CHAPTER 29

Skeletal Dysplasias

Introduction

This chapter describes the major skeletal dysplasias that are seen in the pediatric population. In each of these conditions a structural abnormality in the bone itself leads to disturbances in growth of the trunk and/or extremities. There are more than 200 described bone dysplasias, most of which are extremely rare.[1] Most of the bone dysplasias result in short stature, which is defined as a height that is less than the third percentile for the chronological age of the patient. Short stature can be further described as proportionate or disproportionate, with disproportionate short stature divided into short-limbed and short-trunk forms.

Some of the dysplasias are genetically transmitted, while others are not inherited. In those dysplasias with genetic transmission, recent research has focused on molecular genetics. Not only are scientists discovering which chromosomes the dysplasia is transmitted on, they are also uncovering the precise mutations. In addition, the proteins that are encoded from the genes and the roles these proteins play in skeletal development are now becoming known. Although specific gene therapy is not yet possible, much new information is becoming rapidly available, advancing our understanding of the mechanism of bone dysplasias.

The diagnosis of skeletal dysplasias can most often be made from the history and the physical examination of the child. Short stature is readily identified and is often the chief complaint of the family. At the initial examination, the pattern of shortening should be established. *Rhizomelic* is a term implying shortening that is most prominent in the proximal segments of the limbs (i.e., in the femur or humerus). When the midportion of the limb is shortest, the term *mesomelic* should be used. *Acromelic* describes shortening of the distal limb. Sitting heights and standing heights should be compared with normal growth charts to establish whether the short stature is proportionate or disproportionate (see Chapter 1, Growth and Development).

The physical examination should include careful characterization of the patient's facies. Frontal bossing is seen in achondroplasia, whereas trefoil (triangular) facies is seen in osteogenesis imperfecta. In many dysplasias the patient's teeth are abnormal, a visible reflection of collagen abnormalities common to both the dentition and the bone. Inspection of the patient's ears and skin can narrow down the potential diagnoses as well. Comparison with atlases of skeletal malformations is quite useful.[2] It has been said that children with skeletal dysplasias and syndromes resemble depictions of affected children in atlases more than they resemble their own siblings.

Following the history and physical examination, radiographs are used to identify the area of the bone in which abnormalities are seen. Epiphyseal changes are seen in multiple epiphyseal dysplasia and glycogen storage diseases. Metaphyseal abnormalities are most noticeable in rickets and metaphyseal chondrodysplasias. Spinal radiographs should

always be obtained in the evaluation of a child with a suspected skeletal dysplasia. Dysplastic changes are seen in the spine in several of these conditions, and the presence or absence of spinal involvement can assist the orthopaedic surgeon in establishing the diagnosis. Cervical spine films are also helpful in the diagnosis, and they may reveal troublesome instability that may require attention once it is identified. Hand radiographs are helpful in screening for skeletal dysplasias, as certain dysplasias demonstrate characteristic changes in the metacarpals and phalanges. When the dysplasia is not evident on films, a pediatric orthopaedic radiologist should be consulted to review the radiographs.

Some of the skeletal dysplasias are associated with significant medical findings. One example is the presence of precocious puberty in young girls with Albright's syndrome. Other dysplasias place patients at increased risk for future medical problems. For example, patients with nail-patella syndrome are diagnosed with the condition as children, but they are predisposed to developing renal failure as adults. In these cases the pediatric orthopaedist should counsel patients and their families accordingly and direct them to appropriate medical care.

Referral to a pediatric geneticist is often required when evaluating patients with bone dysplasias. These medical specialists may be very helpful in reaching a diagnosis in vexing cases. Genetic counseling is often of concern for the family, both to estimate the risk in future pregnancies and to obtain information about genetic transmission of the dysplasia when their child reaches reproductive age. Detailed chromosomal studies are now available for some of the skeletal dysplasias.[3]

REFERENCES

Introduction

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2. Jones K: Smith's Recognizable Patterns of Human Malformation. Philadelphia, WB Saunders Co, 1988.
3. Reardon W: Skeletal dysplasias detectable by DNA analysis. Prenat Diagn 1996;16:1221.

Nomenclature and Classification

Sir Thomas Fairbank was among the first to try to classify the skeletal dysplasias, in his *Atlas of General Affections of the Skeleton.*[2] In *Dynamic Classification of Bone Dysplasias,* Rubin further refined the classification schemes, grouping the dysplasias according to the anatomic distribution of bone changes (Fig. 29–1, Table 29–1).[3] The March of Dimes followed with a series of meetings on birth defects, which led to publications describing the skeletal dysplasias.[1] The

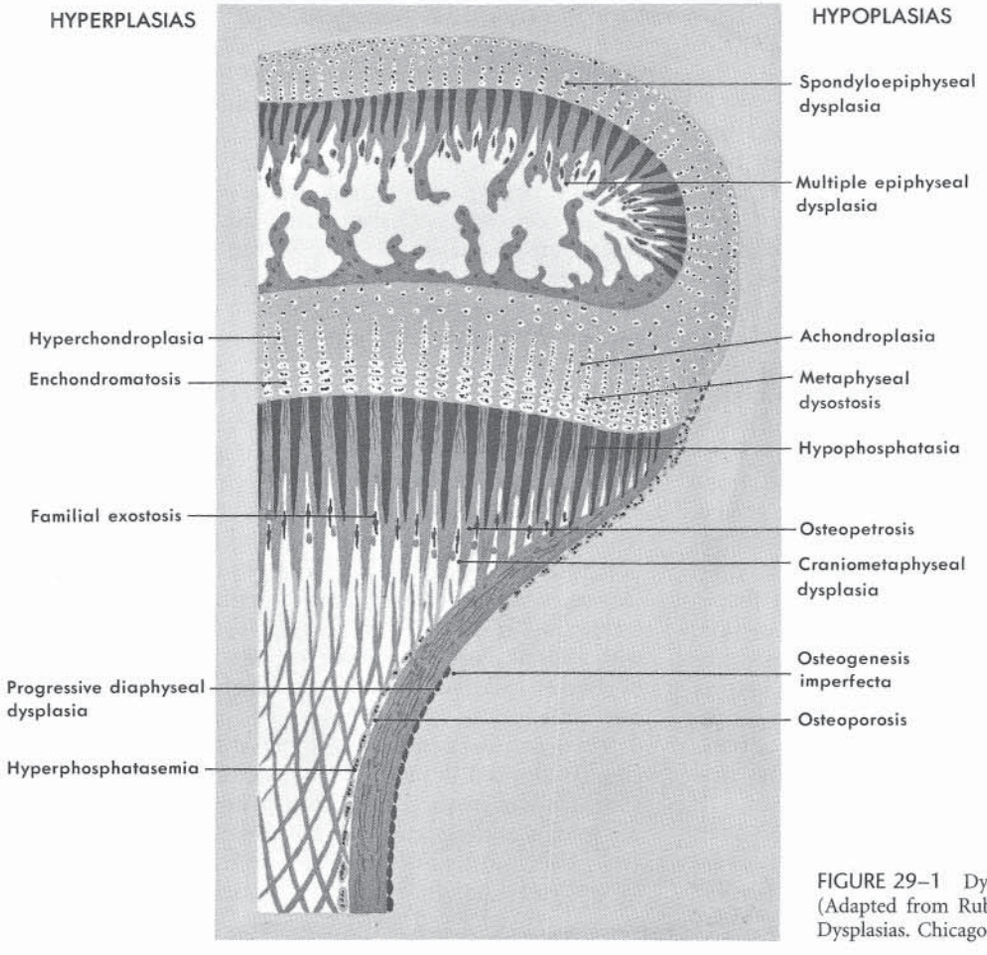

FIGURE 29–1 Dynamic classification of bone dysplasias. (Adapted from Rubin P: Dynamic Classification of Bone Dysplasias. Chicago, Year Book Medical Publishers, 1964.)

TABLE 29–1 Dynamic Classification of Bone Dysplasias

I. Epiphyseal Dysplasias
  A. Epiphyseal hypoplasias
    1. Failure of articular cartilage: spondyloepiphyseal dysplasia congenita and tarda
    2. Failure of ossification center: multiple epiphyseal dysplasia congenita and tarda
  B. Epiphyseal hyperplasia
    1. Excess of articular cartilage; dysplasia epiphysealis hemimelica
II. Physeal Dysplasias
  A. Cartilage hypoplasias
    1. Failure of proliferating cartilage: achondroplasia congenita and tarda
    2. Failure of hypertrophic cartilage: metaphyseal dysostosis congenita and tarda
  B. Cartilage hyperplasias
    1. Excess of proliferating cartilage: hyperchondroplasia
    2. Excess of hypertrophic cartilage: enchondromatosis
III. Metaphyseal Dysplasias
  A. Metaphyseal hypoplasias
    1. Failure to form primary spongiosa: hypophosphatasia congenita and tarda
    2. Failure to absorb primary spongiosa: osteopetrosis congenita and tarda
    3. Failure to absorb secondary spongiosa: craniometaphyseal dysplasia congenita and tarda
  B. Metaphyseal hyperplasias
    1. Excessive spongiosa: multiple exostoses
IV. Diaphyseal Dysplasias
  A. Diaphyseal hypoplasias
    1. Failure of periosteal bone formation: osteogenesis imperfecta congenita and tarda
    2. Failure of endosteal bone formation: idiopathic osteoporosis congenita and tarda
  B. Diaphyseal hyperplasias
    1. Excessive periosteal bone formation: progressive diaphyseal dysplasia
    2. Excessive endosteal bone formation: hyperphosphatasemia

From Rubin P: Dynamic Classification of Bone Dysplasias, p 82. Chicago, Year Book Medical Publishers, 1964.

TABLE 29–2 International Nomenclature of Constitutional Disease of Bone

Osteochondrodysplasias
Abnormalities of cartilage and/or bone growth and development.

Defects of Growth of Tubular Bones and/or Spine
A. Identifiable at birth
  1. Achondrogenesis type I, Parenti-Fraccaro
  2. Achondrogenesis type II, Langer-Saldino
  3. Thanatophoric dysplasia
  4. Thanatophoric dysplasia with cloverleaf skull
  5. Short rib-polydactyly syndrome type I, Saldino-Noonan (perhaps several forms)
  6. Short rib-polydactyly syndrome type II, Majewski's
  7. Chondrodysplasia punctata
    a. Rhizomelic form
    b. Dominant form
    c. Other forms, excluding symptomatic stippling in other disorders (e.g., Zellweger's syndrome, warfarin embryopathy)
  8. Campomelic dysplasia
  9. Other dysplasias with congenital bowing of long bones (several forms)
  10. Achondroplasia
  11. Diastrophic dysplasia
  12. Metatropic dysplasia (several forms)
  13. Chondroectodermal dysplasia, Ellis Van Creveld
  14. Asphyxiating thoracic dysplasia, Jeune's
  15. Spondyloepiphyseal dysplasia congenita
    a. Type Spranger-Wiedemann
    b. Other forms (see B, 11 and 12)
  16. Kniest's dysplasia
  17. Mesomelic dysplasia
    a. Type Nievergelt
    b. Type Langer (probable homozygous dyschondrosteosis)
    c. Type Robinow
    d. Type Rheinhardt
    e. Other forms
  18. Acromesomelic dysplasia
  19. Cleidocranial dysplasia
  20. Larsen syndrome
  21. Otopalatodigital syndrome

Table continued on following page

TABLE 29–2 **International Nomenclature of Constitutional Disease of Bone** *Continued*

B. Identifiable in later life
1. Hypochondroplasia
2. Dyschondrosteosis
3. Metaphyseal chondrodysplasia type Jansen
4. Metaphyseal chondrodysplasia type Schmid
5. Metaphyseal chondrodysplasia type McKusick
6. Metaphyseal chondrodysplasia with exocrine pancreatic insufficiency and cyclic neutropenia
7. Spondylometaphyseal dysplasia
   a. Type Kozlowski
   b. Other forms
8. Multiple epiphyseal dysplasia
   a. Type Fairbank
   b. Other forms
9. Arthro-ophthalmopathy, Stickler
10. Pseudoachondroplasia
    a. Dominant
    b. Recessive
11. Spondyloepiphyseal dysplasia tarda
12. Spondyloepiphyseal dysplasia, other forms (see A, 15 and 16)
13. Dyggve-Melchior-Clausen dysplasia
14. Spondyloepimetaphyseal dysplasia (several forms)
15. Myotonic chondrodysplasia, Catel-Schwartz-Jampel
16. Parastremmatic dysplasia
17. Trichorhinophalangeal dysplasia
18. Acrodysplasia with retinitis pigmentosa and nephropathy Saldino-Mainzer

Disorganized Development of Cartilage and Fibrous Components of Skeleton
1. Dysplasia epiphysealis hemimelica
2. Multiple cartilaginous exostoses
3. Acrodysplasia with exostoses, Giedion-Langer
4. Enchondromatosis, Ollier
5. Enchondromatosis with hemangioma, Maffucci
6. Metachondromatosis
7. Fibrous dysplasia, Jaffe-Lichtenstein
8. Fibrous dysplasia with skin pigmentation and precocious puberty, McCune-Albright
9. Cherubism (familial fibrous dysplasia of the jaws)
10. Neurofibromatosis

Abnormalities of Density of Cortical Diaphyseal Structure and/or Metaphyseal Modeling
1. Osteogenesis imperfecta congenita (several forms)
2. Osteogenesis imperfecta tarda (several forms)
3. Juvenile idiopathic osteoporosis
4. Osteoporosis with pseudoglioma
5. Osteopetrosis with precocious manifestations
6. Osteopetrosis with delayed manifestations (several forms)
7. Pycnodysostosis
8. Osteopoikilosis
9. Osteopathia striata
10. Melorheostosis
11. Diaphyseal dysplasia, Camurati-Engelmann
12. Craniodiaphyseal dysplasia
13. Endosteal hyperostosis
    a. Autosomal dominant, Worth
    b. Autosomal recessive, Van Buchem
14. Tubular stenosis, Kenny-Caffey
15. Pachydermoperiostosis
16. Osteodysplasty, Melnick-Needles
17. Frontometaphyseal dysplasia
18. Craniometaphyseal dysplasia (several forms)
19. Metaphyseal dysplasia, Pyle
20. Sclerosteosis
21. Dysosteosclerosis
22. Osteoectasia with hyperphosphatasia

Dysostoses
Malformation of individual bones singly or in combination.

Dysostoses with Cranial and Facial Involvement
1. Craniosynostosis (several forms)
2. Craniofacial dysostosis, Crouzon
3. Acrocephalosyndactyly, Apert (and others)
4. Acrocephalopolysyndactyly, Carpenter (and others)
5. Mandibulofacial dysostosis
   a. Type Treacher Collins, Franceschetti
   b. Other forms

TABLE 29–2 **International Nomenclature of Constitutional Disease of Bone** *Continued*

6. Oculomandibulofacial syndrome, Hallermann-Streiff-Francois
7. Nevoid basal cell carcinoma syndrome

Dysostoses with Predominant Axial Involvement

1. Vertebral segmentation defects, including Klippel-Feil
2. Cervico-oculoacoustic syndrome, Wildervanck
3. Sprengel anomaly
4. Spondylocostal dysostosis
   a. Dominant form
   b. Recessive forms
5. Oculovertebral syndrome, Weyers
6. Osteo-onychodysostosis
7. Cerebrocostomandibular syndrome

Dysostoses with Predominant Involvement of Extremities

1. Acheiria
2. Apodia
3. Ectodactyly syndrome
4. Aglossia-adactyly syndrome
5. Congenital bowing of long bones (several forms) (see also osteochondrodysplasias)
6. Familial radioulnar synostosis
7. Brachydactyly (several forms)
8. Symphalangism
9. Polydactyly (several forms)
10. Syndactyly (several forms)
11. Polysyndactyly (several forms)
12. Camptodactyly
13. Poland syndrome
14. Rubenstein-Taybi syndrome
15. Pancytopenia-dysmelia syndrome, Fanconi
16. Thrombocytopenia-radialaplasia syndrome
17. Orodigitofacial syndrome
    a. Type Papillon-Leage
    b. Type Mohr
18. Cardiomelic syndrome, Holt-Oram (and others)
19. Femoral facial syndrome
20. Multiple-synostoses (includes some forms of symphalangism)
21. Scapuloiliac dysostosis, Kosenow-Sinios
22. Hand-foot-genital syndrome
23. Focal dermal hypoplasia, Goltz

Idiopathic Osteolyses

1. Phalangeal (several forms)
2. Tarsocarpal
   a. Including Francois form (and others)
   b. With nephropathy
3. Multicentric
   a. Hajdu-Cheney form
   b. Winchester form
   c. Other forms

Chromosomal Aberrations

Specific entities not listed

Primary Metabolic Abnormalities

Calcium and/or Phosphorus

1. Hypophosphatemic rickets
2. Pseudodeficiency rickets, Prader, Royer
3. Late rickets, McCance
4. Idiopathic hypercalcuria
5. Hypophosphatasia (several forms)
6. Pseudohypoparathyroidism (normo- and hypocalcaemic forms, include acrodysostosis)

Complex Carbohydrates

1. Mucopolysaccharidosis, type I (alpha-L-iduronidase deficiency)
   a. Hurler form
   b. Scheie form
   c. Other forms
2. Mucopolysaccharidosis, type II, Hunter (sulfoiduronate sulfatase deficiency)
3. Mucopolysaccharidosis, type III Sanfilippo
   a. Type A (heparin sulfamidase deficiency)
   b. Type B (*N*-acetyl-α-glucosaminidase deficiency)
4. Mucopolysaccharidosis, type IV, Morquio (*N*-acetylgalactosamine-6-sulfate-sulfatase deficiency)
5. Mucopolysaccharidosis, type VI, Maroteaux-Lamy (arylsulfatase B deficiency)
6. Mucopolysaccharidosis, type VII (β-glucuronidase deficiency)
7. Aspartylglucosaminuria (aspartylglucosaminidase deficiency)

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TABLE 29–2 **International Nomenclature of Constitutional Disease of Bone** *Continued*

8. Mannosidosis (α-mannosidase deficiency)
9. Fucosidosis (α-fucosidase deficiency)
10. GMI-gangliosidosis (β-galactosidase deficiency)
11. Multiple sulfatase deficiency, Austin, Thieffry
12. Neuraminidase deficiency (formerly mucolipidosis I)
13. Mucolipidosis II
14. Mucolipidosis III

Lipids
1. Neimann-Pick disease
2. Gaucher disease

Nucleic Acids
1. Adenosine deaminase deficiency and others

Amino Acids
1. Homocystinuria and others

Metals
1. Menkes' kinky hair syndrome and others

From Horan F, Beighton P: Orthopaedic Problems in Inherited Skeletal Disorders. New York, Springer-Verlag, 1982.

European Society of Pediatric Radiologists then arrived at an international nomenclature of constitutional disorders of the bone, which resulted in the classification provided in Table 29–2.

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3. Rubin P: Dynamic Classification of Bone Dysplasias. Chicago, Year Book Medical Publishers, 1964.

Achondroplasia

Achondroplasia is the most common form of dwarfism. Reports of its incidence range between 1.3 per 100,000 live births[2] and 1.5 per 10,000 live births.[52]

GENETICS

Achondroplasia is inherited as an autosomal dominant trait with complete penetrance. Ninety percent of cases are the result of spontaneous mutation.[67] New mutations in the fibroblast growth factor receptor (FGFR) gene have been linked with paternal age greater than 36 years.[53] There are extremely rare reports of familial recurrence of achondroplasia due to mosaicism in subsequent siblings of affected patients born to unaffected parents.[16,23] However, the risk of two parents without achondroplasia producing offspring with achondroplasia is almost negligible. The usual patient with achondroplasia is heterozygous in genotype. Homozygous achondroplasia occurs in the offspring of two achondroplastic parents. In homozygous cases, achondroplasia is usually fatal in the neonatal period.[57]

The gene for achondroplasia is located on chromosome 4p.[20] It encodes for FGFR-3, which acts on growth plate chondrocytes to regulate linear growth.[33] FGFR is expressed in all prebone cartilage, and its function is to slow down or inhibit enchondral ossification. The mutation allows overactivity of the receptor's function.[15] The abnormality in the gene is a glycine to arginine substitution, and there is no variability in the mutation in patients with achondroplasia. Because the mutation is the same for all patients, the phenotype of the disease is similar among unrelated individuals with achondroplasia.[9] The amino acid substitution in the FGFR-3 gene is the most mutable single nucleotide in the human genome.[6]

PATHOPHYSIOLOGY

The abnormality seen in the bone of patients with achondroplasia is failure of enchondral ossification. Intramembranous and periosteal ossification are undisturbed. Histologic studies have shown disarray of the chondrocytes, with loss of columnation and loss of normal chondrocyte proliferation.[44,60] Fibrous tissue is present in the zone of provisional calcification, and what trabeculae are present are irregular.[62] Because enchondral growth is disturbed, the bones remain short. Intramembranous ossification is normal, leading to normal clavicles and skull. Because the width of the long bones is a product of intramembranous periosteal ossification, these bones are of normal diameter.

CLINICAL FEATURES

The most striking clinical feature in children with achondroplasia is their short stature. This is apparent at birth, and has been documented on fetal ultrasound through measurement of femoral length.[40] Trunk height tends to be normal, but arm span and standing height are diminished. Shortening is most severe in the proximal limbs; thus there is *rhizomelic micromelia.* In normal individuals the fingertips reach to the level of the midthighs, but in patients with achondroplasia the fingertips reach only to the greater tro-

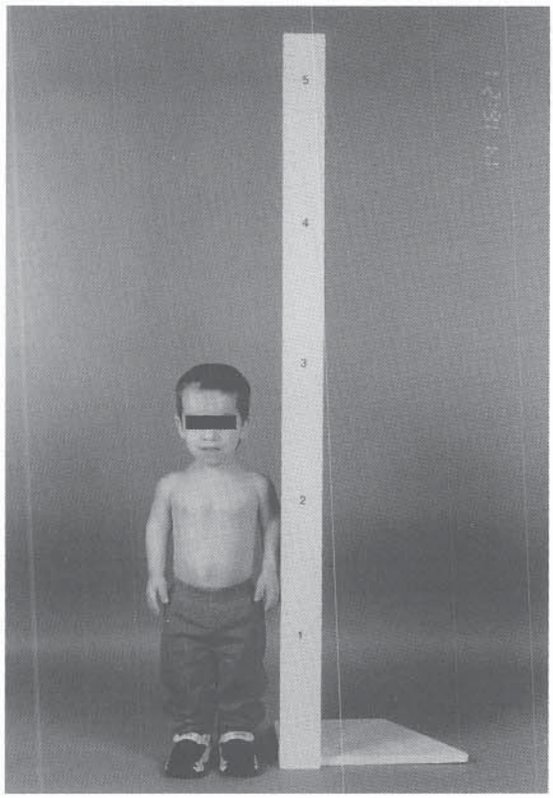


FIGURE 29–2 Six-year-old child with achondroplasia. Note that his fingers reach to the level of his hips.

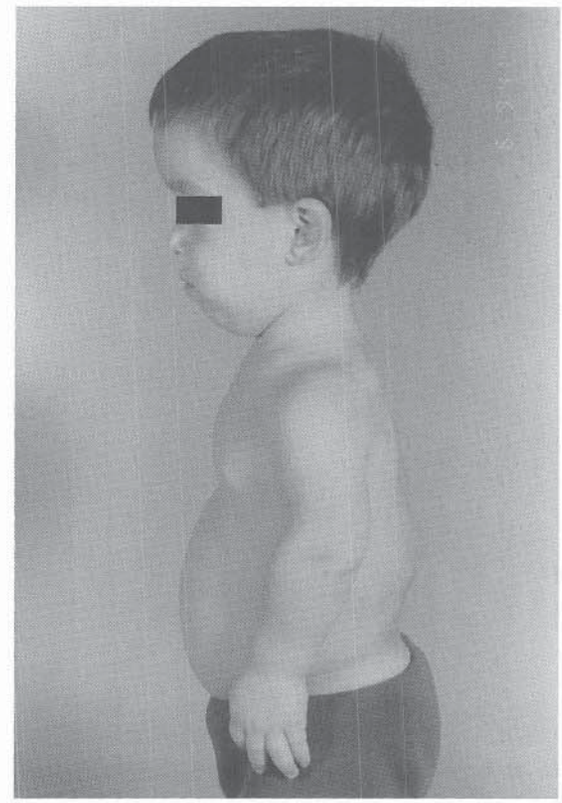


FIGURE 29–3 Facial appearance of a boy with achondroplasia. Note frontal bossing and apparent enlargement of the head, especially in relation to limb size.

chanters (Fig. 29–2). Normally, the midpoint of stature is at the umbilicus, but in patients with achondroplasia the midpoint of height may be as high as the inferior end of the sternum. Ultimate height usually is about 4 feet 3.5 inches (131 cm) for males and 4 feet 1 inch (124 cm) for females.

Facial features include frontal bossing, small maxillae, relatively prominent mandibles, and apparent enlargement of the head (Fig. 29–3). The children are often suspected of having hydrocephalus because of the increased size of the head relative to limb size. The skull appears flattened in the anteroposterior (AP) plane and broad when viewed from the front. The nasal bridge is depressed and flattened. Dentition is normal.

The hands are short and broad. The middle finger is shorter than usual, resulting in all of the digits being of equal length (referred to as *starfish hand*). There is a separation between the middle and ring fingers, which has been described as *trident hand* or *main en trident* by Marie (Fig. 29–4).[43]

The upper limbs are short, and flexion contractures of the elbows may be present. The contractures may be the result of dislocations of the radial head (Fig. 29–5). The lower limbs are also short, and may be bowed in varus. There is relative shortening of the tibia compared to the fibula. The ends of the bones are enlarged. The patient may have a waddling gait.

The muscular development of the limbs is usually accentuated. The skin and soft tissues appear overabundant in relation to the length of the limbs. The abdomen is protuberant, and obesity is a problem in many patients.[54]

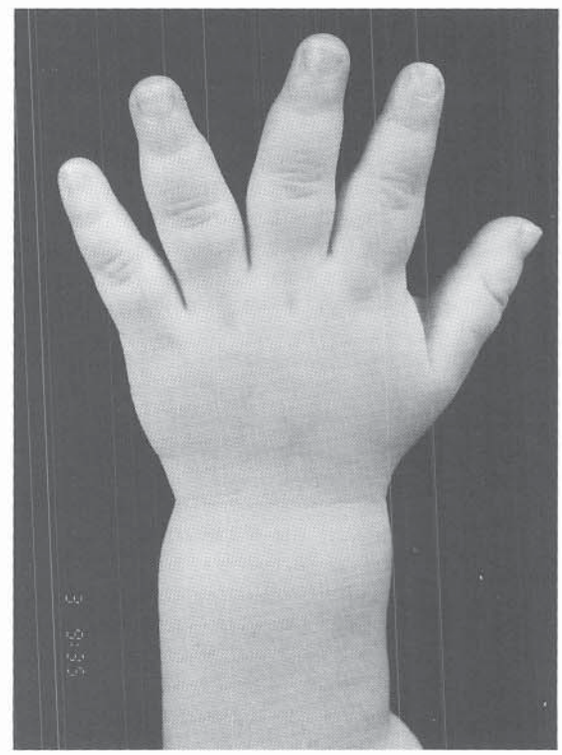


FIGURE 29–4 Trident hand characteristic of achondroplasia. Note space separating the middle finger from the ring finger.

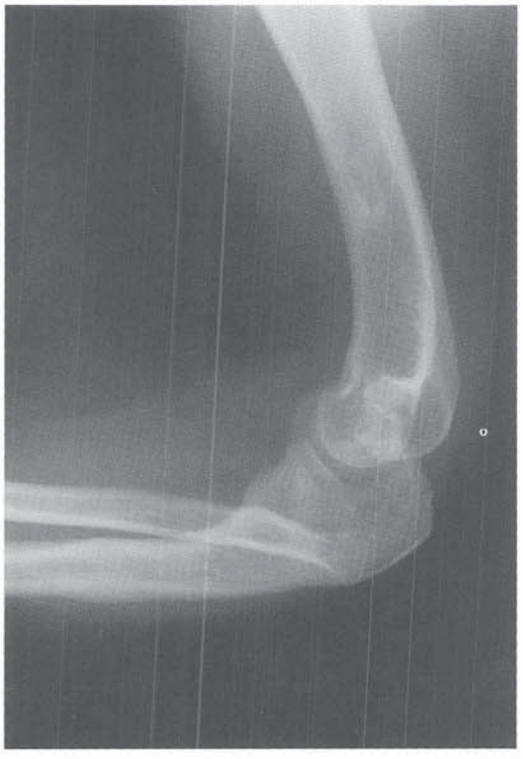


FIGURE 29–5 Radial head dislocation in a 16-year-old girl with achondroplasia.

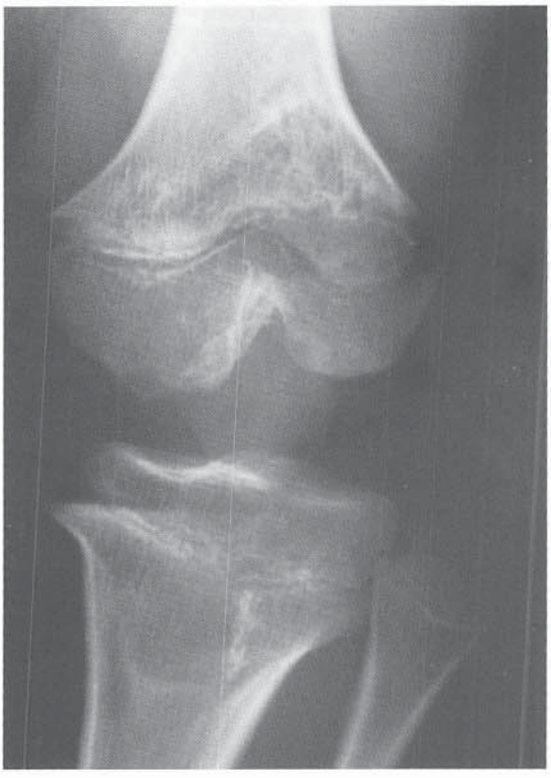


FIGURE 29–6 AP radiograph of an 8-year-old girl with achondroplasia. The distal femoral physis is V-shaped.

Patients with achondroplasia usually have normal intelligence.

RADIOGRAPHIC FINDINGS

The characteristic radiographic findings in achondroplasia are shortness of the tubular long bones, with an apparent increase in bony diameter and density. The metaphyses are widened and flared, but the epiphyses are uninvolved. The growth plates are U-shaped or V-shaped. This is best seen at the distal femur (Fig. 29–6). The two limbs of the V of the metaphysis appear to embrace the epiphysis. The long bones, especially the tibia, may be bowed. The metacarpal, metatarsal, and phalangeal bones are short and thick.

In achondroplasia the pelvis characteristically appears broad and flat, with squared iliac wings (Fig. 29–7).[10] The broad appearance of the ilium is due to the fact that the pelvis is formed almost entirely by intramembranous ossification, which is undisturbed in achondroplasia. The sciatic notches are small. The acetabulae are horizontal and may be notched in very young patients. Ponseti found that disturbances in enchondral ossification at the triradiate cartilage lead to abnormal vertical growth of the iliac contribution to the acetabulum and therefore to radiographic flattening.[62] Because the width of the pelvic inlet is greater than its depth, the pelvis takes on the appearance of a champagne glass.

The proximal femoral metaphyses are widened and the femoral necks are short as a result of the abnormalities in longitudinal growth. The greater trochanter is formed by periosteal ossification and is normal in size, leading to a decrease in the articulotrochanteric distance. True coxa vara

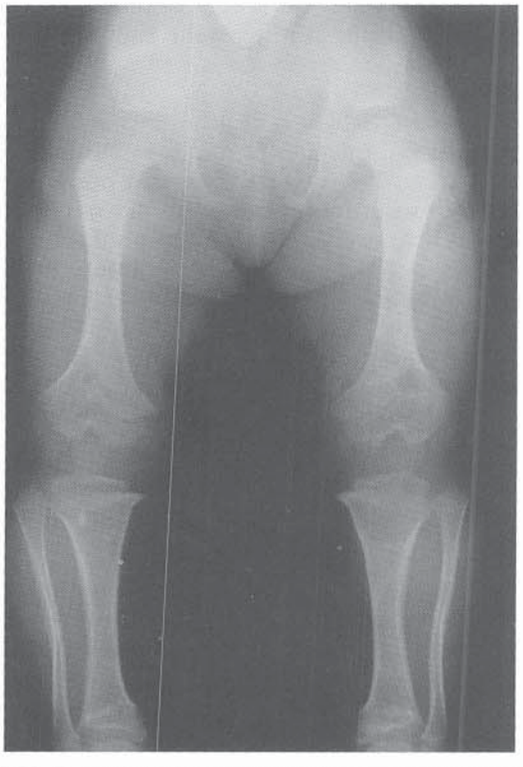


FIGURE 29–7 Radiographic appearance of the pelvis in achondroplasia. Characteristically iliac wings are short and broad, and the inlet of the pelvis has the shape of a champagne glass (width greater than depth).

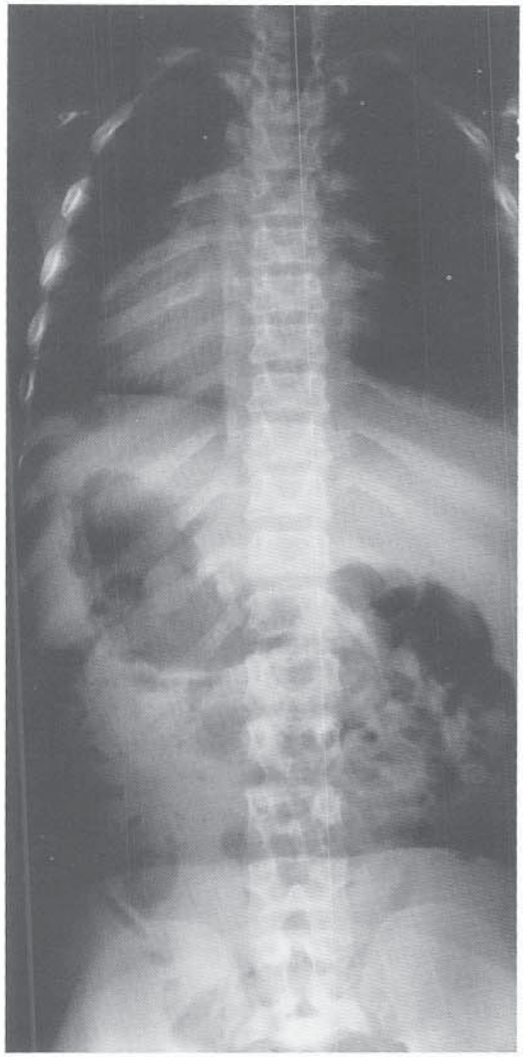


FIGURE 29–8 AP radiograph of an achondroplastic spine. The interpedicular distance progressively decreases distally in the lumbar spine rather than increasing.

is not present, but the overgrowth of the greater trochanter leads to the appearance of varus.[5]

The spine also has a unique appearance in patients with achondroplasia. The spinal canal, as measured by the interpedicular distance, normally widens as one proceeds distally in the lumbar spine from L1 to L5. However, in patients with achondroplasia the spinal canal narrows and the interpedicular distance decreases (Fig. 29–8). Wynne-Davies and associates found interpedicular narrowing from L1 to L5 in 69 percent of achondroplastic patients. No patient with achondroplasia showed widening of the interpedicular distance.[83] The progressive decrease in size of the lumbar spinal canal is due to premature synostosis between the vertebral bodies and their arches. The pedicles are short and broad, a feature best seen on lateral radiographs. The posterior vertebral bodies may appear scalloped in the lumbar spine (Fig. 29–9).

The thoracolumbar spine in the toddler with achondroplasia may appear kyphotic in alignment, with abnormal anterior vertebral growth in severe cases.

Skull radiographs show marked shortness of the base of the skull. The foramen magnum is smaller than normal.[30,31] The frontal region of the skull protrudes to accommodate the enlarging brain.

PRENATAL DIAGNOSIS

A great deal of attention has been paid to the prenatal diagnosis of achondroplasia. Ultrasound does reveal decreased femoral length for gestational age. However, confusion arises in distinguishing achondroplasia from more severe and even lethal forms of dwarfism. If achondroplasia seems likely, based on ultrasound findings, studies of the FGFR gene may confirm the diagnosis.[45,65,69]

DIFFERENTIAL DIAGNOSIS

In the newborn with achondroplasia, the diagnosis usually is easy to make. At birth, achondroplasia must be distinguished from lethal forms of short-limbed dwarfism, such as thanatophoric dwarfism and achondrogenesis.[71] In the older child, achondroplasia may be confused with the mucopolysaccharidoses (such as Morquio's syndrome) and with hypochondroplasia, which is less severe than achondroplasia but has similar radiographic findings.

ORTHOPAEDIC CONSIDERATIONS

Craniocervical Stenosis. Most of the orthopaedic problems encountered in patients with achondroplasia are related to the spine.[4] Young babies are predisposed to cervical cord compression because of hypoplasia of the foramen magnum.[30,41,50] Sudden death has been reported in infants less

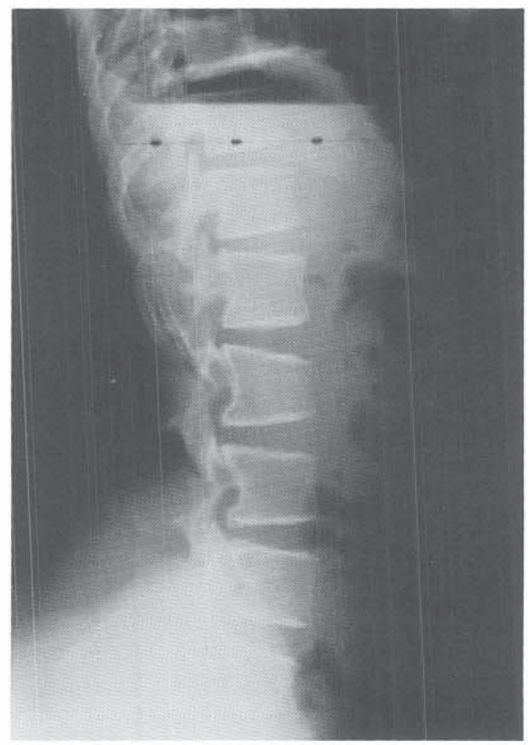


FIGURE 29–9 Lateral radiograph of an achondroplastic lumbar spine showing posterior scalloping of the vertebral bodies and shortened pedicles.

than 1 year old with achondroplasia, and cervical cord compression has been suggested as the cause.[8,29,59] Presenting symptoms in babies with brain stem and upper cervical cord compression consist of sleep apnea and hypotonia. Physical examination reveals hypotonia, but decreased tone and a developmental delay of 3 to 6 months in achieving motor milestones are common in most infants with achondroplasia.[78] The presence of clonus and lower limb hyperreflexia should generate concern.[58]

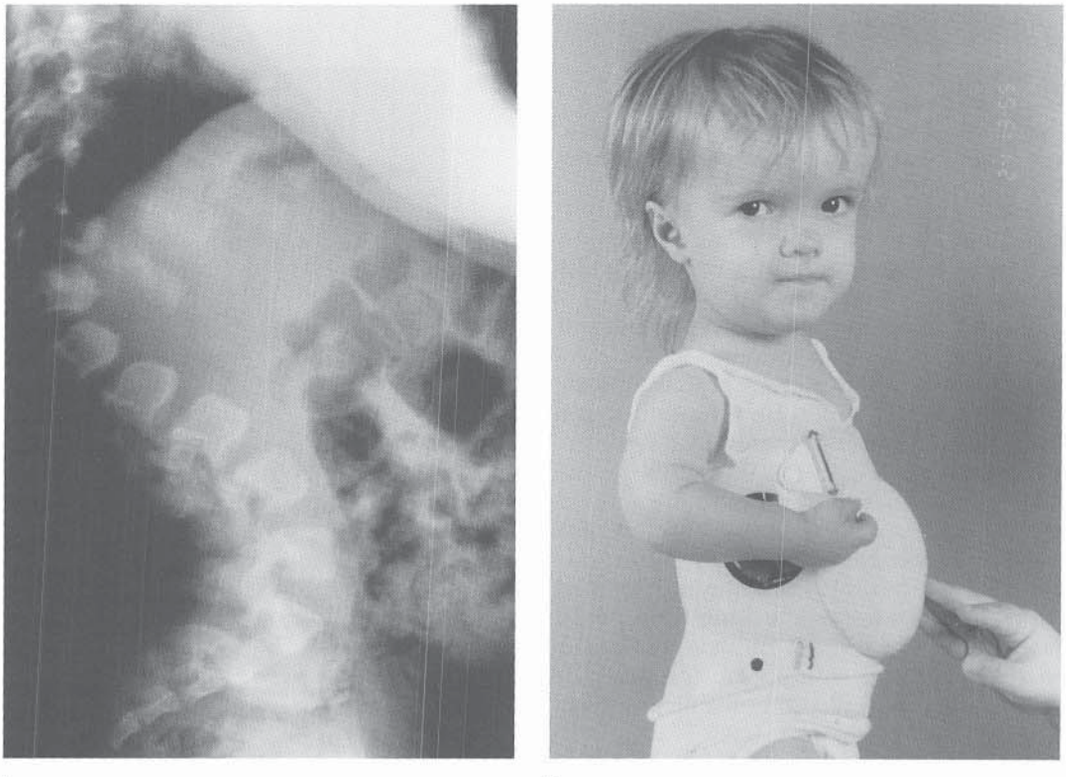
Sleep apnea may result from two mechanisms.[66] Central sleep apnea is caused by compression of the upper cervical spinal cord,[21,79] while obstructive sleep apnea (also common in children with achondroplasia) is due to upper airway obstruction as a result of midface hypoplasia. Sleep studies may be able to differentiate the two forms.[32,81,87] Somatosensory-evoked potentials may also confirm the presence and neurologic significance of foramen magnum stenosis.[12,49,68] Magnetic resonance imaging (MRI) is useful in delineating the myriad abnormalities of the cranial, cerebral, and cervicomedullary junction present in children with achondroplasia.[37,77] The treatment of central sleep apnea is neurosurgical craniocervical decompression.[3] Alternatively, some children have been placed on apnea monitors and closely observed without surgery. Distinguishing between children who need decompression and those who do not remains difficult and controversial.[79] The treatment of obstructive sleep apnea involves the otolaryngologist and may require tonsillectomy, adenoidectomy, or, in very rare cases, tracheostomy.[25,46,73] Although orthopaedic surgery is not needed for either form of sleep apnea, the orthopaedist often oversees the care of the achondroplastic child and must be aware of these potentially dangerous problems so that timely referrals can be made.

The appearance of an enlarged head in children with achondroplasia may raise concern about the presence of hydrocephalus. Hydrocephalus does occur on rare occasions in children with achondroplasia.[17,22] Chiari malformations have also been seen.[86] Growth and head circumference charts specific to children with achondroplasia are available.[35,48] Any deviation from these charts merits attention.

Cervical spine instability is rare in patients with achondroplasia. Some authors advocate posterior fusion in individual cases.[28]

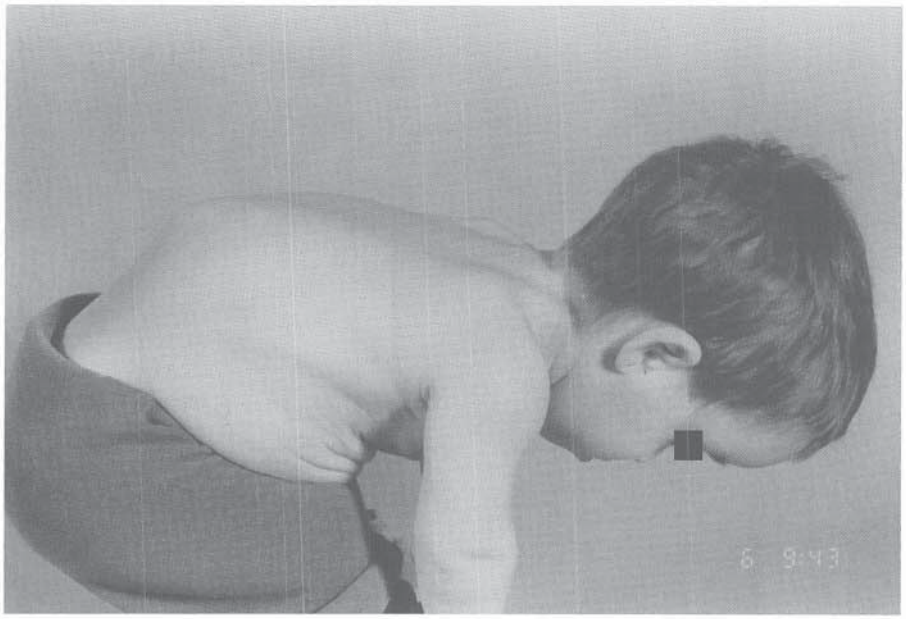
Thoracolumbar Kyphosis. Thoracolumbar kyphosis is a developmental problem that becomes evident in the slightly older infant with achondroplasia. Kyphosis at the thoracolumbar junction is seen in almost all young babies who are not yet able to walk. It has been proposed that the large head size of the infant, combined with low muscular tone, lack of trunk control, and a tendency toward hip flexion, leads to the kyphotic deformity. The kyphosis is most noticeable when the baby is placed in a sitting position. As the child learns to walk, muscle tone and trunk control improve and the kyphosis usually resolves without treatment.[39]

The role of sitting in the young infant in the development of thoracolumbar kyphosis has been investigated by Hall[26] and Pauli and associates.[56] The authors suggested that unsupported sitting by hypotonic infants with achondroplasia leads to the development of kyphosis. Pauli and associates



A B

FIGURE 29–10 **A,** Lateral radiograph of a 1+9-year-old girl with achondroplasia. Note the beaklike irregularities of the anterior vertebral bodies at the thoracolumbar junction. **B,** The child was treated with a TLSO orthosis.



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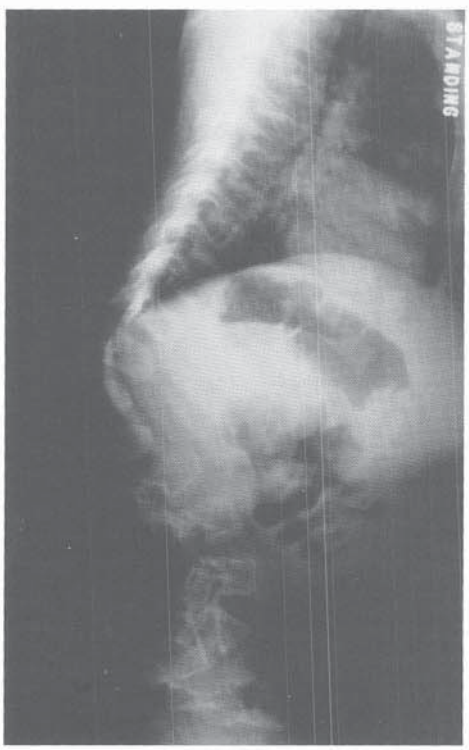

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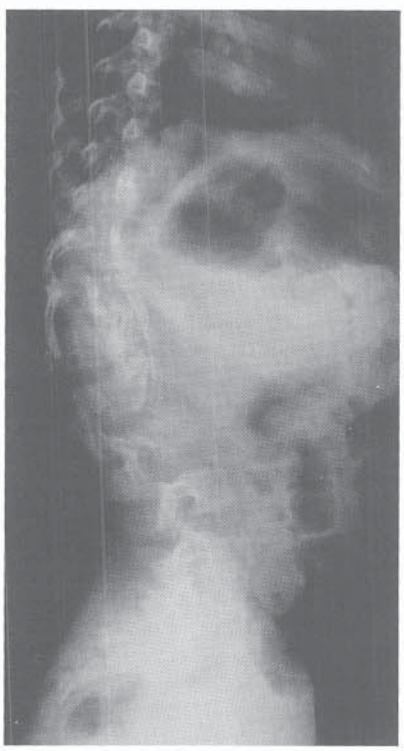


C

FIGURE 29–11 **A,** A 5-year-old boy with persistent thoracolumbar kyphosis despite bracing. **B,** Anterior vertebral body changes are seen in the apex of the kyphosis. **C,** Anterior spinal fusion with two rib strut grafts and posterior spinal fusion without instrumentation was performed.

have advocated prohibiting unsupported sitting in achondroplastic infants.[56] They also recommend early bracing with TLSO (thoracolumbosacral orthoses) in infants with kyphosis, stating that structural changes in the anterior vertebral bodies (e.g., anterior beaking and wedging) may be prevented with earlier support. More commonly, brace treatment is reserved for children whose kyphosis is still present at 3 years of age[79] or in whom the kyphosis does not resolve when the child becomes ambulatory (Fig. 29–10).

Surgical intervention is required for the few young children who have persistent kyphosis. Untreated kyphosis, when combined with spinal stenosis, has led to the development of neurologic deficits in later childhood. For that reason, Tolo recommends surgery for patients with progressive kyphosis, and for children 5 years old or older who have 30 degrees of residual kyphosis at the thoracolumbar junction.[79] Surgery consists of anterior and posterior spinal arthrodesis.[7] Anterior surgery combines diskectomy with anterior strutting with rib graft (Fig. 29–11). Posterior fusion may be

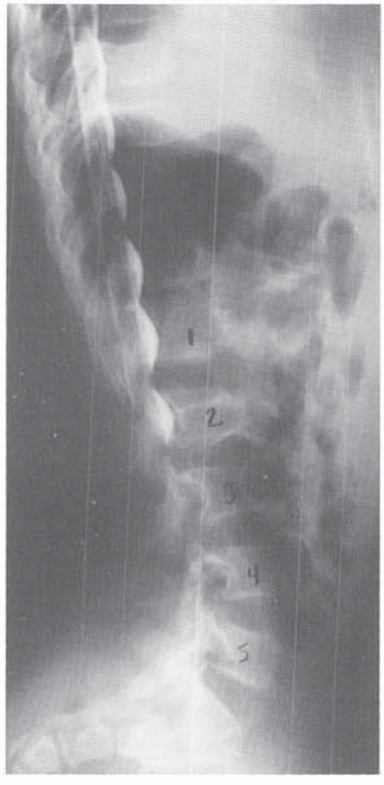


FIGURE 29–12 Myelographic appearance in a 6-year-old girl with spinal stenosis secondary to achondroplasia. Myelography shows indentation of the narrowed dye column and confirms significant lumbar stenosis.

accomplished without the use of internal hardware. If posterior instrumentation is used, great care should be exercised. The stenotic spinal canal and lack of subarachnoid fluid space leave little room for the use of instrumentation in the canal. Paraplegia has been reported as a complication of posterior instrumentation.[79]

Spinal Stenosis. Interpedicular narrowing in the lumbar spine results from abnormal growth of the pedicles in the achondroplastic spine. Anatomic changes seen in the lumbar spine include thickening of the pedicles, hypertrophy of the facets, and enlargement of the laminae.[27] These abnormalities lead to spinal stenosis, which becomes symptomatic most often in the third decade of life but earlier (in the teen years) in some patients. One-third of patients with achondroplasia and symptomatic spinal stenosis present by age 15 years.

Patients with spinal stenosis complain of neurogenic claudication, or pain in the lower back and legs that is exacerbated by activity.[19] The patients relieve the pain by bending over or squatting, which reduces the amount of lumbar lordosis and thereby increases the size of the spinal canal. As the stenosis continues, walking endurance decreases and neurologic signs such as clonus, hyperreflexia, lower extremity weakness, and myelopathy may develop.[79] Paresthesias are quite common, whereas sensory changes occur less frequently.

Not all patients with achondroplasia develop symptomatic stenosis, even though all do have anatomic stenosis. In a study by Kahanovitz and associates, the presence of a thoracolumbar kyphosis (regardless of its magnitude), an L1 interpedicular distance less than 20 mm, an L5 interpedicular distance less than 16 mm, and a large structural lumbar lordosis were found more frequently in patients with disabling symptoms.[36] Of the patients in this study who developed symptoms of spinal stenosis, 91 percent did so by age 30 years. Wynne-Davies and associates also found that the coexistence of thoracolumbar kyphosis with stenosis led to neurologic compromise.[83] The additive effects of thoracolumbar junction kyphosis, degenerative disk narrowing, lumbar hyperlordosis, and interpedicular narrowing lead to critical narrowing of the spinal canal and a predisposition to neurologic deficits.[79]

MRI is useful in identifying the extent of the stenosis. Computed tomography (CT) myelography documents the stenosis very well (Fig. 29–12). When myelography is performed, a cisternal puncture is required, as a lumbar puncture may exacerbate neurologic compromise.[75] MRI and myelography are used not only to identify the number of levels with significant stenosis, but also to assess the intervertebral disks for other pathology that would affect the neurologic status of the child (Fig. 29–13).

Treatment is by surgical posterior decompression. Laminectomy usually is insufficient in decompressing enough of the neural elements, and a more lateral decompression (including undercutting of the facet joints) usually is necessary.[42] If possible, the facet resection should be minimal, consisting of undercutting and removal of the medial portion of the inferior facet. A wide decompression must be performed in combination with foraminotomies of the lateral recesses. Some authors suggest that the decompression extend three levels cephalad to the myelographic block, at

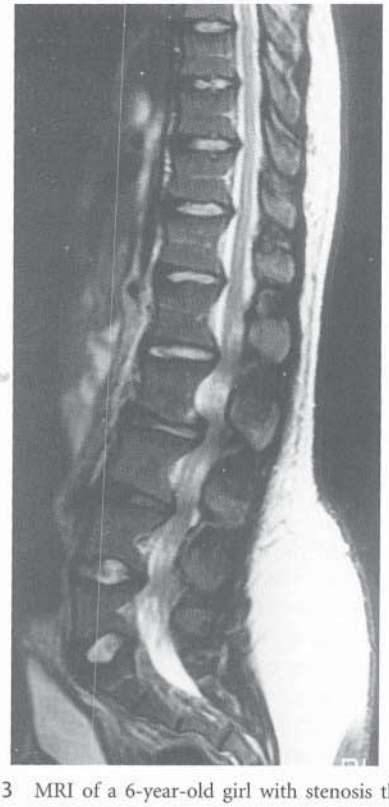


FIGURE 29–13 MRI of a 6-year-old girl with stenosis throughout the lumbar spine.

least to S2, and laterally at least to the facets.[64] The common error in decompressing stenosis in achondroplasia is to address too few levels.

Because of the stenosis and preexisting neurologic symptoms, intraoperative somatosensory-evoked potential monitoring usually is not possible. Additional technical difficulty is encountered in safely removing the laminae in the absence of a normal subarachnoid space. High-speed burs are used to thin the laminae, followed by curettage to gently remove the remaining bone. There may be no room in the canal for the usual Kerrison rongeurs.[79]

Because instability rarely develops, even after wide decompression, primary fusion is generally not indicated.[80] When fusion is performed, instrumentation within the canal is contraindicated because of the risk of paraplegia. Tolo advocates fusion in achondroplastic spinal stenosis only when thoracolumbar kyphosis is present.[79] He performs the fusion posterolaterally, with postoperative immobilization in a cast when the apical vertebrae in the kyphotic segment are only mildly wedged and there is no preexisting neurologic compromise. If there are neurologic deficits, he recommends anterior decompression and fusion with rib or fibular strut grafting, and posterolateral fusion with laminectomies. Instrumentation posteriorly with pedicle screw fixation is possible as well, as the fixation does not violate the decompressed canal.

Neurologic deficits of short duration are usually reversible with surgical decompression.[47] Some patients have, or later develop, compression adjacent to the myelographic site of the stenosis, and some patients develop hypertrophic scarring at the site of initial decompression. Recurrence of neurologic compromise requires additional decompression.[64] Long multisegmental decompression of 10 or more segments results in a lesser likelihood of recurrent symptoms.[74]

Angular Deformities of the Lower Extremities. Angular deformities of the lower extremities may develop during childhood in patients with achondroplasia. Genu varum and tibia vara are more common than valgus deformity.[5] Relative overgrowth of the fibula compared to the tibia has been proposed as the cause of the varus.[62] Despite the presence of angular deformity, degenerative arthritic changes in the knees are quite rare. For that reason, surgery is suggested only for patients whose varus is symptomatic or for those who find their deformity unacceptable cosmetically. Bracing has not been successful in the management of genu varum in patients with achondroplasia. Orthotic use for genu varum has led to peroneal nerve palsy in these patients.[4]

Fibular epiphyseodesis has been recommended for the treatment of tibia vara and fibular overgrowth in patients with achondroplasia.[62] Successful correction of varus has been seen in patients between 7 and 10 years of age. Although unpublished reports looked promising, others have found the procedure unpredictable.[5]

Surgical treatment of genu varum in achondroplasia most commonly consists of proximal tibial and fibular osteotomy with fixation (Fig. 29–14). Stabilization of the osteotomy has been achieved with crossed pins, internal fixation, and external fixation. Except in severe cases, proximal level osteotomies are sufficient to correct both the genu varum and the varus at the ankle.[5] Patients with achondroplasia have ligamentous laxity. Thus, during surgery, attention must be directed toward restoring the mechanical axis through precise bony realignment rather than through the knee joint, by stressing the loose medial collateral ligament.

Hip flexion contractures are commonly seen in patients with achondroplasia. However, surgical release of the contractures is not necessary.

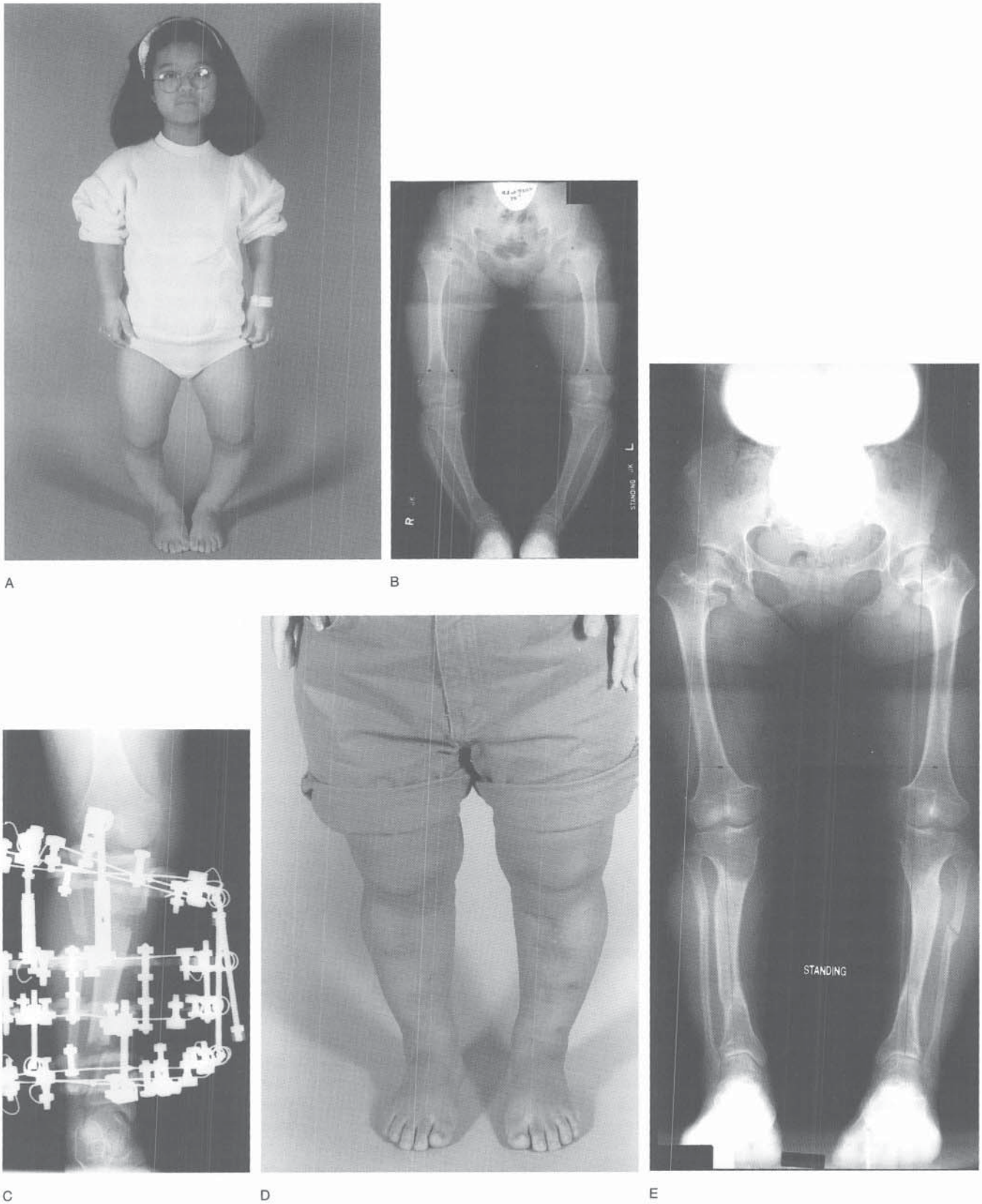
Short Stature. Significant controversy exists regarding the lengthening of short extremities in patients with achondroplasia to achieve a taller stature. Little People of America, a support group of patients and families with bone dysplasias, does not support the use of surgical lengthening to increase height. Nonetheless, lengthening is being performed in various centers, particularly in Europe.

Adolescence usually is the time when lengthening is undertaken (Fig. 29–15).[24,55,85] Seven to 15 cm usually is the length achieved with a single surgical lengthening,[1,13,63] although some authors report greater gains in length.[11,14] Price found that lengthening of approximately 35 percent of initial bone length could be achieved, but complications occurred when greater lengthening was attempted.[63] Leg lengthening does add height. However, the usual gains seen as a result of surgical lengthening do not place the patient within the range of normal height, but instead place him or her at the tall end of height for dwarfism. A marked increase in height may be achieved by staged lengthenings of both tibiae and femora,[61] but this approach subjects the child to multiple operations and hospitalizations. In a small study comparing body image before and after leg lengthening, an improvement in self-image was found after lengthening, but achondroplastic patients still had a more negative body image than a normal control group despite the lengthening.[18]

Some centers advocate simultaneous bilateral femoral or tibial lengthenings, while others find that the lengthenings are better tolerated if one femur and the contralateral tibia are lengthened together. Unilateral tibial and femoral lengthenings are not recommended, because if the patient does not tolerate the lengthening and either refuses or is unable to undergo the contralateral procedure, the child is left with a limb length discrepancy. Lengthening of the humeri follows the lower extremity lengthenings.

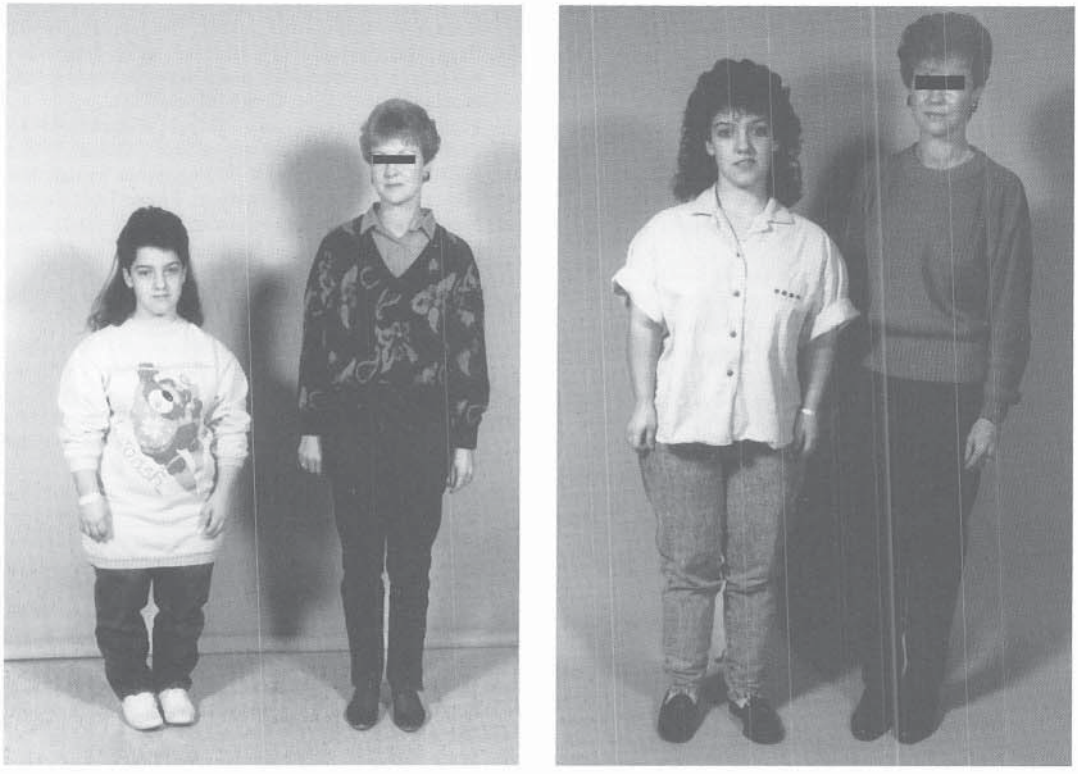
The technical considerations that pertain to lengthening via callotasis or chondrodiastasis are discussed in greater detail in Chapter 23, Limb Length Discrepancy. The tissues in patients with achondroplasia, such as muscle and nerve, tolerate lengthening with fewer problems than in other shortening conditions, such as congenital short femur, probably because the muscle lengths exceed bone lengths before lengthening.[55] Nonetheless, complications such as infection, joint stiffness, and even death have been reported in patients with achondroplasia. Patients with achondroplasia seem to be at increased risk of developing peroneal nerve palsy during lengthening, with foot drop noted in up to one-third of patients.[13]

Growth hormone is currently being used to augment the height of patients with achondroplasia.[51,84] Early results indicate that some, but not all, children with achondroplasia experience increased longitudinal growth while receiving growth hormone.[34,72,82] The greatest acceleration in growth velocity has been seen during the first year of treatment.[38,72] Treatment with growth hormone has not led to an increase



A B C D E

FIGURE 29–14 **A,** Twelve-year-old female with achondroplasia and symptomatic genu varum. **B,** Radiographs of the lower extremities reveal bilateral tibia vara. **C,** Correction by bilateral proximal and distal tibial osteotomy and Ilizarov fixation. **D,** Postoperative appearance of lower extremities following valgus osteotomy with external fixation of tibias. **E,** Radiograph following healing and removal of fixators.



A B

FIGURE 29–15 **A,** A 14-year-old girl with achondroplasia, and her mother, prior to limb lengthening. **B,** Postoperative appearance of the child after lengthening of the lower extremities.

in the body disproportion.[70,76] Administration of growth hormone continues on an investigational basis, and final judgment of its efficacy should be reserved until the patients involved in these studies reach their final adult height.

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Hypochondroplasia

Hypochondroplasia is a rare form of dwarfism that resembles achondroplasia but is less severe.

GENETICS

Hypochondroplasia also is transmitted as an autosomal dominant trait, and its gene defect also encodes for FGFR-3. The genetic difference between achondroplasia and hypochondroplasia is the specific amino acid mutation.[3,11] There is more variability in the mutation that causes hypochondroplasia; thus, there is more variability in the clinical expression of the gene.[4] The estimated incidence of hypochondroplasia is three to four per million live births.[16,17]

CLINICAL FEATURES

The condition cannot be detected at birth and, if mild, may remain undiagnosed throughout the person's life. Clinically, patients with hypochondroplasia are short, but less so than those with achondroplasia. The spectrum of severity is wide, ranging from quite severe short-limbed dwarfism to short, apparently normal prepubertal children who manifest disproportion only after failure to achieve a pubertal growth spurt.[2] The sitting height to standing height ratio is increased, but the body disproportion may not be apparent until puberty. Final height has been reported between 118 and 165 cm.[9] The head appears only slightly enlarged compared with the limbs, but the forehead is large and high. Some patients have small hands.[13]

RADIOGRAPHIC FINDINGS

Hall outlined the following radiographic criteria for the diagnosis of hypochondroplasia.[8] The primary criteria are (1) a narrowed or unchanged lumbar interpedicular distance, (2) squared, shortened ilia, (3) a short, broad femoral neck, (4) short tubular bones, with metaphyseal flaring, and (5) mild to moderate brachydactyly. Secondary criteria are (1) AP shortening of lumbar pedicles, (2) dorsal concavity of the lumbar spine, (3) a long distal fibula, (4) a short distal ulna, and (5) a long ulnar styloid.

ORTHOPAEDIC CONSIDERATIONS

Orthopaedic problems are similar to those seen in achondroplasia. Lumbar lordosis usually is accentuated, and mild interpedicular narrowing can predispose some patients with hypochondroplasia to symptomatic spinal stenosis. The fibula is longer than the tibia,[12] and genu varum may develop in approximately 8 percent of patients.[17] Mild flexion contractures of the elbow and knee develop in some cases.

TREATMENT

Leg lengthening has been performed in patients with hypochondroplasia and can result in enough gain in length to place the child in the low-normal range.[1,6,7,15,18] Growth hormone therapy remains investigational at this time.[2,10,14] The response to growth hormone is greatest during the first year of use.[5] The response varies among patients, perhaps because of the genetic heterogeneity of the disease.

Disabling symptoms do not occur, and patient life expectancy is normal.

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Thanatophoric Dwarfism

Thanatophoric dwarfism is the most common lethal form of dwarfism.

GENETICS

The genetic basis for the disease is found on the same FGFR gene responsible for achondroplasia and hypochondro-

plasia, but the mutation is different.[1,14–16] Because the disease is fatal, all cases result from spontaneous mutations. The incidence of thanatophoric dwarfism is between 0.2 and 0.5 per 10,000 births.[11] As with achondroplasia, there is a link with older paternal age.[12]

PRENATAL DIAGNOSIS

Prenatal diagnosis of this condition is possible with ultrasound.[3,4,8] Images reveal short, squat upper and lower limbs, a narrow thorax, polyhydramnios, and relative enlargement

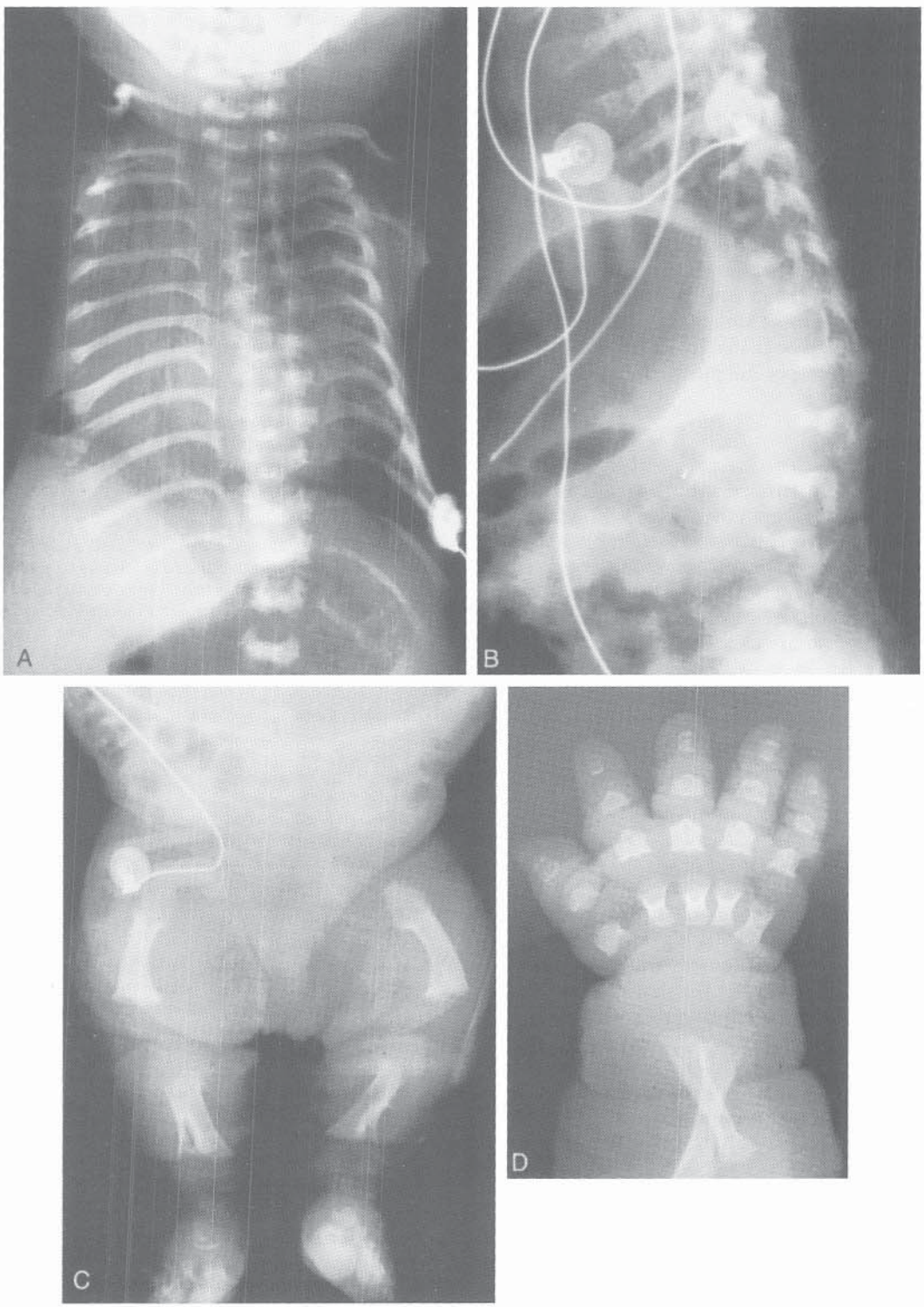

FIGURE 29–16 Thanatophoric dwarfism, characterized by a large head, very short limbs, and a narrow thorax. **A** and **B,** AP and lateral views of the thorax. Note the short, horizontal ribs and platyspondyly with notched end-plates. **C,** AP view of the femora and tibiae. The long bones are shortened and bowed. The femora are shaped like telephone receivers. **D,** AP view of the right hand and forearm. Note the short, broad phalanges, metacarpals, radius, and ulna.

of the head.[2,7] Obstetric plain radiographs may be required to support the diagnosis.[13] Severe platyspondyly is a characteristic feature on both ultrasound and plain radiographs with thanatophoric dysplasia.

TYPE 1 AND 2 FORMS

Two forms of thanatophoric dwarfism exist and are differentiated by the absence (type 1) or presence (type 2) of a "cloverleaf" skull. Type 1 is more common. Histopathology reveals significant brain malformations in both types.[5,17] Severe disturbances of ossification at the growth plate are seen on histologic studies.[6] Type 2 thanatophoric dwarfism is differentiated from the classic type 1 histologically by many bone-lined, penetrating vascular canals in the physis and by hyperactive osteoblasts and osteoclasts in the metaphysis.[18] In type 1 the femurs are curved, while in type 2, straight femurs are associated with a cloverleaf skull.[14]

RADIOGRAPHIC FINDINGS

The radiographic features of thanatophoric dysplasia include markedly flattened vertebral bodies with a typical U-shaped deformity, a flat squat pelvis, and short extremities with flaring and irregularity of the metaphyses.[10] The thorax is narrow, with short horizontal ribs (Fig. 29–16).

PROGNOSIS

Cardiorespiratory failure uniformly results in death in the neonatal period.[10] Thanatophoric dwarfism and the other less common lethal chondrodysplasias are discussed in detail by Maroteaux and associates.[9]

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Pseudoachondroplasia

Pseudoachondroplasia is characterized by short-limbed dwarfism in which both the epiphyses and metaphyses are involved. Affected individuals have significantly short stature and a predisposition to premature osteoarthritis. Pseudoachondroplasia was first described by Maroteaux and Lamy in 1959.[13] In 1961, Ford and associates clearly differentiated pseudoachondroplasia from achondroplasia and spondyloepiphyseal dysplasia.[9] The prevalence of pseudoachondroplasia is estimated at four per million.

GENETICS

Pseudoachondroplasia is usually transmitted as an autosomal dominant trait. The question of whether autosomal recessive forms exist or whether familial recurrence of pseudoachondroplasia is the result of mosaicism remains debated.[8] In either case, the two types of inheritance are not distinguishable radiographically or clinically. Wynne-Davies and associates proposed that four forms exist: autosomal dominant severe, autosomal dominant mild, autosomal recessive severe, and autosomal recessive mild.[20]

Most cases are the result of spontaneous mutations. There has been a genetic linkage of pseudoachondroplasia to the pericentromeric region of chromosome 19.[5,10] This region encodes for cartilage oligomeric matrix protein (COMP), which plays a role in calcium binding within cartilage.[3] Dietz and Mathews summarized that a disruption of calcium-dependent proteoglycan binding by COMP may result in the accumulation of proteoglycan in chondrocytes.[7] Similar mutations are seen in the COMP gene in multiepiphyseal dysplasia (MED), indicating phenotypic overlap between pseudoachondroplasia and MED.[4]

PATHOLOGY

Histologic studies of cartilage from patients with pseudoachondroplasia reveal noncollagenous protein accumulated in the rough endoplasmic reticulum of chondrocytes.[16] Electron microscopy studies of iliac crest specimens have demonstrated abnormalities in proteoglycans.[15]

CLINICAL FEATURES

The appearance of newborns with pseudoachondroplasia is normal, and the dysplasia is not clinically apparent until 1 to 3 years of age, when rhizomelic shortening becomes

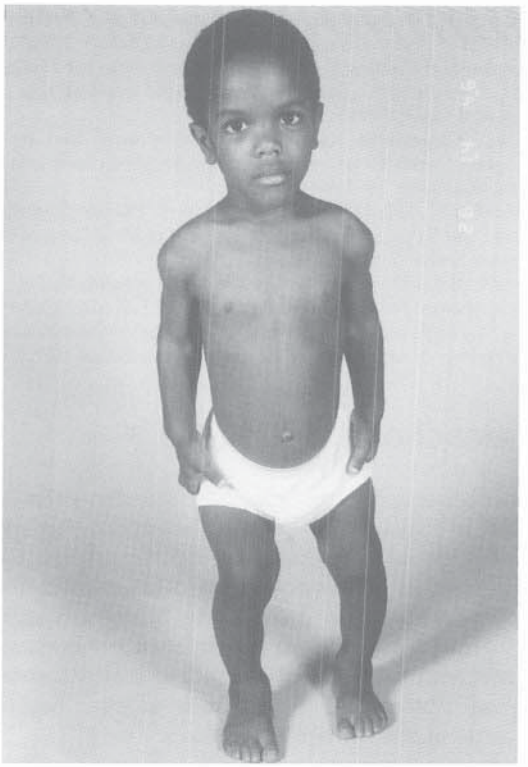

FIGURE 29–17 Boy age 5 years 4 months with pseudoachondroplasia. His face appears normal; his limbs are short, with valgus of the right knee and varus of the left knee.

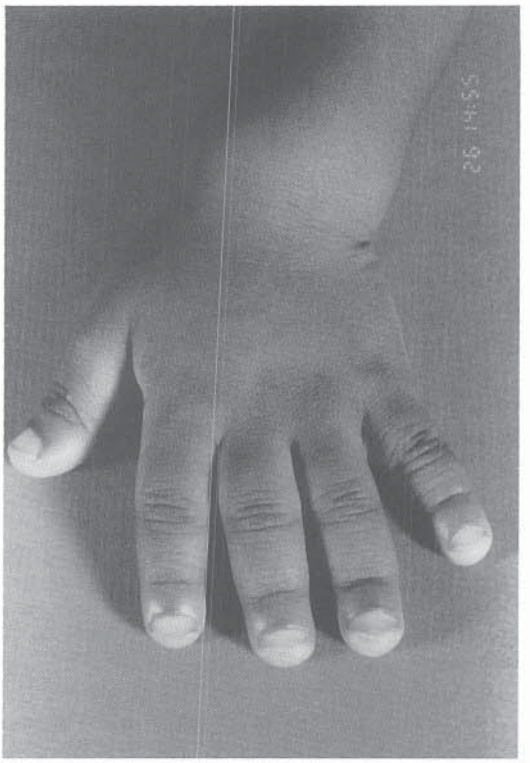

FIGURE 29–18 In pseudoachondroplasia the fingers are short and stubby.

noticeable. Adult height ranges from 106 to 130 cm.[1] Growth curve charts specific to pseudoachondroplasia are available.[11]

The skull and facies in pseudoachondroplasia are normal, and this is helpful in differentiating it from achondroplasia, in which frontal bossing and midface hypoplasia are present (Fig. 29–17). The features distinguishing between pseudoachondroplasia and achondroplasia are summarized in Table 29–3.

The fingers and toes of patients with pseudoachondroplasia are short and thick (Fig. 29–18).

Patients may have mild thoracolumbar kyphosis, and a few patients develop scoliosis. Lumbar lordosis usually is pronounced (Fig. 29–19).

Angular deformity of the lower extremities is common in pseudoachondroplasia. Genu valgum or varum may occur. Some children develop "windswept" deformities of the knees, in which genu valgum is present on one side and genu varum on the other (Fig. 29–17). Patients with pseudo-

TABLE 29–3 **Features Distinguishing Pseudoachondroplasia and Achondroplasia**

Features	Pseudoachondroplasia	Achondroplasia
Inheritance	Heterogeneous; both autosomal dominant and recessive Most sporadic	Autosomal dominant Almost all new mutants
Skull and facies	Normal	Bulging forehead; low nasal bridge Sometimes hydrocephalic
Spine	Lumbar lordosis No progressive narrowing of interpedicular distance Platyspondyly with anterior central breaking	Severe lumbar lordosis Progressive narrowing of interpedicular distance in lumbar spine No platyspondyly; short pedicles
Long bones	Both epiphysis and metaphysis affected Epiphysis delayed in ossification, irregular, and fragmented Metaphysis flared	Epiphysis normal (only metaphysis affected) Metaphysis wide
Pelvis and sciatic notch	Shallow acetabulum Wide great sciatic notch Iliac wings flared	Horizontal acetabular roof Great sciatic notch narrowed to a slit Iliac wing squared
Problems and complications	Degenerative arthritis due to incongruous weightbearing (hip and knee joints) Tibia vara	Spinal stenosis due to narrow spinal canal Tibia vara

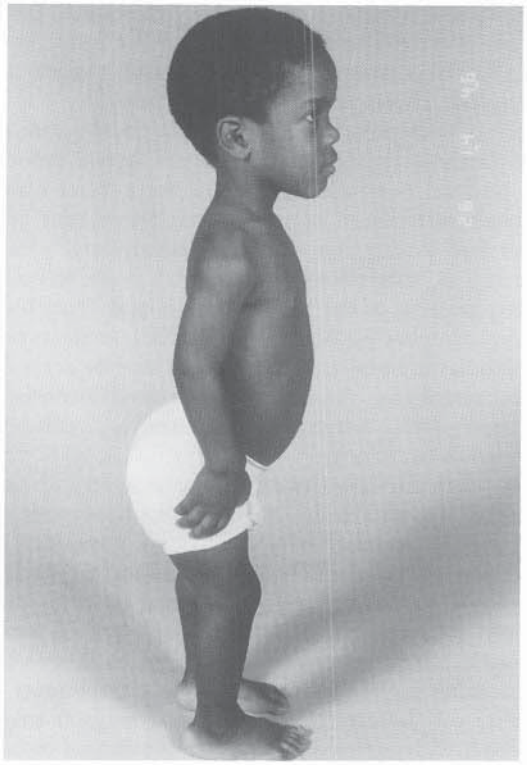

FIGURE 29–19 Increased lumbar lordosis occurs in pseudoachondroplasia as a result of hip flexion contractures.

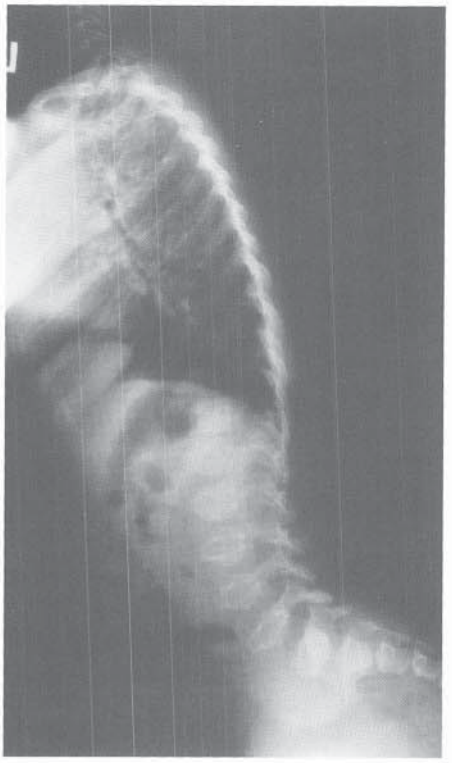

FIGURE 29–20 Platyspondyly with anterior tongue-like projections and increased lumbar lordosis, characteristic of pseudoachondroplasia.

achondroplasia have marked ligamentous laxity,[19] which can accentuate angular deformity of the lower extremities. Pes planus is common.

RADIOGRAPHIC FINDINGS

Spinal radiographs reveal mild platyspondyly, with anterior tongue-like projections and irregular end-plates (Fig. 29–20). The interpedicular distance in the lumbar spine is normal in pseudoachondroplasia, unlike achondroplasia (Fig. 29–21). Scoliosis may be present in teenage patients.

Cervical spinal radiographs may reveal odontoid hypoplasia, such as that seen in other spondyloepiphyseal dysplasias. Atlantoaxial instability may be evident on flexion-extension lateral cervical spine radiographs.

The long bones are short and broad, with flaring of the metaphyses. Ossification of the epiphyses is delayed. When the epiphyses do ossify, they appear irregular and fragmented. The hip and knee are most severely affected (Fig. 29–22).

The appearance of fragmented ossific nuclei of the femoral heads may resemble what is seen in other spondyloepiphyseal dysplasias and even bilateral Legg-Calvé-Perthes disease. Distinguishing features of pseudoachondroplasia that distinguish it from bilateral Legg-Calvé-Perthes disease are synchronous symmetric involvement and the fact that the epiphyses do not develop progressive lucencies in pseudoachondroplasia.[6] The pelvis has normal sciatic notches. The acetabulae are shallow but not horizontal. The triradiate cartilage is widened. There is widening of the ischiopubic junction. Epiphyseal involvement leads to flattening and enlargement of the femoral heads, with subluxation of the

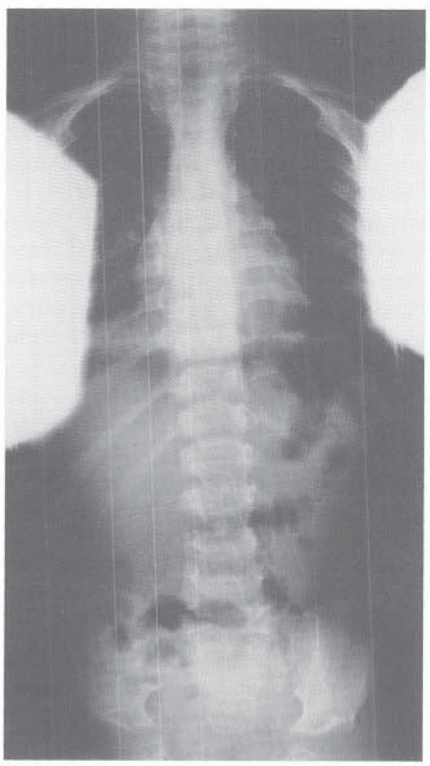

FIGURE 29–21 PA radiograph in pseudoachondroplasia showing normal interpedicular distance in the lumbar spine. In achondroplasia, by contrast, there is progressive narrowing of the lumbar interpedicular distance.

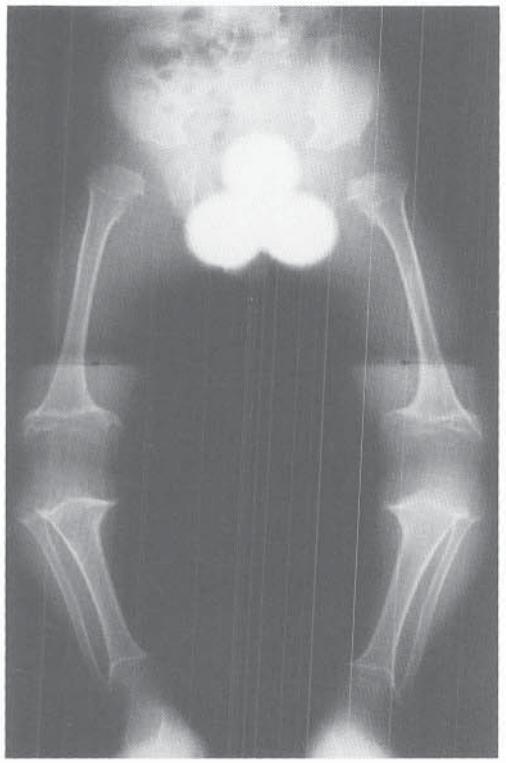

FIGURE 29–22 Flared metaphyses and irregular epiphyses are features of pseudoachondroplasia. Note the absence of proximal femoral ossific nuclei at the hip in this 5-year-old child.

hip. Degenerative arthritis develops in response to the incongruity.

ORTHOPAEDIC CONSIDERATIONS

Lower extremity malalignment usually requires corrective osteotomies. In genu varum associated with achondroplasia, the deformity is present solely within the tibia; however, in pseudoachondroplasia, bony deformity often is evident in both the proximal tibia and distal femur. For this reason, careful preoperative planning with weightbearing radiographs of the entire lower extremity is necessary to fully correct the malalignment. When distal femoral varus is present, valgus osteotomy of the distal femur should be performed. It may be difficult to assess correction of the knee intraoperatively because of the epiphyseal malformation. Thus, arthrography at the time of surgery may be helpful in documenting knee alignment.[1] Care must be taken in assessing the contribution of ligamentous laxity to the skeletal deformity. Recurrence of deformity with growth is common.[12]

Surgical treatment of the hip in pseudoachondroplasia is difficult owing to the incongruity of the femoral head with the acetabulum. The femoral head is flattened and poorly covered by the small, shallow acetabulum. Varus osteotomy of the proximal femur usually creates more incongruity. Valgus osteotomy of the proximal femur may improve joint congruity and enhances abductor function by moving the greater trochanter distally and laterally.[2] Redirectional osteotomies of the pelvis, such as the Salter osteotomy or the triple innominate osteotomy of Steel, are not helpful in pseudoachondroplasia because a prerequisite for these osteotomies is concentric congruity of the joint. In a few cases, a Chiari osteotomy or shelf acetabular augmentation may improve coverage of the femoral head.[2]

Patients with pseudoachondroplasia develop premature osteoarthritis of the hip due to the epiphyseal deformities of the femoral heads. In a study of the natural history of pseudoachondroplasia, approximately 50 percent of adult patients had undergone total hip arthroplasty.[14] Joint replacement in this patient population is technically demanding because of the joint dysplasia and short bones.

Thoracolumbar kyphosis is rarely problematic in pseudoachondroplasia. Lumbar hyperlordosis may be accentuated. Tolo proposed that the cause of increased lordosis is hip flexion contracture, which may be treated by proximal femoral extension osteotomy.[18]

Cervical atlantoaxial instability is associated with pseudoachondroplasia and is due to odontoid hypoplasia in the setting of ligamentous laxity. Neurologic symptoms range from increased fatigability and decreased walking endurance to myelopathy. Flexion-extension lateral cervical spine radiographs are used to quantify the amount of abnormal movement, but MRI performed with the patient in flexion and extension is the best way to observe the impact of the instability on the cervical spinal cord. Surgical treatment of patients with neurologic signs or symptoms consists of atlantoaxial posterior fusion with immobilization in a halo brace.[17] An important part of any pre-anesthetic evaluation of children with pseudoachondroplasia should be radiographic studies for C1–2 instability.

Scoliosis may occur in patients with pseudoachondroplasia. Posterior fusion should be performed when indicated. Instrumentation may be safely employed in patients with pseudoachondroplasia, since they do not have spinal stenosis.[18]

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Spondyloepiphyseal Dysplasia

Spondyloepiphyseal dysplasia (SED) is characterized by disproportionate dwarfism with progressive involvement of the spine and epiphyses of the long bones. There are two major types of SED. The congenita type is detectable at birth, while a milder tarda type presents later in childhood.

SPONDYLOEPIPHYSEAL DYSPLASIA CONGENITA

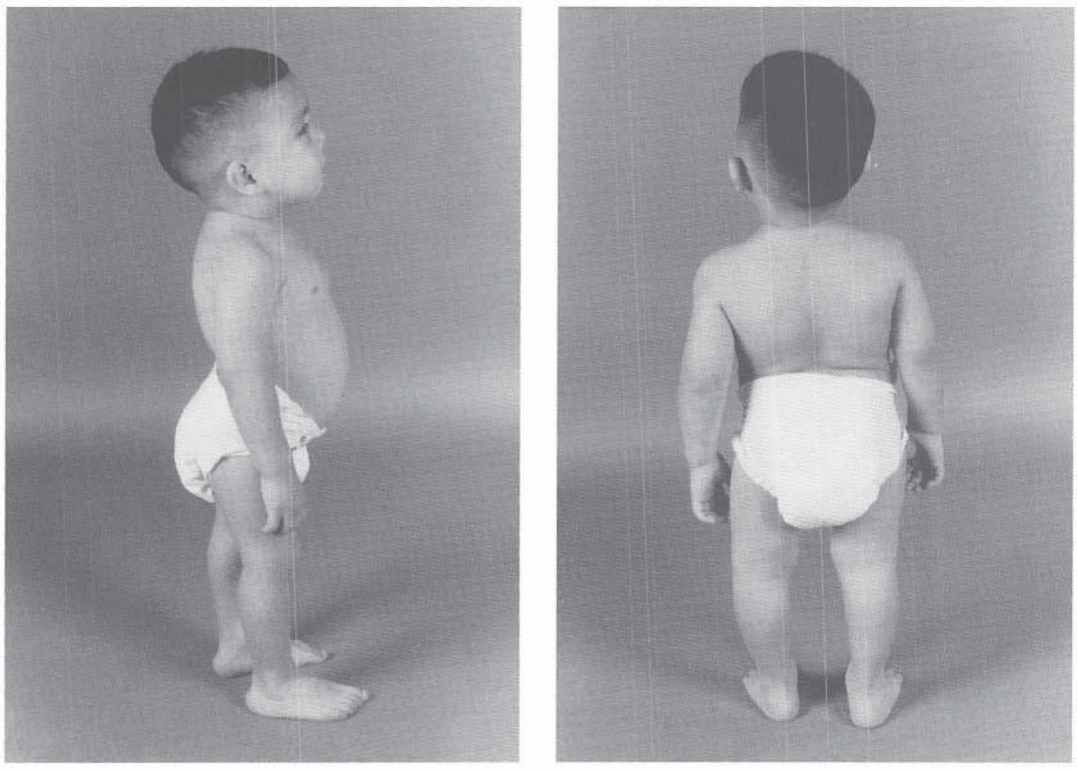
SED congenita results in obvious short-trunk dwarfism and variable degrees of coxa vara, with abnormal epiphyses and vertebral flattening. Shortening is rhizomelic and mesomelic, with relative sparing of the hands and feet.

Genetics. Inheritance is by autosomal dominant transmission, but most cases are sporadic in nature. SED congenita is caused by mutations in the COL2A1 locus on chromosome 12.[18] These result in abnormal type II collagen.[2,7,9] The mutations seen in patients with SED congenita are closely related to those that cause Kniest's dysplasia.[8]

Clinical Features. Clinically, short stature is present (Fig. 29–23).[13] The patient's eyes are wide-set, the neck is short, and the chest appears barrel-shaped. Angular deformity of the lower extremities is common, particularly genu valgum. Lumbar lordosis may be accentuated and is usually due to hip flexion contractures. The lordosis gives the abdomen a protuberant appearance. A waddling gait is produced by the coxa vara. Clubfoot deformity can be seen in patients with SED congenita.

Associated anomalies in SED congenita are cleft palate, myopia with retinal detachment, cataracts, deafness, and herniae.[16,21] A rare form of SED congenita is associated with nephrotic syndrome.[6,26,27]

Radiographic Findings. Radiographic findings include the delayed appearance of the epiphyses.[10] The femoral heads are not apparent on radiographs until the patient is approxi-



A B

FIGURE 29–23 **A** and **B,** Clinical appearance of a 3-year-old boy with spondyloepiphyseal dysplasia (SED) congenita. The short neck and increased lumbar lordosis are obvious.

mately 5 years old. The ossification centers of the carpals and tarsals are delayed, as are the secondary centers of ossification of the long tubular bones. When the epiphyses do appear, they are flattened and irregular in shape. The hands and feet show minimal shortening on radiographs.

Coxa vara is present, and the disorder is further subdivided into a group in which coxa vara is severe and a group in which it is mild. Young infants with coxa vara may have radiographic findings similar to those seen in developmental dislocation of the hip. The iliac wings are small and the acetabulae are usually horizontal (Fig. 29–24).

Platyspondyly is seen (Fig. 29–25), and kyphoscoliosis may be apparent. Odontoid hypoplasia or os odontoideum may be present, and cervical spine films should be routinely obtained in these patients to assess for atlantoaxial instability. The radiographic appearance of the spine is identical to that of Morquio's syndrome and other mucopolysaccharidoses.

Orthopaedic Considerations. Orthopaedic treatment begins with the cervical spine. Signs of cervical instability include hypotonia, sleep apnea, respiratory insufficiency, and myelopathy.[23] Respiratory insufficiency has been seen in babies with SED congenita secondary to thoracic dysplasia[11,20] and secondary to cervical cord compression. Thus, children with pulmonary problems must be carefully assessed for upper cervical instability. Significant instability has been described in infants less than 1 year old with SED congenita. For this reason, flexion and extension cervical radiographs should be obtained prior to the administration of any anesthetic in children with SED.[25] In children with odontoid hypoplasia, instability may be present with extension because the odontoid is not sufficiently large enough to prevent posterior migration of C1 (Figs. 29–26 and 29–27). When odontoid hypoplasia produces atlantoaxial instability, posterior cervical fusion from the occiput or C1 to C2 with halo vest immobilization is necessary.[17,29,30] Instability of 8 mm or more or the presence of myelopathic symptoms is an indication for surgery. The posterior ring of C1 may be incomplete, and this situation should be considered in the preoperative planning.[30]

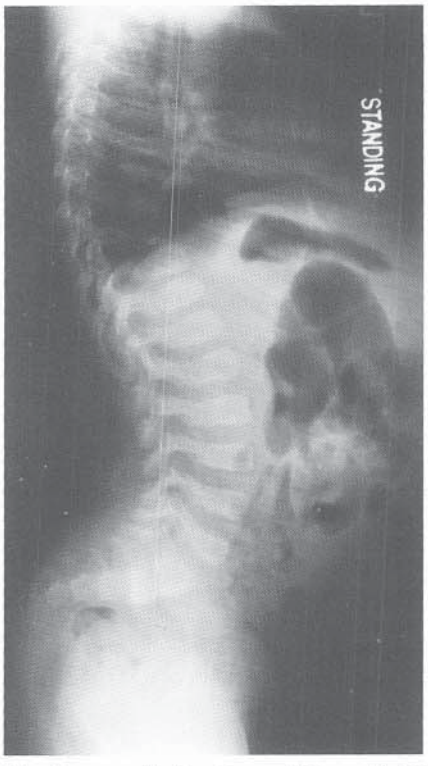


FIGURE 29–25 Platyspondyly in a 2-year-old boy with SED congenita.

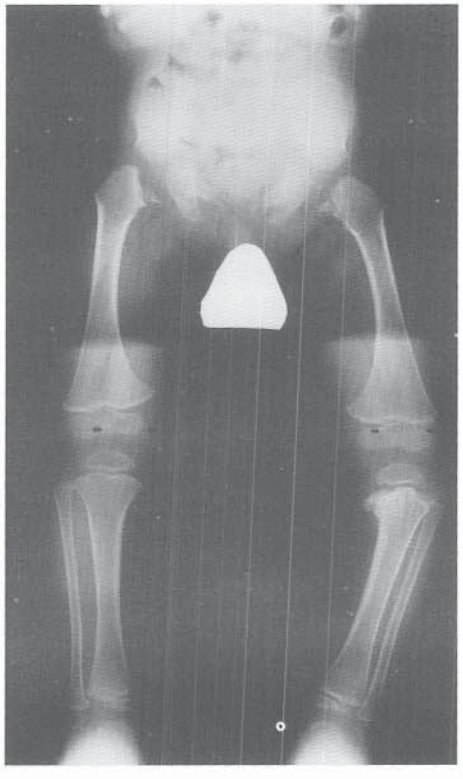


FIGURE 29–24 Radiographic abnormalities in SED congenita include delay in ossification of the femoral heads and coxa vara.

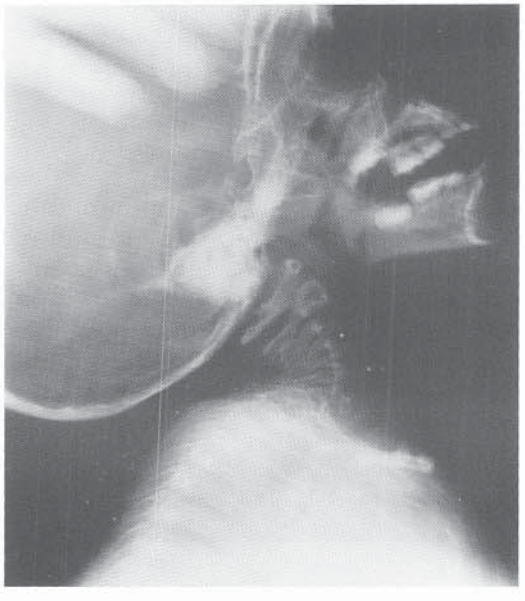


FIGURE 29–26 Patients with SED have hypoplasia of the odontoid which may lead to posterior instability at C1–2.

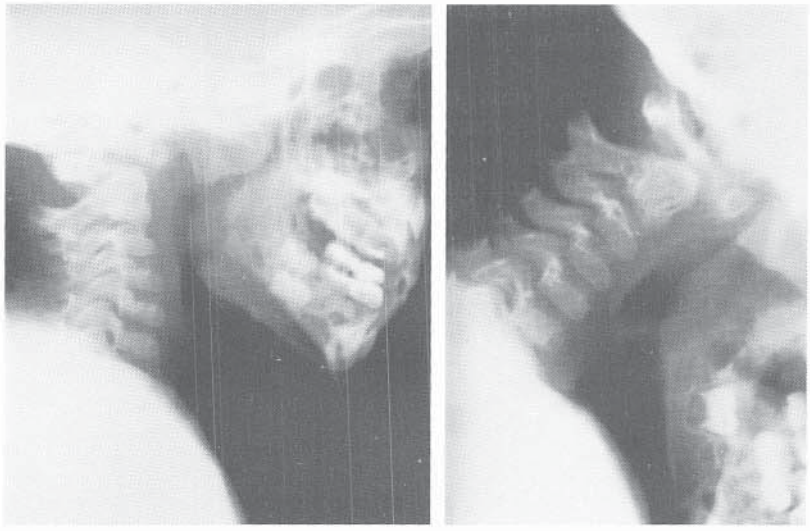


FIGURE 29–27 Spondyloepiphyseal dysplasia in a 4-year-old girl. **A** and **B,** Neutral and flexion lateral views of the cervical spine. Note atlantoaxial instability.

A B

Other spinal deformities associated with SED congenita include scoliosis and lumbar hyperlordosis.[31] Scoliosis may require bracing, although the response to bracing in patients with SED is somewhat unpredictable. Scoliosis may be associated with severe kyphosis. When the scoliosis exceeds 50 degrees or is associated with significant kyphosis, fusion with standard instrumentation is effective.[5,30] Because the spinal canal is not narrowed by the bone dysplasia, instrumentation may be used.

Lumbar lordosis does not require spinal surgery, but attention must be directed to the hips. Extension osteotomy of the proximal femur is occasionally performed to address hip flexion contractures leading to increased lumbar lordosis.

Coxa vara may be severe and may result in discontinuity of the femoral neck. Bassett recommends valgus osteotomy when the neck-shaft angle is less than 100 degrees, when the Hilgenreiner-epiphyseal angle is greater than 60 degrees, when the varus is progressive, or when an inverted triangular fragment is present (Fig. 29–28).[3] Hip dislocation has been seen in conjunction with coxa vara and, when present, further complicates surgical treatment. Open reduction with femoral and acetabular osteotomies has been performed to treat hip dislocation due to SED.

Genu valgum is quite common in SED congenita. Proximal femoral valgus osteotomy for the treatment of coxa vara further accentuates the distal femoral valgus. A distal femoral varus osteotomy is performed to surgically correct the condition. Recurrence is a frequent complication.

Premature osteoarthritis results from the epiphyseal deformity (Fig. 29–29). Whether osteotomies delay the onset of degenerative arthritis remains unknown.

SPONDYLOEPIPHYSEAL DYSPLASIA TARDA

SED tarda is a milder form of SED that is not clinically apparent at birth. Most patients present in older childhood

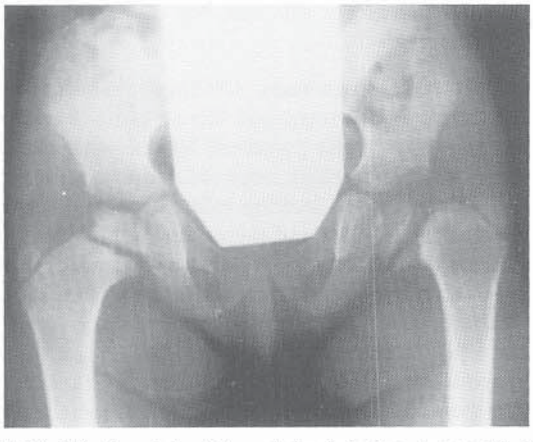


FIGURE 29–28 Spondyloepiphyseal dysplasia in a 4-year-old girl. AP view of the pelvis shows irregular ossification of the femoral heads. The left hip exhibits a severe coxa vara deformity with elevation of the greater trochanter.

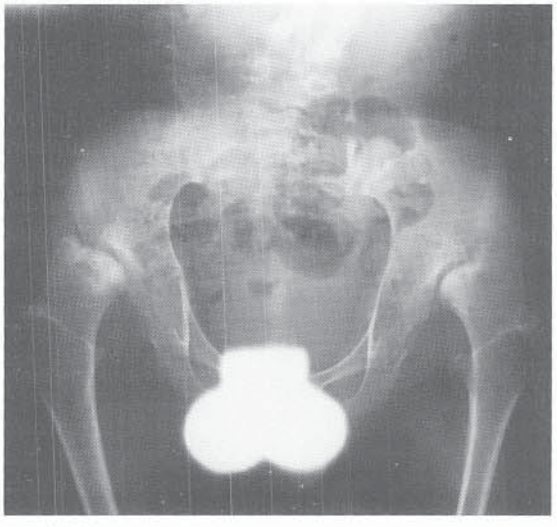
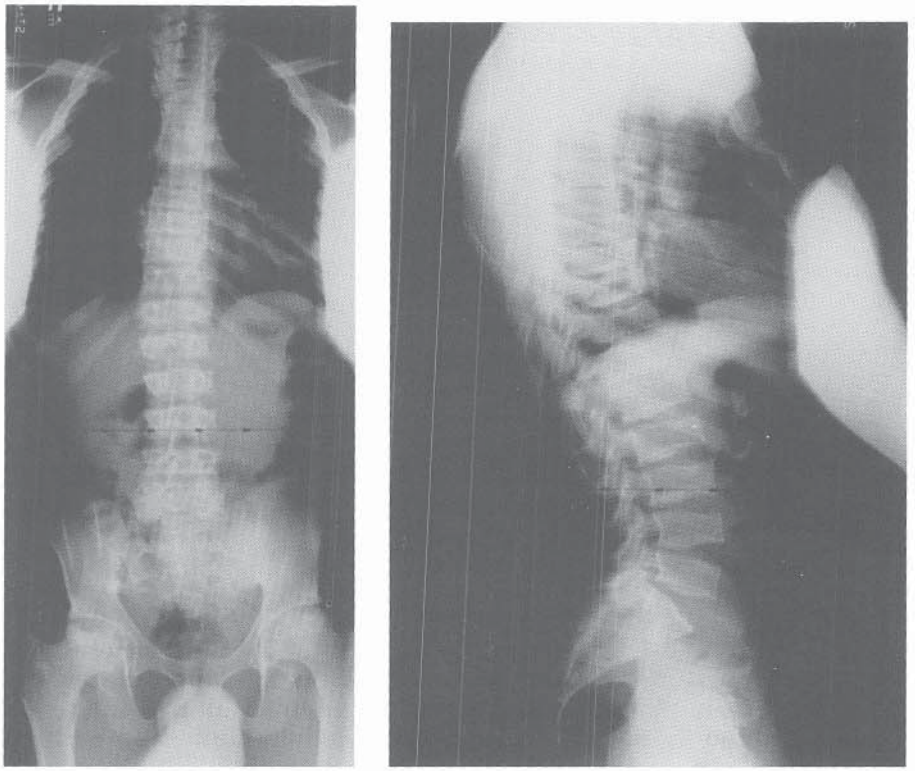


FIGURE 29–29 Severe degenerative arthritis in a 15-year-old individual with SED and dislocated hips.



A B

FIGURE 29–30 **A** and **B,** Mild platyspondyly and proximal femoral epiphyseal irregularities in a 16-year-old patient with SED tarda.

or adolescence with complaints of hip pain. Height is only minimally affected.

Genetics. The inheritance of SED tarda usually is autosomal recessive.[1,15] An X-linked form has also been described and mapped to the Xp22 region.[4,12] SED tarda is genetically distinct from SED congenita.[19] Rare autosomal dominant forms of SED tarda have also been reported.[22,24,28] Thus, there is genetic heterogeneity in SED tarda.

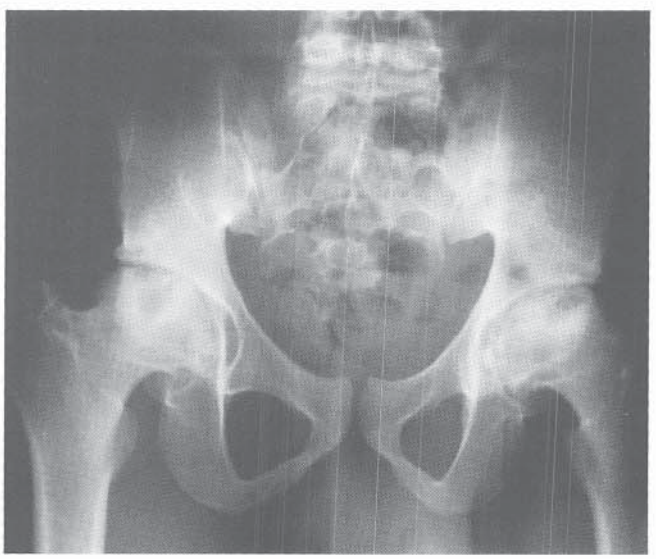


FIGURE 29–31 Joint space narrowing and epiphyseal irregularities in both hips in a 17-year-old patient with SED tarda.

Clinical Features. The dysplasia is not recognized at birth but becomes apparent as the growth rate of the child slows in mid-childhood or adolescence. The presenting complaint is either short stature or hip pain.

Radiographic Findings. Radiographically, the dysplasia may be confused with Legg-Calvé-Perthes disease. However, in SED, involvement is symmetric, while in bilateral Legg-Calvé-Perthes disease involvement is discordant, with one hip more radiographically affected than the other.[10] Coxa magna with flattening and extrusion can be seen on pelvic radiographs. Abnormalities of other epiphyses (usually the proximal humerus), platyspondyly, and narrowed disk spaces of the spine help establish the correct diagnosis of SED tarda (Fig. 29–30).

Orthopaedic Considerations. Orthopaedic surgery is directed at treating the precocious hip arthritis (Fig. 29–31). Valgus osteotomy of the proximal femur, with acetabular augmentation when needed, has been proposed for younger patients with SED tarda, but the influence of the osteotomy on the long-term outcome of these hips has not been established. Degenerative arthritis associated with SED tarda in adulthood is treated by total joint arthroplasty in early adulthood. Custom components may be necessary due to the anatomy and length of the femur.[14]

Platyspondyly is present in patients with SED tarda, and odontoid hypoplasia may lead to instability requiring stabilization in some patients. Patients with SED tarda may have back pain, but they rarely need surgery on the spine.[30] If scoliosis is present, bracing or fusion should be performed, following guidelines similar to those for idiopathic scoliosis.

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Multiple Epiphyseal Dysplasia

Multiple epiphyseal dysplasia (MED) is a condition characterized by a delay in the appearance of the epiphyses, irregular, symmetric epiphyseal formation, mild short stature, and early-onset osteoarthritis. Fairbank first described this entity, calling it dysplasia epiphysealis multiplex.[12,13] It soon became apparent that there were several forms of the dysplasia. The two most common forms are the Fairbank form, known as type I, and a milder form, described by Ribbing,[23] that is known as type II. In a Danish study the prevalence of MED was 9.0 per 100,000.[1] Wynne-Davies previously published a possible prevalence of 11 per million index patients.[30] MED is being detected with increasing frequency.

GENETICS

In the majority of patients, the dysplasia is inherited by autosomal dominant transmission. A rare autosomal recessive form also exists.[20] There is genetic variability between families,[10] which is expected since there are variable forms of the disease. Type I has been mapped to chromosome 19, and its gene product is COMP, the same gene that is abnormal in pseudoachondroplasia. Therefore Fairbank type I MED and pseudoachondroplasia are allelic.[6,7,18] Type II MED is caused by a different mutation, with the abnormality located on chromosome 1 in the gene encoding for the alpha-2 polypeptide chain of type IX collagen.[5,21] Type IX collagen is located on the surface of type II collagen fibrils and is necessary for the long-term integrity of articular cartilage.[11]

PATHOLOGY

The basic defect in MED is a disturbance in the development of the epiphyseal ossification centers. Enchondral ossification is disorganized, and epiphyseal cartilage cells are irregular, with disordered columns and areas of degeneration.[15] Funnelization, diaphyseal cylindrization, and modeling are not affected. The articular cartilage is initially normal but becomes secondarily misshapen during life because of the lack of underlying osseous support. The articular deformities are permanent, with degenerative changes and osteoarthritis developing early in adult life, especially in the weightbearing joints.

Electron microscopy shows intracytoplasmic inclusions within the chondrocytes. These inclusions are dilations of

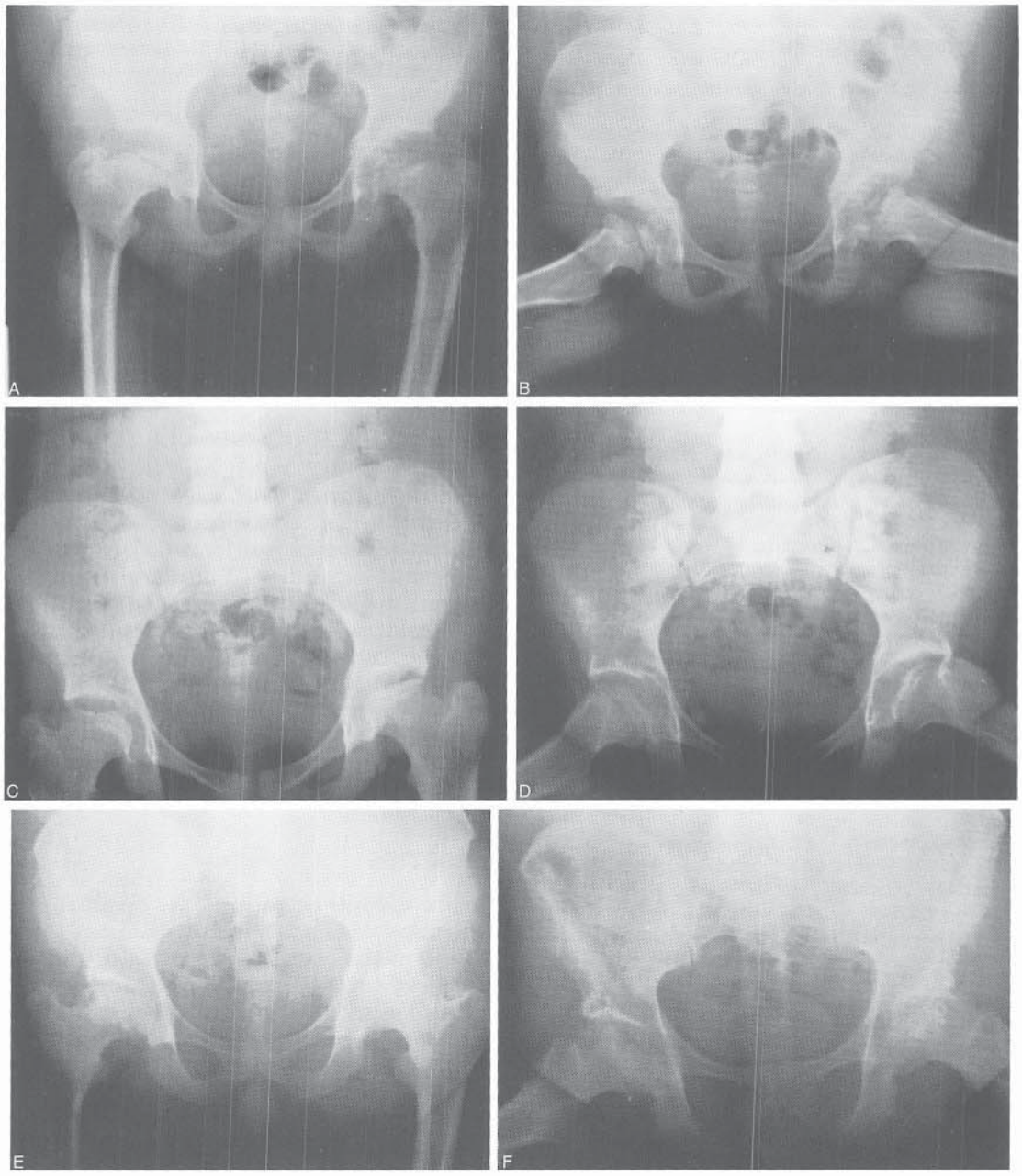


FIGURE 29–32 Multiple epiphyseal dysplasia in two sisters and their 40-year-old father. The disorder is inherited as an autosomal dominant trait. **A** and **B,** AP and frog-leg lateral radiographs of both hips of a 12-year-old girl. Note the irregularity and flattening of the capital femoral epiphyses. Involvement is bilateral. **C** and **D,** AP and lateral views of both hips of the 14-year-old sister showing similar changes. **E** and **F,** AP and lateral radiographs of the father's hips. Note the irregularity of the femoral heads and marked degenerative arthritis in both hips.

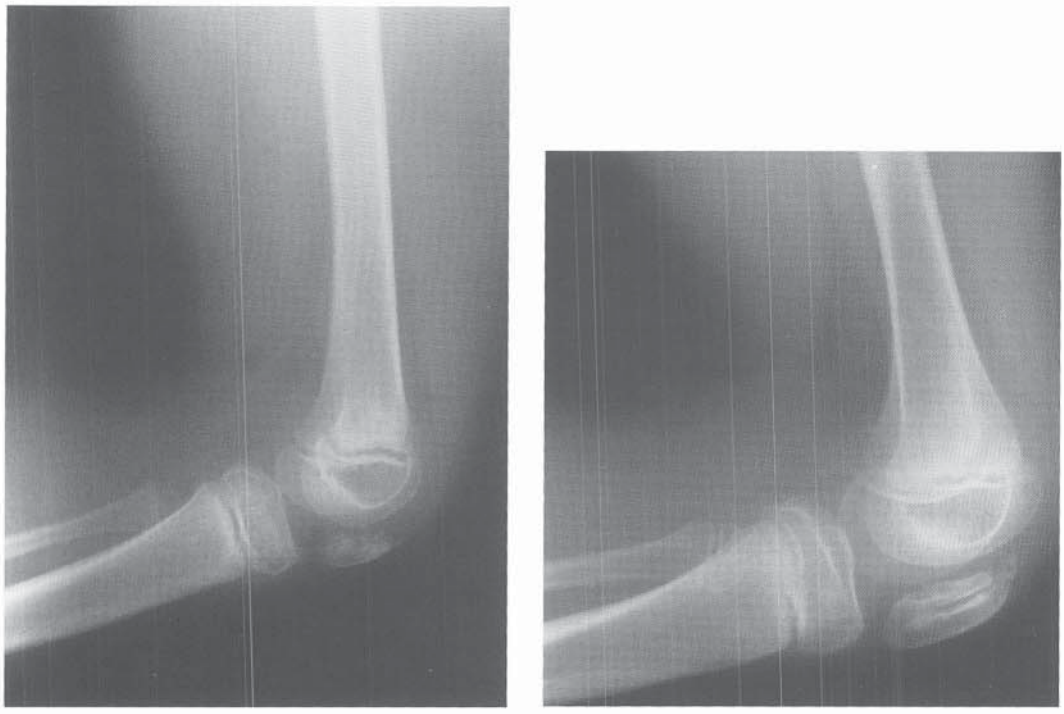
the rough endoplasmic reticulum and resemble those seen in pseudoachondroplasia, lending further support to the opinion that these two dysplasias are genetically related.[26]

The epiphyses most commonly affected are those of the femoral and humeral heads. The short tubular bones of the hands and feet may also be involved. The skull, vertebrae, and pelvis are normal.

CLINICAL FEATURES

The dysplasia is not recognizable at birth. The first sign may be a delay in walking. Often the diagnosis is not made until early adolescence. Initial presenting complaints include joint stiffness or contractures, pain, a limp, or a waddling gait. As the child grows older, the shorter stature becomes more evident. However, true dwarfism is not associated with this condition, as many patients are above the third percentile for height.[3]

The fingers and, to a lesser extent, the toes are short and stubby. Flexion contractures of the elbows and knees are common. Genu valgum or varum may develop. Pain from degenerative arthritis may be present in adolescence or early adulthood. Arthritic changes in the shoulder are frequently accompanied by symptomatic stiffness.[17]



A B

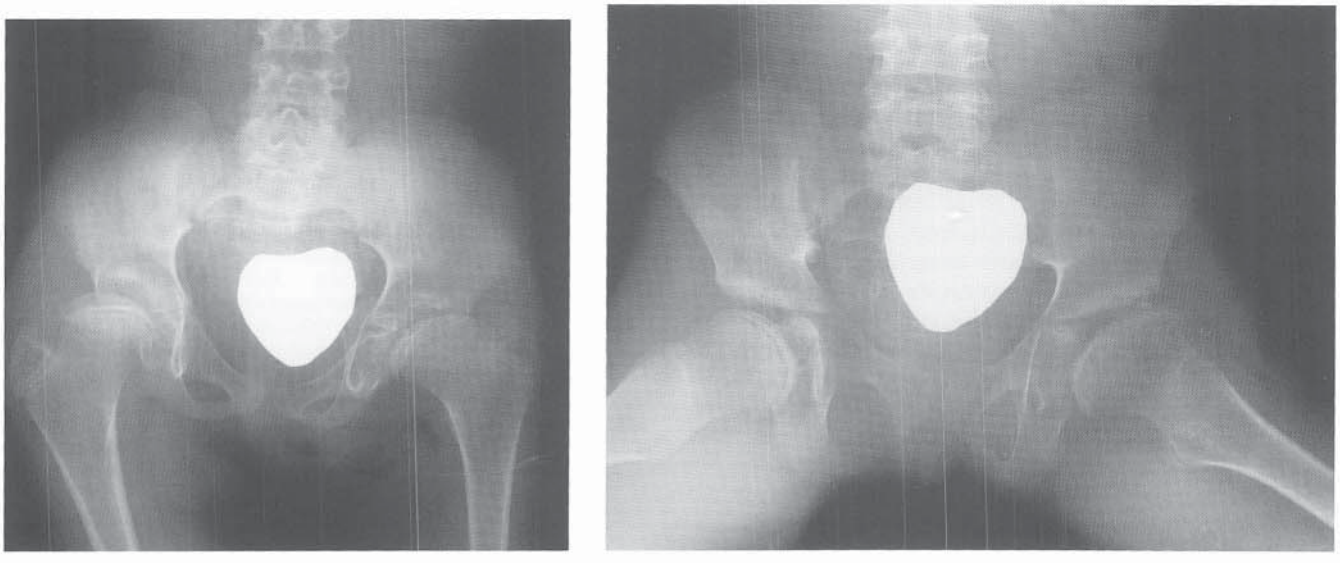
FIGURE 29–33 **A,** Lateral radiograph of the knee of a 5-year-old girl with multiple epiphyseal dysplasia. Ossification of the patella is irregular. **B,** By age 8, the patella appears to be double-layered.

There are no associated neurologic findings. Intelligence is not affected.

RADIOGRAPHIC FINDINGS

The principal finding on radiographs is a delay in the appearance of the ossification centers. When the epiphyses do appear, they are fragmented, mottled, and flattened (Fig. 29–32). There are numerical indices for the normal height of the epiphyses, particularly at the distal femur. Measurement of epiphyseal height and carpal height, both of which are decreased in MED, may assist in reaching an early diagnosis before degenerative arthritis begins.[16,24,28]

The proximal femur is most often affected. The findings on hip radiographs may be easily confused with those of bilateral Legg-Calvé-Perthes disease. Clues to the diagnosis



A B

FIGURE 29–34 **A** and **B,** AP and frog-leg radiographs of a 9-year-old girl with multiple epiphyseal dysplasia. Both femoral heads are irregular and mushroom-shaped.

are the presence of symmetric involvement in MED versus the metachronous findings in Legg-Calvé-Perthes disease.[2] In Legg-Calvé-Perthes disease, usually one hip is involved before the other, so that each hip is in a different stage of the disease. This is not the case in MED.[8] In addition, acetabular changes are seen more frequently in MED. Metaphyseal cysts are seen in Legg-Calvé-Perthes disease, but not in MED.[2] When bilateral Legg-Calvé-Perthes disease is suspected, radiographic examination of other joints should be performed. In MED, epiphyseal irregularities will be visible in other locations, such as the shoulders and knees.

Correctly diagnosing MED is further hampered by the fact that avascular necrosis (AVN) occurs frequently in the hips of patients with MED.[29] Because AVN may be present in MED, the distinction from bilateral Legg-Calvé-Perthes disease cannot be made by bone scan or MRI, since these imaging studies will demonstrate avascularity and subsequent changes for both diseases.[19] Radiographic changes in patients with MED and AVN include subchondral fractures, increased radiodensity of the ossific nucleus, resorption of ossified cartilage, reossification, and asymmetric images.[19]

Coxa vara may occur but is not necessarily bilateral. The femoral necks appear short. Other angular deformities, such as genu varum or valgum, may be present on plain radiographs. Lateral radiographs of the knee may demonstrate a peculiar finding seen in MED, the double-layered patella (Fig. 29–33). When this is present, it is characteristic for MED.[9,14,25] On AP radiographs the femoral condyles appear squared off and flat, and the intercondylar notch is shallow.

The metacarpals and phalanges usually are short. Their epiphyses are irregular.

MED is distinguished from spondyloepiphyseal dysplasia by the absence of severe vertebral changes. Mild end-plate irregularities may be present.[4] Radiographic findings in hypothyroidism may resemble those in MED, and the distinction is made with thyroid function studies.

ORTHOPAEDIC CONSIDERATIONS

Orthopaedic treatment is rarely necessary in early childhood. Once the diagnosis is established, maintenance of range of motion is initiated. The patient and parents should be cautioned regarding weight gain.

Despite findings resembling those of Legg-Calvé-Perthes disease, there is no evidence to support the use of containment orthoses or prophylactic containment surgery in MED. Arthrography of the hip demonstrates the flat, mushroom-shaped femoral head (Figs. 29–34 and 29–35). If hinge abduction is present on arthrography, a valgus proximal femoral osteotomy may improve congruency and therefore relieve pain. Bassett has also recommended shelf acetabular augmentation in some patients with MED to improve coverage of the misshapen femoral head.[3] When MED is complicated by AVN, the prognosis for degenerative arthritis worsens. Nonetheless, varus osteotomy is contraindicated because of preexisting coxa vara.[3]

Osteotomies may be helpful in realigning the lower extremities when angular deformities exist, particularly at the knee. For optimal surgical correction, the level of the deformity must be ascertained preoperatively.[3] Valgus osteotomy of the proximal femur is the treatment for coxa vara, but recurrence is quite common.

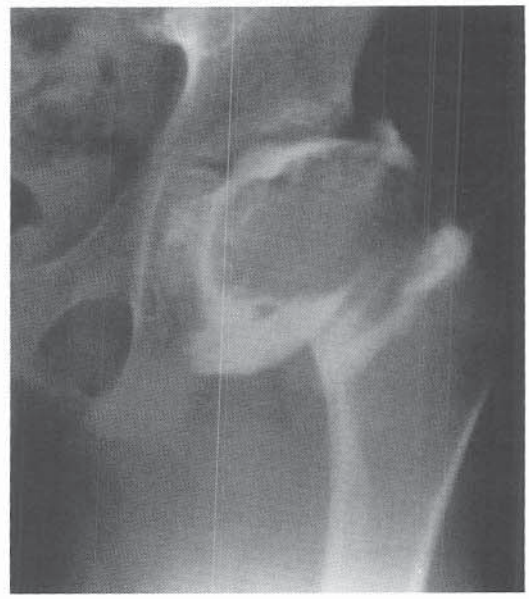


FIGURE 29–35 Arthrogram of the left hip of the 9-year-old child whose x-rays are shown in Figure 29–34. Articular irregularity can be seen.

Degenerative arthritis in children is treated symptomatically.[3,22] Osteoarthritis is present by 30 years of age in those hips that are incongruent with large, flat heads and poor acetabular coverage.[27] If the femoral head is well formed at maturity, the onset of arthritis is delayed. Affected family members seem to develop arthritis at similar ages.[27] Total joint replacement in adulthood is possible.

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Diastrophic Dysplasia (Diastrophic Dwarfism)

In 1960 Lamy and Maroteaux distinguished a very rare form of micromelic dwarfism from that of achondroplasia.[17] They named it *nanisme diastrophique,* deriving the word *diastrophic* from the Greek word meaning crooked or twisted. In this condition, severe short stature is associated with rigid clubfeet, scoliosis, and "hitchhiker's thumb."

GENETICS

Diastrophic dysplasia is inherited as an autosomal recessive trait. The responsible gene is located on the distal part of the long arm of chromosome 5.[10] This gene encodes a unique sulfate transporter. Impaired function of the gene's product leads to undersulfation of proteoglycans in cartilage matrix,[9,24] which impairs the growth response of these cells to fibroblast growth factor (FGF), thus stunting enchondral growth.[22] Abnormalities are seen in type IX collagen, which is responsible for establishing the lattice of type II collagen.[4,5] Mutations at the same locus are responsible for lethal forms of dwarfism such as achondrogenesis.[24]

PATHOLOGY

Abnormal cross-linking of cartilage has been seen, leading to mechanically weaker cartilage.[1] Light microscopy shows atypical chondrocytes, with extreme variation in size and shape, and premature cytoplasmic degeneration. The chondrocytes are larger and clearer than normal, with more rounded nuclei.[25] Prominent, densely staining fibrotic foci are present throughout the cartilage. The collagen in these foci is remarkably abnormal.[23] The cartilage matrix demonstrates an increase in fibrous tissue as well. Abnormalities are seen in the chondrocytes of the entire skeleton, including the trachea.[25]

CLINICAL FEATURES

The condition is easily diagnosed at birth. The affected newborn is severely dwarfed, with very short limbs and marked bilateral clubfeet (Fig. 29–36). During the first 2 weeks of life, swelling of the external ears develops that subsequently calcifies and ossifies, forming the "cauliflower ear" deformity characteristic of diastrophic dysplasia (Fig. 29–37).

The face appears "cherubic" because of the fullness of the cheeks around the mouth. The nasal bridge is narrow, and the nostrils are flared. A cleft palate is present in 56 percent of patients.[14,20]

The hands are short and broad. The thumb deformity, referred to as "hitchhiker's thumb," is a distinctive feature of the dysplasia (Fig. 29–38). It is caused by excessive shortening of the first metacarpal (which is triangular in shape), leading to radial subluxation of the metacarpophalangeal joint of the thumb (Fig. 29–39). The thumb is nearly perpendicular to the index finger.

Equinovarus of the foot is another distinctive feature of the dysplasia. In a study by Ryoppy and associates, only 7

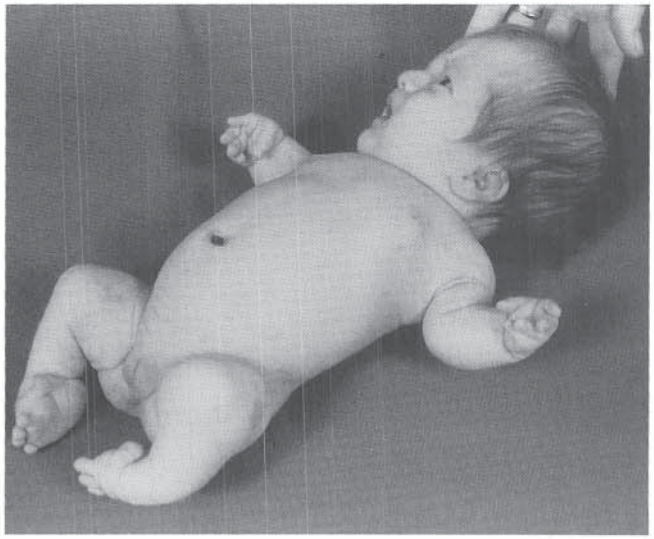


FIGURE 29–36 Baby with diastrophic dysplasia. The legs and arms are very short, and the clubfeet bilaterally are obvious.

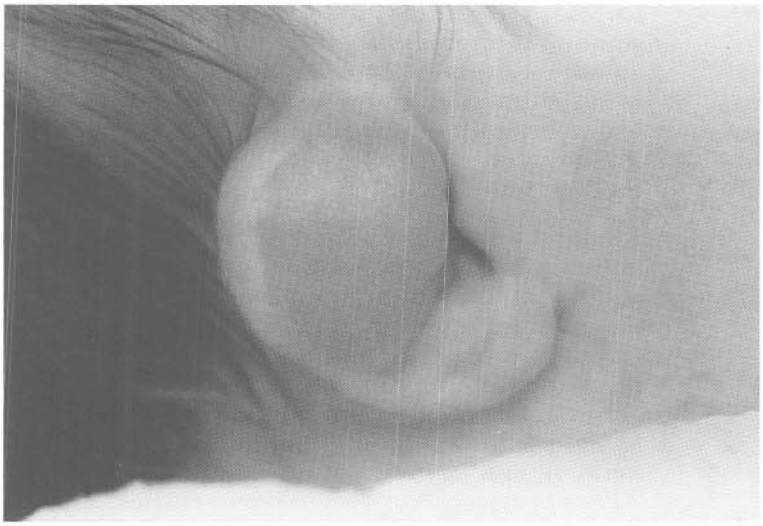


FIGURE 29–37 Swollen external ear in a baby with diastrophic dysplasia.

percent of 208 feet in children with diastrophic dysplasia were normal.[21] The equinovarus of diastrophic dysplasia differs from the deformity present in idiopathic clubfoot. In diastrophic dysplasia, the first metatarsal is short and triangular (like the first metacarpal in the hand). The forefoot is medially deviated, and extreme hallux varus is present. The hindfoot and ankle are in severe equinus (Fig. 29–40). The Achilles tendon consists of a band of fanlike fibers and is not a distinct cord. The foot deformity is rigid and resistant to correction.

The joints may be hyperextensible because of excessive ligamentous laxity, or they may have limited range of motion. Most patients have the "stiff joint" variant. Flexion contractures of the hips, knees, and elbows are present at birth. The contractures may be progressive, leading to impairment in standing and walking. Hip dislocation may be present in affected infants. Genu valgum and patellar dislocation can develop at the knee. Radial head dislocation is commonly seen.

The spine appears normal at birth, but as the child becomes ambulatory, scoliosis and kyphosis develop (Fig. 29–41). Spinal deformity is progressive in nearly all cases.

Cervical kyphosis is present in some cases. There is no abnormality of the odontoid process in diastrophic dysplasia, but the disorder has a high rate of association with hypoplasia of the cervical vertebral bodies. Spina bifida occulta of the upper cervical spine is present (Fig. 29–42). Myelopathy can result from cord compression.

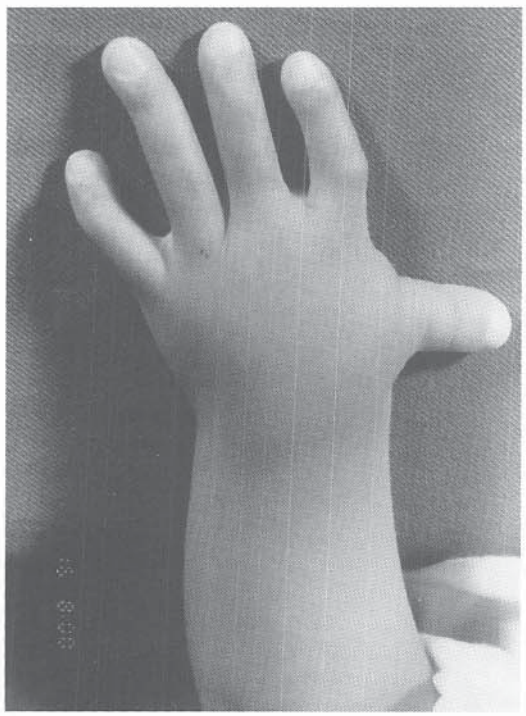


FIGURE 29–38 "Hitchhiker's thumb" is characteristic of diastrophic dysplasia.

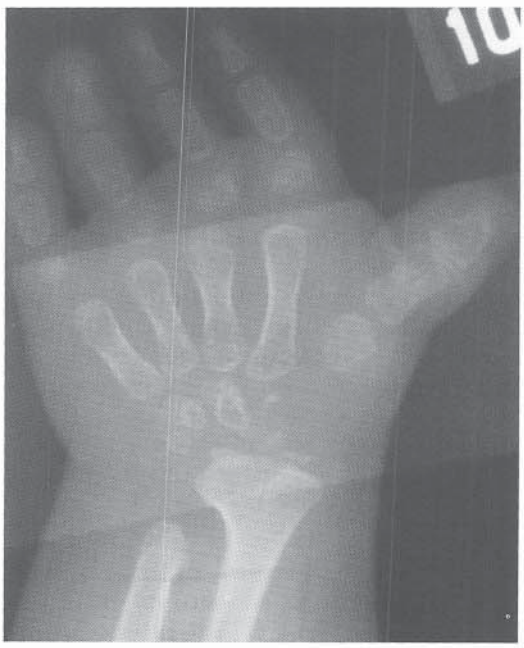


FIGURE 29–39 "Hitchhiker's thumb" results from severe shortening of the first metacarpal, which appears triangular in shape.

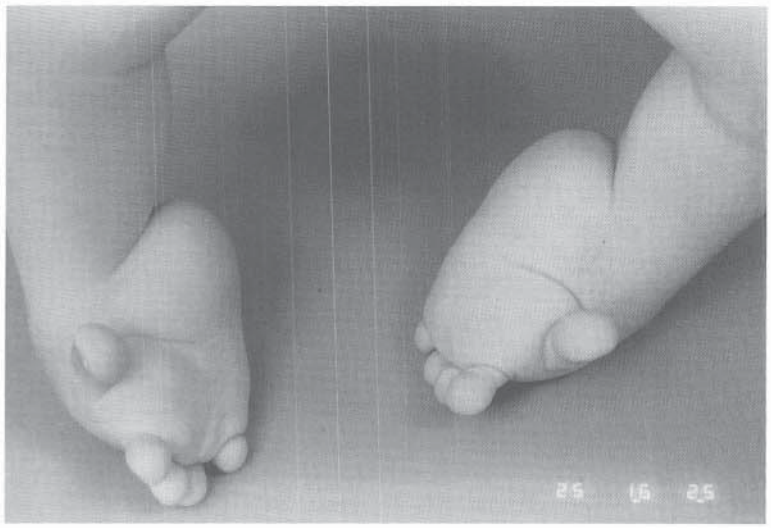


FIGURE 29–40 Equinovarus deformity of the feet in diastrophic dysplasia. The great toe deformity is similar to hitchhiker's thumb.

Thoracolumbar kyphosis is present in almost all patients. Lumbar lordosis is markedly increased and is linked to flexion contractures of the hip. Spinal stenosis is an uncommon feature of diastrophic dysplasia.

Stature is markedly reduced, with adult height reaching 80 to 140 cm (2 feet 7 inches to 4 feet 7 inches). The limbs are excessively short compared with the trunk.

Patient intelligence is normal.

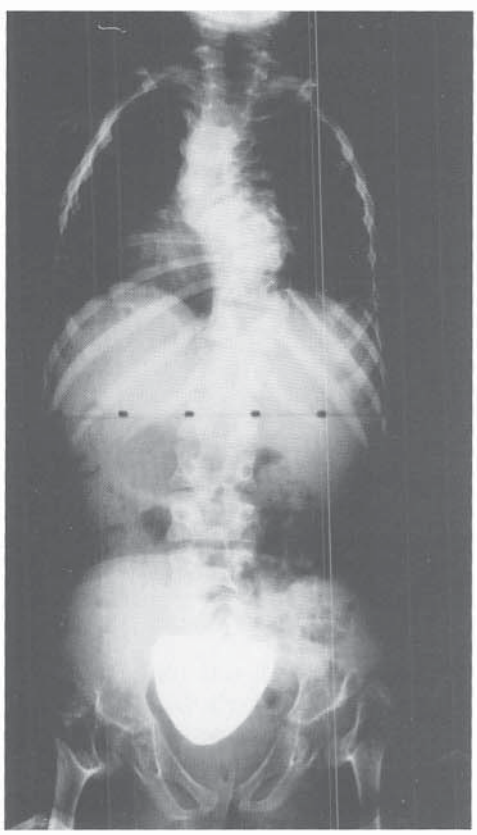


FIGURE 29–41 Rigid scoliosis in an 8-year-old girl with diastrophic dysplasia. She also has bilateral hip dislocations.

RADIOGRAPHIC FINDINGS

Radiographic findings associated with diastrophic dysplasia include a short, broad appearance of long bones with flared metaphyses. There is a delay in the radiographic appearance of the epiphyses, and the distal femoral epiphyses are not apparent at birth. Development of the proximal femoral ossific nuclei is distinctly delayed,[28] and the proximal femoral metaphysis has a saucer-like indentation (Fig. 29–43).[2] When the epiphysis does ossify, it is flattened and irregular in shape. Coxa vara is common, and hip dislocation is present in about 25 percent of patients.[29] Valgus angulation is frequently present at the knee (Fig. 29–44). There is relative shortening of the fibula compared with the tibia.[2]

The first metacarpal and first metatarsal are triangular, leading to the hitchhiker's thumb in the upper extremity. Symphalangism of the proximal interphalangeal joints of the hand is present.

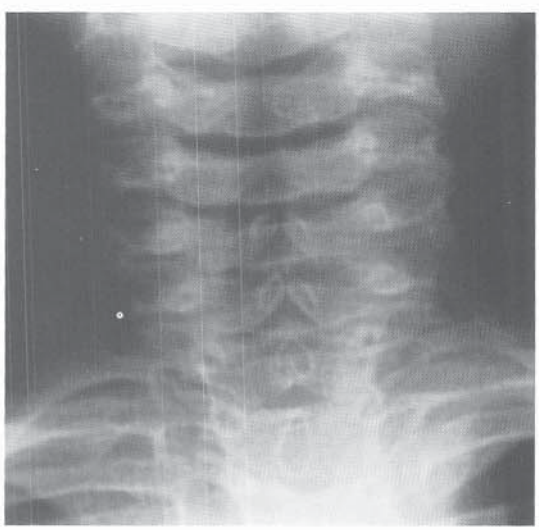


FIGURE 29–42 Spina bifida occulta of the cervical spine is a feature of diastrophic dysplasia.

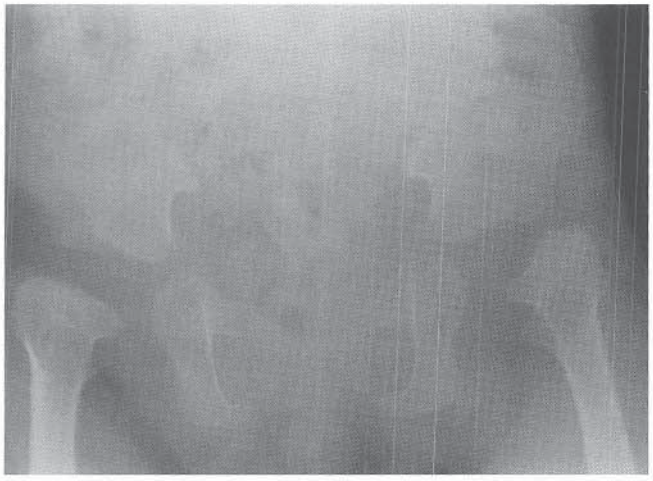


FIGURE 29–43 Ossification of the femoral heads is delayed in this 23-month-old girl with diastrophic dysplasia.

Spinal radiographs show the characteristic findings.[3,12,27] There is cervical kyphosis of varying severity, with hypoplasia of the third, fourth, and fifth cervical vertebral bodies.[6] In severe cases, the odontoid may come to lie in a position parallel to the foramen magnum (Fig. 29–45). Spina bifida of the cervical spine is common. In the lumbar spine, there may be mild wedging of the vertebral bodies at the thoracolumbar junction. The interpedicular distance may increase, remain the same, or decrease from the upper to the lower lumbar spine.[3] Scoliosis may be present, and segmentation defects resembling congenital scoliosis are associated with diastrophic dysplasia.[27]

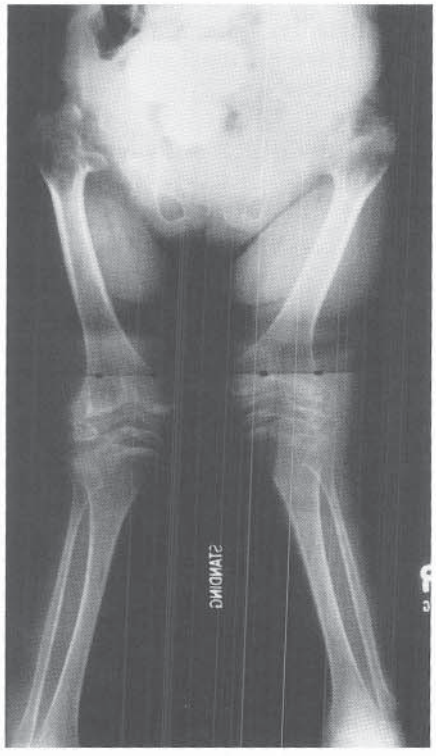
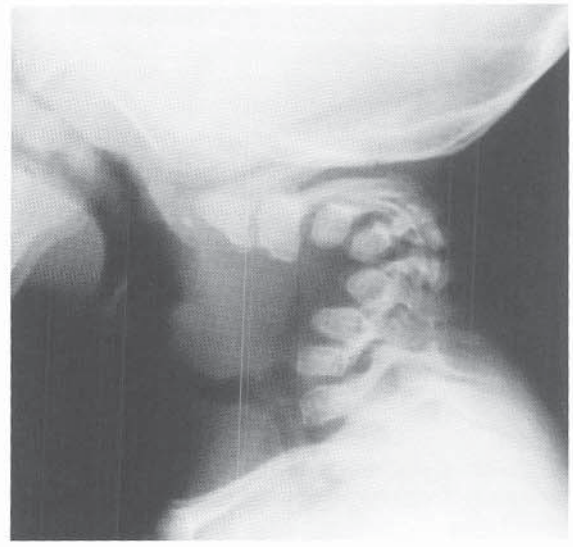


FIGURE 29–44 Hip dislocations and genu valgum in diastrophic dysplasia. The metaphyses are broad and flared.



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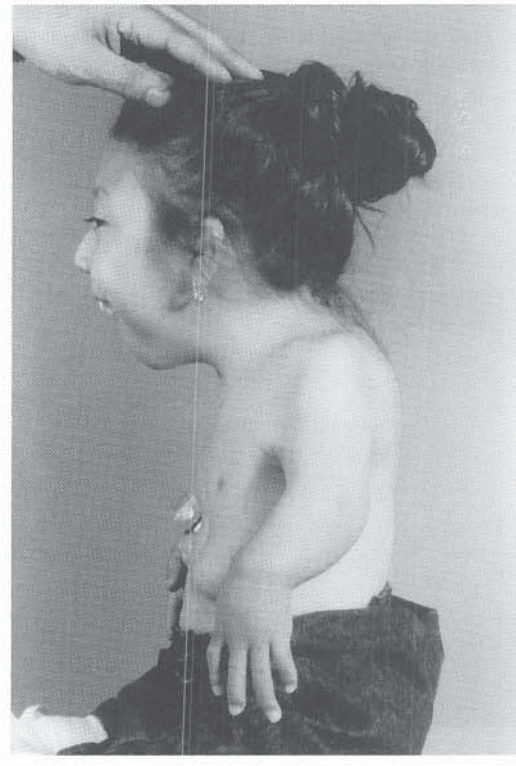


B

FIGURE 29–45 **A** and **B,** Cervical kyphosis in diastrophic dysplasia.

PRENATAL DIAGNOSIS

Prenatal diagnosis is possible with ultrasound, which shows the short limbs and hitchhiker's thumbs.[7,8,13] DNA analysis may now provide a reliable means of prenatal diagnosis during the first trimester of pregnancy.[11]

DIFFERENTIAL DIAGNOSIS

In infants, one should rule out dysplasias with short-limbed dwarfism, such as achondroplasia, chondrodysplasia punc-

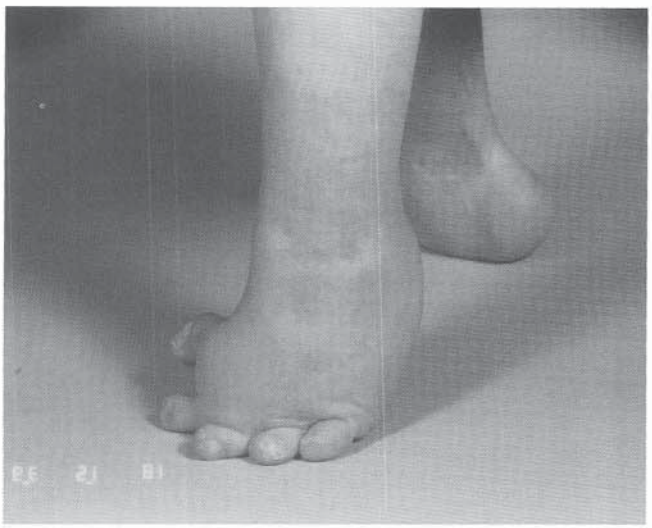


FIGURE 29–46 Clinical appearance of the feet in diastrophic dysplasia after surgery. Recurrent deformity is very difficult to treat.

tata (Conradi's disease), and spondyloepiphyseal dysplasia congenita. Arthrogryposis may be mistaken for diastrophic dysplasia because of the multiple joint contractures and dislocations. The diagnosis of diastrophic dysplasia is most easily made by the presence of hitchhiker's thumbs and cauliflower ears.

ORTHOPAEDIC CONSIDERATIONS

The orthopaedic management of diastrophic dysplasia is exceptionally difficult. Deformities are rigid and likely to recur following surgery, yet nearly all patients with diastrophic dysplasia are able to walk.

Equinovarus of the foot requires correction through surgery. It is best to perform soft tissue release when the child is about to learn to walk, which usually is at or slightly older than 1 year of age. The deformity may be very resistant, even to aggressive release. Postoperative bracing with ankle-foot orthoses (AFOs) is recommended to delay recurrence. Recurrent deformity requires repeat surgery, which is even less likely to achieve and maintain a plantigrade foot (Fig. 29–46). Talectomy and talar decancellation have been necessary in this patient population.

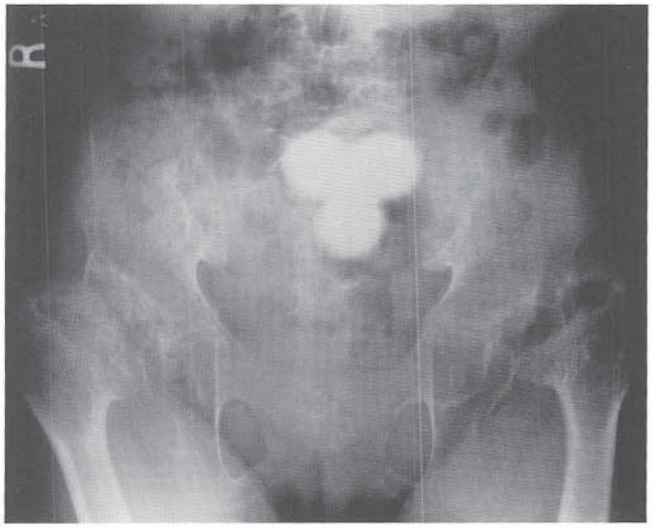
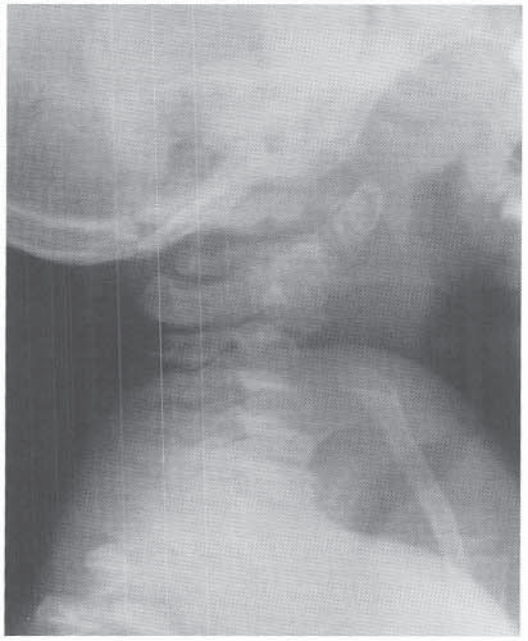


FIGURE 29–47 Femoral head deformity and hip dislocation in diastrophic dysplasia.

Hip dislocation is quite common in diastrophic dysplasia (Fig. 29–47). However, femoral head deformity and joint contractures make reduction of the dislocated hip challenging. The dislocations are teratologic in nature and therefore do not respond to closed forms of treatment. Open reduction has been performed in some hips, yet Tachdjian felt that there are hips "so resistant that sometimes it is good



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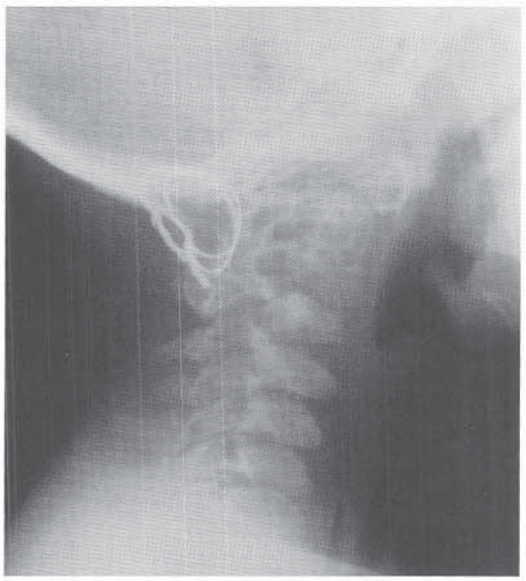
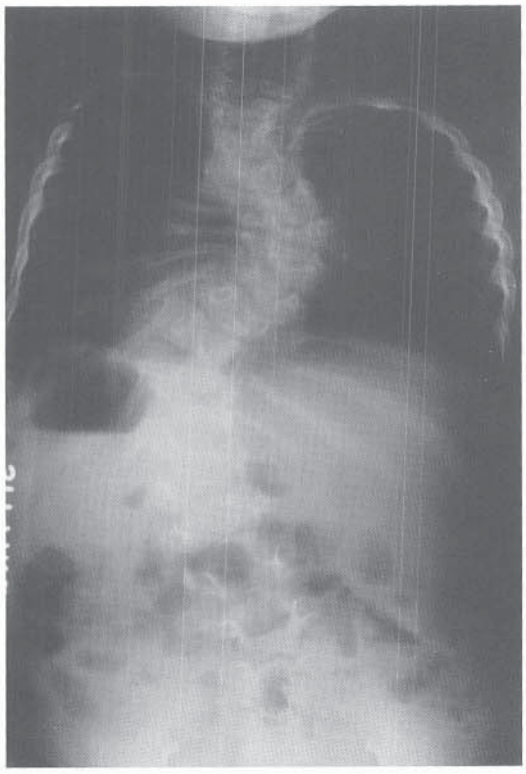


B

FIGURE 29–48 **A** and **B,** Atlantoaxial instability may occur in diastrophic dysplasia. Posterior spinal fusion was performed in this child.



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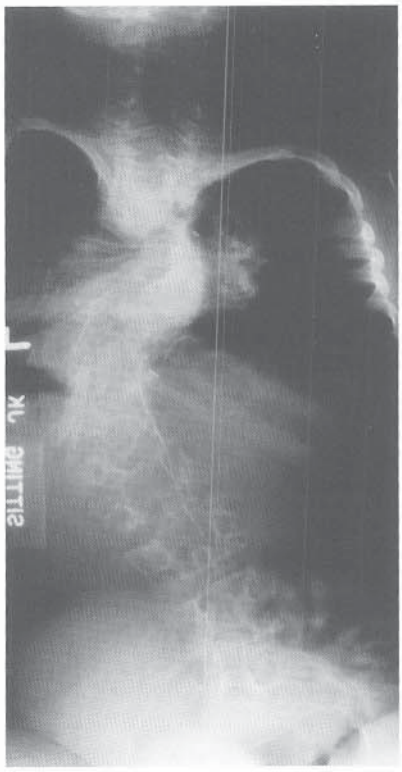

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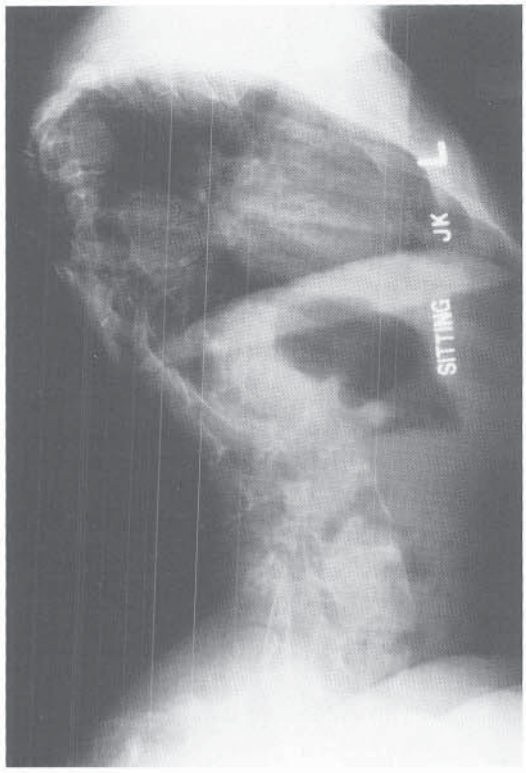


C

FIGURE 29–49 A to C, Progression of kyphoscoliosis from age 3 to age 13 in a patient with diastrophic dysplasia.

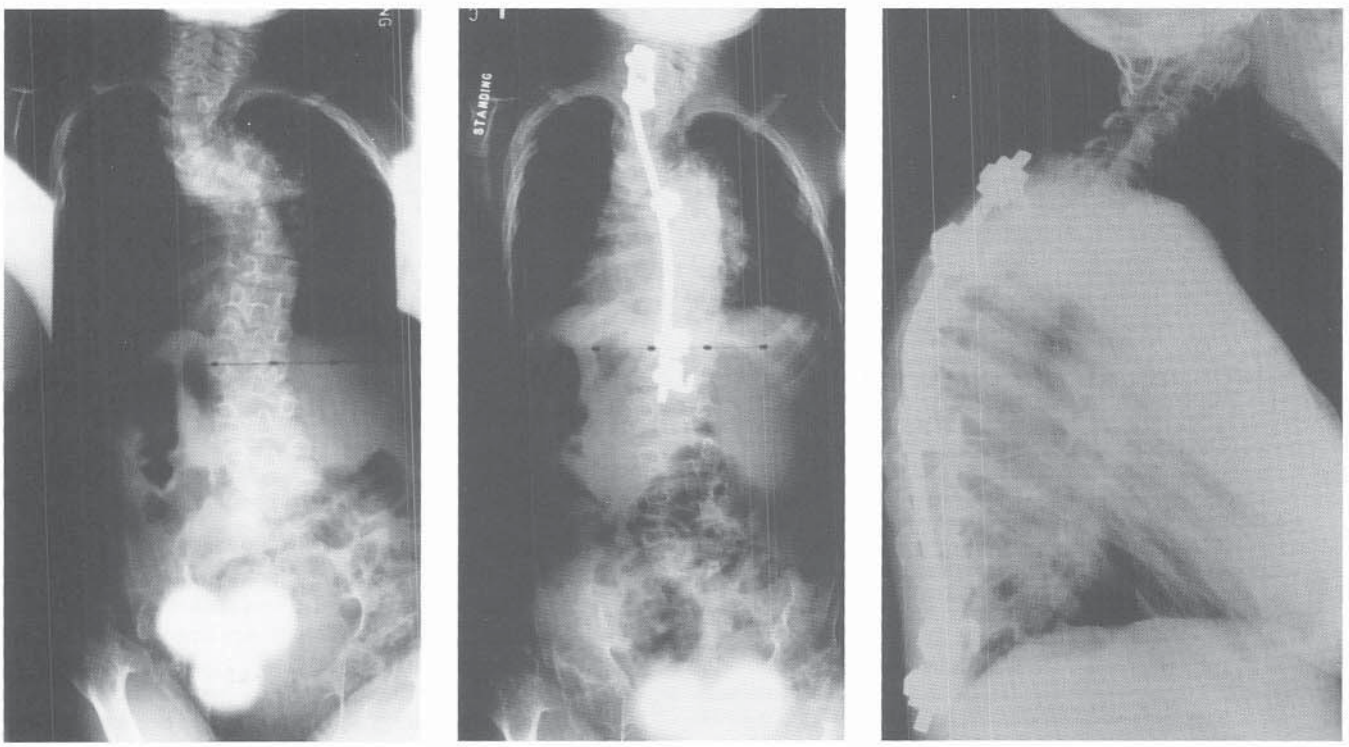
judgment to leave them dislocated."[26] Lack of containment and incongruity lead to premature osteoarthritis. Because the irregularity of the femoral head is inherent to the dysplasia, surgical treatment in early childhood does not prevent degenerative changes. Joint contractures may require osteotomy to improve gait, and valgus extension proximal femoral osteotomy is helpful for some patients.

Genu valgum also is common in patients with diastrophic dysplasia but does not require corrective osteotomy in most cases.[2] Patellofemoral dislocation should be treated surgically. Knee flexion contractures require surgical soft tissue release, which should be combined with simultaneous release of the hip flexion contractures. Bony abnormalities at the knee and hip are inevitable in diastrophic dysplasia. Thus, while soft tissue release may improve soft tissue contractures, skeletal malalignment and intra-articular pathology can prevent achieving full correction of the joint contractures. Extension osteotomy may be necessary. Recurrence is very common.

Spinal deformity associated diastrophic dysplasia is universal. Cervical kyphosis has resolved spontaneously in some young patients.[3,27] When spontaneous resolution of kyphosis does occur, it does so by 5 years of age.[18] Severe, progressive kyphosis necessitates spinal fusion. Anterior fusion with fibular strut grafting and posterior fusion with halo immobilization have met with success.[12] Deficiencies of the posterior elements of the cervical spine make posterior spinal fusion more difficult. Failure to stabilize severe kyphosis has led to quadriplegia and death.[3,15] Atlantoaxial instability has also been described in diastrophic dysplasia (Fig. 29–48).[19] Any preoperative evaluation of a young child with diastrophic dysplasia (e.g., prior to clubfoot surgery) must include radiographic documentation of normal cervical alignment. Failure to do so could lead to devastating neurologic sequelae or even death.

Scoliosis is particularly problematic in the diastrophic dwarfism population. In a study comprising 101 Finnish diastrophic patients (where the incidence of diastrophic dysplasia is highest), scoliosis was present in 49 percent of females and 22 percent of males.[28] Tolo and Kopits reported a higher incidence of scoliosis in their referral practices, with 70 percent of patients having curves of more than 10 degrees but only 30 percent of patients having curves of more than 30 degrees.[16,27] Curves may be apparent as early as age 6 months[12] but more commonly become apparent around 5 years of age. The rate of progression varies considerably in reported series, from universal[12] to occasional[21] (Fig. 29–49).

Tolo differentiates two types of curves.[27] The first type resembles idiopathic scoliosis and accordingly responds to bracing and surgery. Bethem and associates were successful in treating milder curves with Milwaukee braces.[3] The second type of curve is short and sharp and is associated with kyphosis. Bracing has been used to treat this type as well, but with little success. Early surgery may be necessary, even as early as 2 to 3 years of age if the curves are severe.[27] Delaying surgery to allow for further trunk growth at the expense of worsening deformity will only lead to stiffer deformities at the time of surgery and greater difficulty in operative treatment. Spinal cord monitoring should be performed as neurologic problems have been reported sec-



A B C

FIGURE 29–50 A to C, Radiographs of a 9-year-old child with scoliosis secondary to diastrophic dysplasia. Spinal fusion was performed using TSRH instrumentation.

ondary to surgical correction.[27] Instrumentation has been used safely in some patients with diastrophic dysplasia (Fig. 29–50).[27]

Lumbar hyperlordosis is common in diastrophic dysplasia; however, it usually is not progressive, and surgical correction is not indicated.[12]

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Kniest's Dysplasia (Pseudometatropic Dysplasia)

Kniest's dysplasia is a rare, severe form of chondrodysplasia characterized by dwarfism, progressive joint stiffness and contractures, retinal detachment, cleft palate, midface hypoplasia, and hearing loss.[8,12] Kyphoscoliosis is a hallmark of the disease.[7,8] The prenatal diagnosis of Kniest's dysplasia has been described.[1]

GENETICS

Kniest's dysplasia is an autosomal dominant disorder. The dysplasia is the result of mutations of COL2A1, which leads to defective type II collagen.[9,12] These mutations result in alternate splicing and interruption of the triple helix of alpha-1 (II) chains of type II collagen.[2,3,13] Genetically, Kniest's dysplasia is related to spondyloepiphyseal dysplasia congenita and Stickler's syndrome.[11]

PATHOLOGY

Pathologic findings include a disorganized physeal growth plate, soft, crumbly cartilage with a "Swiss cheese" appearance, and intracytoplasmic inclusions in the resting chondrocytes.[4,10]

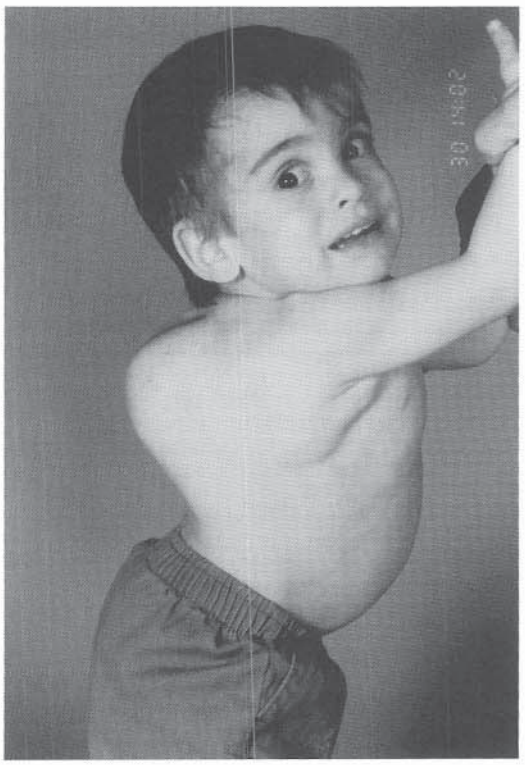
CLINICAL FEATURES

The dysplasia usually can be detected at birth. The child's limbs are short, with a rhizomelic involvement. There is a characteristic facial appearance, with a depressed midface and prominent eyes and forehead. Contractures begin to appear around 1 year of age. Affected children cannot fully close the hand into a fist because of contractures. The joints appear enlarged owing to the flaring of the metaphyses. Cleft palate is present in about 50 percent of babies.

RADIOGRAPHIC FINDINGS

Radiographic findings include osteopenia, short bowed tubular bones with exaggerated metaphyseal flare, platyspondyly with vertical clefts of the vertebral bodies, and characteristically shaped iliac bones.[4] The ilia are hypoplastic and the acetabulae are small and shallow.

The appearance of the epiphyses, in particular the femoral heads, is delayed. Patchy, sclerotic changes are seen within the epiphyses when they do appear.[2] The epiphyses are irregular in shape and therefore lead to angular deformities of the lower extremities. MRI of the femoral head has revealed large cartilaginous "megaepiphyses."[6]



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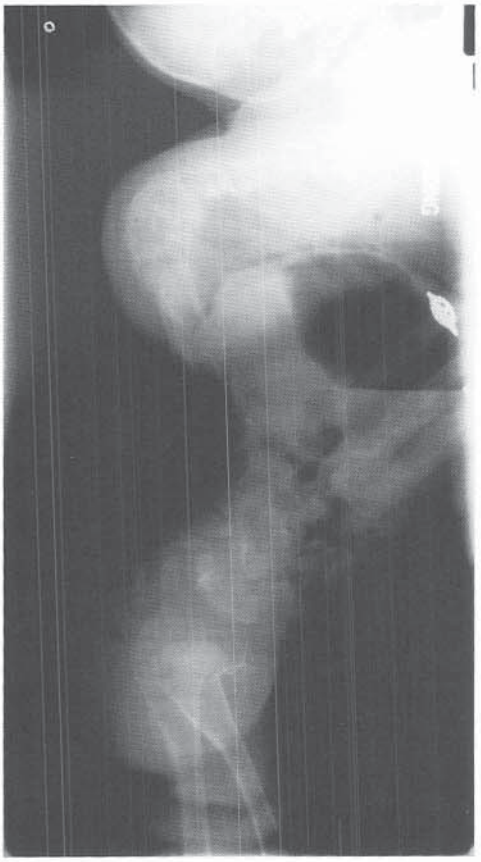

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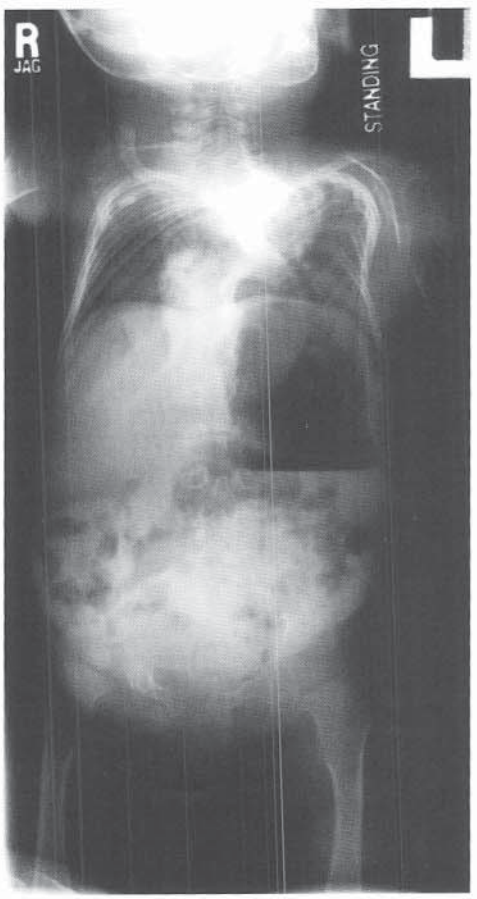

C

FIGURE 29–51 **A** to **C,** Severe kyphoscoliosis in a child age 1 year 7 months with Kniest's dysplasia.

The presence of enlarged cartilaginous epiphyses and sclerosis within the epiphysis differentiates Kniest's dysplasia from spondyloepiphyseal dysplasia congenita.[2] Kniest's dysplasia resembles Morquio's syndrome radiographically[7]; however, the two conditions can be distinguished by laboratory testing of the urine.

TREATMENT

Treatment during the neonatal period focuses on respiratory care, as the collagenopathy may lead to tracheomalacia.[2] Aggressive treatment of upper respiratory infections may prevent hearing loss. Cleft palates are repaired when the infants are medically stable.

ORTHOPAEDIC CONSIDERATIONS

Orthopaedic treatment often focuses on correction of the spinal deformity. Cervical atlantoaxial instability has been reported in Kniest's dysplasia. Surgical treatment is posterior cervical fusion with halo immobilization.[5] Kyphoscoliosis develops in infancy and is very resistant to treatment, as the dysplastic bone resists attempts at surgical fusion (Fig. 29–51).

Loss of joint motion creates functional difficulties for patients with Kniest's dysplasia. Therefore, physical therapy (and occupational therapy for hand involvement) is recommended. Angular deformities of the lower extremities are best treated by osteotomy in the ambulatory patient, although recurrence of deformity is common. Degradation of articular cartilage leads to severe arthritis during adolescence, and few patients are able to continue to walk.

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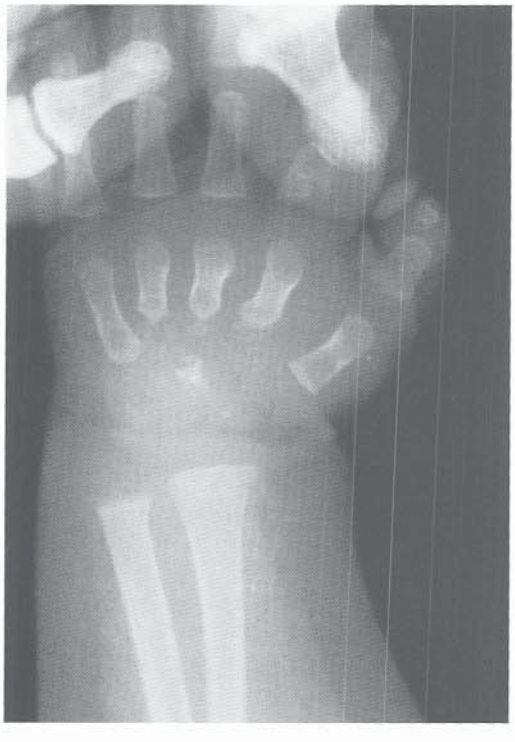

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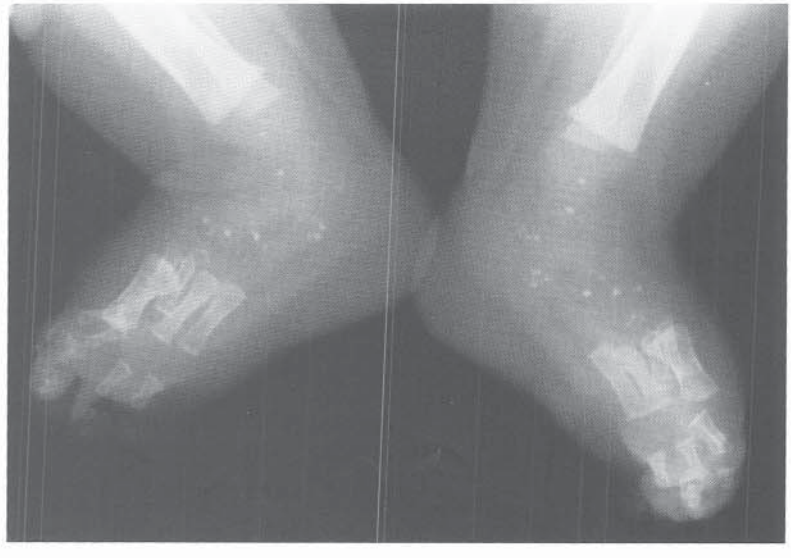
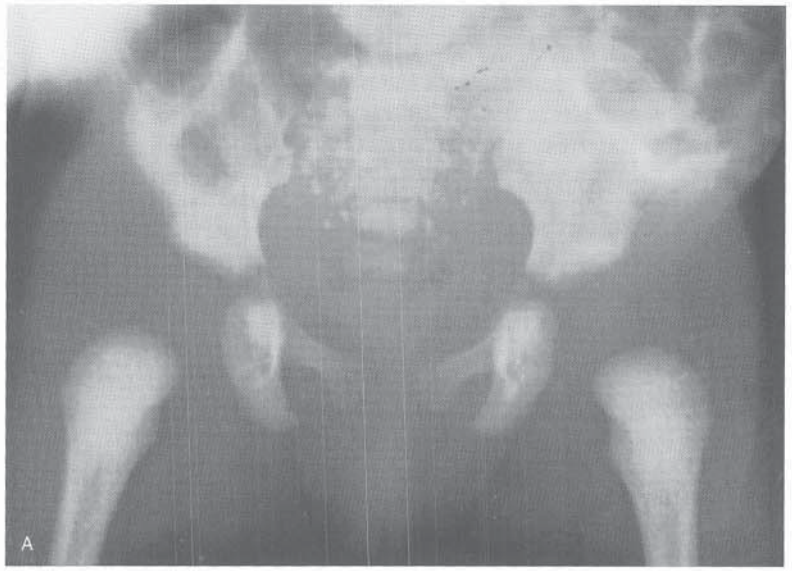


B

FIGURE 29–52 **A** and **B,** Punctate calcifications are seen throughout the carpals and tarsals of a 5-month-old child with chondrodysplasia punctata.



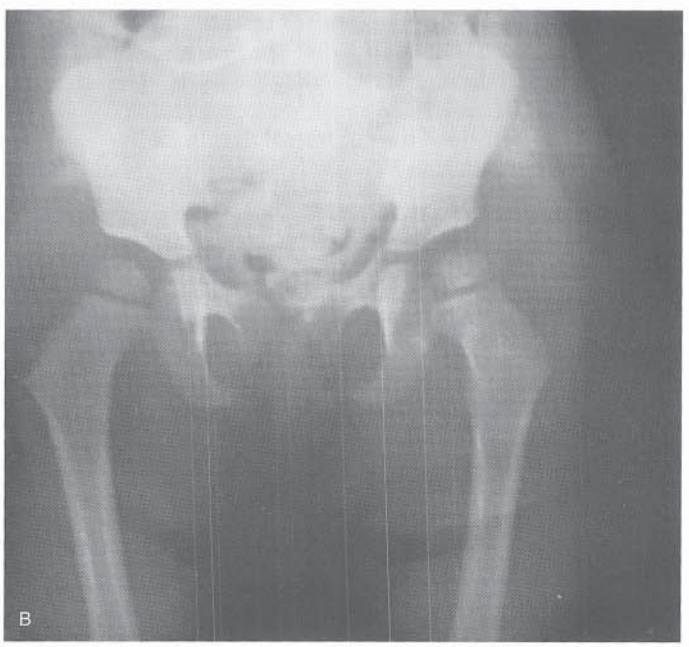


FIGURE 29–53 **A,** Multiple areas of calcification are evident in the pelvis and proximal femur of an infant. **B,** At age 1 year 6 months, the calcified areas have disappeared.

Chondrodysplasia Punctata

Chondrodysplasia punctata is a group of dysplasias characterized by stippled calcifications within the epiphyses in infancy (Figs. 29–52 and 29–53) and associated with short stature, dry and scaly skin, occasional heart defects, and cataracts.[9] The most common form is Conradi-Hünermann syndrome, which is inherited as an X-linked recessive or autosomal dominant trait. A rarer autosomal recessive form exists, characterized by a rhizomelic pattern of dwarfism, that is often fatal within the first year of life. Other forms of the disease exist and are becoming better understood as the molecular genetics of the subtypes are discovered.[27]

GENETICS

Conradi-Hünermann syndrome is inherited as an autosomal dominant trait with variable expression.[24] The X-linked forms of chondrodysplasia have been localized to the arylsulfatase E (ARSE) gene, a member of the sulfatase gene family in the Xp22 region for the X-linked recessive type[7,11,20] and in the Xp28 region for the X-linked dominant variant.[18,25] The severe rhizomelic form of chondrodysplasia punctata is genetically very interesting, as it results from mutations in PEX7 that produce deficiencies in hepatic peroxisomal proteins.[4,19,22]

PATHOLOGY

Specimens obtained from patients with rhizomelic chondrodysplasia punctata exhibit marked irregularity of vascularization of the epiphyses, disturbance of chondroblastic maturation, and mucoid degeneration of cartilage.[6,28] In other forms of the dysplasia there are irregular areas of calcification and cyst formation within the epiphyseal cartilage.

CLINICAL FEATURES

Rhizomelic chondrodysplasia punctata is characterized clinically by symmetric shortening of the proximal limbs. The shortening is notable at birth. Contractures of the joints, including dislocation of the hips, are common. There is a characteristic dysmorphic face with a depressed nasal bridge. Bilateral cataracts are present in 75 percent of patients with the rhizomelic form. Other systemic abnormalities may include congenital heart disease, upper airway obstruction, and tracheoesophageal fistulas.[5,10,23]

In the milder type of chondrodysplasia punctata, limb shortening is less severe and may be asymmetric. The facial appearance is similar to that seen in patients with the rhizomelic form, with a flat nasal bridge. Similarly, the skin is dry and scaly, an appearance termed *ichthyosiform erythroderma.*[14] The clinical appearance of the child may be subtle enough that the disorder is not diagnosed at the time of birth.

Cataracts are suggested as a diagnostic marker to differentiate between the different forms of chondrodysplasia punctata. In both the rhizomelic and the X-linked dominant types, cataracts are present in about two-thirds of cases. In the rhizomelic type, the opacities tend to be bilateral and symmetric. In the X-linked dominant type, they are usually asymmetric and often unilateral. In contrast, the consistent lack of cataracts is characteristic of the autosomal dominant form of chondrodysplasia punctata.[15]

RADIOGRAPHIC FINDINGS

The hallmark of the disease is multiple punctate opacities in the unossified cartilage at the ends of the long bones, the tarsals, the pelvis, and the vertebrae (see Fig. 29–52). The radiographic picture of epiphyseal punctate calcifications is typical, but early diagnosis is important, because the characteristic calcifications disappear within the first year of life (see Fig. 29–53).[1] Although they are the hallmark of chondrodysplasia punctata, the calcifications are nonspecific and have been seen in a variety of disorders. These include Zellweger syndrome; warfarin, dilantin, alcohol, and rubella embryopathies; vitamin K-epoxide-reductase deficiency; chromosome trisomies 18 and 21; the Smith-Lemil-Opitz syndrome; hypothyroidism; and other rare disorders.[17,27] Stippling may also occur in the trachea and larynx and can result in upper airway obstruction.

Other radiographic findings include cranial stenosis, which can lead to cervical cord compression.[13] Upper cervical spine abnormalities, such as os odontoideum and instability, have also been described (Fig. 29–54).[3] Congenital vertebral anomalies and scoliosis or kyphosis are often present. In the lateral projection, vertebral bodies may show separate centers of ossification anteriorly, separated by a cleft posteriorly. Platyspondyly is not present.

The appearance of the secondary centers of ossification is often delayed. After the stippling has resolved, the radiographic appearance of the long bones resembles that of epiphyseal dysplasia. Coxa vara may be present.

PRENATAL DIAGNOSIS

The prenatal diagnosis of chondrodysplasia punctata has been made with ultrasound.[12,21] The punctate calcifications can be seen in late pregnancy in the rhizomelic form, while limb shortening is apparent earlier.[2,8] Amniocentesis has also been useful in diagnosing the rhizomelic form.[16]

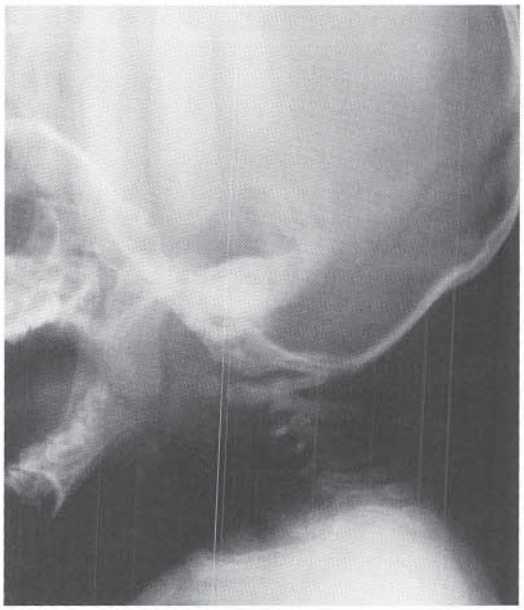


FIGURE 29–54 Vertebral body irregularity in the cervical spine of a 1-year-old child with chondrodysplasia punctata.

ORTHOPAEDIC CONSIDERATIONS

Orthopaedic treatment consists primarily of managing the scoliosis. Because the curves may be quite severe in young patients, surgical management is quite difficult. Bracing is rarely useful. Treatment consists of early anterior and posterior spinal fusion.

Upper cervical instability may be detected on flexion and extension lateral cervical spine radiographs. Occasionally, surgical stabilization is necessary.

Coxa vara, when severe, is treated by valgus osteotomy of the proximal femur. Limb length equalization by epiphyseodesis or lengthening may be helpful in adolescent patients.

PROGNOSIS

Most babies with the rhizomelic form of chondrodysplasia punctata die in infancy from respiratory complications. In patients who survive, there is a high rate of associated spasticity, psychomotor retardation, growth failure, seizures, thermoregulatory instability, feeding difficulty, and pneumonia.[26] Patients with Conradi-Hünermann syndrome have normal life spans.

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Metaphyseal Chondrodysplasia

Metaphyseal chondrodysplasia denotes a group of bone dysplasias characterized by failure of normal mineralization of the zone of provisional calcification, leading to widened physes and enlarged knobby metaphyses. Histologic studies of the growth plate show abnormalities in columnation, with nests and clusters of chondrocytes present instead of orderly rows.[3] Because the longitudinal growth of the bone is affected, affected patients are quite short and angular deformities may occur. In all types of this dysplasia the epiphyses are spared, and thus arthritis rarely develops. There are many different types of metaphyseal chondrodysplasia, with the most common described below.[8]

JANSEN TYPE

The Jansen type is the most severe, but also the rarest, form of metaphyseal chondrodysplasia.

Genetics. The genetic abnormality is a mutation of the PTH-PTHrP receptor on chromosome 3.[16,19]

Clinical Features. The disorder is usually apparent at birth because of the severe short stature, widely spaced eyes, and exophthalmos. The forearms and legs are very short. The lower limb tends to develop angular deformities, with angulation present at the junction of the metaphysis and diaphysis.

Radiographic Findings. Radiographs show bulbous expansion of the metaphyses, with mottling and fragmentation.[17] The metaphyses are quite wide, resembling what is seen in rickets.[20] The epiphyses are normal once they appear. The hands and feet are involved. The metacarpals and metatarsals are cupped, with dense, sclerotic bone on the side of the metaphysis.

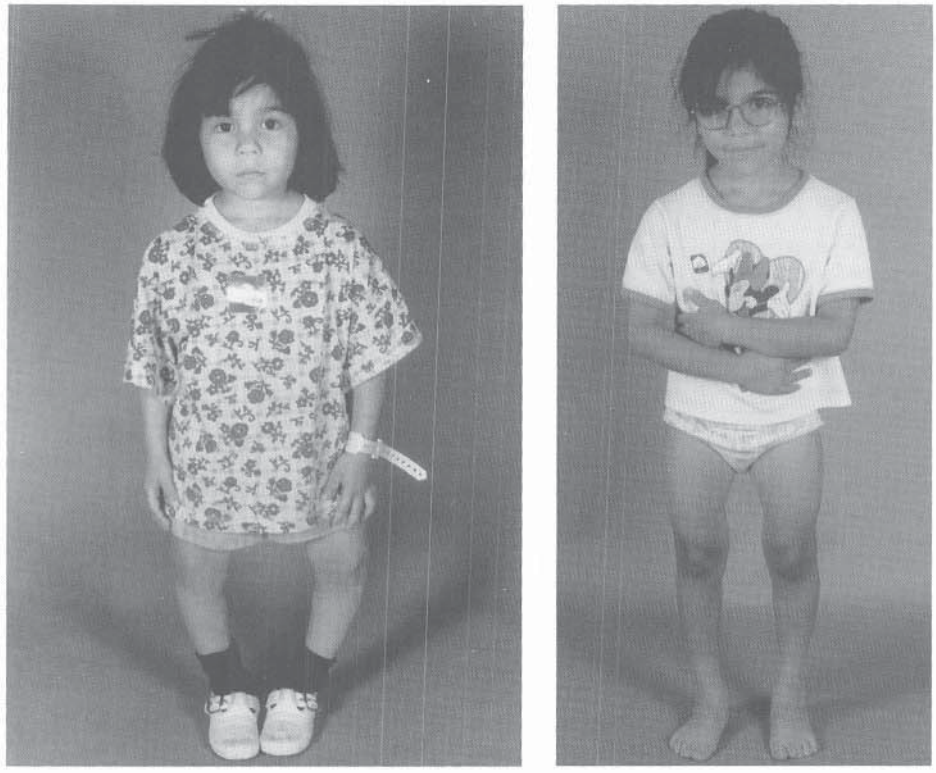
Endocrine Abnormalities. Severe hypercalcemia and hypophosphatasia are seen in patients with the Jansen type of metaphyseal chondrodysplasia, despite low levels of parathyroid hormone (PTH).[5,16] PTH/PTH-related peptide (PTHrP) receptors normally mediate the endocrine actions of PTH that are required for the control of calcium homeostasis. This action is disturbed in Jansen's metaphyseal chondrodysplasia.[6]

SCHMID TYPE

The Schmid type is the most common form of metaphyseal chondrodysplasia.

Genetics. Inheritance is autosomal dominant. Mutations present on chromosome 6 affect the alpha-1 (X) chain of type X collagen (COL10A1) in Schmid's metaphyseal chondrodysplasia.[23,24] Type X collagen is synthesized specifically by hypertrophic chondrocytes at sites of endochondral ossification. Knowledge of the precise mutation responsible for Schmid's metaphyseal chondrodysplasia has led to successful prenatal diagnosis via chorionic villous sampling.[15]

Clinical Features. This dysplasia is characterized by predominant involvement of the proximal femora and moderate short stature. Skeletal changes are not present at birth. They develop with weightbearing at 3 to 5 years of age, when bowing of the lower extremities becomes apparent.[1] Angular deformities, particularly genu varum, are common because the child has been walking for a few years (Fig. 29–55). Despite the normal appearance of the patient's face, this type has often been mistaken for achondroplasia.[25]



A B

FIGURE 29–55 **A,** Girl age 4 years 9 months with Schmid's metaphyseal chondrodysplasia. **B,** Clinical appearance of the child after a right proximal tibial osteotomy and left distal femoral and proximal tibial osteotomies were performed.

Radiographic Findings. The epiphyses are normal in Schmid's metaphyseal chondrodysplasia. The skull, spine, thorax, and pelvis are not involved. The metaphyses are widened and the physes are abnormally thick. Radiographs show splaying, irregularity, and cupping of the metaphyses (Fig. 29–56). The proximal femoral metaphysis is particularly irregular and splayed, and there is medial beaking.[9] Coxa vara is present to varying degrees. A triangular bone fragment may be present on the inferior aspect of the femoral neck when the coxa vara is severe.

Differential Diagnosis. Entities to be ruled out before diagnosing Schmid's metaphyseal chondrodysplasia include nutritional and vitamin D–resistant rickets.[4] The diagnosis of Schmid's metaphyseal chondrodysplasia is based on normal serum chemistry values.

Orthopaedic Considerations. Orthopaedic treatment is primarily confined to the lower extremities. Valgus osteotomy of the proximal femur may be indicated for children with significant coxa vara. Indications for surgical correction include a triangular fragment in the inferior femoral neck and progressive deformity.[1] Usually the entire femur has a varus bow, with the clinical appearance of genu varum. The varus alignment may improve spontaneously during childhood.[18] If the femoral condyles are parallel to the floor, corrective osteotomy may not lead to improved functional results.[1] If surgical realignment of genu varum is performed, distal femoral as well as proximal tibial osteotomies are usually required (Fig. 29–57). Following osteotomies, recurrence of deformity with growth is common.

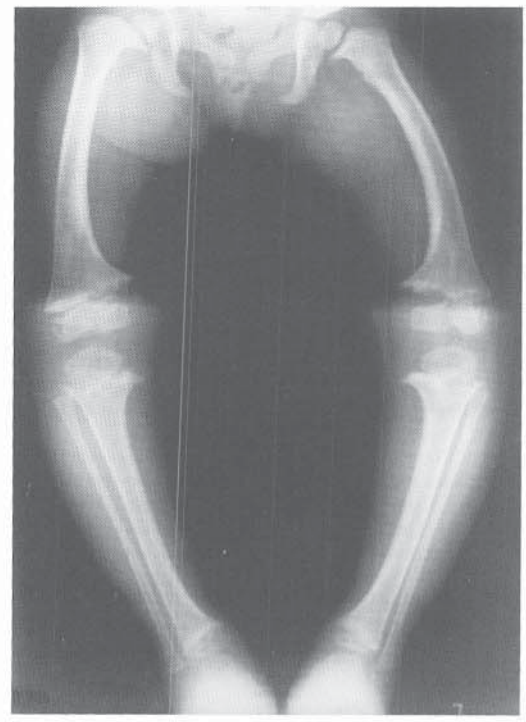


FIGURE 29–56 Genu varum in a 4-year-old girl with Schmid's metaphyseal chondrodysplasia. The physes are widened, and there is metaphyseal cupping that resembles rickets.

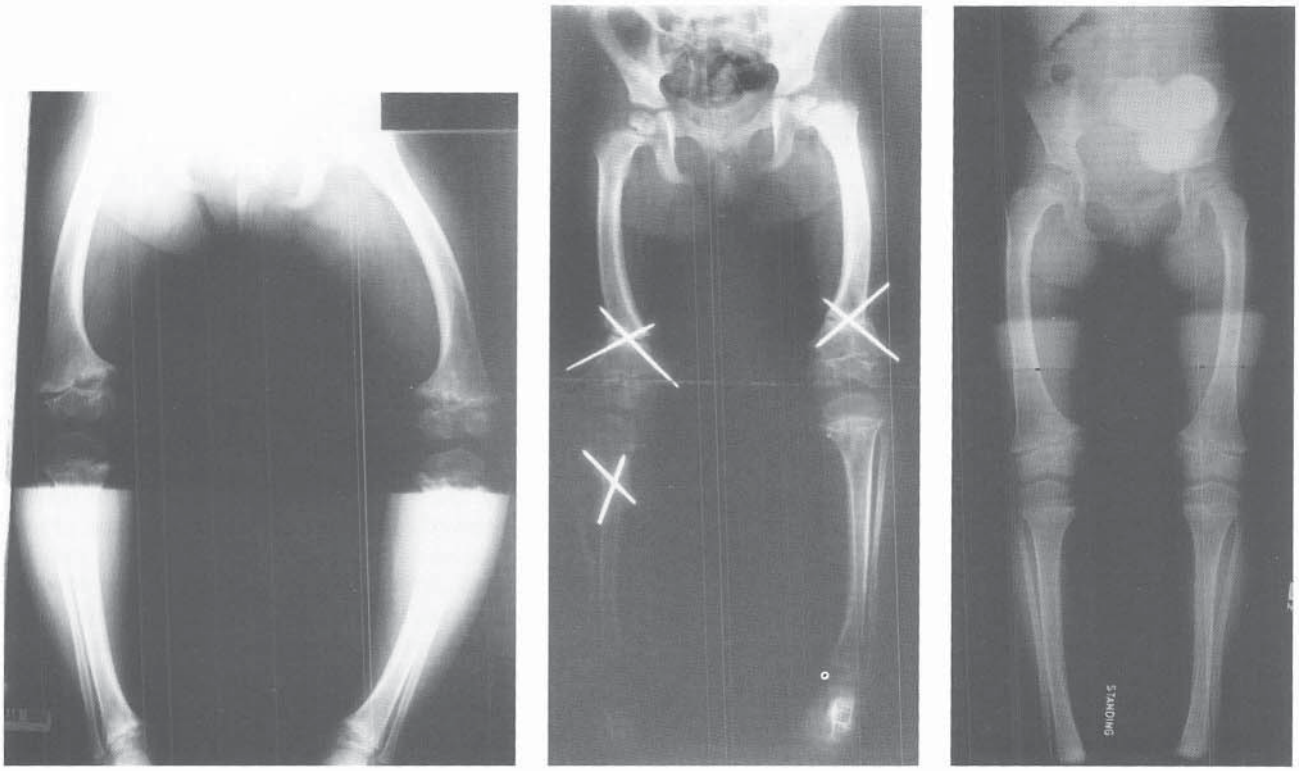


FIGURE 29–57 AP radiographs of the child age 4 years 9 months with Schmid's metaphyseal chondrodysplasia from Fig. 29–55 before, immediately after, and 2 years after realignment osteotomies.

CARTILAGE-HAIR HYPOPLASIA (McKUSICK TYPE)

Genetics. This chondrodysplasia is transmitted as an autosomal recessive trait. It is particularly prevalent in Finland[11, 12] and in the Amish population.[1] The CHH gene has recently been mapped to chromosome 9.[7,21]

Clinical Features. Clinically, affected patients are short, usually shorter than those with Schmid's metaphyseal chondrodysplasia. Height is severely diminished, with adult stature ranging from 105 cm to 157 cm (3 feet 5 inches to 5 feet 2 inches). The fingers and toes are shortened and hyperextensible. Elbow extension may be limited. Genu varum usually is mild and rarely requires treatment. Ankle deformity is caused by unusually long fibulas, leading to hindfoot varus, with midfoot and forefoot valgus. Scoliosis may be present in up to one-fourth of patients with CHH dysplasia. Lumbar lordosis is usually increased.[11,12] The milder clinical appearance in infancy may cause a delay in the diagnosis.[10] The presence of fine, sparse, short, brittle hair is the distinguishing feature. The eyelashes and brows are also affected.[13,14] Unlike the other metaphyseal chondrodysplasias, this dysplasia is associated with immunodeficiency.[2]

Radiographic Findings. Radiographic findings resemble those seen with the Schmid type. Coxa vara may be present but is usually milder than that associated with Schmid's metaphyseal chondrodysplasia.[1] The epiphyses are normal. Odontoid hypoplasia is present in some patients. In the hands, the metaphyses of the phalanges are cupped and the epiphyses appear delta-shaped. In the spine, the vertebral bodies are oval in shape.

Orthopaedic Considerations. Orthopaedic treatment is usually directed toward the ankle and foot. Tachdjian recommended a calcaneal sliding osteotomy as treatment for hindfoot varus but cautioned the surgeon to assess the ankle for ligamentous laxity prior to osteotomy to improve results.[22] Bassett advocated supramalleolar osteotomy as treatment for ankle varus secondary to fibular overgrowth.[1]

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Osteopetrosis

Osteopetrosis is a rare bone dysplasia that was first described by Albers-Schönberg in 1904[1] and, according to Hamersma, given the name *osteopetrosis* by Karshner in 1926.[20] The dysplasia is characterized by failure of bone resorption due to functional deficiency of the osteoclasts. Calcified chondroid and primitive bone persist, leading to osteosclerosis and increased brittleness of the bones.

There are several forms of the disease. The classic congenital form is known as malignant osteopetrosis. A second form is known as benign or tarda osteopetrosis. There also are described cases of osteopetrosis of intermediate severity between the congenital and tarda forms that have been grouped as intermediate forms. A last form of osteopetrosis is linked to renal tubular acidosis. Rare cases of osteopetrosis associated with congenital brain malformations and syringomyelia have been reported.[38,39]

GENETICS

Malignant osteopetrosis is transmitted as an autosomal recessive trait and maps to chromosome 11q13.[21] Osteopetrosis tarda is inherited in an autosomal dominant pattern,[7] and its genetic locus is suspected to be on chromosome 1p21.[51] Autosomal dominant osteopetrosis has been divided into subtypes.[7,19,49] The intermediate forms of osteopetrosis are believed to be autosomal recessive in inheritance.[4,17,24,53] Osteopetrosis associated with renal tubular acidosis also is autosomal recessive in inheritance and is due to a lack of carbonic anhydrase II.[35]

PATHOLOGY

Abnormal osteoclastic activity leads to the inability to absorb cartilage and bone. Shapiro and associates performed histologic, ultrastructural, and biochemical studies of osteopetrotic bone.[43] The bone contained an increased number of osteoclasts, but the osteoclasts were not resorbing bone, as evidenced by the absence of ruffled borders and clear zones. The osteoclasts were unable to respond to PTH. There is an inherent inability to activate macrophages and monocytes.[54]

Pathologic changes in osteopetrosis are due to failure to resorb enchondral cartilage and bone. Formation proceeds normally, leading to the presence of too much immature bone. Calcified cartilage and woven bone persist down into the metaphysis and diaphysis. The metaphysis widens and becomes bulbous as a result of lack of funnelization, and the cortex thickens. Because the overabundant bone is immature, there are fewer collagen fibrils than is normal, and the bones are brittle and prone to break.

Microscopically, there is a characteristic histologic picture of irregular patches of immature chondro-osseous tissue embedded in matrices of coarse fiber bone (Fig. 29–58). Cement lines are wide and prominent. The bone marrow spaces are obliterated by the dense bands of immature bony tissue.

Intramembranous bone formation and bone resorption are also affected. The cranial nerves are pinched by the bony overgrowth of the cranial foramina.

MALIGNANT OSTEOPETROSIS

In malignant osteopetrosis, clinical manifestations appear at birth or in early infancy. Obliteration of the marrow cavity by bony overgrowth results in inability of the bone marrow to participate in hematopoiesis. Pancytopenia develops, resulting in presenting symptoms of abnormal bleeding, easy bruising, progressive anemia, and failure to thrive. Hepatosplenomegaly occurs in response to the anemia. Dentition is delayed, and the teeth have multiple caries. Bony overgrowth of the cranial foramina causes cranial nerve palsies, which result in blindness and deafness. Pathologic fractures occur in the fragile, brittle bones. The clinical course is rapidly progressive and is lethal at a very young age in the absence of a bone marrow transplant.

BENIGN OR TARDA OSTEOPETROSIS

The onset of benign osteopetrosis varies.[6] Often the dysplasia is diagnosed incidentally following radiographic examination of an asymptomatic patient. Approximately 40 percent of patients with benign osteopetrosis are asymptomatic.[5] Clinical findings are limited to mild anemia, pathologic fractures, and premature osteoarthritis. In general, the patients are healthy and have normal life spans. In rare cases, osteomyelitis of the mandible may occur.

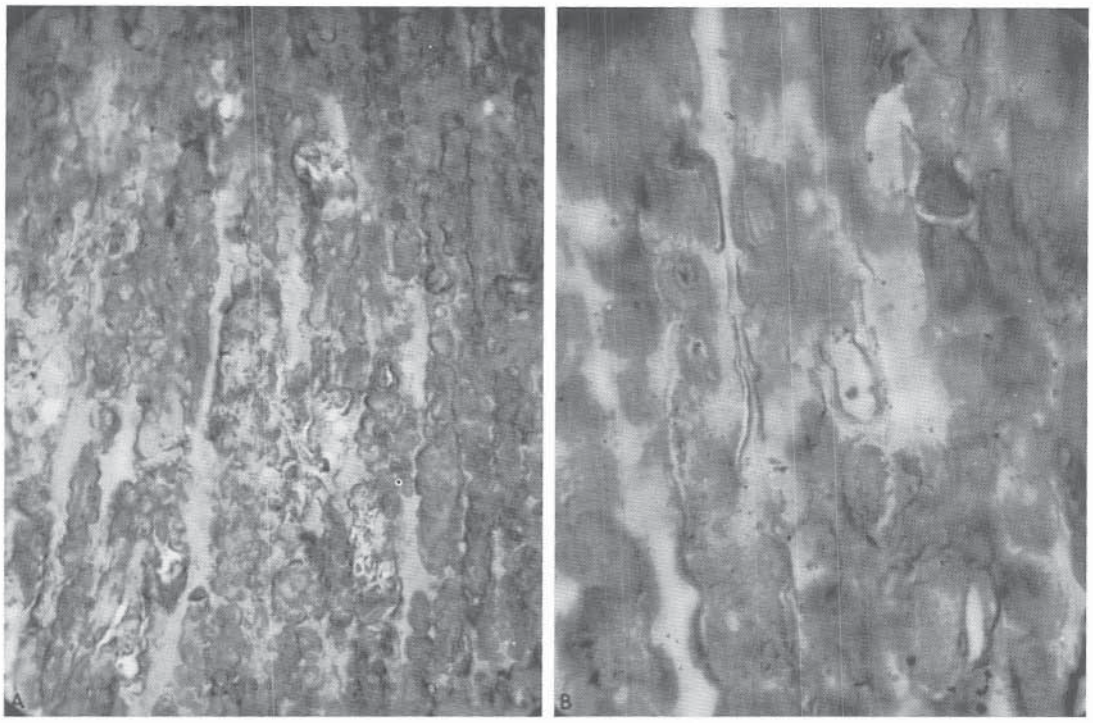

FIGURE 29–58 Histologic findings in osteopetrosis. **A,** ×100. **B,** ×400. Note the irregular patches of immature chondro-osseous tissue embedded in a matrix of coarse fiber bone with wide and prominent cement lines.

OSTEOPETROSIS ASSOCIATED WITH RENAL TUBULAR ACIDOSIS

In a series of patients with this form of osteopetrosis, dental caries, cerebral calcifications, and optic atrophy were common, while anemia was usually not present.[37]

RADIOGRAPHIC FINDINGS

The hallmark of osteopetrosis is the increased radiopacity of the bones. There is no distinction between cortical and cancellous bone, because the intramedullary canal is filled with bone (Fig. 29–59).[14]

With excellent radiographic technique, transverse striations can be seen in the long bones. The transverse bands are composed of alternating zones of sclerosis and relative lucency, which correlate with the activity of the disease. Longitudinal striations may be seen that represent vascular columns.

Endobones, known as os-in-os or bone-within-a-bone, are miniaturized, radiodense tissues that resemble tiny bones inside the cortices of the tubular bones (Fig. 29–60). They are pathognomonic for osteopetrosis. Endobones are most noticeable in early childhood and are best seen in the tarsals, tibia, fibula, radius, ulna, vertebrae, and pelvis.

Flaring of the metaphysis is present due to failure of normal bone modeling and tubulation. Flaring is best seen at physes with the most rapid growth, such as the distal femur.

In early childhood the vertebral bodies are uniformly radiodense. In adolescence and adulthood the spine shows a "rugger jersey" appearance (Fig. 29–61). The vertebrae appear like sandwiches, with osteosclerosis adjacent to the end-plates but relative radiolucency in the middle of the vertebral body.

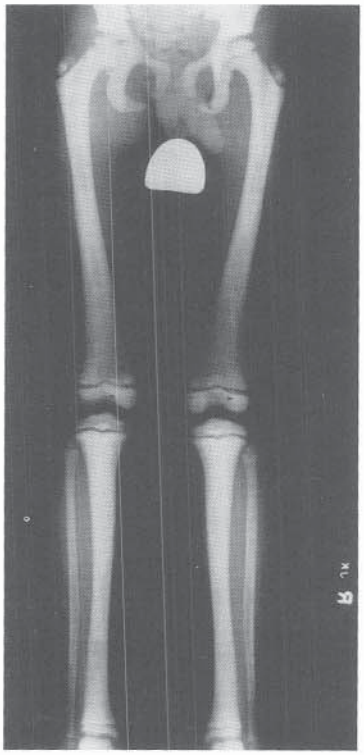

FIGURE 29–59 Osteopetrosis in a 5-year-old child. The intramedullary canal has been filled with bone. There is no distinction between cortical and cancellous bone.

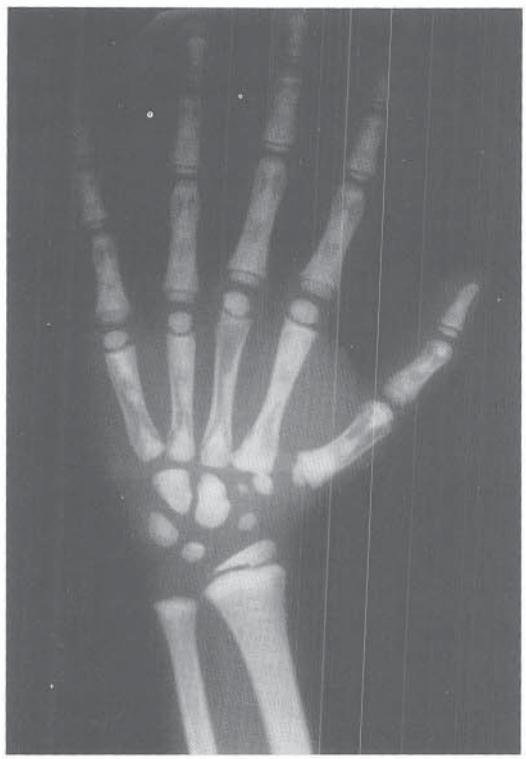

FIGURE 29–60 Endobones in the metacarpals and phalanges of the hand. Note the transverse striations in the distal radius.

On skeletal scintigraphy there is increased uptake of tracer, particularly in the distal femur and proximal tibia. Dual x-ray absorptiometry (DEXA) of the lumbar spine, femur, and total body shows a marked increase in bone mineral density.[13] Bone mineral content is also increased in osteopetrosis.[19]

The skull is radiodense, and the fossae are underdeveloped. Skull CT has been performed in patients with osteopetrosis. Internal carotid artery stenosis has been seen, due to documented bony overgrowth of the petrous carotid canal.[11] Doppler studies of the ophthalmic artery have been used to document optic nerve encroachment and impending blindness in infants.[22]

LABORATORY FINDINGS

Serum calcium, phosphate, and PTH levels are normal. Alkaline phosphatase levels may be elevated; and acid phosphatase levels are elevated. In osteopetrosis associated with renal tubular acidosis, plasma pH will reveal metabolic acidosis.[35] Hypokalemia may be present.

PRENATAL DIAGNOSIS

Prenatal diagnosis has been accomplished in the 25th week of pregnancy with the use of fetal radiography, which reveals sclerosis of osteopetrotic bone and metaphyseal splaying and clubbing of the femurs.[36] Ultrasound has also been used to identify affected fetuses.[41] Prenatal molecular genetic testing has been used in osteopetrosis with renal tubular acidosis.[48]

DIFFERENTIAL DIAGNOSIS

Osteopetrosis must be differentiated from other sclerosing bone conditions. In pyknodysostosis, anemia is not present, whereas hypoplasia of the clavicles and distal phalanges and mandibular changes (seen as a small chin) are present. In progressive diaphyseal dysplasia (Camurati-Engelmann disease), anemia is not present and the ends of the bones are not clubbed, as the sclerosis involves only the diaphysis. Pathologic fractures are not seen. Other, rarer dysplasias can be confused with osteopetrosis, such as craniometaphyseal dysplasia, metaphyseal dysplasia (Pyle's disease), and frontometaphyseal dysplasia. In none of these conditions does anemia occur. Medical conditions that may produce osteosclerosis are metal poisoning, syphilis, and myelofibrosis.

PROBLEMS AND COMPLICATIONS

Pathologic fractures are common in osteopetrosis because of the brittle nature of the "marble bones." The fracture line generally is transverse, but epiphyseal separations have also been seen.[34,42] Fracture callus is produced, but healing usually is slow. Histologically, the callus is normal; however, subsequent normal remodeling into mature bone with a developed haversian canal does not occur.[12] Callus can envelop the existing bone. The proximal femur is particularly prone to fracture.[18] Coxa vara may develop as a result of the shear stresses across the osteopetrotic femoral neck. Osteomyelitis is common in patients with osteopetrosis because

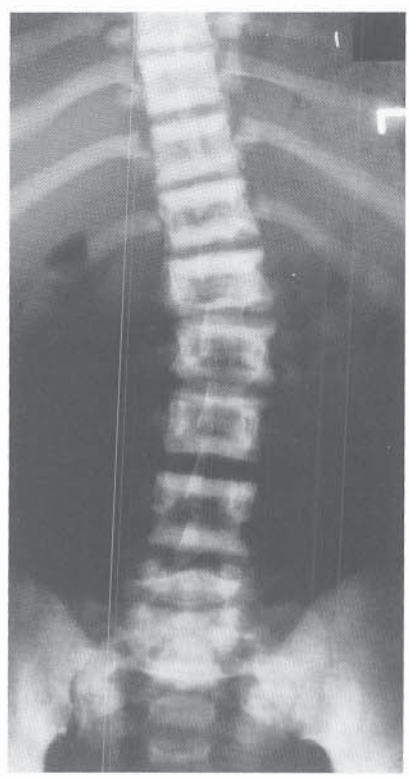

FIGURE 29–61 "Rugger jersey" spine in 16-year-old individual with osteopetrosis.

of a reduced resistance to infection. The mandible is most frequently involved.[3,23]

TREATMENT

Treatment for the congenital form of osteopetrosis is directed at the life-threatening pancytopenia. In a European study conducted from 1972 to 1988 and comprising 33 patients with autosomal recessive osteopetrosis, the probability of survival to age 6 years was approximately 30 percent for the group.[25] The risk of developing visual or hematologic impairment in the first year of life was about 75 percent. Patients with early hematologic impairment (i.e., before age 3 months), especially when combined with early visual impairment, had a very poor prognosis regarding life expectancy.

Congenital osteopetrosis is treated by bone marrow transplantation to provide monocytic osteoclast precursors.[44] In 1975, Walker discovered that osteopetrosis in the rat could be cured by transplanting osteoclast precursors from bone marrow and spleen.[52] This animal research led to the ability to cure previously fatal malignant osteopetrosis by transplanting human bone marrow into an affected infant. Transplantation of marrow from genotype-matched HLA identical donors leads to a 5-year survival rate of 79 percent. When the HLA type is not identical, the success rate following bone marrow transplantation deteriorates, with patients who receive mismatched HLA marrow transplants from a relative having only a 13 percent 5-year survival rate.[15] Myeloablative chemotherapy prior to transplantation maximizes the potential for success.[44] Hypercalcemia may develop following successful bone marrow transplantation, as the osteoclasts resorb the excessive bone.[15]

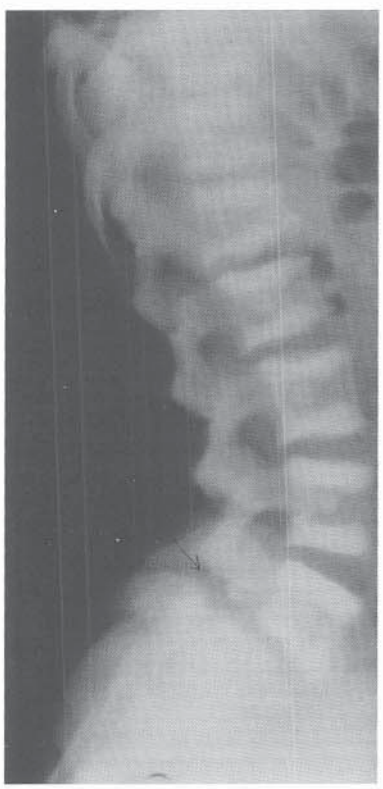

FIGURE 29–62 Spondylolysis of L5 secondary to osteopetrosis. Note the "rugger jersey" appearance of the spine.

In successful bone marrow transplants, normalization of the bone marrow occurs, with normal osteoclastic activity seen on bone marrow biopsy. Bone marrow scintigraphy is useful in confirming restoration of the marrow.[50] Radiographs of the long bones and hands show resolution of the osteosclerosis and new normal bone formation with remodeling.[10,40]

Recently, umbilical cord blood transplantation has been reported to be successful in the treatment of congenital osteopetrosis. The advantages of this approach are the ability to use unrelated donors and a lower incidence of graft-versus-host disease.[30]

The pharmacologic treatment of patients with osteopetrosis is being investigated. Prednisone improves the anemia but does not reduce bone mass. Thyroid hormone therapy has been shown to stimulate bone resorption.[7] Calcitriol in high doses has been reported to result in clinical improvement.[25] Interferon-gamma has been used to allow bone resorption by enhancing superoxide production.[26,27] Blood counts improved significantly, and bone marrow scans demonstrated improved marrow production. However, some patients cannot tolerate the side effects of interferon and actually develop greater immunosuppression.[29] Erythropoietin has been used in an adult case of transfusion-dependent osteopetrosis, with resultant improvement in red cell and platelet counts.[33] All of these medical therapies ameliorate osteopetrosis, but they do not cure the condition.[25]

Cranial nerve impingement is treated by neurosurgical decompression of the bony impingement at the cranial neural foramina. Upper airway obstruction may require a tracheostomy.[47]

ORTHOPAEDIC CONSIDERATIONS

Fractures are treated by conventional methods, but they may be slow to heal. Internal fixation of fractures is technically demanding, as the osteopetrotic bone is difficult to drill or ream.[42] Nonunions may occur, particularly at the proximal femur, and reconstructive osteotomy can fail if fixation is inadequate.[46]

Coxa vara is the most common orthopaedic deformity in patients with benign osteopetrosis. The condition develops as a result of multiple stress fractures of the femoral neck. Corrective osteotomy is difficult to perform because of problems with internal fixation.[28,32]

Total joint arthroplasty of the hip has been performed in patients with benign osteopetrosis who had symptomatic nonunions of the subtrochanteric femur and premature osteoarthritis.[2,8,32] However, preparation of the femur is extremely difficult due to the lack of the intramedullary canal and the brittle nature of the bone. Proximal tibial osteotomy and total knee arthroplasty have also been performed in adult patients with osteoarthritis; the technical challenges are similar.[9,45]

Cervical and lumbar spondylolysis are commonly seen in children with osteopetrosis. Lumbar spondylolysis may produce low back pain (Fig. 29–62). Progressive spondylo-

listhesis does not occur. Conservative treatment with orthoses can help reduce symptoms of pain.[31]

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Progressive Diaphyseal Dysplasia (Camurati-Engelmann Disease)

This rare syndrome was first described by Camurati in 1922[3] and then by Engelmann in 1929.[5] The dysplasia is characterized by widened fusiform diaphyses, with excessive periosteal and endosteal new bone formation occurring *only* in the diaphysis. The muscles and subcutaneous tissue are atrophic and weak over the affected area of the limb.[7,14]

GENETICS

The disease is inherited as an autosomal dominant trait.[18] There is variation in the expression of the disorder. The prevalence is less than one per million. There is a slight male predominance.

PATHOLOGY

The bony cortex is markedly thickened, with some hypertrophy of the periosteum. Microscopic examination shows an increase in the fibrous component of the periosteum. There is marked osteoblastic and osteoclastic activity. The trabeculae are thickened but otherwise normal. The medullary cavity is slightly narrowed. Later in the disease, the compact bone may change to cancellous bone. The marrow is normal early on, but later consists of loose mesenchymal fibrous tissue with occasional foci of hematopoiesis.[4,17]

CLINICAL FEATURES

The disease usually manifests by age 10 years. Involvement of the long bones is bilateral and symmetric. The tibia is the most frequently affected bone. Other common sites of

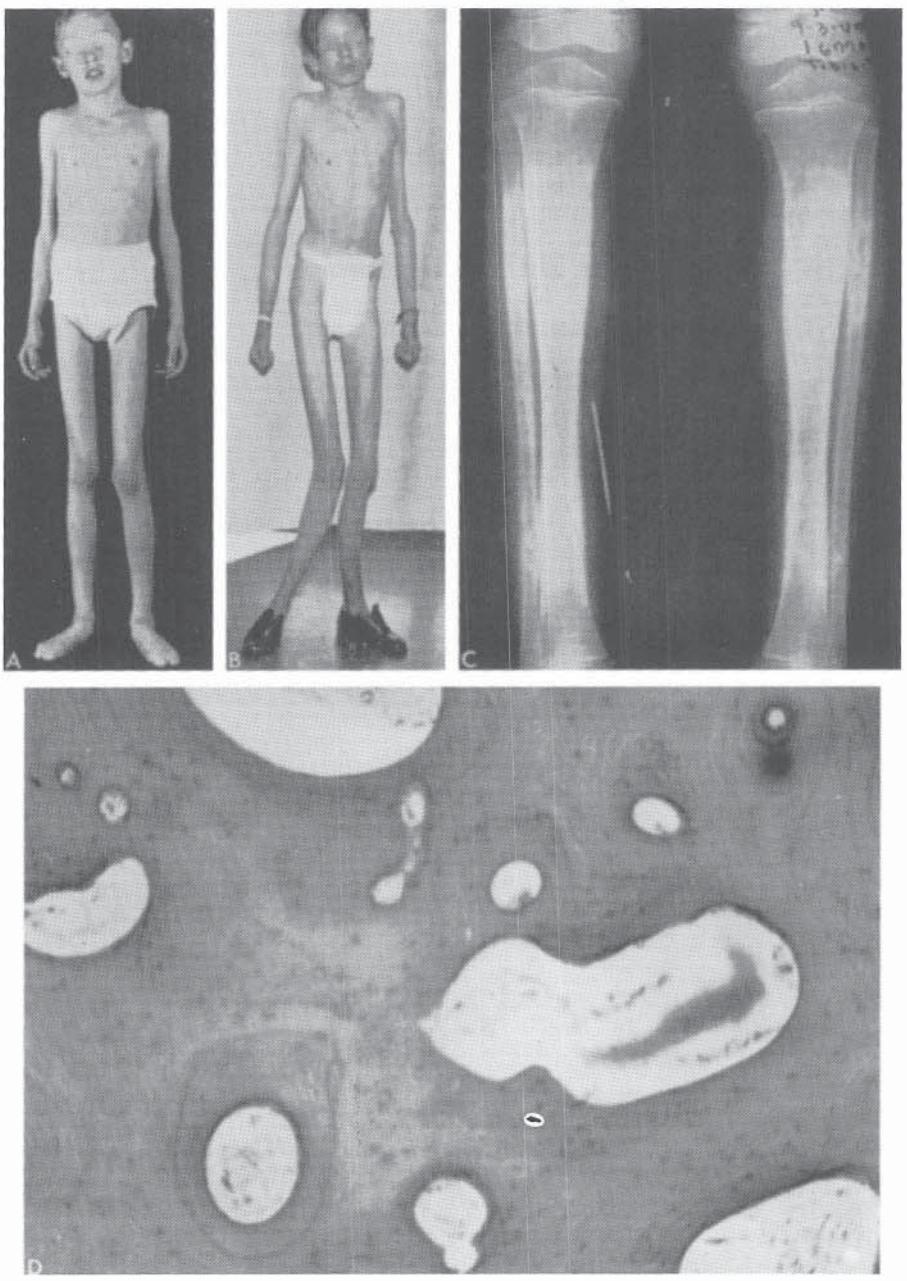

FIGURE 29–63 Camurati-Engelmann disease in a young boy. **A** and **B,** Clinical appearance at age 10 and again at age 18. Note asthenic habitus, lack of physical development, marked genu valgum, and external tibial torsion. **C,** AP radiographs of the tibiae at age 7 years show diaphyseal sclerosis with both endosteal and periosteal thickening and relatively normal epiphyses and metaphyses. **D,** Histologic section of specimen obtained at time of osteotomy reveals thickened trabeculae with normal haversian systems (×100). (From Clawson DK, Loop JW: Progressive diaphyseal dysplasia [Engelmann's disease]. J Bone Joint Surg 1964; 46-A:143.)

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Osteopathia Striata

Osteopathia striata is a dysplasia characterized by striations in the metaphyseal regions of cancellous bone, with sclerosis of the base and vault of the skull. It was first described by Voorhoeve and named by Fairbank in 1924.[5,6,19]

GENETICS

The dysplasia is inherited as an autosomal dominant trait, and its prevalence is less than 0.1 per million.[10,16,18] A second, X-linked form of the disease associated with significant cranial abnormalities has been proposed.[15] There is a high degree of variability in the clinical expression of the disease.[11–13,17]

CLINICAL FEATURES

Skull abnormalities lead to abnormal facies. The forehead is high, with frontal bossing. A broad nasal bridge is present. Cleft palate has been seen in patients with skull deformity.[13,20] Some patients are mentally retarded. The skeletal lesions are asymptomatic.

RADIOGRAPHIC FINDINGS

Usually there is symmetric involvement of one bone or of the entire skeleton.[9] The striations are radiodense and are parallel to the long axis of the bone (Fig. 29–65).[7] They may extend into the epiphysis. The most common sites are in the long bones at areas of rapid growth.[8] When present in the ilia, the radiating lines have a "fanlike sunburst" appearance. The pathognomonic feature of osteopathia striata is sclerosis of the skull base.[3] The bone striations do not change with age.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes osteopoikilosis, the autosomal dominant form of osteopetrosis, and hyperostosis corticalis generalisata.[1] Osteopathia striata may be present in patients with mixed sclerosing bone dysplasias (see previous section, Osteopoikilosis).

CLINICAL COURSE

There are no orthopaedic complications, and no treatment is necessary. The occurrence of visual impairment and deafness as a result of cranial nerve impingement has been reported.[2,4,14]

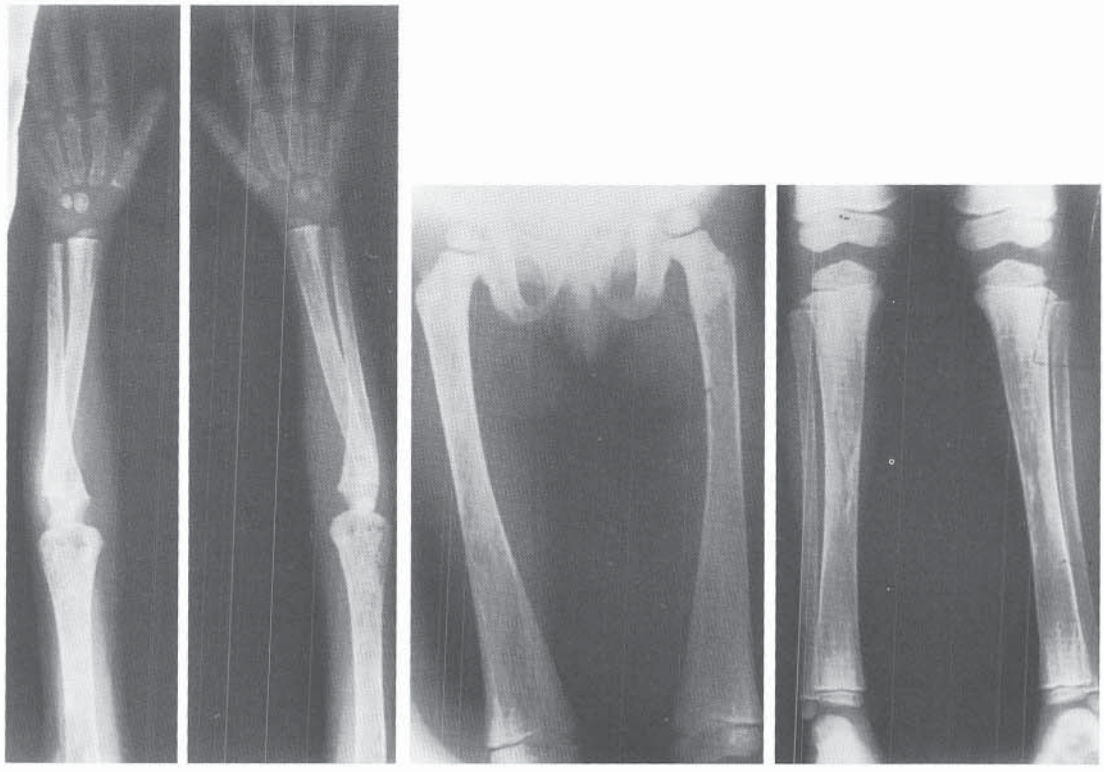

FIGURE 29–65 Osteopathia striata. AP radiographs of upper and lower limbs show the striations parallel to the longitudinal axis. They are especially marked in the metaphyseal areas.

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Melorheostosis

Melorheostosis is a rare dysplasia characterized by a "flowing" hyperostosis of the cortex. The radiographic appearance has been likened to "dripping wax down the side of a candle." Unlike most of the other osteosclerotic dysplasias, melorheostosis is not believed to be a genetic disorder. Its prevalence is estimated at one per million.

ETIOLOGY

The etiology of melorheostosis remains unknown. There is a peculiar tendency for the hyperostosis to involve only one side of the bone, following a sclerotomal pattern.[18] Theories have been proposed linking melorheostosis to peripheral neuropathy resembling herpes zoster.[14,23]

PATHOLOGY

Pathologic examination of bone and soft tissue reveals no pathognomonic features. Histology shows osteosclerosis, with thickening of the bony trabeculae and narrowing of

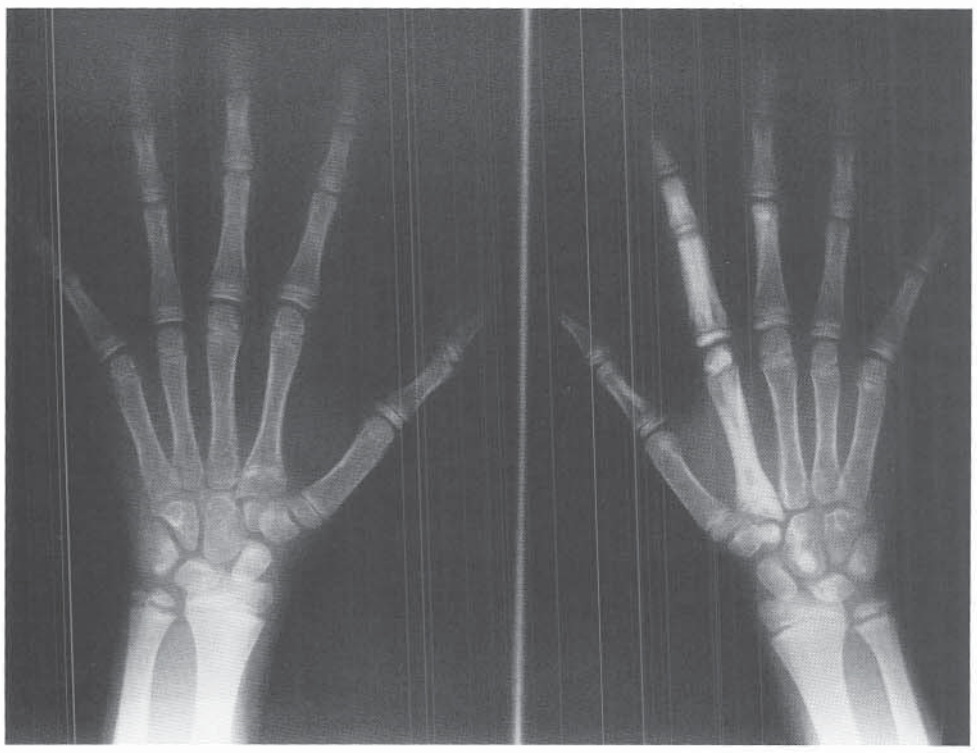


FIGURE 29–66 Melorheostosis. Sclerosis is seen in the right hand, most prominently the second metacarpal. There is also sclerosis present in the carpals and phalanges. The left hand is normal.

the medullary cavity. The haversian canals are surrounded by thick and irregular laminae. The bone appears primitive, particularly on the periosteal surface. The abnormal bony deposition begins at the proximal end of the bone and proceeds distally.[14] The bone marrow appears fibrous.[7]

Periosseous fibrosis of soft tissues is common. Fibrosis of the skin and subcutaneous tissues is frequently noted. Periarticular calcifications or ossification may occur.[12,40]

CLINICAL FEATURES

The disease usually becomes apparent in childhood or adolescence. Presenting complaints consist of soft tissue contracture and fibrosis in children and bone pain in adolescents and adults. The disease may affect one bone, one limb, or multiple sites.

Limitation of joint motion is present in all patients. Contractures result from periarticular calcification, soft tissue fibrosis, and bony deformity. Flexion contractures of the hips and knees, abduction contractures of the hips leading to pelvic obliquity, equinus, and varus or valgus of the feet are all seen.[30] Genu valgum may be present. Finger and toe flexion contractures also occur.[3,27,28,31,33] Melorheostosis of the hand can lead to carpal tunnel syndrome, even in young children.[5,6,8]

The affected limb appears enlarged. Leg length inequality is common, but the affected extremity may be longer or shorter.

The soft tissue is tense, thickened, and shiny or erythematous. The underlying subcutaneous tissue feels woody.

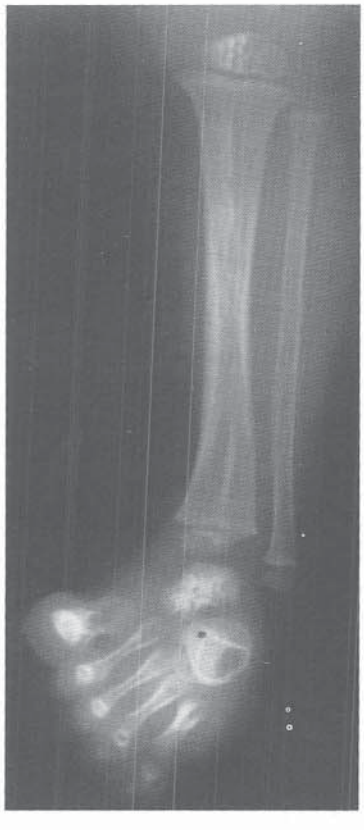
RADIOGRAPHIC FINDINGS

The classic radiographic finding is asymmetric, irregular osteosclerosis along the axes of the long bones (Fig. 29–66). There is a distinct border between pathologic and normal bone. In children the sclerosis in the long bones is endosteal, whereas in adults it is subperiosteal or extracortical. Epiphyseal sclerosis may be present in children (Fig. 29–67).

Bone scintigraphy in melorheostosis shows increased uptake with asymmetric cortical activity that may cross the joints.[10,13,19,35] Blood pool imaging on bone scans shows increased tracer uptake.[20]

CLINICAL COURSE

The clinical course of melorheostosis is one of slow but constant progression into adulthood.[9] A number of associated conditions have been documented in patients with melorheostosis, including scleroderma,[22,34,36] neurofibromatosis, tuberous sclerosis,[15] rheumatoid arthritis,[37] and hemangioma.[14] Melorheostosis may be a component, along



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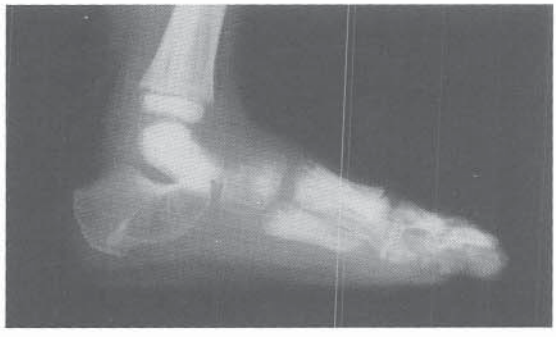

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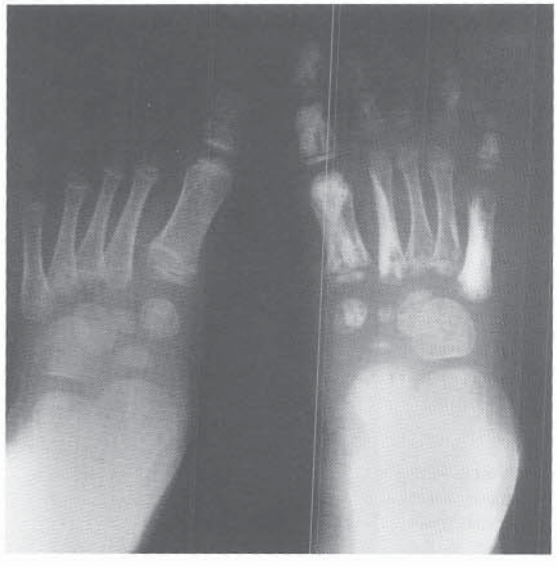

C

FIGURE 29–67 A to C, Melorheostosis involving the femur, tibia, tarsals, and foot in a child. Epiphyseal sclerosis can be seen.

with osteopoikilosis and osteopathia striata, in patients with mixed sclerosing bone dysplasia,[24,25,38]

Vascular anomalies, including aneurysms and renal artery stenosis, have been described in patients with melorheostosis.[1,11,16,26,29] Ischemia leading to amputation has been reported.[39]

Malignant transformation in isolated cases has been described.[4,17]

DIFFERENTIAL DIAGNOSIS

Osteomyelitis, osteopetrosis, osteopoikilosis, and osteopathia striata should all be considered in the differential diagnosis. The presence of joint contractures in an infant may suggest arthrogryposis, but the radiographic appearance of hyperostosis will differentiate arthrogryposis from melorheostosis. Soft tissue fibrosis resembles scleroderma. Limb pain may mimic acute rheumatic fever or poliomyelitis.

TREATMENT

Medical treatment is recommended to control the bone pain.[32]

ORTHOPAEDIC CONSIDERATIONS

Orthopaedic management of the contractures is difficult. Soft tissue contractures are resistant to release, and recurrence of deformity following surgery is extremely common.[28] Manipulation, casting, soft tissue releases, capsulotomies, and osteotomies have all resulted in a high recurrence rate.[39]

Fixed contractures are treated by release, with extensive capsulotomy and tendon resections rather than lengthening, as in the treatment of arthrogryposis. Orthoses are used postoperatively to delay recurrence. Osteotomies may be needed to correct deformity. Gradual correction of deformity with the Ilizarov technique has been reported.[2,21]

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Infantile Cortical Hyperostosis (Caffey's Disease)

Infantile cortical hyperostosis (Caffey's disease) is a self-limited disorder characterized by soft tissue swelling, sub-

periosteal new bone formation, cortical thickening of underlying bones, fever, and irritability.[5] Classically, the onset of the disease occurs before the fifth month of life, with resolution by 3 years of age. There are rare cases of documented cortical hyperostosis in older children that in every way resemble Caffey's disease.[14]

GENETICS

The occurrence of the disease in isolated cases or in multiple members in families suggests that there are two different forms, namely a sporadic form and a familial form.[25] Reported cases of sporadic cases are becoming less common.[22] In the sporadic form the mandible is mostly affected, whereas in the familial form the tibia is the predominant bone known to be affected.[3] The familial form is inherited as an autosomal dominant trait with variable penetrance.[1,9] The age at onset in the familial form is younger than in the sporadic form, with the familial form manifest in about 24 percent of patients at birth.[22] An even more severe autosomal recessive form may exist whose onset is in the prenatal period.[8]

PATHOLOGY

In the early stages of the disease, there is a marked inflammatory process involving the periosteum and adjacent soft tissues. Gradually the inflammation subsides, leaving a thickened periosteum and subperiosteal immature lamellar bone. Vascular fibrous tissue occupies the bone marrow space (Fig. 29–68). Biopsy of more mature bony lesions reveals only hyperplasia of the lamellar cortical bone, without inflammation or subperiosteal hemorrhage.[7,16,24]

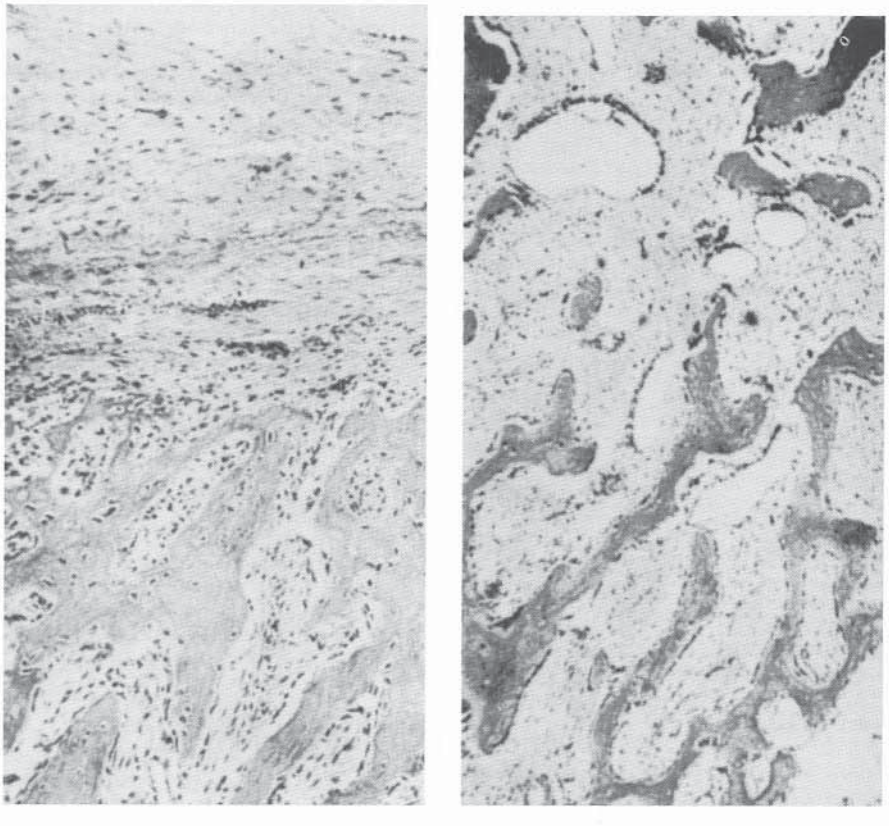
CLINICAL FEATURES

The average age at presentation is 9 weeks, with almost all cases apparent by 5 months of age. The disease may be present at birth.

In the sporadic form, the mandible is the most common site of involvement, with mandibular abnormality present in 75 to 80 percent of cases. The most common clinical manifestations at presentation are hyperirritability and the presence of a local mass, often over the mandible. The swelling appears suddenly, is deep and firm, and may be tender. There is no local heat or redness. Fever may be present, and the sedimentation rate and serum alkaline phosphatase levels are elevated, mimicking infection. Affected babies may refuse to eat because of mandibular pain, and failure to thrive may develop.[23] Anemia may be present.

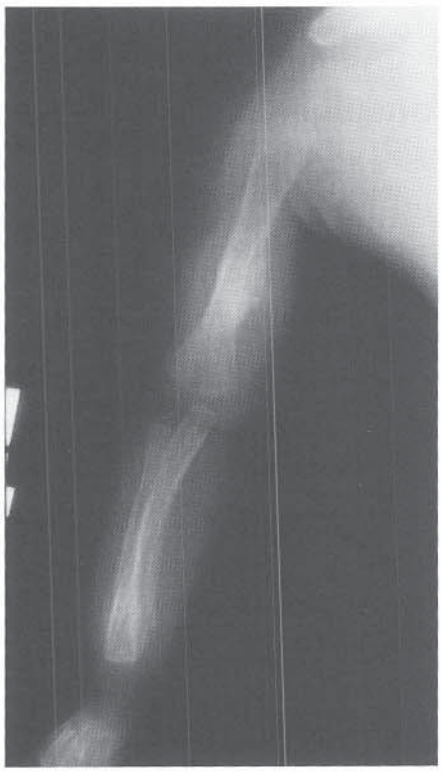
Of the limbs, the ulna and tibia are most frequently involved, with the tibia most often affected in the familial form of the disease. Next in frequency of involvement are the clavicles, scapulae, and ribs. The humerus, femur, and fibula are less often involved. Occasional involvement of the skull, ilium, scapulae, and metatarsals has been described.[11,12] Multifocal involvement is common, but the disease usually is asymmetric.[10,14]

Late recurrence or persistence of symptoms with deformity is quite rare.[2,3,18,26]



A B

FIGURE 29–68 Infantile cortical hyperostosis—pathologic findings. **A,** Histologic section. Note the thickened periosteum with underlying immature bone. **B,** Photomicrograph showing the filling of marrow spaces with vascular fibrous tissue. (From Staheli LT, Church CC, Ward BH: Infantile cortical hyperostosis [Caffey's disease]. JAMA 1968;203:98.)



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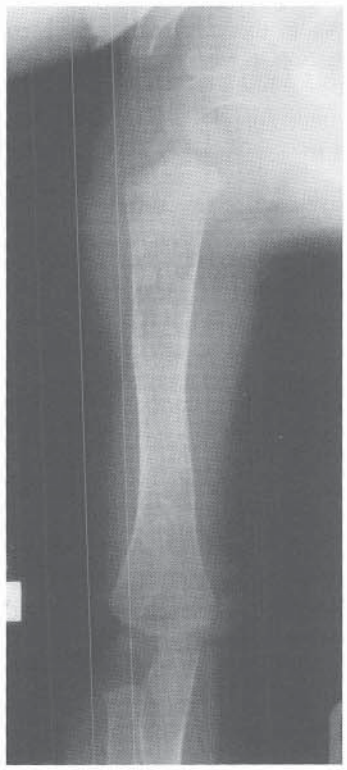

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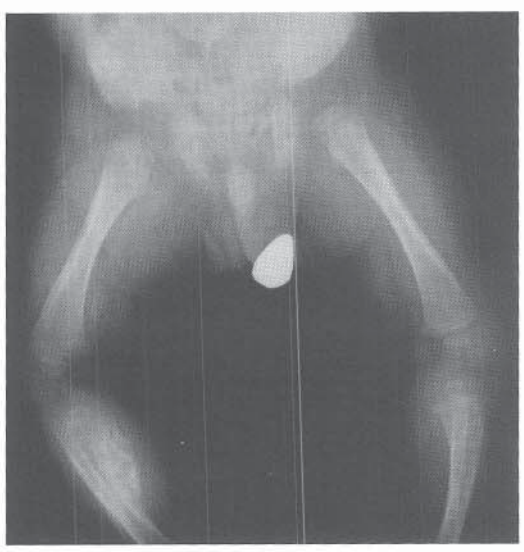

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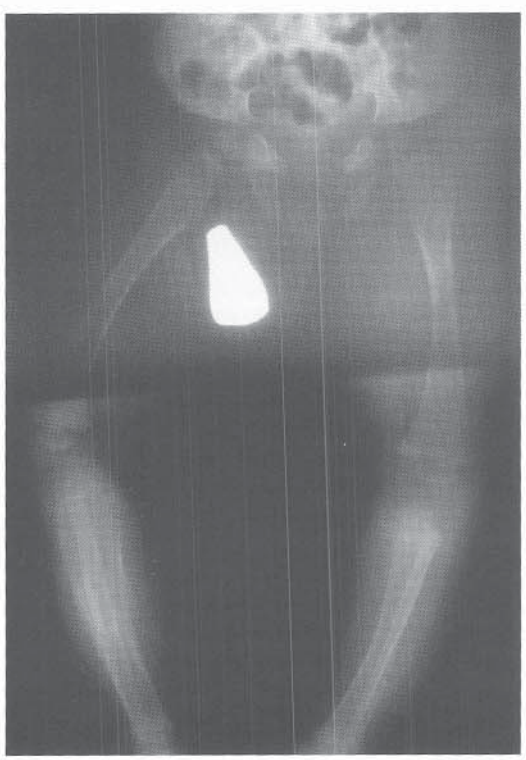

E

FIGURE 29–69 **A,** Radiograph of a 3-month-old boy with Caffey's disease in the upper extremity. **B,** Radiograph obtained 1 month later shows maturation of the periosteal new bone. **C,** Follow-up radiograph obtained at age 7 months is normal. **D,** Involvement of the tibia was also present at age 3 months. **E,** At age 7 months, the right tibia remains widened compared to the left.

RADIOGRAPHIC FINDINGS

The characteristic finding on plain radiographs is the formation of periosteal new bone engulfing the diaphysis but not the epiphysis of the existing bone. The diameter of the bone increases. Soft tissue swelling will be evident. Over time, the periosteal bone increases in density and becomes homogeneous with the underlying cortex. Over months to years, the appearance of the bone becomes normal (Fig. 29–69).[17]

The MRI appearance of Caffey's disease has been described.[20] Marked periosteal reaction appeared as a discretely visualized area of even thickness and intermediate signal intensity encircling the femoral diaphysis. Marked edema and swelling of the adjacent soft tissues of the periosteal segment were also present. MRI provides excellent images for differentiating bony and soft tissue structures and for evaluating the extent of soft tissue involvement, but it has no additional value in clinical management.[21]

DIAGNOSIS

The diagnostic features of infantile cortical hyperostosis are specific: (1) the narrow age range for presentation (between birth and 5 months of age), (2) the triad of irritability, swelling, and bone lesions, and (3) mandibular involvement. Laboratory tests may help rule out other conditions. Biopsy of the lesion usually is not indicated. However, when the possibility of malignancy cannot be ruled out, biopsy may be necessary.

PRENATAL DIAGNOSIS

Prenatal diagnosis of the prenatal form of Caffey's disease is possible with ultrasound. The appearance on ultrasound resembles osteogenesis imperfecta.[15]

DIFFERENTIAL DIAGNOSIS

The condition may be mistaken for osteomyelitis or a result of child abuse.[29] Congenital syphilis and hypervitaminosis A may also resemble Caffey's disease (Table 29–4).[30] Other diseases in the differential diagnosis include scurvy, Ewing's sarcoma, and metastatic neuroblastoma.

The administration of prostaglandin E in young infants with cardiac malformations has been shown to produce periosteal reaction with new bone formation.[32,33] The hyperostosis associated with the use of prostaglandin can be differentiated from Caffey's disease by the site of involvement. With prostaglandin-associated hyperostosis, the mandible is not affected, whereas in Caffey's disease the mandible is most often involved.[19]

TREATMENT

There is no specific treatment for Caffey's disease. Corticosteroids are effective in alleviating the acute systemic manifestations but do not change the bony lesions. Steroid treatment is reserved for infants with extensive disease.[4] Nonsteroidal anti-inflammatory medication has been used successfully to treat a child with recurrent Caffey's disease.[28]

TABLE 29–4 **Features Distinguishing Pyknodysostosis, Osteopetrosis, and Cleidocranial Dysplasia**

Features	Pyknodysostosis	Osteopetrosis	Cleidocranial Dysplasia
Inheritance	Autosomal recessive	Congenital malignant type (autosomal recessive) Mild tarda type (autosomal dominant)	Autosomal dominant
Stature	Short stature—short-limbed type	Short in congenital type Normal in tarda type	Usually normal Sometimes minimal shortness
Prevalence	<1 per million	3 per million	<1 per million
Facies	Micrognathia with obtuse mandible, small maxilla; delayed eruption of disorganized teeth	Normal	Low nasal bridge with bulging frontal and parietal regions teeth Disordered eruption of failure of fusion of mandibular symphisis
Skull	Dysplasia with widened sutures; wormian bones Persistent open fontanelles No cranial foramina impingement No cranial nerve palsy	Thickened vault, base Cranial foramina impingement with bone overgrowth Cranial nerve palsy	Wormian bones Open fontanelles in childhood No cranial nerve palsy
Clavicle	Hypoplastic, sometimes absent in lateral portion	Present and normal	Partially or completely absent
Hands, feet	Hypoplasia or absence of terminal phalanges of digits	Normal	Normal
Pelvis-hips	Flattened femoral heads, short and deformed femoral necks	Endobones and transverse bands of increased and decreased radiopacity Coxa vara may be present	Wide symphysis pubis Triradiate cartilages and sacroiliac joints wide
Bone texture	Osteosclerosis without obliteration of intermedullary canals	Osteosclerosis with obliteration of intramedullary canals	Normal
Hematologic picture	Normal	Aplastic anemia	Normal
Liver, spleen	Normal	Hepatosplenomegaly	Normal

ORTHOPAEDIC CONSIDERATIONS

Residual deformity may result from severe disease with intermittent recurrences. The medullary canal may remain expanded, with thinning of the cortex. Fusion of the ribs, the tibia and fibula, and the radius and ulna has been described. The radial head may dislocate. Leg length inequality may result from asymmetric involvement.[13,24,27]

CLINICAL COURSE

The disease is self-limiting, and complete recovery within 6 to 9 months can usually be expected. Spontaneous remissions may occur. On rare occasions, death may occur in the severe prenatal form of Caffey's disease.[6,31]

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Pyknodysostosis

Pyknodysostosis was first described by Maroteaux and Lamy in 1962.[14,15] The term *pyknodysostosis* was derived from the Greek word *pycnos,* meaning thick or dense; *dys,* meaning defective; and *osteon,* meaning bone. The dysplasia enjoys the celebrity of counting the French painter Henri de Toulouse Lautrec (1864–1901) among those afflicted.

GENETICS

Pyknodysostosis is inherited as an autosomal recessive trait. The locus for the dysplasia has been mapped to chromosome 1q21.[7,18] Mutations in this region lead to cathepsin K deficiency. Cathepsin K is a cysteine protease that is highly

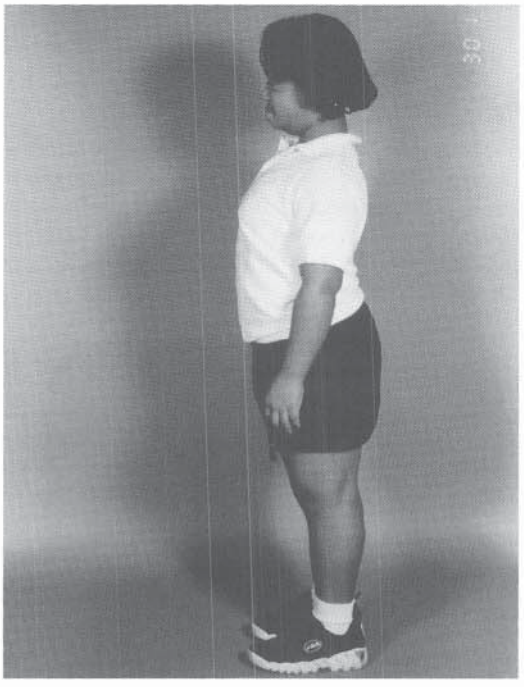


FIGURE 29–70 Clinical appearance of a female patient with pyknodysostosis. Her chin is very small.

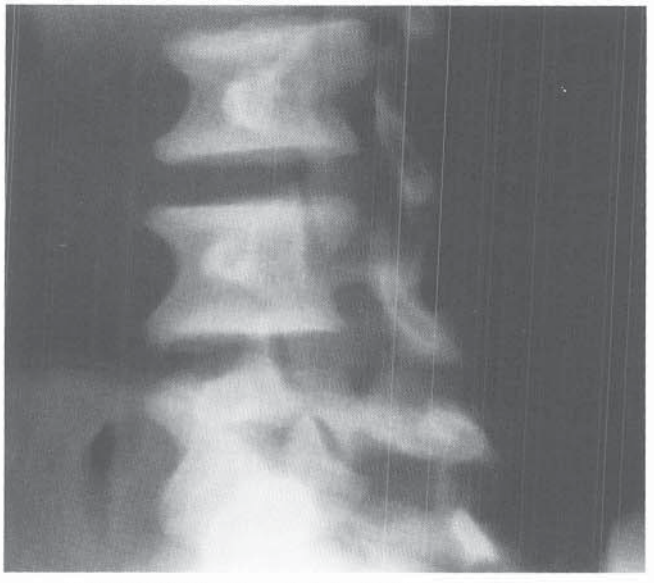


FIGURE 29–71 Spondylolysis of L5 in pyknodysostosis.

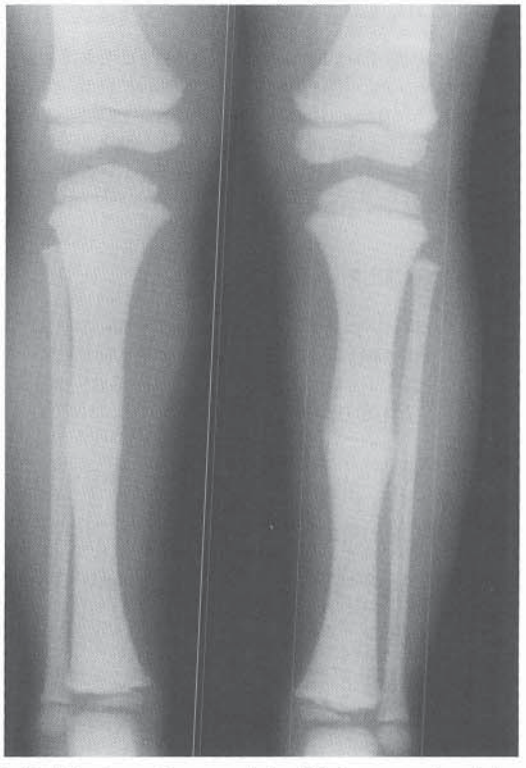


FIGURE 29–72 Stress fracture of the tibia in osteosclerotic bone of a child with pyknodysostosis.

expressed in osteoclasts.[8] The estimated prevalence of pyknodysostosis is one per million.

PATHOLOGY

The mechanism for the development of the diffuse sclerotic process associated with pyknodysostosis is not clearly understood.[12] Findings from microscopic examination of bone biopsy specimens are similar to those in osteopetrosis.[4] Meredith and associates proposed that normal osteoblasts and osteoclasts fail to respond as they should to the demands of stress on the bone.[16] Although osteoclasts are present, they do not appear to function properly in resorbing bone. At fracture sites, all cellular elements of fracture repair are present.[13,16]

CLINICAL FEATURES

This dysplasia is characterized by short-limbed short stature. There is hypoplasia or absence of the lateral portion of the clavicles, and hypoplasia of the terminal phalanges of the digits (termed *acro-osteolysis*), leading to short, stubby hands with large fingernails. The skull has widened sutures and persistent open fontanels, even into adulthood. The mandible is small, and the angle of the mandible is described as obtuse, leading to a very small chin (Fig. 29–70). The nose is protuberant. The teeth are delayed in appearance and disordered when present.[5,10,17]

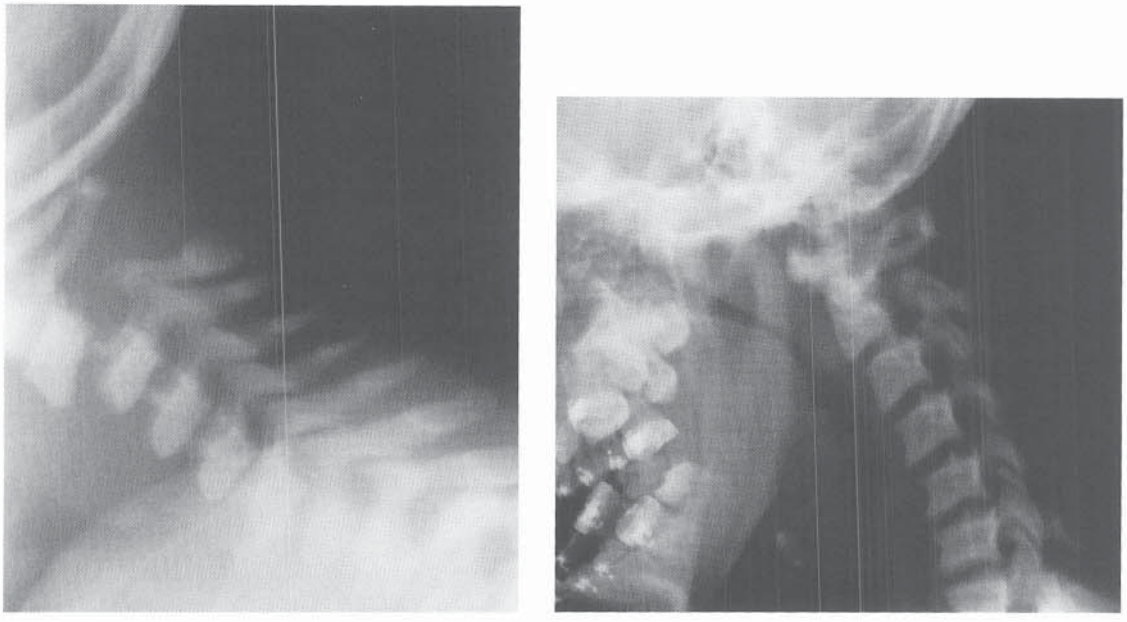
RADIOGRAPHIC FINDINGS

Radiographs show generalized osteosclerosis. The medullary canal is always present, but it is small and irregular. Spinal radiographs may show failure of segmentation of the atlas from the axis and again in the lower lumbar spine. Spondylolisthesis and spondylolysis are common (Fig. 29–71).[1,4,6] Hand radiographs show the hypoplasia or resorption of the distal phalanges.

The sclerotic bone has a propensity to fracture, with

TABLE 29–5 **Features Distinguishing Infantile Cortical Hyperostosis and Hypervitaminosis A**

Features	Infantile Cortical Hyperostosis	Hypervitaminosis A
Age at onset	Birth–6 mo.	≥1 yr
Involvement of mandible	Present (almost always)	Universally absent
Metatarsal involvement	Rare	Usual
Fever	Present	Absent
Cortical hyperostosis	Present	Present
Tender soft tissue swelling	Present	Present
Vitamin A level	Normal	Elevated
Response to low-vitamin diet	None	Amelioration of symptoms within 1 mo
Response to corticosteroid therapy	Alleviation of acute systemic manifestations	No response
Inheritance	Possibly autosomal dominant	Nonhereditary



A B

FIGURE 29–73 **A,** Spondylolysis of C2 in a 2-year-old with pyknodysostosis. **B,** Same child at age 13 years. No treatment had been performed.

fractures generally occurring in the lower extremities. The fracture lines are characteristically transverse on radiographs and located in the mid-diaphysis. Comminution is not seen.[4]

Bone formation and resorption are simultaneously diminished. Bone densitometry shows values of up to 291 percent of age-matched normal controls (the increased bone density was mainly in the trabecular bone and not in the cortical bone). MRI studies have shown the cortex to be of normal thickness, whereas the space within the medullary canal was limited as a result of the increase in trabecular bone. Bone scan reveals increased uptake.[13]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes osteopetrosis. Unlike osteopetrosis, pyknodysostosis does not lead to aplastic anemia, because the medullary canal is partially preserved.[19] Cleidocranial dysostosis may be considered because of the hypoplasia of the clavicles; however, osteosclerosis is not seen in cleidocranial dysostosis (Table 29–5).[9] Rare conditions that may be confused with pyknodysostosis are progressive diaphyseal dysplasia (Camurati-Engelmann disease) and idiopathic nonfamilial acro-osteolysis.[9]

ORTHOPAEDIC CONSIDERATIONS

Orthopaedic treatment consists of fracture care. Stress fractures can occur with minimal trauma (Fig. 29–72). Fracture healing has been reported as normal by some authors,[4,20] while other authors report that callus formation is poor.[16] Most stress fractures result in little if any pain, even when they occur in weightbearing bones.[3]

Spondylolysis may occur. Apparent spondylolysis at the second cervical vertebra, resembling the "hangman's fracture," results from clefts in the pedicles of C2 but rarely leads to instability (Fig. 29–73).[2,3]

CLINICAL COURSE

Life expectancy is normal. Adult height reaches 130 to 150 cm. Growth hormone has been used in physiologic replacement doses to accelerate growth in these short patients.[21] Chronic osteomyelitis of the jaw occurs frequently and is resistant to standard forms of treatment.[11,22]

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Cleidocranial Dysostosis

Cleidocranial dysostosis was first described by Marie and Sainton in 1898.[9] It is a disorder in which the bones formed by intramembranous ossification are abnormal (primarily the clavicles, cranium, and pelvis). The characteristic finding in cleidocranial dysostosis is hypoplasia or absence of the clavicles. Although the most significant abnormalities are seen in the bones formed by intramembranous ossification, enchondral growth is disturbed to a lesser degree, resulting in mild dwarfism.

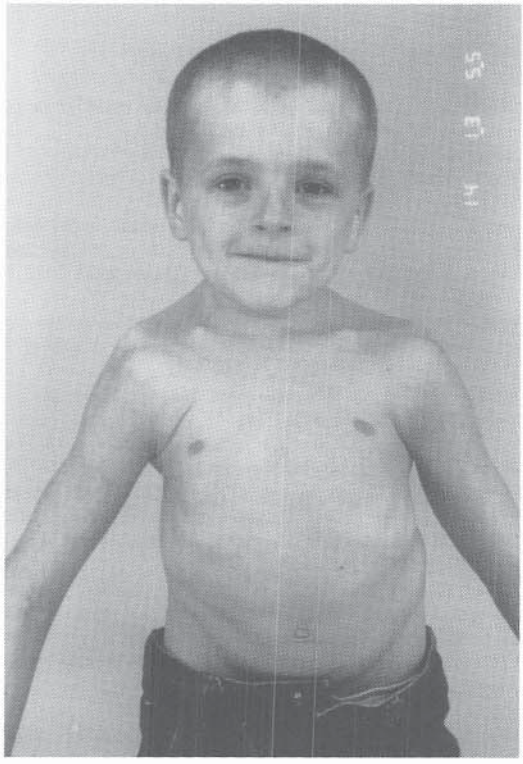
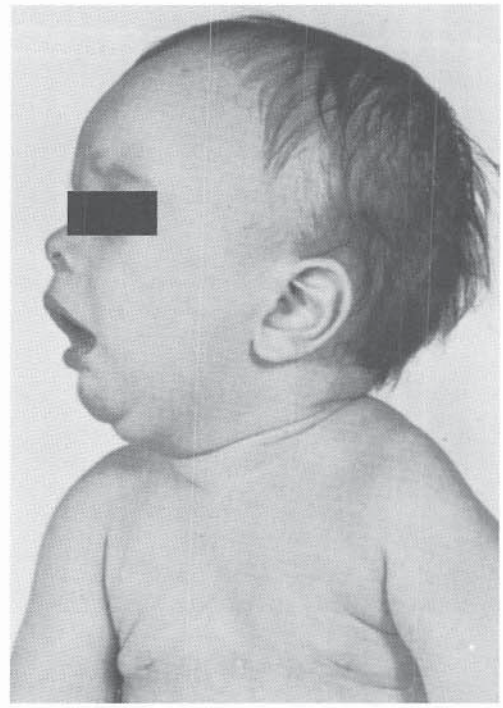


FIGURE 29–74 Appearance of a child with cleidocranial dysostosis.



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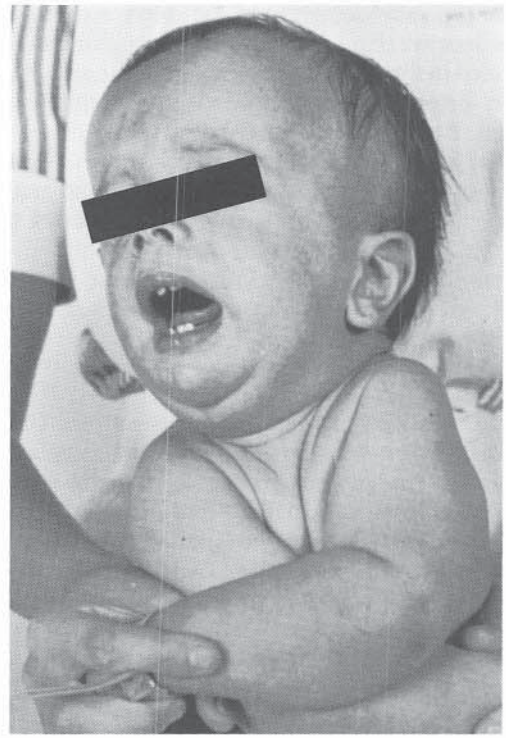

B

FIGURE 29–75 **A** and **B,** In cleidocranial dysostosis the shoulders can be approximated because of the absence of the clavicles.

GENETICS

Cleidocranial dysostosis is inherited as an autosomal dominant trait. The gene responsible for the dysplasia is located on chromosome 6p21.[2,8] The gene has been cloned and is called CBFA1, an osteoblast-specific transcription factor and

a regulator of osteoblast differentiation.[8] Approximately two-thirds of cases are familial and one-third are new mutations.[11]

CLINICAL FEATURES

Typically, the disease is identified within the first 2 years of life. Affected children have large heads with elfin faces (the skull is wider than normal, but the face appears small) (Fig. 29–74). The eyes are slightly wide-set. The palate is high and narrow. Deciduous teeth erupt normally, but permanent teeth are delayed. When they do appear, they are maldeveloped.

The shoulders look droopy, and the chest appears narrow.[12] Sternal abnormalities result from the abnormal intramembranous ossification, and pectus excavatum is common.

One or both clavicles may be underdeveloped or missing altogether.[1] The most common defect is loss of the lateral end of the clavicle, with failure of development of the middle third of the clavicle second in frequency. The defect may be palpable. When it is bilateral, the child can touch the shoulders together in front of the chest due to hypermobility. The scapulae appear small, and winging may be noticeable (Fig. 29–75).

Patients with cleidocranial dysplasia are short-statured. The average adult height in males ranges between the fifth and the 50th percentiles. Females have more significant dwarfism, with adult height less than the fifth percentile.[7]

RADIOGRAPHIC FINDINGS

Hypoplasia or absence of the clavicles is obvious on radiographs. Absence of the clavicles has even been seen on prenatal ultrasound.[5,6]

Skull radiographs show multiple wormian bones and poor mineralization of the cranium. Closure of the sutures is markedly delayed, and the anterior fontanelle is enlarged. In some patients the anterior fontanelle never closes. The nasal, lachrymal, and malar bones may be hypoplastic or

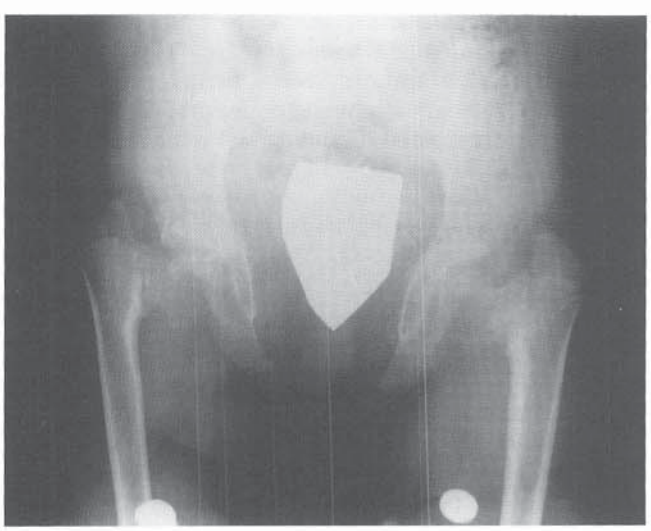

FIGURE 29–76 Pelvic radiograph of a 9-year-old child with cleidocranial dysostosis. The symphysis pubis is wide, and coxa vara is present bilaterally.

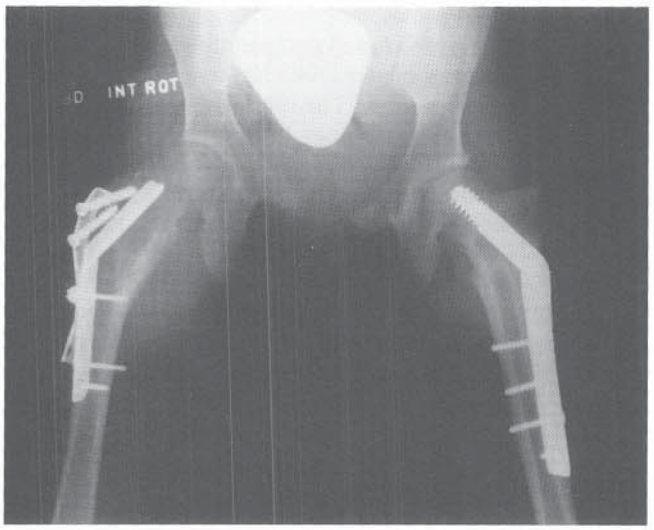

FIGURE 29–77 Postoperative radiograph following valgus osteotomy of the proximal femurs performed on the child whose pretreatment radiograph is shown in Figure 29–76.

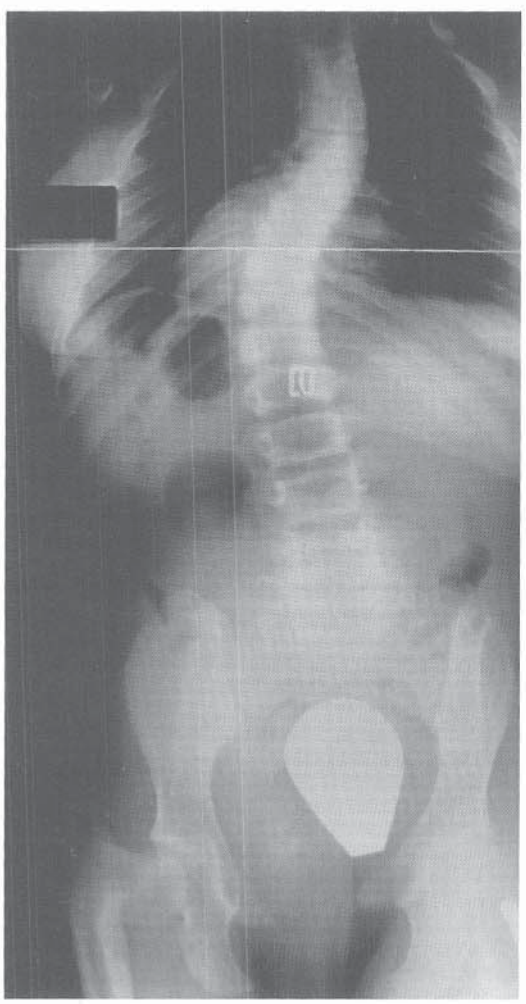

FIGURE 29–78 Scoliosis in a 12-year-old child with cleidocranial dysostosis. Note the absent clavicles.

absent, and the zygomas are poorly developed. The maxilla is small, and the symphysis of the mandible may fail to fuse.

The pelvis shows bilateral involvement. The symphysis pubis remains quite wide.[4] The rami also are incompletely fused and may appear thinner than usual. The sacroiliac joint may be wide. The iliac wings appear small. Coxa vara is associated with cleidocranial dysplasia, and the femoral necks are very short (Fig. 29–76). Hip dislocations occur infrequently.

Spina bifida occulta may be present in the thoracic and lumbar spine. Scoliosis is seen in this patient population. Lumbar spondylolysis has also been reported in 24 percent of patients.[7]

Ossification of the carpal and tarsal bones is delayed. The terminal phalanges are short, pointed, hypoplastic, or even absent. The second through the fifth metatarsals and metacarpals have epiphyses at both their proximal and distal ends. The second metacarpal is unusually long.

ORTHOPAEDIC CONSIDERATIONS

There may be absence or hypoplasia of the musculature that originates or inserts on the clavicle, specifically the anterior portion of the deltoid and the clavicular head of the sternocleidomastoid muscle. Brachial plexus irritation occurs on rare occasions and manifests with pain and numbness. Excision of the clavicular fragments can decompress the brachial plexus.

Coxa vara is treated by valgus osteotomy of the proximal femur (Fig. 29–77). Indications for surgery are identical to those for developmental coxa vara (i.e., a neck-shaft angle of less than 90 degrees, a Hilgenreiner-epiphyseal angle of 60 degrees or more, or progression of deformity). Younger patients may show progressive acetabular remodeling following osteotomy. In older children, pelvic osteotomy to improve the containment of the hip is advised.[10]

Scoliosis should be treated in a manner similar to idiopathic scoliosis (Fig. 29–78).

An association between cleidocranial dysplasia and syringomyelia has been described.[3]

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Idiopathic Osteolysis

Idiopathic osteolysis, or "disappearing bone disease," is an extremely rare condition characterized by the spontaneous onset of rapid destruction and resorption of a single bone or multiple bones. This results in severe deformities, with joint subluxation and instability.

GORHAM'S MASSIVE OSTEOLYSIS

Gorham's disease is the most common form of idiopathic osteolysis. It is not genetically transmitted. The age at onset of osteolysis is variable, and the disease has been seen in children. It may appear in any part of the skeleton and has been described in the shoulder, pelvis, proximal femur, skull, and spine. It often involves multiple contiguous bones (i.e., ribs and spine; or pelvis, proximal femur, and sacrum) (Fig. 29–79). Although previously thought to be benign, the course of the disease varies with the site of involvement. Gorham's disease has led to death when it involved the spine.* The disease may be multifocal.[24]

The massive osteolysis results from vascular proliferation or angiomatosis within the involved bones and the surrounding soft tissue. Histologic study reveals ectatic vessels covered with endothelium that resemble hemangiomas.[20,23] Cytokine studies have shown increased levels of interleukin-6 in patients with Gorham's disease, leading to a hypothesis that the disease may be due to enhanced osteoclast activity stimulated by cytokine mediators.[6]

HEREDITARY MULTICENTRIC OSTEOLYSIS WITH DOMINANT TRANSMISSION

The age of onset of this genetically transmitted dysplasia usually is between 2 and 7 years. The child complains of pain and swelling in the hands and feet. There may be a history of previous trauma. Over a period of a few years the carpals and tarsals completely resorb. The proximal metacarpals are tapered on radiographs, and the distal radius, ulna, and proximal humerus may also be involved (Fig. 29–80). Wrist instability and ankle deformity result. The disease usually stabilizes in adolescence, but it may reappear in later adulthood.

HEREDITARY MULTICENTRIC OSTEOLYSIS WITH RECESSIVE INHERITANCE

This form resembles the dominantly transmitted type, with the addition of generalized osteoporosis of the appendicular skeleton.

*See references 1, 4, 5, 8, 10, 11, 13–15, 17, 18, 21–23.

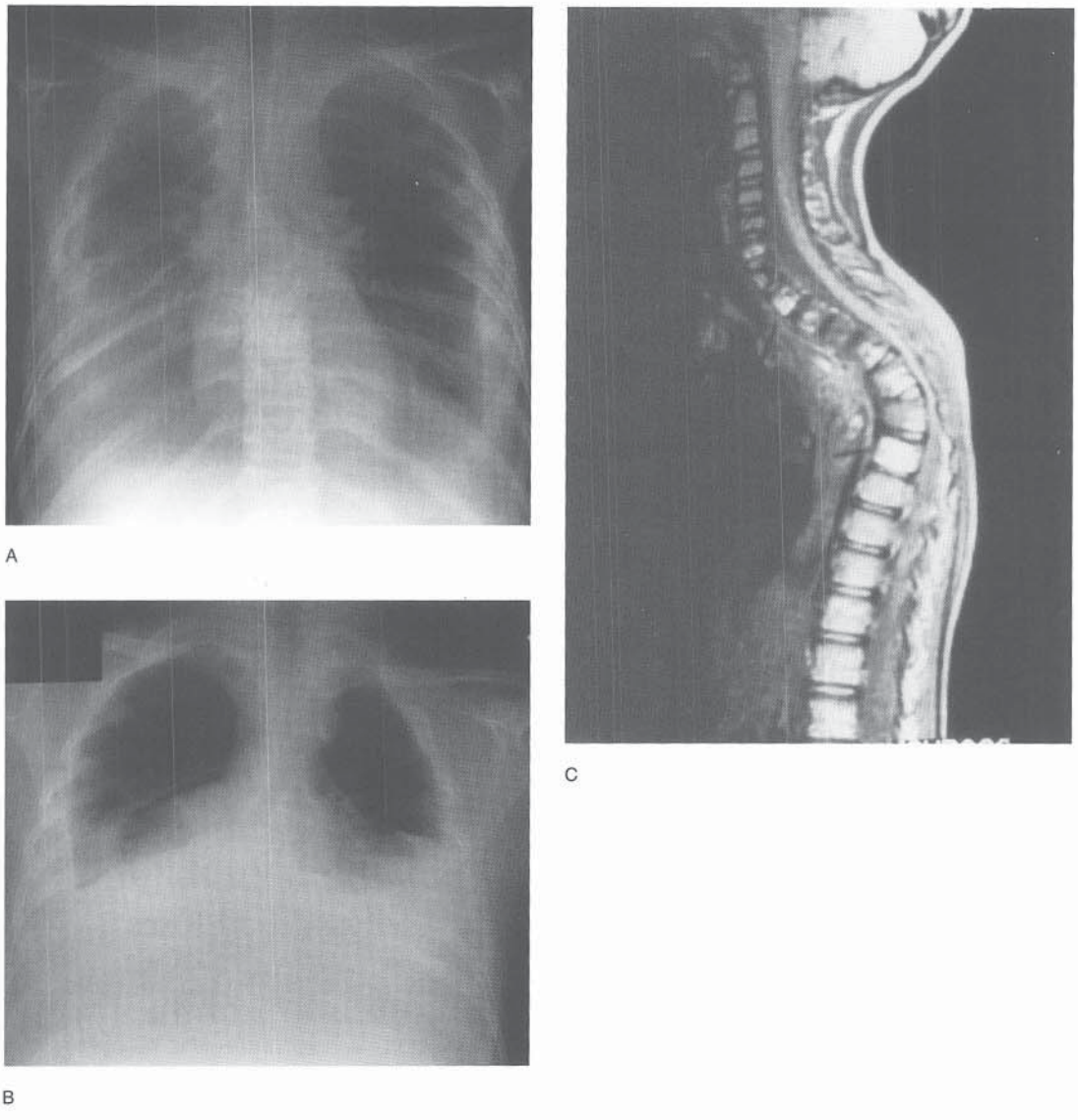

FIGURE 29–79 **A,** Chest radiograph of a 12-year-old child with Gorham's disease of the spine. The upper spinal cortices are indistinct on x-ray. **B,** Intractable chylothoraces developed secondary to the dysplasia. **C,** MRI disclosed kyphosis in the area of disappearing bone, with spinal cord compromise.

NONHEREDITARY MULTICENTRIC OSTEOLYSIS WITH NEPHROPATHY

In this form there is greater involvement of the hand and wrist than of the foot. The carpus begins resorbing between the ages of 2 and 5 years, at which time the children complain of pain and swelling. The metacarpals look like sucked peppermint sticks. At the same time of bone resorption, severe renal disease occurs, manifesting with proteinuria, glomerulonephritis, and malignant hypertension. The disease usually is fatal in adolescence.

RADIOGRAPHIC FINDINGS

The CT and MRI appearances of Gorham's disease have been well described.[3,4,7,18,22,26]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis should include inflammatory disorders of bone, malignant osteoclast tumors, arterial vascular disease, posttraumatic osteolysis, and AVN.

TREATMENT

Surgical treatment of Gorham's disease is fraught with complications. Bone grafts resorb as readily as the host bone does. Attempts have been made to surgically stabilize the disappearing spine, but they are usually unsuccessful.

Radiation therapy has met with some success in patients with Gorham's disease.[9,12,15,16] Orthotic stabilization of the spine with a halo, combined with radiation, has been used in a few patients.

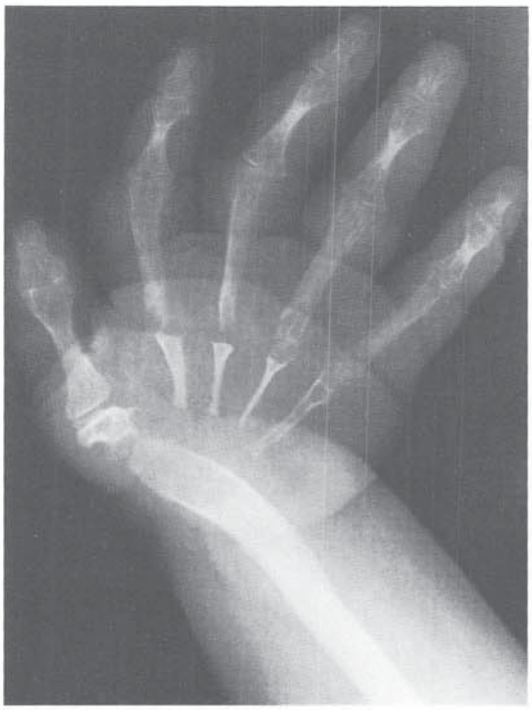

FIGURE 29–80 Osteolysis—carpotarsal form. Note marked erosion of the base of the metacarpals and absence of the carpal bones. The proximal phalanges appear bizarre and elongated. The hand is in marked ulnar deviation. (From Poznanski AK: The Hand in Radiologic Diagnosis. Philadelphia, WB Saunders Co, 1984.)

Chylothorax and pleural effusions are particularly problematic in patients with osteolysis of the spine and have been linked to a high mortality rate. Surgical and medical treatments have been proposed.[2,19,25]

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Mucopolysaccharidoses

The mucopolysaccharidoses constitute the largest group of lysosomal storage diseases (Table 29–6). The intracellular degradation of micromolecular compounds by lysosomal enzymes is abnormal in this group of diseases, leading to intracellular accumulation of semidegraded compounds. The overall incidence of the mucopolysaccharidoses is one in 25,000 live births.[61] The mucopolysaccharidoses are subdivided based on their enzyme deficiency and the type of substance that accumulates. The most common of the mucopolysaccharidoses are Morquio's and Hurler's syndromes.

DIAGNOSIS

Heparan sulfate, dermatan sulfate, and keratan sulfate are the mucopolysaccharides that accumulate and are excreted by the urine. Biochemical analysis of the urine can lead to the diagnosis of the specific mucopolysaccharidosis. There are many different techniques used to isolate the glycosaminoglycans (GAGs) from the urine. The ease with which abnormal GAGs are detected on biochemical testing varies with the different mucopolysaccharidoses.[20,38,43,95]

Identification of the mucopolysaccharidoses is also possible through skin fibroblast culture.[7] The fibroblasts are assayed for specific enzyme activity known to be abnormal in the different mucopolysaccharidoses. This assay has also been used with chorionic villous sampling and amniotic fluid cells to establish the prenatal diagnosis in affected fetuses.[39,89,96,97]

TABLE 29–6 **Characteristic Features Distinguishing the Mucopolysaccharidoses**

Type	Enzyme Defect	Increased Urinary Excretion of Acid Muccopoly-saccharide	Inheritance	Age at Which Features Present	Facies	Corneal Clouding	Deafness	Hepato-splenomegaly	Cardio-vascular Abnormality	Stature	Skeletal Changes	Mental Retardation	Prognosis
Hurler's syndrome MPS I	Deficient α-L-iduronidase	Dermatan sulfate ++ Heparan sulfate +	Autosomal recessive	First few months May appear normal at birth	Grotesque; gargoyle	Present	Present	Present	Present	Normal at birth, later may be moderately short	Moderate dorsolumbar kyphosis Anterior-inferior beaking of body of L2 or L1	Severe	Progressive disease; usually death by age 10 yr due to heart disease or respiratory infection
Hunter syndrome MPS II	Low sulfoiduronate sulfatase	Heparan sulfate ++ Dermatan sulfate +	Sex-linked recessive All patients male	6–12 mo	Similar to Hurler's; less severe	Absent	Frequent	Present	Present Pulmonary hypertension	Normal at birth, later may be moderately short	Moderate, absence of lumbar kyphosis	Late in onset, less severe than in Hurler's	Survival possible into the third decade of life Eventual death from cardiopulmonary disease
Sanfilippo syndrome MPS III	Low *N*-heparan sulfatase or α-acetylglucosaminidase	Heparan sulfate ++	Autosomal recessive	Early childhood	Not coarse	Absent	Present	Minimal or moderate	Absent	Normal	Minimal widening of clavicles at medial ends, no kyphosis	Severe	Survival into third or fourth decade
Morquio's syndrome MPS IV	*N*-Ac-Gal-6 sulfate sulfatase	Keratan sulfate ++ (diminishes with age)	Autosomal recessive	2–4 yr	Not coarse; wide mouth; prominent maxilla	Present, slowly progressive	Present	Usually absent	Minimal, if present aortic regurgitation	Markedly short (under 4 ft)	Severe and diffuse platyspondyly with central tongue Capital femoral epiphyses irregular, eventually disappear	Absent	Normal longevity Respiratory failure due to rib cage rigidity
Scheie's syndrome MPS I-S	α-L-Iduronidase	Heparan sulfate + Dermatan sulfate ++	Autosomal recessive	Late childhood	Somewhat coarse	Present	Present	Absent	Present; aortic valve disease	Normal	Small epiphysis on hands	Absent	Normal longevity
Maroteaux-Lamy syndrome MPS VI	*N*-Ac-Gal-4 sulfatase	Dermatan sulfate ++	Autosomal recessive	Early to late childhood	Coarse	Present, poor vision	Present	Hepatomegaly rather than splenomegaly	Absent	Normal at birth, later markedly short	Severe (same as Hurler's)	Absent	Guarded, death from cardiovascular complications

As molecular genetic research determines the specific mutations that result in mucopolysaccharidoses, genetic testing has become a means of establishing the diagnosis. Specific mutations are described individually for each type of mucopolysaccharidosis.

RADIOGRAPHIC FINDINGS

All of the mucopolysaccharidoses lead to abnormally short stature. Radiographic changes are also seen in the skull, leading to abnormal facies. The skull is enlarged, with a thick calvarium. The clavicles are broad, especially medially. The scapulae are short and stubby. The ribs are oar-shaped and broader anteriorly than posteriorly. The vertebral bodies are ovoid when immature. Scoliosis and kyphosis are frequently present. The iliac wings are flared and the acetabulae are dysplastic. Coxa valga is common. The long bones often have thickened cortices. The second through fifth metacarpals are pointed at their proximal ends, and the phalanges are bullet-shaped. There is a delay in ossification of the carpal bones.

It is not possible to differentiate the various types of mucopolysaccharidoses on the basis of radiographic features alone. The distinctive features of the various mucopolysaccharidoses are summarized in Table 29–6.

MUCOPOLYSACCHARIDOSIS I (HURLER'S SYNDROME)

Genetics. Hurler's syndrome is an autosomal recessive disorder characterized by a deficiency in α-L-iduronidase.[5] The enzyme defect leads to an accumulation of both dermatan and, in lesser amounts, heparan sulfates, which are excreted in the urine.[21,58] Hurler's syndrome is seen equally in males and females and has been described in all ethnic groups.[53] There is a spectrum of clinical severity in α-L-iduronidase deficiency, ranging from the very severe (Hurler's syndrome) through an intermediate form (Hurler's/Scheie's syndrome) to a relatively mild form (Scheie's syndrome). Numerous mutations of the gene encoding α-L-iduronidase are known in Hurler's syndrome, and different mutations have been found to cause the milder subtypes.[47,85] As noted, prenatal diagnosis is available through amniocentesis, and the carrier state can be identified by assaying leukocytes for enzyme activity.[93]

Pathology. Deposits of abnormal mucopolysaccharide are seen in many tissues, including the CNS and peripheral ganglia, the retina, the parenchymal and Kupffer cells of the liver, the reticulum cells of the spleen and lymph nodes, the pituitary glands, and the testes.[57] Deposits are also seen in the heart, especially in the valves and coronary arteries.[14,71] Chondrocytes and osteocytes are enlarged and have vacuoles. The chondrocytes of the growth plate are disorganized.[79] Neutrophils, lymphocytes, and eosinophils show coarse violet granules, termed *Reilly granules,* on Wright's stain.

Clinical Features. Affected infants are normal in the neonatal period because the changes seen in Hurler's syndrome do not occur until the mucopolysaccharide accumulates. The average age at diagnosis is 9 months.[17]

The facies of affected infants becomes coarse and heavy (Fig. 29–81). The head is enlarged, and hydrocephalus may result from meningeal deposits.[78] The skull is abnormally shaped, and the forehead is low. Premature closure of the sagittal and metopic sutures of the skull leads to a prominent longitudinal ridge that may cross the forehead. The ears are low and the eyes are wide-set. The teeth are poorly formed and widespread. The nostrils are wide, and the nose has a depressed bridge and broad tip. The lips are everted, the tongue is enlarged, and the mouth is open. "Chronic rhinitis" with noisy mouth breathing is always present and is due to narrowing of the nasopharynx by enlarged adenoids and mucosal deposits. This, combined with the presence of hernias, may be the presenting signs of the disease.[17] Obstructive sleep apnea may result from upper airway obstruction and may result in death.[77]

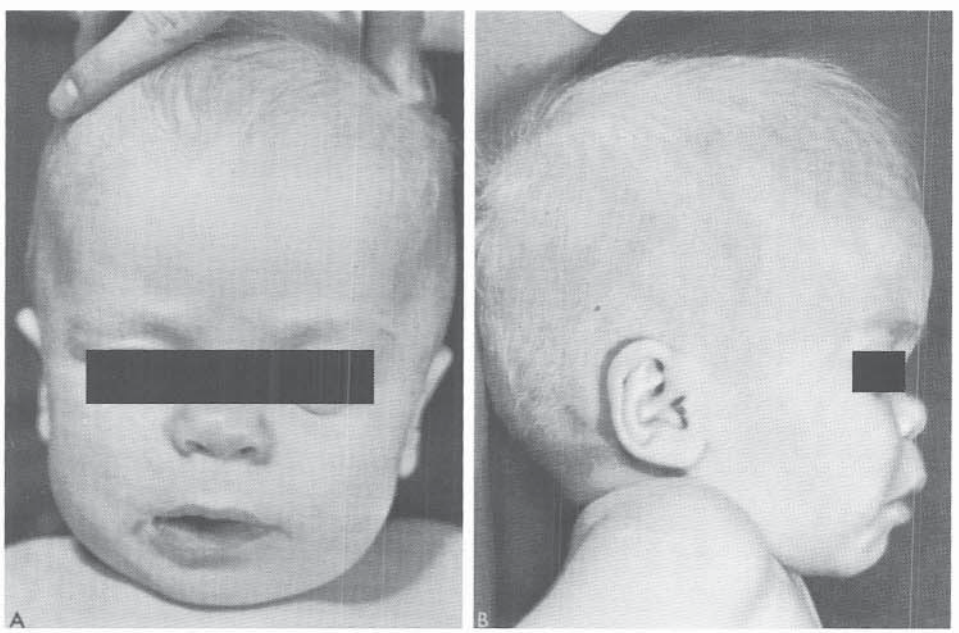


FIGURE 29–81 Hurler's syndrome (mucopolysaccharidosis I) in an infant. **A** and **B,** Typical deformity of the head.

Clouding of the cornea is a universal feature of the disease. There is progressive degeneration of the retina, which, combined with the clouded cornea, leads to blindness. Glaucoma in early childhood has been described.[65]

The patient has a short neck. The rib cage is deformed, with flaring of its lower portion. The abdomen is protuberant due to hepatosplenomegaly.

Thoracolumbar kyphosis can be seen in children as young as 6 months (Fig. 29–82). The presence of a gibbus deformity in a child with motor delays should raise the suspicion of Hurler's syndrome.[9] Flexion contractures of the joints are common. The little finger is curved radially. The hands are broad, with short, stubby fingers. Genu valgum and flatfeet may be present. Stature usually is short.

Mental retardation is a consistent, progressive feature of Hurler's syndrome. Cardiac problems result from myocardial deposits, which lead to stiff walls and to valve malfunction, most commonly of the mitral valve.[71] In the absence of treatment, cardiomyopathy is relentlessly progressive.[19]

Radiographic Findings. The skeletal changes in Hurler's syndrome resemble those seen in Morquio's syndrome, with a few exceptions. The skull is normal in infancy but becomes enlarged in the AP diameter and short in height due to premature closure of the sutures. The sella turcica is elongated and J-shaped. The mandible is short and wide.

Dysplastic changes develop in the vertebrae in the first few months of life. In the lateral view, the biconvex shape persists, and mild thoracolumbar kyphosis may be appreciated. Between 1 and 2 years of age, the kyphosis at the thoracolumbar junction becomes pronounced. An anterior-inferior beak develops on the vertebral body (Fig. 29–83A) that differs from the central tongue-like projection seen in patients with Morquio's disease. Odontoid hypoplasia and atlantoaxial instability may be seen in patients with Hurler's syndrome.[84]

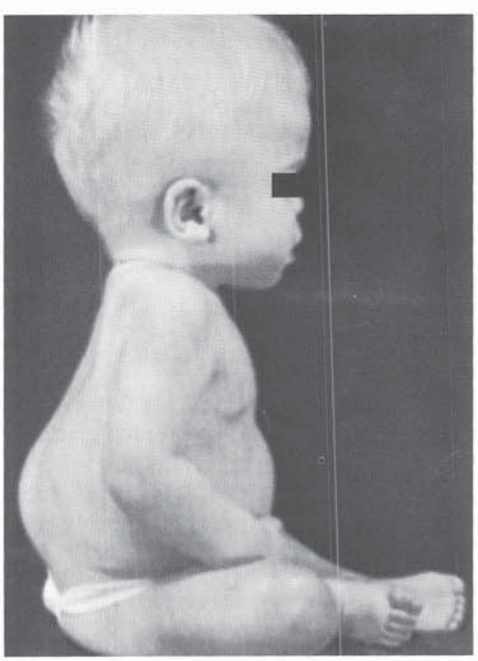


FIGURE 29–82 Lateral view of an infant with Hurler's syndrome shows localized kyphosis at the dorsolumbar junction.

The pelvis is flared and the acetabula are dysplastic. Coxa valga is marked. Ossification of the capital femoral epiphysis is delayed. Subluxation or dislocation of the hips is frequent (Fig. 29–83B).[54]

Chest radiographs reveal cardiomegaly. The ribs are abnormal, being broad anteriorly and narrow posteriorly. The clavicles are hypoplastic at their lateral ends and thick medially.

The long bones have widened diaphyses. The humerus is short and thick, while the distal radius and ulna are tapered, with their physes pointing toward each other. In the hand, the metacarpals are tapered proximally and the phalanges are short and broad (Fig. 29–83C).

CT and MRI of the brain reveal abnormalities. Small cystic lesions and increased signal intensity are noted in the periventricular white matter on brain MRI.[2,45]

Treatment. Hurler's syndrome has been treated successfully with bone marrow transplantation. The preferred donor is an HLA-identical sibling.[30] Following successful transplantation, accumulation of the mucopolysaccharide stops. There is improvement in the coarse facies, hepatosplenomegaly, and possibly hearing. Unfortunately, the neurologic abnormalities persist; however, they do not worsen.[30] To avoid serious neurologic deterioration in infancy, it is crucial that the diagnosis of Hurler's syndrome be made as soon as possible.[9]

If untreated, Hurler's syndrome is fatal, usually before age 10 years. The usual cause of death is cardiac complications.

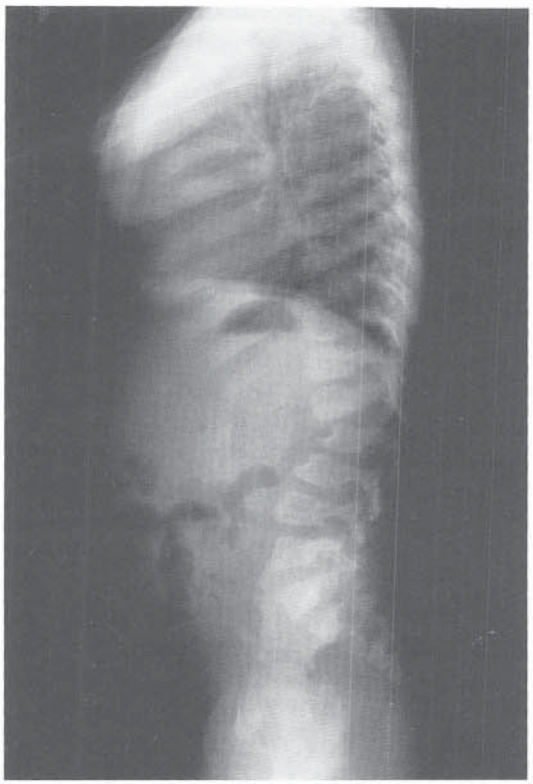
Research is currently under way in the field of gene therapy for Hurler's syndrome. Genetically modified hematopoietic progenitor cells infected with retroviruses carrying human α-L-iduronidase cDNA have successfully produced α-L-iduronidase in vitro and thus may be potentially useful for the gene therapy of Hurler's syndrome.[22,36]

Anesthesia is complicated in children with Hurler's syndrome. Up to 53 percent of affected children have been reported to have airway difficulty during surgery.[35] The trachea is infiltrated with abnormal deposits, making airway obstruction problematic.[1] Myocardial abnormalities may also pose anesthetic risks.[42]

Orthopaedic Considerations. Orthopaedic manifestations of Hurler's syndrome are not responsive to bone marrow transplantation.[30] Hip flexion contractures are very common in these children. Hip dysplasia often requires surgical reconstruction, including reduction, femoral osteotomy, and pelvic osteotomy.[54] Increasing valgus deformity of the knees and progressive generalized myopathy typically result in loss of mobility as the child enters adolescence.[23] Now that patients can survive childhood, it remains to be seen whether surgery will improve their long-term gait.

Carpal tunnel syndrome is nearly always present in children with Hurler's syndrome. The condition is bilateral. Symptoms are rare, but signs such as decreased sweating, pulp atrophy, thenar wasting, and manual clumsiness are common.[12,33] Median nerve compression is due to accumulations around the nerve and within the carpal tunnel. Treatment is surgical decompression. Trigger fingers may also develop, and respond to surgical release (Fig. 29–84).[32]

Cervical instability may be present in children with Hurler's syndrome. C1-C2 fusion may be necessary in children with instability due to odontoid hypoplasia.



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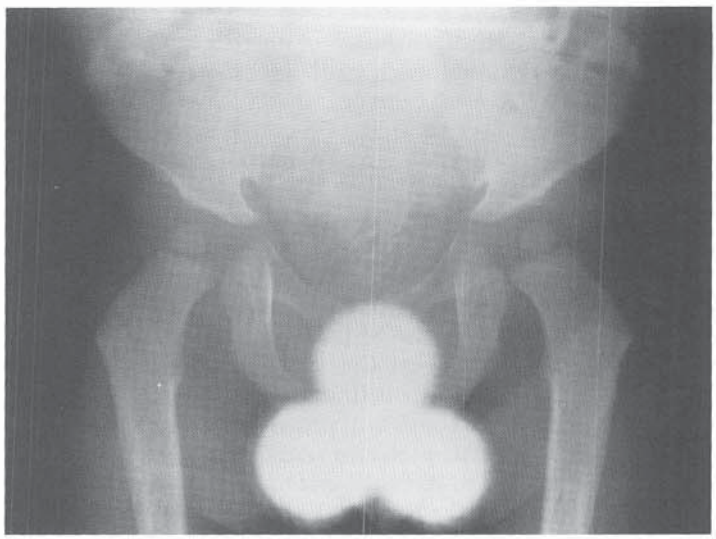

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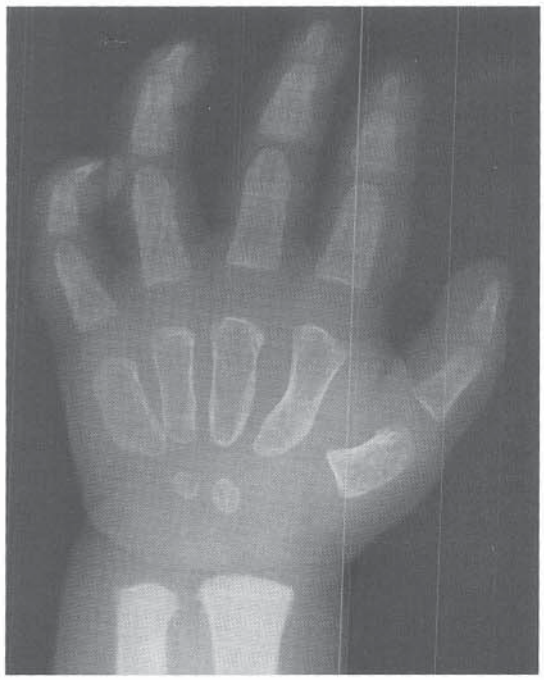


C

FIGURE 29–83 **A,** Thoracolumbar kyphosis in a 3-year-old child with Hurler's disease. The anterior-inferior beaking of the vertebral bodies is apparent. **B,** Dysplastic acetabula and coxa valga are seen in Hurler's syndrome. **C,** Short, tapered metacarpals are also present.

MUCOPOLYSACCHARIDOSIS II (HUNTER'S SYNDROME)

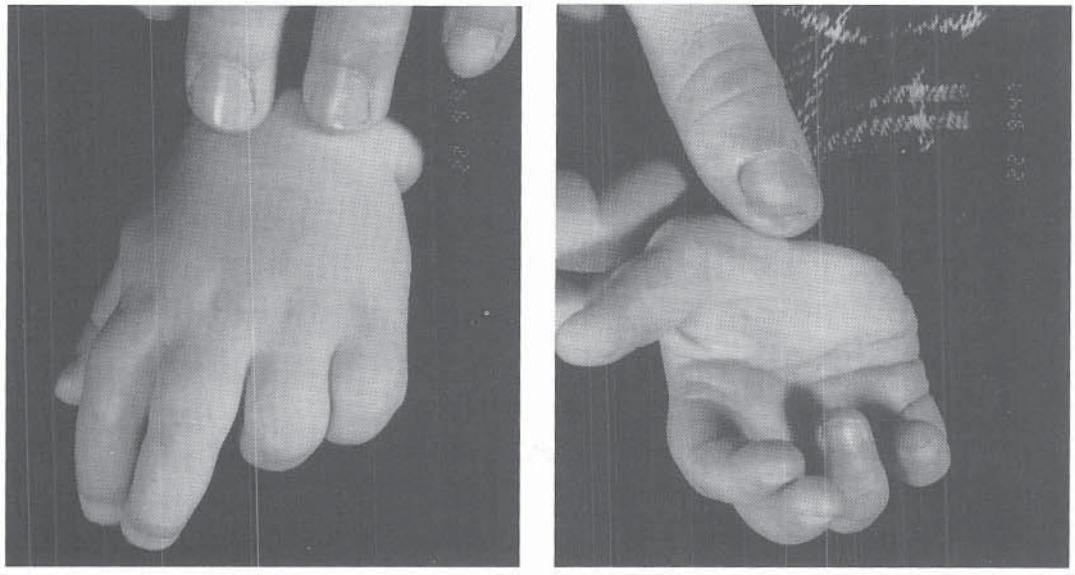
Genetics. Hunter's syndrome is a rare sex-linked recessive disorder caused by a deficiency in the enzyme iduronate-2-sulfatase (IDS). All affected patients are male, while carriers are female. The genetic abnormality is in the IDS gene located at the Xq27–q28 region. Several different mutations have been described in this area in patients with Hunter's syndrome.[16,25,66,86] The variability in the molecular genetic abnormality produces variability in the clinical phenotype. Carrier status can be identified with DNA testing.[87]

Pathology. Patients with Hunter's syndrome excrete large amounts of heparan sulfate and lesser amounts of dermatan sulfate in the urine. As in Hurler's syndrome, these substances accumulate in the tissues of affected patients.

Clinical Features. The distinguishing features are absence of corneal clouding and lack of thoracolumbar kyphosis. Mental retardation is later in onset and slower in progression than in Hurler's syndrome. Deafness occurs in 50 percent of patients. Carpal tunnel syndrome is common.[12,64]

Radiographic Findings. Radiographic findings are similar to those seen in Hurler's syndrome but are less severe.

Treatment. Bone marrow transplantation has been used in isolated cases of Hunter's syndrome.[49,56] Gene therapy is being investigated.[13]



A B

FIGURE 29–84 **A** and **B,** Flexion of the fourth and fifth fingers secondary to trigger finger deformity in a child with Hurler's syndrome.

Clinical Course. The clinical course is milder and more variable than in Hurler's syndrome. Although most patients die by 18 years of age if not treated, some survive into adulthood. The usual causes of death are airway obstruction[28,46,77] or cardiac failure.[19]

MUCOPOLYSACCHARIDOSIS III (SANFILIPPO SYNDROME)

Genetics. Sanfilippo syndrome is a group of four autosomal recessive enzyme deficiencies, all leading to an inability to metabolize heparan sulfate. Sanfilippo A syndrome is due to a defect in the lysosomal enzyme sulfamidase.[11,76] Sanfilippo B syndrome is caused by a deficiency of α-*N*-acetylglucosaminidase.[8,75,98] Sanfilippo D syndrome is caused by a deficiency of *N*-acetylglucosamine-6-sulfatase.[26]

Pathology. Patients with Sanfilippo syndrome excrete excessive amounts of heparan sulfate in the urine, but routine screening of urine may fail to identify the abnormal substance.[70] Accumulation of heparan sulfate in lysosomes results in degeneration of the CNS.

Clinical Features. CNS deterioration is manifested by progressive mental retardation, combined with hyperactivity and aggressive behavior.[94] Colville and Bax reported that the presenting symptom in 56 percent of patients with Sanfilippo syndrome was a delay or regression in language.[18]

Corneal clouding and cardiac abnormalities are extremely rare in these disorders. Hepatosplenomegaly, skeletal deformities, and short stature are milder than in Hurler's syndrome. There are no specific musculoskeletal problems.

Treatment. As with the other mucopolysaccharidoses, bone marrow transplantation and gene therapy are being investigated.[10,92]

MUCOPOLYSACCHARIDOSIS IV (MORQUIO'S SYNDROME)

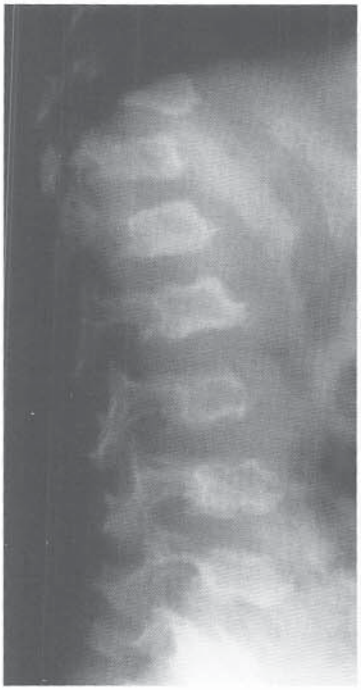
Genetics. Morquio's syndrome is an autosomal recessive dysplasia caused by a deficiency in the enzyme *N*-acetylgalactosamine-6-sulfatase, which is essential for the degradation of keratan sulfate and chondroitin-6-sulfate.[80] The gene for this lysosomal enzyme is located on chromosome 16.[6,60]

Diagnosis. The diagnosis of Morquio's syndrome is made with a positive test for urinary keratan sulfate.[38] There is variability among patients in the clinical severity of the disease, and children with the milder form of the dysplasia may not excrete keratan sulfate in their urine, making differentiation from spondyloepiphyseal dysplasia difficult.[27] The incidence of Morquio A syndrome is one per 76,000 live births.[61]

A second form of Morquio's syndrome is mucopolysaccharidosis IV-B, which is caused by a deficiency in β-galactosidase.[91] Morquio B dysplasia tends to present at a later age.[7] Affected individuals have normal intelligence and no neurologic abnormalities. This form of Morquio's syndrome does produce dysostosis multiplex, dwarfism, odontoid anomalies, and cloudy corneas.[29] Keratan sulfate is present in the urine of these patients also.[90]

Histology. Histopathology reveals physeal abnormalities, including vacuolization of the chondrocytes and disruption of the orderly arrangement of the proliferating chondrocytes. Provisional calcification is sparse.[55]

Clinical Features. Patients usually appear normal at birth but exhibit growth failure and spondyloepiphyseal dysplasia as infants. Most children are brought to a physician for investigation of what the parents perceive as an abnormal appearance by 12 to 18 months of age.[18] Intelligence is normal in this condition, unlike in the other mucopolysaccharidoses.



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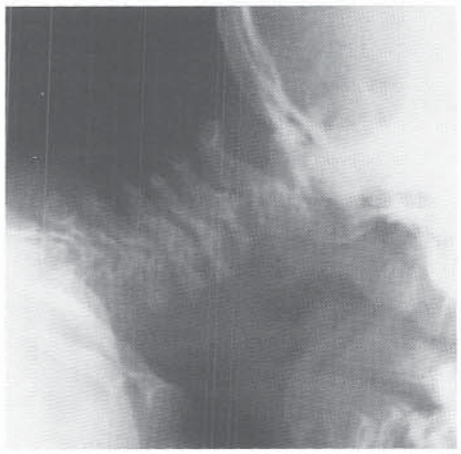

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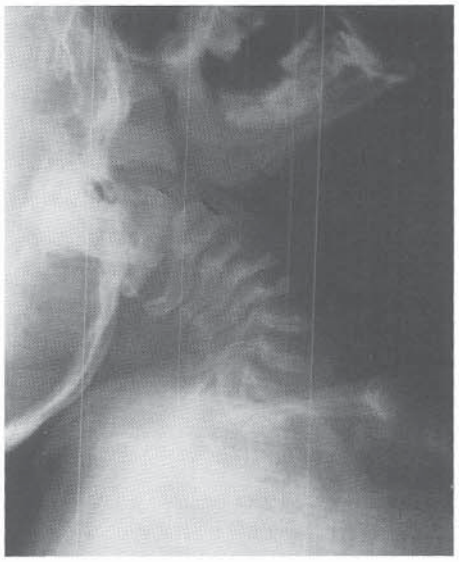

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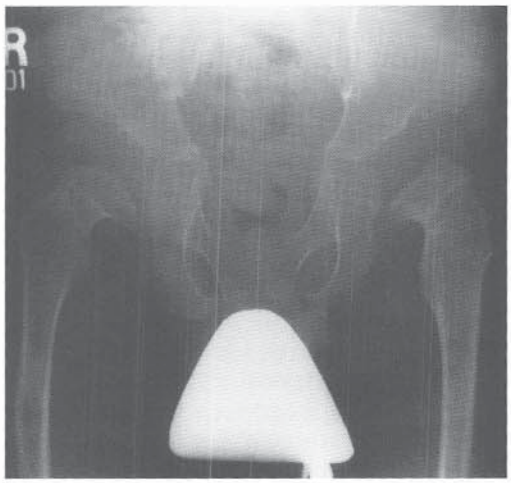

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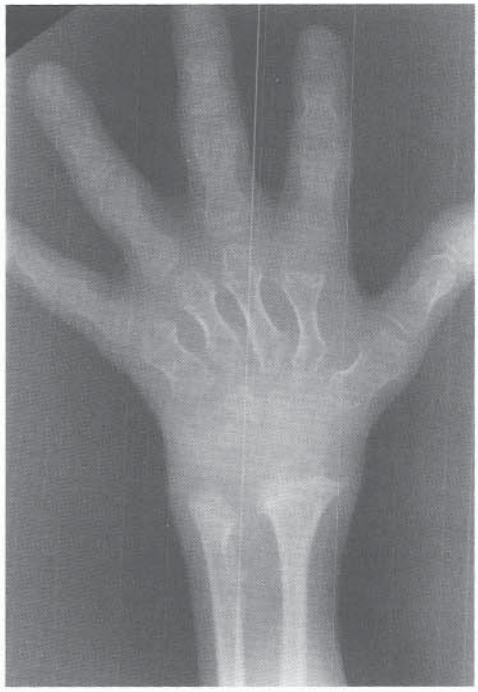


E

FIGURE 29–85 **A,** Lateral radiograph of the spine in a 3-year-old girl with Morquio's syndrome. A central tongue-like beak can be seen on the vertebral bodies. **B** and **C,** Flexion-extension radiographs demonstrate C1–2 instability secondary to hypoplasia of the odontoid. **D,** Pelvic radiograph of a 14-year-old child with Morquio's syndrome. The acetabula are dysplastic and there is failure of ossification of the femoral heads. **E,** Radiographic appearance of the hand in Morquio's syndrome.

Thoracolumbar kyphosis may be the first deformity noted by the parents. The child will also have genu valgum. Dwarfing is primarily due to shortness of the trunk rather than the limbs. The neck is short. The child stands with the knees and hips flexed in a crouched position and the head thrust forward and sunk between the high shoulders. The eyes are wide-set, the nasal bridge is depressed, and the maxilla is prominent. The abdomen may protrude, but hepatosplenomegaly is not associated with this particular mucopolysaccharidosis.

The epiphyses of the knees, elbows, shoulders, wrists, and ankles appear enlarged. Generalized joint laxity is a feature of Morquio's syndrome, making it distinctly different from the other mucopolysaccharidoses, in which joint stiff-

ness is the rule. Ankle valgus and flatfeet are present. Muscle weakness may be noted. The gait is waddling, and the hands and feet are short.

Corneal opacities develop later. Nearly all patients have hearing loss by the end of the first decade.[72] Silent cardiac abnormalities are found in many patients with Morquio's syndrome, particularly mitral and aortic valve thickening and stenosis.[41] Restrictive lung disease results from abnormalities in the shape and mechanics of the chest wall.[15] Pectus carinatum is present. The sternal segments fuse prematurely, with consequent restriction of chest excursion and reduced vital capacity.

Radiographic Findings. The radiographic features of Morquio's disease are distinctive. The vertebral bodies in the thoracic and lumbar spine are ovoid in infancy, but with time they become flattened (termed *platyspondyly*). A central tongue or anterior beak becomes obvious in the lower thoracic and upper lumbar vertebrae (Fig. 29–85A). The disks are narrower than normal. Kyphosis is common. Hypoplasia or absence of the odontoid process is a characteristic feature of Morquio's syndrome (Figs. 29–85B and C).

The epiphyses of the long bones ossify irregularly and, as a result, are broad and flat. Ossification of the femoral heads is delayed, and the femoral necks are widened. Coxa vara or valga may occur (Fig. 29–85D). The acetabula are dysplastic. The pelvis becomes narrow with growth, resulting in a "wineglass" shape to the inner pelvic contour. The iliac wings are flared laterally.

A delay in the ossification of the lateral proximal tibial epiphysis is common. The metaphyses are widened, but the diaphyses are relatively normal. The carpals and tarsals are irregular and their ossification is delayed also. There is central constriction of the diaphyses of the metacarpals, phalanges, and metatarsals. The bases of the second through fifth metacarpals are pointy (Fig. 29–85E).

Prenatal Diagnosis. Prenatal diagnosis of Morquio's syndrome is possible. Cells present in the amniotic fluid are assayed for the presence of *N*-acetylgalactosamine-6-sulfatase. An absence of enzyme activity is predictive of the diagnosis of Morquio A syndrome.

Orthopaedic Considerations. Morquio's syndrome is the most common of the mucopolysaccharidoses to produce upper cervical instability.[88] Odontoid hypoplasia leads to upper cervical cord compression, due to instability between C1 and C2.[59] The odontoid hypoplasia is present in all patients with Morquio A disease.[62,63]

Patients usually become symptomatic between 4 and 6 years of age, when they complain of difficulty walking.[44] Parents often attribute the change in ambulation to genu valgum (Fig. 29–86). The treating orthopaedist must be aware of the potential cervical spinal cord problems, and lateral flexion-extension radiographs must be obtained before surgical treatment of the genu valgum is considered. In most cases the patient's decreased endurance is due to subtle myelopathy rather than lower extremity malalignment.

Evaluation of cervical spine instability in a patient with Morquio's syndrome begins with lateral flexion-extension plain radiographs. Translation of the anterior arch of C1 and/or splaying of the posterior elements with flexion indicates instability (Figs. 29–87A and B). CT scans obtained in flexion and extension have also been used to document instability and spinal cord compression,[73] but MRI images the spinal cord better.[45] Posterior indentation of the spinal cord by the posterior arch of C1 can be seen. A few studies report the presence on MRI or myelography of an anterior soft tissue mass at C1 that further compromises the space available for the spinal cord in patients with Morquio's syndrome.[37,81] Somatosensory-evoked potentials have also been used to document the physiologic effect of upper cervical instability on the spinal cord.[83] In our experience, when spinal cord compression is suspected on imaging studies, surgical treatment should proceed, with preoperative somatosensory-evoked potentials unnecessary.

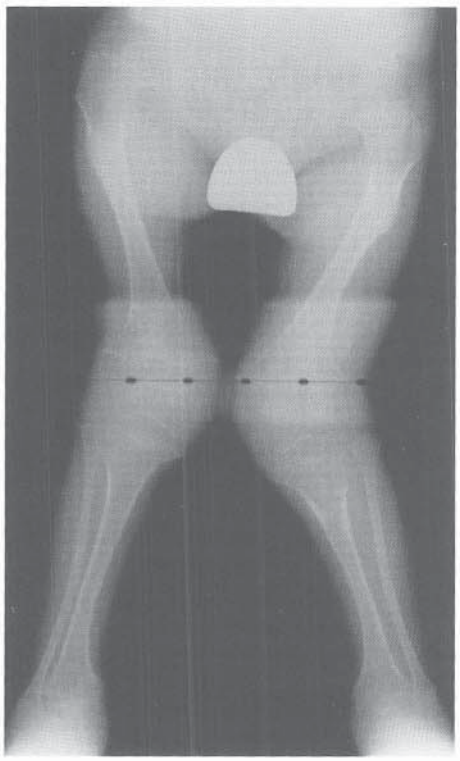
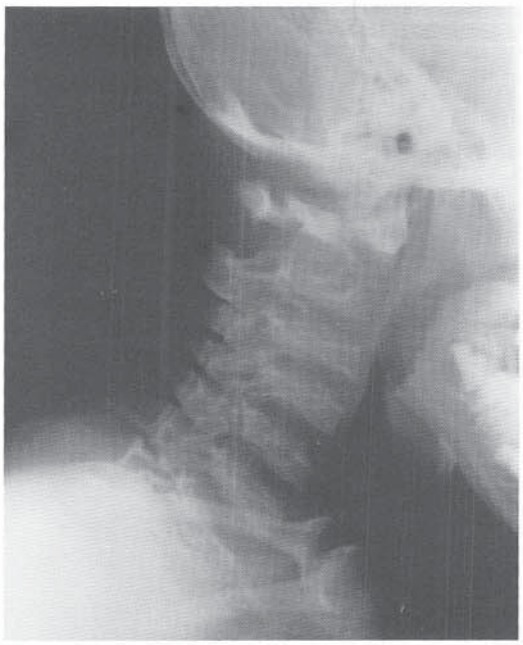


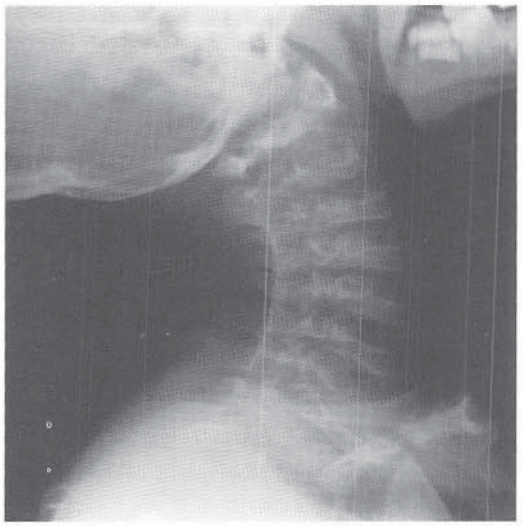
FIGURE 29–86 Excessive genu valgum in a 5-year-old boy with Morquio's syndrome and difficulty walking.

Atlantoaxial instability in Morquio's syndrome is treated by posterior spinal fusion (Fig. 29–87C).[81,88] Postoperative immobilization in a halo vest is necessary. If untreated, myelopathic changes progress rapidly, and traumatic quadriparesis and death due to respiratory arrest have both been described.[31,51] Because myelopathy rarely resolves completely following surgery, performing surgery at the first sign of instability is imperative to preserve neurologic function.[51,82,88] Some authors advocate prophylactic posterior occipitocervical fusion in patients with Morquio's syndrome, stating that once myelopathy occurs, neurologic compromise is generally permanent.[69]

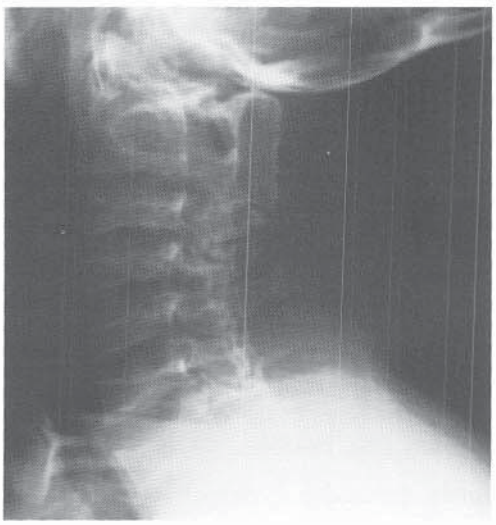
When significant anterior compression exists, anterior transoral decompression has been performed in conjunction with posterior occipitocervical fusion in patients with Morquio's syndrome. The addition of an anterior decompression adds to the difficulty of the surgery by increasing the instabil-



A



B



C

FIGURE 29–87 **A** and **B,** C1–2 instability secondary to odontoid hypoplasia in a 5-year-old boy with Morquio's syndrome who complained of difficulty walking. The genu valgum shown in Figure 29–86 was noted by the parents. **C,** Lateral radiograph obtained 3 years after successful C1–2 posterior fusion.

ity already present, but the procedure has been found necessary in a few patients with Morquio's syndrome.[4,68]

Thoracolumbar kyphosis is also commonly seen in patients with Morquio's syndrome. Anterior wedging of the T12 or L1 vertebra is often present. Occasionally the wedging does not resolve with growth and leads to a progressive kyphosis that requires orthotic treatment or even surgical fusion.[88] Left untreated, the kyphosis may progress and cause neurologic compromise.[48]

Genu valgum may be treated by realignment osteotomy after cervical instability has been ruled out or treated. Proximal femoral osteotomy for coxa vara is occasionally performed. Wrist instability usually can be treated by splinting.

MUCOPOLYSACCHARIDOSIS V (SCHEIE'S SYNDROME)

Mucopolysaccharidosis V has now been recategorized as a subtype of mucopolysaccharidosis I (Hurler's syndrome). The enzyme deficiency has been identified as α-L-iduronidase, the same defect seen in patients with Hurler's syndrome. In contrast to Hurler's syndrome, progressive neurologic deterioration is not seen, and stature is nearly normal. Musculoskeletal problems usually do not occur.

MUCOPOLYSACCHARIDOSIS VI (MAROTEAUX-LAMY SYNDROME)

This very rare mucopolysaccharidosis is due to a deficiency in arylsulfatase B, also known as *N*-acetylgalactosamine-4-sulfatase. It is inherited as an autosomal recessive trait, as are most enzyme deficiencies. There is an abnormal accumulation of the GAG dermatan sulfate.

The disease usually manifests at 2 to 3 years of age, when shortness of the trunk and limbs, genu valgum, lumbar kyphosis, and pectus carinatum become apparent. Spinal cord compression may occur.[50,74] Corneal opacities and hepatosplenomegaly are present. Cardiomyopathy may be seen in young children.[34] Skeletal abnormalities closely resemble

those seen in Hurler's syndrome, but intelligence is normal in Maroteaux-Lamy syndrome.

There is a spectrum of clinical involvement. This is supported by molecular genetic research, which shows several mutations that produce various forms of the syndrome.[40,52] Bone marrow and stem cell transplants and gene therapy have been proposed as treatments.[3,24,67]

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Niemann-Pick Disease

Niemann-Pick disease has been subtyped into three major forms. In types A and B, there is a deficiency in sphingomyelinase, which results in the accumulation of large foam cells containing phospholipids.[1] Type A presents with severe neurodegeneration in infancy and is lethal. Type B presents in childhood and has a milder course without neurologic involvement.[3] Type C is due to a defect in cholesterol transport, resulting in accumulation of intracellular, unesterified cholesterol.[4] All three forms produce hepatosplenomegaly, while types A and C cause neurologic deterioration and mental retardation. All three disorders are inherited as autosomal recessive traits. The gene for type C has been localized to chromosome 18.[2]

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