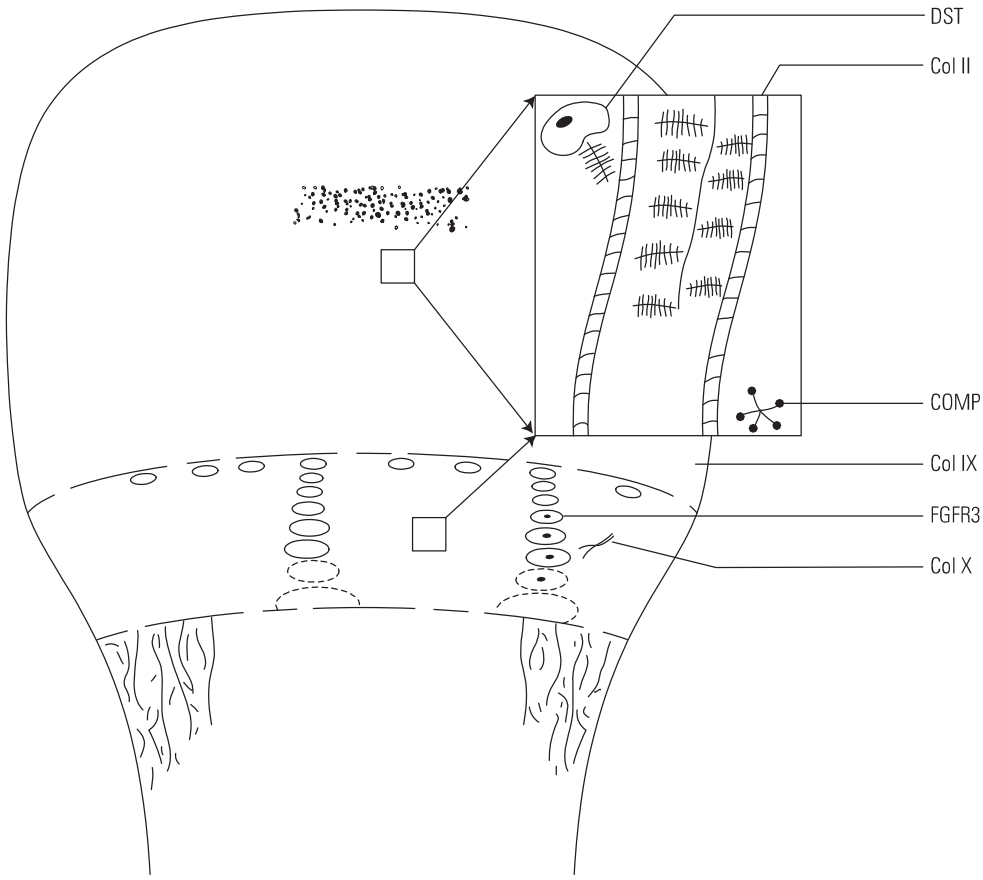


FIGURE 7-1. Schematic illustration of the sites and effects of the known cartilage defects in the skeletal dysplasias. Section of cartilage matrix of physis and epiphysis is simplified and enlarged; genetic abnormalities often affect both regions. *DST,* diastrophic sulfate transporter, deficiency of which leads to undersulfation of proteoglycans in epiphysis and physis of DD and achondrogenesis types 1B and 2; *Col II,* type-II collagen, which is defective in Kneist dysplasia and SED; *COMP,* cartilage oligomeric matrix protein, abnormal pseudoachondroplasia, and some forms of MED; *Col IX,* type-IX collagen, which is closely linked to type-II collagen and is abnormal in some forms of MED; *FGFR3,* fibroblast growth factor receptor 3, which inhibits chondrocyte proliferation in achondroplasia, hypochondroplasia, and thanatophoric dysplasia; *Col X,* type-X collagen, which is synthesized only by the hypertrophic cells of the growth plate and is abnormal in Schmidt-type metaphyseal chondrodysplasia.

is usually shorter than normal in patients with achondroplasia, SED, and most dysplasias but not in those with pseudoachondroplasia or storage disorders. Head circumference is usually larger than normal in patients with achondroplasia. Respiratory difficulty in infancy may occur as a result of restrictive problems in the syndromes with a small thorax, neurologic problems such as foramen magnum stenosis in achondroplasia, or upper airway obstruction in various conditions. A history of heart disease suggests the possibilities of chondroectodermal dysplasia, which may be associated with congenital heart malformations, or storage disorders, such as Hurler or Morquio syndromes, in which cardiac dysfunction may be acquired. A history of immune deficiency or malabsorption is common in cartilage-hair hypoplasia. Retinal detachment may occur with Kneist syndrome or SED. The clinician should elicit information about a family history of short stature or dysmorphism any previous skeletal surgery the patient may have had.

The presence of unusual facial characteristics, a cleft palate, or extremity malformations should be noted. Height percentile for age should be determined using standard charts. Most skeletal dysplasias result in adult height of <60 in. Measurement of the upper:lower segment ratio may be helpful in distinguishing disproportion early. This value can be obtained by measuring the distance from the top of the pubic symphysis to the sole of the plantigrade foot and subtracting it from the overall length. The normal ratio is 1.6 at birth (given that extremities develop later than the trunk) and diminishes to 0.93 in adults and teens. If shortening of the extremities is noted, it is helpful to classify it as rhizomelic (shortest in the humerus and femur), as in achondroplasia, mesomelia (shortest in the forearms and the legs), or acromelia (shortest distally). The extremities should be examined for ligamentous laxity or contracture (6, 7).

A thorough neurologic examination is needed because of the frequent incidence of spinal compromise at the upper cervical level in SED, DD, Larsen syndrome, and metatropic dysplasia, or at any level in achondroplasia.

A skeletal survey should be ordered, including lateral radiographs of skull and neck and anteroposterior views of the

entire spine, pelvis, arms, hands, and legs. Much of this information can be gleaned from reviewing previous radiographs of the child's chest and abdomen that may have been obtained. Sometimes, pathognomonic features will be revealed, such as the caudal narrowing of the interpediculate distances in achondroplasia, double-layered patella in MED, and the iliac horns in nail–patella syndrome. Flexion–extension radiographs of the cervical spine should be ordered if instability is suspected to be causing delay in reaching milestones, loss of strength, or loss of endurance. In many syndromes in which cervical instability is common, such as SED, such radiographs should be ordered as a matter of course. Magnetic resonance imaging (MRI) in flexion and extension may be helpful in some cases to determine if the instability is causing critical risk. However, the limitation of this test is that it often must be done under anesthesia or sedation and the degree of cervical movement is less. If conventional radiographs show substantial motion and a static MRI shows signal changes at the same location, then flexion and extension images are usually not needed.

Laboratory tests may include calcium, phosphate, alkaline phosphatase, and protein to rule out metabolic disorders such as hypophosphatemia or hypophosphatasia. If a progressive disorder is found, the patient's urine should be screened for storage products (under the guidance of a geneticist). To rule out hypothyroidism, serum thyroxine should be measured if the fontanels in an infant are bulging and bone development is delayed. After the differential diagnosis is clinically focused, DNA testing for mutation analysis is increasingly being done in the clinical setting for patients with skeletal dysplasias. A geneticist should be consulted to help establish a diagnosis and a prognosis and to address medical problems. The geneticist sometimes functions as a primary physician for a patient with a genetic disorder because a geneticist has the best overview of the medical issues facing the patient.

Treatment. An orthopaedic surgeon caring for a person with skeletal dysplasia should focus on three aspects: prevention of future limitations, treatment of current deformity, and treatment of pain. The patient's parents should be counseled about the mode of inheritance and the risk of recurrence so that they can make future family plans appropriately. In most cases, it is advisable to see such patients on a routine basis for surveillance so that skeletal problems can be detected at the optimum time for treatment. Weight management is a continuing challenge for many and requires attention. One study of the quality of life in patients with achondroplasia has shown that, although many individuals are able to function at a high level, as a group there are significantly lower scores in all domains (8). Physical difficulties in an environment that is not scaled for such individuals were some of the most commonly cited factors, indicating that treatments to increase stature may have functional benefit.

If surgery becomes necessary for a person with skeletal dysplasia, special considerations apply. Anesthetic management is more difficult if the dysplasia involves oropharyngeal malformations, limited neck mobility, cervical instability, or stenosis (9). Cervical instability is so common in the skeletal dysplasias that the surgeon should make a point of ruling it out by knowledge of the patient or by knowledge of the condition and whether cervical instability is associated with it, or by obtaining special radiographs in flexion and extension (10–12). Restrictive airway problems accompany some dysplasias, and laryngotracheomalacia affects many young diastrophic children. Skeletal distortion may make deep venous access challenging and, in some cases, a general surgeon should be consulted in advance. Intraoperative positioning must accommodate small stature and any contractures that are present. Limb lengthening is an option for many patients who do not have a high risk of DJD. In the tibia, for instance, concomitant stabilization of the tibiofibular joints during lengthening and Achilles lengthening can decrease complications (13). However, the achievement of substantial lengthening in multiple extremities requires a major commitment of a patient's time. Total joint arthroplasty is more difficult in individuals with skeletal dysplasia because of patients' contractures and abnormal skeletal shape and size and because extensive soft-tissue releases may be necessary. However, pain and function scores have been shown to improve substantially after arthroplasty (13).

Postoperative planning must be done in advance because most of these patients have a decreased ability to accommodate postoperative immobilization, stiffness, or functional restrictions. In some situations, postoperative placement in a rehabilitative setting may be most helpful to the patient and family. The Little People of America organization (www.lpaonline.org) may be an important resource for information and support.

ACHONDROPLASIA

Overview. Achondroplasia, an abnormality of endochondral ossification, is the most common form of skeletal dysplasia and occurs in approximately 1 of 25,000 live births (14, 15).

Achondroplasia is caused by a gain of function in the mutation of a gene that encodes for fibroblast growth factor receptor 3 (*FGFR3*) (16–19). Achondroplasia arises from a point mutation on the short arm of chromosome 4 at nucleotide 1138 of the *FGFR3* gene. The mutation is located on the distal short arm of chromosome 4. The result of this mutation is endochondral-ossification-engendered underdevelopment and shortening of the long bones that does not involve intramembranous or periosteal components.

Achondroplasia is inherited as a fully penetrant autosomal dominant trait, but more than 80% of such cases are sporadic, meaning both parents are unaffected (20). If one of the parents is affected, there is a 50/50 chance that the child will develop achondroplasia (14, 15, 20). However, because there is also an increased incidence when the parents are more than 33 years old at the time of conception, a *de novo* mutation is implied (21).

Etiology. The cause of achondroplasia is a single-point mutation in the gene that encodes for *FGFR3. FGFR3* mutations have also been found in individuals with thanatophoric dysplasia and hypochondroplasia. Almost all people with achondroplasia have the same recurrent *G-380Rlocus* mutation, which causes a change in a single amino acid. This mutation substitutes an arginine for a glycine residue in the transmembrane domain of the tyrosine-coupled transmembrane receptor in the physis (1, 22). *FGFR3* is expressed in the cartilaginous precursors of bone, where it is believed to decrease chondrocyte proliferation in the proliferative zone of the physis and to regulate growth by limiting endochondral ossification (23). However, in persons with achondroplasia, articular cartilage formation, articular cartilage development, and the intramembranous and periosteal ossification processes are unaffected (24).

It is not known why the proximal portions of the long bones (rhizomelic) are affected more than the distal aspects.

Clinical Features. In the achondroplastic population, the extremities are most affected, that is, they are shorter than those in an unaffected individual. The most commonly affected bones are the humerus and femur, which present a rhizomelic appearance (25). The trunk length is within normal limits or at the lower end of normal limits. This combination typically results in the fingertips reaching only to the tops of the greater trochanter (26), a condition that can lead to possible difficulties in personal hygiene and care and that can worsen as decreasing amount of flexibility occurs in the normal aging process (Fig. 7-2).

The hands are described as trident in nature, that is, the individual is unable to oppose the third and the fourth ray, leaving a space that cannot be closed. There are flexion contractures at the elbow and decreased ability to supinate, most often secondary to the fact that the radial head can be subluxed, as evidenced on radiographs. None of the above features are clinically important, but a nonknowledgeable physician might misdiagnose such a presentation as a "nursemaid's elbow" and incorrectly attempt a reduction.

The facial appearance of patients with achondroplasia is characterized by an enlarged head, mandibular protrusion, frontal bossing (flattened or depressed nasal bridge), and midface hypoplasia. The bones in the midface are more affected than the other facial bones because of their endochondral origin (16).

Although the lower extremities are typically in varus secondary to knee and ankle morphology, the lower extremities can be straight or occasionally in valgus, and internal tibial torsion may also be seen. Typically, the knee and ankle joints have excessive laxity, although usually such patients do not develop premature arthritis. The femoral necks are often shortened, giving an appearance of coxa breva.

In terms of the spine, kyphosis at the thoracolumbar junction is very common and is typically seen in the first 1 to 2 years of life (Fig. 7-3). In most children, this condition will correct spontaneously within a few months of ambulation, although ambulation is often delayed in patients with achondroplasia (27). As kyphosis improves, lumbosacral lordosis may seem to progress.

FIGURE 7-2. Photograph of a 5-year-old male with achondroplasia. Note the typical bowing and fingertips reaching to the top of the hips.

One study found that life expectancy is not substantially diminished in individuals with achondroplasia (28), but a more recent report has indicated a higher mortality rate in 30- to 50-year-old people with achondroplasia compared with age-matched controls (29). This reported increased mortality is typically secondary to heart disease. One indicator for heart disease is abnormal blood pressure, but it is possible that standard blood pressure cuffs may underestimate the pressures in the achondroplastic population, leading to the nonidentification and nontreatment of a large number of patients with high blood pressure. New cuffs have been developed and their use for this population is being reviewed.

Growth and Development. In most children with achondroplasia, growth and development fall behind those of unaffected children.

Widely available growth charts (25) indicate that the infant with achondroplasia is shorter than an unaffected infant, a

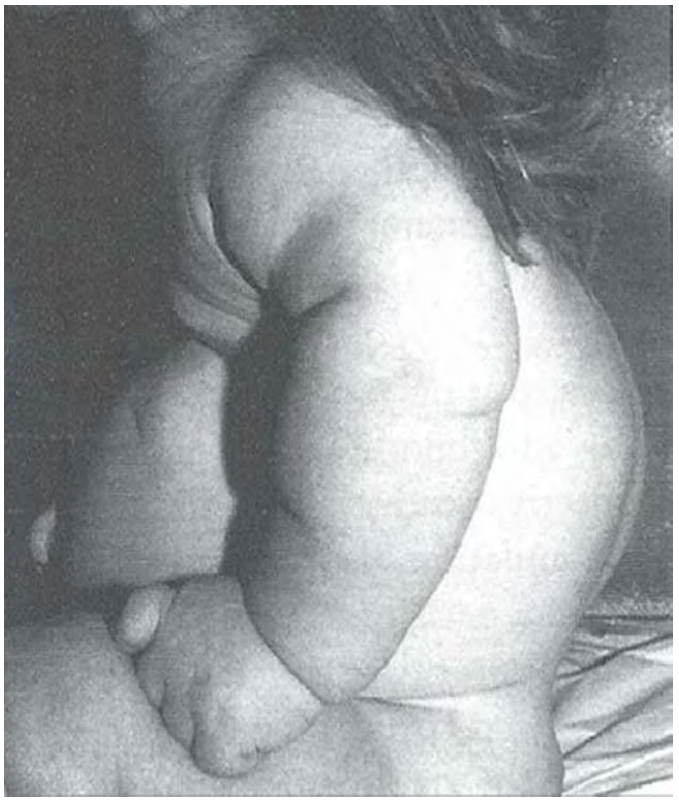


FIGURE 7-3. Photograph of an 18-month-old female with achondroplasia sitting with typical postural kyphosis.

height deficit that increases markedly during the first few years of life and becomes even more marked during the growth spurt at puberty (30). The average height for an adult with achondroplasia is 132 cm for men and 125 cm for women (20).

Children with achondroplasia also have delayed motor milestones (head control, 4 months; sitting up independently, 10 months; ambulation, 18 to 20 months) (31, 32), and three-quarters of them have ventriculomegaly (33).

Historically, hydrocephalus was thought to be the cause, leading also to macrocephaly, but only a very small subset has been shown to have clinically significant hydrocephalus (34); standardized head circumference charts can help track such children (35). Ventricular peroneal shunting is indicated only for rapid progression of head circumference, or for signs and symptoms of increased intracranial pressure.

Mental development is typically normal in children with achondroplasia, but physical manifestations are often delayed, especially in the first 2 to 3 years of life (36). Typically, motor development normalizes by 3 years of age. There are standardized developmental charts that are available for monitoring such children.

Foramen magnum stenosis is one of the earliest serious health consequences faced by some children with achondroplasia. Its symptoms, which most commonly occur in the first 2 years of life but which may present later (37), include chronic brain stem compression, sleep apnea, lower cranial nerve dysfunction, difficulty in swallowing, hyperreflexia, hypotonia, weakness, paresis or clonus, and severe developmental delay, and are quantified in sleep studies (34, 38–42). The most common presenting symptom of foramen magnum stenosis is respiratory difficulty with excessive snoring or apnea (43). Apnea can be central in nature (because of brainstem compression) or just obstructive because of the individual's small midface. The American Academy of Pediatrics recommends screening for foramen magnum stenosis with polysonography and computed tomography (CT) or MRI in all infants with achondroplasia. Because CT and MRI in the first year of life require sedation, the child who is developing well, has no abnormal reflexes, and is alert, oriented, and meeting all milestones can typically just be followed clinically. If head circumference changes or if a patient is not reaching milestones, a sleep study should be ordered. If the sleep study is abnormal, then a CT or an MRI scan should be obtained. We prefer MRI because, in our opinion, it produces a better image of the brain stem and the upper cervical spinal cord.

Some studies have shown a high mortality rate (2% to 5%) in infants with achondroplasia and have indicated foramen magnum stenosis as the responsible factor (33).

Radiographic Characteristics. There are several features typically seen on the radiographs of individuals with achondroplasia, but caution should be exercised in interpreting the absence of such findings: not all affected individuals exhibit such radiographic characteristics.

The key feature is the typical narrowing intrapedicular distance from L1 to L5 seen on the anteroposterior radiographs of affected individuals (44, 45); in the unaffected population, the intrapedicular distance from L1 to L5 increases. The presence of such narrowing is an absolute indicator of achondroplasia, but the lack of such narrowing does not rule out the presence of achondroplasia. In addition, pedicles in those with achondroplasia are approximately 30% to 40% thicker than those in unaffected individuals (46). In this patient population, the vertebral bodies have a scalloped appearance (20), lumbar lordosis increases to the sacrum segment and may even become horizontal, and severe scoliosis is rare but can be seen; however, the incidence of cervical instability is not higher than that in the unaffected population (20, 46).

Other radiographic abnormalities include underdeveloped facial bones, skull base, and foramen magnum; square iliac rings; rhizomelic shortening; and flared metaphysis of the long bones. Affected individuals also have a pronounced, inverted "v" shape of the distal femoral physis with normal distal femoral epiphysis, and the metacarpals and metatarsals are almost all equal in length. The iliac wings have a squared appearance. The metaphysis of all long bones is flared in appearance. Despite being short, the diaphyses of all long bones are thick. The sites of major muscle insertions, such as the tibial tubercle, greater trochanter, and insertion of the deltoid, are more prominent than usual. The epiphysis throughout the skeleton is normal in appearance and development; consequently, degenerative joint arthritis or changes are rarely seen.

General Medical Treatment. Although children with achondroplasia are typically healthier than those with other dysplasias, infants and young children with achondroplasia should be closely monitored and evaluated, especially during the first few years of life, for signs and symptoms of foramen magnum stenosis (see earlier). If the diagnosis is made clinically, an MRI should be ordered to show the stenosis. At this point, neurosurgery can enlarge the foramen magnum. Sometimes, surgeons may need to perform a durotomy or an expansion of the dura and a C1 laminectomy. Many of these children also have dilatation of the veins of their cranium secondary to venous distension, which can also be relieved by such surgery. As indicated earlier, children with achondroplasia have delayed motor milestones; for example, most unaffected children walk by 12 months, whereas most of those with achondroplasia do not walk until 18 months. Postsurgery, patients typically are able to start achieving milestones much more quickly and progress rapidly (38, 40). In addition, children with achondroplasia have a higher risk of respiratory complications than do unaffected children, not only because of midface hypoplasia and upper airway obstruction, but also because of a decreased respiratory drive that can be secondary to foramen magnum stenosis. Early brain stem decompression can decrease the risk (37).

Otolaryngeal problems are also prevalent: 90% of the patients with achondroplasia can experience otitis media before they are 2 years old (47), and many require ear tube placements. Adenoid and tonsil hypertrophy in the presence of midface hypoplasia can cause obstructive sleep apnea. The otitis media and adenotonsil hypertrophy may result in conductive hearing loss that can impair speech development and delay.

Achieving and maintaining an ideal body weight is also difficult and a lifelong struggle. Currently, because there are no standardized charts for size and weight, observing skin-fold thickness and noting general appearance may be the best clinical option (48, 49).

Children with achondroplasia are typically not deficient in growth hormone levels, but there is a substantial amount of research with regard to the administration of growth hormone to supplement height (18, 50, 51). Typically, in the first year of receiving growth hormone treatment, there is an increase in the growth height velocity, but it diminishes over the next 2 to 3 years, with a net result of no real increase. There has been speculation that too much growth hormone can hasten the development of spinal stenosis, which is one of the worst complications of achondroplasia (18, 50, 51).

There are several other otolaryngologic problems that are usually secondary to the underdevelopment of midface skeletal structures. Maxillary hypoplasia can lead to dental overcrowding and malocclusion (52). Many children with this condition require orthodontic attention. In such children, Eustachian tubes often do not function properly because the children are smaller than the unaffected population and more horizontally than vertically positioned, decreasing the ability to drain middle ear fluid (53).

Orthopaedic problems include angular deformities of the lower extremities, genu varum at the knees, thoracolumbar kyphosis, and spinal stenosis (which can occur at any level of the spinal canal). Malalignment of the lower extremities is typically secondary to genu varum or ankle varus (24, 54). A very small percentage of patients have genu valgum, which rarely becomes severe enough to require treatment, but genu varum may progress to cause substantial pain and difficulty in ambulation (24, 55). Some clinicians have postulated that the longer fibula is the cause of this pain, but others have shown that the length of the fibula has no direct relationship on the amount of bowing on the knee (56–58) (Fig. 7-4). Leg malalignment has been shown to be the result of ankle, distal femur, or proximal tibia deformity, or from a combination thereof. Incomplete ossification epiphysis often makes it quite challenging to elicit the source of this malalignment. Arthrograms are typically used at our institution to help identify the exact location of the deformity and are especially helpful in patients <8 years old (12). Although bracing has been used elsewhere to help control ligamentous laxity and to try to correct bowing, we have found that the short and often pendulous nature of the legs of patients with achondroplasia makes it difficult to provide a brace with proper fit and enough of a mechanical advantage to correct the malalignment. During the past 10 years of our practice, no brace has been used to control malalignment, and surgical decisions are not made until the child is at least 3 years old. The indication for surgery is persistent pain that is secondary to malalignment (not to spinal stenosis) deformity severe enough to cause a fibular thrust, resulting in a gap between the proximal tibia and the femur on ambulation (40, 57, 59). Again, in our practice, if the decision has been made for surgical intervention, an arthrogram is obtained to evaluate the optimal location of the osteotomy. Such arthrography also often identifies internal tibial torsion, which can then be corrected concurrently. Although fibular shortening has been advocated in the past (55), we and others (60, 61) do not think it is ever indicated. Treatment indications are difficult to define clearly because there are no natural history studies showing which degree of deformity causes early degeneration.

Short Stature and Limb Lengthening. Infants with achondroplasia are shorter than other individuals and the deficit progresses until skeletal maturity.

Everyday difficulties as the result of short stature include using public restrooms, face washing in public restrooms, hair combing, engaging in hobbies involving physical activity, playing sports with average-statured individuals, conducting routine business transactions (often at countertop level), and driving a car. Nevertheless, the decision to augment stature is difficult and controversial because the procedure is time consuming, complicated (40, 62), and fraught with complications (38, 40).

First, surgical lengthening can achieve quite a bit of height if done safely and correctly (13, 63, 64), but because it is a time-consuming process, it removes these children from their normal activities of school and socialization. The psychologic impact can be tremendous, especially if the lengthening goals

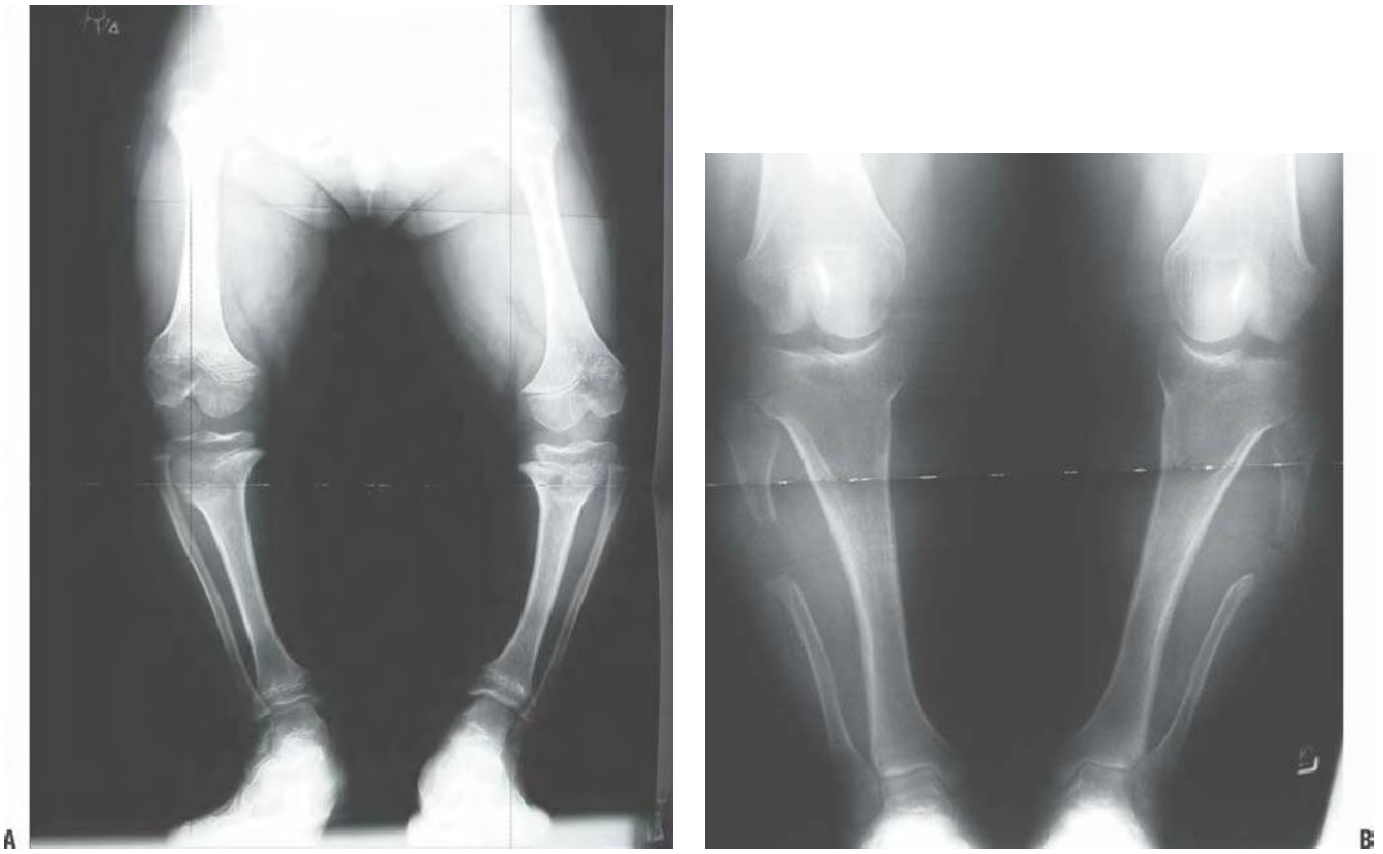


FIGURE 7-4. Prefibulectomy **(A)** and postfibulectomy **(B)** (without change of alignment) radiographs of a 14-year-old male with achondroplasia and tibia vara.

are not achieved. At some centers, lengthening is performed at two separate time intervals, the first typically at the age of 7 years old and the second at preadolescence. The overall time frame for surgery and postoperative therapy may be up to 3 years. Some centers prefer to delay lengthening until early adolescence to increase the patient's participation for the rehabilitation process and also the decision making as to whether or not the lengthening should be done. We know of only one child with achondroplasia who has had limb lengthening and whose parents were also affected.

Second, surgical limb lengthening is a very complicated endeavor (40, 62), and one that is fraught with complications (38, 40). In one study by Aldegheri and Dall'Oca (65), 43% of the patients who underwent limb lengthening had complications, including fracture, failure of premature consolidation, malunion, malalignment, joint stiffness, and infection. One report in the literature indicates increased symptoms of lumbar spinal stenosis (66). The effect of limb lengthening on spinal stenosis needs additional investigation. Humeral lengthening, often is combined with lower extremity limb lengthening, may be the most functionally appreciated because it makes it is easier to perform personal care, put on shoes and socks, and perform extended reaching. The procedure also has lower risks than lower limb lengthening.

Despite the fact that limb lengthening has been a procedure in frequent use for several decades, to our knowledge, the functional benefits after elective limb lengthening have never been studied.

Spinal Aspects Thoracolumbar kyphosis develops in most infants with achondroplasia. A newborn with achondroplasia typically has a thoracolumbar kyphosis centered at approximately T12–L1. When sitting begins, the infant slumps forward because of trunk hypotonia, in combination with a relatively large head, flat chest, and protuberant abdomen. The apex of the vertebral deformity becomes wedge-shaped anteriorly, although it usually is a reversible phenomenon. This condition should not be confused with a diagnosis of congenital kyphosis. Most of these patients improve by the 2nd or the 3rd year of life, after walking begins and muscle strength increases (15, 27, 67, 68). However, persistent kyphosis can increase the risk of symptomatic stenosis, putting pressure on the conus (Fig. 7-5). To prevent persistent kyphosis, Pauli et al. (27) recommended early parental counseling (before the infant is 1 year old) for prohibition of unsupported sitting or sitting up at more than a 45-degree angle and for the use of the following measures: firm, back-seating devices; curling the infant into a "C" position; hand counterpressure when holding the infant; and bracing as needed. In the study by Pauli et al. (27), bracing is initiated for patients who develop kyphosis that does not correct to <30 degrees on prone lateral radiographs. Those authors initially used bracing but found it cumbersome

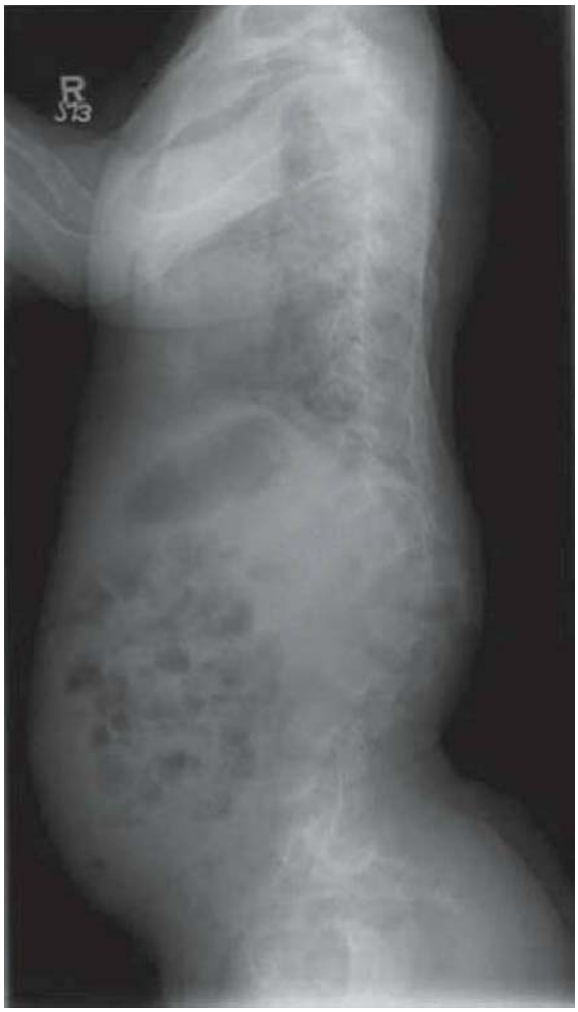


FIGURE 7-5. Radiograph of a 4-year-old patient with achondroplasia and thoracolumbar wedging and kyphosis.

and not very helpful. In addition, the braced patient may be at an increased risk for falls because of the brace's large size and the patient's small body, poor trunk control, and developmental delay. Bracing may also have a detrimental effect on pulmonary function in children with small thoracic cages. In our practice, we have found that bracing has delayed the onset of walking. If wedging of the vertebrae persists beyond the ages of 4 or 5 years, and surgical intervention is not sought, we recommend a trial of using hyperextension casts to see if it will help with the wedging. Although some surgeons have used this technique with some benefit (69), we have seen several instances of such use that have resulted in numerous complications, including skin breakdowns, the inability to tolerate the casts, decreased ability to ambulate, and others. Currently, the indication for safe surgical intervention in our practice is kyphosis ≥50 degrees at 5 years of age with no sign of improvement (70). The key is twofold: (a) no hooks, wires, or any other hardware in the canal and (b) no overcorrection. Correction should limited to what is obtainable preoperatively with the awake child hyperextended laterally over a bolster. The threshold for performing an anterior arthrodesis has decreased with increased rigidity instrumentation by the placement of pedicle screws at every level (70–76).

For the child with achondroplasia, thoracolumbar kyphosis, and concurrent spinal stenosis symptoms, MRI will be obtained; if it shows anterior cord impingement, a corpectomy via an anterior approach will be performed. In this situation, we would not perform a vertebral body resection posteriorly because we think the achondroplastic spinal cord is not mobile enough to tolerate such a procedure. Currently, any child >3 years old who can accommodate pedicle screws, including cervical spine screws, is not placed in a cast or brace postoperatively. However, for a child <3 years old with pedicle screws, a bracing protocol is instituted for 3 months.

Lumbar stenosis typically can present during the second or third decade of life of an individual with achondroplasia, but it can be seen as early as 18 months (Fig. 7-6). Patients typically present with complaints of lower back pain, leg pain, progressive weakness of the extremities, numbness, and tingling, symptoms that often are decreased or alleviated completely by squatting or bending over—maneuvers that reduce the lumbar lordosis, increase the size of the canal, and relieve the pressure. Surgical indications include myelopathy, progressive signs and symptoms, inability to ambulate more than one or two city

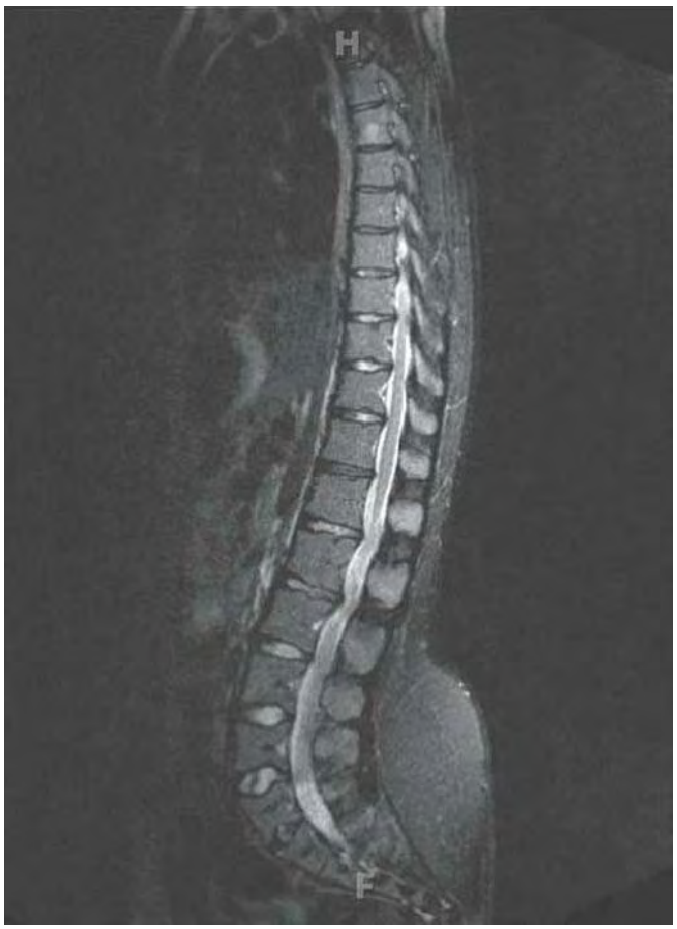


FIGURE 7-6. T2-weighted MRI of a 12-year-old patient with achondroplasia and lumbar stenosis.

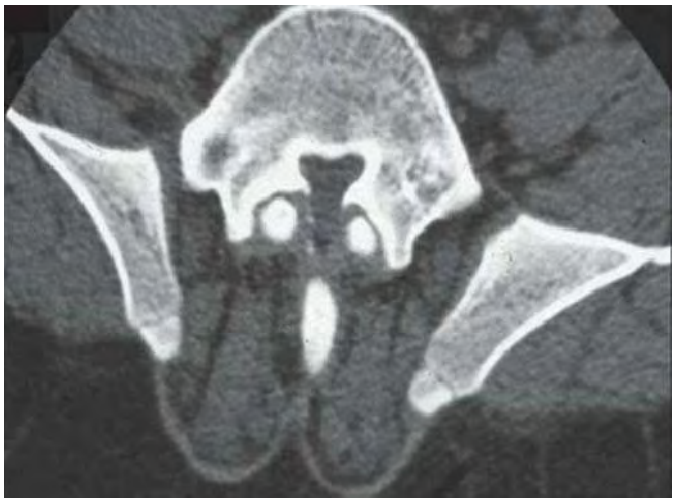


FIGURE 7-7. CT myelogram in a patient with achondroplasia and severe lumbar/sacral stenosis.

blocks without having to stop or squat to relieve the pressure. Preoperative workup includes MRI and possibly a CT scan (Fig. 7-7). By correlating the physical examination and the MRI study, the clinician can identify the approximate level of the most severe stenosis. Usually, treatment is a wide decompression that extends at least two levels above the point of the most severe stenosis and down to the sacrum. In skeletally immature patients, a posterior spinal fusion with pedicle screw instrumentation needs to be done concurrently to prevent progressive kyphosis. If the patient is skeletally mature and has no underlying kyphosis, posterior decompression can be done alone, without a concurrent fusion (40, 46, 71–74, 77).

HYPOCHONDROPLASIA

Etiology and Pathogenesis. Hypochondroplasia is an autosomal dominant disorder, and the chance of passing it on to offspring is approximately 50% (1). Although hypochondroplasia and achondroplasia have similar names and are similar phenotypically (individuals with mild achondroplasia can appear similar to individuals with severe hypochondroplasia), they are two distinct disorders. The mutation that causes hypochondroplasia is located on the short arm of chromosome 4, in gene *FGFR3,* as it is in achondroplasia and thanatophoric dysplasia. However, the nucleotide change is in a different region, the tyrosine kinase domain. In hypochondroplasia, the mutation results in increased activation of factors that slow cell growth (16, 78–81).

Clinical Features. Hypochondroplasia can usually be identified at birth, but it can also be unrecognized until early puberty if the individual is only mildly affected. The presentation is more varied than that of achondroplasia; foramen magnum stenosis and thoracolumbar stenosis are extremely rare in patients with hypochondroplasia.

Compared with the achondroplastic population, individuals with hypochondroplasia have less of a height discrepancy (118 to 160 cm) (20, 82); similar, but less pronounced, facial characteristics; limbs shorter than the trunk, but to a lesser extent; milder other features such as thoracolumbar kyphosis, spinal stenosis, and genu varum; and mesomelic rather than rhizomelic long-bone shortening. In addition, the need for surgical intervention for patients with hypochondroplasia is much lower than that for those with achondroplasia. In our practice, we have surgically treated several hundred patients who had achondroplasia with spinal stenosis and/or kyphosis, but only a few patients with hypochondroplasia have required surgical intervention. Unlike individuals with achondroplasia, in whom intelligence is normal, a small portion (<10%) of those with hypochondroplasia have been associated with mental retardation (83).

Radiographic Features. Hall and Spranger (84) have proposed primary and secondary criteria for making this diagnosis. Primary criteria are narrowing of the pedicles in the lumbar spine, squaring of the iliac crest, broad femoral necks, mild metaphyseal flaring, and brachydactyly. Secondary criteria are shortening lumbar pedicles, mild posterior scalloping of the vertebral bodies, elongation of the distal fibula, and ulnar styloid. In patients with achondroplasia, the sciatic notches are narrow in nature; in patients with hypochondroplasia, the notches are unaffected and normal in appearance.

Differential Diagnosis. Compared with achondroplasia, hypochondroplasia is a much milder form of skeletal dysplasia and has a much more variable presentation; it can also go unrecognized until early puberty. However, severe cases of hypochondroplasia can overlap mild forms of achondroplasia. Occasionally, hypochondroplasia can be confused with Schmidt metaphyseal dysplasia because both disorders have mild short stature, typically normal faces, and mild genu varum.

Treatment. Surgery is rarely indicated. The administration of growth hormone therapy can have a positive initial impact (51, 85, 86), but to our knowledge, no long-term studies have been done. If limb lengthening is chosen, the risks and complications are the same as those for individuals with achondroplasia, but the benefits may be greater because the patients are taller initially and successful lengthening may enable them to achieve low-to-normal adult height and stature. However, patients should still be advised of all of the risks and complications and that there are no long-term studies.

METATROPIC DYSPLASIA

Overview. The term "metatropic dwarfism" comes from the Greek word metatropos, or "changing form," because patients with this condition appear to have short-limb dwarfism early in life, but later develop a short-trunk pattern as spinal length is lost with the development of kyphosis and scoliosis. The condition has been likened to Morquio syndrome because of the enlarged appearance of the metaphyses and the contractures (87).

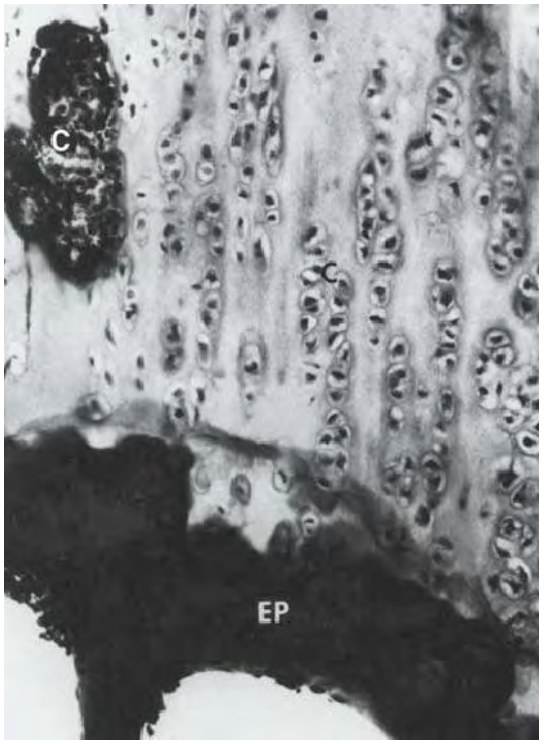


FIGURE 7-8. Histology of the growth plate in metatropic dysplasia, showing relatively normal columns of proliferating chondrocytes (*C*), but absence of the hypertrophic or the degenerating zones, as well as a "seal," or bony end plate (*EP*), over the metaphysis. (From Boden SD, Kaplan FS, Fallon MD, et al. Metatropic dwarfism: uncoupling of endochondral and perichondral growth. *J Bone Joint Surg Am* 1987;69:174, with permission.)

It is a rare condition that may be inherited in an autosomal dominant or recessive manner (88). The cause of this dysplasia has not been elucidated. However, histologic abnormalities of the growth plate have been studied and appear to be characteristic, as shown in the study by Boden et al. (89). The physis shows relatively normal columns of proliferating chondrocytes. However, there is an abrupt arrest of further development, with absence of a zone of hypertrophic or degenerating chondrocytes. Instead, there is a mineralized seal of bone over the metaphyseal end of the growth plate (Fig. 7-8). The perichondral ring remains intact, and circumferential growth is preserved. This uncoupling of endochondral and perichondral growth appears to account for the characteristic "knobby" metaphyses and the platyspondyly. Additional understanding of the defect in this disorder will shed light on the normal maturation of the physis.

Clinical Features. One of the most characteristic features of this condition is the presence of the "coccygeal tail," a cartilaginous prolongation of the coccyx that is not present in other dysplasias (Fig. 7-9A,B). It is usually a few centimeters long and arises from the gluteal fold. The facial appearance includes a high forehead, and there may be a high arched palate. The sternum may display a pectus carinatum, the limbs have flexion contractures of up to 30 to 40 degrees from infancy, and other joints may have ligamentous laxity. The limbs appear relatively short with respect to the trunk. The metaphyses are enlarged, which, when combined with underdeveloped musculature, gives a "bulky" appearance to the limbs. Some patients have been reported to have ventriculomegaly or hydrocephalus (90) or to develop upper cervical spine instability and/or stenosis (90, 91). Scoliosis develops in early childhood and is progressive (92, 93). Some restrictive lung disease is usually present,

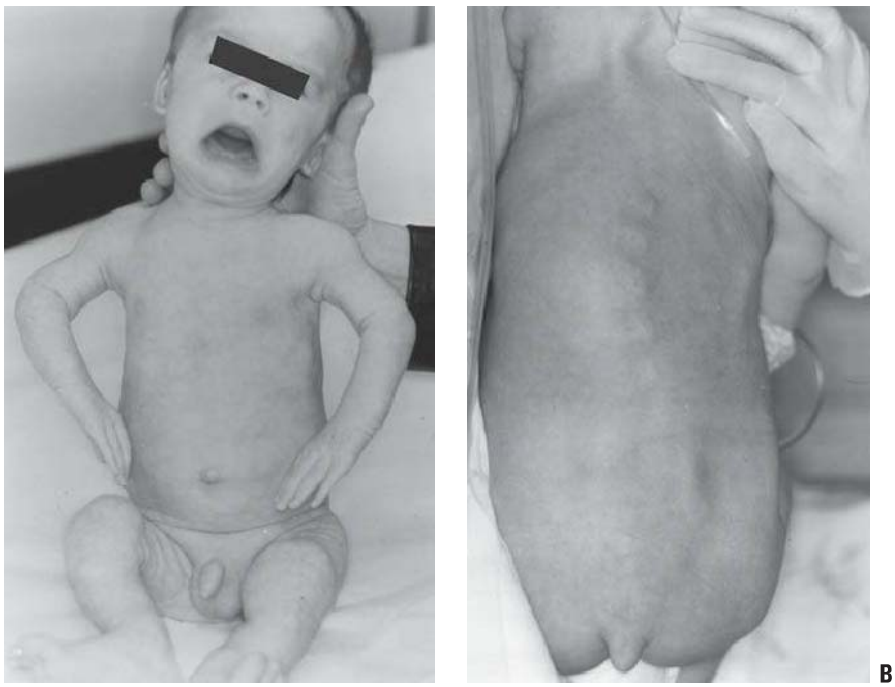


FIGURE 7-9. A 1-year-old infant with metatropic dysplasia, illustrating knee-flexion contractures, "bulky" metaphyses **(A)**, and a coccygeal tail **(B)**.

and it may cause death in infancy for the one-third of patients who are afflicted by the autosomal recessive form of the disease (88, 93). However, for those who survive into adulthood, height varies from 110 to 120 cm.

Radiographic Features. Prenatal sonographic diagnosis may be possible in the first or second trimester, with the finding of substantial dwarfism, narrow thorax, and enlarged metaphyses (94, 95). Odontoid hypoplasia frequently exists in patients with this condition, as in many patients with skeletal dysplasia. In infancy, the vertebrae are markedly flattened throughout the spine, but normal in width. Kyphosis and scoliosis develop in most patients. The ribs are short and flared, with cupping at the costochondral junctions (Fig. 7-10).

The epiphyses and metaphyses are enlarged, giving the long bones an appearance that has been likened to that of a barbell (Fig. 7-11). The epiphyses have delayed and irregular ossification. Protrusio acetabuli has been reported (93). Genu varum of mild-to-moderate degree usually develops. Degenerative changes of major joints often occur in adulthood.

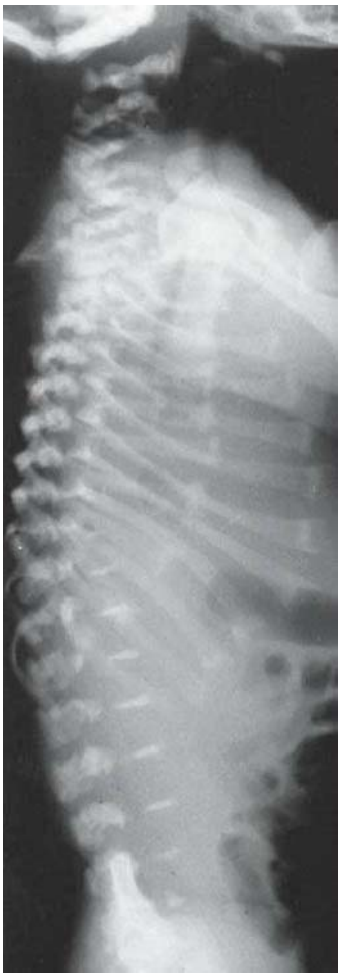


FIGURE 7-10. Newborn with metatropic dysplasia. Note platyspondyly with delayed vertebral ossification and flared ribs. (Courtesy of Judy Hall, Vancouver, BC.)

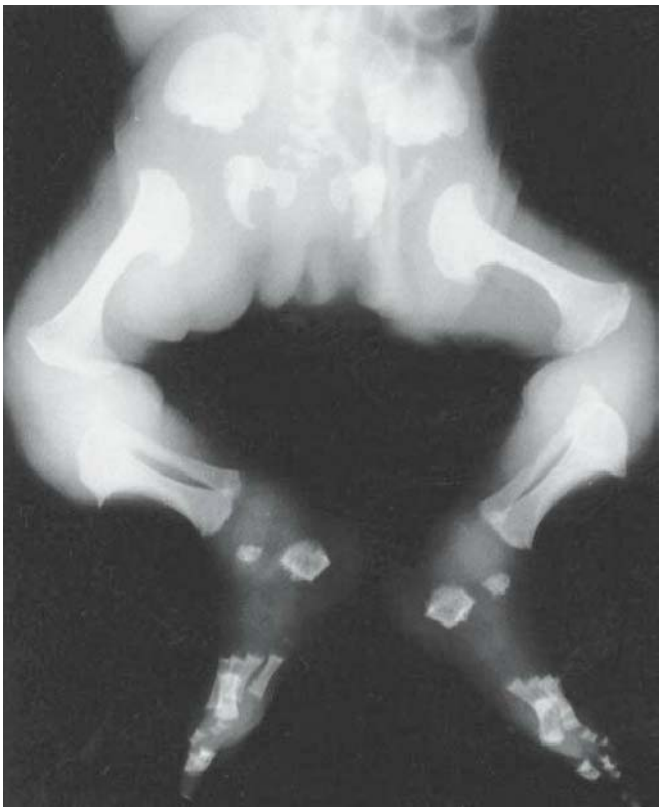


FIGURE 7-11. Newborn with metatropic dysplasia. The diaphyses are short and the metaphyses are broad and flared; their appearance has been likened to dumbbells. The iliac wings are flared, and the acetabulae are deep. (Courtesy of George S. Bassett, MD.)

Treatment/Orthopaedic Considerations. Respiratory problems often dominate infancy and may be fatal. They result from the small thorax and may also result, in part, from cervical instability. Such children need to be observed on a follow-up basis at a center with clinicians who have pediatric pulmonary expertise. The neck should be imaged early with MRI and possibly flexion–extension radiographs. Because cervical quadriplegia has been reported (91), fusion is recommended if atlantooccipital translation is more than approximately 8 mm, or neurologic compromise is present. If a patient has atlantoaxial instability of 5 to 8 mm but is neurologically intact, MRI should be obtained in flexion and extension. Fusion should be recommended if cord compromise is seen. Severe stenosis should be decompressed (91).

The patients should be examined early for spinal curvature. There is no documentation of efficacy of brace treatment for this condition. It may be tried in small curves (<45 degrees) in young patients or those who need support to sit, but it has no proven value for large curves, even if the patients are young and still actively growing. Spinal fusion for scoliosis may be advisable in patients with more severe curves. Deciding exactly when to intervene is more of an informed judgment call than a science. To document medical health and to have a chance of bone size adequate for instrumentation, we recommend observation and accepting a larger curve

threshold for surgery in patients <10 years old. However, progressive, sharp, angular kyphosis with paraparesis may occur in metatropic dysplasia and should be treated early with growth-sparing procedures or fusion if, in the surgeon's estimation, neurologic compromise is a risk. When surgery is undertaken, anterior as well as posterior fusion should be considered if the patient is able to tolerate it, because rigid fixation is difficult and there is a high rate of pseudarthrosis in this condition (10). Given that the curves are often rigid, only the amount of correction that can be achieved safely should be attempted. Halo-cast immobilization is an option if patient size, stenosis, or poor bone density make instrumentation inadvisable.

CHONDROECTODERMAL DYSPLASIA

Overview. Chondroectodermal dysplasia is an uncommon disorder. It is also known as Ellis-Van-Creveld syndrome and is prevalent among the Amish (96). It results in disproportional short stature and abnormalities in the teeth, limbs, and cardiac areas. The pathognomonic characteristic of this condition is severe flattening or wedging of the lateral proximal tibial physis, which leads to the severe genu valgum (Fig. 7-12).

It is a defect in *EVC* gene, or in the short arm of chromosome 4 (97–99). It results in the defect of maturation of endochondral ossification. It is transmitted as an autosomal recessive condition.

Orthopaedic Treatment. The first priority for patients with chondroectodermal dysplasia is stabilization of the heart.

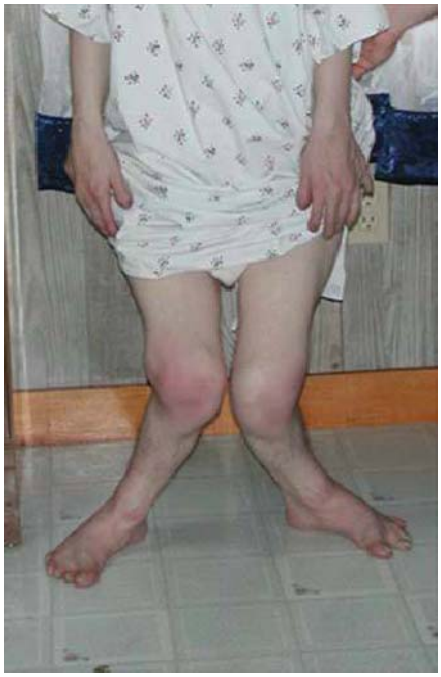


FIGURE 7-12. Photograph of a 16-year-old Amish male with Ellis-Van-Creveld syndrome and severe genu valgum.

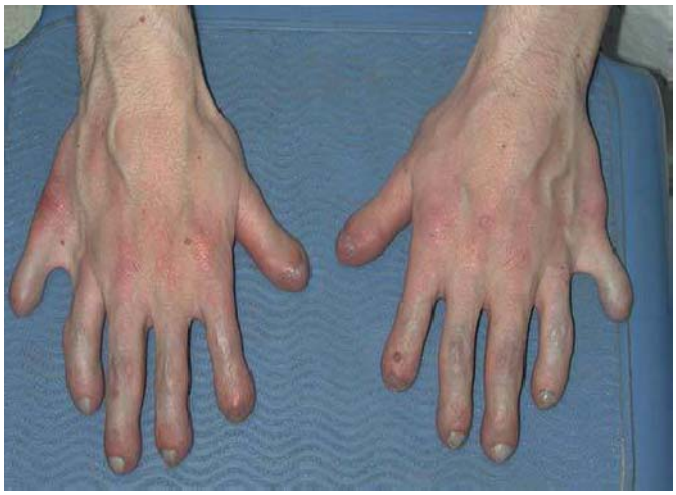


FIGURE 7-13. Photograph of a 21-year-old male with Ellis-Van-Creveld syndrome who did not undergo polydactyly correction.

Approximately one-third of these infants die in the first few weeks of life (100). In the first year, most patients with this condition have polydactyly, which can be reconstructed (Fig. 7-13). Genu valgum frequently occurs and can be quite severe. If seen early, genu valgum can be treated with guided growth, such as a hemiepiphysiodesis with an 8-plate. In our practice, bracing has had no effect on this condition and does not help control the severe ligamentous laxity. If surgical intervention (i.e., osteotomies) is warranted because of severe valgus angulation, rotational malalignment should be considered along with any genu valgum. The distal femur is typically externally rotated, and the tibia is internally rotated. It appears as though there is a flexion contracture in the lower extremities, but after correcting the malrotation, the flexion contracture typically disappears and then the malalignment needs to be corrected (62, 101). Clinicians can correct the malalignment with external or internal fixation. In these children and young adults, there is an increased risk of patellar subluxation and dislocation. Many times, lateral release, medial reefing, and even tibial tubercle osteotomies are required. In the presence of genu valgum, after correcting the malrotation, lateral proximal tibial elevation can also be entertained. Before the plateau elevation, an external fixator across the knee can be placed to open the lateral joint line. Osteotomy is necessary in severe cases because there is a high rate of recurrence.

Clinical Features. Approximately half of the children with chondroectodermal dysplasia have cardiac defects, most commonly atrial septal defects. One-third of children with this condition die during the neonatal period, most from cardiac abnormalities.

Patients with this disorder develop hypospadious and epispadious. They have narrow chests, abnormal dentition (with crooked, sparse, and sometimes lost teeth), abnormal nails, and postaxial polydactyly. This condition presents as acromesomelic shortening of the middle and distal segments

of the upper and lower extremities (102–105). The spine is typically uninvolved. The lower extremities have significant genu valgum secondary to a hypoplastic proximal laterotibial plateau and lax ligaments, and rotational abnormalities (such as external rotation of the femur or internal rotation of the tibia) are often present, as though there were a flexion contracture.

Radiographic Features. The ribs are short, the chest is narrow, and there is uneven growth of the proximal tibial epiphysis laterally. Exostosis can develop from the proximal tibial epiphysis medially and acetabular spike of the medial and lateral edges. The greater trochanteric epiphyses are quite pronounced, and the wrists can display fusion of the capitates, hamate, and (sometimes) other carpal bones. Carpal bones typically have delayed maturation, in contrast to the accelerated maturation of the phalanges.

DIASTROPHIC DYSPLASIA

Overview. DD is perhaps the dysplasia with the most numerous, disparate, and severe skeletal abnormalities. The term "diastrophic" comes from a Greek root meaning "distorted," which aptly describes the ears, spine, long bones, and feet. Before the current level of understanding of the skeletal dysplasias was developed, early authorities referred to this condition as "achondroplasia with clubbed feet" (106, 107). Certainly, the skeletal abnormalities are much more extensive than that.

The disorder is autosomal recessive and is extremely rare, except in Finland, where between 1% and 2% of the population are carriers, and there are more than 160 people known to be affected because of an apparent founder effect (108). The defect is on chromosome 5 in the gene that codes for a sulfate transporter protein (aptly named "diastrophic dysplasia sulfate transporter" or *DTDST*) (109, 110). This protein is expressed in virtually all cell types. Decreased content of sulfate in cartilage from patients with DD has been shown (111). A defect in this gene leads to undersulfation of proteoglycan in the cartilage matrix. If one considers proteoglycans to be the "hydraulic jacks" of cartilage at the ultrastructural level, it is understandable that there should be such impairment of performance of physeal, epiphyseal, and articular cartilage throughout the body. Achondrogenesis types 1B and 2 are more serious disorders causing mutations on the same gene.

Histopathology reveals that chondrocytes appear to degenerate prematurely, and collagen is present in excess (112, 113). Tracheal cartilage has some of the same abnormalities seen in other cartilage types, but it still does not explain some of the specific focal malformations seen in DD, such as proximal interphalangeal joint fusion in the hands, short first metacarpal causing hitchhiker thumbs, or cervical spina bifida. Additional work on the role of this sulfate transporter on skeletal growth and development must be done to explain these curious findings.

Clinical Features. Prominent cheeks gave rise to the previously used name "cherub dwarf" (Fig. 7-14). The nasal bridge is flattened. Up to one-half of patients have a cleft palate, which may contribute to aspiration pneumonia (112). The cartilage of the trachea is abnormally soft, and its diameter may be narrowed. The ear is normal at birth but develops a peculiar acute swelling of the pinna at 3 to 6 weeks in 80% to 85% of cases (114). The reasons for this event and this timing are not known. The cartilage hardens in a deformed shape—the "cauliflower ear," which is one of the pathognomonic features of this dysplasia.

Patients with diastrophism have a slightly increased [approximately 5% (106, 107)] perinatal mortality as a result of respiratory problems, especially aspiration pneumonia and tracheomalacia. Motor milestones are delayed: sitting occurs at a mean age of 8 months, pulling up to a stand at 13 months, and walking at 24 months (115).

The skeleton displays abnormalities from the cervical spine down to the feet (6). The posterior arches of the lower cervical spine are often bifid. There are no external clues to this occult underlying abnormality. Cervical kyphosis is seen in one-third to one-half of patients (11, 116); it may be present in infancy, and its course is variable. Spontaneous resolution has been reported in a number of patients, even with curves of up to

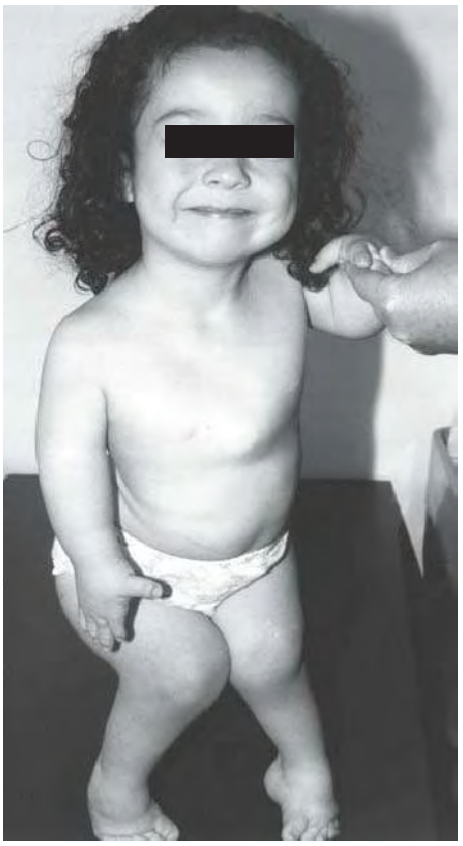


FIGURE 7-14. A 5-year-old girl with DD. Note prominent cheeks, circumoral fullness, equinovarus feet, valgus knees with flexion contracture, and abducted or "hitchhiker" thumbs.

80 degrees (117, 118) (Fig. 7-15A–C). However, others progress, and several reports of quadriparesis from this deformity exist (11, 119). Scoliosis develops in at least one-third of patients (116), but many curves do not exceed 50 degrees. Tolo (120) has stated that the scoliosis may be one of two types: idiopathic-like or sharply angular. The sharply angular type is usually characterized by kyphosis at the same level as the scoliosis. Spinal stenosis is not common, in contrast to achondroplasia. Most patients have substantial lumbar lordosis, likely to compensate for the hip flexion contractures in diastrophism.

The extremities display rhizomelic shortening. The shoulders may be subluxated, as may the radial heads (possibly because of ulnar shortening). The hands are short, broad, and ulnarly deviated. The hitchhiker thumb is the result of a short, proximally placed, often triangular, first metacarpal that may be hypermobile. This finding is seen in up to 95% of persons with DD (106). The proximal interphalangeal joints of the fingers are often fused (symphalangism).

The hips maintain a persistent flexion contracture. The proximal femoral epiphyses progressively deform, and even subluxate, in some patients. Epiphyseal flattening and hinge abduction develop in many patients (121). Arthritic changes develop by early to middle adulthood. The knees usually have flexion contractures, which result from a combination of ligamentous contracture and epiphyseal deformation (Fig. 7-16A,B). Excessive valgus is also common. Up to one-fourth of patients

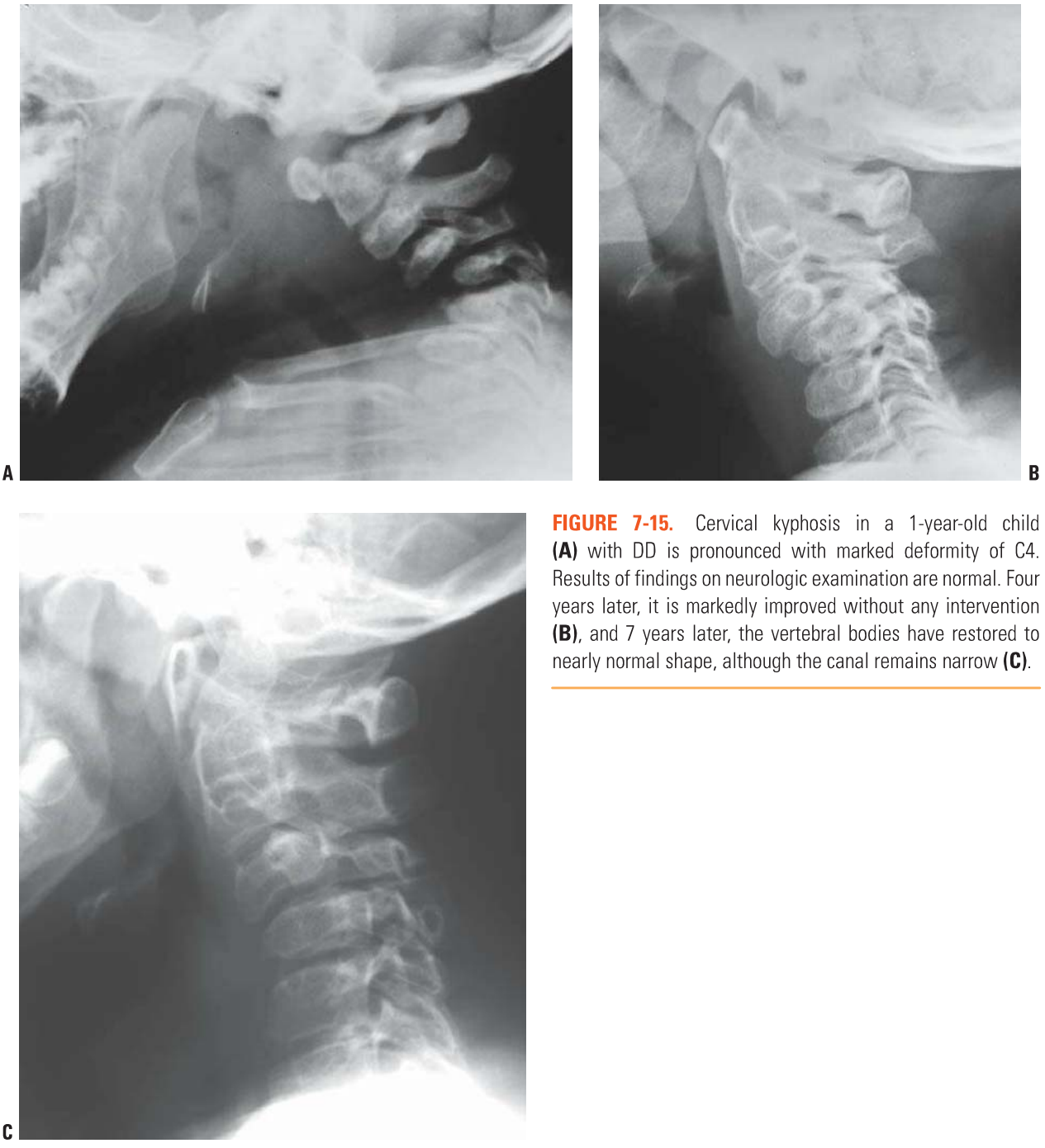


FIGURE 7-15. Cervical kyphosis in a 1-year-old child **(A)** with DD is pronounced with marked deformity of C4. Results of findings on neurologic examination are normal. Four years later, it is markedly improved without any intervention **(B)**, and 7 years later, the vertebral bodies have restored to nearly normal shape, although the canal remains narrow **(C)**.

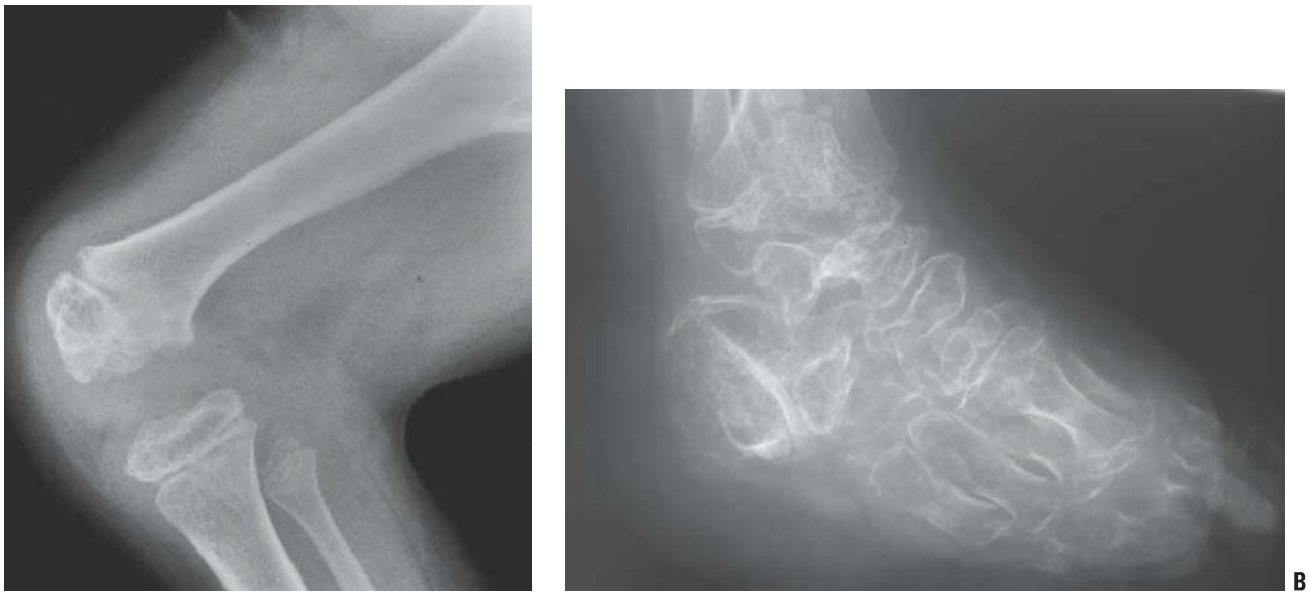


FIGURE 7-16. The extremities and the feet are involved in DD. Joint contracture is accompanied by epiphyseal deformity, as this knee radiograph illustrates **(A)**. A rigid, severe equinovarus foot is common **(B)**.

have a dislocated patella (106). DJD of the hips and knees develops in early to midadulthood.

The feet of diastrophic persons are commonly described as being clubfeet, but many different variations exist. In the large Finnish series by Ryoppy et al. (107), the most common finding was adduction and valgus (seen in 43%), followed in prevalence by equinovarus in 37%, and then by pure equinus. Diastrophic feet have significantly marked differences from idiopathic clubfeet (122). In the former, the equinus is more extreme, and the talocalcaneal joint is usually in valgus. Cavus often occurs with wedging of the calcaneocuboid joint. Adduction of the foot occurs mostly through the cuneiforms and metatarsals. The great toe may be in varus beyond the degree commonly seen in idiopathic clubfoot, analogous to the hitchhiker thumb. The foot deformities are very stiff and involve bony malformations, contracture, and malalignment. These feet are as difficult to correct as any type of clubfoot, and rarely have substantial or lasting improvement from serial cast treatment (122).

There is great variation in the severity of DD. Height is related to overall severity of involvement, with taller people being less severely affected (123, 124). The variation in stature is an example of the same spectrum of disorder. Growth curves for persons with DD are available (125). The median adult height is 136 cm for males and 129 cm for females (126). Therefore, people with achondroplasia are shorter in stature, and are approximately equal to those with pseudoachondroplasia and SED congenita. The pubertal growth spurt is diminished or absent, so the overall growth failure is progressive, suggesting that the physes are unable to respond to normal hormonal influences.

The life expectancy of persons with DD is not substantially less than that of the unaffected population, except for a small number of patients [approximately 8% (106)] who die in infancy from respiratory causes or during childhood from cervical myelopathy. Patients with severe spinal deformities are more prone to develop respiratory problems. Many patients are able to lead productive work and family lives, but walking ability is progressively limited and 10% do not walk at all, mostly because of the limitation of joint movement (127).

Radiographic Features. Prenatal diagnosis may be made by sonography in the second trimester with demonstration of long-bone measurements at least 3 standard deviations below normal, as well as clubfeet and adducted thumbs. In infancy, calcification develops in the pinna of the ear, and later in the cranium and the costal cartilages. The vertebrae are poorly ossified. The lower cervical spine may show kyphosis in infancy and early childhood, usually having an apex at approximately C4; this finding tends to decrease with time (118). MRI may be necessary to judge the severity of this condition in relation to the spinal cord. To our knowledge, only one case (116) of atlantoaxial instability has been reported in this condition. The vertebral "wedging" decreases with time in most patients (128). Spina bifida occulta is seen in more than three-fourths of patients (128). Unlike the spine in achondroplasia, the interpediculate distances in individuals with DD narrow only slightly at descending levels of the lumbar spine. Scoliosis may occur in the form of either a sharp, angular curve or a gradual, idiopathic-like one (Fig. 7-17A,B).

Images of the hand are characterized by several findings. The first metacarpal is small, oval, and proximally placed. Although the proximal interphalangeal joints of the digits are ankylosed, a radiolucent space is present early and later

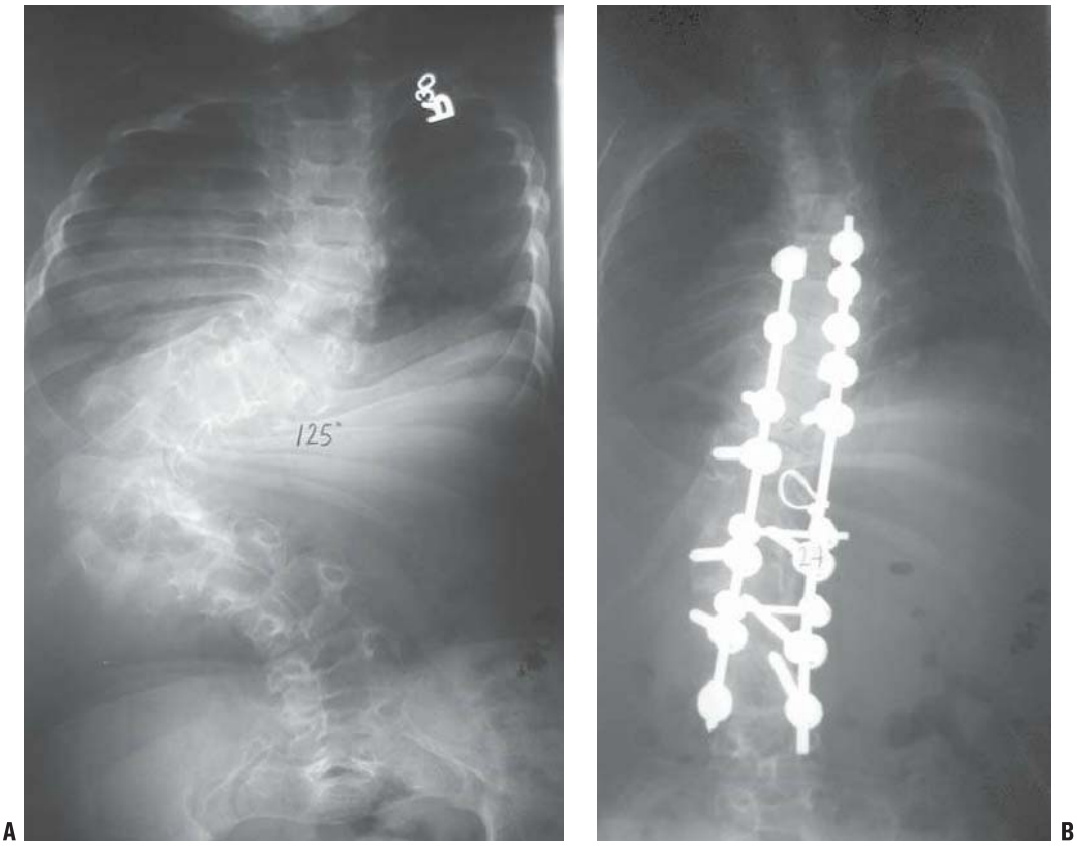


FIGURE 7-17. Severe scoliosis may occur early in DD, as in this 125-degree curve in an 8-year-old child **(A)**. After correction **(B)**.

fuses. The ulna and the fibula are shortened, contributing to the valgus of the knees and the radial head subluxation, which is sometimes seen. The diaphyses of the long bones are short and broad. The epiphyses of the proximal and the distal femur are delayed in appearance. The capital femoral epiphyses may show signs of osteonecrosis well into childhood. Arthrograms show flattening of the proximal and the distal femur, accounting for the stiffness observed clinically. The proximal femur is usually in varus, but, even so, hip dysplasia or subluxation may develop progressively with time.

Treatment

Cervical Spine. A neurologic examination should be performed periodically on all children, and a lateral cervical radiograph should also be obtained during the first 2 years of life. If cervical kyphosis is noted, the patient should be followed with clinical and radiographic examinations every 6 months. The behavior of the kyphosis appears to be related to the severity of the DD (121). If the kyphosis is nonprogressive, and there is no neurologic deficit, the only treatment should be observation because most kyphosis in this disorder will improve with time and growth, probably as a result of strengthening of the extensor muscles (121, 123). However, if the kyphosis progresses, but there is no neurologic deficit, bracing may be used. Successful control of cervical kyphosis by full-time use of the Milwaukee brace was reported by Bethem et al. (10, 11). If the curve continues to progress despite the brace, or a neurologic deficit occurs, posterior fusion should be performed. The surgeon should be cognizant of the bifid lamina during the exposure. Instrumentation may not be technically possible. If adequate bone graft is not available from the iliac crests, it may be taken from the proximal tibia(s) or other sources. Immobilization by a halo and vest is needed for 2 to 4 months postoperatively. For children, the pins should be inserted at a lower torque than in adults (4 inch-pounds), and the surgeon may elect to use a slight distractive moment and a slight posterior translation of the head. A pad may be used behind the apex of the kyphosis to help keep it from increasing. If neurologic deficit is present along with the curve, MRI in a neutral position and in extension will help to determine the degree of anterior compression and the type of procedure required. If there is severe anterior cord compression, corpectomy and strut graft may be indicated. Posterior fusion is also indicated.

Thoracolumbar Spine. Scoliosis affects more than one-half of diastrophic patients (116), follows one of three patterns (early progressive, idiopathic-like, or mild nonprogressive) (129), and has been shown to be unrelated to the type of mutation in *DTST* (108, 128). To our knowledge, the success of bracing in preventing or slowing curve progression has not been documented. It seems reasonable to offer it to patients, if the curve is <45 degrees, but to discontinue it for those in whom there would be no apparent benefit. Large curves often continue to progress in adulthood (116), and surgery has a role

in preventing progression for curves >~50 degrees. Posterior fusion is the mainstay of treatment (120). For younger patients, or those whose associated kyphosis is >50 degrees, anterior fusion may also be added. Instrumentation should be used carefully, bearing in mind the short stature, the stiffness of the spine, and the slightly diminished bone density. Small hooks may be used if needed (120). Spinal stenosis is seen in this condition much less often than it is in achondroplasia, but it may occur if degenerative changes are superimposed on the baseline canal size. Mild stenosis may be masked in some cases by the patients' relative inactivity.

Hips. Hip flexion contractures and knee flexion contractures should be assessed together. If they are severe (>40 degrees), release may be considered if an arthrogram shows no epiphyseal flattening and good potential for gaining range of motion. If there is epiphyseal flattening, it is probably better to avoid releases, given that recurrence is likely. Hip dysplasia is often progressive because of deformation of the abnormal cartilage under muscle forces and body weight. No long-term series has been done to show the ability of surgery to arrest this process. Therefore, the surgeon should use individual judgment as to whether an acetabular augmentation or a femoral osteotomy will help provide good coverage without restricting range of motion or function. Nonoperative treatment cannot be faulted in this condition.

Degenerative changes in the hip are one of the main reasons for decreasing walking ability in those with diastrophism. Hip joint arthroplasty is an option, when the pain becomes severe enough. Small or custom components are needed (130). The femur often has an increased anterior bow, probably in compensation for the hip flexion contracture. The isthmus of the femur is only 13 mm on average. Femoral shortening osteotomy is often needed. Contracture release (adductor, rectus, and sartorius) may be needed along with the arthroplasty, but femoral nerve palsy may follow if it is done extensively. Autograft augmentation of the acetabulum is often necessary. The largest series of hip arthroplasty in this condition is by Helenius et al. (131), with 41 hips in 10 patients (mean age, 41 years). Trochanteric transfer was performed in nearly one-half of the hips. Two patients had femoral palsies, but recovered. Hip range of motion was increased slightly, and Harris hip score nearly doubled. At a mean follow-up of 8 years, revision rate was 24%; all involved the acetabular side.

Knees. The knees in diastrophism usually lack flexion and extension. Complete correction of knee flexion contractures is prohibited by the shape of the condyles, which may be triangular, creating a bony block to flexion, extension, or both. Residual contracture at maturity may be diminished by distal femoral osteotomy. Patellar subluxation is present in one-fourth of those with DD (106); correcting it may help improve extensor power.

Knee arthroplasty often becomes necessary because of pain. Unique features of the procedure for patients with DD include extensive lateral release with patellar relocation, use of constrained prostheses whose stems must be shortened or bent, and femoral osteotomy (132). Mean age at surgery is similar to that for total hip arthroplasty (mid-40s). Pain and function are improved, although many patients lose a slight amount of knee motion (132).

Feet. Although the classic foot deformity in this condition is equinovarus, other types may be seen, including isolated equinus, forefoot adduction, or valgus. The feet are rigid, and cast treatment is usually futile. A plantigrade foot is the goal of treatment. Surgical treatment should be deferred until the feet are large enough to work on (usually after 1 year), and the neck is free of marked kyphosis. If soft-tissue release is performed, it should be as extensive as needed to correct the deformity. Sometimes, it requires release of the posteroinferior tibiofibular ligament to bring the dome of the talus into the mortise. Partial recurrence of deformity is common (107), and salvage procedures include talectomy, talocalcaneal decancellation, and arthrodesis (in the older child).

KNEIST SYNDROME

Overview. This syndrome results from a type-II collagen defect. Most mutations occur between exons 12 and 24 of the *COL2A1* gene. There have been numerous mutations described in literature, but all are phenotypically similar. It behaves as an autosomal dominant condition. Pathologically, the cartilage has been termed "soft" and "crumbly," with a "Swiss cheese" appearance (133).

The syndrome is characterized by large, stiff and knobby joints, with substantial contractures (134, 135). Patients with Kneist syndrome have unique facial features. This type of dysplasia results in severe disability. The spine and the epiphysis are also involved.

Clinical Features. The characteristic facial features of patients with Kneist syndrome are prominent eyes and forehead and a depressed midface. The joints appear enlarged, are very pronounced (secondary to the broad metaphysis of the long bones), and very stiff. The stiffness, which affects the large joints (e.g., the knees and hips) and the small joints of the fingers, progresses as the patients age and delays ambulation and fine motor skills. There is an increased incidence of inguinal and abdominal hernias. Many patients have a cleft palate, which can result in aspiration, a broad trunk, and a depressed sternum. Intellectual development is normal.

Compared with unaffected individuals, patients with Kneist syndrome have a higher incidence of aspiration secondary to the cleft palate or tracheal malacia and of otitis media (which can result in chronic hearing loss and myopia). Other eye problems include glaucoma and retinal detachment, which can lead to blindness early in life (135).

Radiographic Features. There is a generalized osteopenia of the spine and extremities, most probably secondary to disuse from increasing pain on ambulation, myelopathy, and

difficulty in ambulation from joint stiffness and premature arthritis.

Atlantoaxial instability is seen and can be secondary to odontoid hypoplasia. The vertebrae are flattened, and the vertebral bodies have clefts. As patients age, they can develop a severe kyphoscoliosis that needs to be corrected.

The femoral necks are short and broad with a substantial loss of joint space seen early into adolescence. There are regular calcifications in the epiphyseal and the metaphyseal regions. The epiphyses are flattened and irregular. Valgus can develop in the distal femur and the proximal tibia, leading to severe genu valgum.

Orthopaedic Treatment. Cervical instability must be checked routinely every 3 years with flexion and extension radiographs (136). If the space available for the cord is <13 mm or if the atlantodens internal is >8 mm, prophylactic cervical fusion is indicated. For many patients, halo-cast immobilization is used.

Kyphosis or scoliosis can present early and be progressive. We have found brace treatment to be ineffective in these patients. Early on, when the spine is still growing, growing rods can be used, followed by a definitive fusion at maturity.

For many of these patients with dysplasia, joint stiffness, and early arthritis, aqua therapy is recommended to keep the muscles strong and help preserve some joint motion (130).

Osteotomies around the hip for containment of the femoral head can be done. Arthrograms are recommended, especially for lower extremity malalignment, when surgical correction is performed. Many of these patients also have substantial flexion contractures, and using some extension in the osteotomies can help or diminish the arc of motion rather than increase it.

Clubfoot is seen fairly commonly. In our experience, the Ponseti method (137) has been less than satisfying in such patients. Aggressive posterior releases are recommended but a painful hallux can develop. Fusion of this joint can also be beneficial for hallux rigidus.

SPONDYLOEPIPHYSEAL DYSPLASIA CONGENITA

Overview. SED congenita is a rare disorder with an estimated prevalence of approximately 3 to 4 per 1 million people (1, 2). Its key features include substantial spinal and epiphyseal involvement, without metaphyseal enlargement or contractures of other joints (138). It is heritable in an autosomal dominant form, but most patients acquire the disease because of a new mutation. The etiology of this disorder has been characterized as a defect type-II collagen, the gene for which is located on chromosome 1293. This gene is the predominant protein of the cartilage matrix, and mutations have been observed in the α1 chain, resulting in alteration in length (139). As for many skeletal dysplasias, electron microscopy has shown intracellular inclusions in SED, which are probably a result of intracellular retention of procollagen (140).

Clinical Features. In general, the face is taut, and the mouth is small. Cleft palate is common. The trunk and extremities are shortened, although the extremities are more shortened proximally because of the coxa vara (Fig. 7-18A,B). Pectus carinatum develops, possibly because the rib growth outpaces the increase in trunk height. There are similarities to Morquio syndrome but a lack of visceral involvement. Scoliosis and kyphosis usually develop before the teen years. Back pain is also common by this time.

The hips are most commonly in varus, but this finding varies. The degree of varus has been thought to be the best marker for the severity of the disease (141), which varies. If the varus is severe, it is often accompanied by a substantial hip flexion contracture. Patients often walk with the trunk and head held back to compensate for this contracture. The knees are often in mild varus, and a combination of external rotation of the femora and internal rotation of the tibiae often coexists.

The most common foot deformity is equinovarus, but this it is not nearly as stiff as it is when associated with DD. Growth curves are available for this condition (141). Adult height varies from 90 to 125 cm.

Radiographic Features. One of the traits of this condition is that ossification is delayed in almost all regions (142, 143). There is often odontoid hypoplasia or os odontoideum. Flattened vertebral ossification centers with posterior wedging give the vertebral appearance, on lateral view, a pear shape. If scoliosis is present, it is often sharply angulated over a few vertebrae (Fig. 7-19). Disc spaces become narrow and irregular by maturity. Ossification of the pubis is delayed. The proximal femora are in varus with short necks, but the degree of this involvement varies. The proximal femur may not ossify for up to 9 years (141). Often, the varus is progressive (Fig. 7-20), and there may be progressive extrusion of the femoral head, which requires an arthrogram to show it clearly. The distal femoral metaphyses are flared. Genu valgum is more common than genu varum. Early osteoarthritis is likely in the hips, more so than in the knee. The carpal bones are delayed in ossification, but the tubular bones of the hands are near normal.

Medical Problems. Respiratory problems occur in infants, often because of a small thorax. The most common disabling problem in this syndrome involves the eyes: retinal detachment is frequent. It is reported to occur especially during the adolescent growth spurt (144). Regular ophthalmologic examinations are recommended. Hearing impairment is noted in a minority of patients.

Orthopaedic Problems and Treatment. Orthopaedically, the most potentially serious sequelae can involve neck instability. Os odontoideum, odontoid hypoplasia, or aplasia may all cause instability and, potentially, myelopathy (Fig. 7-21A–C). Numerous cases have been reported (10). Careful neurologic examination should be done at each clinic visit. Flexion-extension radiographs should be performed

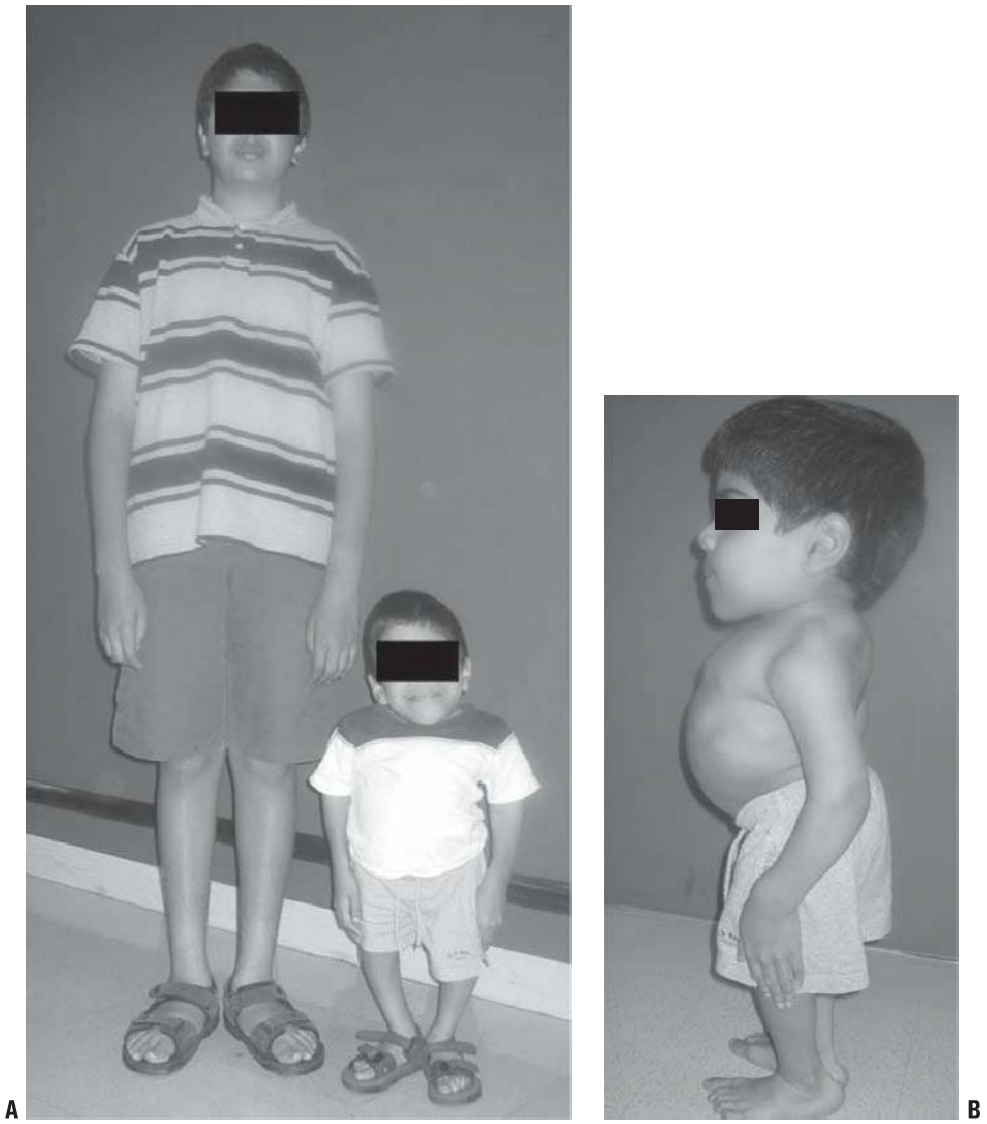


FIGURE 7-18. SED congenita produces the most extreme short stature. This 12-year-old boy is with his 14-year-old brother **(A)**. Note extreme spinal shortening, increased lumbar lordosis, and hip flexion contracture **(B)**.

approximately every 3 years if an upper cervical anomaly is identified. If the odontoid is difficult to see, one can use CT or MRI. Stenosis often coexists and makes subluxation more critical. It is recommended to fuse the atlantoaxial interval if instability exceeds 8 mm, or if symptoms develop. If severe stenosis exists, or if a fixed subluxation cannot be reduced, it may be necessary to perform a decompression of the atlas and, consequently, fusion to the occiput (145). Transarticular screw fixation is often possible after children are 6 to 8 years old. However, in younger children, bone strength or size of the neural arches may make rigid internal fixation impractical; in such patients, bone graft and halo-cast immobilization are usually successful. Scoliosis is present in more than one-half of patients with SED (138, 139, 142), and it may become severe. Curve control with a brace may be attempted if the curve is <40 degrees. However, long-term efficacy has not been shown. Fusion may be necessary if the curve is progressive. Thoracolumbar stenosis is not as severe as in achondroplasia. Instrumentation is not contraindicated but should be used judiciously. If internal stabilization is not judged to be strong, the use of halo-brace immobilization postoperatively should be considered. Correction is usually modest [17% in one series (10)]. Anterior surgery should be used if the patient is young (<11 years old) or the curve is rigid (correcting to <45 degrees). Kyphosis is also common; use of a Milwaukee brace has been shown to be effective if it can be worn until maturity (10).

Hip osteotomies are indicated if the neck-shaft angle is <100 degrees. Insufficient correction makes recurrence more likely. It is helpful to correct any flexion contracture at the same time, leaving adequate flexion for function. Malrotation should be also corrected. If a patient is experiencing painful hinge abduction, a valgus osteotomy may improve symptoms (146). An arthrogram may help in operative planning.

Hip subluxation may be reconstructed using a combination of femoral and iliac osteotomies. When doing any procedure on the hip, knee alignment should be assessed at the same time and corrected if necessary. The clinician should also consider the effect that knee angular correction will have on the hip. For instance, correction of severe knee valgus deformity

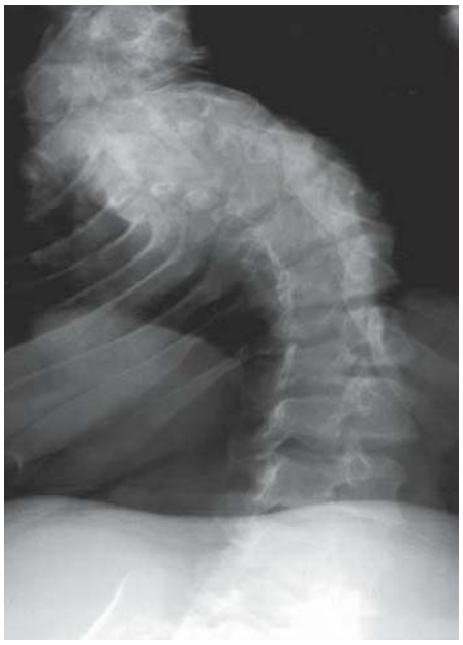


FIGURE 7-19. Scoliosis, with a sharp apex concentrated over a limited number of vertebrae, is characteristic of SED congenita.

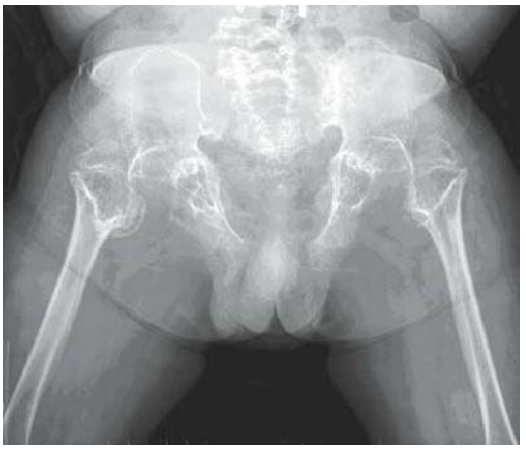
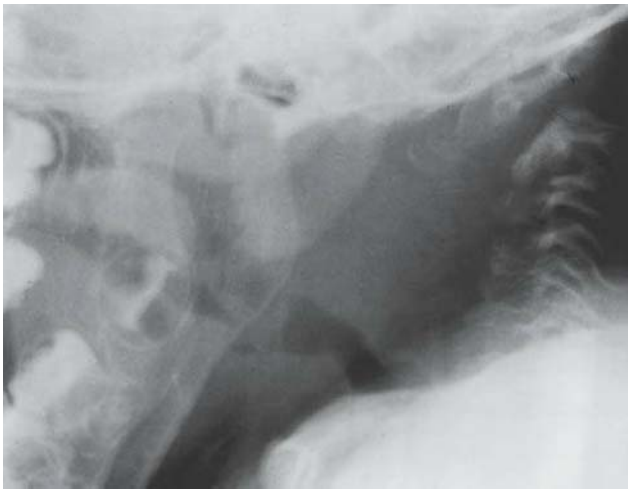
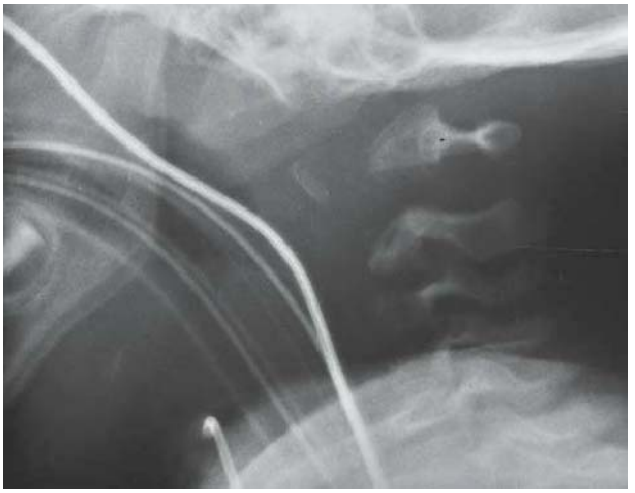


FIGURE 7-20. The hips in this 15-year-old with SED congenita show severe coxa vara, with delayed ossification of the capital femoral epiphyses and metaphyses.



A



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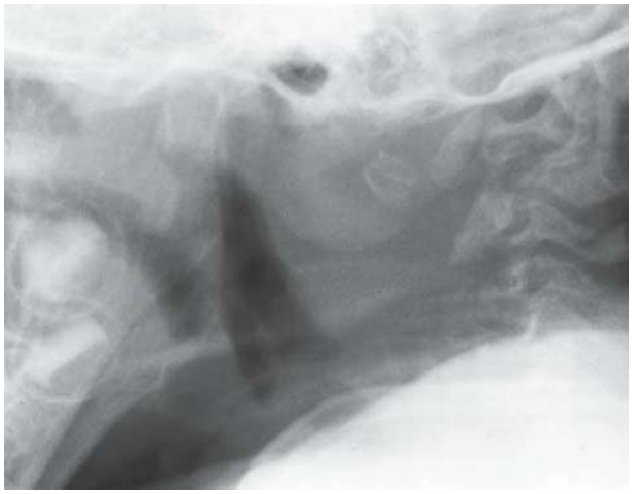


C

FIGURE 7-21. Atlantoaxial instability is common in SED congenita. This 2-year-old patient had delayed motor milestones. The upright lateral radiograph **(A)** of the cervical spine shows odontoid hypoplasia with marked atlantoaxial subluxation. Less evident is the stenosis of the ring of the atlas. When supine in a neutral position **(B)**, the alignment improved. After decompression of the atlas and fusion of occiput to C2 **(C)**, he gained the ability to walk.

has the same effect on hip congruity as does a varus osteotomy of the proximal femur.

Total joint replacement is a very difficult procedure: the hip is stiff, custom components are often needed, and concomitant osteotomy is sometimes necessary (130).

Foot deformities can usually be treated according to standard clubfoot principles. If the foot is stiff, an osteotomy or a decancellation of the talus, calcaneus, and/or cuboid may be needed.

SPONDYLOEPIPHYSEAL DYSPLASIA TARDA

Overview. SED tarda is distinguished from the congenita form by later age at diagnosis and milder features. Manifestations first appear in later childhood, or even in adulthood. The spine and only the larger joints are affected. Several genetic patterns of transmission have been reported (105, 147, 148). The most common is X-linked, in which male patients are more commonly or more severely affected and female patients may show milder (or no) manifestations. It is the result of a defect in the gene *SEDL* (149), whose function is not yet known. A recessive form has also been reported. SED tarda is one of several conditions (termed the *COL2A1* group or the SED family), which may result from a mutation in type-II collagen (14, 78). The mechanism by which the particular mutation for this condition produces the mildest phenotype in this family has yet to be elucidated.

Clinical Features. In the earliest cases, manifestations are first called to clinical attention when the child is approximately 4 years old. Stature is mildly shortened. Arm span is substantially longer than height. The condition may be first diagnosed as bilateral Perthes syndrome (150). Back pain and hip or knee pain may be present in childhood. Joint range of motion is minimally limited, if at all. Varus or valgus deformities are rare. Degenerative changes may occur in the hip or the knee by young adulthood. Adult height may be 60 in. or more (105).

Radiographic Features. Involvement of shoulders, hips, and knees predominates. The hips manifest varying degrees of coxa magna, epiphyseal flattening (Fig. 7-22), or epiphyseal extrusion, differing markedly even within the same family. A minority of patients present with bilateral coxa vara. Odontoid hypoplasia or os odontoideum may cause atlantoaxial instability. Spinal involvement ranges from mild platyspondyly (Fig. 7-23), with axe-like configuration of the vertebral bodies on the lateral view, to isolated disc-space narrowing. Mild-to-moderate scoliosis develops in a minority of patients.

Orthopaedic Problems and Treatment. The severity of orthopaedic conditions varies widely, even within a family. There are undoubtedly many affected individuals whose problems are so mild that no diagnosis is ever made. In one large family, only 4 of the 31 affected members requested any orthopaedic treatment (151). This condition should be considered whenever spine, hip, and/or knee pains run in a family, and the radiographs seem to be just a little atypical. Bracing may be recommended if scoliosis exceeds 30 degrees in the skeletally immature patient. Surgery should be offered for the rare patient in whom it exceeds 50 degrees. All patients should be screened for atlantoaxial instability. Fusion should be recommended if the spine is unstable in either flexion or extension, according to criteria given earlier for the congenita form. The role for procedures to increase coverage of the dysplastic, extruded femoral head by the acetabulum during the childhood years is not well documented. However, it may

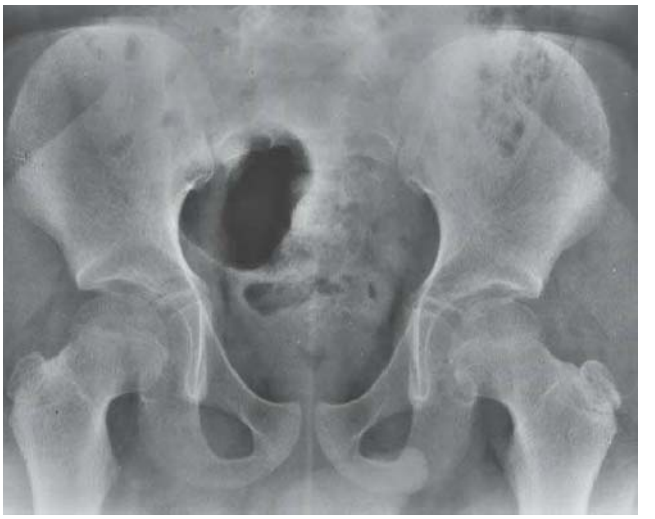


FIGURE 7-22. The pelvis in this patient with SED tarda shows small, flattened epiphyses.

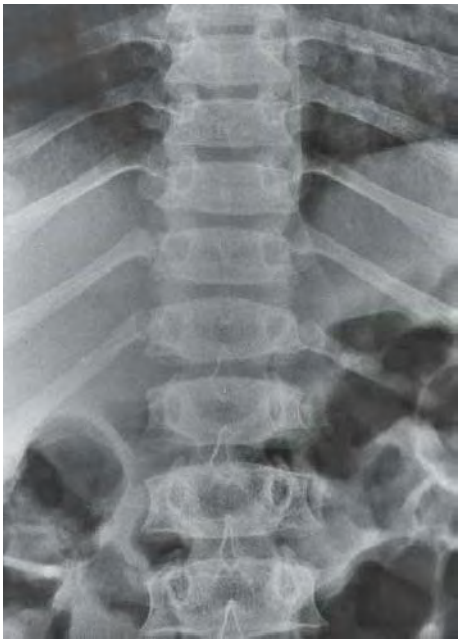


FIGURE 7-23. The spine in this patient with SED tarda shows typical mild flattening of the vertebral bodies, but no scoliosis.

be helpful in the rare young patient with increasing extrusion and persistent pain, in whom the hip contact surface is markedly compromised. If hip pain becomes a problem after the femoral heads are mature or nearly mature, osteotomy may help to increase congruity or decrease hinge abduction. Usually, a valgus or valgus-extension osteotomy is most appropriate, as long as there is reasonable joint space and adequate contact remaining. A preoperative arthrogram is helpful in the young patient to see the full outline of the articular surface. Osteotomies of knees or ankles are rarely needed. Total joint arthroplasty is often needed for the hips or knees, at an age much younger than that for the general population.

PSEUDOACHONDROPLASIA

Overview. Pseudoachondroplasia is one of the more common forms of skeletal dysplasia, occurring in approximately 4 per 1 million live births in the United States (152). Although the name is similar to achondroplasia, it is a phenotypically and genotypically distinct condition. It was originally described by Maroteaux and Lamy (153) in 1959, at which time they identified it as a subset of SED. Later on, it became its own distinct dysplasia. Clinical features are not recognized during the first few years of life, and there is less involvement of the spine than is seen in SED.

Pseudoachondroplasia results from a mutation in the COMP protein (154, 155). This protein is the same as that seen in MED. Chondrocytes of people affected with pseudoachondroplasia have lamellae inclusion bodies located within the endoplasmic reticulum.

MED and pseudoachondroplasia have been described as a family of dysplasias, with MED being the milder and pseudoachondroplasia being the more severe form. COMP is a large extracellular matrix glycol-protein that is found surrounding chondrocytes and also in the extracellular matrix of ligaments and tendons. Multiple mutations in the COMP gene have been found to result in pseudoachondroplasia. In this case, it is an overproduction of COMP gene, not a deletion, that results in pseudoachondroplasia. Abnormal COMP deposits in the rough endoplasmic reticulum of chondrocytes and into the extracellular matrix (92, 156) leads to an abnormal, flatter cell shape (157, 158). Somatic and germinal line mosaicism is present, which allows this condition to act as a recessive disorder in terms of inheritance, even though it is a dominant gene.

Clinical Features. This is one of the skeletal dysplasias that are not recognized until later on in life because it is essentially a storage disorder. It is typically recognized between 2 and 4 years old. As patients age, more COMP is deposited and the condition progresses. The height of children with pseudoachondroplasia is within the normal parameters at birth, but trails down to less than the 5th percentile at 2 years old (125). In addition, the atypical normal faces prevent the diagnosis of this condition until later on in life (159, 160).

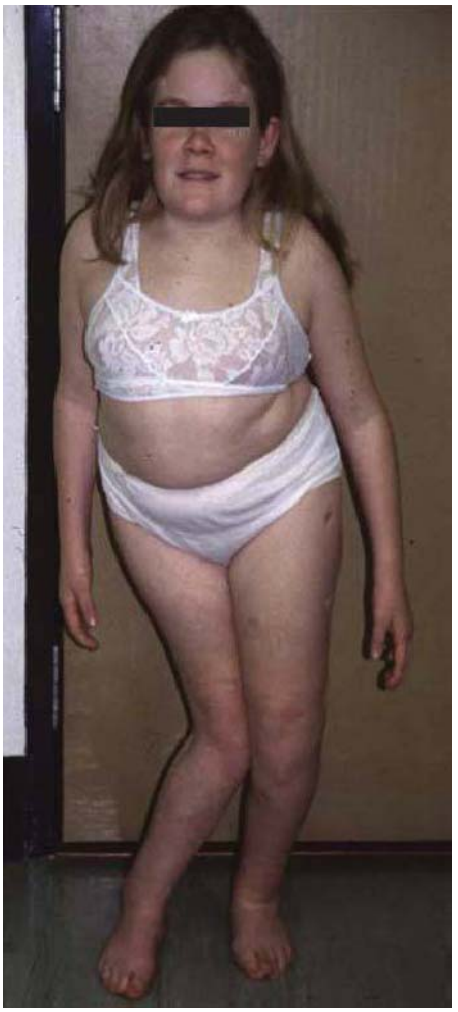


FIGURE 7-24. Photograph of a 16-year-old female with pseudoachondroplasia and windswept deformity.

Patients with pseudoachondroplasia have a rhizomelic appearance of shortening of the extremities, the same as that seen in achondroplasia. However, the trident hand, typically seen in achondroplasia, is not seen in pseudoachondroplasia. These children typically develop substantial malalignment of the lower extremities, with genu varum on one side and genu valgum on the other side (i.e., the windswept deformity) (Fig. 7-24). Femoral heads typically get misshapen with time and are flattened. The hips, knees, and ankles develop premature arthritis in early adulthood. Spinal involvement is to a lesser degree. Cervical instability that will need stabilization may occur with this disorder (12); therefore, it needs to be checked on a routine basis. There is an increased kyphosis and lumbar lordosis (157). Scoliosis can also affect these patients.

Typically, these people have normal life expectancies and intelligence. They do not develop changes outside of the skeleton.

Radiographic Features. The vertebral bodies are very flat with anterior indentation, which is seen early on in life. It would be very helpful to identify these patients early on and make a diagnosis.

Cervical instability is common, secondary to odontoid hypoplasia. These patients need to be monitored in a routine fashion, with radiographs every 2 to 3 years in flexion and extension.

The epiphyses are regularly shaped and ossify later in life. In the long bones, the metaphyses are broad, irregular at the ends, and flared. The pubic rami and the greater trochanteric apophyses are delayed in closing (161).

As the femoral head enlarges, it takes on a flattened appearance and can sublux from the acetabulum. An arthrogram can be helpful in eliciting the cause and identifying the surgical options. Much of the ossification between the carpals is delayed, which can make it challenging to decide how to correct the malalignment of lower extremities, which is why we think arthrograms are critical.

Orthopaedic Problems and Treatment. The cervical spine should be evaluated early on and often. If the atlantodens interval is >8 mm, or if the space available for the cord is <14 mm, prophylactic posterior fusion (Fig. 7-25) is indicated with a halo brace. If myelopathy develops, it is another indication for surgical treatment. Even with internal fixation, a halo brace has been found to be helpful (162), and using it may increase the rate of union. Kyphosis and scoliosis are seen, and we use the same indications for surgical treatment as those for patients of average stature. However, in our experience, brace treatment is not helpful. Although stenosis is not usually seen, we prefer to use pedicle screws during operative treatment. If a large curve is seen early on in life, growing rods can be an effective interim treatment before a definitive fusion.

With hip subluxation, the cause is important. If it is secondary to valgus at the knees, it needs to be addressed first. If it is primary to hip abnormality, then this also needs to be addressed. Arthrograms are obtained to see if surgical varus of the hip, which can be combined with an iliac osteotomy, would be appropriate. Typically, an acetabular shelf augmentation can also be done to increase the volume in the acetabulum. However, despite a clinician's best efforts, many of these hips will develop premature arthritis (22, 130, 157). Total hip arthroplasty for patients with pseudoachondroplasia can be done safely and effectively at facilities that have experience with this procedure and patient population (130).

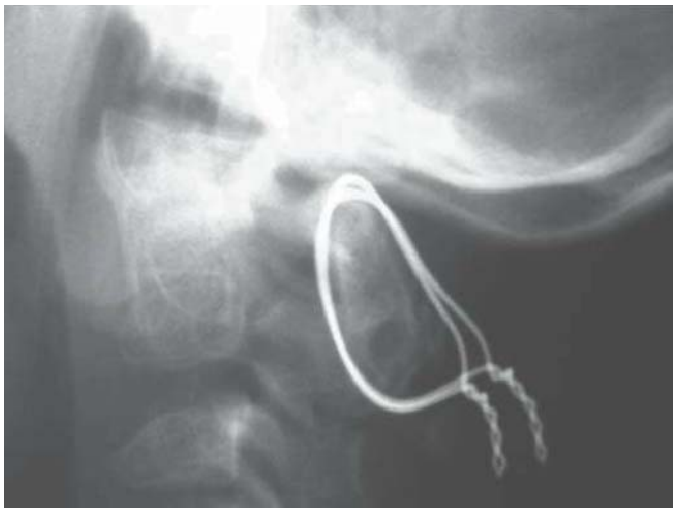


FIGURE 7-25. Radiograph of a 4-year-old with pseudoachondroplasia after cervical fusion and sublaminar wiring for cervical instability.

In such patients, lower extremity malalignment usually consists of the "windswept deformity," that is, varus of one limb and valgus of the other. Arthrograms followed by lower extremity osteotomies can be helpful, but overcorrection must be avoided, or the same problems will rapidly develop in the opposite direction. As with the hips, these knees can develop premature arthritis, requiring total knee arthroplasty, which requires a constrained prosthesis because the arthritis is secondary to ligamentous laxity. We have seen nonconstrained prosthesis in total knee arthroplasties dislocating immediately after surgery.

MULTIPLE EPIPHYSEAL DYSPLASIA

Overview. MED is one of the most widely known, variable, and commonly occurring skeletal dysplasias. It is usually dominantly inherited, although recessive cases have recently been described as a result of mutations in transport protein (152). It affects many epiphyses, produces symptoms mainly in those with substantial load bearing, and has few changes in the physes or metaphyses. Historically, it was described as occurring in two separate forms, with eponyms that are still used today: Ribbing dysplasia, having mild involvement, or Fairbank dysplasia, a more severe type (163–165). However, with the current understanding of the genetic basis, this distinction may not be scientific, and a wide variability is recognized (166).

Histologically, intracytoplasmic inclusions are seen that are similar to, but not as severe as, those seen in pseudoachondroplasia. Growth plate organization is still noticeably abnormal, despite the minimal changes seen in the metaphyses. The genetic basis for this disorder is now reasonably well understood. It is a heterogeneous disorder. Mutations in many patients have been found in the gene for the matrix glycoprotein COMP on chromosome 19, as in pseudoachondroplasia. This product accumulates in cartilage cells and causes premature apoptosis. It also weakens the integrity of the matrix, allowing deformation and wear under normal loads. However, in other cases of MED, abnormalities have been found in the α_2 fibers of collagen type IX (*COL9A2*). Collagen type IX is normally a trimer that is found on the surface of type-II collagen in cartilage. It may form a macromolecular bridge between type-II collagen fibrils and other matrix components—it therefore may be important for the adhesive properties of cartilage. A *COL9A2* mutation has been described in one large family, with peripheral joint involvement only (167). In addition, dominant MED in some cases is caused by defects in matrilin-3, another oligomeric extracellular matrix protein (152, 168). Rarer, recessive forms of MED are caused by mutations in transporters (152). Therefore, it appears that MED is a very heterogeneous disorder, which may help clinicians to

understand some of the more common epiphyseal cartilage disorders such as Perthes disease, osteochondritis dissecans, and osteoarthritis (152).

Clinical Features. Patients typically present later in childhood for one of several reasons. They may be referred for joint pain in the lower extremities, decreased range of motion, gait disturbance, or angular deformities of the knees (169). There may be flexion contractures of knees or elbows. Symptoms may develop as late as adulthood. These patients have minimal short stature, ranging in height from 145 to 170 cm (164). The face and the spine are normal. There is no visceral involvement.

Radiographic Features. Most changes in MED involve the epiphyses; any of the ossification centers may be delayed in appearance. There are occasional irregularities of streaking in the metaphyses, but they are minor. The appearances of the epiphyses in the immature and in the mature patients are characteristic (170). In the growing patient, the epiphyses are fragmented and small in size (Fig. 7-26). The epiphyseal ossification centers eventually coalesce, but the overall shape of the epiphysis is smaller. An arthrogram may be helpful for assessing the shape of the joint surface. The more fragmentation there is in the capital femoral epiphysis, the earlier is the onset of osteoarthritis (171). Coxa vara occurs in some patients. By maturity, there is some degree of flattening of the major load-bearing epiphyses: flattening of the femoral condyles, an ovoid femoral head, decreased sphericity of the humeral head, and squaring of the talus. In adulthood, major joints develop premature osteoarthritis. This condition is most common and most severe in the hips.

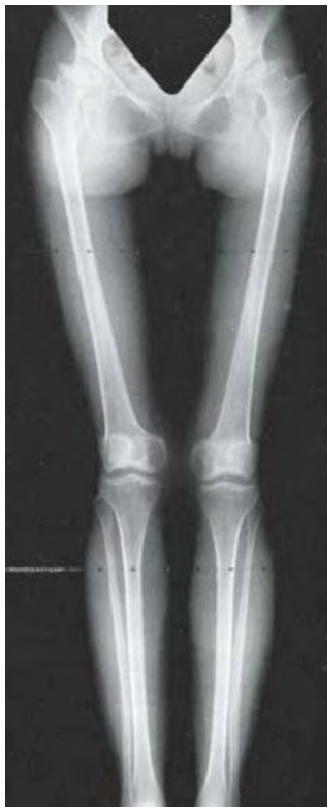


FIGURE 7-26. Multiple epiphyseal dysplasia.

Avascular necrosis may be superimposed on MED, a combination that occurs in approximately one-half of the femoral heads (172). It can be recognized by the appearance of a crescent sign, resorption of bone that had already been formed, and, sometimes, by the presence of metaphyseal cysts (172). MRI at this time may show loss of signal in a portion of the femoral head. A "sagging rope sign" may develop later (173).

An orthopaedic surgeon must be able to differentiate MED from Perthes disease (150). Several radiographic clues may be helpful. In MED, abnormalities in the acetabulum are primary and are more pronounced. The radiographic changes are symmetric and fairly synchronous. It is also helpful to obtain radiographs of the knees, ankles, shoulders, and wrists.

Radiographs of the knees show that the femoral condyles are flattened and may be in valgus. There may be irregular ossification, just as in the hip. The condyles are somewhat squared on lateral view. Osteochondritis dissecans may be superimposed. MED patients with a *DTDST* mutation also show a double-layered patella on the lateral view (174, 175). This is a complete or partial double radiodensity, which is rarely seen in other conditions.

The ankles in MED are also in valgus; changes occur in the talus and in the distal tibia. Upper extremity involvement is less severe; there may be irregularities in the proximal and distal humerus and radius. The humeral head involvement in adulthood has been termed a "hatchet-head" appearance, and results from undergrowth of the head and neck. It occurs in children more severely affected with MED. Radial ray hypoplasia may occur sporadically (176). The carpal ossification centers are delayed in appearing. The hand and wrist involvement may predict stature, that is more severely disordered epiphyses (177). The spine may be normal, or it may have slight endplate irregularities or ossification defects on the anterior margins of the vertebrae (178).

Orthopaedic Implications. The orthopaedic surgeon may become involved in the care of the patient with MED in one of two periods. There is a small role for realignment procedures in the early, deforming period of the hip if there is progressive subluxation or pain. However, with substantial delay in epiphyseal ossification, recurrent deformity has been reported (179). Pain is more likely to occur in cases in which avascular necrosis has supervened (172). Although the principle of coverage is the same as that used in Perthes disease, there is often a degree of coxa vara pre-existing in hips with MED, which may contraindicate the use of a femoral osteotomy. Acetabular shelf augmentation is a worthwhile procedure in these instances (180, 181).

Not all patients need surgical treatment; however, it can help some. Hemiepiphysiodesis may guide growth to help correct knee and ankle deformities. Even though the physes

may not be normal, correction of 15 to 20 degrees has been reported in 18 months (182). Severe deformities may be corrected by osteotomy at maturity in the femur or tibia, depending on the site of abnormality. Patients having a double-layered patella may have symptoms because of the relative movement of one over the other. This situation may be treated by excision of one or fusion of the two segments, as appropriate (183). DJD is the biggest problem, and it occurs in the second or third decade. It results not so much from malalignment of the joints, but from intrinsic defect in cartilage. It produces stiffness, from an early age, and pain leading to a total joint arthroplasty. Differences from standard osteotomy include a shallow or an anteverted acetabulum or narrow femoral canal (184). Even the shoulder is commonly affected by degeneration, and shoulder arthroplasty may be necessary (185).

CHONDRODYSPLASIA PUNCTATA

Overview. This skeletal dysplasia is named for a radiographic finding of calcification in skeletal cartilage, which can arise through several different pathways (186). It is also known by the synonym "congenital stippled epiphysis." Key features include depressed nasal bridge and multiple punctate calcifications in infancy, which are best visualized on the newborn's radiographs (187). There are many different types, the most common being an X-linked dominant type (Conradi-Hünermann syndrome), followed by an autosomal recessive rhizomelic type (which is usually fatal in infancy) and a rare X-linked recessive type. Four other types have been described that are even more rare (188). Although the appearance of neonatal epiphyseal calcification is striking, it is not very specific. There are various conditions that may present with the same phenomenon: Zellweger (cerebrohepatorenal) syndrome, gangliosidosis, rubella, trisomy 18 or 21, vitamin K deficiency, hypothyroidism, or fetal alcohol or hydantoin syndromes (188–193). Rhizomelic chondrodysplasia punctata is a peroxisomal deficiency of dihydroxyacetone-phosphate acyltransferase that is often (but not always) fatal in the first year of life (194, 195). The genetic defect and pathogenesis of the Conradi-Hünermann syndrome is related to a defect in sterol metabolism (186). The final common pathway of the various types is a defect in cholesterol synthesis (196) or peroxisomal enzymes. Histologic examination shows perilacunar calcifications throughout the cartilage matrix (197).

Clinical Features. Patients with Conradi-Hünermann syndrome are characterized by hypertelorism, a depressed nasal bridge, and a bifid nasal tip (198–201). In addition, many have alopecia, congenital heart and/or renal malformations, and mental retardation. In rhizomelic chondrodysplasia punctata, findings include microcephaly, a high incidence of congenital cataracts, growth retardation, and a well-formed nasal bridge (202–205). Some have feeding difficulties, and many succumb to death from respiratory issues or seizures in the first year. Diagnosis may be made by amniocentesis, with measurement of plasmalogen biosynthesis and phytanic acid oxidation.

Skeletal findings in the extremities include limb-length inequality, coxa vara, and clubfoot or other foot deformities (206). Spinal findings include atlantoaxial instability, congenital scoliosis, spinal stenosis or kyphosis (196, 207, 208).

Radiographic Features. Skeletal calcifications are visible at birth, but most disappear by 1 year. These calcifications involve the epiphyses, carpal bones, ribs, and pelvis (209) (Fig. 7-27A,B). Extraskeletal sites include the trachea and larynx. The appearance is of small flecks of calcium, "which appear as if paint had been flecked on by a brush" (210). The

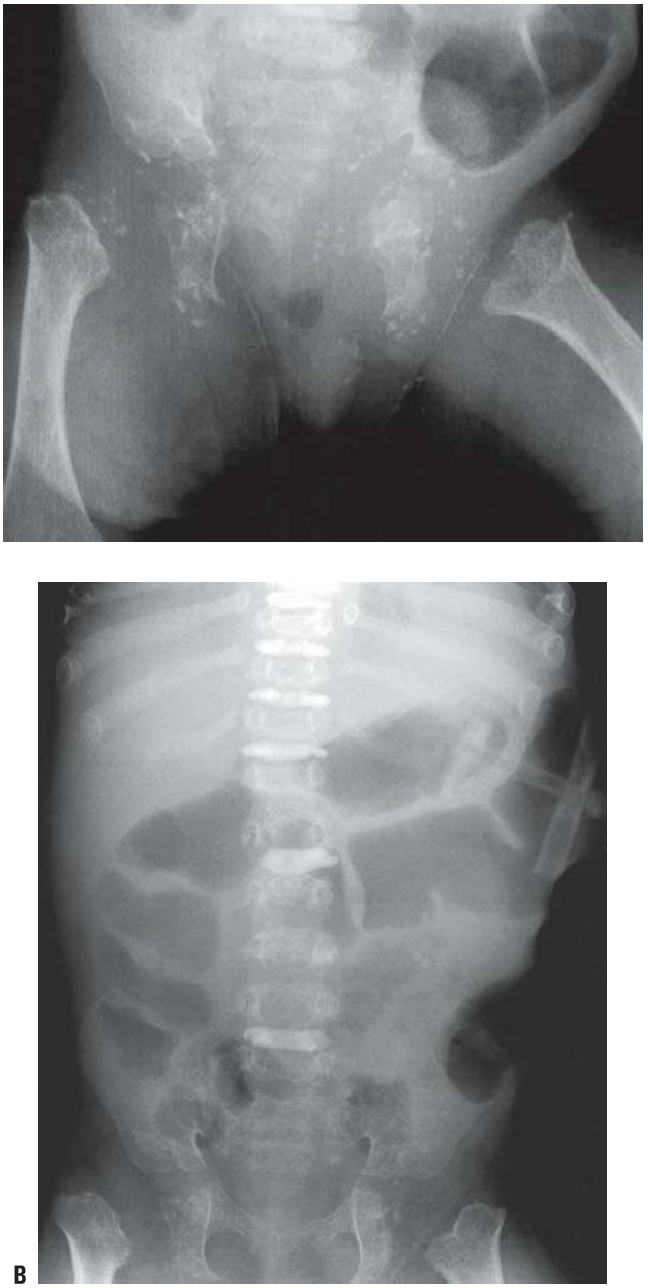


FIGURE 7-27. **A:** Diffuse punctate epiphyseal calcifications in infancy are a hallmark for which chondrodysplasia punctata was named. **B:** At 2.5 years old, the epiphyseal calcifications are mostly resolved, but calcification of the intervertebral discs persists.

ossification centers themselves may be delayed in appearance. Coxa vara may affect one or both hips, or it may be absent (211). The fibula often substantially overgrows the tibia. Spine radiographs may have the appearance of a hemivertebra or a congenital bar. Calcification of the intervertebral discs may develop (Fig. 7-27B). Odontoid hypoplasia and os odontoideum have been described (208).

Orthopaedic Implications. Because of the risk of cervical instability or stenosis, each patient should have a lateral cervical radiograph and, if instability appears possible, a flexion-extension view. Scoliosis may occur early because of secondary congenital anomalies. It may require early fusion if progression is documented and the patient, medically, is a candidate. Anterior structural grafting, followed by posterior fusion and cast immobilization, has the highest rate of success (196). Coxa vara should be treated if it is symptomatic and the neck-shaft angle is <100 degrees. Lower limb-length inequality should be monitored and treated appropriately.

METAPHYSEAL CHONDRODYSPLASIAS

Overview. Metaphyseal chondrodysplasias are a family of disorders resulting in metaphyseal irregularities and limb deformity (211–214); however, the epiphyses are uninvolved. There are four named disorders in this family: McKusick type, Schmidt type, Jansen metaphyseal dysplasia, and Kozlowski type.

McKusick Type. Also known as *cartilage-hair dysplasia*, the McKusick type is most commonly found among the Amish population in Lancaster, Pennsylvania, but it can also be found outside this community. The condition is autosomal recessive and maps to chromosome 9 (215). The defect is in the *RMRP* gene, which encodes a mitochondrial RNA process (216).

FIGURE 7-28. Photograph of a 24-year-old Amish female with McKusick-type dysplasia and mild genu varum.

Clinical Features. Individuals with McKusick-type dysplasia have light, fine, and sparse hair (Fig. 7-28). They might have a change in T-cell immunity, which causes an increased risk of infection, especially varicella zoster (217, 218).

Anemia occurs frequently in young children, but the incidence lessens as they become adolescents (219). A high risk of malignancies, such as lymphoma, sarcoma, and skin cancers, can be seen in this patient population (217, 220), and life expectancy is decreased, warranting medical treatment into adulthood more than with most of the other dysplasias.

In addition, individuals with McKusick-type dysplasia have generalized ligamentous laxity of the elbows and can develop substantial instability even though they might have flexion contractures. Pectus deformities can also develop. These individuals also have genu varum that might require operative intervention. Bracing is ineffective in controlling the genu varum in these patients, so if it is progressive and painful, operative intervention is warranted.

Radiographic Features. Compared with individuals who have Schmidt-type dysplasia, those with McKusick-type dysplasia have more shortening and less varus of the long bones. The metaphyseal involvement is seen uniformly throughout and there is a distal fibula overgrowth. Atlantoaxial instability has been reported secondary to odontoid hypoplasia, but it is not common in this population (220).

Orthopaedic Implications. Routine radiographs with flexion/extension every 3 years are warranted. If there is more than 8 mm of movement, prophylactic fusion is indicated. Early observation of scoliosis is warranted; if the scoliosis is progressive or reaches more than 45 degrees, posterior spinal fusion is indicated. If the individual is still skeletally immature, growing rods can be used. Bracing in this population has not been helpful.

Hip dislocation occurs in approximately 3% of the population (220). Traditional treatment can be used with good success, but it must be implemented early and aggressively (217). Lower extremity malalignment can be corrected if it is progressive or causing pain. Later on in life, if premature arthritis develops, total hip and total knee arthroplasty can be done safely with good results.

Schmidt Type. This type is more common than the McKusick type; it is autosomal dominant. The defect is seen in the α-1 chain of type-X collagen (221–223). Histologically, cartilage islands that extend into the metaphyses are visible. Sometimes, it is necessary to differentiate this type of dysplasia from rickets or hypophosphatasia.

Clinical Features. The adult height is minimally shortened. Minimal features with typical normal faces are seen. Patients can develop leg pain later in life, with mild varus at the knees and ankles accompanied by a mild form of short stature, and it may be at this late presentation that it is first diagnosed.

Radiographic Features. Radiographically, the metaphysis of the long bones are wedged and flared and can contain cysts. The physes are slightly widened, there may be mild varus at the knees, and atlantoaxial instability can be seen, although the latter is not very common.

Orthopaedic Implications. These patients do not develop premature arthritis. Occasionally, clinicians may see varus needing operative correction, secondary to progressive pain.

Jansen Metaphyseal Dysplasia. This type of dysplasia is less common than the other two and is an autosomal dominant disorder that is linked to a defect in the receptor for parathyroid hormone and parathyroid hormone–related proteins (224).

Patients with this disorder can develop hypercalcemia and have more pronounced metaphyseal changes than those seen in the Schmidt and McKusick types.

Kozlowski Type. This autosomal dominant disorder is fairly rare. It is characterized by spinal metaphyseal involvement seen in the first few years of life, secondary to short stature, and a progressive kyphosis. Patients with this disorder can have limitation of movement, a Trendelenburg gait, and an early onset of arthritic changes.

Mild platyspondyly is seen, which is in direct contrast to the other three metaphyseal chondrodysplasias previously described. The most visible area to detect metaphyseal dysplasia in the Kozlowski type is in the proximal femur. The bone age of the carpals and tarsals is delayed.

DIAPHYSEAL ACLASIA (HEREDITARY MULTIPLE EXOSTOSES)

Overview. Although solitary exostoses do not qualify as skeletal dysplasias, it is clear that patients with hereditary multiple exostoses (HME) have a generalized disturbance of skeletal growth. The condition has been localized to mutations on chromosomes 8 and 11. The genes involved are referred to as *EXT1* and *EXT2*. The differing locations of mutation account for the phenotypic variability of the condition. Patients affected because of a mutation in *EXT1* have a more severe phenotype (225). These genes produce transmembrane glycoproteins that affect cell signaling, interact with fibroblast growth factor, and affect endochondral development and maturation (226). Most cases of HME are transmitted in an autosomal dominant fashion, but a large number of patients acquire it as a spontaneous mutation. The metaphysis of a person with HME is characterized by thinning of the cortex, innumerable small bumps, and cartilage rests extending into the trabecular bone.

Clinical Features. The condition is not usually diagnosed until the child is 3 to 4 years old, at which time the first exostoses are noted and other features develop. The features become progressively more pronounced until maturity, at which point exostoses should cease to grow. Affected persons are at the low end of normal for stature. The metaphyses are circumferentially enlarged throughout the body, not only in the regions in which there are obvious exostoses. This enlargement gives the child a rather "stocky" appearance, which is then further exaggerated by the appearance of the exostoses. The exostoses may cause soreness when they arise under tendons or in an area vulnerable to contusion, such as the knee or shoulder. The exostoses tend to steal from the longitudinal growth of the long bones. The categories of problems caused by HME are fourfold:

1. Localized pressure on tendons, vessels and nerves, among other places. Peroneal palsy may arise from a lateral exostosis, and it may occur in such a way as to cause brachial plexus compression. Intraspinal lesions have been reported in a substantial minority of patients (227). Pseudoaneurysms may occur.
2. Angular growth of two-bone segments—the arms and forearms. Usually, the thinner of these two bones is more inhibited in its growth than the wider one, so it tethers the growth of the latter. Valgus may develop at the wrist, knee, and ankle. The radial head may subluxate or dislocate.
3. Limb-length inequality. Often, one limb is more involved than the other with exostoses, and it may undergrow as much as 4 cm.
4. Malignant degeneration. Transformation to chondrosarcoma occurs in approximately 5% of patients after maturity (226). It is more likely in *EXT1* than *EXT2* mutations (228). Such change may be signaled by increased growth of an exostosis, or pain over an exostosis. Bone scans every 2 years in adulthood have been advocated as one way to detect this change. Self-examination and periodic orthopaedic examination, with MRI in the case of an apparent change, is another way to follow these patients in adulthood (226).

Radiographic Features. The metaphyses are very wide, and internal irregularities can be seen. The exostoses may be sessile or pedunculated, and have continuity with the main cortex, as do solitary exostoses. Exostoses on the undersurface of the scapula may be identified on conventional radiographs, but they are best evaluated by CT. The femoral necks are usually wide and in valgus (Fig. 7-29). Valgus is much more common than varus at the knee (Fig. 7-30), and the distal

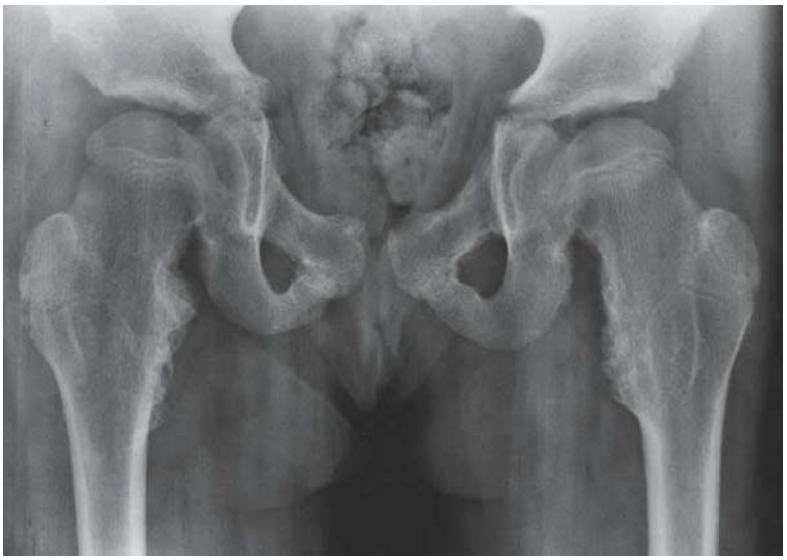


FIGURE 7-29. The hips in diaphyseal aclasia are characterized by broad, irregular femoral necks that are usually in valgus. There are osteochondromas and irregularities in formation of the pelvis also, which can be difficult to monitor over time.

tibial epiphysis may be triangular if the fibula is pulling the ankle into valgus. Radial head subluxation may occur with ulnar shortening, and the resultant carpal subluxation can readily be identified by wrist radiographs.

Orthopaedic Implications. Monitoring in childhood should mostly be done by clinical examination because all bones are affected and the lesions are too numerous to image routinely. Clinicians should perform a brief neurologic examination; check joint range of motion; measure knee, ankle, elbow, and wrist angulation and limb lengths; and remove any exostoses that are causing severe symptoms, but warn the patients that the metaphyseal widening will persist, so the effect on appearance may not match expectations. Removal of lesions impairing radioulnar motion may result in slight increase in range of motion, especially if an exostosis is located on only the ulna but not on the radius (229). Ulnar lengthening may help avert radial head subluxation. However, studies of the function after osteotomies of the forearm show that there is not often functional benefit (229, 230). Hemiepiphysiodesis is a minimally invasive way to correct angulation at the wrist, knee, and ankle (231). Valgus angulation at the distal tibia is correlated with degenerative changes in the long term (232). If the patient is near maturity and needs correction, osteotomy may be indicated. Limb-length inequality can be corrected by the standard methods. Patients with HME are more likely than others to form keloids (233). Some experts recommend screening patients with HME by MRI for intraspinal lesions at least once during growing years (227) (Fig. 7-31).

Patients should be taught to examine themselves for signs of growth after maturity because it may signal malignant degeneration. A bone scan may be a helpful adjunct if a problem is suspected.

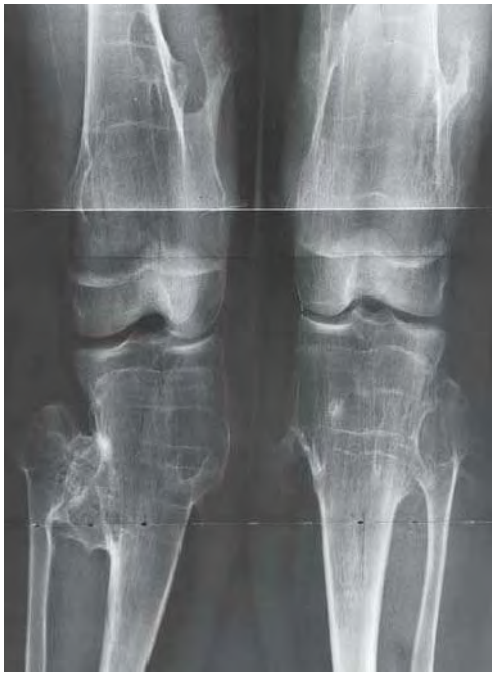


FIGURE 7-30. This figure of the knees in a patient with diaphyseal aclasia best illustrates that this defect is a systemic abnormality of bone formation, rather than a series of discrete tumors. The metaphyses are broad and irregular in the region where the exostoses are located. The knees are developing a valgus alignment because of the short fibulae, as are the ankles (not shown).

DYSCHONDROSTEOSIS (LERI-WEILL SYNDROME)

Overview. Dyschondrosteosis, which was described by Leri and Weill (234) in 1929, is characterized by mild mesomelic short stature (middle segments of the limbs are shortest) (235, 236). This growth disturbance of the middle segments is most notable in the distal radius, which usually develops a Madelung deformity (234, 237, 238). It is inherited in an autosomal dominant fashion, with approximately 50% penetrance (237, 239). The expression is more severe in female patients than in males. It has

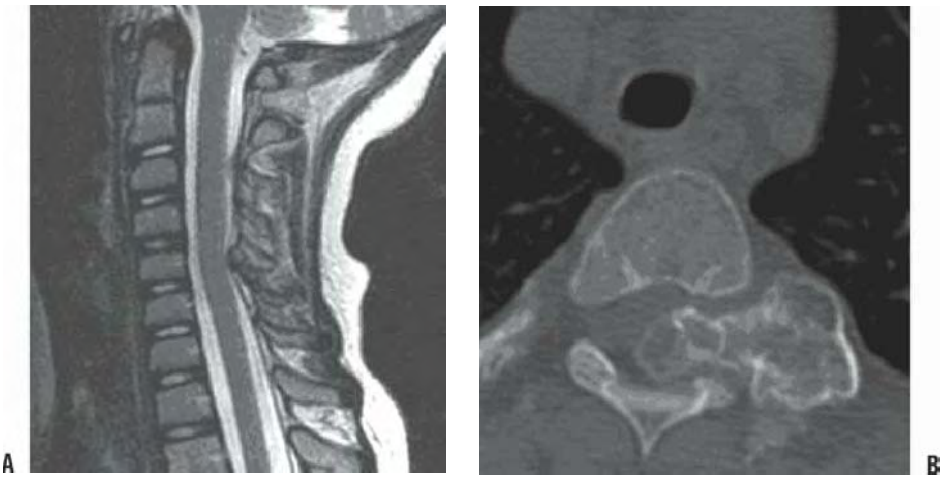


FIGURE 7-31. Two patients with multiple hereditary osteochondromas had severe lesions in the spinal canal that were not visible on conventional radiographs. **A:** MRI scan showing osteochondroma arising from the undersurface of the C5 lamina in one patient. **B:** CT scan showing lesion arising from a rib and invading the spinal canal in another patient. (Figures courtesy of Dr. James Roach.)

been shown to involve a mutation or deletion in the *S*hort-stature *H*omeobox-containing gene *O*n chromosome *X* [*SHOX* (240)], which also causes the short stature seen in Turner syndrome and other causes of short stature (241, 242).

Clinical Features. Patients usually present in juvenile or adolescent years because of short stature, forearm disproportion or deformity, or wrist pain or deformity (243). The deformity of the distal forearm, or Madelung deformity, is characterized by a deficiency of growth of the volar-ulnar portion of the radius. The differential diagnosis of this phenomenon includes Turner syndrome, trauma, Ollier disease, or multiple hereditary exostoses. Most patients begin to experience pain in the wrist during adolescence, and limitation of pronation and supination. A variation on this theme, seen in some patients with dyschondrosteosis, is shortening of both radius and ulna without angulation. The mesomelic shortening also involves the lower extremities, specifically the tibiofibular segments. There, however, angular deformity is not pronounced—only a mild genu varum or an ankle valgus usually exists. Short stature is usually, but not always, a feature; adult height ranges from 135 to 170 cm. In one series of patients, deficiency in growth hormone was found, and stature was increased by growth hormone supplementation (244).

Radiographic Features. Madelung deformity is a failure of development of the volar-ulnar part of the distal radial epiphysis. The distal radial epiphysis develops a triangular appearance and a tilt of joint surface (243) (Fig. 7-32A,B). A physeal bar may be seen on CT at the lunate facet (239). The ulna is subluxated or dislocated dorsally. In contrast to other causes of Madelung deformity, the ulna is as long as, or longer than, the radius (244). The tibia and fibula are short, with the fibula longer than the tibia at the ankle and/or the knee. There may be some degree of genu varum or ankle valgus. Cubitus valgus, hypoplasia of the humeral head, short fourth metacarpal, and coxa valga have all been noted, but rarely do all occur in the same patient.

Orthopaedic Implications. Human growth hormone treatment may produce a sustained response, and patients concerned about short stature may be referred to an endocrinologist for discussion of this treatment (244, 245). Patients who experience wrist pain may be treated initially by a wrist splint and anti-inflammatory agents. If still symptomatic, a reconstruction with a double osteotomy of the distal radius and an ulnar recession can provide good results (246). In one study, this procedure provided improvement in symptoms and clinical appearance, but lunate subluxation, grip strength, and range of motion were minimally influenced (238). Although it has been described, it is unclear whether bar resection can allow normal growth to occur. Osteotomy of the tibia is occasionally indicated to correct genu varum (237).

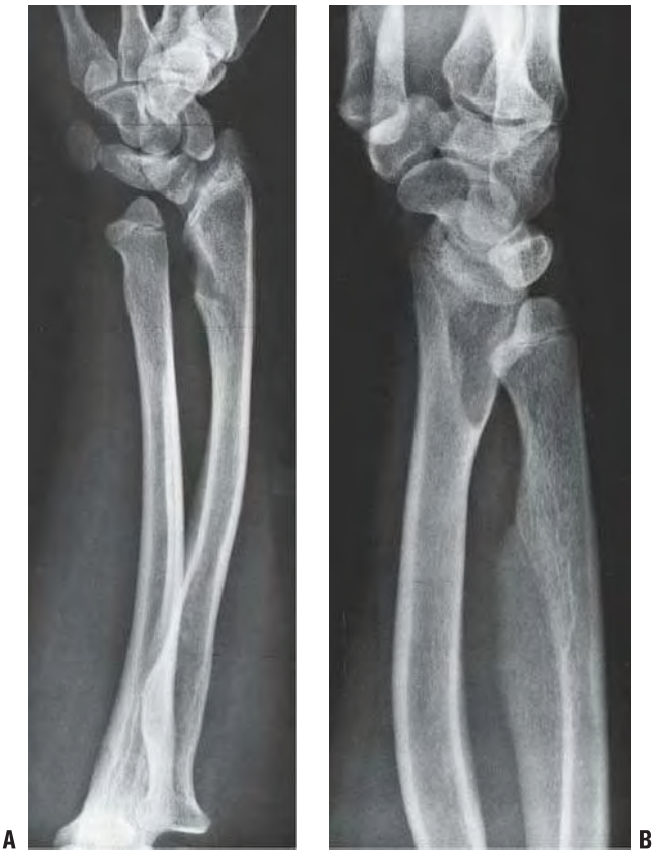


FIGURE 7-32. **A:** Madelung deformity in the forearm of a patient with dyschondrosteosis. **B:** The distal radial epiphysis has a markedly triangular epiphysis, and the ulna is dorsally subluxated.

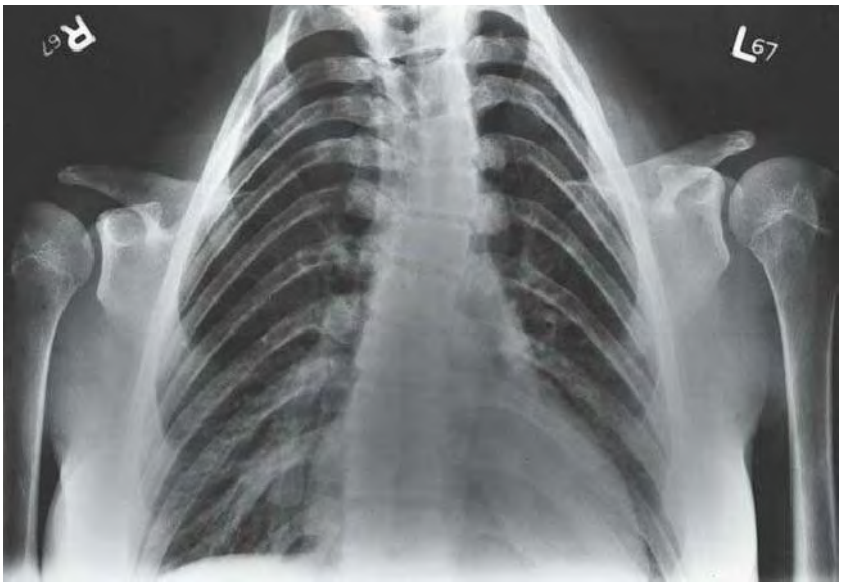


FIGURE 7-33. The clavicles are completely absent in the patient with cleidocranial dysplasia, although in many patients they are merely hypoplastic. There is also a characteristic mild scoliosis and an occult bifid lamina of T2.

CLEIDOCRANIAL DYSPLASIA

Overview. Cleidocranial dysplasia is a true skeletal dysplasia because it affects the growth of many bones in all parts of the skeleton, primarily those of membranous origin. Classic features include a widening of the cranium, and dysplasia of the clavicle and the pelvis (247, 248). The incidence is estimated at 1 per 200,000 (249). It is transmitted as an autosomal dominant condition, and the defect is in the *RUNX2/CFBA1* gene on chromosome 6, which encodes an osteoblast-specific transcription factor required for osteoblast differentiation (250–252). *RUNX2* activity is regulated by mechanical stress (253).

Clinical Features. Although the name suggests that only two bones are affected, there are numerous abnormalities. Patients have mildly to moderately diminished stature, with most male and some female patients below the 5th percentile for age. Mean adult height for males is 64 in. There is bossing in the frontal parietal and occipital regions. The maxillary region is underdeveloped, giving apparent exophthalmos and maxillary micrognathism. Cleft palate and dental abnormalities are common (254–257).

The clavicles are partially or completely absent (256); there is complete absence only 10% of the time (256). This clavicle deficit causes the shoulders to drop and the neck to appear longer. The classic diagnostic feature is that the shoulders can be approximated, which is an ability that helped one college wrestler to escape holds (257). The pelvis is narrow. The hips are occasionally unstable at birth. Coxa vara may occur, causing limitation of abduction and a Trendelenburg gait. There is an increased incidence of scoliosis and, often, a double thoracic curve. Syringomyelia has been reported in several patients with cleidocranial dysplasia and scoliosis (258–260). It has been recommended that MRI be obtained for patients with this dysplasia who have progressive scoliosis.

Radiographic Features. Prenatal radiographic diagnosis may be made on the basis of small or absent clavicles (Fig. 7-33). Nomograms are available for clavicular size during gestation (261). If there is uncertainty, molecular prenatal diagnosis may be performed. If a portion of the clavicle is present, it is usually the medial end. The skull of a newborn with this disorder has the maturation of a 20-week fetus (254). Wormian bones are present in the skull. The anterior fontanel may be open in adulthood (Fig. 7-34). In the vertebral column, spina bifida occulta and spondylolysis are common (262). The pelvis

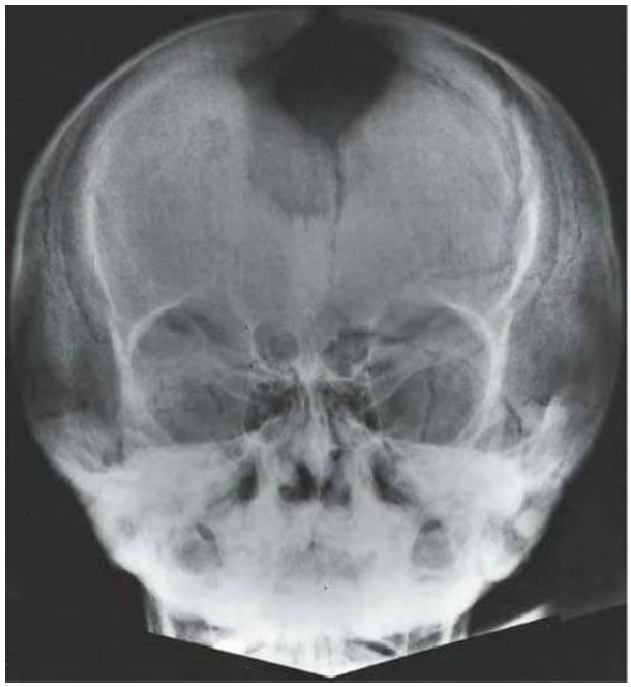


FIGURE 7-34. The skull in this teenager with cleidocranial dysplasia shows an enlarged cranium, widened sutures, and a persistent anterior fontanel.

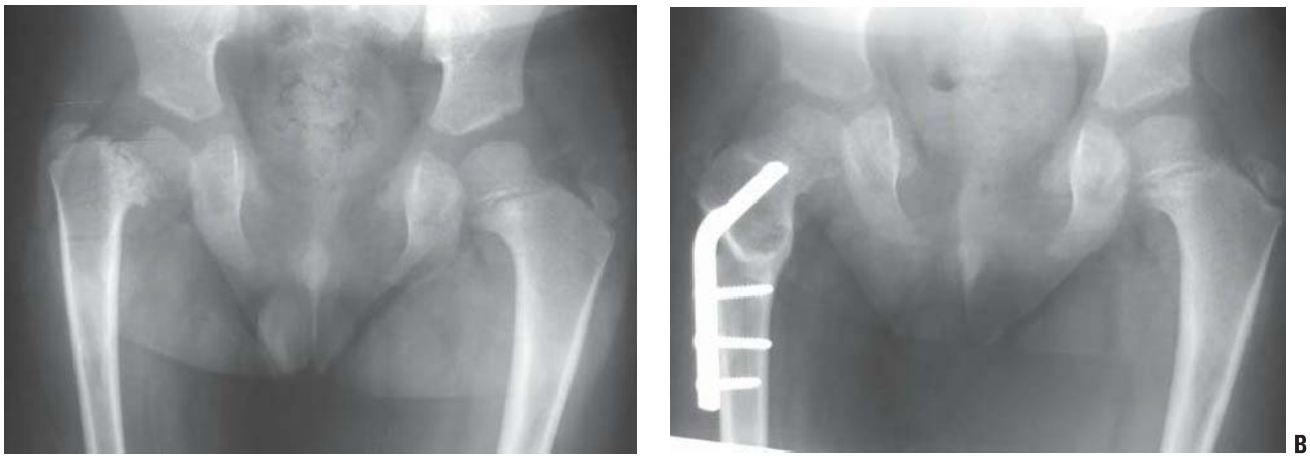


FIGURE 7-35. In cleidocranial dysplasia, the pelvis is narrow, the symphysis pubis is widened, the ischiopubic synchondrosis is unossified, and there may be coxa vara. Preoperative **(A)** and postoperative **(B)** radiographs.

is narrow and shows widening of the triradiate cartilage, delay in pubic ossification, and progressive deformation of the base of the femoral neck into varus (Fig. 7-35A,B), with a triangular metaphyseal fragment typical of coxa vara (263). Skeletal maturation may be delayed.

Orthopaedic Implications. No treatment is indicated for the clavicles. Scapulothoracic arthrodesis has been reported for symptomatic shoulder dysfunction (264). The coxa vara may be treated by valgus-rotational osteotomy if the neck shaft angle is <100 degrees and the patient has a Trendelenburg gait (265). If acetabular dysplasia is present, it should be corrected first. Scoliosis should be treated according to usual guidelines. MRI should be obtained if the curve is progressive because of the increased risk of syringomyelia.

Cesarean section is often necessary. Craniofacial surgery may be helpful in correcting the skull defects, and many dental problems may develop. Affected pregnant women may have cephalopelvic disproportion, especially if the fetus has the same disorder, because of the mother's narrow pelvis and the fetus' enlarged cranium.

LARSEN SYNDROME

Overview. This syndrome was first described in 1950; the six patients were described having the unique combination of hypertelorism, multiple joint dislocations, and focal bone deformities (266). This syndrome has been reported in autosomal dominant and -recessive patterns. The gene is on chromosome 3 near, but distinct from, *COL7A1* locus 4207 (267). The dominant form has been associated with a mutation in filamin B, a cytoskeletal structural protein (268, 269). It remains a rare condition, with an incidence estimated at 1 per 100,000 (270).

Clinical Features. The facial appearance involves widely spaced eyes, a depressed nasal bridge, and a prominent forehead. Cleft palate is common. The thumb has a wide distal phalanx, and the fingers do not taper distally. Hypotonia has also been reported, but it may result from cervical compression (271). Sudden death has been reported (266, 272); most instances were likely a result of exacerbation of this compression. Dislocations most commonly involve the elbows (or radial heads), hips, and knees (Fig. 7-36), followed by the midfoot and shoulders. Characteristic foot deformities involve equinovarus or equinovalgus. Atrial and ventricular septal defects have been reported (267). Within the range of abnormalities just described, every patient with this syndrome is unique in his or her pattern of associated problems.

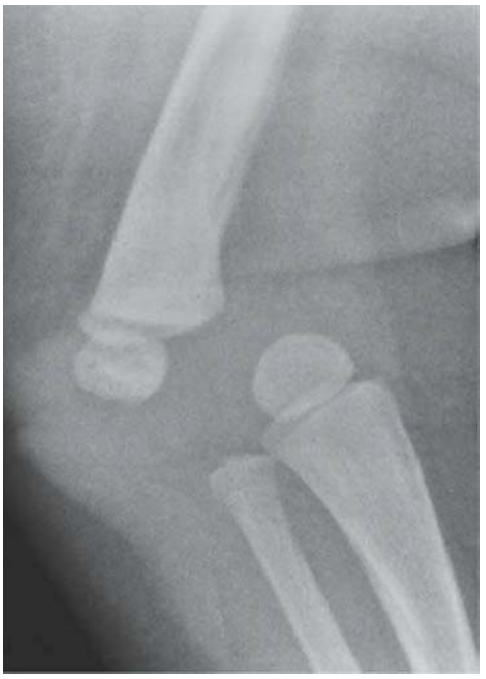
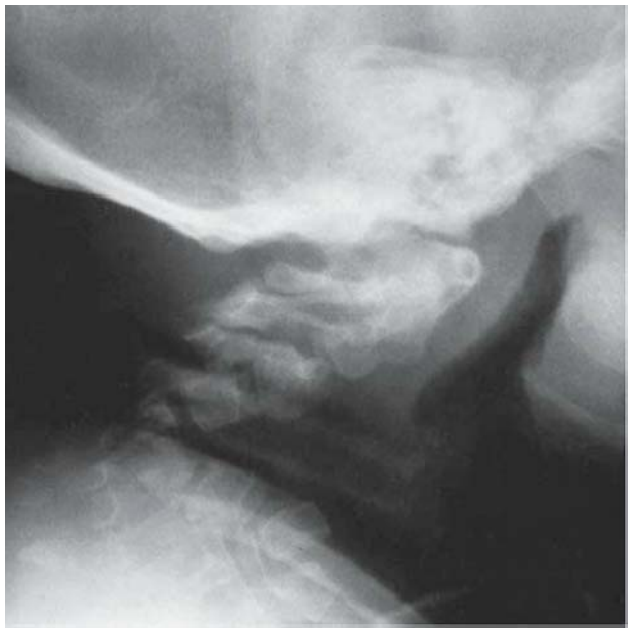
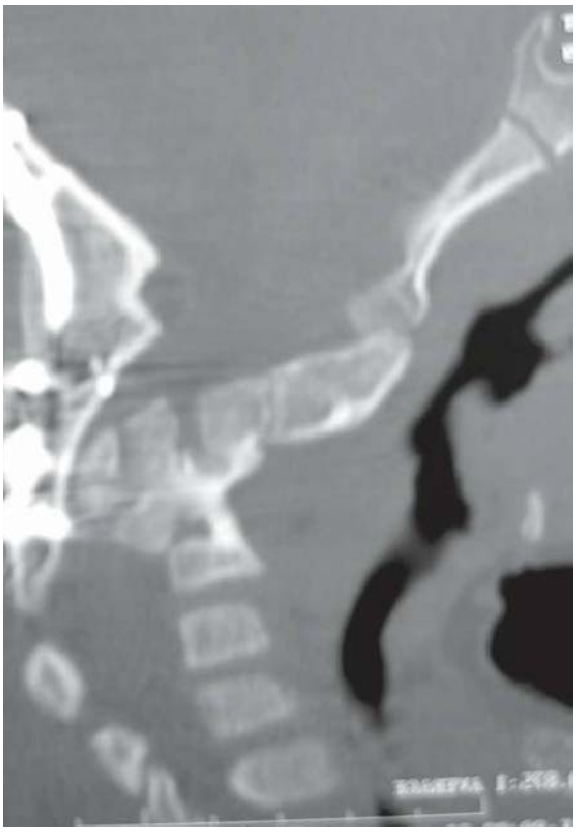


FIGURE 7-36. Congenital anterior knee dislocation is common in Larsen syndrome.

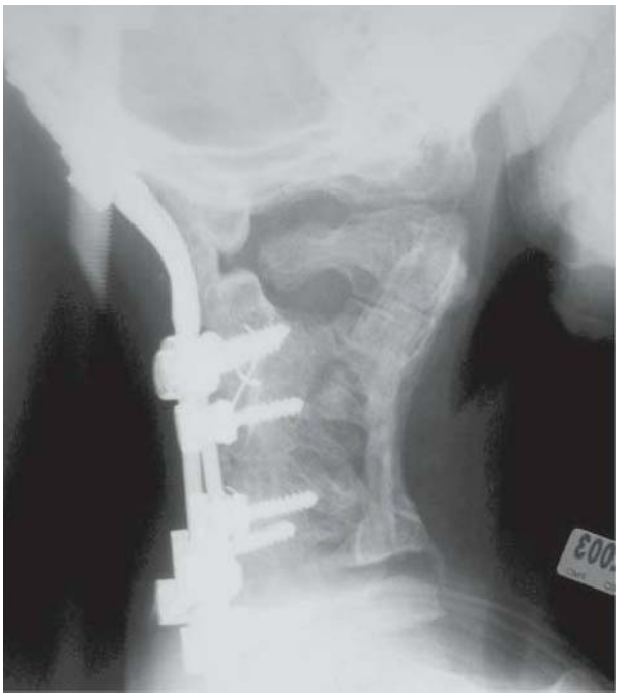
Radiographic Features. There does not appear to be a theme to the radiographic findings in this syndrome. Virtually every patient described, however, has some abnormality in some part of the spine. The cervical spine is the most commonly and severely affected, and spina bifida is very common in that location. Perhaps as a result, the cervical vertebrae may develop progressive kyphosis (Fig. 7-37A–C). The vertebral bodies in this situation, especially C4 and C5, are very hypoplastic. It is not clear whether this vertebral hypoplasia is a result of pressure from the kyphosis, or a separate, coincidental phenomenon that coexists with the posterior element deficiency. The reported incidence of cervical kyphosis ranges from none to 60% (270, 271, 273). Other cervical problems that may occur include atlantoaxial or subaxial instability (273)



A



B



C

FIGURE 7-37. Cervical kyphosis occurs in many patients with Larsen syndrome, in association with spina bifida occulta of this region **(A)**. The disorder is usually progressive **(B)** and may require decompression and fusion if myelopathy from focal kyphosis occurs **(C)**.

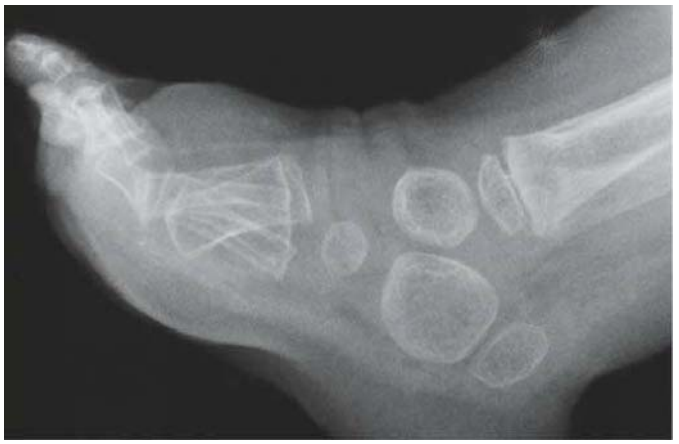


FIGURE 7-38. The feet in Larsen syndrome are usually in equinovarus and show a characteristic accessory calcaneal ossification center.

and spondylolisthesis of vertebrae. The thoracic spine may also manifest spina bifida; scoliosis is seen in many individuals, but it is usually mild and rarely requires treatment (273). In the lumbar spine, spondylolysis, kyphosis, scoliosis, and back pain may occur (273). Sacral spina bifida is common, but no neurologic compromise is reported.

One of the characteristic (although not universal) findings in Larsen syndrome is the presence of accessory calcaneal or carpal ossification centers (Fig. 7-38). Shortened metacarpals are also noted.

Orthopaedic Implications. At the beginning of treatment, the orthopaedic surgeon must rule out the cervical kyphosis that may accompany this syndrome because of the catastrophic complications, such as paraparesis, that have been reported. It may be easy to ascribe any developmental delay to the many other skeletal problems these children have, when in fact the cervical kyphosis may cause a neurologic basis for it. Because spontaneous improvement has not been reported with this kyphosis, as it has been with DD, the involved cervical segments should be fused posteriorly if the kyphosis exceeds 35 to 45 degrees. At this level, posterior fusion alone over the involved segments may be successful and may result in spontaneous correction with growth by acting as a posterior tether. Segmental fixation may be helpful in obtaining and maintaining some correction. If the kyphosis progresses to the point of myelopathy, an anterior corpectomy and fusion may be needed, and anterior growth will not occur (274). If enough iliac crest bone is not available for fusion, tibial bone may be used. After surgery, the patient should be in a brace or cast for 4 to 6 months (271). Laryngotracheomalacia may complicate induction of anesthesia.

The lower extremity problems are usually treated in a sequence beginning with the feet and the knees, and then the hips. Treatment for clubfeet may be started early, because some respond to manipulation and cast treatment with tenotomy. Recurrence is common and should be treated with complete subtalar release and shortening osteotomy or decancellation, as necessary. Knees that are hyperextended or subluxatable may also be treated with casts, but this treatment is unlikely to succeed for patients with complete dislocation who usually require open reduction with V-Y quadricepsplasty, anterior capsulotomy, and release of the anterior portions of the collateral ligaments. A successful result after serial cast treatment and quadriceps tenotomy has been reported (275). If cruciate deficiency leads to persistent anterior instability, reconstruction using parapatellar fascia is usually successful.

Whether to reduce hip dislocations in this condition remains controversial. Some series report that they are resistant to treatment (270, 273), whereas others report some successful results (270, 272). A dislocated hip after failed treatment is less functional than one left untreated. A reasonable approach is to consider treatment of those hips in which the dislocation is not too high and the acetabulum is not too shallow, for patients with otherwise good prospects for activity. The medial approach may be used for infants, but for older children or those with a shallow acetabulum, an anterolateral approach is preferred, with osteotomy or augmentation. If the hip subluxates easily or has a narrow safe zone, the clinician should not hesitate to perform a femoral shortening and derotation. We prefer to begin cast treatment for the feet and knees together, then to operate on the knees if, as usual, they are resistant, then the feet if they are resistant. By that time, the surgeon will have a better idea of the patient's potential and can decide on the most appropriate approach to the hips.

PERINATAL LETHAL SKELETAL DYSPLASIAS

With the increasing use of prenatal diagnostic tests, the orthopaedic surgeon may be questioned about some of the lethal dysplasias that would not otherwise be encountered in practice. These dysplasias are mentioned here to provide some basic information. The combined incidence of lethal dysplasias has been estimated at 15 per 100,000 births in one population. The natural history of these conditions should be considered carefully if one is facing a decision to provide respiratory support.

Thanatophoric dysplasia is characterized by disproportionately small limbs, normal trunk length, a protuberant abdomen, and a large head with frontal bossing. The chest is narrow and the lungs are hypoplastic. The femora are bowed, and their appearance has been likened to old-style telephone receivers. There is phenotypic resemblance to homozygous achondroplasia, and in fact this condition results from a mutation in the same gene, *FGFR3*. Only a few children with this disorder have been reported to survive past 2 years old, even with full respiratory support (1).

Achondrogenesis is characterized by a short trunk, large head, distended abdomen, and severely underdeveloped limbs. It has been subclassified into four types. It may be autosomal dominant or recessive. Achondrogenesis type I results from a mutation in the *DTDST*.

Survival beyond birth is very rare. Currently, there is no treatment available for prolonging the lifespan. Atelosteogenesis,

of which there are two types, is characterized by dislocations of large joints and, in some cases, clubfeet. Midface hypoplasia, micrognathism, and a narrow chest are also seen. At least one of the two types results from a mutation in the *DTDST.*

Short-rib-polydactyly syndrome is autosomal recessive and is characterized by polydactyly, which is classically postaxial but may be preaxial, short horizontal ribs, and defects in the kidneys and lungs.

Osteogenesis imperfecta type II is arguably a skeletal dysplasia. Because of the poor prognosis, some of these children have been treated by bone marrow transplants, with reportedly prolonged survival (276).

Conditions that may be, but are not always, fatal in the neonatal period include achondroplasia (homozygous form), rhizomelic chondrodysplasia punctata, camptomelic dysplasia, and a congenital form of hypophosphatasia.

APPENDIX 1: SUMMARIES OF IMPORTANT SKELETAL DYSPLASIAS

Achondroplasia

Genetic Transmission: Autosomal dominant, but most patients have *de novo* mutation

Gene Defect: Highly uniform mutation in *FGFR3* (gain of function)

Key Clinical Features: Stenosis of spine (especially lumbar) or foramen magnum; thoracolumbar kyphosis; genu varum

Key Treatment Points: Brace thoracolumbar kyphosis if more than 2 years old; decompress symptomatic stenosis; cervical spine is stable; osteotomies for genu varum if symptomatic.

Hypochondroplasia

Genetic Transmission: Autosomal dominant

Genetic Defect: Most in *FGFR3* (different domain)

Key Clinical Features: Mild short stature; mild spinal stenosis

Key Treatment Implications: May benefit from growth hormone and/or limb lengthening

Metatropic Dysplasia

Genetic Transmission: Autosomal dominant or recessive

Genetic Defects: Unknown

Key Clinical Features: Infant mortality risk; coccygeal tail, enlarged metaphyses, and contractures; kyphoscoliosis

Key Treatment Points: Rule out cervical instability; possible role for spine fusion.

Chondroectodermal Dysplasia

Genetic Transmission: Autosomal recessive

Genetic Defect: *EVC* with defective maturation or endochondral ossification

Key Clinical Features: Cardiac defects, teeth and nails abnormal, postaxial polydactyly; genu valgus, external femoral rotation

Key Treatment Points: Lateral knee subluxation and depression of tibial plateau are pathognomonic features.

Diastrophic Dysplasia

Genetic Transmission: Autosomal recessive

Genetic Defect: Diastrophic dysplasia sulfate transporter abnormal in all cartilage

Key Clinical Features: "Hitchhiker" thumbs and "cauliflower" ears; joint contractures, cervical kyphosis; scoliosis; DJD, equinovarus feet

Key Treatment Points: Monitor cervical kyphosis, fuse if increasing; correct feet; treat scoliosis, DJD

Kneist Dysplasia

Genetic Transmission: Autosomal dominant

Genetic Defect: Type-II collagen, *COL2A1,* usually exons 12 to 24

Key Clinical Features: Large stiff joints; equinovarus; risk retinal detachment and odontoid hypoplasia

Key Treatment Points: Severe scoliosis and epiphyseal dysplasia occur.

SED Congenita

Genetic Transmission: Autosomal dominant

Genetic Defect: Type-II collagen, *COL2A1*

Key Clinical Features: Severely short stature, C1–C2 instability, scoliosis, hip dysplasia, possible equinovarus foot

Key Treatment Points: Rule out cervical instability. Monitor for scoliosis.

SED Tarda

Genetic Transmission: X-linked most common

Genetic Defect: Type-II collagen (*COL2A1*) or SEDLIN

Key Clinical Features: Hip, back, or knee pain develop in later childhood/adolescence; mild scoliosis

Key Treatment Points: Monitor for scoliosis and kyphosis. Premature DJD may occur.

Pseudoachondroplasia

Genetic Transmission: Autosomal dominant

Genetic Defect: COMP

Key Clinical Features: Ligamentous laxity, windswept knees; size normal at birth, but falls behind

Key Treatment Points: Correct windswept knees; screen for cervical instability. Degenerative changes in hips and knees may occur in adulthood.

Multiple Epiphyseal Dysplasia

Genetic Transmission: Autosomal dominant

Genetic Defect: COMP, other forms from type-IX collagen or Maitrilin 3

Key Clinical Features: Near-normal stature; epiphyseal deformation of large joints with symptoms in late childhood or adulthood

Key Treatment Points: Observation versus acetabular coverage in childhood; joint replacement in adulthood

Chondrodysplasia Punctata

Genetic Transmission: Multiple

Genetic Defect: Rhizomelic form from peroxisomal enzyme deficiency; other forms affect cholesterol synthesis

Key Clinical Features: Neonatal stippling of epiphyses; early mortality (most rhizomelic patients)

Key Treatment Points: Evaluate and treat atlantoaxial instability, congenital scoliosis, coxa vara.

Metaphyseal Chondrodysplasias

Genetic Transmission and Defect: McKusick, autosomal recessive; Schmidt, Jansen, and Kozlowski, autosomal dominant

Key Clinical Features: Metaphyseal irregularities with normal epiphyses; genu varum, mild short stature, fine sparse hair; immune and gastrointestinal disorders in McKusick type

Key Treatment Points: Rule out rare atlantoaxial instability; correct genu varum if severe; monitor medical problems in McKusick type.

Diaphyseal Aclasia (Multiple Osteocartilaginous Exostosis)

Genetic Transmission: Autosomal dominant

Genetic Defect: *EXT1* and *EXT2* gene mutations found on chromosomes 8 and 11, respectively

Key Clinical Features: Short stature, impingement on tendons and nerves, angular deformities, limb-length inequality, malignant degeneration

Key Treatment Points: Monitor for growth disturbances, remove symptomatic exostoses, educate about signs of slight malignant degeneration, monitor spine

Dyschondrosteosis (Leri-Weill Syndrome)

Genetic Transmission: Autosomal dominant

Genetic Mutation: Short stature homeobox gene on chromosome X(*SHOX*)

Key Clinical Features: Mild mesomelic short stature, mild knee angulation, bilateral Madelung deformities

Key Treatment Points: Osteotomies may be indicated to correct forearm deformities.

Cleidocranial Dysplasia

Genetic Transmission: Autosomal dominant

Genetic Defect: Defect in human *RUNX2* (*CBFA1*) gene

Key Clinical Features: Widened cranium, clavicles partially or completely absent, unossified pubic rami; hip abnormalities

Key Treatment Points: Hip surgery for dysplasia or varus; care of dental, cranial, and obstetric problems

Larsen Syndrome

Genetic Transmission: Autosomal dominant or recessive

Genetic Defect: Defect in filamin B, a cytoskeletal protein

Key Clinical Features: Widely spaced eyes, depressed nasal bridge, multiple joint dislocations, cervical kyphosis

Key Treatment Points: Screen for, and aggressively treat, cervical kyphosis. Joint dislocations treated according to standard principles.

REFERENCES

1. Beighton P, ed. *McKusick's Heritable Disorders of Connective Tissue.* St. Louis, MO: Mosby, 1993.
2. Rimoin DL, Cohn D, Krakow D, et al. The skeletal dysplasias: clinical-molecular correlations. *Ann N Y Acad Sci* 2007;1117:302.
3. Boyadjiev SA, Jabs EW. Online Mendelian Inheritance in Man (OMIM) as a knowledge base for human developmental disorders. *Clin Genet* 2000;57:253.
4. Beighton P, Giedion A, Gorlin R, et al. International classification of osteochondrodysplasias. *Am J Med Genet* 1992;44:223.
5. Dreyer SD, Zhou G, Lee B. The long and the short of it: developmental genetics of the skeletal dysplasias. *Clin Genet* 1998;54:464.
6. Walker BA, Scott CI, Hall JG, et al. Diastrophic dwarfism. *Medicine (Baltimore)* 1972;51:41.
7. Unger S. A genetic approach to the diagnosis of skeletal dysplasia. *Clin Orthop Relat Res* 2002;401:32.
8. Gollust SE, Thompson RE, Gooding HC, et al. Living with achondroplasia in an average-sized world: an assessment of quality of life. *Am J Med Genet A* 2003;120:447.
9. Tobias JD. Anesthetic implications of Larsen syndrome. *J Clin Anesth* 1996;8:255.
10. Bethem D, Winter RB, Lutter L, et al. Spinal disorders of dwarfism. Review of the literature and report of eighty cases. *J Bone Joint Surg Am* 1981;63:1412.
11. Bethem D, Winter RB, Lutter L. Disorders of the spine in diastrophic dwarfism. A discussion of nine patients and review of the literature. *J Bone Joint Surg Am* 1980;62:529.
12. Ain MC, Chaichana KL, Schkrohowsky JG. Retrospective study of cervical arthrodesis in patients with various types of skeletal dysplasia. *Spine (Phila Pa 1976)* 2006;31:E169.
13. Aldegheri R. Distraction osteogenesis for lengthening of the tibia in patients who have limb-length discrepancy or short stature. *J Bone Joint Surg Am* 1999;81:624.
14. Dietz FR, Mathews KD. Update on the genetic bases of disorders with orthopaedic manifestations. *J Bone Joint Surg Am* 1996;78:1583.
15. Hall JG. The natural history of achondroplasia. *Basic Life Sci* 1988;48:3.
16. Horton WA. Fibroblast growth factor receptor 3 and the human chondrodysplasias. *Curr Opin Pediatr* 1997;9:437.
17. Muenke M, Schell U. Fibroblast-growth-factor receptor mutations in human skeletal disorders. *Trends Genet* 1995;11:308.
18. Seino Y, Moriwake T, Tanaka H, et al. Molecular defects in achondroplasia and the effects of growth hormone treatment. *Acta Paediatr Suppl* 1999;88:118.
19. 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.
20. Wynne-Davies R, Walsh WK, Gormley J. Achondroplasia and hypochondroplasia. Clinical variation and spinal stenosis. *J Bone Joint Surg Br* 1981;63:508.
21. Giudicelli MD, Serazin V, Le Sciellour CR, et al. Increased achondroplasia mutation frequency with advanced age and evidence for G1138A mosaicism in human testis biopsies. *Fertil Steril* 2008;89:1651.
22. McKeand J, Rotta J, Hecht JT. Natural history study of pseudoachondroplasia. *Am J Med Genet* 1996;63:406.
23. Maynard JA, Ippolito EG, Ponseti IV, et al. Histochemistry and ultrastructure of the growth plate in achondroplasia. *J Bone Joint Surg Am* 1981;63:969.
24. Ponseti IV. Skeletal growth in achondroplasia. *J Bone Joint Surg Am* 1970;52:701.
25. Nehme AME, Riseborough EJ, Tredwell SJ. Skeletal growth and development of the achondroplastic dwarf. *Clin Orthop Relat Res* 1976;116:8.
26. Bailey JA II. Orthopaedic aspects of achondroplasia. *J Bone Joint Surg Am* 1970;52:1285.

27. Pauli RM, Breed A, Horton VK, et al. Prevention of fixed, angular kyphosis in achondroplasia. *J Pediatr Orthop* 1997;17:726.
28. Mahomed NN, Spellmann M, Goldberg MJ. Functional health status of adults with achondroplasia. *Am J Med Genet* 1998;78:30.
29. Wynn J, King TM, Gambello MJ, et al. Mortality in achondroplasia study: a 42-year follow-up. *Am J Med Genet A* 2007;143:2502.
30. Scott CI Jr. Achondroplastic and hypochondroplastic dwarfism. *Clin Orthop Relat Res* 1976;114:18.
31. Ireland PJ, Johnson S, Donaghey S, et al. Developmental milestones in infants and young Australasian children with achondroplasia. *J Dev Behav Pediatr* 2010;31:41.
32. Trotter TL, Hall JG. Health supervision for children with achondroplasia. *Pediatrics* 2005;116:771.
33. Keiper GL Jr, Koch B, Crone KR. Achondroplasia and cervicomedullary compression: prospective evaluation and surgical treatment. *Pediatr Neurosurg* 1999;31:78.
34. Pauli RM, Horton VK, Glinski LP, et al. Prospective assessment of risks for cervicomedullary-junction compression in infants with achondroplasia. *Am J Hum Genet* 1995;56:732.
35. Pierre-Kahn A, Hirsch JF, Renier D, et al. Hydrocephalus and achondroplasia. A study of 25 observations. *Childs Brain* 1980;7:205.
36. Todorov AB, Scott CI Jr, Warren AE, et al. Developmental screening tests in achondroplastic children. *Am J Med Genet* 1981;9:19.
37. Bagley CA, Pindrik JA, Bookland MJ, et al. Cervicomedullary decompression for foramen magnum stenosis in achondroplasia. *J Neurosurg* 2006;104:166.
38. Hecht JT, Nelson FW, Butler IJ, et al. Computerized tomography of the foramen magnum: achondroplastic values compared to normal standards. *Am J Med Genet* 1985;20:355.
39. Hecht JT, Horton WA, Reid CS, et al. Growth of the foramen magnum in achondroplasia. *Am J Med Genet* 1989;32:528.
40. Shirley ED, Ain MC. Achondroplasia: manifestations and treatment. *J Am Acad Orthop Surg* 2009;17:231.
41. Waters KA, Everett F, Sillence DO, et al. Treatment of obstructive sleep apnea in achondroplasia: evaluation of sleep, breathing, and somatosensory-evoked potentials. *Am J Med Genet* 1995;59:460.
42. Zucconi M, Weber G, Castronovo V, et al. Sleep and upper airway obstruction in children with achondroplasia. *J Pediatr* 1996; 129:743.
43. Reynolds KK, Modaff P, Pauli RM. Absence of correlation between infantile hypotonia and foramen magnum size in achondroplasia. *Am J Med Genet* 2001;101:40.
44. Lutter LD, Longstein JE, Winter RB, et al. Anatomy of the achondroplastic lumbar canal. *Clin Orthop Relat Res* 1977;126:139.
45. Lutter LD, Langer LO. Neurological symptoms in achondroplastic dwarfs—surgical treatment. *J Bone Joint Surg Am* 1977;59:87.
46. Srikumaran U, Woodard EJ, Leet AI, et al. Pedicle and spinal canal parameters of the lower thoracic and lumbar vertebrae in the achondroplast population. *Spine (Phila Pa 1976)* 2007;32:2423.
47. Collins WO, Choi SS. Otolaryngologic manifestations of achondroplasia. *Arch Otolaryngol Head Neck Surg* 2007;133:237.
48. Hoover-Fong JE, Schulze KJ, McGready J, et al. Age-appropriate body mass index in children with achondroplasia: interpretation in relation to indexes of height. *Am J Clin Nutr* 2008;88:364.
49. Hecht JT, Francomano CA, Horton WA, et al. Mortality in achondroplasia. *Am J Hum Genet* 1987;41:454.
50. Horton WA, Hecht JT, Hood OJ, et al. Growth hormone therapy in achondroplasia. *Am J Med Genet* 1992;42:667.
51. Tanaka H, Kubo T, Yamate T, et al. Effect of growth hormone therapy in children with achondroplasia: growth pattern, hypothalamic-pituitary function, and genotype. *Eur J Endocrinol* 1998;138:275.
52. Berkowitz RG, Grundfast KM, Scott C, et al. Middle ear disease in childhood achondroplasia. *Ear Nose Throat J* 1991;70:305.
53. Glass L, Shapiro I, Hodge SE, et al. Audiological findings of patients with achondroplasia. *Int J Pediatr Otorhinolaryngol* 1981;3:129.
54. Stanley G, McLoughlin S, Beals RK. Observations on the cause of bowlegs in achondroplasia. *J Pediatr Orthop* 2002;22:112.
55. Kopits SE. Correction of bowleg deformity in achondroplasia. *Johns Hopkins Med J* 1980;146:206.
56. Lee ST, Song HR, Mahajan R, et al. Development of genu varum in achondroplasia. Relation to fibular overgrowth. *J Bone Joint Surg Br* 2007;89:57.
57. Ain MC, Shirley ED, Pirouzmanesh A, et al. Genu varum in achondroplasia. *J Pediatr Orthop* 2006;26:375.
58. Beals RK, Stanley G. Surgical correction of bowlegs in achondroplasia. *J Pediatr Orthop B* 2005;14:245.
59. Bober M, Johnson C, Nicholson L, et al. Scott sign: a clinical measure of ligamentous laxity in achondroplastic infants. *Am J Med Genet A* 2008;146:2291.
60. Dietz FR, Weinstein SL. Spike osteotomy for angular deformities of the long bones in children. *J Bone Joint Surg Am* 1988;70:848.
61. Rab GT. Oblique tibial osteotomy for Blount's disease (tibia vara). *J Pediatr Orthop* 1988;8:715.
62. Paley D, Tetsworth K. Mechanical axis deviation of the lower limbs. Preoperative planning of multiapical frontal plane angular and bowing deformities of the femur and tibia. *Clin Orthop Relat Res* 1992; 280:65.
63. Aldegheri R. Femoral callotasis. *J Pediatr Orthop B* 1997;6:42.
64. Kashiwagi N, Suzuki S, Seto Y, et al. Bilateral humeral lengthening in achondroplasia. *Clin Orthop Relat Res* 2001;391:251.
65. Aldegheri R, Dall'Oca C. Limb lengthening in short stature patients. *J Pediatr Orthop B* 2001;10:238.
66. Park HW, Kim HS, Hahn SB, et al. Correction of lumbosacral hyperlordosis in achondroplasia. *Clin Orthop Relat Res* 2003;414:242.
67. Siebens AA, Hungerford DS, Kirby NA. Curves of the achondroplastic spine: a new hypothesis. *Johns Hopkins Med J* 1978;142:205.
68. Kopits SE. Orthopedic complications of dwarfism. *Clin Orthop Relat Res* 1976;114:153.
69. Tolo VT. Surgical treatment of kyphosis in achondroplasia. In: Nicoletti B, Kopits SE, Ascani E, et al., eds. *Human Achondroplasia: A Multidisciplinary Approach.* New York, NY: Plenum Press, 1988: 257.
70. Ain MC, Shirley ED. Spinal fusion for kyphosis in achondroplasia. *J Pediatr Orthop* 2004;24:541.
71. Sciubba DM, Noggle JC, Marupudi NI, et al. Spinal stenosis surgery in pediatric patients with achondroplasia. *J Neurosurg* 2007;106:372.
72. Ain MC, Chang TL, Schkrohowsky JG. Laminectomies and achondroplasia: does body mass index influence surgical outcomes? *Am J Med Genet A* 2007;143A:1032.
73. Schkrohowsky JG, Carlisle ES, Chaichana KL, et al. Intraoperative dural tears secondary to lumbar decompression in adults with achondroplasia. *Neurosurg Q* 2006;16:92.
74. Ain MC, Shirley ED, Pirouzmanesh A, et al. Postlaminectomy kyphosis in the skeletally immature achondroplast. *Spine (Phila Pa 1976)* 2006;31:197.
75. Ain MC, Browne JA. Spinal arthrodesis with instrumentation for thoracolumbar kyphosis in pediatric achondroplasia. *Spine (Phila Pa 1976)* 2004;29:2075.
76. Farmer KW, Brinkley MF, Skolasky RL, et al. Lumbar fusion in achondroplasia. Does fusion to the sacrum affect function? *J Pediatr Orthop* 2009;29:476.
77. Ain MC, Chang TL, Schkrohowsky JG, et al. Rates of perioperative complications associated with laminectomies in patients with achondroplasia. *J Bone Joint Surg Am* 2008;90:295.
78. Horton WA. Evolution of the bone dysplasia family [editorial comment]. *Am J Med Genet* 1996;63:4.
79. Rousseau F, Bonaventure J, Legeai-Mallet L, et al. Clinical and genetic heterogeneity of hypochondroplasia. *J Med Genet* 1996;33:749.
80. Cohen MM Jr. Some chondrodysplasias with short limbs: molecular perspectives. *Am J Med Genet* 2002;112:304.

81. Su WC, Kitagawa M, Xue N, et al. Activation of Stat1 by mutant fibroblast growth-factor receptor in thanatophoric dysplasia type II dwarfism. *Nature* 1997;386:288.
82. Beals RK. Hypochondroplasia. A report of five kindreds. *J Bone Joint Surg Am* 1969;51:728.
83. Wynne-Davies R, Patton MA. The frequency of mental retardation in hypochondroplasia [letter to the editor]. *J Med Genet* 1991;28:644.
84. Hall BD, Spranger J. Hypochondroplasia: clinical and radiological aspects in 39 cases. *Radiology* 1979;133:95.
85. Oberklaid F, Danks DM, Jensen F, et al. Achondroplasia and hypochondroplasia. Comments on frequency, mutation rate, and radiological features in skull and spine. *J Med Genet* 1979;16:140.
86. Ramaswami U, Hindmarsh PC, Brook CG. Growth hormone therapy in hypochondroplasia. *Acta Paediatr Suppl* 1999;88:116.
87. Rimoin DL, Siggers DC, Lachman RS, et al. Metatropic dwarfism, the Kniest syndrome and the pseudoachondroplastic dysplasias. *Clin Orthop Relat Res* 1976;114:70.
88. Genevieve D, Le Merrer M, Feingold J, et al. Revisiting metatropic dysplasia: presentation of a series of 19 novel patients and review of the literature. *Am J Med Genet A* 2008;146:992.
89. Boden SD, Kaplan FS, Fallon MD, et al. Metatropic dwarfism: uncoupling of endochondral and perichondral growth. *J Bone Joint Surg Am* 1987;69:174.
90. Shohat M, Lachman R, Rimoin DL. Odontoid hypoplasia with vertebral cervical subluxation and ventriculomegaly in metatropic dysplasia. *J Pediatr* 1989;114:239.
91. Leet AI, Sampath JS, Scott CI Jr, et al. Cervical spinal stenosis in metatropic dysplasia. *J Pediatr Orthop* 2006;26:347.
92. Beck M, Roubicek M, Rogers JG, et al. Heterogeneity of metatropic dysplasia. *Eur J Pediatr* 1983;140:231.
93. Maroteaux P, Spranger J, Wiedemann HR. Metatrophic dwarfism. *Arch Kinderheilkd* 1966;173:211.
94. Gordienko IY, Grechanina EY, Sopko NI, et al. Prenatal diagnosis of osteochondrodysplasias in high risk pregnancy. *Am J Med Genet* 1996;63:90.
95. Manouvrier-Hanu S, Devisme L, Zelasko MC, et al. Prenatal diagnosis of metatropic dwarfism. *Prenat Diagn* 1995;15:753.
96. Ellis RWB, Van Creveld S. A syndrome characterized by ectodermal dysplasia, polydactyly, chondro-dysplasia and congenital morbus cordis. Report of three cases. *Arch Dis Child* 1940;15:65.
97. Ide SE, Ortiz de Luna RI, Francomano CA, et al. Exclusion of the MSX1 homeobox gene as the gene for the Ellis van Creveld syndrome in the Amish. *Hum Genet* 1996;98:572.
98. Polymeropoulos MH, Ide SE, Wright M, et al. The gene for the Ellis-van Creveld syndrome is located on chromosome 4p16. *Genomics* 1996;35:1.
99. McKusick VA. Ellis-van Creveld syndrome and the Amish. *Nat Genet* 2000;24:203.
100. Baujat G, Le Merrer M. Ellis-Van Creveld syndrome. *Orphanet J Rare Dis* 2007;2:27.
101. Kruse RW, Bowen JR, Heithoff S. Oblique tibial osteotomy in the correction of tibial deformity in children. *J Pediatr Orthop* 1989;9:476.
102. Qureshi F, Jacques SM, Evans MI, et al. Skeletal histopathology in fetuses with chondroectodermal dysplasia (Ellis-van Creveld syndrome). *Am J Med Genet* 1993;45:471.
103. McKusick VA, Egeland JA, Eldridge R, et al. Dwarfism in the Amish I. The Ellis-Van Creveld syndrome. *Bull Johns Hopkins Hosp* 1964;115:306.
104. Kaitila II, Leisti JT, Rimoin DL. Mesomelic skeletal dysplasias. *Clin Orthop Relat Res* 1976;114:94.
105. Pinelli G, Cottafava F, Senes FM, et al. Ellis-Van Creveld syndrome: description of four cases. Orthopaedic aspects. *Ital J Orthop Traumatol* 1990;16:113.
106. Hollister DW, Lachman RS. Diastrophic dwarfism. *Clin Orthop Relat Res* 1976;114:61.
107. Ryoppy S, Poussa M, Merikanto J, et al. Foot deformities in diastrophic dysplasia. An analysis of 102 patients. *J Bone Joint Surg Am* 1992;74:441.
108. Remes VM, Hastbacka JR, Poussa MS, et al. Does genotype predict development of the spinal deformity in patients with diastrophic dysplasia? *Eur Spine J* 2002;11:327.
109. Hastbacka 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.
110. Hastbacka J, Sistonen P, Kaitila I, et al. A linkage map spanning the locus for diastrophic dysplasia (DTD). *Genomics* 1991;11:968.
111. Superti-Furga A, Rossi A, Steinmann B, et al. A chondrodysplasia family produced by mutations in the diastrophic dysplasia sulfate transporter gene: genotype/phenotype correlations. *Am J Med Genet* 1996;63:144.
112. Lamy M, Maroteaux P. Diastrophic nanism. *Presse Med* 1960;68:1977.
113. Qureshi F, Jacques SM, Johnson SF, et al. Histopathology of fetal diastrophic dysplasia. *Am J Med Genet* 1995;56:300.
114. Godbersen GS, Hosenfeld D, Pankau R. Diastrophic dysplasia. A congenital syndrome with remarkable changes of the external ear and stridor. *HNO* 1990;38:256.
115. Crockett MM, Carten MF, Hurko O, et al. Motor milestones in children with diastrophic dysplasia. *J Pediatr Orthop* 2000;20:437.
116. Poussa M, Merikanto J, Ryoppy S, et al. The spine in diastrophic dysplasia. *Spine (Phila Pa 1976)* 1991;16:881.
117. Herring JA. The spinal disorders in diastrophic dwarfism. *J Bone Joint Surg Am* 1978;60:177.
118. Remes V, Marttinen E, Poussa M, et al. Cervical kyphosis in diastrophic dysplasia. *Spine (Phila Pa 1976)* 1999;24:1990.
119. Kash IJ, Sane SM, Samaha FJ, et al. Cervical cord compression in diastrophic dwarfism. *J Pediatr* 1974;84:862.
120. Tolo VT. Spinal deformity in skeletal dysplasias. In: Weinstein SL, ed. *The Pediatric Spine: Principles and Practice.* New York, NY: Raven Press, 1994:369.
121. Vaara P, Peltonen J, Poussa M, et al. Development of the hip in diastrophic dysplasia. *J Bone Joint Surg Br* 1998;80:315.
122. Weiner DS, Jonah D, Kopits S. The 3-dimensional configuration of the typical foot and ankle in diastrophic dysplasia. *J Pediatr Orthop* 2008;28:60.
123. Horton WA, Rimoin DL, Lachman RS, et al. The phenotypic variability of diastrophic dysplasia. *J Pediatr* 1978;93:609.
124. Merrill KD, Schmidt TL. Occipitoatlantal instability in a child with Kniest syndrome. *J Pediatr Orthop* 1989;9:338.
125. Horton WA, Hall JG, Scott CI, et al. Growth curves for height for diastrophic dysplasia, spondyloepiphyseal dysplasia congenita, and pseudoachondroplasia. *Am J Dis Child* 1982;136:316.
126. Makitie O, Kaitila I. Growth in diastrophic dysplasia. *J Pediatr* 1997;130:641.
127. Remes V, Poussa M, Lonnqvist T, et al. Walking ability in patients with diastrophic dysplasia: a clinical, electroneurophysiological, treadmill, and MRI analysis. *J Pediatr Orthop* 2004;24:546.
128. Remes VM, Marttinen EJ, Poussa MS, et al. Cervical spine in patients with diastrophic dysplasia—radiographic findings in 122 patients. *Pediatr Radiol* 2002;32:621.
129. Remes V, Poussa M, Peltonen J. Scoliosis in patients with diastrophic dysplasia: a new classification. *Spine (Phila Pa 1976)* 2001;26:1689.
130. Ain MC, Andres BM, Somel DS, et al. Total hip arthroplasty in skeletal dysplasias: patient selection, preoperative planning, and operative techniques. *J Arthroplasty* 2004;19:1.
131. Helenius I, Remes V, Tallroth K, et al. Total hip arthroplasty in diastrophic dysplasia. *J Bone Joint Surg Am* 2003;85:441.
132. Helenius I, Remes V, Lohman M, et al. Total knee arthroplasty in patients with diastrophic dysplasia. *J Bone Joint Surg Am* 2003;85:2097.
133. Gilbert-Barnes E, Langer LO Jr, Opitz JM, et al. Kniest dysplasia: radiologic, histopathological, and scanning electron microscopic findings. *Am J Med Genet* 1996;63:34.
134. Kneist W. Zur abgrenzung der dysostosis endochondralis von der chondrodystrophie. *Z Kinder* 1952;70:633.
135. Spranger J, Winterpacht A, Zabel B. Kniest dysplasia: Dr. W. Kniest, his patient, the molecular defect. *Am J Med Genet* 1997;69:79.
136. Siggers CD, Rimoin DL, Dorst JP, et al. The Kniest syndrome. *Birth Defects Orig Artic Ser* 1974;10:193.
137. Dobbs MB, Gurnett CA. Update on clubfoot: etiology and treatment. *Clin Orthop Relat Res* 2009;467:1146.

138. Cole WG, Hall RK, Rogers JG. The clinical features of spondyloepiphyseal dysplasia congenita resulting from the substitution of glycine 997 by serine in the alpha 1(II) chain of type II collagen. *J Med Genet* 1993;30:27.
139. Harrod MJE, Friedman JM, Currarino G, et al. Genetic heterogeneity in spondyloepiphyseal dysplasia congenita. *Am J Med Genet* 1984;18:311.
140. Tiller GE, Weis MA, Polumbo PA, et al. An RNA-splicing mutation (G + 5IVS20) in the type II collagen gene (COL2A1) in a family with spondyloepiphyseal dysplasia congenita. *Am J Hum Genet* 1995;56:388.
141. Wynne-Davies R, Hall C. Two clinical variants of spondylo-epiphysial dysplasia congenita. *J Bone Joint Surg Br* 1982;64:435.
142. Spranger JW, Langer LO Jr. Spondyloepiphyseal dysplasia congenita. *Radiology* 1970;94:313.
143. Williams BR, Cranley RE. Morphologic observations on four cases of SED congenita. *Birth Defects Orig Artic Ser* 1974;10:75.
144. Ikegawa S, Iwaya T, Taniguchi K, et al. Retinal detachment in spondyloepiphyseal dysplasia congenita. *J Pediatr Orthop* 1993;13:791.
145. LeDoux MS, Naftalis RC, Aronin PA. Stabilization of the cervical spine in spondyloepiphyseal dysplasia congenita. *Neurosurgery* 1991;28:580.
146. Shetty GM, Song HR, Lee SH, et al. Bilateral valgus-extension osteotomy of hip using hybrid external fixator in spondyloepiphyseal dysplasia: early results of a salvage procedure. *J Pediatr Orthop B* 2008;17:21.
147. Kaibara N, Takagishi K, Katsuki I, et al. Spondyloepiphyseal dysplasia tarda with progressive arthropathy. *Skeletal Radiol* 1983;10:13.
148. Yang SS, Chen H, Williams P, et al. Spondyloepiphyseal dysplasia congenita. A comparative study of chondrocytic inclusions. *Arch Pathol Lab Med* 1980;104:208.
149. Fiedler J, Bergmann C, Brenner RE. X-linked spondyloepiphyseal dysplasia tarda: molecular cause of a heritable disorder associated with early degenerative joint disease. *Acta Orthop Scand* 2003;74:737.
150. Crossan JF, Wynne-Davies R, Fulford GE. Bilateral failure of the capital femoral epiphysis: bilateral Perthes disease, multiple epiphyseal dysplasia, pseudoachondroplasia, and spondyloepiphyseal dysplasia congenita and tarda. *J Pediatr Orthop* 1983;3:297.
151. Diamond LS. A family study of spondyloepiphyseal dysplasia. *J Bone Joint Surg Am* 1970;52:1587.
152. Briggs MD, Chapman KL. Pseudoachondroplasia and multiple epiphyseal dysplasia: mutation review, molecular interactions, and genotype to phenotype correlations. *Hum Mutat* 2002;19:465.
153. Maroteaux P, Lamy M. Pseudo-achondroplastic forms of spondyloepiphyseal dysplasias. *Presse Med* 1959;67:383.
154. Deere M, Sanford T, Francomano CA, et al. Identification of nine novel mutations in cartilage oligomeric matrix protein in patients with pseudoachondroplasia and multiple epiphyseal dysplasia. *Am J Med Genet* 1999;85:486.
155. Ferguson HL, Deere M, Evans R, et al. Mosaicism in pseudoachondroplasia. *Am J Med Genet* 1997;70:287.
156. Cooper RR, Ponseti IV, Maynard JA. Pseudoachondroplastic dwarfism. A rough-surfaced endoplasmic reticulum storage disorder. *J Bone Joint Surg Am* 1973;55:475.
157. Hecht JT, Montufar-Solis D, Decker G, et al. Retention of cartilage oligomeric matrix protein (COMP) and cell death in redifferentiated pseudoachondroplasia chondrocytes. *Matrix Biol* 1998;17:625.
158. Pedrini-Mille A, Maynard JA, Pedrini VA. Pseudoachondroplasia: biochemical and histochemical studies of cartilage. *J Bone Joint Surg Am* 1984;66:1408.
159. Hall JG. Pseudoachondroplasia. *Birth Defects Orig Artic Ser* 1975;11:187.
160. Hall JG, Dorst JP. Pseudoachondroplastic SED, recessive Maroteaux-Lamy type. *Birth Defects Orig Artic Ser* 1969;5:254.
161. Wynne-Davies R, Hall CM, Young ID. Pseudoachondroplasia: clinical diagnosis at different ages and comparison of autosomal dominant and recessive types. A review of 32 patients (26 kindreds). *J Med Genet* 1986;23:425.
162. Leet AI, Pichard CP, Ain MC. Surgical treatment of femoral fractures in obese children: does excessive body weight increase the rate of complications? *J Bone Joint Surg Am* 2005;87:2609.
163. Fairbank T. Dysplasia epiphysealis multiplex. *Br J Surg* 1947;34:225.
164. Ribbing S. Studien uber hereditare, multiple epiphysenstorungen. *Acta Radiol Suppl* 1937;34:1.
165. Stanescu R, Stanescu V, Muriel MP, et al. Multiple epiphyseal dysplasia, Fairbank type: morphologic and biochemical study of cartilage. *Am J Med Genet* 1993;45:501.
166. Posey KL, Hecht JT. The role of cartilage oligomeric matrix protein (COMP) in skeletal disease. *Curr Drug Targets* 2008;9:869.
167. van Mourik JB, Hamel BC, Mariman EC. A large family with multiple epiphyseal dysplasia linked to COL9A2 gene. *Am J Med Genet* 1998;77:234.
168. Makitie O, Mortier GR, Czarny-Ratajczak M, et al. Clinical and radiographic findings in multiple epiphyseal dysplasia caused by MATN3 mutations: description of 12 patients. *Am J Med Genet A* 2004;125:278.
169. Jacobs PA. Dysplasia epiphysialis multiplex. *Clin Orthop Relat Res* 1968;58:117.
170. Schlesinger AE, Poznanski AK, Pudlowski RM, et al. Distal femoral epiphysis: normal standards for thickness and application to bone dysplasias. *Radiology* 1986;159:515.
171. Treble NJ, Jensen FO, Bankier A, et al. Development of the hip in multiple epiphyseal dysplasia. Natural history and susceptibility to premature osteoarthritis. *J Bone Joint Surg Br* 1990;72:1061.
172. Mackenzie WG, Bassett GS, Mandell GA, et al. Avascular necrosis of the hip in multiple epiphyseal dysplasia. *J Pediatr Orthop* 1989;9:666.
173. Apley AG, Wientroub S. The sagging rope sign in Perthes' disease and allied disorders. *J Bone Joint Surg Br* 1981;63:43.
174. Hodkinson HM. Double patellae in multiple epiphyseal dysplasia. *J Bone Joint Surg Br* 1962;44:569.
175. Vatanavicharn N, Lachman RS, Rimoin DL. Multilayered patella: similar radiographic findings in pseudoachondroplasia and recessive multiple epiphyseal dysplasia. *Am J Med Genet A* 2008;146A:1682.
176. Eddy MC, Steiner RD, McAlister WH, et al. Bilateral radial ray hypoplasia with multiple epiphyseal dysplasia. *Am J Med Genet* 1998;77:182.
177. Haga N, Nakamura K, Takikawa K, et al. Stature and severity in multiple epiphyseal dysplasia. *J Pediatr Orthop* 1998;18:394.
178. Spranger J. The epiphyseal dysplasias. *Clin Orthop Relat Res* 1976;114:46.
179. Trigui M, Pannier S, Finidori G, et al. Coxa vara in chondrodysplasia: prognosis study of 35 hips in 19 children. *J Pediatr Orthop* 2008;28:599.
180. Kruse RW, Guille JT, Bowen JR. Shelf arthroplasty in patients who have Legg-Calve-Perthes disease. A study of long-term results. *J Bone Joint Surg Am* 1991;73:1338.
181. Willett K, Hudson I, Catterall A. Lateral shelf acetabuloplasty: an operation for older children with Perthes' disease. *J Pediatr Orthop* 1992;12:563.
182. Cho TJ, Choi IH, Chung CY, et al. Hemiepiphyseal stapling for angular deformity correction around the knee joint in children with multiple epiphyseal dysplasia. *J Pediatr Orthop* 2009;29:52.
183. Ramachandran G, Mason D. Double-layered patella: marker for multiple epiphyseal dysplasia. *Am J Orthop (Belle Mead NJ)* 2004;33:35.
184. Pavone V, Costarella L, Privitera V, et al. Bilateral total hip arthroplasty in subjects with multiple epiphyseal dysplasia. *J Arthroplasty* 2009;24:868.
185. Ingram RR. The shoulder in multiple epiphyseal dysplasia. *J Bone Joint Surg Br* 1991;73:277.
186. Irving MD, Chitty LS, Mansour S, et al. Chondrodysplasia punctata: a clinical diagnostic and radiological review. *Clin Dysmorphol* 2008;17:229.
187. Andersen PE Jr, Justesen P. Chondrodysplasia punctata. Report of two cases. *Skeletal Radiol* 1987;16:223.
188. Wulfsberg EA, Curtis J, Jayne CH. Chondrodysplasia punctata: a boy with X-linked recessive chondrodysplasia punctata due to an inherited X-Y translocation with a current classification of these disorders. *Am J Med Genet* 1992;43:823.
189. Borg SA, Fitzer PM, Young LW. Roentgenologic aspects of adult cretinism. Two case reports and review of the literature. *Am J Roentgenol Radium Ther Nucl Med* 1975;123:820.
190. Hanson JW, Smith DW. The fetal hydantoin syndrome. *J Pediatr* 1975;87:285.
191. Harrod MJE, Sherrod PS. Warfarin embryopathy in siblings. *Obstet Gynecol* 1981;57:673.

192. Pauli RM, Lian JB, Mosher DF, et al. Association of congenital deficiency of multiple vitamin K-dependent coagulation factors and the phenotype of the warfarin embryopathy: clues to the mechanism of teratogenicity of coumarin derivatives. *Am J Hum Genet* 1987;41:566.
193. Pike MG, Applegarth DA, Dunn HG, et al. Congenital rubella syndrome associated with calcific epiphyseal stippling and peroxisomal dysfunction. *J Pediatr* 1990;116:88.
194. Curry CJR, Magenis RE, Brown M, et al. Inherited chondrodysplasia punctata due to a deletion of the terminal short arm of an X chromosome. *N Engl J Med* 1984;311:1010.
195. Wardinsky TD, Pagon RA, Powell BR, et al. Rhizomelic chondrodysplasia punctata and survival beyond one year: a review of the literature and five case reports [see comments]. *Clin Genet* 1990;38:84.
196. Mason DE, Sanders JO, Mackenzie WG, et al. Spinal deformity in chondrodysplasia punctata. *Spine (Phila Pa 1976)* 2002;27:1995.
197. Gilbert EF, Opitz JM, Spranger JW, et al. Chondrodysplasia punctata—rhizomelic form. Pathologic and radiologic studies of three infants. *Eur J Pediatr* 1976;123:89.
198. Happle R. X-linked dominant chondrodysplasia punctata. Review of literature and report of a case. *Hum Genet* 1979;53:65.
199. Manzke H, Christophers E, Wiedemann HR. Dominant sex-linked inherited chondrodysplasia punctata: a distinct type of chondrodysplasia punctata. *Clin Genet* 1980;17:97.
200. Silengo MC, Luzzatti L, Silverman FN. Clinical and genetic aspects of Conradi-Hunermann disease. A report of three familial cases and review of the literature. *J Pediatr* 1980;97:911.
201. Spranger JW, Opitz JM, Bidder U. Heterogeneity of chondrodysplasia punctata. *Humangenetik* 1971;11:190.
202. Heymans HSA, Oorthuys JWE, Nelck G, et al. Rhizomelic chondrodysplasia punctata: another peroxisomal disorder [letter to the editor]. *N Engl J Med* 1985;313:187.
203. Hoefler S, Hoefler G, Moser AB, et al. Prenatal diagnosis of rhizomelic chondrodysplasia punctata. *Prenat Diagn* 1988;8:571.
204. Mueller RF, Crowle PM, Jones RAK, et al. X-linked dominant chondrodysplasia punctata: a case report and family studies. *Am J Med Genet* 1985;20:137.
205. Rittler M, Menger H, Spranger J. Chondrodysplasia punctata, tibia-metacarpal (MT) type. *Am J Med Genet* 1990;37:200.
206. Burck U. Mesomelic dysplasia with punctate epiphyseal calcifications—a new entity of chondrodysplasia punctata? *Eur J Pediatr* 1982;138:67.
207. Khanna AJ, Braverman NE, Valle D, et al. Cervical stenosis secondary to rhizomelic chondrodysplasia punctata. *Am J Med Genet* 2001;99:63.
208. Bethem D. Os odontoideum in chondrodystrophia calcificans congenita. A case report. *J Bone Joint Surg Am* 1982;64:1385.
209. Sheffield LJ, Halliday JL, Danks DM, et al. Clinical, radiological and biochemical classification of chondrodysplasia punctata. *Am J Hum Genet* 1989;45:A64.
210. Fairbank HAT. Dysplasia epiphysialis punctata: synonyms—stippled epiphyses, chondrodystrophia calcificans congenita (Hunermann). *J Bone Joint Surg Br* 1949;31:114.
211. Lawrence JJ, Schlesinger AE, Kozlowski K, et al. Unusual radiographic manifestations of chondrodysplasia punctata. *Skeletal Radiol* 1989;18:15.
212. Cooper RR, Ponseti IV. Metaphyseal dysotosis: description of an ultrastructural defect in the epiphyseal plate chondrocytes. *J Bone Joint Surg Am* 1973;55:485.
213. Evans R, Caffey J. Metaphyseal dysostosis resembling vitamin D-refractory rickets. *AMA J Dis Child* 1958;95:640.
214. Kozlowski K. Metaphyseal and spondylometaphyseal chondrodysplasias. *Clin Orthop Relat Res* 1976;114:83.
215. Sulisalo T, van der Burgt I, Rimoin DL, et al. Genetic homogeneity of cartilage-hair hypoplasia. *Hum Genet* 1995;95:157.
216. Ridanpaa M, Jain P, McKusick VA, et al. The major mutation in the RMRP gene causing CHH among the Amish is the same as that found in most Finnish cases. *Am J Med Genet C Semin Med Genet* 2003;121:81.
217. Makitie O, Kaitila I. Cartilage-hair hypoplasia—clinical manifestations in 108 Finnish patients. *Eur J Pediatr* 1993;152:211.
218. Makitie O, Marttinen E, Kaitila I. Skeletal growth in cartilage-hair hypoplasia. A radiological study of 82 patients. *Pediatr Radiol* 1992;22:434.
219. Juvonen E, Makitie O, Makipernaa A, et al. Defective in-vitro colony formation of haematopoietic progenitors in patients with cartilage-hair hypoplasia and history of anaemia. *Eur J Pediatr* 1995;154:30.
220. van der Burgt I, Haraldsson A, Oosterwijk JC, et al. Cartilage hair hypoplasia, metaphyseal chondrodysplasia type McKusick: description of seven patients and review of the literature. *Am J Med Genet* 1991;41:371.
221. Wasylenko MJ, Wedge JH, Houston CS. Metaphyseal chondrodysplasia, Schmid type. A defect of ultrastructural metabolism: case report. *J Bone Joint Surg Am* 1980;62:660.
222. Paschalis EP, Jacenko O, Olsen B, et al. Fourier transform infrared microspectroscopic analysis identifies alterations in mineral properties in bones from mice transgenic for type X collagen. *Bone* 1996;19:151.
223. Wallis GA, Rash B, Sykes B, et al. Mutations within the gene encoding the alpha 1 (X) chain of type X collagen (COL10A1) cause metaphyseal chondrodysplasia type Schmid but not several other forms of metaphyseal chondrodysplasia. *J Med Genet* 1996;33:450.
224. Schipani E, Jensen GS, Pincus J, et al. Constitutive activation of the cyclic adenosine 3′,5′-monophosphate signaling pathway by parathyroid hormone (PTH)/PTH-related peptide receptors mutated at the two loci for Jansen's metaphyseal chondrodysplasia. *Mol Endocrinol* 1997;11:851.
225. Alvarez C, Tredwell S, De Vera M, et al. The genotype-phenotype correlation of hereditary multiple exostoses. *Clin Genet* 2006;70:122.
226. Jones KB, Morcuende JA. Of hedgehogs and hereditary bone tumors: re-examination of the pathogenesis of osteochondromas. *Iowa Orthop J* 2003;23:87.
227. Roach JW, Klatt JW, Faulkner ND. Involvement of the spine in patients with multiple hereditary exostoses. *J Bone Joint Surg Am* 2009;91:1942.
228. Porter DE, Lonie L, Fraser M, et al. Severity of disease and risk of malignant change in hereditary multiple exostoses. A genotype-phenotype study. *J Bone Joint Surg Br* 2004;86:1041.
229. Ishikawa J, Kato H, Fujioka F, et al. Tumor location affects the results of simple excision for multiple osteochondromas in the forearm. *J Bone Joint Surg Am* 2007;89:1238.
230. Akita S, Murase T, Yonenobu K, et al. Long-term results of surgery for forearm deformities in patients with multiple cartilaginous exostoses. *J Bone Joint Surg Am* 2007;89:1993.
231. Beals RK, Shea M. Correlation of chronological age and bone age with the correction of ankle valgus by surface epiphysiodesis of the distal medial tibial physis. *J Pediatr Orthop B* 2005;14:436.
232. Noonan KJ, Feinberg JR, Levenda A, et al. Natural history of multiple hereditary osteochondromatosis of the lower extremity and ankle. *J Pediatr Orthop* 2002;22:120.
233. Hosalkar H, Greenberg J, Gaugler RL, et al. Abnormal scarring with keloid formation after osteochondroma excision in children with multiple hereditary exostoses. *J Pediatr Orthop* 2007;27:333.
234. Leri A, Weill J. Une affection congenitale et symetrique du developpement osseux: la dyschondrosteose. *Bull Mem Soc Med Hosp (Paris)* 1929;53:1491.
235. Felman AH, Kirkpatrick JA Jr. Dyschondrosteose. Mesomelic dwarfism of Lwei and Weill. *Am J Dis Child* 1970;120:329.
236. Langer LO Jr. Dyschondrosteosis, a hereditable bone dysplasia with characteristic roentgenographic features. *Am J Roentgenol Radium Ther Nucl Med* 1965;95:178.
237. Dawe C, Wynne-Davies R, Fulford GE. Clinical variation in dyschondrosteosis. A report on 13 individuals in 8 families. *J Bone Joint Surg Br* 1982;64:377.
238. Murphy MS, Linscheid RL, Dobyns JH, et al. Radial opening wedge osteotomy in Madelung's deformity. *J Hand Surg Am* 1996;21:1035.
239. Mohan V, Gupta RP, Helmi K, et al. Leri-Weill syndrome (dyschondrosteosis): a family study. *J Hand Surg Br* 1988;13:16.
240. Shears DJ, Vassal HJ, Goodman FR, et al. Mutation and deletion of the pseudoautosomal gene SHOX cause Leri-Weill dyschondrosteosis. *Nat Genet* 1998;19:70.

241. Marchini A, Rappold G, Schneider KU. SHOX at a glance: from gene to protein. *Arch Physiol Biochem* 2007;113:116.
242. Rappold GA, Shanske A, Saenger P. All shook up by SHOX deficiency. *J Pediatr* 2005;147:422.
243. Cook PA, Yu JS, Wiand W, et al. Madelung deformity in skeletally immature patients: morphologic assessment using radiography, CT, and MRI. *J Comput Assist Tomogr* 1996;20:505.
244. Thuestad IJ, Ivarsson SA, Nilsson KO, et al. Growth hormone treatment in Leri-Weill syndrome. *J Pediatr Endocrinol Metab* 1996;9:201.
245. Burren CP, Werther GA. Skeletal dysplasias: response to growth hormone therapy. *J Pediatr Endocrinol Metab* 1996;9:31.
246. Vickers D, Nielsen G. Madelung deformity: surgical prophylaxis (physiolysis) during the late growth period by resection of the dyschondrosteosis lesion. *J Hand Surg Br* 1992;17:401.
247. Marie P, Sainton P. On hereditary cleido-cranial dysostosis. *Clin Orthop Relat Res* 1968;58:5.
248. Marie P, Seinton P. Observation d'hydrocephalie hereditaire (pere et fils) par vice de developpement du crane et du cerveau. *Rev Neurol* 1897;5:394.
249. Martinez-Frias ML, Herranz I, Salvador J, et al. Prevalence of dominant mutations in Spain: effect of changes in maternal age distribution. *Am J Med Genet* 1988;31:845.
250. Geoffroy V, Corral DA, Zhou L, et al. Genomic organization, expression of the human CBFA1 gene, and evidence for an alternative splicing event affecting protein function. *Mamm Genome* 1998;9:54.
251. Lee B, Thirunavukkarasu K, Zhou L, et al. Missense mutations abolishing DNA binding of the osteoblast-specific transcription factor OSF2/CBFA1 in cleidocranial dysplasia. *Nat Genet* 1997;16:307.
252. Otto F, Thornell AP, Crompton T, et al. Cbfa1, a candidate gene for cleidocranial dysplasia syndrome, is essential for osteoblast differentiation and bone development. *Cell* 1997;89:765.
253. Ziros PG, Basdra EK, Papavassiliou AG. Runx2: of bone and stretch. *Int J Biochem Cell Biol* 2008;40:1659.
254. Jensen BL. Somatic development in cleidocranial dysplasia. *Am J Med Genet* 1990;35:69.
255. Jensen BL, Kreiborg S. Development of the skull in infants with cleidocranial dysplasia. *J Craniofac Genet Dev Biol* 1993;13:89.
256. Miles PW. Cleidocranial dysostosis: a survey of six new cases and 126 from the literature. *J Kansas Med Soc* 1940;41:462.
257. Gupta SK, Sharma OP, Malhotra S, et al. Cleido-cranial dysostosis—skeletal abnormalities. *Australas Radiol* 1992;36:238.
258. Dore DD, MacEwen GD, Boulos MI. Cleidocranial dysostosis and syringomyelia. Review of the literature and case report. *Clin Orthop Relat Res* 1987;214:229.
259. Taglialavoro G, Fabris D, Agostini S. A case of progressive scoliosis in a patient with craniocleidopelvic dysostosis. *Ital J Orthop Traumatol* 1983;9:507.
260. Vari R, Puca A, Meglio M. Cleidocranial dysplasia and syringomyelia. Case report. *J Neurosurg Sci* 1996;40:125.
261. Hamner LH III, Fabbri EL, Browne PC. Prenatal diagnosis of cleidocranial dysostosis. *Obstet Gynecol* 1994;83:856.
262. Jarvis JL, Keats TE. Cleidocranial dysostosis. A review of 40 new cases. *Am J Roentgenol Radium Ther Nucl Med* 1974;121:5.
263. Kim HT, Chambers HG, Mubarak SJ, et al. Congenital coxa vara: computed tomographic analysis of femoral retroversion and the triangular metaphyseal fragment. *J Pediatr Orthop* 2000;20:551.
264. Krishnan SG, Hawkins RJ, Michelotti JD, et al. Scapulothoracic arthrodesis: indications, technique, and results. *Clin Orthop Relat Res* 2005;435:126.
265. Richie MF, Johnston CE II. Management of developmental coxa vara in cleidocranial dysostosis. *Orthopedics* 1989;12:1001.
266. Larsen LJ, Schottstaedt ER, Bost FC. Multiple congenital dislocations associated with characteristic facial abnormality. *J Pediatr* 1950;37:574.
267. Vujic M, Hallstensson K, Wahlstrom J, et al. Localization of a gene for autosomal dominant Larsen syndrome to chromosome region 3p21.1–14.1 in the proximity of, but distinct from, the COL7A1 locus. *Am J Hum Genet* 1995;57:1104.
268. Krakow D, Robertson SP, King LM, et al. Mutations in the gene encoding filamin B disrupt vertebral segmentation, joint formation and skeletogenesis. *Nat Genet* 2004;36:405.
269. Zhang D, Herring JA, Swaney SS, et al. Mutations responsible for Larsen syndrome cluster in the FLNB protein. *J Med Genet* 2006;43:e24.
270. Laville JM, Lakermance P, Limouzy F. Larsen's syndrome: review of the literature and analysis of thirty-eight cases. *J Pediatr Orthop* 1994;14:63.
271. Johnston CE II, Birch JG, Daniels JL. Cervical kyphosis in patients who have Larsen syndrome. *J Bone Joint Surg Am* 1996;78:538.
272. Micheli LJ, Hall JE, Watts HG. Spinal instability in Larsen's syndrome: report of three cases. *J Bone Joint Surg Am* 1976;58:562.
273. Bowen JR, Ortega K, Ray S, et al. Spinal deformities in Larsen's syndrome. *Clin Orthop Relat Res* 1985;197:159.
274. Sakaura H, Matsuoka T, Iwasaki M, et al. Surgical treatment of cervical kyphosis in Larsen syndrome: report of 3 cases and review of the literature. *Spine (Phila Pa 1976)* 2007;32:E39.
275. Dobbs MB, Boehm S, Grange DK, et al. Congenital knee dislocation in a patient with Larsen syndrome and a novel filamin B mutation. *Clin Orthop Relat Res* 2008;466:1503.
276. Bodian DL, Chan TF, Poon A, et al. Mutation and polymorphism spectrum in osteogenesis imperfecta type II: implications for genotype-phenotype relationships. *Hum Mol Genet* 2009;18:463.